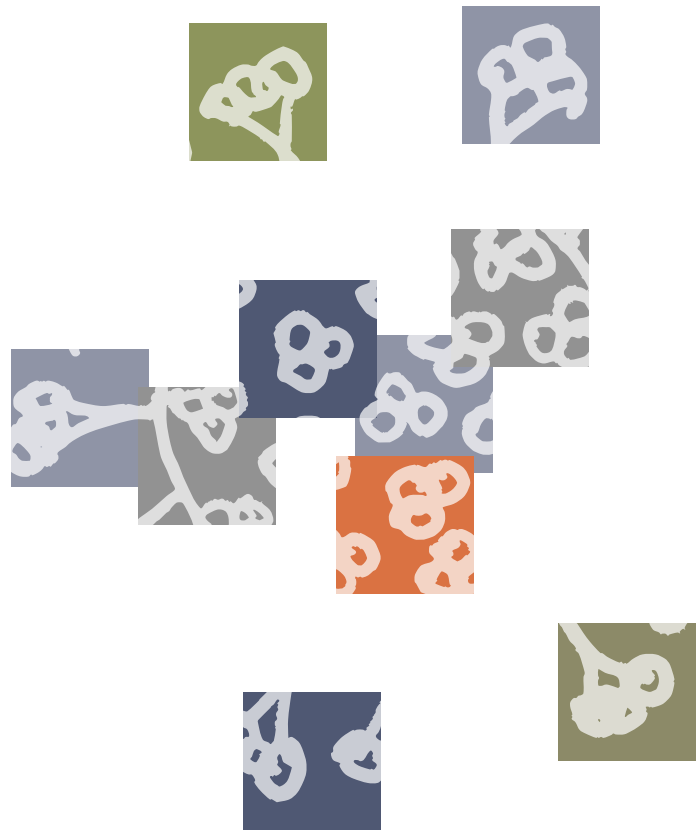
Christian Hoffmann
Bernd Sebastian Kamps

COVID REFERENCE *top10*

Daily Science vol. 1/2



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COVID Reference Top 10
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Volume 1

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Daily Science
Volume 1

Steinhäuser Verlag

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Preface

Here we publish in a single PDF the daily Top 10 scientific papers we have presented ever since COVID Reference's first edition on 29 March 2020. There is no secret to our procedure: the daily scanning of the literature helps us to stay afloat in the never-ending waves of new publications about SARS-CoV-2 and COVID-19. Many papers discussed in the Top 10 will eventually make it into subsequent editions of COVID Reference.

We dedicate this book to our students. May this selection of approx. 1,000 fine articles and full-text links deepen their understanding of the new coronavirus and prepare them for the challenges ahead.

Christian Hoffmann & Bernd Sebastian Kamps

15 July 2020

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First Authors

The authors of the articles presented before June will be added in a future update.

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6 September	586	26 September	659		

22 Papers

If you don't read anything, read at least the following 22 papers.

1. Guan WJ, Ni ZY, Hu Y, et al. **Clinical Characteristics of Coronavirus Disease 2019 in China.** N Engl J Med. 2020 Apr 30;382(18):1708-1720. PubMed: https://pubmed.gov/32109013. Full-text: https://doi.org/10.1056/NEJMoa2002032 ●● (Outstanding)

2. van Doremalen N, Bushmaker T, Morris DH, et al. **Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1.** N Engl J Med. 2020 Mar 17. PubMed: https://pubmed.gov/32182409. Fulltext: https://doi.org/10.1056/NEJMc2004973 ●● (Outstanding)

3. Cao B, Wang Y, Wen D, et al. **A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19.** N Engl J Med. 2020 Mar 18. PubMed: https://pubmed.gov/32187464. Fulltext: https://doi.org/10.1056/NEJMoa2001282 ●● (Outstanding)

4. Yu F, Yan L, Wang N, et al. **Quantitative Detection and Viral Load Analysis of SARS-CoV-2 in Infected Patients.** Clin Infect Dis. 2020 Mar 28. PubMed: https://pubmed.gov/32221523. Fulltext: https://doi.org/10.1093/cid/ciaa345 ●● (Outstanding) | Is sputum sufficient for diagnosis? In a total of 323 samples from 76 pts, the average viral load in sputum (17429 copies/test) was significantly higher than in throat swabs (2552) and nasal swabs (651). Viral load was also higher in the early and progressive stages than in the recovery stage. If these data are confirmed, collection of specimen would be much easier.

5. Wölfel R, Corman VM, Guggemos W. et al. **Virological assessment of hospitalized patients with COVID-2019**. Nature 2020, April 1. Full-text: https://doi.org/10.1038/s41586-020-2196-x ●● (Outstanding) | Important work, showing active virus replication in upper respiratory tract tissues (in contrast to SARS). In a detailed virological analysis of nine cases, pharyngeal virus shedding was very high during the first week of symptoms (peak at 7.11×10^8 RNA copies per throat swab, day 4), more than 1000 times higher than seen with SARS-CoV. Infectious virus was readily

isolated from throat- and lung-derived samples, but not from stool samples, in spite of high virus RNA concentration. Blood and urine never yielded virus. Shedding of viral RNA from sputum continued after the end of symptoms.

6. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. **Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2.** Science. 2020 Mar 27;367(6485):1444-1448. PubMed: https://pubmed.gov/32132184. Full-text: https://doi.org/10.1126/science.abb2762 ●● (Outstanding) | Using cryo–electron microscopy, it is shown how SARS-CoV-2 binds to human cells. The first step in viral entry is the binding of the viral trimeric spike protein to the human receptor angiotensin-converting enzyme 2 (ACE2). Authors present the structure of human ACE2 in complex with a membrane protein that it chaperones, B0AT1. The structures provide a basis for the development of therapeutics targeting this crucial interaction.

7. Lan J, Ge J, Yu J, et al. **Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor.** Nature. 2020 May;581(7807):215-220. PubMed: https://pubmed.gov/32225176. Full-text: https://doi.org/10.1038/s41586-020-2180-5 ●● (Outstanding) | To elucidate the SARS-CoV-2 RBD and ACE2 interaction at a higher resolution/atomic level, authors used X-ray crystallography. Binding mode was very similar to SARS-CoV, arguing for convergent evolution of both viruses. The epitopes of two SARS-CoV antibodies targeting the RBD were also analysed with the SARS-CoV-2 RBD, providing insights into the future identification of cross-reactive antibodies.

8. Leung NHL, Chu DKW, Shiu EYC, et al. **Respiratory virus shedding in exhaled breath and efficacy of face masks.** Nat Med. 2020 May;26(5):676-680. PubMed: https://pubmed.gov/32371934. Full-text: https://doi.org/10.1038/s41591-020-0843-2 ●● (Outstanding) | Do face masks work? Yes, but it depends. This important study from Hong Kong (performed 2013-16) quantified virus in respiratory droplets and aerosols in exhaled breath. In total, 111 participants (infected with seasonal coronavirus, influenza or rhinovirus) were randomized to wear (or not) a simple surgical face mask. Results suggested that masks could be used by ill people to reduce onward transmission. But note the small numbers: in respiratory droplets, seasonal coronavirus was found in 0/11 droplets

(aerosols: 0/11) from participants wearing face masks, compared to 3/10 (aerosols: 4/10) without masks. Influenza viruses were detected in 1/27 (aerosols 6/27!) with face masks, compared to 6/23 (8/23) without. For rhinovirus, there were no significant differences at all. Of note, authors also identified virus in some participants who did not cough at all during the 30-min exhaled breath collection, suggesting droplet and aerosol routes of transmission from individuals with no obvious signs or symptoms.

9. He X, Lau EHY, Wu P, et al. **Temporal dynamics in viral shedding and transmissibility of COVID-19**. Nat Med. 2020 Apr 15. PubMed: https://pubmed.gov/32296168. Full-text: https://doi.org/10.1038/s41591-020-0869-5 ●● (Outstanding) | Important work on viral shedding: this may begin 2 to 3 days before the appearance of the first symptoms and infectiousness profile may more closely resemble that of influenza than that of SARS. Analyzing a total of 414 throat swabs in 94 patients, the highest viral load was found at the time of symptom onset. Infectiousness started from 2.3 days (95% CI, 0.8–3.0 days) before symptom onset and peaked at 0.7 days (95% CI, -0.2–2.0 days) before symptom onset. The authors estimated that 44% (95%CI 25-69%) of secondary cases were infected during the index cases' presymptomatic stage. Infectiousness was estimated to decline quickly within 7 days.

10. Long QX, Liu BZ, Deng HJ, et al. **Antibody responses to SARS-CoV-2 in patients with COVID-19.** Nat Med. 2020 Jun;26(6):845-848. PubMed: https://pubmed.gov/32350462. Full-text: https://doi.org/10.1038/s41591-020-0897-1 ●● (Outstanding) | One of the largest studies to date, reporting on acute antibody responses (using magnetic chemiluminescence enzyme immunoassay) in 285 patients (mostly non-severe COVID-19, 39 treated at ICU). Within 19 days after symptom onset, 100% of patients tested positive for antiviral IgG. Seroconversion for IgG and IgM occurred simultaneously or sequentially. Both IgG and IgM titers plateaued within 6 days after seroconversion. The median day of seroconversion for both IgG and IgM was 13 days post-symptom onset. No association between plateau IgG levels and clinical characteristics of the patients was found.

11. Wang C, Li W, Drabek D, et al. **A human monoclonal antibody blocking SARS-CoV-2 infection**. Nat Commun. 2020 May 4;11(1):2251. PubMed: https://pubmed.gov/32366817. Full-text: https://doi.org/10.1038/s41467-020-16256-y ●● (Outstanding) | The first report of a human monoclonal antibody that neutralizes SARS-CoV-2. 47D11 binds a conserved epitope on the spike RBD explaining its ability to cross-neutralize SARS-CoV and SARS-CoV-2, using a mechanism that is independent of receptor-binding inhibition. This antibody could be useful for development of antigen detection tests and serological assays targeting SARS-CoV-2.

12. Vabret N, Britton GJ, Gruber C, et al. **Immunology of COVID-19: Current State of the Science.** Immunity. 2020 Jun 16;52(6):910-941. PubMed: https://pubmed.gov/32505227. Full-text: https://doi.org/10.1016/j.immuni.2020.05.002 ●● (Outstanding) | Brilliant review on the current knowledge of innate and adaptive immune responses elicited by SARS-CoV-2 infection and the immunological pathways that likely contribute to disease severity and death.

13. Grifoni A, Weiskopf D, Ramirez SI, et al. **Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals.** Cell. 2020 Jun 25;181(7):1489-1501.e15. PubMed: https://pubmed.gov/32473127. Full-text: https://doi.org/10.1016/j.cell.2020.05.015 ●● (Outstanding) | Cellular response is a major knowledge gap. This important study identified circulating SARS-CoV-2–specific CD8 and CD4 T cells in around 70 and 100% of 20 COVID-19 convalescent patients, respectively. CD4 T cell responses to the spike protein were robust and correlated with the magnitude of IgG titers. Of note, the authors detected SARS-CoV-2–reactive CD4 T cells in 40-60% of unexposed individuals, suggesting cross-reactive T cell recognition between circulating seasonal coronaviruses and SARS-CoV-2.

14. Blanco-Melo D, Nilsson-Payant BE, Liu WC, et al. **Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19.** Cell. 2020 May 28;181(5):1036-1045.e9. PubMed: https://pubmed.gov/32416070. Full-text: https://doi.org/10.1016/j.cell.2020.04.026 ●● (Outstanding) | Incredible in-depth analysis of host response to SARS-CoV-2 and other human respiratory viruses in cell lines, primary cell cultures, ferrets, and COVID-19 patients. Data consistently revealed a unique

and inappropriate inflammatory response to SARS-CoV-2 which is imbalanced with regard to controlling virus replication versus activation of the adaptive immune response. It is defined by low levels of type I and III interferons juxtaposed to elevated chemokines and high expression of IL-6. The authors propose that reduced innate antiviral defenses coupled with exuberant inflammatory cytokine production are the defining and driving features of COVID-19. Given this dynamic, treatments for COVID-19 have less to do with the IFN response and more to do with controlling inflammation.

15. Zhang X, Tan Y, Ling Y, et al. **Viral and host factors related to the clinical outcome of COVID-19.** Nature. 2020 May 20. PubMed: https://pubmed.gov/32434211. Full-text: https://doi.org/10.1038/s41586-020-2355-0 ●● (OUTSTANDING) | Viral variants do not affect outcome. This important study on 326 cases found at least two major lineages with differential exposure history during the early phase of the outbreak in Wuhan. Patients infected with these different clades did not exhibit significant difference in clinical features, mutation rate or transmissibility. Lymphocytopenia, especially a reduced CD4+ and CD8+ T cell counts upon admission, was predictive of disease progression. High levels of IL-6 and IL-8 during treatment were observed in patients with severe or critical disease and correlated with decreased lymphocyte count. The determinants of disease severity seemed to stem mostly from host factors such as age, lymphocytopenia, and its associated cytokine storm.

16. Docherty AB, Harrison EM, Green CA, et al. **Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study.** BMJ. 2020 May 22;369:m1985. PubMed: https://pubmed.gov/32444460. Full-text: https://doi.org/10.1136/bmj.m1985 ●● (OUTSTANDING) | Clinical data from 20,133 patients, admitted to (or diagnosed in) 208 acute care hospitals in the UK until April 19. Median age was 73 years (interquartile range 58-82) and 60% were men. Comorbidities were common, namely chronic cardiac disease (31%), diabetes (21%), non-asthmatic chronic pulmonary disease (18%). Overall, 41% of patients were discharged alive, 26% died, and 34% continued to receive care. 17% required admission to high dependency or intensive care units; of these, 28% were discharged alive, 32% died, and 41% continued to receive care.

Of those receiving mechanical ventilation, 17% were discharged alive, 37% died, and 46% remained in hospital. Increasing age, male sex, and comorbidities including chronic cardiac disease, non-asthmatic chronic pulmonary disease, chronic kidney disease, liver disease and obesity were associated with higher mortality in hospital.

17. Somsen GA, van Rijn C, Kooij S, Bem RA, Bonn D. **Small droplet aerosols in poorly ventilated spaces and SARS-CoV-2 transmission**. Lancet Respir Med. 2020 May 27. PubMed: https://pubmed.gov/32473123. Full-text: https://doi.org/10.1016/S2213-2600(20)30245-9 ●● (Outstanding) | Doors and windows open! Important study, analyzing droplet production due to coughs and speech by measuring the droplet size distribution, travel distance and velocity, and the airborne time in relation to the level of air ventilation (no ventilation, mechanical ventilation only, and mechanical ventilation supported by the opening of an entrance door and a small window). In the best ventilated room, after 30 s the number of droplets had halved, whereas with no ventilation this took about 5 min!

18. Boulware DR, Pullen MF, Bangdiwala AS, et al. **A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19.** N Engl J Med. 2020 Jun 3:NEJMoa2016638. PubMed: https://pubmed.gov/32492293. Full-text: https://doi.org/10.1056/NEJMoa2016638 ●● (Outstanding) | In total, 821 asymptomatic participants were randomized to receive hydroxychloroquine or placebo within 4 days after exposure (88% with a high-risk exposure). Incidence of confirmed SARS-CoV-2 was 11.8% with CQ and 14.3% with placebo. Side effects were more common with hydroxychloroquine than with placebo (40.1% vs. 16.8%), but no serious adverse reactions were reported. This is bad news because after high-risk or moderate-risk exposure to Covid-19, HCQ did not prevent infection when used as post-exposure prophylaxis within 4 days after exposure.

19. Day T, Gandon S, Lion S, et al. **On the evolutionary epidemiology of SARS-CoV-2.** Curr Biol 2020, June 11. Full-text: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7287426 ●● (Outstanding) | Outstanding essay about what little is currently known about the evolution of SARS-CoV-2. At present, there is a lack of compelling evidence that any existing variants impact the progression, severity, or transmission of COVID-19 in an adaptive manner. The authors discuss

the potential evolutionary routes that SARS-CoV-2 might take and dispel some of the current misinformation that is circulating in the media.

20. Major J, Crotta S, Llorian M, et al. **Type I and III interferons disrupt lung epithelial repair during recovery from viral infection.** Science. 2020 Jun 11:eabc2061. PubMed: https://pubmed.gov/32527928. Full-text: https://doi.org/10.1126/science.abc2061 ●● (Outstanding) | Key message: Interferon may be helpful during early infection and harmful at later stages. IFN-λ mainly signals in epithelia, inducing localized antiviral immunity, and has a key role in the reduction of epithelial proliferation and differentiation during lung repair. In animal and cell experiments, the authors show that IFN-induced p53 directly reduces epithelial proliferation and differentiation, increasing disease severity and susceptibility to bacterial superinfections. Excessive or prolonged IFN production may aggravate viral infection by impairing lung epithelial regeneration.

21. Pfeifer M, Ewig S, Voshaar T, et al. **Position Paper for the State-of-the-Art Application of Respiratory Support in Patients with COVID-19**. Respiration. 2020 Jun 19:1-21. PubMed: https://pubmed.gov/32564028. Full-text: https://doi.org/10.1159/000509104 ●● (Outstanding) | Important statements including observations about the pathophysiology of acute respiratory failure (ARF). Pulmonary damage in advanced COVID-19 often differs from acute respiratory distress syndrome (ARDS). Two types (type L and type H) are differentiated, corresponding to early- and late-stage lung damage. This differentiation should be taken into consideration in respiratory support. Based on current knowledge, inhalation therapy, nasal high-flow therapy (NHF), continuous positive airway pressure (CPAP), or non-invasive ventilation (NIV) can be performed without an increased risk of infection to staff if PPE is provided. In ARF, NIV should be carried out in an intensive care unit or a comparable setting by experienced staff. If the ARF progresses under CPAP/NIV, intubation should be implemented without delay in patients who do not have a "do not intubate".

22. Bouhaddou M, Memon D, Meyer B, et al. **The Global Phosphorylation Landscape of SARS-CoV-2 Infection.** Cell. 2020 Jun 28:S0092-8674(20)30811-4. PubMed: https://pubmed.gov/32645325. Full-text: https://doi.org/10.1016/j.cell.2020.06.034 ●● (Outstanding) | Nothing to do next weekend? Then read this incredible work of 66 pages (> 400 references!). In brief: proteomics approaches that globally quantify changes in

protein abundance and phosphorylation represent a powerful tool to elucidate mechanisms of viral pathogenesis by providing a snapshot of how cellular pathways and processes are rewired upon infection. Using a quantitative mass spectrometry-based phosphoproteomics survey of SARS-CoV-2 infection in Vero E6 cells, the 78 (!) authors present the global phosphorylation and protein abundance landscape of SARS-CoV-2 infection, map phosphorylation changes to disrupted kinases and pathways, and use these profiles to find drugs with the potential to treat SARS-CoV-2 infection. In total, 87 compounds (10 FDA-approved drugs) were identified.

Pre-Top 10 Era

New Year 2020

30 December

ProMed (International Society for Infectious Diseases). **Undiagnosed pneumonia - China (HU): RFI.** Archive Number: 20191230.6864153. Full-text: https://promedmail.org/promed-post/?id=6864153 ●●

This email is the first message that alerted the world to what was to become the worst health crisis in 100 years.

8 January

Cyranoski D. **New virus identified as likely cause of mystery illness in China.** Nature (News). Full-text: https://www.nature.com/articles/d41586-020-00020-9 ●●

The first news report in a major scientific journal. A day later, an updated version reports a new coronavirus as the likely cause of the pneumonia-like illness. The virus's genome is sequenced.

14 January

Hui DS, I Azhar E, Madani TA, Ntoumi F, Kock R, Dar O, Ippolito G, Mchugh TD, Memish ZA, Drosten C, Zumla A, Petersen E. **The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China.** Int J Infect Dis. 2020 Feb; 91:264-266. PubMed: https://pubmed.gov/31953166. Full-text: https://doi.org/10.1016/j.ijid.2020.01.009

These two articles by Hui et al. and Bogoch et al. relate the questioning of researchers during the first two SARS-CoV-2 weeks of the year 2020. At that *neonatal* stage of the pandemic there was still "no clear evidence of human to human transmission."

On January 14, SARS-CoV-2 was still called *2019-nCov*.

Bogoch II, Watts A, Thomas-Bachli A, Huber C, Kraemer MUG, Khan K. **Pneumonia of unknown aetiology in Wuhan, China: potential for international spread via commercial air travel.** J Travel Med. 2020 Mar 13;27(2):taaa008. PubMed: https://pubmed.gov/31943059. Full-text: https://doi.org/10.1093/jtm/taaa008

The authors evaluate international travel patterns from Wuhan in order to anticipate the spread of a new coronavirus. The top 7 destination cities for passengers arriving from Wuhan (January to March 2018) were Bangkok, Hong Kong, Tokyo, Taipei, Phuket, Seoul and Singapore.

17 January

Imai N, et al. (Imperial College London) **Estimating the potential total number of novel Coronavirus cases in Wuhan City, China.** Full-text: https://doi.org/10.25561/77149

The authors contradict official figures published by the People's Republic of China, estimating that a total of more than 1,700 cases of 2019-nCoV in Wuhan City had onset of symptoms by 12 January 2020 – while officially, less than 100 cases were reported by mid-January. How did they do the math? They analyzed the volume of international travel from Wuhan.

24 January

Huang C, Wang Y, Li X, et al. **Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.** Lancet. 2020 Feb 15;395(10223):497-506. PubMed: https://pubmed.gov/31986264. Full-text: https://doi.org/10.1016/S0140-6736(20)30183-5 ● (IMPORTANT)

The first clinical paper about what would later be called COVID-19. The authors describe 41 patients with a median age of 49 years admitted by 2 January to Jin Yin-Tan Hospital (金银潭医院), Wuhan. Thirteen patients (32%) needed ICU care and 6 patients died (15%). The paper offers the first glimpse at laboratory prognostic markers.

Chan JF, Yuan S, Kok KH, et al. **A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster.** Lancet. 2020 Feb 15;395(10223):514-523. PubMed: https://pubmed.gov/31986261. Fulltext: https://doi.org/10.1016/S0140-6736(20)30154-9 ● (IMPORTANT)

The first paper on person-to-person transmission. It is also an excellent exercise: try and find your way through the intricate relationships of a family of 6 travellers from Shenzhen (two grandparents, their daughter and son-in-law and two grandchildren) and their five relatives in Wuhan.

30 January

Chen N, Zhou M, Dong X, et al. **Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study.** Lancet. 2020 Feb 15;395(10223):507-513. PubMed: https://pubmed.gov/32007143. Full-text: https://doi.org/10.1016/S0140-6736(20)30211-7

The second clinical paper, again from Jin Yin-Tan Hospital. In this extended investigation of the previous report (see 24 January, Huang C et al.), 49 of 99 patients had a history of exposure to the Huanan seafood market. The average age of the patients was 55.5 years. Two thirds of the patients were men and 51% had previous chronic diseases. The authors identify older men with comorbidities as a special risk group.

Rothe C, Schunk M, Sothmann P, et al. **Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany.** N Engl J Med 2020;382:970-971. https://pubmed.gov/32003551. Full-text: https://doi.org/10.1056/NEJMc2001468 ● (IMPORTANT)

The authors report the case of a businesswoman from Shanghai who infected at least one business partner during a trip to Germany. During her stay, she had apparently been well with no signs or symptoms of infection but had become ill on her flight back to China, where she tested positive for SARS-CoV-2 a few days after her return. The authors suggest that asymptomatic persons may be potential sources of SARS-CoV-2 infection. (And right they were! To clarify whether the index patient in question has been correctly described as asymptomatic, the authors spoke with her by telephone on 5 February 2020. Read the summary of the call.)

February 2020

3 February

Zhou P, Yang XL, Wang XG, et al. **A pneumonia outbreak associated with a new coronavirus of probable bat origin.** Nature. 2020 Mar;579(7798):270-273. PubMed: https://pubmed.gov/32015507. Full-text: https://doi.org/10.1038/s41586-020-2012-7

The authors report the identification and characterization of a new coronavirus and obtain full-length genome sequences from five patients at an early stage of the outbreak. The sequences are almost identical and share 80% sequence identity to SARS-CoV. The virus is also 96% identical at the whole-genome level to a bat coronavirus. The authors confirm that the new virus uses the same cell entry receptor—angiotensin converting enzyme II (ACE2)—as SARS-CoV.

4 February

Wang M, Cao R, Zhang L, et al. **Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro.** Cell Res. 2020 Mar;30(3):269-271. PubMed: https://pubmed.gov/32020029. Full-text: https://doi.org/10.1038/s41422-020-0282-0

The paper that was at the origin of the hydroxychloroquine frenzy. In human trials, hydroxychloroquine was subsequently shown to have no clinical benefit. Likewise, the clinical effect of remdesivir is, at best, modest.

5 February

Zumla A, Hui DS, Azhar EI, Memish ZA, Maeurer M. **Reducing mortality from 2019-nCoV: host-directed therapies should be an option.** Lancet. 2020 Feb 22;395(10224):e35-e36. PubMed: https://pubmed.gov/32035018. Full-text: https://doi.org/10.1016/S0140-6736(20)30305-6

The first discussion of host-directed therapies. The authors remind us that during the SARS-CoV-1 and MERS-CoV outbreaks, several unique opportunities to evaluate a range of treatment interventions were missed. The SARS-

CoV-2 pandemic may elucidate questions about coronavirus pathogenesis that remained unanswered during the previous coronavirus epidemics.

7 February

Shen K, Yang Y, Wang T, et al. **Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement.** World J Pediatr. 2020 Feb 7. PubMed: https://pubmed.gov/32034659. Fulltext: https://doi.org/10.1007/s12519-020-00343-7

The first Chinese consensus statement on pediatric COVID-19 informs that most infected children have mild clinical manifestations. They have no fever or symptoms of pneumonia with a good prognosis. Most of them recover within 1–2 weeks after disease onset. Only a few children progress to lower respiratory infections.

12 February

Shang L, Zhao J, Hu Y, Du R, Cao B. **On the use of corticosteroids for 2019-nCoV pneumonia.** Lancet. 2020 Feb 29;395(10225):683-684. PubMed: https://pubmed.gov/32122468. Full-text: https://doi.org/10.1016/S0140-6736(20)30361-5

A group of physicians from the Chinese Thoracic Society propose to use corticosteroids prudently in critically ill patients with 2019-nCoV pneumonia; to be particularly cautious with patients who have hypoxemia due to underlying diseases or who regularly use corticosteroids for chronic diseases; and to use low-to-moderate doses (≤0·5 – 1 mg/kg per day methylprednisolone or equivalent) for ≤ 7 days.

Chen H, Guo J, Wang C, et al. **Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records.** Lancet. 2020 Mar 7;395(10226):809-815. PubMed: https://pubmed.gov/32151335. Full-text: https://doi.org/10.1016/S0140-6736(20)30360-3

The authors report 9 pregnant women with laboratory-confirmed COVID-19 pneumonia who were admitted to Zhongnan Hospital of Wuhan University. The clinical characteristics were similar to those reported for non-pregnant adult patients who developed COVID-19 pneumonia. The authors find no evidence for intrauterine SARS-CoV-2 infection in late pregnancy. A comment of

the paper three weeks later by Qiao J: **What are the risks of COVID-19 infection in pregnant women?** Lancet. 2020 Mar 7;395(10226):760-762. PubMed: https://pubmed.gov/32151334. Full-text: https://doi.org/10.1016/S0140-6736(20)30365-2

21 February

Bai Y, Yao L, Wei T, et al. **Presumed Asymptomatic Carrier Transmission of COVID-19. JAMA.** 2020 Feb 21. PubMed: https://pubmed.gov/32083643. Fulltext: https://doi.org/10.1001/jama.2020.2565 ● (IMPORTANT)

The authors describe a familial cluster of 5 patients with COVID-19 pneumonia in Anyang, China. Four were women, and ages ranged from 42 to 57 years. None of the patients had visited Wuhan or been in contact with any other people who had traveled to Wuhan – except an asymptomatic family member who lived in Wuhan and traveled to Anyang on January 10, 2020. The authors warn that if their findings of presumed transmission by an asymptomatic carrier are replicated, the prevention of COVID-19 infection would prove challenging.

24 February

Wu Z, McGoogan JM. **Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention.** JAMA. 2020 Feb 24. PubMed: https://pubmed.gov/32091533. Fulltext: https://doi.org/10.1001/jama.2020.2648 ● (IMPORTANT)

A bonanza of data at a fairly early stage of the pandemic – and shocking numbers at a moment when local epidemics were taking off in Europe. A must-read for everyone.

Spectrum of disease:

- Mild: 81%
- Severe: 14%
- Critical: 5%

Case-fatality rate:

- 14.8% in patients aged ≥ 80 years
- 8.0% in patients aged 70-79 years

* Summaries of the articles from
24 February until 27 March will be added later. *

Pan Y, Zhang D, Yang P, Poon LLM, Wang Q. **Viral load of SARS-CoV-2 in clinical samples.** Lancet Infect Dis. 2020 Feb 24. PubMed: https://pubmed.gov/32105638. Fulltext: https://doi.org/10.1016/S1473-3099(20)30113-4

The first description of two patients who had positive results on RT-PCR a day before symptom onset, suggesting that infected individuals can be infectious before they become symptomatic.

Cheung JC, Ho LT, Cheng JV, Cham EYK, Lam KN. **Staff safety during emergency airway management for COVID-19 in Hong Kong.** Lancet Respir Med. 2020 Apr;8(4):e19. PubMed: https://pubmed.gov/32105633. Full-text: https://doi.org/10.1016/S2213-2600(20)30084-9

25 February

Ji Y, Ma Z, Peppelenbosch MP, Pan Q. **Potential association between COVID-19 mortality and health-care resource availability.** Lancet Glob Health. 2020 Apr;8(4):e480. PubMed: https://pubmed.gov/32109372. Full-text: https://doi.org/10.1016/S2214-109X(20)30068-1

26 February

Ai T, Yang Z, Hou H, et al. **Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases.** Radiology. 2020 Feb 26:200642. PubMed: https://pubmed.gov/32101510. Fulltext: https://doi.org/10.1148/radiol.2020200642

27 February

Stebbing J, Phelan A, Griffin I, et al. **COVID-19: combining antiviral and anti-inflammatory treatments.** Lancet Infect Dis. 2020 Apr;20(4):400-402.

PubMed: https://pubmed.gov/32113509. Full-text: https://doi.org/10.1016/S1473-3099(20)30132-8

Lan L, Xu D, Ye G, et al. **Positive RT-PCR Test Results in Patients Recovered From COVID-19.** JAMA. 2020 Feb 27. PubMed: https://pubmed.gov/32105304. Fulltext: https://doi.org/10.1001/jama.2020.2783

28 February

Guan WJ, Ni ZY, Hu Y, et al. **Clinical Characteristics of Coronavirus Disease 2019 in China.** N Engl J Med. 2020 Apr 30;382(18):1708-1720. PubMed: https://pubmed.gov/32109013. Full-text: https://doi.org/10.1056/NEJMoa2002032 ●● (OUTSTANDING)

European Centre for Disease Prevention and Control. **Checklist for hospitals preparing for the reception and care of coronavirus 2019 (COVID-19) patients.** ECDC: Stockholm; 2020. Full-text: https://bit.ly/3iC4ASL

March 2020

3 March

Xia Y, Jin R, Zhao J, Li W, Shen H. **Risk of COVID-19 for patients with cancer.** Lancet Oncol. 2020 Apr;21(4):e180. PubMed: https://pubmed.gov/32142622. Full-text: https://doi.org/10.1016/S1470-2045(20)30150-9

5 March

Hoffmann M, Kleine-Weber H, Schroeder S, et al. **SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor.** Cell. 2020 Apr 16;181(2):271-280.e8. PubMed: https://pubmed.gov/32142651. Full-text: https://doi.org/10.1016/j.cell.2020.02.052 ● (IMPORTANT)

10 March

Hong H, Wang Y, Chung HT, Chen CJ. **Clinical characteristics of novel coronavirus disease 2019 (COVID-19) in newborns, infants and children.** Pediatr Neonatol. 2020 Mar 10. PubMed: https://pubmed.gov/32199864. Fulltext: https://doi.org/10.1016/j.pedneo.2020.03.001

13 March

Wu C, Chen X, Cai Y, et al. **Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China.** JAMA Intern Med. 2020 Mar 13:e200994. PubMed: https://pubmed.gov/32167524. Full-text: https://doi.org/10.1001/jamainternmed.2020.0994

16 March

Ferguson N, et al. (Imperial College COVID-19 Response Team) **Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand.** 16 March 2020. Full-text: https://doi.org/10.25561/77482 ● (IMPORTANT)

17 March

van Doremalen N, Bushmaker T, Morris DH, et al. **Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1.** N Engl J Med. 2020 Mar 17. PubMed: https://pubmed.gov/32182409. Fulltext: https://doi.org/10.1056/NEJMc2004973 ●● (OUTSTANDING)

Wang Y, Liu Y, Liu L, Wang X, Luo N, Li L. **Clinical Outcomes in 55 Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Who Were Asymptomatic at Hospital Admission in Shenzhen, China.** J Infect Dis. 2020 May 11;221(11):1770-1774. PubMed: https://pubmed.gov/32179910. Full-text: https://doi.org/10.1093/infdis/jiaa119

18 March

Cao B, Wang Y, Wen D, et al. **A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19.** N Engl J Med. 2020 Mar 18. PubMed: https://pubmed.gov/32187464. Fulltext: https://doi.org/10.1056/NEJMoa2001282 ●● (OUTSTANDING)

Liu D, Li L, Wu X, et al. **Pregnancy and Perinatal Outcomes of Women With Coronavirus Disease (COVID-19) Pneumonia: A Preliminary Analysis.** AJR Am J Roentgenol. 2020 Jul;215(1):127-132. PubMed: https://pubmed.gov/32186894. Full-text: https://doi.org/10.2214/AJR.20.23072

Luo M, Cao S, Wei L, et al. **Precautions for Intubating Patients with COVID-19. Anesthesiology.** 2020 Mar 19. PubMed: https://pubmed.gov/32195703. Fulltext: https://doi.org/10.1097/ALN.0000000000003288

19 March

Liu Y, Yan LM, Wan L, et al. **Viral dynamics in mild and severe cases of COVID-19.** Lancet Infect Dis. 2020 Mar 19. PubMed: https://pubmed.gov/32199493. Fulltext: https://doi.org/10.1016/S1473-3099(20)30232-2

Wu JT, Leung K, Bushman M, et al. **Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China.** Nat Med. 2020 Apr;26(4):506-510. PubMed: https://pubmed.gov/32284616. Full-text: https://doi.org/10.1038/s41591-020-0822-7 ● (IMPORTANT)

20 March

Zhang L, Lin D, Sun X, et al. **Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors.** Science. 2020 Apr 24;368(6489):409-412. PubMed: https://pubmed.gov/32198291. Full-text: https://doi.org/10.1126/science.abb3405

Hanley B, Lucas SB, Youd E, Swift B, Osborn M. **Autopsy in suspected COVID-19 cases.** J Clin Pathol. 2020 Mar 20. PubMed: https://pubmed.gov/32198191. Fulltext: https://doi.org/10.1136/jclinpath-2020-206522

Basile C, Combe C, Pizzarelli F, et al. **Recommendations for the prevention, mitigation and containment of the emerging SARS-CoV-2 (COVID-19) pandemic in haemodialysis centres.** Nephrol Dial Transplant. 2020 Mar 20. PubMed: https://pubmed.gov/32196116. Fulltext: https://doi.org/10.1093/ndt/gfaa069

Wu Y, Guo C, Tang L, et al. **Prolonged presence of SARS-CoV-2 viral RNA in faecal samples.** Lancet Gastroenterol Hepatol. 2020 Mar 19. PubMed: https://pubmed.gov/32199469. Fulltext: https://doi.org/10.1016/S2468-1253(20)30083-2 ● (IMPORTANT)

21 March

Guo L, Ren L, Yang S, et al. **Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19).** Clin Infect Dis. 2020 Mar 21. PubMed: https://pubmed.gov/32198501. Fulltext: https://doi.org/10.1093/cid/ciaa310

Clerkin KJ, Fried JA, Raikhelkar J, et al. **COVID-19 and Cardiovascular Disease.** Circulation. 2020 May 19;141(20):1648-1655. PubMed: https://pubmed.gov/32200663. Full-text: https://doi.org/10.1161/CIRCULATIONAHA.120.046941

23 March

To KK, Tsang OT, Leung WS, et al. **Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study.** Lancet Infect Dis. 2020 Mar 23. PubMed: https://pubmed.gov/32213337. Fulltext: https://doi.org/10.1016/S1473-3099(20)30196-1 ● (IMPORTANT)

24 March

Swiss Society Of Intensive Care Medicine. **Recommendations for the admission of patients with COVID-19 to intensive care and intermediate care units (ICUs and IMCUs).** Swiss Med Wkly. 2020 Mar 24;150:w20227. PubMed: https://pubmed.gov/32208493. Full-text: https://doi.org/10.4414/smw.2020.20227

Swiss Academy Of Medical Sciences. **COVID-19 pandemic: triage for intensive-care treatment under resource scarcity.** Swiss Med Wkly. 2020 Mar 24;150:w20229. PubMed: https://pubmed.gov/32208495. Full-text: https://doi.org/10.4414/smw.2020.20229

Thomas-Rüddel D, Winning J, Dickmann P, et al. **Coronavirus disease 2019 (COVID-19): update for anesthesiologists and intensivists March 2020.** Anaesthesist. 2020 Mar 24:1-10. PubMed: https://pubmed.gov/32211920. Fulltext: https://doi.org/10.1007/s00101-020-00760-3

Patel AB, Verma A. **COVID-19 and Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers: What Is the Evidence?** JAMA. 2020 Mar 24. PubMed: https://pubmed.gov/32208485. Full-text: https://doi.org/10.1001/jama.2020.4812

25 March

Mizumoto K, Kagaya K, Zarebski A, Chowell G. **Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020.** Euro Surveill. 2020 Mar;25(10):2000180. PubMed: https://pubmed.gov/32183930. Full-text: https://doi.org/10.2807/1560-7917.ES.2020.25.10.2000180 ● (IMPORTANT)

26 March

Poston JT, Patel BK, Davis AM. **Management of Critically Ill Adults With COVID-19.** JAMA. 2020 Mar 26. PubMed: https://pubmed.gov/32215647. Full-text: https://doi.org/10.1001/jama.2020.4914

Zeng L, Xia S, Yuan W, et al. **Neonatal Early-Onset Infection With SARS-CoV-2 in 33 Neonates Born to Mothers With COVID-19 in Wuhan, China.** JAMA Pediatr. 2020 Mar 26. PubMed: https://pubmed.gov/32215598. Fulltext: https://doi.org/10.1001/jamapediatrics.2020.0878

27 March

Shen C, Wang Z, Zhao F, et al. **Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma.** JAMA. 2020 Mar 27;323(16):1582-9. PubMed: https://pubmed.gov/32219428. Full-text: https://doi.org/10.1001/jama.2020.4783 ● (IMPORTANT)

Daily Top 10

30 March

Fauci AS, Lane HC, Redfield RR. **Covid-19 – Navigating the Uncharted.** N Engl J Med. 2020 Mar 26;382(13):1268-1269. PubMed: https://pubmed.gov/32109011. Full-text: https://doi.org/10.1056/NEJMe2002387

Brief overview of current research topics from opinion leaders.

Hospital

Sorbello M, El-Boghdadly K, Di Giacinto I, et al. **The Italian COVID-19 outbreak: experiences and recommendations from clinical practice.** Anaesthesia. 2020 Mar 27. PubMed: https://pubmed.gov/32221973. Full-text: https://doi.org/10.1111/anae.15049

Detailed practical recommendations, based on experiences during the Italian outbreak. Key elements of clinical management, airway management, personal protective equipment and non-technical aspects are described.

Cook TM, El-Boghdadly K, McGuire B, McNarry AF, Patel A, Higgs A. **Consensus guidelines for managing the airway in patients with COVID-19.** Anaesthesia. 2020 Mar 27. PubMed: https://pubmed.gov/32221970. Full-text: https://doi.org/10.1111/anae.15054

Consented principles from the UK Association of Anaesthetists for airway management, including emergency tracheal intubation, predicted or unexpected difficult tracheal intubation, cardiac arrest, anesthetic care and tracheal extubation.

Matthay MA, Aldrich JM, Gotts JE. **Treatment for severe acute respiratory distress syndrome from COVID-19.** Lancet Respir Med. 2020 Mar 20. PubMed: https://pubmed.gov/32203709. Full-text: https://doi.org/10.1016/S2213-2600(20)30127-2

Brief overview of therapeutic options for severe acute respiratory distress syndrome.

Clinical

Chen G, Wu D, Guo W, et al. **Clinical and immunologic features in severe and moderate Coronavirus Disease 2019.** J Clin Invest. 2020 Mar 27. PubMed: https://pubmed.gov/32217835. Full-text: https://doi.org/137244

First study on immunologic characteristics of 21 patients (retrospective). Total lymphocytes but also CD4+ and CD8+ T cells decreased in nearly all patients, and were markedly lower in severe cases (294, 178 and 89 x 10^6/L) than moderate cases (641, 382 and 254 x 10^6/L). Immunological markers may be of importance due to their correlation with disease severity in COVID-19.

Risk factors, comorbidities

McMichael TM, Currie DW, Clark S, et al. **Epidemiology of Covid-19 in a Long-Term Care Facility in King County, Washington.** N Engl J Med. 2020 Mar 27. PubMed: https://pubmed.gov/32220208. Full-text: https://doi.org/10.1056/NEJMoa2005412 ● (IMPORTANT)

Important paper that highlights the severity of COVID-19 in older people. A total of 167 confirmed cases affecting 101 residents in a long-term care facility, 50 health care personnel (HCP), and 16 visitors. The case fatality rate for residents was 33.7% (34 of 101) and 0% among HCP.

Guan WJ, Liang WH, Zhao Y, et al. **Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis.** Eur Respir J. 2020 Mar 26. PubMed: https://pubmed.gov/32217650. Full-text: https://doi.org/10.1183/13993003.00547-2020 ● (IMPORTANT)

More on the role of comorbidities. 1,590 hospitalised patients from 575 hospitals across mainland China. After adjusting for age and smoking status, COPD [hazards ratio (HR) 2.681, 95% confidence interval (95%CI) 1.424-5.048], diabetes (HR 1.59, 95%CI 1.03-2.45), hypertension (HR 1.58, 95%CI 1.07-2.32) and malignancy (HR 3.50, 95%CI 1.60-7.64) were risk factors of reaching endpoints.

Inciardi RM, Lupi L, Zaccone G, et al. **Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19).** JAMA Cardiol. 2020 Mar 27. PubMed: https://pubmed.gov/32219357. Full-text: https://doi.org/10.1001/jamacardio.2020.1096

Interesting case report on myopericarditis with systolic dysfunction which highlights cardiac involvement as a complication, even without symptoms and signs of interstitial pneumonia.

Kutikov A, Weinberg DS, Edelman MJ, Horwitz EM, Uzzo RG, Fisher RI. **A War on Two Fronts: Cancer Care in the Time of COVID-19.** Ann Intern Med. 2020 Mar 27. PubMed: https://pubmed.gov/32219410. Full-text: https://doi.org/10.7326/M20-1133

Inspiring thoughts on treatment and care for patients with cancer. No new data.

Chen T, Wu D, Chen H, et al. **Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study.** BMJ. 2020 Mar 26;368:m1091. PubMed: https://pubmed.gov/32217556. Full-text: https://doi.org/10.1136/bmj.m1091

Retrospective case series of 113 deceased patients. The median time from disease onset to death was 16 (IQR 12.0-20.0) days. Common complications observed more frequently in deceased patients included acute respiratory distress syndrome (100%), type I respiratory failure (51%), sepsis (100%), acute cardiac injury (77%), heart failure (49%), alkalosis (40%), hyperkalemia (37%), acute kidney injury (25%), and hypoxic encephalopathy (20%).

Little P. **Non-steroidal anti-inflammatory drugs and covid-19. BMJ.** 2020 Mar 27;368:m1185. PubMed: https://pubmed.gov/32220865. Full-text: https://doi.org/10.1136/bmj.m1185

Discussion of a possible link between NSAIDs and both respiratory and cardiovascular adverse effects in COVID-19. Recommends pragmatic approach: regular NSAID use should probably not be recommended first line.

Pregnancy, pediatric patients

Wang SS, Zhou X, Lin XG, et al. **Experience of Clinical Management for Pregnant Women and Newborns with Novel Coronavirus Pneumonia in Tongji Hospital, China.** Curr Med Sci. 2020 Mar 26. PubMed: https://pubmed.gov/32219626. Full-text: https://doi.org/10.1007/s11596-020-2174-4

Updated and very detailed recommendations for the clinical management for pregnant women and their newborns with SARS-CoV-2. Experience from Wuhan. No data.

Zeng H, Xu C, Fan J, et al. **Antibodies in Infants Born to Mothers With COVID-19 Pneumonia.** JAMA. 2020 Mar 26. PubMed: https://pubmed.gov/32215589. Full-text: https://doi.org/10.1001/jama.2020.4861

Among 6 mothers with confirmed COVID-19, SARS-CoV-2 was not detected in the serum or throat swab by RT-PCR in any of their newborns. However, virus-specific antibodies (IgG) were detected in 5 neonatal blood sera samples.

31 March

Diagnostics

Yu F, Yan L, Wang N, et al. **Quantitative Detection and Viral Load Analysis of SARS-CoV-2 in Infected Patients**. Clin Infect Dis. 2020 Mar 28. PubMed: https://pubmed.gov/32221523. Fulltext: https://doi.org/10.1093/cid/ciaa345 ●● (Outstanding)

Is sputum sufficient for diagnosis? In a total of 323 samples from 76 pts, the average viral load in sputum (17429 copies/test) was significantly higher than in throat swabs (2552) and nasal swabs (651). Viral load was also higher in the early and progressive stages than in the recovery stage. If these data are confirmed, collection of specimen would be much easier.

Zhao J, Yuan Q, Wang H, et al. **Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019**. Clin Infect Dis. 2020 Mar 28. PubMed: https://pubmed.gov/32221519. Fulltext: https://doi.org/10.1093/cid/ciaa344

More on antibody response. Among 173 patients, the seroconversion rate (median time) for Ab, IgM and IgG was 93.1% (11 days), 82.7% (12 days) and 64.7% (14 days), respectively. A higher titer of Ab was independently associated with a worse clinical classification.

Comorbidities

Vaduganathan M, Vardeny O, Michel T, McMurray JV, Pfeffer MA, Solomon SD. **Renin–Angiotensin–Aldosterone System Inhibitors in Patients with**

Covid-19. NEJM, March 30, 2020. Fulltext: https://www.nejm.org/doi/full/10.1056/NEJMsr2005760?

Fantastic review of an interdisciplinary expert panel on the use, risks and benefit of RAAS inhibitors (ACE inhibitors and sartans) in the COVID-19 era. Bottom line: We don't know enough. Until further data are available, RAAS inhibitors can be continued.

Joob B, Wiwanitkit V. **SARS-CoV-2 and HIV**. J Med Virol. 2020 Mar 27. PubMed: https://pubmed.gov/32220066. Fulltext: https://doi.org/10.1002/jmv.25782

A few new thoughts on HIV infection and COVID-19.

Zhu F, Cao Y, Xu S, Zhou M. **Co-infection of SARS-CoV-2 and HIV in a patient in Wuhan city, China** [published online ahead of print March 11, 2020]. J Med Virol. https://doi.org/10.1002/jmv.25732

First case report of patient with undiagnosed HIV infection (low CD4 counts), recovering from a coronavirus-related pneumonia. Argues against deleterious effect of HIV.

Pregnancy

Li Y, Zhao R, Zheng S, et al. **Lack of Vertical Transmission of Severe Acute Respiratory Syndrome Coronavirus 2, China**. Emerg Infect Dis. 2020 Jun 17;26(6). PubMed: https://pubmed.gov/32134381. Fulltext: https://doi.org/10.3201/eid2606.200287

Case report on a cesarean section, suggesting that mother-to-child transmission is unlikely.

Epidemiology

Hellewell J, Abbott S, Gimma A, et al. **Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts**. Lancet Glob Health. 2020 Apr;8(4):e488-e496. PubMed: https://pubmed.gov/32119825. Fulltext: https://doi.org/10.1016/S2214-109X(20)30074-7

Excellent work with implications for future outbreaks and the time after lockdown. Using a stochastic transmission model, contact tracing and isolation of cases was sufficient to control a new outbreak.

Clinical

Bhatraju PK, Ghassemieh BJ, Nichols M. **Covid-19 in Critically Ill Patients in the Seattle Region — Case Series**. NEJM March 30, 2020. Full-text: https://doi.org/10.1056/NEJMoa2004500

More than "Ok, COVID-19 has reached the US": this paper describes in detail the demographic characteristics, coexisting conditions, imaging findings, and outcomes among 21 critically ill patients admitted at ICUs.

Nickel CH, Bingisser R. **Mimics and chameleons of COVID-19**. Swiss Med Wkly. 2020 Mar 23;150:w20231. PubMed: https://pubmed.gov/32202647. https://doi.org/10.4414/smw.2020.20231

An older patient with COVID-19 and non-specific symptoms is described, as well as another case with heart failure, mimicking COVID-19. Both cases underline the need for extensive testing.

Vaccine

Lurie N, Saville M, Hatchett R, Halton J. **Developing Covid-19 Vaccines at Pandemic Speed. NEJM March 30, 2020.** Full-text: https://doi.org/10.1056/NEJMp2005630

Excellent review on vaccine development. Outlook on new platforms for RNA and DNA vaccines that can be made quickly because they require no culture or fermentation, instead using synthetic processes. Hope and despair.

April 2020

1 April

Virology

Ceraolo C, Giorgi FM. **Genomic variance of the 2019-nCoV coronavirus**. J Med Virol. 2020 May;92(5):522-528. PubMed: https://pubmed.gov/32027036. Full-text: https://doi.org/10.1002/jmv.25700

Analysis of 56 genomic sequences from distinct patients, showing high sequence similarity (> 99%). A few variable genomic regions exist, mainly at the ORF8 locus (coding for accessory proteins).

Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. **The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2**. Nat Microbiol. 2020 Apr;5(4):536-544. PubMed: https://pubmed.gov/32123347. Full-text: https://doi.org/10.1038/s41564-020-0695-z ● (IMPORTANT)

Consensus statement (a little wordy), defining the place of SARS-CoV-2 (provisionally named 2019-nCoV) within the Coronaviridae.

Letko M, Marzi A, Munster V. **Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses**. Nat Microbiol. 2020 Apr;5(4):562-569. PubMed: https://pubmed.gov/32094589. Full-text: https://doi.org/10.1038/s41564-020-0688-y

Important work on viral entry, using a rapid and cost-effective platform with allows to functionally test large groups of viruses for zoonotic potential. Host protease processing during viral entry is a significant barrier for several lineage B viruses. However, bypassing this barrier allows several coronaviruses to enter human cells through an unknown receptor.

Clinical

Verity R, Okell LC, Dorigatti I, et al. **Estimates of the severity of coronavirus disease 2019: a model-based analysis**. Lancet Infect Dis. 2020; (published online March 30.) Full-text: https://doi.org/10.1016/S1473-3099(20)30243-7

Defining the case fatality rate (CFR) remains challenging and simply dividing the number of deaths by the number of cases can be misleading. Using indi-

vidual-case data and after careful modelling, CFR was 1.38% (95% CI, 1.23–1.53) in this analysis. The mean duration from symptom onset to death was 17.8 days (95% 16.9–19.2).

Comorbidities

Yao H, Chen JH, Xu YF. **Patients with mental health disorders in the COVID-19 epidemic. Lancet Psychiatry**. 2020 Apr;7(4):e21. Full-text: https://doi.org/10.1016/S2215-0366(20)30090-0

Don't forget people with mental health conditions! A few thoughts on these patients who could be more substantially affected, resulting in relapses or worsening of an already existing mental health condition because of high susceptibility to stress compared with the general population.

Chen Q, Liang M, Li Y, et al. **Mental health care for medical staff in China during the COVID-19 outbreak**. Lancet Psychiatry. 2020 Apr;7(4):e15-e16. PubMed: https://pubmed.gov/32085839. Full-text: https://doi.org/10.1016/S2215-0366(20)30078-X

And don't forget the staff! Some thoughts on how to maintain staff mental health during such a crisis.

Jin XH, Zheng KI, Pan KH, Xie YP, Zheng MH. **COVID-19 in a patient with chronic lymphocytic leukaemia**. Lancet Haematol. 2020 Apr;7(4):e351-e352. Full-text: https://doi.org/10.1016/S2352-3026(20)30074-0

Interesting case report on a patient with CLL. Clinical and biochemical features of COVID-19 might be partly masked by coexisting CLL. Longer incubation period was presumed.

Diagnostics

Chen C, Gao G, Xu Y, et al. **SARS-CoV-2-Positive Sputum and Feces After Conversion of Pharyngeal Samples in Patients With COVID-19.** Ann Intern Med. 2020 Jun 16;172(12):832-834. PubMed: https://pubmed.gov/32227141. Full-text: https://doi.org/10.7326/M20-0991

Among 133 patients, 22 patients who had positive RT-qPCR results for SARS–CoV-2 in the sputum or feces (up to 39 and 13 days, respectively) after pharyngeal swabs became negative. Although uncontrolled, this study raises concern about whether patients with negative pharyngeal swabs are truly virus-free, or sampling of additional body sites is needed.

Therapy and Procedures

Kim AH, Sparks JA, Liew JW. **A Rush to Judgment? Rapid Reporting and Dissemination of Results and Its Consequences Regarding the Use of Hydroxychloroquine for COVID-19**. Ann Intern Med 2020. Full-text: https://doi.org/10.7326/M20-1223

Harsh criticism at the Gautret-Study (on a potential benefit of hydroxychloroquine), making clear that essential standards of data generation and interpretation were lacking, leading to undesirable downstream effects.

Yazdany J, Kim AHJ. **Use of Hydroxychloroquine and Chloroquine During the COVID-19 Pandemic: What Every Clinician Should Know.** Ann Intern Med. 2020 Jun 2;172(11):754-755. PubMed: https://pubmed.gov/32232419. Full-text: https://doi.org/10.7326/M20-1334 ● (IMPORTANT)

Extensive comment on someone's swanky twitter claiming that the combination of HCQ and azithromycin has "a real chance to be one of the biggest game changers in the history of medicine" (March 21). Careful review about the risks of HCQ and how pretentious dissemination of overpromised data may cause severe harm.

2 April

Epidemiology

Chan KH, Yuen KY. **COVID-19 epidemic: disentangling the re-emerging controversy about medical face masks from an epidemiological perspective**. Int J Epidem March 31, 2020. dyaa044. Full-text: https://doi.org/10.1093/ije/dyaa044

Review of data and inconsistencies in official guidelines and expert opinions about face masks, confusing both the public and health care professionals. Still wondering, after reading this review.

Dudly JP, Lee NT. **Disparities in Age-Specific Morbidity and Mortality from SARS-CoV-2 in China and the Republic of Korea**. Clin Inf Dis 2020, March 31. Full-text: https://doi.org/10.1093/cid/ciaa354

Morbidity in China exhibited a Gaussian distribution (peak 50-59 years), while morbidity in ROK had a bimodal distribution (peak 20-29 years). Careless youth? Authors speculate that this was possibly due to differences in public

health intervention practices and age-related sociocultural factors (lower rates of compliance among younger people with social distancing and self-quarantine recommendations).

Patrick GT, Whittaker C, Watson O, et al. **The Global Impact of COVID-19 and Strategies for Mitigation and Suppression**. Imperial College London 2020, published March 26. Full-text: https://doi.org/10.25561/77735.

Elegant models illustrating the potential impact of the COVID-19 pandemic globally and highlighting the challenging decisions faced by governments. In the absence of interventions, COVID-19 would have resulted in 7.0 billion infections and 40 million deaths globally this year. Mitigation strategies focussing on shielding the elderly (60% reduction in social contacts) and slowing but not interrupting transmission (40% reduction) could reduce this burden by half, saving 20 million lives.

Wells CR, Sah P, Moghadas SM, et al. **Impact of international travel and border control measures on the global spread of the novel 2019 coronavirus outbreak**. Proc Natl Acad Sci U S A. 2020 Mar 13. PubMed: https://pubmed.gov/32170017. Full-text: https://doi.org/10.1073/pnas.2002616117

Complex epidemiological models, showing that border controls, airport screening and travel restrictions likely slowed the rate of exportation from mainland China to other countries, but were insufficient to contain the global spread of COVID-19. Rapid contact tracing remains essential.

Clinical

Wu P, Duan F, Luo C, et al. **Characteristics of Ocular Findings of Patients With Coronavirus Disease 2019 (COVID-19) in Hubei Province, China**. JAMA Ophthalmol. Published online March 31, 2020. Full-text: https://doi.org/10.1001/jamaophthalmol.2020.1291

In a case series from China, 12/38 patients (32%, more common in severe COVID-19 cases) had ocular manifestations consistent with conjunctivitis, including conjunctival hyperemia, chemosis, epiphora, or increased secretions. Two patients had positive PCR results from conjunctival swabs.

Bonow RO, Fonarow GC, O´Gara PT, Yancy CW. **Association of Coronavirus Disease 2019 (COVID-19) With Myocardial Injury and Mortality**. JAMA Cardiol. 2020 Mar 27. PubMed: https://pubmed.gov/32219362. Full-text: https://doi.org/10.1001/jamacardio.2020.1105

Brief review on the potential for direct and indirect adverse effects of SARS-CoV-2 on the heart and especially so in those with already established heart disease.

Comorbidities

Kaiser UB, Mirmira RG, Stewart PM. **Our Response to COVID-19 as Endocrinologists and Diabetologists**. J Clin Endocrin Metabol, 105, May 2020, published 31 March 2020, dgaa148, https://doi.org/10.1210/clinem/dgaa148

Thoughts on diabetes management, glucocorticoid use, pituitary or other neuroendocrine diseases.

CDC COVID-19 Response Team. **Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019 — United States, February 12–March 28, 2020**. MMWR Morb Mortal Wkly Rep. ePub: 31 March 2020. Full-text: http://dx.doi.org/10.15585/mmwr.mm6913e2

No, the situation in the US does not differ from other countries. Among 7,162 patients with underlying health conditions or potential risk factors reported to the CDC, those with these conditions were more likely admitted to the hospital and to an ICU. And yes, "persons with underlying health conditions who have symptoms of COVID-19 should immediately contact their health care provider".

Diagnostics

Wölfel R, Corman VM, Guggemos W. et al. **Virological assessment of hospitalized patients with COVID-2019**. Nature 2020, April 1. Full-text: https://doi.org/10.1038/s41586-020-2196-x ●● (OUTSTANDING)

Important work, showing active virus replication in upper respiratory tract tissues (in contrast to SARS). In a detailed virological analysis of nine cases, pharyngeal virus shedding was very high during the first week of symptoms (peak at 7.11×10^8 RNA copies per throat swab, day 4), more than 1000 times higher than seen with SARS-CoV. Infectious virus was readily isolated from throat- and lung-derived samples, but not from stool samples, in spite of high

virus RNA concentration. Blood and urine never yielded virus. Shedding of viral RNA from sputum continued after the end of symptoms.

Treatment

Liu S, Zheng Q, Wang Z. **Potential covalent drugs targeting the main protease of the SARS-CoV-2 coronavirus**. Bioinformatics April 1, 2020. btaa224, Full-text: https://doi.org/10.1093/bioinformatics/btaa224

Some new ideas on treatment. Using a computer-aided drug discovery protocol, possible covalent drugs targeting 3CLpro protease of SARS-CoV-2 were identified. For drug repurposing, the following ones (indication) might have priority: Telcagepant (migraine), Vidupiprant (asthma), Poziotinib (breast cancer), and Fostamatinib (rheumatoid arthritis).

3 April

Virology

Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. **Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2**. Science. 2020 Mar 27;367(6485):1444-1448. PubMed: https://pubmed.gov/32132184. Full-text: https://doi.org/10.1126/science.abb2762 ●● (Outstanding)

Using cryo–electron microscopy, it is shown how SARS-CoV-2 binds to human cells. The first step in viral entry is the binding of the viral trimeric spike protein to the human receptor angiotensin-converting enzyme 2 (ACE2). Authors present the structure of human ACE2 in complex with a membrane protein that it chaperones, B0AT1. The structures provide a basis for the development of therapeutics targeting this crucial interaction.

Lan J, Ge J, Yu J, et al. **Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor.** Nature. 2020 May;581(7807):215-220. PubMed: https://pubmed.gov/32225176. Full-text: https://doi.org/10.1038/s41586-020-2180-5 ●● (Outstanding)

To elucidate the SARS-CoV-2 RBD and ACE2 interaction at a higher resolution/atomic level, authors used X-ray crystallography. Binding mode was very similar to SARS-CoV, arguing for convergent evolution of both viruses. The epitopes of two SARS-CoV antibodies targeting the RBD were also analysed with the SARS-CoV-2 RBD, providing insights into the future identification of cross-reactive antibodies.

Shang J, Ye G, Shi K. **Structural basis of receptor recognition by SARS-CoV-2.** Nature 2020, March 30. https://doi.org/10.1038/s41586-020-2179-y ● (IMPORTANT)

How well does SARS-CoV-2 recognize hACE2? Better than other coronaviruses. Compared to SARS-CoV and RaTG13 (isolated from bats), ACE2 binding affinity is higher. Functionally important epitopes in SARS-CoV-2 RBM are described that can potentially be targeted by neutralizing antibody drugs.

Epidemiology

Luo C, Yao L, Zhang L, et al. **Possible Transmission of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in a Public Bath Center in Huai′an, Jiangsu Province, China**. JAMA Netw Open. 2020 Mar 2;3(3):e204583. PubMed: https://pubmed.gov/32227177. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.4583

A cluster-spreading event in Huai'an, China, in which a patient may have transmitted the virus to 8 other individuals via bathing in a public bath center (sauna, bath, 25 to 41° C and humidity of approximately 60%). Transmissibility appears not to be reduced in warm and humid conditions.

Cereda D, Tirani M, Rovida F, et al. **The early phase of the COVID-19 outbreak in Lombardy, Italy**. Preprint. Full-text: https://arxiv.org/abs/2003.09320

Still looking for patient zero in Italy (not found). However, this important study of 6,000 laboratory-confirmed cases tracks how the outbreak unfolded in the region. By the time the first case was detected, the virus had already spread (since January) to most towns and cities in southern Lombardy.

Comorbidities

Bousquet J, Akdis C, Jutel M, et al. **Intranasal corticosteroids in allergic rhinitis in COVID-19 infected patients: An ARIA-EAACI statement**. Allergy. 2020 Mar 31. PubMed: https://pubmed.gov/32233040. Full-text: https://doi.org/10.1111/all.14302

A joint statement of the European Academy of Allergology and Clinical Immunology, following the results of a questionnaire. Bottom line: Stopping intranasal steroids is not advised, until we know better.

Clinical

Back A, Tulsky JA, Arnold RM. **Communication Skills in the Age of COVID-19**. Ann Intern Med 2020, April 2. Full-text: https://doi.org/10.7326/M20-1376

Thoughts about how to communicate as a clinician in this crisis. Talking maps for communication tasks that none of us have faced before, including facilitating virtual goodbyes between family members and dying patients with restricted access. And explaining decisions on why a particular patient will not receive a scarce resource: "I can see how it feels unfair". Phew. Could anyone ever have imagined that?

Procedures

Zhang Y, Zhang X, Liu L, Wang H, Zhao Q. **Suggestions for infection prevention and control in digestive endoscopy during current 2019-nCoV pneumonia outbreak in Wuhan, Hubei province, China**. Endoscopy. 2020 Apr;52(4):312-314. PubMed: https://pubmed.gov/32212122. Full-text: https://doi.org/10.1055/a-1128-4313

Brief workflow to prevent SARS-CoV-2 transmission in the endoscopy center.

Diagnostics

Qiu L, Liu X, Xiao M, et al. **SARS-CoV-2 is not detectable in the vaginal fluid of women with severe COVID-19 infection**. Clin Infect Dis 2020, April 2, ciaa375, full-text: https://doi.org/10.1093/cid/ciaa375

Is the virus everywhere? No. Not in the vaginal fluid (of 10 women with severe COVID-19).

Saito M, Adachi E, Yamayoshi S, et al. **Gargle lavage as a safe and sensitive alternative to swab samples to diagnose COVID-19: a case report in Japan**. Clinical Infectious Diseases 2020, April 2, ciaa377, https://doi.org/10.1093/cid/ciaa377

Case report of a patient who did not produce sputum. Gargle lavage testing was sensitive. If confirmed by larger studies, this can be done by patients themselves without putting healthcare professionals at increased risk.

4 April

Epidemiology

Ferretti L, Wymant C, Kendall M, et al. **Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing**. Science 31 Mar 2020. https://doi.org/10.1126/science.abb6936

Using an analytically solvable model, authors show that viral spread is too fast to be contained by manual contact tracing. Spread could be controlled if this process was faster, more efficient and happened at scale. A contact-tracing app that builds a memory of proximity contacts and immediately notifies contacts of positive cases can achieve epidemic control if used by enough people, without need for lockdowns.

Flaxman S, Mishra S, Gandy A. **Estimating the number of infections and the impact of non-pharmaceutical interventions on COVID-19 in 11 European countries**. March 30. https://doi.org/10.25561/77731

Infection-control measures such as national lockdowns in many European countries are reducing the spread of coronavirus. Across 11 countries, between 21,000 and 120,000 deaths were probably avoided by the end of March, according to a model by a group at Imperial College London.

Leung NHL, Chu DKW, Shiu EYC, et al. **Respiratory virus shedding in exhaled breath and efficacy of face masks.** Nat Med. 2020 May;26(5):676-680. PubMed: https://pubmed.gov/32371934. Full-text: https://doi.org/10.1038/s41591-020-0843-2 ●● (Outstanding)

Do face masks work? Yes, but it depends. This important study from Hong Kong (performed 2013-16) quantified virus in respiratory droplets and aerosols in exhaled breath. In total, 111 participants (infected with seasonal coronavirus, influenza or rhinovirus) were randomized to wear (or not) a simple surgical face mask. Results suggested that masks could be used by ill people to reduce onward transmission. But note the small numbers: in respiratory droplets, seasonal coronavirus was found in 0/11 droplets (aerosols: 0/11) from participants wearing face masks, compared to 3/10 (aerosols: 4/10) without masks. Influenza viruses were detected in 1/27 (aerosols 6/27!) with face masks, compared to 6/23 (8/23) without. For rhinovirus, there were no significant differences at all. Of note, authors also identified virus in some participants who did not cough at all during the 30-min exhaled breath collection, suggesting droplet and aerosol routes of transmission from individuals with no obvious signs or symptoms.

Chin AW, Chu JT, Perera MR, et al. **Stability of SARS-CoV-2 in different environmental conditions**. The Lancet Microbe 2020, April 02. Full-text: https://doi.org/10.1016/S2666-5247(20)30003-3 ● (IMPORTANT)

Don't put your masks in the fridge for recycling! Heating is probably better. This important work shows that the virus was highly stable at 4°C (almost no reduction on day 14) but sensitive to heat (70° C: inactivation 5 min, 56°: 30 min, 37°: 2 days). It also depends on the surface: No infectious virus could be recovered from printing and tissue papers after 3 hours, from treated wood and cloth on day 2, from glass and banknotes on day 4, stainless steel and plastic on day 7. Strikingly, a detectable level of infectious virus (~0·1% of the original inoculum) could still be present on the outer layer of a surgical mask on day 7.

Clinical

Gane SB, Kelly C, Hopkins C. **Isolated sudden onset anosmia in COVID-19 infection. A novel syndrome?** Rhinology. 2020 Apr 2. PubMed: https://pubmed.gov/32240279. Full-text: https://doi.org/10.4193/Rhin20.114

Case report and series on isolated sudden onset anosmia, urging to consider this presentation.

Comorbidities

Meng J, Xiao G, Zhang J, et al. **Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension**. Emerg Microbes Infect. 2020 Dec;9(1):757-760. PubMed: https://pubmed.gov/32228222. Full-text: https://doi.org/10.1080/22221751.2020.1746200

First study arguing against any deleterious effect of RAAS inhibitors (ACE inhibitors or sartans) in COVID-19! Among 42 of 417 patients admitted to Shenzhen Hospital while on antihypertensive therapy, those receiving RAAS inhibitors had a lower rate of severe diseases than patients without (5/17 compared to 12/25) and a trend toward a lower level of IL-6 in peripheral blood.

The Lancet Oncology. **COVID-19: global consequences for oncology**. Lancet Oncol. 2020 Apr;21(4):467. PubMed: https://pubmed.gov/32240603. Full-text: https://doi.org/10.1016/S1470-2045(20)30175-3

Thoughts on how the pandemic affects treatment of patients with cancer and how it will hit the wider oncology community. Substantial changes for re-

search, education, and collaboration are expected, including reduced international travel and increased remote networking and telemedicine.

Procedures

Tay JK, Koo ML, Loh WS. **Surgical Considerations for Tracheostomy During the COVID-19 PandemicLessons Learned From the Severe Acute Respiratory Syndrome Outbreak**. JAMA Otolaryngol Head Neck Surg. Published online March 31, 2020. Full-text: https://doi.org/10.1001/jamaoto.2020.0764

Patients with prolonged ventilation may require tracheostomy to optimize weaning from ventilatory support. Review of the literature and practical issues.

Diagnostics

Petherick A. **Developing antibody tests for SARS-CoV-2.** Lancet. 2020 Apr 4;395(10230):1101-1102. PubMed: https://pubmed.gov/32247384. Full-text: https://doi.org/10.1016/S0140-6736(20)30788-1

Brief report about current knowledge and development on antibody testing.

Treatment

Chen C, Huang J, Cheng Z, et al. **Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial**. Posted March 27, medRxiv 2020.03.17.20037432. Full-text: https://doi.org/10.1101/2020.03.17.20037432

Important open-label, randomized trial conducted in 3 hospitals in China, comparing arbidol and favipiravir in 236 patients with COVID-19 pneumonia. Primary outcome was the 7-day clinical recovery rate (recovery of fever, respiratory rate, oxygen saturation and cough relief). In "ordinary" COVID-19 patients (not critical), the recovery rates were 56% with arbidol (n = 111) and 71% (n = 98) with favipiravir (p = 0.02) that was well tolerated, except for some elevated serum uric acid levels. Striking! But can we trust? In the whole study population, no difference was evident. Many cases were not confirmed by PCR. There were also imbalances between subgroups of "ordinary" patients and even favipiravir was incorrectly spelt 7 times: 3x famiravir, 4x fabiravir (come on guys - did anybody read the manuscript?). This paper needs a careful (and major) review...

5 April

Epidemiology

Scott SE, Zabel K, Collins J, et al. **First Mildly Ill, Non-Hospitalized Case of Coronavirus Disease 2019 (COVID-19) Without Viral Transmission in the United States — Maricopa County, Arizona, 2020**. Clinical Infectious Diseases 2020, 02 April, ciaa374, https://doi.org/10.1093/cid/ciaa374

Is symptom severity a proxy for infectivity? Case report of a patient with mild illness and positive tests for up to 18 days after diagnosis, without evidence of transmission to 16 close contacts, among them 10 high-risk contacts.

Lu J, Gu J, Li K, et al. COVID-19 **Outbreak Associated with Air Conditioning in Restaurant, Guangzhou, China, 2020**. Emerg Infect Dis. 2020 Apr 2;26(7). PubMed: https://pubmed.gov/32240078. Full-text: https://doi.org/10.3201/eid2607.200764

Outbreak in a restaurant. The distances between index patient and persons at other tables were all > 1 m, suggesting that droplet transmission was prompted by air-conditioned ventilation.

Kwon SY, Kim EJ, Jung YS, Jang JS, Cho NS. **Post-donation COVID-19 identification in blood donors**. Vox Sang. 2020 Apr 2. PubMed: https://pubmed.gov/32240537. Full-text: https://doi.org/10.1111/vox.12925

Korean study of seven asymptomatic blood donors who were later identified as COVID-19 confirmed cases. None out of 9 recipients of platelets or red blood cell transfusions tested positive for SARS-CoV-2 RNA. Transfusion transmission is unlikely.

Chang L, Zhao L, Gong H, Wang L, Wang L. **Severe Acute Respiratory Syndrome Coronavirus 2 RNA Detected in Blood Donations.** Emerg Infect Dis. 2020 Apr 3;26(7). PubMed: https://pubmed.gov/32243255. Full-text: https://doi.org/10.3201/eid2607.200839

With screening of 2,430 donations in real-time, including 1,656 platelet and 774 whole blood donations from Wuhan, the authors found plasma samples positive for viral RNA from 4 asymptomatic donors. It remains unclear whether detectable RNA signifies infectivity.

Diagnostics

Vetrugno L, Bove T, Orso D, et al. **Our Italian Experience Using Lung Ultrasound for Identification, Grading and Serial Follow-up of Severity of Lung Involvement for Management of Patients with COVID-19**. Echocardiography. 2020 Apr 1. PubMed: https://pubmed.gov/32239532. Full-text: https://doi.org/10.1111/echo.14664

Experience from Italy with lung ultrasound as a bedside tool to improve evaluation of lung involvement, and also reduce the use of chest x-rays and CT. A point scoring system is employed by region and ultrasound pattern.

Clinical

Kimball A, Hatfield KM, Arons M, et al. **Asymptomatic and Presymptomatic SARS-CoV-2 Infections in Residents of a Long-Term Care Skilled Nursing Facility - King County, Washington, March 2020**. MMWR Morb Mortal Wkly Rep. 2020 Apr 3;69(13):377-381. PubMed: https://pubmed.gov/32240128. Full-text: https://doi.org/10.15585/mmwr.mm6913e1

Outbreak in a long-term care facility: Test them all, immediately! Following identification of a case of SARS-CoV-2 in a health care worker, 13/23 residents who tested positive were asymptomatic or presymptomatic on the day of testing.

Comorbidities

Bavishi C, Maddox TM, Messerli FH. **Coronavirus Disease 2019 (COVID-19) Infection and Renin Angiotensin System Blockers.** JAMA Cardiol. 2020 Apr 3. PubMed: https://pubmed.gov/32242890. Full-text: https://doi.org/10.1001/jamacardio.2020.1282

This mini-review outlines the mechanisms by which RAAS inhibitors (ACEIs/ARBs) may be of benefit in COVID-19. Overview of the current recommendations for their use in infected patients. According to the authors, the biological plausibility of the salutary effects of RAAS inhibitors is intriguing and several trials of starting losartan in patients with COVID-19 are currently being planned.

Al-Shamsi HO, Alhazzani W, Alhuraiji A, et al. **A Practical Approach to the Management of Cancer Patients During the Novel Coronavirus Disease 2019 (COVID-19) Pandemic: An International Collaborative Group.** Oncologist. 2020 Apr 3. PubMed: https://pubmed.gov/32243668. Full-text: https://doi.org/10.1634/theoncologist.2020-0213

Detailed and important review for oncologists, addressing current challenges associated with managing cancer patients during theCOVID-19 pandemic.

Volkow ND. **Collision of the COVID-19 and Addiction Epidemics**. Ann Intern Med. 2020 Apr 2. PubMed: https://pubmed.gov/32240293. Full-text: https://doi.org/10.7326/M20-1212

Don't forget or marginalize persons with substance use disorders during this crisis!

Fried JA, Ramasubbu K, Bhatt R, et al. **The Variety of Cardiovascular Presentations of COVID-19.** Circulation. 2020 Apr 3. PubMed: https://pubmed.gov/32243205. Full-text: https://doi.org/10.1161/CIRCULATIONAHA.120.047164

Four COVID-19 cases with cardiovascular presentations are described. In patients presenting with what appears to be a typical cardiac syndrome, COVID-19 infection should be in the differential during the current pandemic, even in the absence of fever or cough.

6 April

Epidemiology

Klompas M, Morris CA, Sinclair J, Pearson M, Shenoy ES. **Universal Masking in Hospitals in the Covid-19 Era**. N Engl J Med. 2020 Apr 1. PubMed: https://pubmed.gov/32237672. Full-text: https://doi.org/10.1056/NEJMp2006372

Thoughts on universal masking in hospitals. Pros and cons. Bottom line: The main value is probably psychological: giving health care workers the confidence to absorb and implement prevention practices.

Tian H, Liu Y, Li Y, et al. **An investigation of transmission control measures during the first 50 days of the COVID-19 epidemic in China**. Science. 2020 Mar 31. PubMed: https://pubmed.gov/32234804. Full-text: https://doi.org/10.1126/science.abb6105

"All models are wrong, but some are useful", statistician George Box supposedly once said. This model shows how non-pharmaceutical measures have worked in China. Without the Wuhan travel ban, there would have been 744,000 cases by February 19, day 50 of the epidemic. With the Wuhan travel ban alone, the number of cases would have decreased to 202,000. Other control measures such as the national emergency response, together with the travel ban, limited the number of cases, 96% fewer than expected in the absence of interventions.

Normile D. **As normalcy returns, can China keep COVID-19 at bay?** Science. 2020 Apr 3;368(6486):18-19. PubMed: https://pubmed.gov/32241931. Full-text: https://doi.org/10.1126/science.368.6486.18

China is now addressing an issue every country and location in the world will eventually (hopefully) face: how to normalize and restore societal activities, while at the same time minimizing disease-related dangers from the outbreak.

Ghinai I, McPherson TD, Hunter JC, et al. **First known person-to-person transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the USA**. Lancet. 2020 Apr 4;395(10230):1137-1144. PubMed: https://pubmed.gov/32178768. Full-text: https://doi.org/10.1016/S0140-6736(20)30607-3

Infection of health-care workers (HCWs) is not inevitable! A female in her 60s who travelled to Wuhan on Dec 25, 2019, and returned to Illinois on Jan 13, 2020, transmitted the infection to her husband. Although both were hospitalised in the same facility and shared hundreds (n = 348) of contacts with HCWs, nobody else became infected, supporting recommendations regarding appropriate infection control.

Diagnostics

Pan Y, Long L, Zhang D, et al. **Potential false-negative nucleic acid testing results for Severe Acute Respiratory Syndrome Coronavirus 2 from thermal inactivation of samples with low viral loads**. Clin Chem. 2020 Apr 4. PubMed: https://pubmed.gov/32246822. Full-text: https://doi.org/10.1093/clinchem/hvaa091

Don't put your swabs in the sun! In this small study, all samples were inactivated by incubation in a water bath at 56° for 30 minutes. 7/15 specimens with low virus levels converted to false negative. Longer storage could also cause false-negative results.

Virology

Monto AS, DeJonge P, Callear AP, et al. **Coronavirus occurrence and transmission over 8 years in the HIVE cohort of households in Michigan**. J Infect Dis. 2020 Apr 4. PubMed: https://pubmed.gov/32246136. Full-text: https://doi.org/10.1093/infdis/jiaa161

Let's pray that SARS-CoV-2 remembers its origins. And that it behaves like other human coronaviruses (hCoVs). A longitudinal surveillance cohort study of children and their households from Michigan found that hCoV infections were sharply seasonal, showing a peak for different hCoV types (229E, HKU1, NL63, OC43) in February. Over 8 years, almost no hCoV infections occurred after March. Will SARS-CoV-2 remember this? It's April....

Procedures

Lyons C, Callaghan M. **The use of high-flow nasal oxygen in COVID-19**. Anaesthesia. 2020 Apr 4. PubMed: https://pubmed.gov/32246843. Full-text: https://doi.org/10.1111/anae.15073 ● (IMPORTANT)

Careful and well-balanced review about the pros and cons of this treatment strategy.

Treatment

Du YX, Chen XP. **Favipiravir: pharmacokinetics and concerns about clinical trials for 2019-nCoV infection**. Clin Pharmacol Ther. 2020 Apr 4. PubMed: https://pubmed.gov/32246834. Full-text: https://doi.org/10.1002/cpt.1844

This mini-review (not open access) focusses on the pharmacokinetics of favipiravir and potential drug-drug interactions (DDIs). As the parent drug un-

dergoes metabolism in the liver mainly by aldehyde oxidase (AO), potent AO inhibitors such as cimetidine, amlodipine, or amitriptyline are expected to cause relevant DDIs.

Pregnancy

Poon LC, Yang H, Kapur A, et al. **Global interim guidance on coronavirus disease 2019 (COVID-19) during pregnancy and puerperium from FIGO and allied partners: Information for healthcare professionals**. Int J Gynaecol Obstet. 2020 Apr 4. PubMed: https://pubmed.gov/32248521. Full-text: https://doi.org/10.1002/ijgo.13156

For those of you who are not gynecologists: No, it's not Luís Figo. It's FIGO, the International Federation of Gynaecology and Obstetrics which gives "interim" recommendations about how to deal with pregnant women: 46 pages on ambulatory antenatal care, management in the setting of the obstetrical triage, intra/postpartum management and neonatal care. Among others, IRCCS, PAHO, ECDC, SIN, SEGO, RCOG, SOGC, SOAP, ISUOG and RANZCOG also contributed.

7 April

Diagnostics

Pan Y, Long L, Zhang D, et al. **Potential false-negative nucleic acid testing results for Severe Acute Respiratory Syndrome Coronavirus 2 from thermal inactivation of samples with low viral loads**. Clin Chem. 2020 Apr 4. PubMed: https://pubmed.gov/32246822. Full-text: https://doi.org/10.1093/clinchem/hvaa091

Don't put your swabs in the sun! In this small study, all samples were inactivated by incubation in a water bath at 56˚ for 30 minutes. Of note, 7/15 specimens with low virus levels converted into false negative. Longer storage also caused false negative results in a few cases.

Yuan M, Wu NC, Zhu X, et al. **A highly conserved cryptic epitope in the receptor-binding domains of SARS-CoV-2 and SARS-CoV**. Science. 2020 Apr 3. PubMed: https://pubmed.gov/32245784. Full-text: https://doi.org/10.1126/science.abb7269

Insights into antibody recognition and how SARS-CoV-2 can be targeted by the humoral response, revealing a conserved epitope shared between SARS-

CoV and SARS-CoV-2. This epitope could be used for vaccines and the development of cross-protective antibodies.

Clinical

Grasselli G, Zangrillo A, Zanella A, et al. **Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy**. JAMA. 2020 Apr 6. PubMed: https://pubmed.gov/32250385. Full-text: https://doi.org/10.1001/jama.2020.5394 ● (IMPORTANT)

Important work, providing sobering evidence about the burden of critical illness. Over a period of 28 days, 1,591 COVID-19 patients (88% requiring endotracheal intubation and ventilatory support) were admitted to 72 Italian ICUs, an average of 22 patients per ICU (median length of stay was 9 days). Of note, 82% were male and median age was only 63 years (IQR 56-70), suggesting that older age alone is not a risk factor for admission to the ICU. As of March 25, ICU mortality was 26%. However, 58% were still in the ICU. Scary study, telling us a lot about the fragility of health care systems in even the wealthiest countries.

Wunsch H. **The outbreak that invented intensive care**. Nature, World View, April 3, 2020. Full-text: https://www.nature.com/articles/d41586-020-01019-y

Interesting article on Copenhagen's polio epidemic in 1952, when over 300 patients (see below) developed respiratory paralysis within a few weeks, completely overwhelming the ventilator facilities. Does this remind you of something?

West JB. **The physiological challenges of the 1952 Copenhagen poliomyelitis epidemic and a renaissance in clinical respiratory physiology**. J Appl Physiol 2005 Aug;99(2):424-32. PubMed: https://pubmed.gov/16020437. Full-text: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1351016/

Yes, it's old. But, please, read this incredible story on hope and despair, on enormous medical challenges and true heroes, highly topical after almost 60 years. A comprehensive review about a forgotten epidemic occurring 1952 at the Belgdam Hospital in Copenhagen, Denmark: about 3,000 polio patients were admitted between August and December, among them 1,250 with paralysis and 345 with respiratory failure - due to bulbar or bulbospinal polio affecting brainstem or nerves that control breathing. The heroic solution was to recruit 1,500 medical and dental students, providing round-the-clock man-

ual ventilation using rubber bags, with only the patient's appearance to guide them. For a total of 165,000 hours. Think about it. The students were flying by sight. Sometimes, only the patients' rolling back eyes signalled that more ventilation was needed. Watery eyes while reading this heartbreaking article. A perfect story for anti-vaxxers (if these damned trolls would take notice). And about how fast we forget!

Procedures

Lyons C, Callaghan M. **The use of high-flow nasal oxygen in COVID-19**. Anaesthesia. 2020 Apr 4. PubMed: https://pubmed.gov/32246843. Full-text: https://doi.org/10.1111/anae.15073

Careful and well-balanced review about the pros and cons of this treatment strategy.

8 April

Epidemiology

Bae S, Kim MC, Kim JY, et al. **Effectiveness of Surgical and Cotton Masks in Blocking SARS-CoV-2: A Controlled Comparison in 4 Patients**. Ann Intern Med. 2020 Apr 6. PubMed: https://pubmed.gov/32251511. Full-text: https://doi.org/10.7326/M20-1342

Very small study, but both surgical and cotton masks appear to be ineffective in preventing the virus dissemination from the coughs of patients with COVID-19 to the environment and external mask surface.

Diagnostics

Chapman AR, Bularga A, Mills NL. **High-Sensitivity Cardiac Troponin Can Be An Ally in the Fight Against COVID-19**. Circulation. 2020 Apr 6. PubMed: https://pubmed.gov/32251612. Full-text: https://doi.org/10.1161/CIRCULATIONAHA.120.047008

Nice review on how to use and interpret troponin results in COVID-19 patients. According to the authors, clinicians must recognize that troponin is not a test for myocardial infarction, and it never was. No biomarker has ever had the ability to detect acute atherothrombotic occlusion in a coronary artery. Elevations of cardiac troponin can inform the diagnosis of a number of cardiac conditions related to COVID-19.

Clinical

Omer SB, Malani P, Del Rio C. **The COVID-19 Pandemic in the US: A Clinical Update.** JAMA. 2020 Apr 6. PubMed: https://pubmed.gov/32250388. Full-text: https://doi.org/10.1001/jama.2020.5788

Short but interesting viewpoint on current clinical insights and key questions. Is PCR always positive? What about reinfection, immunity? What do we know about transmission?

Comorbidities

Schiffrin EL, Flack J, Ito S, Muntner P, Webb C. **Hypertension and COVID-19**. Am J Hypertens. 2020 Apr 6. PubMed: https://pubmed.gov/32251498. Full-text: https://doi.org/10.1093/ajh/hpaa057

Is hypertension a true risk factor for severe COVID-19 courses? According to the authors, there is as yet (March 29) "no evidence" that hypertension is related to outcomes of COVID-19, or that ACE inhibitor or ARB use is harmful, or for that matter beneficial.

Pasha SB, Fatima H, Ghouri YA. **Management of Inflammatory Bowel Diseases in the Wake of COVID-19 Pandemic**. J Gastroenterol Hepatol. 2020 Apr 4. PubMed: https://pubmed.gov/32246874. Full-text: https://doi.org/10.1111/jgh.15056

Some thoughts on how to manage patients suffering from Inflammatory Bowel Diseases, regarding their ongoing immunosuppressive therapies which could render them more susceptible to acquire COVID-19 infection and develop severe courses.

Treatment

Duan K, Liu B, Li C, et al. **Effectiveness of convalescent plasma therapy in severe COVID-19 patients**. PNAS 2020, April 6. https://doi.org/10.1073/pnas.2004168117

A single dose (200 mL) of convalescent plasma was given to 10 patients (9 treated with umifenovir, 6 with methylprednisolone, 1 with remdesivir). In all 7 patients with viremia, serum SARS-CoV-2 RNA decreased to an undetectable level within 2-6 days. Meanwhile, clinical symptoms and paraclinical criteria rapidly improved within three days. Using antibodies from convalescents could be an option in severe cases. It's now time for larger studies.

Pregnancy, pediatrics

Choi SH, Kim HW, Kang JM, Kim DH, Cho EY. **Epidemiology and Clinical Features of Coronavirus disease 2019 in Children**. Clin Exp Pediatr. 2020 Apr 6. PubMed: https://pubmed.gov/32252139. Full-text: https://doi.org/10.3345/cep.2020.00535

Summarized in this nice review published on April 6, "what is known about COVID-19 in children and adolescents until now". No, not until now. Until March 12, 2020 (a far-off age). What has happened since then?

9 April

Virology

Kim YI, Kim SG, Kim SM, et al. **Infection and Rapid Transmission of SARS-CoV-2 in Ferrets**. Cell Host Microbe. 2020 Apr 5.. PubMed: https://pubmed.gov/32259477. Full-text: https://doi.org/10.1016/j.chom.2020.03.023

Ferrets shed the virus in nasal washes, saliva, urine, and feces up to 8 days post-infection. They may represent an infection and transmission animal model of COVID-19 that may facilitate development of SARS-CoV-2 therapeutics and vaccines.

Clinical

Miller DG, Pierson L, Doernberg S. **The Role of Medical Students During the COVID-19 Pandemic**. Ann Intern Med. 2020 Apr 7. PubMed: https://pubmed.gov/32259194. Full-text: https://doi.org/10.7326/M20-1281

The American Association of Medical Colleges (AAMC) recommends that "unless there is a critical health care workforce need locally, we strongly suggest that medical students not be involved in any direct patient care activities". The authors disagree (for good reasons).

Cheung KS, Hung IF, Chan PP, et al. **Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples from the Hong Kong Cohort and Systematic Review and Meta-analysis**. Gastroenterology. 2020 Apr 3. PubMed: https://pubmed.gov/32251668. Full-text: https://doi.org/10.1053/j.gastro.2020.03.065

In a meta-analysis of 60 studies comprising 4,243 patients, the pooled prevalence of gastrointestinal symptoms was 17.6% (95% CI, 12.3% - 24.5%). Preva-

lence was lower in studies from China than other countries. Pooled prevalence of stool samples that were positive for virus RNA was 48.1% and could persist for up to ≥ 33 days from onset of illness even after viral RNA negativity in respiratory specimens. Stool viral RNA was detected at higher frequency among those with diarrhea.

Shanafelt T, Ripp J, Trockel M. **Understanding and Addressing Sources of Anxiety Among Health Care Professionals During the COVID-19 Pandemic**. JAMA. 2020 Apr 7. PubMed: https://pubmed.gov/32259193. Full-text: https://doi.org/10.1001/jama.2020.5893

This viewpoint summarizes key considerations for supporting the health care workforce.

Comorbidities

Dave M, Seoudi N, Coulthard P. **Urgent dental care for patients during the COVID-19 pandemic**. Lancet. 2020 Apr 3. PubMed: https://pubmed.gov/32251619. Full-text: https://doi.org/10.1016/S0140-6736(20)30806-0

Don't forget the dentists! And test them with the same high priority as that of medical health-care workers in hospitals!

Sun J, Aghemo A, Forner A, Valenti L. **COVID-19 and liver disease**. Liver Int. 2020 Apr 6. doi: https://doi.org/10.1111/liv.14470. [Epub ahead of print]

"Since December 2019, patients with unexplained pneumonia have been found in Wuhan, Hubei Province, China, which was caused by a novel coronavirus that had not been previously identified (1). Tentatively defined as 2019 novel coronavirus (2019-nCoV), the pathogen has now been named Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) (2), while the disease termed Coronavirus Disease 2019 (COVID-19)." This abstract was published on April 6, with references. In all seriousness. Come on guys, we all know that already! Is it to be feared that nobody will read your interesting mini-review on mechanisms and clinical implications of liver injury, unmet clinical needs and main research questions?

Treatment

Praveen D, Chowdary PR, Aanandhi MV. **Baricitinib - a januase kinase inhibitor - not an ideal option for management of COVID-19**. Int J Antimicrob Agents. 2020 Apr 4:105967. PubMed: https://pubmed.gov/32259575. Full-text: https://doi.org/10.1016/j.ijantimicag.2020.105967

Several studies have speculated that baricitinib could act on AT2 cells and AAK1 mediated endocytosis. The authors argue that the drug would not be an ideal option, due to the fact that baricitinib causes lymphocytopenia, neutropenia and viral reactivation. Sounds reasonable.

Perinel S, Launay M, Botelho-Nevers E, et al. **Towards Optimization of Hydroxychloroquine Dosing in Intensive Care Unit COVID-19 Patients**. Clin Infect Dis. 2020 Apr 7. PubMed: https://pubmed.gov/32255489. Full-text: https://doi.org/10.1093/cid/ciaa394

Ongoing clinical trials with HCQ use different dosing regimens. In this PK study on 13 patients critically ill with COVID-19, 200 mg three times daily was inappropriate to reach a supposed target blood level of 1 - 2 mg/L. Authors proposed 800 mg once daily on day 1, followed by 200 mg twice daily for 7 days. Further PK studies needed.

Bloch EM, Shoham S, Casadevall A, et al. **Deployment of convalescent plasma for the prevention and treatment of COVID-19**. J Clin Invest. 2020 Apr 7. Full-text: https://doi.org/1387454

An overview of treatment with convalescent plasma on current evidence of benefit, regulatory considerations, logistical work-flow (recruitment of donors, etc) and proposed clinical trials.

Procedures

Loftus RW, Dexter F, Parra MC, Brown JR. **Importance of oral and nasal decontamination for patients undergoing anesthetics during the COVID-19 era**. Anesth Analg. 2020 Apr 3. PubMed: https://pubmed.gov/32250978. Full-text: https://doi.org/10.1213/ANE.0000000000004854

According to the authors, the evidence shows a favourable risk/benefit profile for patient decolonization with nasal povidone and oral chlorhexidine rinse to help mitigate the perioperative spread.

10 April

Diagnostics

Yuan J, Kou S, Liang Y, Zeng J, Pan Y, Liu L. **PCR Assays Turned Positive in 25 Discharged COVID-19 Patients**. Clin Infect Dis. 2020 Apr 8. PubMed: https://pubmed.gov/32266381. Full-text: https://doi.org/10.1093/cid/ciaa398

Among 172 discharged COVID-19 patients, 25 (14.5%) had positive testing again 2 to 13 days after discharge, without aggravation of symptoms. Two negative RT-PCR tests 24 hours apart may not be sufficient for viral clearance evaluation, suggesting the need for additional measures to confirm illness resolution.

Hope MD, Raptis CA, Henry TS. **Chest Computed Tomography for Detection of Coronavirus Disease 2019 (COVID-19): Don´t Rush the Science**. Ann Intern Med. 2020 Apr 8. PubMed: https://pubmed.gov/32267912. Full-text: https://doi.org/10.7326/M20-1382

Can chest CT be used as a primary tool for detecting COVID-19 in epidemic areas? Some early studies from China said yes. The authors comment that this is a cautionary tale about the consequences of rushing the scientific review process: harsh criticism on faulty design, incomplete methods, biased patient cohorts, confounding and scant discussion, calling into question the broad conclusions that were made in these studies. Bottom line: CT should not be used to screen for or as a first-line test to diagnose COVID-19, all the more considering that performing CT safely is problematic.

Nair A, Rodrigues JCL, Hare S, et al. **A British Society of Thoracic Imaging statement: considerations in designing local imaging diagnostic algorithms for the COVID-19 pandemic**. Clin Radiol. 2020 May;75(5):329-334. PubMed: https://pubmed.gov/32265036. Full-text: https://doi.org/10.1016/j.crad.2020.03.008

Same issue. The British Society of Thoracic Imaging has explored different scenarios integrating CT into a diagnostic algorithm. Of note, the clinical value, even in the absence of PCR availability, remains unclear. Again: CT can help, but probably not as a tool for diagnosing COVID-19.

Clinical

Zhang Y, Xiao M, Zhang S, et al. **Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19**. N Engl J Med. 2020 Apr 8. PubMed: https://pubmed.gov/32268022. Full-text: https://doi.org/10.1056/NEJMc2007575

Case series on 3 patients with critical illness, developing antiphospholipid antibodies. These antibodies may rarely lead to thrombotic events that are difficult to differentiate from other causes of multifocal thrombosis in critically patients, such as disseminated intravascular coagulation, heparin-induced thrombocytopenia, and thrombotic microangiopathy.

Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. **Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study**. Eur Arch Otorhinolaryngol. 2020 Apr 6. PubMed: https://pubmed.gov/32253535. Full-text: https://doi.org/10.1007/s00405-020-05965-1 ● (IMPORTANT)

This important study shows that in Europe, otolaryngologic symptoms are much more common than in Asia (it remains unclear whether this is a true difference). Among 417 mild-to-moderate COVID-19 patients (from 12 European hospitals), 86% and 88% reported olfactory and gustatory dysfunctions, respectively. The vast majority was anosmic (hyposmia, parosmia, phantosmia did also occur), and the early olfactory recovery rate was 44%. Females were more affected than males. Olfactory dysfunction appeared before (12%), at the same time (23%) or after (65%) the appearance of other symptoms. There is no doubt that sudden anosmia or ageusia need to be recognized as important symptoms of COVID-19.

Baig AM. **Neurological manifestations in COVID-19 caused by SARS-CoV-2**. CNS Neurosci Ther. 2020 Apr 7. PubMed: https://pubmed.gov/32266761. Full-text: https://doi.org/10.1111/cns.13372

Neuroinvasive propensity has been demonstrated as a common feature of human coronaviruses. These viruses can invade brainstem via a synapse-connected route from the lung and airways. With regard to SARS-CoV-2, early occurrences such as olfactory symptoms (see above) should be further evaluated for CNS involvement. Potential late neurological complications in cured COVID-19 patients are discussed. No data are available yet. However, after reading this, you will ask yourself whether herd immunity (infection of broader populations) is such a good idea.

Epidemiology

Stafford N. Covid-19: **Why Germany´s case fatality rate seems so low**. BMJ. 2020 Apr 7;369:m1395. PubMed: https://pubmed.gov/32265194. Full-text: https://doi.org/10.1136/bmj.m1395

Guess why? It's probably testing and nothing else. The more people with no or mild symptoms you test, the lower the fatality rate. Reliable PCR methods are reported through the end of January. In Germany's public health system, testing is not restricted to a central laboratory as in many other nations but can be conducted at quality-controlled laboratories throughout the country. Within a few weeks, overall capacity reached half a million PCR tests a week. The same low fatality rate is seen in South Korea, another country with high testing rates.

Nussbaumer-Streit B, Mayr V, Dobrescu AI, et al. **Quarantine alone or in combination with other public health measures to control COVID-19: a rapid review**. Cochrane Database Syst Rev. 2020 Apr 8;4:CD013574. PubMed: https://pubmed.gov/32267544. Full-text: https://doi.org/10.1002/14651858.CD013574

A word from Cochrane. Current evidence for COVID-19 "is limited". However, findings "consistently indicate that quarantine is important in reducing incidence and mortality". In order to maintain the best possible balance of measures, "decision makers must constantly monitor the outbreak situation and the impact of the measures implemented". Well.

Pregnancy

Zaigham M, Andersson O. **Maternal and Perinatal Outcomes with COVID-19: a systematic review of 108 pregnancies**. Acta Obstet Gynecol Scand. 2020 Apr 7. PubMed: https://pubmed.gov/32259279. Full-text: https://doi.org/10.1111/aogs.13867

Systematic review among 108 pregnancies published in 18 articles. 91% were delivered by cesarean section. Three maternal intensive care unit admissions were noted but no maternal deaths. One neonatal death and one intrauterine death were also reported.

Bourne T, Kyriacou C, Coomarasamy A, et al. **ISUOG Consensus Statement on rationalization of early-pregnancy care and provision of ultrasonography in context of SARS-CoV-2.** Ultrasound Obstet Gynecol. 2020 Apr 8. PubMed: https://pubmed.gov/32267981. Full-text: https://doi.org/10.1002/uog.22046

Statement on how to rationalize ultrasound and to manage early pregnancy complications in this crisis.

11 April

Virology

Shi J, Wen Z, Zhong G, et al. **Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS-coronavirus 2.** Science. 2020 Apr 8. PubMed: https://pubmed.gov/32269068. Full-text: https://doi.org/10.1126/science.abb7015

SARS-CoV-2 replicates poorly in dogs, pigs, chickens, and ducks. However, ferrets and cats are permissive to infection and cats susceptible to airborne infection. But cat owners can relax. Experiments were done in a small number of cats exposed to high doses of the virus, probably not representing real-life. It remains also unclear if cats secrete enough coronavirus to pass it on to people.

Wang X, Xu W, Hu G, et al. **SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion.** Cell Mol Immunol. 2020 Apr 7. PubMed: https://pubmed.gov/32265513. Full-text: https://doi.org/10.1038/s41423-020-0424-9

It remains unclear whether SARS-CoV-2 can also infect T cells, resulting in lymphocytopenia. Using a model with pseudoviruses, authors showed that SARS-CoV-2 infects (but does not replicate in) T cells through S protein-mediated membrane fusion. T cell lines were significantly more sensitive to SARS-CoV-2 infection when compared with SARS-CoV. Of note, a very low expression level of hACE2 was found, indicating that a novel receptor might mediate SARS-CoV-2 entry into T cells.

Vaccine

Le TT, Andreadakis Z, Kumar A, et al. **The COVID-19 vaccine development landscape**. Nature reviews drug discovery. 09 April 2020. Full-text: https://www.nature.com/articles/d41573-020-00073-5

Brief data-driven overview by seven experts. The conclusion is that efforts are unprecedented in terms of scale and speed and that there is an indication that a vaccine could be available by early 2021. As of 8 April 2020, the global vaccine landscape includes 115 candidates, of which the 5 most advanced candidates have already moved into clinical development, including mRNA-1273 from Moderna, Ad5-nCoV from CanSino Biologicals, INO-4800 from Inovio, LV-SMENP-DC and pathogen-specific aAPC from Shenzhen Geno-Immune Medical Institute. The race is on!

Diagnostics

Xu K, Chen Y, Yuan J, et al. **Factors associated with prolonged viral RNA shedding in patients with COVID-19**. Clin Infect Dis. 2020 Apr 9. PubMed: https://pubmed.gov/32271376. Full-text: https://doi.org/10.1093/cid/ciaa351

In a cohort of 113 symptomatic patients from two hospitals outside Wuhan, the median duration of SARS-CoV-2 RNA detection was 17 days (IQR, 13-22 days) as measured from illness onset. Male sex, delayed hospital admission, and invasive mechanical ventilation were independent risk factors for prolonged SARS-CoV-2 RNA shedding.

Okba NMA, Muller MA, Li W, et al. **Severe Acute Respiratory Syndrome Coronavirus 2-Specific Antibody Responses in Coronavirus Disease 2019 Patients**. Emerg Infect Dis. 2020 Apr 8;26(7). PubMed: https://pubmed.gov/32267220. Full-text: https://doi.org/10.3201/eid2607.200841

Small study, demonstrating that most PCR-confirmed SARS-CoV-2-infected persons seroconverted by 2 weeks after disease onset. Sensitivity varied between the assays (IgA ELISA showed higher sensitivity). It remains crucial to calibrate and standardize assays developed by different laboratories by using well-defined standard references as part of diagnostic assay validation.

Clinical

Wang Y, Lu X, Chen H, et al. **Clinical Course and Outcomes of 344 Intensive Care Patients with COVID-19**. Am J Respir Crit Care Med. 2020 Apr 8. PubMed: https://pubmed.gov/32267160. Full-text: https://doi.org/10.1164/rccm.202003-0736LE

Large single-center case study on 344 severe and critically ill patients admitted to Tongji hospital from January 25 through February 25, 2020. 133 (38.7%) patients died at a median of 15 days. Beside older age, hypertension and COPD were more common in non-survivors but not diabetes. No difference was seen between patients with or without ACE inhibitors.

Ji D, Zhang D, Xu J, et al. **Prediction for Progression Risk in Patients with COVID-19 Pneumonia: the CALL Score.** Clin Infect Dis. 2020 Apr 9. PubMed: https://pubmed.gov/32271369. Full-text: https://doi.org/10.1093/cid/ciaa414

CURB-65 severity score may not be suitable for COVID-19. In 208 patients, a risk factors scoring system was developed, for prediction of progression, based on patients' age, comorbidities, lymphocyte count and serum LDH at presentation. Needs to be validated by larger studies.

Treatment

Grein J, Ohmagari N, Shin D, et al. **Compassionate Use of Remdesivir for Patients with Severe Covid-19**. N Engl J Med. 2020 Apr 10. PubMed: https://pubmed.gov/32275812. Full-text: https://doi.org/10.1056/NEJMoa2007016

A compassionate use program of remdesivir for patients with severe COVID-19 is described. Clinical improvement was observed in 36/53 (68%) patients. Since published yesterday, data are celebrated in the media. Unjustifiably. Although the authors have made some efforts to discuss their data carefully, even more caution is needed. We believe that with this "study", any (*yes, any!*) clinical benefit of remdesivir remains unproven. Moreover, several issues in this data set seem to be very implausible. We have written a correspondence letter to NEJM and will keep you updated.

Sheahan TP, Sims AC, Zhou S, et al. **An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice**. Sci Transl Med. 2020 Apr 6. PubMed: https://pubmed.gov/32253226. Full-text: https://doi.org/10.1126/scitranslmed.abb5883

The ribonucleoside analog beta-D-N(4)-hydroxycytidine (NHC, EIDD-1931) has broad spectrum antiviral activity against all CoVs, as well as increased potency against resistance mutations to the nucleoside analog inhibitor remdesivir. But how long will it take to bring this compound to clinical trials?

Jin Z, Du X, Xu Y, et al. **Structure of M(pro) from COVID-19 virus and discovery of its inhibitors**. Nature. 2020 Apr 9. PubMed: https://pubmed.gov/32272481. Full-text: https://doi.org/10.1038/s41586-020-2223-y ● (IMPORTANT)

Virtual drug screening to identify new drug leads that target the COVID-19 virus main protease M(pro) which plays a pivotal role in mediating viral replication and transcription. Six compounds inhibited M(pro) with IC_{50} values ranging from 0.67 to 21.4 muM, among them with disulfiram and carmofur (a pyrimidine analogue used as an antineoplastic agent), two approved drugs.

12 April

Virology

Chu H, Chan JF, Wang Y, et al. **Comparative replication and immune activation profiles of SARS-CoV-2 and SARS-CoV in human lungs: an ex vivo study with implications for the pathogenesis of COVID-19**. Clin Infect Dis. 2020 Apr 9. PubMed: https://pubmed.gov/32270184. Full-text: https://doi.org/10.1093/cid/ciaa410

Cell experiments on replication capacity and the immune activation profile of SARS-CoV-2 and SARS-CoV infection in human lung tissues. Both viruses were similar in cell tropism, with both targeting types I and II pneumocytes, and alveolar macrophages. SARS-CoV-2 generated 3.20 x more infectious virus particles than SARS-CoV from the infected lung tissues.

Cao X. **COVID-19: immunopathology and its implications for therapy**. Nat Rev Immunol. 2020 Apr 9. PubMed: https://pubmed.gov/32273594. Full-text: https://doi.org/10.1038/s41577-020-0308-3

Some thoughts on the immunopathological changes in patients with COVID-19 and how this may provide potential targets for drug discovery and may be important for clinical management.

Wang Q, Zhang Y, Wu L, et al. **Structural and Functional Basis of SARS-CoV-2 Entry by Using Human ACE2**. Cell. 2020 Apr 7. PubMed: https://pubmed.gov/32275855. Full-text: https://doi.org/10.1016/j.cell.2020.03.045 ● (IMPORTANT)

Atomic details of the crystal structure of the C-terminal domain of SARS-CoV-2 spike protein in complex with human ACE2 are presented. The hACE2 binding mode of SARS-CoV-2 seems to be similar to SARS-CoV, but some key residue substitutions slightly strengthen the interaction and lead to higher affinity for receptor binding. Antibody experiments indicate notable differences in antigenicity between SARS-CoV and SARS-CoV-2.

Epidemiology

Guo ZD, Wang ZY, Zhang SF, et al. **Aerosol and Surface Distribution of Severe Acute Respiratory Syndrome Coronavirus 2 in Hospital Wards, Wuhan, China, 2020**. Emerg Infect Dis. 2020 Apr 10;26(7). PubMed: https://pubmed.gov/32275497. Full-text: https://doi.org/10.3201/eid2607.200885 ● (IMPORTANT)

In hospitals, the virus is everywhere. SARS-CoV-2 was widely distributed in the air and on object surfaces in both the intensive care units and general wards, implying a potentially high infection risk for medical staff. Contamination was greater in ICU. Virus was found on floors, computer mice, trash cans, and sickbed handrails and was detected in air approximately 4 m from patients.

Rossman H, Keshet A, Shilo S, et al. **A framework for identifying regional outbreak and spread of COVID-19 from one-minute population-wide surveys**. Nat Med. 2020 Apr 9. PubMed: https://pubmed.gov/32273611. Full-text: https://doi.org/10.1038/s41591-020-0857-9

Coronavirus infection spreads in clusters, and early identification of these clusters is critical for slowing down the spread of the virus. Short daily population-wide online surveys that assess the development of symptoms could serve as a strategic and valuable tools for identifying such clusters and informing epidemiologists, public health officials and policymakers.

Diagnostics

Guo WL, Jiang Q, Ye F, et al. **Effect of throat washings on detection of 2019 novel coronavirus**. Clin Infect Dis. 2020 Apr 9. PubMed: https://pubmed.gov/32271374. Full-text: https://doi.org/10.1093/cid/ciaa416

Throat washing may be used for monitoring due to its non-invasiveness and reliability. Throat washing was harvested by asking patients to oscillate over the posterior pharyngeal wall with 20 ml sterile normal saline. After 5-10 seconds, they spit out normal saline from their throat to a sterile container. In 24 paired throat washings and nasopharyngeal swab specimens, the positive testing rate of throat washing was much higher than that of swabs.

Xiao AT, Tong YX, Zhang S. **False-negative of RT-PCR and prolonged nucleic acid conversion in COVID-19: Rather than recurrence**. J Med Virol. 2020 Apr 9. PubMed: https://pubmed.gov/32270882. Full-text: https://doi.org/10.1002/jmv.25855

Negative does not mean absolutely negative. Among 70 COVID-19 patients, 15 (21%) experienced a "turn positive" of SARS-CoV-2 PCR after two consecutive negative results (up to 45 days after symptom onset).

Clinical

Mao L, Jin H, Wang M, et al. **Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China**. JAMA Neurol. 2020 Apr 10. PubMed: https://pubmed.gov/32275288. Full-text: https://doi.org/10.1001/jamaneurol.2020.1127

This retrospective, observational case series found 78/214 patients (36%) with neurologic manifestations, ranging from fairly specific symptoms (loss of sense of smell or taste, myopathy, and stroke) to more non-specific symptoms (headache, low consciousness, dizziness, or seizure). Whether these more non-specific symptoms are manifestations of the disease itself remains to be seen.

Cui S, Chen S, Li X, Liu S, Wang F. **Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia**. J Thromb Haemost. 2020 Apr 9. PubMed: https://pubmed.gov/32271988. Full-text: https://doi.org/10.1111/jth.14830

Among 81 severe COVID-19 patients, incidence of venous thromboembolism (VTE) was 25%. A significant increase of D-dimer was a good index for identifying high-risk groups of VTE.

Treatment

Ferner RE, Aronson JK. **Chloroquine and hydroxychloroquine in covid-19**. BMJ. 2020 Apr 8;369:m1432. PubMed: https://pubmed.gov/32269046. Full-text: https://doi.org/10.1136/bmj.m1432

In the year 1925, the BMJ cautiously endorsed Moellgaard's gold treatment for tuberculosis, although it found his pharmacological reasoning "both interesting and instructive". In 2020, the BMJ is similarly cautious about (hydroxyl)chloroquine treatment for SARS-CoV-2. In cell and animal studies, the effects on avian influenza, Epstein-Barr, chikungunya or Zika have been variable. Wide use of these drugs will expose patients to rare but potentially fatal harms, including serious cutaneous adverse reactions, fulminant hepatic failure, and ventricular arrhythmias (especially when prescribed with azithromycin).

13 April

Virology

Gao Y, Yan L, Huang Y, et al. **Structure of the RNA-dependent RNA polymerase from COVID-19 virus**. Science. 2020 Apr 10. PubMed: https://pubmed.gov/32277040. Full-text: https://doi.org/10.1126/science.abb7498 ● (IMPORTANT)

Using cryogenic electron microscopy, the authors describe the structure of the RNA-dependent RNA polymerase, another central enzyme of the viral replication machinery. It is also shown how remdesivir and sofosbuvir bind to this polymerase.

Epidemiology

Danis K, Epaulard O, Benet T, et al. **Cluster of coronavirus disease 2019 (Covid-19) in the French Alps, 2020**. Clin Infect Dis. 2020 Apr 11. PubMed: https://pubmed.gov/32277759. Full-text: https://doi.org/10.1093/cid/ciaa424

Some clusters are described, including a 9-yr-old child who attended three different schools (why 3 is not described) and one ski class while symptomatic. Coinfected with both picornavirus + influenza A(H1N1), the child transmitted only these viruses to others but not SARS-CoV-2, suggesting that these viruses are more easily transmitted than SARS-CoV-2.

Asadi S, Bouvier N, Wexler AS, Ristenpart WD. **The coronavirus pandemic and aerosols: Does COVID-19 transmit via expiratory particles?** Aerosol Sci Technol. 2020 Apr 3;0(0):1-4. PubMed: https://pubmed.gov/32308568. Full-text: https://doi.org/10.1080/02786826.2020.1749229. eCollection 2020

Why is SARS-CoV-2 so highly transmissible? This interesting overview describes current knowledge of airborne transmission. It's not only the "droplet spray", typically greater than 5 µm in diameter. Alternatively, a susceptible person can inhale microscopic aerosol particles consisting of the residual solid components of evaporated respiratory droplets, which are tiny enough to remain airborne for hours. The authors conclude that speech plausibly serves as an underrecognized transmission mechanism: "it is up to 'aerosol scientists' to provide the technology and hard data to either corroborate or reject that." So please, get on the scene, aerosol scientists on this planet!

Clinical

Yousefzadegan S, Rezaei N. **Case Report: Death Due to Novel Coronavirus Disease (COVID-19) in Three Brothers**. Am J Trop Med Hyg. 2020 Apr 10. PubMed: https://pubmed.gov/32277694. Full-text: https://doi.org/10.4269/ajtmh.20-0240

Is there a genetic predisposition for severe diseases? This report from Iran describes three brothers aged 54-66 years, all dying from COVID-19 with a relatively similar pattern after less than 2 weeks of illness. All were previously healthy, without histories of underlying diseases.

Casini A, Alberio L, Angelillo-Scherrer A, et al. **Thromboprophylaxis and laboratory monitoring for in-hospital patients with Covid-19 - a Swiss consensus statement by the Working Party Hemostasis**. Swiss Med Wkly. 2020 Apr 11;150:w20247. PubMed: https://pubmed.gov/32277760. Full-text: https://doi.org/10.4414/smw.2020.20247 ● (IMPORTANT)

All in-hospital COVID-19 patients should receive pharmacological thromboprophylaxis according to a risk stratification score, unless contraindicated. In patients with creatinine clearance > 30 ml/min, low molecular weight heparin (LMWH) should be administered according to the prescribing information. These guidelines also suggest regularly monitoring prothrombin time, D-dimers, fibrinogen, platelet count, LDH, creatinine and ALT daily or at least 2-3 times per week.

Yan CH, Faraji F, Prajapati DP, Boone CE, DeConde AS. **Association of chemosensory dysfunction and Covid-19 in patients presenting with influenza-like symptoms**. Int Forum Allergy Rhinol. 2020 Apr 12. PubMed: https://pubmed.gov/32279441. Full-text: https://doi.org/10.1002/alr.22579

"Flu plus 'loss of smell' means COVID-19". Among 263 patients presenting in March (in a single center in San Diego) with flu-like symptoms, loss of smell was found in 68% of COVID-19 patients (n=59), compared to only 16% in negative patients (n=203). Smell and taste impairment were independently and strongly associated with positivity (anosmia: adjusted odds ratio 11, 95%CI: 5-24). Conversely, sore throat was independently associated with negativity.

Comorbidities

Torres T, Puig L. **Managing Cutaneous Immune-Mediated Diseases During the COVID-19 Pandemic**. Am J Clin Dermatol. 2020 Apr 10. PubMed: https://pubmed.gov/32277351. Full-text: https://doi.org/10.1007/s40257-020-00514-2

Patients with cutaneous immune-mediated diseases (including psoriasis, atopic dermatitis, and hidradenitis suppurativa) may continue their treatment even during the COVID-19 outbreak, preventing disease flares. However, in patients with active COVID-19 infection, it is generally recommended to withhold immunosuppressive or biologic treatment.

Coles CE, Aristei C, Bliss J, et al. **International Guidelines on Radiation Therapy for Breast Cancer During the COVID-19 Pandemic**. Clin Oncol (R Coll Radiol). 2020 May;32(5):279-281. PubMed: https://pubmed.gov/32241520. Full-text: https://doi.org/10.1016/j.clon.2020.03.006

In order to reduce hospital visits to a minimum and to ease pressure on workforce, detailed guidelines on radiation therapy for breast cancer are given, mainly focussing on hypofractionation.

Treatment, procedures

Lentz RJ, Colt H. **Summarizing societal guidelines regarding bronchoscopy during the COVID-19 pandemic**. Respirology. 2020 Apr 11. PubMed: https://pubmed.gov/32277733. Full-text: https://doi.org/10.1111/resp.13824

In whom to perform bronchoscopy and how to perform it safely? This paper describes different guidelines (based on expert opinions).

Grant WB, Lahore H, McDonnell SL, et al. **Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths**. Nutrients. 2020 Apr 2;12(4). PubMed: https://pubmed.gov/32252338. Full-text: https://doi.org/10.3390/nu12040988

Evidence? Well. Serum 25(OH)D concentrations tend to decrease with age, which may be important for COVID-19 because case-fatality rates increase with age. That's the whole story. After all, the "hypothesis that vitamin D supplementation can reduce the risk of influenza and COVID-19 incidence and death should be investigated in trials".

14 April

Virology

Monteil V, Kwon H, Prado P, et al. **Inhibition of SARS-CoV-2 Infections in Engineered Human Tissues Using Clinical-Grade Soluble Human ACE2.** Cell. 2020 May 14;181(4):905-913.e7. PubMed: https://pubmed.gov/32333836. Full-text: https://doi.org/10.1016/j.cell.2020.04.004

This study shows that human recombinant soluble ACE2 (hrsACE2) blocks SARS-CoV-2 infections of different cells, human blood vessel organoids and human kidney organoids. In ARDS patients, hrsACE2 was ineffective but safe at a broad range of doses. Apeiron Biologics plans a randomized study on 200 COVID-19 patients in April.

Epidemiology

van Doremalen N, Bushmaker T, Morris DH, et al. **Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1**. N Engl J Med. 2020 Mar 17. PubMed: https://pubmed.gov/32182409. Full-text: https://doi.org/10.1056/NEJMc2004973

This important work was published a few weeks ago. Today, no less than 6 correspondence letters mainly discuss airborne transmission and viability of SARS-CoV-2 in aerosols. The bottom line: viability was investigated under experimental conditions and should not be used to draw conclusions about airborne transmission. However, according to the authors, aerosol-generating medical procedures should be examined as well as decontamination techniques.

Sutton D, Fuchs K, D´Alton M, Goffman D. **Universal Screening for SARS-CoV-2 in Women Admitted for Delivery.** N Engl J Med. 2020 Apr 13. PubMed: https://pubmed.gov/32283004. Full-text: https://doi.org/10.1056/NEJMc2009316

Between March 22 and April 4, 2020, all pregnant women who delivered infants were tested in a hospital located on the northern tip of Manhattan, New York City. Nasopharyngeal swabs obtained from 210 asymptomatic women were positive in 29 (13.7%). All four women with symptoms of COVID-19 on admission were positive. In other words: **29/33 women were asymptomatic**.

Kong WH, Li Y, Peng MW, et al. **SARS-CoV-2 detection in patients with influenza-like illness**. Nat Microbiol. 2020 Apr 7. PubMed: https://pubmed.gov/32265517. Full-text: https://doi.org/10.1038/s41564-020-0713-1

Re-analysing 640 throat swabs collected from patients in Wuhan with influenza-like-illness from 6 October 2019 to 21 January 2020, the authors found 9 to be positive for SARS-CoV-2. The onset date of the earliest case was 4 January 2020, one week after the outbreak was reported by hospitals.

Clinical

Zini G, Bellesi S, Ramundo F, d´Onofrio G. **Morphological anomalies of circulating blood cells in COVID-19**. Am J Hematol. 2020 Apr 12. PubMed: https://pubmed.gov/32279346. Full-text: https://doi.org/10.1002/ajh.25824

Morphologic changes in the peripheral blood over time in a few COVID-19 patients from Italy. In the early phase of symptom aggravation, a pronounced granulocytic reaction with immaturity, dysmorphism and apoptotic-degenerative morphological evidence was seen. Later the hematologic picture tended to shift toward impressive reactive lymphocyte activation, often with numerical increase, and heterogeneous morphological expression.

Comorbidities

Wang H, Li T, Barbarino P, et al. **Dementia care during COVID-19**. Lancet. 2020 Apr 11; 395(10231):1190-1191. PubMed: https://pubmed.gov/32240625. Full-text: https://doi.org/10.1016/S0140-6736(20)30755-8

Some thoughts on dementia care in this crisis.

Treatment

De Meyer S, Bojkova D, Cinati J, et al. **Lack of Antiviral Activity of Darunavir against SARS-CoV-2**. Full-text: https://doi.org/10.1101/2020.04.03.20052548

Usually we hesitate to refer to www.medrxiv.org. Preprints published at this website are preliminary reports of work that have not been certified by peer review. Well, it's time to make an exception. Because this is important: **Darunavir, an HIV protease inhibitor, is not active against SARS-CoV-2.** There was no *in vitro* antiviral activity against a clinical isolate at clinically relevant concentrations (EC_{50} > 100 μM). Remdesivir, used as a positive control, showed potent activity (EC_{50} = 0.38 μM). However, the clinical trial on 3,040 participants treated with darunavir in Spain is still ongoing (www.clinicaltrials.gov assessment on April 13).

Bartiromo M, Borchi B, Botta A, et al. **Threatening drug-drug interaction in a kidney transplant patient with Coronavirus Disease 2019 (COVID-19)**. Transpl Infect Dis. 2020 Apr 12. PubMed: https://pubmed.gov/32279418. Full-text: https://doi.org/10.1111/tid.13286

If you give HIV PIs, please be always aware of drug-drug interactions. Ritonavir is a strong pharmaco-enhancer. For example, **tacrolimus** has to be **reduced by 10-100 fold** to maintain concentration within the therapeutical range. In this case report, a woman with kidney transplantation was treated with lopinavir/r (the "r" indicates ritonavir) for COVID-19 while receiving the full dose of tacrolimus. Levels went incredibly high and were still above the therapeutic range 9 days after stopping both lopinavir/r and tacrolimus. Fortunately, everything turned out alright.

Feldmann M, Maini RN, Woody JN, et al. **Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed**. Lancet. 2020 Apr 9. PubMed: https://pubmed.gov/32278362. Full-text: https://doi.org/10.1016/S0140-6736(20)30858-8

Treating the inflammatory excess in patients with COVID-19: why anti-tumour necrosis factor (TNF) antibodies could be a good idea.

McEnery T, Gough C, Costello RW. **COVID-19: Respiratory support outside the intensive care unit**. Lancet Respir Med. 2020 Apr 9. PubMed: https://pubmed.gov/32278367. Full-text: https://doi.org/10.1016/S2213-2600(20)30176-4

The debate about the optimal mode of respiratory support (outside ICU) continues. Advocate high flow nasal cannulae (HFNC) over non-invasive ventilation (NIV) or vice versa? In the absence of randomised control trials in the use of either HFNC or NIV in COVID-19, this commentary discusses current knowledge.

15 April

Epidemiology

Gudbjartsson DF, Helgason A, Jonsson H, et al. **Spread of SARS-CoV-2 in the Icelandic Population**. N Engl J Med. 2020 Apr 14. PubMed: https://pubmed.gov/32289214. Full-text: https://doi.org/10.1056/NEJMoa2006100

SARS-CoV-2 in Iceland. As of April 4, a total of 1,221 of 9,199 tested persons (13.3%) were positive. Why is this of interest? Because the country serves as a perfect epidemiological model. Key findings: The percentage of participants who tested positive in population screening remained stable (0.8%) in March, and the infection rates in two screening groups (recruited through open invitation and through random sampling) were not substantially different. Notably, 43% of the participants who tested positive reported having no symptoms.

Stone TE, Kunaviktikul W, Omura M, Petrini M. **Editorial: Facemasks and the Covid 19 pandemic: What advice should health professionals be giving the general public about the wearing of facemasks?** Nurs Health Sci. 2020 Apr 12. PubMed: https://pubmed.gov/32279450. Full-text: https://doi.org/10.1111/nhs.12724

Bottom line of this editorial (addressed to nurses): surgical facemasks by the general public is not recommended unless you are looking after a sick person in a household setting or are suffering from an illness. Far more effective is handwashing and maintaining a safe distance from other people.

Perc M, Miksić NG, Slavinec M et al. **Forecasting COVID-19**. Front. Phys., 08 April 2020 | https://doi.org/10.3389/fphy.2020.00127

Forecasts obtained with a simple iteration method that only needs the daily values of confirmed cases as input. The method takes into account expected recoveries and deaths, and it determines maximally allowed daily growth rates that lead away from exponential increase toward stable and declining

numbers. Keeping the daily growth rates to below 5% is an important target for a promising outlook.

Diagnostic

Cheng MP, Papenburg J, Desjardins M, et al. **Diagnostic Testing for Severe Acute Respiratory Syndrome-Related Coronavirus-2: A Narrative Review**. Ann Intern Med. 2020 Apr 13. PubMed: https://pubmed.gov/32282894. Full-text: https://doi.org/10.7326/M20-1301

Comprehensive review of the current array of tests for SARS-CoV-2, highlighting gaps in current diagnostic capacity, and proposing potential solutions.

Wang X, Yao H, Xu X, et al. **Limits of Detection of Six Approved RT-PCR Kits for the Novel SARS-coronavirus-2 (SARS-CoV-2)**. Clin Chem. 2020 Apr 13. PubMed: https://pubmed.gov/32282874. Full-text: https://doi.org/10.1093/clinchem/hvaa099

Limits of detection of six commercial kits differed substantially (up to 16-fold difference), with the poorest limits likely leading to false-negative results when RT–PCR were used to detect SARS-CoV-2 infection. According to the authors, manufacturers should analyze the existing problems according to the clinical application and further improve their products.

Stam HJ, Stucki G, Bickenbach J. **Covid-19 and Post Intensive Care Syndrome: A Call for Action**. J Rehabil Med. 2020 Apr 14. PubMed: https://pubmed.gov/32286675. Full-text: https://doi.org/10.2340/16501977-2677

One aftershock of the pandemic will be the huge number of post-intensive care survivors who have been mechanically ventilated and will likely experience short- and medium-term consequences. These patients will require not only adequate screening but early rehabilitation and other interventions.

Comorbidities

Daniels MJ, Cohen MG, Bavry AA, Kumbhani DJ. **Reperfusion of STEMI in the COVID-19 Era - Business as Usual?** Circulation. 2020 Apr 13. PubMed: https://pubmed.gov/32282225. Full-text: https://doi.org/10.1161/CIRCULATIONAHA.120.047122

In the current crisis with limited resources to protect the work force, fibrinolytic therapy (FT) may be considered for patients with myocardial infarction (STEMI). FT may even be preferred over primary percutaneous coronary intervention. Arguments for this strategy are summarized.

Zhong Z, Zhang Q, Xia H, et al. **Clinical characteristics and immunosuppressants management of coronavirus disease 2019 in solid organ transplant recipients**. Am J Transplant. 2020 Apr 13. PubMed: https://pubmed.gov/32282986. Full-text: https://doi.org/10.1111/ajt.15928

COVID-19 was observed in two transplant recipients (liver and kidney), with different treatments and prognoses. Both patients recovered.

Treatment

Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. **Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review**. JAMA. 2020 Apr 13. PubMed: https://pubmed.gov/32282022. Full-text: https://doi.org/10.1001/jama.2020.6019

Fantastic review on current knowledge on potential therapies (as of April 5).

Rome BN, Avorn J. **Drug Evaluation during the Covid-19 Pandemic**. N Engl J Med. 2020 Apr 14. PubMed: https://pubmed.gov/32289216. Full-text: https://doi.org/10.1056/NEJMp2009457

Thoughts on how clinical trials should be performed during the current pandemic. And how the processes for evaluating and approving drugs can go awry during a public health crisis.

16 April

Comment on Compassionate Use of Remdesivir for Patients with Severe Covid-19 N Engl J Med. 2020 Apr 10**.**

Today, we will not discuss the Top Ten Papers. Instead, we will talk about remdesivir and give you 10 good reasons to be careful. Last Friday, on April 10, the New England Journal of Medicine published data on patients who were treated with 10 days of remdesivir on a compassionate use basis (Grein 2020). These results gained a lot of media attraction and Daniel O'Day, Gilead's CEO, wrote the same day that "the majority" of patients "demonstrated clinical

improvement". There is no doubt that remdesivir is currently the biggest hope for COVID-19. Results of two large Phase III randomized clinical trials are expected by the end of this month. Remdesivir is also among the four drugs tested in WHO's huge SOLIDARITY trial.

Grein et al. offer an optimistic view on remdesivir. Although viral data were not available, they concluded with a clinical "improvement in 68%" (36/53) and a "noteworthy" low mortality of 13%, seemingly lower than seen in a randomized clinical trial (RCT) of lopinavir/r (Cao 2020). The authors also emphasize repeatedly the severity of disease in their patients, as many required ventilation – more than in the lopinavir/r trial.

Is the author's optimism justified? We don't believe so. We think that, given the published data, remdesivir has only low or at best moderate clinical activity. We are concerned that remdesivir which was not effective against Ebola, will fail in COVID-19 as well.

First, 8/61 patients were not included in the analysis, among them 7 with no post-treatment data. Any reader will wonder what happened to these patients – did they die while on treatment? If these patients had been included in the analysis, we would have observed "improvement in 59%" (36/61).

One patient was excluded due to an "erroneous start date". This is remarkable as at least 13/51 received less than the planned treatment of 10 days but remained in the analysis. The same is true for at least two patients with, let's say, an "erroneous stop date" (treatment given for 13 days). The author's statement that treatment duration was not uniform, "largely because clinical improvement enabled discharge", is misleading. Only 3/13 subjects who were treated for less than 10 days were discharged early.

In the mentioned randomized clinical trial comparing lopinavir/r and standard of care, day 14 clinical improvement rates on a predefined ordinal scale were 46% with lopinavir/r and 30% with standard care (Cao 2020). According to an NEJM editorial commenting on this trial, results were "disappointing" (Baden 2020). Applying the same scale to the "study" presented here, the day 14 rate would have been at best 49% with remdesivir.

The authors emphasize the severity of their patients' health, indicated by the fact that 34/53 required invasive mechanical ventilation (IMV), more than in the lopinavir/r trial. But IMV is not the only indicator for severity. The patients in the lopinavir/r trial were sick, too. Inclusion criteria were CT-confirmed pneumonia and an oxygen saturation of 94 % or less while breathing ambient air.

Age and comorbidities in the lopinavir/r trial looked much the same as in the remdesivir study.

The median duration from onset of disease until treatment initiation was 12 days (IQR 9-15) with remdesivir and 13 days (IQR 11-16) in the lopinavir/r trial. Thus, considering points 4-6, it remains unclear if the remdesivir patients were more severely ill.

If we focus on the 41 remdesivir patients who required at least high-flow oxygen at baseline, clinical improvement at day 14 was seen in only 39%. Is this more than we would have seen with placebo?

This study provided data on ALT, AST, and creatinine. They were "fluctuating" during follow-up. Inexplicably, other easily performed and more important parameters such as lymphocytes, D-dimer and lactate dehydrogenase were unavailable. Several studies have identified these parameters to be highly predictive for clinical progression (Zhou 2020, Ji 2020).

The data quality is poor. For some subjects (31, 32), duration remained (mistakenly?) unclear and subject 43 was discharged while worsening.

The final argument: patients who were too ill for an antiviral agent (the "point of no return") doesn't count. Of 17 patients without IMV at baseline, at least 4 patients worsened during remdesivir treatment.

In conclusion, for a number of reasons, this report published in the New England Journal of Medicine is a cautionary tale for "science in a hurry". Fragmentary data arouse false expectations. This paper is not helpful. Safety of the drug was shown in the Ebola trial. It might have been preferable to postpone the publication – after all, the eagerly awaited results from the randomized clinical trials on remdesivir are just days to a few weeks away.

Will remdesivir be to COVID-19 what AZT was to AIDS? (AZT, approved in 1987, was the first and only antiretroviral drug to treat HIV/AIDS for years. Unfortunately, dosage was complicated and efficacy was minimal.) We hope this is not the case because we badly need efficient drugs in our fight against the SARS-CoV-2 pandemic.

We sincerely hope that our objections to the study by Grein et al. are wrong.

References

Baden LR, Rubin EJ. **Covid-19 – The Search for Effective Therapy.** N Engl J Med. 2020 Mar 18. PubMed: https://pubmed.gov/32187463. Full-text: https://doi.org/10.1056/NEJMe2005477

Cao B, Wang Y, Wen D, et al. **A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19.** N Engl J Med. 2020 Mar 18. PubMed: https://pubmed.gov/32187464. Full-text: https://doi.org/10.1056/NEJMoa2001282

Grein J, Ohmagari N, Shin D, et al. **Compassionate Use of Remdesivir for Patients with Severe Covid-19.** N Engl J Med. 2020 Apr 10. PubMed: https://pubmed.gov/32275812. Full-text: https://doi.org/10.1056/NEJMoa2007016

Ji D, Zhang D, Xu J, et al. **Prediction for Progression Risk in Patients with COVID-19 Pneumonia: the CALL Score.** Clin Infect Dis. 2020 Apr 9. PubMed: https://pubmed.gov/32271369. Full-text: https://doi.org/10.1093/cid/ciaa414

Zhou F, Yu T, Du R, et al. **Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.** Lancet. 2020 Mar 28;395(10229):1054-1062. PubMed: https://pubmed.gov/32171076. Full-text: https://doi.org/10.1016/S0140-6736(20)30566-3

17 April

Epidemiology

Szarpak L, Smereka J, Filipiak KJ, Ladny JR, Jaguszewski M. **Cloth masks versus medical masks for COVID-19 protection**. Cardiol J. 2020 Apr 14. PubMed: https://pubmed.gov/32285928. Full-text: https://doi.org/10.5603/CJ.a2020.0054

Some critical thoughts on the use of cloth masks. The physical properties of a cloth mask, reuse, the frequency and effectiveness of cleaning, and increased moisture retention, may potentially increase the infection risk.

Diagnostics

He X, Lau EHY, Wu P, et al. **Temporal dynamics in viral shedding and transmissibility of COVID-19**. Nat Med. 2020 Apr 15. PubMed: https://pubmed.gov/32296168. Full-text: https://doi.org/10.1038/s41591-020-0869-5 ●● (Outstanding)

Important work on viral shedding: this may begin 2 to 3 days before the appearance of the first symptoms and infectiousness profile may more closely resemble that of influenza than that of SARS. Analyzing a total of 414 throat swabs in 94 patients, the highest viral load was found at the time of symptom onset. Infectiousness started from 2.3 days (95% CI, 0.8–3.0 days) before symptom onset and peaked at 0.7 days (95% CI, -0.2–2.0 days) before symptom onset. The authors estimated that 44% (95%CI 25-69%) of secondary cases were infected during the index cases' presymptomatic stage. Infectiousness was estimated to decline quickly within 7 days.

Raptis CA, Hammer MM, Short RG, et al. **Chest CT and Coronavirus Disease (COVID-19): A Critical Review of the Literature to Date**. AJR Am J Roentgenol. 2020 Apr 16:1-4. PubMed: https://pubmed.gov/32298149. Full-text: https://doi.org/10.2214/AJR.20.23202

A critical review concluding that current evidence does not substantiate the use of CT as a diagnostic test for COVID-19. At present, CT should be reserved for evaluation of complications of COVID-19 pneumonia or for assessment if alternative diagnoses are suspected.

Song C, Wang Y, Li W, et al. **Absence of 2019 Novel Coronavirus in Semen and Testes of COVID-19 Patients**. Biol Reprod. 2020 Apr 16. PubMed: https://pubmed.gov/32297920. Full-text: https://doi.org/10.1093/biolre/ioaa050

The virus was not found in the semen of 12 patients recovering from COVID-19 and in a testis sample of one deceased patient.

Scorzolini L, Corpolongo A, Castilletti C, Lalle E, Mariano A, Nicastri E. **Comment of the potential risks of sexual and vertical transmission of Covid-19 infection**. Clin Infect Dis. 2020 Apr 16. PubMed: https://pubmed.gov/32297915. Full-text: https://doi.org/10.1093/cid/ciaa445

In six women, SARS-CoV-2 was not detected in amniotic fluid, cord blood, neonatal throat swab, or breastmilk samples.

Clinical

Zhan M, Qin Y, Xue X, Zhu S. **Death from Covid-19 of 23 Health Care Workers in China**. N Engl J Med. 2020 Apr 15. PubMed: https://pubmed.gov/32294342. Full-text: https://doi.org/10.1056/NEJMc2005696

In China, among 3387 healthcare workers infected with SARS-CoV-2, 23 persons died. Median age was 55 years (range, 29 to 72). Eleven of these persons had been rehired after retirement and 8 were surgeons. Only 2 of the 23 health care workers were physicians in respiratory medicine who had been specifically assigned to treat patients with COVID-19.

Hendren NS, Drazner MH, Bozkurt B, Cooper LT Jr. **Description and Proposed Management of the Acute COVID-19 Cardiovascular Syndrome**. Circulation. 2020 Apr 16. PubMed: https://pubmed.gov/32297796. Full-text: https://doi.org/10.1161/CIRCULATIONAHA.120.047349

SARS-CoV-2 has the potential to infect cardiomyocytes, pericytes and fibroblasts via the ACE2 pathway leading to direct myocardial injury, but that pathophysiological sequence remains unproven. A second hypothesis to explain COVID-19 related myocardial injury centers on cytokine excess and/or antibody mediated mechanisms. Clinically, COVID-19 can manifest with an acute cardiovascular syndrome (termed "ACovCS"). This review shows surveillance, diagnostic and management strategies for ACovCS that balances potential patient risks and healthcare staff exposure.

Xu P, Zhou Q, Xu J. **Mechanism of thrombocytopenia in COVID-19 patients**. Ann Hematol. 2020 Apr 15. PubMed: https://pubmed.gov/32296910. Full-text: https://doi.org/10.1007/s00277-020-04019-0

Review focussing on thrombocytopenia which is commonly seen in COVID-19. Three mechanisms are discussed: direct infection of bone marrow cells by the virus and inhibition of platelet synthesis, platelet destruction by the immune system and platelet aggregation in the lungs, resulting in microthrombi and platelet consumption.

Treatment

Smereka J, Puslecki M, Ruetzler K, et al. **Extracorporeal membrane oxygenation in COVID-19**. Cardiol J. 2020 Apr 14. PubMed: https://pubmed.gov/32285929. Full-text: https://doi.org/10.5603/CJ.a2020.0053

A brief review on ECMO which remains a therapeutic option in some well selected patients with severe COVID-19.

Di Giambenedetto S, Ciccullo A, Borghetti A, et al. **Off-label Use of Tocilizumab in Patients with SARS-CoV-2 Infection**. J Med Virol. 2020 Apr 16. PubMed: https://pubmed.gov/32297987. Full-text: https://doi.org/10.1002/jmv.25897

The humanized anti-IL-6 receptor antibody tocilizumab was given to three patients with severe COVID-19. All showed rapid relief of respiratory symptoms, resolution of fever and reduction in CRP following tocilizumab administration.

18 April

Epidemiology

CDC Covid Response Team**. Characteristics of Health Care Personnel with COVID-19 - United States, February 12-April 9, 2020**. MMWR Morb Mortal Wkly Rep. 2020 Apr 17;69(15):477-481. PubMed: https://pubmed.gov/32298247. Full-text: https://doi.org/10.15585/mmwr.mm6915e6

During February 12-April 9, among 315,531 COVID-19 cases reported to CDC, 49,370 (16%) included data on whether the patient was a health care worker (HCW). Detailed data were available on 8,945 of these HCW. Most HCW (90%) were not hospitalized; however, severe outcomes, including 27 deaths, occurred across all age groups. ICU admission and death were observed in 2.1–4.9% and 0.3-0.6%, respectively. These rates were markedly higher in HCW older than 65 years, with 6.9-16.0 % and 2.0-4.2%.

Anfinrud P, Stadnytskyi V, Bax CE, Bax A. **Visualizing speech-generated oral fluid droplets with laser light scattering**. N Engl J Med. https://doi.org/10.1056/NEJMc2007800.

You remember Depeche Mode's hit 'Enjoy the Silence'? Then look at this video, a person saying "stay healthy", a laser light-scattering experiment in which speech-generated droplets and their trajectories were visualized. The louder the speech, the higher the numbers of flashes. The number of flashes was highest when the "th" sound in the word "healthy" was pronounced. Depeche Mode were right: "Words are very unnecessary/They can only do harm".

Meselson M. **Droplets and Aerosols in the Transmission of SARS-CoV-2.** N Engl J Med. 2020 Apr 15. PubMed: https://pubmed.gov/32294374. Full-text: https://doi.org/10.1056/NEJMc2009324

These authors emphasize that breathing and talking produce even smaller and much more numerous particles, known as aerosol particles, than those visualized in the (above mentioned) laser experiment. They recommend wearing a suitable mask whenever it is thought that infected persons may be nearby and of providing adequate ventilation of enclosed spaces where such persons are known to be or may recently have been.

Diagnostics

Iwen PC, Stiles KL, Pentella MA. **Safety Considerations in the Laboratory Testing of Specimens Suspected or Known to Contain the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)**. Am J Clin Pathol. 2020 Apr 15;153(5):567-570. PubMed: https://pubmed.gov/32190890. Full-text: https://doi.org/10.1093/ajcp/aqaa047

Brief review on laboratory biosafety practices necessary to safely process clinical specimens.

Huang Y, Chen S, Yang Z, et al. **SARS-CoV-2 Viral Load in Clinical Samples of Critically Ill Patients**. Am J Respir Crit Care Med. 2020 Apr 15. PubMed: https://pubmed.gov/32293905. Full-text: https://doi.org/10.1164/rccm.202003-0572LE

Small study on 16 critically ill patients, demonstrating higher viral load and prolonged shedding in lower respiratory tract specimens, as compared with upper respiratory tract specimens.

Kim H, Hong H, Yoon SH. **Diagnostic Performance of CT and Reverse Transcriptase-Polymerase Chain Reaction for Coronavirus Disease 2019: A Meta-Analysis**. Radiology. 2020 Apr 17:201343. PubMed: https://pubmed.gov/32301646. Full-text: https://doi.org/10.1148/radiol.2020201343

There is a big debate whether chest CT contributes to COVID-19 diagnosis. Chinese researchers say yes, everyone else says no. This meta-analysis found a high sensitivity but low specificity. In areas with low prevalence, chest CT has a low positive predictive value (1.5-30.7%).

Clinical

Goyal P, Choi JJ, Pinheiro LC, et al. **Clinical Characteristics of Covid-19 in New York City**. N Engl J Med. 2020 Apr 17. PubMed: https://pubmed.gov/32302078. Full-text: https://doi.org/10.1056/NEJMc2010419

Clinical characteristics of the first 393 consecutive patients who were admitted to two hospitals in New York City, among them 130 needing invasive mechanical ventilation. The latter were more likely to be male, to be obese, and to have elevated liver-function values and inflammatory markers (ferritin, D-dimer, C-reactive protein, and procalcitonin). Diarrhea (23.7%), and nausea

and vomiting (19.1%) were more frequent than in the reports from China (it remains unclear whether this difference reflects geographic variation or differential reporting).

Bangalore S, Sharma A, Slotwiner A, et al. **ST-Segment Elevation in Patients with Covid-19 - A Case Series**. N Engl J Med. 2020 Apr 17. PubMed: https://pubmed.gov/32302081. Full-text: https://doi.org/10.1056/NEJMc2009020

In this case series of 18 patients who had ST-segment elevation, there was variability in presentation, a high prevalence of non-obstructive disease, and a poor prognosis. 6/9 patients undergoing coronary angiography had obstructive disease. Of note, all 18 patients had elevated D-dimer levels.

Gong J, Ou J, Qiu X, et al. **A Tool to Early Predict Severe Corona Virus Disease 2019 (COVID-19) : A Multicenter Study using the Risk Nomogram in Wuhan and Guangdong, China**. Clin Infect Dis. 2020 Apr 16. PubMed: https://pubmed.gov/32296824. Full-text: https://doi.org/10.1093/cid/ciaa443

A risk prediction nomogram for severe COVID-19 was evaluated, including older age, and higher serum lactate dehydrogenase, C-reactive protein, the coefficient of variation of red blood cell distribution width, blood urea nitrogen, direct bilirubin and lower albumin. Interesting, but needs to be validated in larger trials.

Helms J, Kremer S, Merdji H, et al. **Neurologic Features in Severe SARS-CoV-2 Infection**. N Engl J Med. 2020 Apr 15. PubMed: https://pubmed.gov/32294339. Full-text: https://doi.org/10.1056/NEJMc2008597

In this observational series of 58 patients, ARDS due to SARS-CoV-2 infection was associated with encephalopathy, prominent agitation and confusion, and corticospinal tract signs. It remained unclear which of these features were due to critical illness–related encephalopathy, cytokines, or the effect or withdrawal of medication, and which features were specific to SARS-CoV-2 infection.

19 April

Epidemiology

Nickbakhsh S, Ho A, Marques DFP, McMenamin J, Gunson RN, Murcia PR**. Epidemiology of seasonal coronaviruses: Establishing the context for COVID-19 emergence**. J Infect Dis. 2020 Apr 15. PubMed: https://pubmed.gov/32296837. Full-text: https://doi.org/10.1093/infdis/jiaa185 ● (IMPORTANT)

Interesting and incredibly diligent work on seasonal coronaviruses (sCoVs) and other co-circulating viruses over a thirteen years period in Western Scotland, UK. Different sCoVs were detected in 4.0% (2,958/74,519) of tested patients overall, contributing to 10.7% of all respiratory virus detections. All were winter pathogens, on average peaking between January and March, alongside influenza viruses and RSV. However, there were notable variations between sCoV types and between years. A potential for cross-protective immunity was also seen between some subtypes.

Diagnosis

Abdalhamid B, Bilder CR, McCutchen EL, Hinrichs SH, Koepsell SA, Iwen PC. **Assessment of Specimen Pooling to Conserve SARS CoV-2 Testing Resources**. Am J Clin Pathol. 2020 Apr 18. PubMed: https://pubmed.gov/32304208. Full-text: https://doi.org/10.1093/ajcp/aqaa064

Experimental pools were created, mixing positive and negative nasopharyngeal specimens. Results: if the incidence rate of SARS-CoV-2 infection is 10% or less, group testing will result in the saving of reagents and personnel time with an overall increase in testing capability of at least 69%.

Abbasi J. **The Promise and Peril of Antibody Testing for COVID-19**. JAMA. 2020 Apr 17. PubMed: https://pubmed.gov/32301958. Full-text: https://doi.org/10.1001/jama.2020.6170

Comprehensive review on recent (last two weeks) developments in antibody testing, a very rapidly evolving field of research. Brief overview on promises and perils of different testing systems, including ELISA and lateral flow assays.

Ashcroft J. **Keep older healthcare workers off the covid-19 front line**. BMJ. 2020 Apr 17;369:m1511. PubMed: https://pubmed.gov/32303493. Full-text: https://doi.org/10.1136/bmj.m1511

Older age is a risk factor for severe disease. This also applies to HCW. In China 11/23 deceased HCWs had been reactivated from retirement. In Italy, most of the 74 doctors who died were in their 60s, and only four were women. This brief letter to BMJ addresses this issue. Author declared the following competing interests: "I am an older, male GP".

Clinical

Chow EJ, Schwartz NG, Tobolowsky FA, et al. **Symptom Screening at Illness Onset of Health Care Personnel With SARS-CoV-2 Infection in King County, Washington**. JAMA. 2020 Apr 17. PubMed: https://pubmed.gov/32301962. Full-text: https://doi.org/10.1001/jama.2020.6637

Detailed analysis of symptoms of all laboratory-confirmed SARS-CoV-2 infections in HCP residing in King County. Screening only for fever, cough, shortness of breath, or sore throat might have missed 17% of symptomatic HCP at the time of illness onset; expanding criteria for symptoms screening to include myalgias and chills may still have missed 10%.

Chong VCL, Lim EKG, Fan EB, Chan SSW, Ong KH, Kuperan P. **Reactive lymphocytes in patients with Covid-19**. Br J Haematol. 2020 Apr 16. PubMed: https://pubmed.gov/32297330. Full-text: https://doi.org/10.1111/bjh.16690

Examination of the peripheral blood films of 32 patients found reactive lymphocytes in 72%. This seems to be in stark contrast to the SARS outbreak where reactive lymphocytes of this type were only rarely seen.

Treatment

Hillaker E, Belfer JJ, Bondici A, Murad H, Dumkow LE**. Delayed Initiation of Remdesivir in a COVID-19 Positive Patient**. Pharmacotherapy. 2020 Apr 13. PubMed: https://pubmed.gov/32281114. Full-text: https://doi.org/10.1002/phar.2403

Were we wrong with our critical review on remdesivir? Again, we hope so. A case of successful late initiation of remdesivir is presented. Sixty hours after starting the drug, the patient was extubated and was able to transition to room air within 24 hours of extubation.

Zhu Z, Lu Z, Xu T, et al. **Arbidol Monotherapy is Superior to Lopinavir/ritonavir in Treating COVID-19.** J Infect. 2020 Apr 10. PubMed: https://pubmed.gov/32283143. Full-text: https://doi.org/10.1016/j.jinf.2020.03.060

Retrospective case series, comparing lopinavir/r (34 cases) and arbidol (16 cases). On day 14 after the admission, no viral load was detected in the arbidol group, but the viral load was found in 15 (44.1%) patients treated with lopinavir/ritonavir. Patients in the arbidol group had a shorter duration of positive RNA test compared to those in the lopinavir/ritonavir group ($P < 0.01$).

Pregnancy

Chen L, Li Q, Zheng D, et al. **Clinical Characteristics of Pregnant Women with Covid-19 in Wuhan, China**. N Engl J Med. 2020 Apr 17. PubMed: https://pubmed.gov/32302077. Full-text: https://doi.org/10.1056/NEJMc2009226

Experience from Wuhan. A total of 109 of 118 women (92%) had mild disease, and 9 (8%) had severe disease (hypoxemia), 1 of whom received non-invasive mechanical ventilation (critical disease). There were 3 spontaneous abortions, 2 ectopic pregnancies, and 4 induced abortions (all owing to patients' concerns about COVID-19).

Alzamora MC, Paredes T, Caceres D, Webb CM, Valdez LM, La Rosa M. **Severe COVID-19 during Pregnancy and Possible Vertical Transmission.** Am J Perinatol. 2020 Apr 18. PubMed: https://pubmed.gov/32305046. Full-text: https://doi.org/10.1055/s-0040-1710050

Case report from Lima, Peru, describing a severe presentation of COVID-19 in pregnancy requiring invasive ventilatory support, suggesting possible vertical transmission.

20 April

Epidemiology

Normile D. **'Suppress and lift': Hong Kong and Singapore say they have a coronavirus strategy that works**. Science Mag Apr 13, 2020. Full-text https://www.sciencemag.org/news/2020/04/suppress-and-lift-hong-kong-and-singapore-say-they-have-coronavirus-strategy-works#

The bottom line: the tighter you control the infected, the less restriction you have to impose on the uninfected. With this strategy, Hong Kong and Singapore are very successful. But look at the controls: hospitalizing all those who test positive, regardless of whether they have symptoms, two weeks of self-quarantine to all close contacts, electronic wristbands, etc. You want to see where the infected people in Hong Kong are? You'll find them here: https://chp-dashboard.geodata.gov.hk/covid-19/en.html

Cheng KK, Lam TH, Leung CC. **Wearing face masks in the community during the COVID-19 pandemic: altruism and solidarity**. Lancet. 2020 Apr 16. PubMed: https://pubmed.gov/32305074. Full-text: https://doi.org/10.1016/S0140-6736(20)30918-1

The authors review current recommendations and conclude that mass masking for source control is a useful and low-cost adjunct to social distancing and hand hygiene, shifting the focus from self-protection to altruism, actively involving every citizen, and is a symbol of social solidarity in the global response to the pandemic.

Virology/Pathogenesis

Rockx B, Kuiken T, Herfst S, et al. **Comparative pathogenesis of COVID-19, MERS, and SARS in a nonhuman primate model**. Science 17 Apr 2020: eabb7314. Full text: https://science.sciencemag.org/content/early/2020/04/16/science.abb7314 ● (IMPORTANT)

This animal study was performed to understand the pathogenesis, showing SARS-CoV-2-infected macaques provide a new model to test therapeutic strategies. Virus was excreted from nose and throat in the absence of clinical signs, and detected in type I and II pneumocytes *in foci* of diffuse alveolar damage and in ciliated epithelial cells of nasal, bronchial, and bronchiolar mucosae. In SARS-CoV infection, lung lesions were typically more severe, while they were milder in MERS-CoV infection, where virus was detected mainly in type II pneumocytes.

Diagnostics

Atkinson B, Petersen E. **SARS-CoV-2 shedding and infectivity**. Lancet. 2020 Apr 15. PubMed: https://pubmed.gov/32304647. Full-text: https://doi.org/10.1016/S0140-6736(20)30868-0

Brief but important comment on several papers reporting on prolonged viral shedding. PCR does not distinguish between infectious virus and non-infectious nucleic acid. This is well known from many viral infections such as Ebola or measles.

Clinical

Toscano G, Palmerini F, Ravaglia S, et al. **Guillain-Barre Syndrome Associated with SARS-CoV-2**. N Engl J Med. 2020 Apr 17. PubMed: https://pubmed.gov/32302082. Full-text: https://doi.org/10.1056/NEJMc2009191

Observational cohort from Italy, involving five patients with COVID-19–associated Guillain-Barré syndrome which probably should be distinguished from critical illness neuropathy and myopathy, which tend to appear later in the course of critical COVID-19 illness.

Gutierrez-Ortiz C, Mendez A, Rodrigo-Rey S, et al. **Miller Fisher Syndrome and polyneuritis cranialis in COVID-19**. Neurology. 2020 Apr 17. PubMed: https://pubmed.gov/32303650. Full-text: https://doi.org/10.1212/WNL.0000000000009619

The next paper on neurological complications seen with COVID-19, probably due to an aberrant immune response.

Chen R, Liang W, Jiang M, et al. **Risk factors of fatal outcome in hospitalized subjects with coronavirus disease 2019 from a nationwide analysis in China**. Chest. 2020 Apr 15. PubMed: https://pubmed.gov/32304772. Full-text: https://doi.org/10.1016/j.chest.2020.04.010

It's only age. Multivariate analysis of a retrospective cohort of 1590 hospitalized subjects with COVID-19 throughout China revealed the following factors associated with mortality: Age 75 or older (HR: 7.86, 95% CI: 2.44-25.35), Age 65-74 years (HR: 3.43, 95% CI: 1.24-9.5), coronary heart disease (HR: 4.28, 95% CI: 1.14-16.13), cerebrovascular disease(HR: 3.1, 95% CI: 1.07-8.94), dyspnea (HR: 3.96, 95% CI:1.42-11), procalcitonin > 0.5ng/ml (HR: 8.72, 95% CI:3.42-

22.28), AST > 40 U/L (HR: 2.2, 95% CI: 1.1- 6.73). Not very new, but by now the largest cohort with detailed information.

Comorbidities

Brojakowska A, Narula J, Shimony R, Bander J. **Clinical Implications of SARS-Cov2 Interaction with Renin Angiotensin System**. J Am Coll Cardiol. 2020 Apr 14. PubMed: https://pubmed.gov/32305401. Full-text: https://doi.org/10.1016/j.jacc.2020.04.028

Don't stop your sartans or ACE inhibitors! The authors hypothesize that the benefits of treatment with renin-angiotensin system inhibitors in SARS-COV-2 may outweigh the risks and at the very least should not be withheld.

Kennedy NA, Jones GR, Lamb CA, et al. **British Society of Gastroenterology guidance for management of inflammatory bowel disease during the COVID-19 pandemic**. Gut. 2020 Apr 17. PubMed: https://pubmed.gov/32303607. Full-text: https://doi.org/10.1136/gutjnl-2020-321244

Making recommendations in the absence of data is not that easy. The authors have made heroic attempts to balance the risk of immune modifying drugs with the risk associated with active disease.

Severe COVID-19

Moore JB, June CH. **Cytokine release syndrome in severe COVID-19**. Science 17 Apr 2020: eabb8925. Full-text: https://science.sciencemag.org/content/early /2020/04/16/science.abb8925 ● (IMPORTANT)

Brief but fantastic overview about the current knowledge and the pathways leading to cytokine release syndrome.

21 April

Vacation

22 April

Vaccine

Callaway E. **Hundreds of people volunteer to be infected with coronavirus**. Nature 22 April 2020. Full-text: https://www.nature.com/articles/d41586-020-01179-x

What about a 'human challenge' vaccine study? Such a trial would be much faster: a much smaller group of young, healthy volunteers would receive a candidate vaccine and then be intentionally infected with the virus, to judge the efficacy of the immunization. No trial is yet planned, but the debate is on. The approach is also gaining some political support.

Epidemiology

Cowling BJ, Ali ST, Ng TWY, et al. **Impact assessment of non-pharmaceutical interventions against coronavirus disease 2019 and influenza in Hong Kong: an observational study**. Lancet Public Health. 2020 Apr 17. PubMed: https://pubmed.gov/32311320. Full-text: https://doi.org/10.1016/S2468-2667(20)30090-6

Detailed paper from Hong Kong modeling the effects of non-pharmaceutical interventions (NPIs, including border restrictions, quarantine and isolation, distancing, and changes in population behaviour). NPIs were associated with reduced transmission of COVID-19 and were also likely to have substantially reduced influenza transmission. Findings strongly suggest that social distancing and population behavioural changes – that have a social and economic impact that is less disruptive than a total lockdown – can meaningfully control COVID-19.

Wu X, Fu B, Chen L, Feng Y. **Serological tests facilitate identification of asymptomatic SARS-CoV-2 infection in Wuhan, China**. J Med Virol. 2020 Apr 20. PubMed: https://pubmed.gov/32311142. Full-text: https://doi.org/10.1002/jmv.25904

Forget herd immunity! Overall prevalence is still incredibly low. Even in hotspots like Wuhan! From April 3 to 15, SARS-CoV-2-specific IgG positive rate among 1,021 people applying for a permission to resume travel, only 98 (9.60%) were IgG positive and IgM and NAT (SARS-CoV-2 nucleic acid test) negative.

Diagnostics

Wilson NM, Norton A, Young FP, Collins DW. **Airborne transmission of severe acute respiratory syndrome coronavirus-2 to healthcare workers: a narrative review**. Anaesthesia. 2020 Apr 20. PubMed: https://pubmed.gov/32311771. Full-text: https://doi.org/10.1111/anae.15093

Evidence suggestive of airborne spread is growing. Authors discuss several 'aerosol-generating procedures' and current evidence (limited). A precautionary approach should be considered to assure healthcare worker safety.

Marty M, Chen K, Verrill KA. **How to Obtain a Nasopharyngeal Swab Specimen**. NEJM 2020. April 17, 2020. Full-text: https://www.nejm.org/doi/full/10.1056/NEJMvcm2010260?query=featured_home

It's not that trivial to obtain a NP-swab. Watch this video on protection, preparation, equipment, handling, removing personal protective equipment, etc.

Xiang F, Wang X, He X, et al. **Antibody Detection and Dynamic Characteristics in Patients with COVID-19**. Clin Infect Dis. 2020 Apr 19. PubMed: https://pubmed.gov/32306047. Full-text: https://doi.org/10.1093/cid/ciaa461 ● (IMPORTANT)

More on antibodies, as a complementary approach for PCR. The seroconversion of specific IgM and IgG antibodies were observed as early as the 4th day after symptom onset. In the confirmed patients with COVID-19, sensitivity, specificity, positive predictive value of IgM were 77.3% (51/66), 100% and 100%, and those of IgG were 83.3% (55/66), 95.0% and 94.8%. Both antibodies performed well in serodiagnosis for COVID-19 and rely on great specificity. The antibodies against SARS-CoV-2 can be detected in the middle and later stage of the illness.

Clinical

Effenberger M, Grabherr F, Mayr L, et al. **Faecal calprotectin indicates intestinal inflammation in COVID-19**. Gut. 2020 Apr 20. PubMed: https://pubmed.gov/32312790. Full-text: https://doi.org/10.1136/gutjnl-2020-321388

Fecal calprotectin (FC) has evolved as a reliable fecal biomarker allowing detection of intestinal inflammation in inflammatory bowel diseases and infectious colitis. This report on 40 patients provides some evidence that SARS-

CoV-2 infection instigates an inflammatory response in the gut, as elevated FC (largely expressed by neutrophil granulocytes) and diarrhea.

Severe COVID-19

Barnes BJ, Adrover JM, Baxter-Stoltzfus A, et al. **Targeting potential drivers of COVID-19: Neutrophil extracellular traps**. J Exp Med. 2020 Jun 1;217(6). PubMed: https://pubmed.gov/32302401. Full-text: https://doi.org/10.1084/jem.20200652

Case report of a patient who succumbed to COVID-19. Hypothesis that a powerful function of neutrophils – the ability to form neutrophil extracellular traps (NETs) – may contribute to organ damage and mortality in COVID-19. Targeting NETs directly and/or indirectly with existing drugs may reduce clinical severity.

Spiezia L, Boscolo A, Poletto F, et al. **COVID-19-Related Severe Hypercoagulability in Patients Admitted to Intensive Care Unit for Acute Respiratory Failure**. Thromb Haemost. 2020 Apr 21. PubMed: https://pubmed.gov/32316063. Full-text: https://doi.org/10.1055/s-0040-1710018

Case series of 22 patients with acute respiratory failure present a severe hypercoagulability rather than consumptive coagulopathy. Fibrin formation and polymerization may predispose to thrombosis and correlate with a worse outcome.

Treatment

Bhimray A, Morgan RL, Shumaker. **Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19**. Published by IDSA, 4/11/2020. Full-text: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

Evidence-based guidelines which are, in the absence of large RCTs, not very helpful. Recommendations for all drugs acknowledge the current “knowledge gap”. HCQ, lopinavir/r, tocilizumab and convalescent plasma should be given "only in the context of a clinical trial". Great.

23 April

Epidemiology

Jiang XL, Zhang XL, Zhao XN, et al. **Transmission potential of asymptomatic and paucisymptomatic SARS-CoV-2 infections: a three-family cluster study in China**. J Infect Dis. 2020 Apr 22. PubMed: https://pubmed.gov/32319519. Full-text: https://doi.org/10.1093/infdis/jiaa206

Detailed cluster analysis, confirming that transmission by individuals with asymptomatic or paucisymptomatic infections is possible. An asymptomatic mother transmitted the virus to her son, and a paucisymptomatic father transmitted the virus to his three-month-old daughter. SARS-CoV-2 was detected in the environment of one household.

Diagnostics

Zheng S, Fan J, Yu F, et al. **Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study**. BMJ. 2020 Apr 21;369:m1443. PubMed: https://pubmed.gov/32317267. Full-text: https://doi.org/10.1136/bmj.m1443

Among 96 consecutively admitted patients (22 mild, 74 severe COVID-19), RNA viral load was measured in 3,497 respiratory, stool, serum, and urine samples. Infection was confirmed in all patients by testing sputum and saliva samples, in the stool of 59% and in the serum of 41%. The median duration of virus in stool (22 days) was significantly longer than in respiratory (18 days, severe cases: 21 days) and serum samples (16 days). However, the main limitation is that RNA PCR cannot distinguish between viable and non-viable virus.

Clinical

Richardson S, Hirsch JS, Narasimhan M, et al. **Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area**. JAMA. 2020 Apr 22. PubMed: https://pubmed.gov/32320003. Full-text: https://doi.org/10.1001/jama.2020.6775 ● (IMPORTANT)

The numbers are becoming huge now. This case series from New York included 5,700 COVID-19 patients admitted to 12 hospitals between March 1 and April 4, 2020. Median age was 63 years (IQR 52-75), the most common comorbidities were hypertension (57%), obesity (42%), and diabetes (34%). At triage,

31% of patients were febrile, 17% had a respiratory rate greater than 24 breaths/minute, and 28% received supplemental oxygen. Of 2,634 patients with an available outcome, 14% (median age 68 years, IQR 56-78, 33% female) were treated in ICU, 12% received invasive mechanical ventilation and 21% died. Mortality for those requiring mechanical ventilation was 88.1%.

Pan Y, Yu X, Du X, et al. **Epidemiological and clinical characteristics of 26 asymptomatic SARS-CoV-2 carriers**. J Infect Dis. 2020 Apr 22. PubMed: https://pubmed.gov/32318703. Full-text: https://doi.org/10.1093/infdis/jiaa205

Retrospective analysis of 26 persistently asymptomatic patients. The median period from contact to the last positive nucleic acid test was 21.5 days (10-36 days). At least 10 patients had typical ground-glass or patchy opacities on CT.

Spinato G, Fabbris C, Polesel J, et al. **Alterations in Smell or Taste in Mildly Symptomatic Outpatients With SARS-CoV-2 Infection**. JAMA. 2020 Apr 22. PubMed: https://pubmed.gov/32320008. Full-text: https://doi.org/10.1001/jama.2020.6771

Telephone survey, analyzing 202 adult COVID-19 patients with mild symptoms, 5-6 after the positive swab was performed. Any altered sense of smell or taste was reported by 130 patients (64%, 95% CI, 57%-71%, more frequent in women, 73%). This was seen in 12% before, in 23% at the same time and in 27% after other symptoms. An altered sense of smell or taste was reported as the only symptom by 6 patients (3.0%).

Finsterer J, Stollberger C. **Causes of hypogeusia/hyposmia in SARS-CoV2 infected patients**. J Med Virol. 2020 Apr 20. PubMed: https://pubmed.gov/32311107. Full-text: https://doi.org/10.1002/jmv.25903

Some thoughts on the pathogenesis of hyposmia. According to the authors, the most likely cause for transient hypogeusia and hyposmia in SARS-CoV-2-infected patients is a direct contact and interaction of the virus with gustatory receptors or olfactory receptor cells.

Comorbidities

Sattar N, McInnes IB, McMurray JJV. **Obesity a Risk Factor for Severe COVID-19 Infection: Multiple Potential Mechanisms**. Circulation. 2020 Apr 22. PubMed: https://pubmed.gov/32320270. Full-text: https://doi.org/10.1161/CIRCULATIONAHA.120.047659

Brief review on obesity as a unifying risk factor for severe COVID-19 infection, reducing both protective cardiorespiratory reserve as well as potentiating the immune dysregulation. Possible patho-mechanisms are discussed.

Treatment

Prokunina-Olsson L, Alphonse N, Dickenson RE, et al. **COVID-19 and emerging viral infections: The case for interferon lambda**. J Exp Med. 2020 May 4;217(5). PubMed: https://pubmed.gov/32289152. Full-text: https://doi.org/10.1084/jem.20200653

In this Viewpoint article, the authors present their opinion on the benefits and potential limitations of using IFN-λ to prevent, limit, and treat SARS-CoV-2 infections.

Severe COVID-19

Caputo ND, Strayer RJ, Levitan R. **Early Self-Proning in Awake, Non-intubated Patients in the Emergency Department: A Single ED's Experience during the COVID-19 Pandemic**. Acad Emerg Med. 2020 Apr 22. PubMed: https://pubmed.gov/32320506. Full-text: https://doi.org/10.1111/acem.13994

Proning helps, even in awake, non-intubated patients. Among 50 patients, the median SpO2 at triage was 80%. After application of supplemental oxygen was given to patients on room air it was 84%. After 5 minutes of proning was added, SpO2 improved to 94%.

Pediatric

Lu X, Zhang L, Du H, et al. **SARS-CoV-2 Infection in Children**. N Engl J Med. 2020 Apr 23;382(17):1663-1665. PubMed: https://pubmed.gov/32187458. Full-text: https://doi.org/10.1056/NEJMc2005073 ● (IMPORTANT)

Of 171 children with confirmed SARS-CoV-2 infection in Wuhan, most appeared to have a milder clinical course. Asymptomatic infections were not uncommon (16%). During the course of hospitalization, 3 patients (all with co-

existing conditions) required intensive care support and invasive mechanical ventilation.

24 April

Virology

Sungnak W, Huang N, Bécavin C, et al. **SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes**. Nature Medicine, Published: 23 April 2020. Full-text: https://www.nature.com/articles/s41591-020-0868-6 ● (IMPORTANT)

Elegant paper, confirming the expression of ACE2 in multiple tissues shown in previous studies, with added information on tissues not previously investigated, including nasal epithelium and cornea and its co-expression with TMPRSS2. Potential tropism was analyzed by surveying expression of viral entry-associated genes in single-cell RNA-sequencing data from multiple tissues from healthy human donors. These transcripts were found in specific respiratory, corneal and intestinal epithelial cells, potentially explaining the high efficiency of SARS-CoV-2 transmission.

Epidemiology

Giordano G, Blanchini F, Bruno R, et al. **Modelling the COVID-19 epidemic and implementation of population-wide interventions in Italy**. Nat Med. 2020 Apr 22. PubMed: https://pubmed.gov/32322102. Full-text: https://doi.org/10.1038/s41591-020-0883-7

Interesting new model that predicts the course of the epidemic, considering eight stages of infection: susceptible (S), infected (I), diagnosed (D), ailing (A), recognized (R), threatened (T), healed (H) and extinct (E), collectively termed SIDARTHE. The model discriminates between infected individuals depending on whether they have been diagnosed and on the severity of their symptoms. Authors demonstrate that restrictive social-distancing measures will need to be combined with widespread testing and contact tracing to end the ongoing pandemic.

Peto J, Alwan NA, Godfrey KM, et al. **Universal weekly testing as the UK COVID-19 lockdown exit strategy**. Lancet. 2020 Apr 20. PubMed: https://pubmed.gov/32325027. Full-text: https://doi.org/10.1016/S0140-6736(20)30936-3

They have a dream: These UK researchers recommend the evaluation of weekly antigen testing of the whole population after lockdown. As they say, "a voluntary Dunkirk spirit" would be the only way for 10 million tests to be done daily.

Transmission

Park SY, Kim YM, Yi S, et al. **Coronavirus Disease Outbreak in Call Center, South Korea**. Emerg Infect Dis. 2020 Apr 23;26(8). PubMed: https://pubmed.gov/32324530. Full-text: https://doi.org/10.3201/eid2608.201274

Epidemiologic characteristics of a COVID-19 outbreak centered in a call center in South Korea, indicating an attack rate of 8.5% within the whole building. If results were restricted to one floor, the attack rate was as high as 43.5%. Among the 97 confirmed case-patients, 92% were symptomatic at the time of investigation and 4% were presymptomatic. Only 4% remained asymptomatic after 14 days of isolation.

Keshtkar-Jahromi M, Sulkowski M, Holakouie-Naieni K. **Public Masking: An Urgent Need to Revise Global Policies to Protect against Novel Coronavirus Disease (COVID-19)**. Am J Trop Med Hyg. 2020 Apr 22. PubMed: https://pubmed.gov/32323645. Full-text: https://doi.org/10.4269/ajtmh.20-0305

Brief review. The authors highly recommend mass masking around the world during the pandemic. Whereas surgical masks are the preferred recommendation for the general public, cloth masks should be considered as a substitute if supplies are limited or surgical masks are not available.

Clinical

Varga Z, Flammer AJ, Steiger P, et al. **Endothelial cell infection and endotheliitis in COVID-19**. Lancet. 2020 Apr 20. PubMed: https://pubmed.gov/32325026. Full-text: https://doi.org/10.1016/S0140-6736(20)30937-5

The ACE2 receptor is widely expressed on endothelial cells. Three cases, indicating direct viral infection of the endothelial cell and diffuse endothelial inflammation, induced by SARS-CoV-2 infection.

Grillet F, Behr J, Calame P, Aubry S, Delabrousse E. **Acute Pulmonary Embolism Associated with COVID-19 Pneumonia Detected by Pulmonary CT Angiography**. Radiology. 2020 Apr 23:201544. PubMed: https://pubmed.gov/32324103. Full-text: https://doi.org/10.1148/radiol.2020201544

In 100 patients with severe COVID-19, a high prevalence (23%, 95%CI 15-33%) of acute pulmonary embolism was found. Pulmonary embolus was diagnosed at mean of 12 days from symptom onset. In multivariable analysis, requirement for mechanical ventilation (OR = 3.8, 95%CI 1.02-15) remained associated with acute pulmonary embolus.

Comorbidities

Sriram K, Insel PA. **Risks of ACE inhibitor and ARB usage in COVID-19: evaluating the evidence. Clin Pharmacol Ther**. 2020 Apr 22. PubMed: https://pubmed.gov/32320478. Full-text: https://doi.org/10.1002/cpt.1863

Nice review. Data from 12 animal studies and from 12 human studies overwhelmingly imply that administration of ACEIs/ARBs does not increase ACE2 expression. Available evidence does not support the hypothesis that ACEI/ARB use increases ACE2 expression and the risk of complications from COVID-19. The authors conclude that patients being treated with ACEIs and ARBs should continue their use for approved indications.

Zhang P, Zhu L, Cai J, et al. **Association of Inpatient Use of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers with Mortality Among Patients With Hypertension Hospitalized With COVID-19**. Circ Res. 2020 Apr 17. PubMed: https://pubmed.gov/32302265. Full-text: https://doi.org/10.1161/CIRCRESAHA.120.317134

Same idea: in this retrospective, multi-center study of 1128 adult patients with hypertension diagnosed with COVID-19, 188 patients taking ACEI/ARB were compared with 940 patients without using ACEI/ARB. Unadjusted mortality rate was lower in the ACEI/ARB group versus the non-ACEI/ARB group (3.7% vs. 9.8%). In a Cox model, after adjusting for age, gender, comorbidities, and in-hospital medications, the detected risk for all-cause mortality was lower in the ACEI/ARB group (adjusted HR 0.42; 95%CI, 0.19-0.92).

Treatment

Chorin E, Dai M, Shulman E. **The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin**. Nature Medicine. Published: 24 April 2020. Full-Text: https://www.nature.com/articles/s41591-020-0888-2 ● (IMPORTANT)

Check ECG if you do this! In this important study, authors followed the corrected QT (QTc) interval in a consecutive cohort of 84 patients receiving hydroxychloroquine and azithromycin which were administered orally for 5 days. A prolongation of the QTc from a baseline average of 435 ± 24 ms to a maximal average value of 463 ± 32 ms was found, occurring on day 3.6 ± 1.6 of therapy. In a subset of nine (11%) patients, the QTc was severely prolonged to > 500 ms, a known marker of high risk of malignant arrhythmia and sudden cardiac death. Five of nine patients with severe QTc prolongation had a normal QTc at baseline.

25 April

Epidemiology

Gatto M, Bertuzzo E, Mari L, et al. **Spread and dynamics of the COVID-19 epidemic in Italy: Effects of emergency containment measures**. Proc Natl Acad Sci USA. 2020 Apr 23. PubMed: https://pubmed.gov/32327608. Full-text: https://doi.org/10.1073/pnas.2004978117

Complex models from Italy, quantifying the effect of local containment measures. The bottom line: the sequence of restrictions posed to mobility and human-to-human interactions have reduced transmission by 45% (42 to 49%). Models unquestionably support strong governmental decisions like those made in Italy.

Transmission

Arons MM, Hatfield KM, Reddy SC, et al. **Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility**. N Engl J Med. 2020 Apr 24. PubMed: https://pubmed.gov/32329971. Full-text: https://doi.org/10.1056/NEJMoa2008457

The next outbreak in King County, Washington: a skilled nursing facility facing rapid and widespread transmission of the virus, leading to 17 deaths in 57 residents. Of note, 27/48 with positive test results were asymptomatic at the

time of testing and most likely contributed to transmission. Infection-control strategies focussing solely on symptomatic residents are not sufficient! Test them all, immediately!

Tobias A, Molina T. **Is temperature reducing the transmission of COVID-19?** Environ Res. 2020 Apr 18;186:109553. PubMed: https://pubmed.gov/32330766. Full-text: https://doi.org/10.1016/j.envres.2020.109553

Measuring temperature's impact on transmission rates is almost impossible in such a dynamic pandemic. The authors have made a heroic attempt, showing that the number of diagnosed cases may increase below a maximum temperature of 10° C and linearly decreasing afterward. Thus, the arrival of summer could reduce the transmission of the COVID-19. However, this is only a first clue that has to be confirmed.

Diagnostics

Torres R, Rinder HM. **Double-Edged Spike: Are SARS-CoV-2 Serologic Tests Safe Right Now?** Am J Clin Pathol. 2020 Apr 23. PubMed: https://pubmed.gov/32322898. Full-text: https://doi.org/10.1093/ajcp/aqaa071

Brief but excellent review on the pitfalls and problems of antibody tests. At present, a positive antibody result does not guarantee non-infectious status nor immunity. What about asymptomatic or minimally symptomatic persons? The molecular heterogeneity of SARS-CoV-2 subtypes, imperfect performance of available tests and cross-reactivity with seasonal CoVs are discussed.

Xiao AT, Tong YX, Zhang S. **Profile of RT-PCR for SARS-CoV-2: a preliminary study from 56 COVID-19 patients**. Clin Infect Dis. 2020 Apr 19. PubMed: https://pubmed.gov/32306036. Full-text: https://doi.org/10.1093/cid/ciaa460

The dynamics profile of SARS-CoV-2 shedding from 56 recovered patients. The negative results of RT-PCR test for SARS-CoV-2 (throat or deep nasal cavity swab samples) began to be dominant from week 4 after onset of symptoms and by the end of follow-up (6 weeks), all results of RT-PCR test were negative.

Yongchen Z, Shen H, Wang X, et al. **Different longitudinal patterns of nucleic acid and serology testing results based on disease severity of COVID-19 patients**. Emerg Microbes Infect. 2020 Apr 20:1-14. PubMed: https://pubmed.gov/32306864. Full-text: https://doi.org/10.1080/22221751.2020.1756699

Do asymptomatic individuals develop antibodies? Serial investigation on 21 individuals from Jiangsu Province, including 17 COVID-19 patients and 5 asymptomatic carriers, using gold immunochromatography assay supplied by Innovita (China). All of 17 symptomatic patients were seropositive by week 6. Only 1/5 asymptomatic cases generated SARS-CoV-2 specific antibody responses within the first 4 weeks.

Comorbidities

Pereira MR, Mohan S, Cohen DJ, et al. **COVID-19 in Solid Organ Transplant Recipients: Initial Report from the US Epicenter**. Am J Transplant. 2020 Apr 24. PubMed: https://pubmed.gov/32330343. Full-text: https://doi.org/10.1111/ajt.15941

The first large cohort of COVID-19 in transplant recipients. Of 90 patients (median age 57 years), 46 were kidney recipients, 17 lung, 13 liver, 9 heart and 5 dual-organ transplants. Sixteen patients died (18% overall, 24% of hospitalized, 52% of ICU), indicating that transplant recipients appear to have more severe outcomes.

Akalin E, Azzi Y, Bartash B. **Covid-19 and Kidney Transplantation**. N Engl J Med. 2020 Apr 24. PubMed: https://pubmed.gov/32329975. Full-text: https://doi.org/10.1056/NEJMc2011117

Single center experience with 36 kidney transplant recipients. Patients appear to have less fever as an initial symptom, lower CD3/4/8 cell counts and more rapid clinical progression: after 21 days, 10 died.

French JA, Brodie MJ, Caraballo R, et al. **Keeping people with epilepsy safe during the Covid-19 pandemic**. Neurology. 2020 Apr 23. PubMed: https://pubmed.gov/32327490. Full-text: https://doi.org/10.1212/WNL.0000000000009632

Some helpful recommendations on how to modify clinical care for people with epilepsy and what general advice can be given to these patients during this crisis.

Treatment

Dai W, Zhang B, Su H, et al. **Structure-based design of antiviral drug candidates targeting the SARS-CoV-2 main protease**. Science. 2020 Apr 22. PubMed: https://pubmed.gov/32321856. Full-text: https://doi.org/10.1126/science.abb4489

More on a key enzyme, SARS-CoV-2's main protease (Mpro). The authors synthesized two lead compounds (11a and 11b) targeting Mpro, exhibiting good inhibitory activity, good PK properties and low toxicity in animal experiments. Pre-clinical.

26 April

Epidemiology

Chinazzi M, Davis JT, Ajelli M, et al. **The effect of travel restrictions on the spread of the 2019 novel coronavirus (COVID-19) outbreak**. Science. 2020 Apr 24;368(6489):395-400. PubMed: https://pubmed.gov/32144116. Full-text: https://doi.org/10.1126/science.aba9757

Complex transmission models, using epidemiological data from China. The authors concluded that the travel quarantine introduced in Wuhan on 23 January 2020 only delayed epidemic progression by 3 to 5 days within China, but international travel restrictions did help slow spread elsewhere by nearly 80% in the world until mid-February. The results suggest that even sustained 90% travel restrictions to and from mainland China only modestly affect the epidemic trajectory. Early detection, hand washing, self-isolation, and household quarantine will likely be more effective.

Transmission

Canova V, Lederer Schlapfer H, Piso RJ, et al. **Transmission risk of SARS-CoV-2 to healthcare workers -observational results of a primary care hospital contact tracing**. Swiss Med Wkly. 2020 Apr 25;150:w20257. PubMed: https://pubmed.gov/32333603. Full-text: https://doi.org/Swiss Med Wkly. 2020;150:w20257

Good news. Among 21 healthcare workers who had contact with an initially undiagnosed COVID-19 case, transmission risk was low, especially during short contacts.

Comorbidities

Cai G, Bosse Y, Xiao F, Kheradmand F, Amos CI. **Tobacco Smoking Increases the Lung Gene Expression of ACE2, the Receptor of SARS-CoV-2**. Am J Respir Crit Care Med. 2020 Apr 24. PubMed: https://pubmed.gov/32329629. Full-text: https://doi.org/10.1164/rccm.202003-0693LE

Brand new information: smoking is not the best idea. However, this is particularly true in the current pandemic. Ever having smoked significantly and substantially increased pulmonary ACE2 expression by 25%. The significant smoking effect on ACE2 pulmonary expression may suggest an increased risk for viral binding and entry of SARS-CoV-2 in lungs of smokers.

Severe COVID-19

Wadman M, Couzin-Frankel J, Kaiser J, et al. **A rampage through the body**. Science 24 Apr 2020: Vol. 368, Issue 6489, pp. 356-360. Full-text: https://science.sciencemag.org/content/368/6489/356 ● (IMPORTANT)

Is there anybody still twaddling about herd immunity? Let him read this detailed feature, describing the map of the devastation that COVID-19 can inflict not only on the lungs but on other organs as well, including blood vessels, heart, brain, kidneys and other organs. Scientists are just beginning to probe the nature of that harm.

Servick K. **Survivors' burden**. Science 24 Apr 2020: Vol. 368, Issue 6489, pp. 359. https://science.sciencemag.org/content/368/6489/359

Discharge from ICU is not the end of it. Clinicians are now turning their attention to potential lingering effects of both the virus and the emergency treatments that allow people to survive. Scarring can cause long-term breathing problems. This article also discusses other topics of concern such as muscle atrophy and weakness, mental problems but also cognitive impairment after leaving long-term intensive care.

Marini JJ, Gattinoni L. **Management of COVID-19 Respiratory Distress**. JAMA. 2020 Apr 24. PubMed: https://pubmed.gov/32329799. Full-text: https://doi.org/10.1001/jama.2020.6825

Useful review on the unique lung injury induced by SARS-CoV-2 infection. It has become clear that acute respiratory distress syndrome (ARDS) in COVID-19 is different from ARDS. “CARDs” appears to include an important vascular insult that potentially mandates a different treatment approach than cus-

tomarily applied for ARDS. The authors review their experiences and propose to categorize patients. In type L (low lung elastance, high compliance, low response to PEEP), infiltrates are often limited in extent and initially characterized by a ground-glass pattern on CT that signifies interstitial rather than alveolar edema. Many patients do not appear overtly dyspneic and may stabilize at this stage without deterioration. Others may transit to a clinical picture more characteristic of typical ARDS: Type H shows extensive CT consolidations, high elastance (low compliance) and high PEEP response. Clearly, types L and H are the conceptual extremes of a spectrum that includes intermediate stages.

Poissy J, Goutay J, Caplan M, et al. **Pulmonary Embolism in COVID-19 Patients: Awareness of an Increased Prevalence**. Circulation. 2020 Apr 24. PubMed: https://pubmed.gov/32330083. Full-text: https://doi.org/10.1161/CIRCULATIONAHA.120.047430

Case series from Lille, France showing a high prevalence of Pulmonary Embolism (PE) in severe COVID-19. Among the first 107 COVID-19 patients admitted to the ICU for pneumonia in March, the authors identified 22 (20.6%) cases. It is of note that at the time of diagnosis of PE, 20/22 were receiving prophylactic antithrombotic treatment (UFH or LWMH) according to the current guidelines in critically ill patients.

Treatment

Borba MGS, Val FFA, Sampaio VS, et al. **Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial**. JAMA Netw Open. 2020 Apr 24;3(4.23):e208857. PubMed: https://pubmed.gov/32330277. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.8857 ● (IMPORTANT)

Less is more? This double-masked, randomized, Phase IIb clinical trial in Manaus, Brazil allocated severe COVID-19 patients to receive high-dose CQ (600 mg BID for 10 days) or low-dose CQ (450 mg BID on day 1, QD for 4 days). The data safety monitoring board terminated the trial after 81/440 individuals had been enrolled. By day 13 of enrolment, 6 of 40 patients (15%) in the low-dose group had died, compared with 16 of 41 patients (39%) in the high-dose group. Viral RNA was detected in 78% and 76%, respectively. This trial also shows how dramatically mechanisms to execute research have accelerated: the first patient had been enrolled in this trial on March 26, 2020.

Mathian A, Mahevas M, Rohmer J, et al. **Clinical course of coronavirus disease 2019 (COVID-19) in a series of 17 patients with systemic lupus erythematosus under long-term treatment with hydroxychloroquine**. Ann Rheum Dis. 2020 Apr 24. PubMed: https://pubmed.gov/32332072. Full-text: https://doi.org/10.1136/annrheumdis-2020-217566

People with lupus (SLE) who take hydroxychloroquine (HCQ) are not protected. This cohort describes 17 SLE patients with COVID-19, among them several severe cases. The duration of HCQ treatment prior to COVID-19 was relatively long, with a median of 7.5 years. Some patients were also treated with prednisone and/or with immunosuppressants.

Sheahan TP, Sims AC, Zhou S, et al. **An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice**. Sci Transl Med. 2020 Apr 6. PubMed: https://pubmed.gov/32253226. Full-text: https://doi.org/10.1126/scitranslmed.abb5883

What if remdesivir doesn't work? The next nucleoside analog is on its way. Beta-D-N(4)-hydroxycytidine (NHC, EIDD-1931) has broad spectrum antiviral activity against all human and bat CoVs, including CoVs resistant to remdesivir. In mice, both prophylactic and therapeutic administrations improved pulmonary function and reduced virus titer.

27 April

Epidemiology

Pearce N, Vandenbroucke JP, VanderWeele TJ, Greenland S. **Accurate Statistics on COVID-19 Are Essential for Policy Guidance and Decisions**. Am J Public Health. 2020 Apr 23:e1-e3. PubMed: https://pubmed.gov/32324422. Full-text: https://doi.org/10.2105/AJPH.2020.305708

Review of key epidemiological concepts and discussion of some of the preventable methodologic errors.

Mosites E, Parker EM, Clarke KE, et al. **Assessment of SARS-CoV-2 Infection Prevalence in Homeless Shelters — Four U.S. Cities, March 27–April 15, 2020**. MMWR, Early Release / April 22, 2020 / 69. Full-text: https://www.cdc.gov/mmwr/volumes/69/wr/mm6917e1.htm?s_cid=mm6917e1_w

Outbreaks in homeless shelters. If you test more than one person to be PCR positive, you already have many positive cases. Overall, 1,192 residents and 313 staff members were tested in 19 shelters from 4 US cities. When testing followed identification of a cluster, high proportions of positive tests were found, ranging from 16-66%. Testing in shelters where only one or no previous case had been identified found low prevalence (1-5%).

Arias-Reyes C, Zubieta-DeUrioste N, Poma-Machicao L, et al. **Does the pathogenesis of SAR-CoV-2 virus decrease at high-altitude?** Respir Physiol Neurobiol. 2020 Apr 22:103443. PubMed: https://pubmed.gov/32333993. Full-text: https://doi.org/10.1016/j.resp.2020.103443

Interesting idea. Epidemiological data from Tibet, Bolivia and Ecuador suggest that COVID-19 infection is decreased in populations living at an altitude of above 3,000 m. Highland inhabitants may be less susceptible to SARS-CoV-2 virus infection due to physiological acclimatization to hypoxia. High-altitude environmental factors may contribute to reduce the virulence of SARS-CoV-2. But can we be sure? The methods section of this paper contains one sentence. And the fact that the virus was written incorrectly even in the title, does not enhance credibility.

Virology

Cohen J. **COVID-19 vaccine protects monkeys from new coronavirus, Chinese biotech reports**. Science April 23, 2020. Full-text: https://www.sciencemag.org/news/2020/04/covid-19-vaccine-protects-monkeys-new-coronavirus-chinese-biotech-reports

Preliminary results of an old-fashioned vaccine consisting of a chemically inactivated version of the virus (which could be produced easily and in huge quantities). The vaccine worked in 8 rhesus macaques, while no obvious side effects were observed. Sinovac Biotech, an experienced vaccine maker from China, has now started Phase I clinical trials in 144 healthy volunteers to evaluate safety.

Transmission

Schwierzeck V, König JC, Kühn J, et al. **First reported nosocomial outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in a pediatric dialysis unit**. Clinical Infectious Diseases, 27 April 2020. Full-text: https://doi.org/10.1093/cid/ciaa491

The next outbreak, occurring in a pediatric dialysis unit in Münster, Germany, comprising a total of 12 cases. After careful investigation, the authors found that none of 32 persons with type II exposure became infected (= shared indoor environment without cumulative 15 minutes face-to-face contact, HCWs exposed during treatment or nursing in a distance of > 2 meters, without appropriate personal protective equipment such as surgical masks, etc.).

Atkinson B, Petersen E. **SARS-CoV-2 shedding and infectivity**. Lancet. 2020 Apr 25;395(10233):1339-1340. PubMed: https://pubmed.gov/32304647. Full-text: https://doi.org/10.1016/S0140-6736(20)30868-0

Several reports from China have suggested prolonged shedding of the virus by measuring viral RNA in different body fluids. The authors emphasize an important issue in the current discussion. The presence of nucleic acid alone **cannot** be used to define viral shedding or infection potential. For many viral diseases including SARS-CoV or MERS-CoV, it is well known that viral RNA can be detected long after the disappearance of infectious virus.

Diagnostics

Qu J, Wu C, Li X. **Profile of IgG and IgM antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)**. Clinical Infectious Diseases. 2020. Full-text: https://doi.org/10.1093/cid/ciaa489

Seroconversion patterns of IgM and IgG antibodies using 347 serum samples from 41 patients. Using combined N and S proteins as capture antigen to increase sensitivity of their in-house assay, IgG and IgM antibodies were found in the majority of the patients during the first three weeks of the disease. Of note, the seroconversion time of IgG antibody was earlier than IgM. IgG antibody reached the highest concentration on day 30, while IgM antibody peaked on day 18, and then began to decline.

Severe COVID-19

Matheny Antommaria AH, Gibb TS, McGuire AL, et al. **Ventilator Triage Policies During the COVID-19 Pandemic at U.S. Hospitals Associated With Members of the Association of Bioethics Program Directors**. Ann Intern Med. 2020 Apr 24. PubMed: https://pubmed.gov/32330224. Full-text: https://doi.org/10.7326/M20-1738

Triage? Nobody is prepared, according to this survey among 67 Bioethics Program Directors from North American hospitals. Over one half of respondents did not have ventilator triage policies. Policies have substantial heterogeneity, and many omit guidance on fair implementation. Of note, among the most frequently cited triage criteria was "lottery" (35%). Great.

Treatment

Ledford H. **Chloroquine hype is derailing the search for coronavirus treatments**. Nature Medicine, 24 April 2020. Full-text https://www.nature.com/articles/d41586-020-01165-3

After hearing politicians touting the potential benefits, many patients are turning away from clinical trials of other therapies that would require them to give up chloroquine treatments. This report reviews these issues which have already led to serious delays in trial enrolment, muddled efforts to interpret data and endangered clinical research on COVID-19.

Borrell B. **New York clinical trial quietly tests heartburn remedy against coronavirus**. Science April 26, 2020. Full-text: https://www.sciencemag.org/news/2020/04/new-york-clinical-trial-quietly-tests-heartburn-remedy-against-coronavirus

Famotidine for COVID-19? By reviewing 6212 Chinese patient records, it became obvious that many survivors had been suffering from chronic heartburn and were on famotidine rather than the more expensive omeprazole. On 7 April, the first COVID-19 patients at Northwell Health in the New York City area began receiving famotidine intravenously, at nine times the heartburn dose. Interim results of this clinical trial which has enrolled an incredibly huge number of patients, will be available within a few weeks. Don't tell your politicians.

28 April

Epidemiology

Oliver N, Lepri B, Sterely H. **Mobile phone data for informing public health actions across the COVID-19 pandemic life cycle**. Science Advances 27 Apr 2020. Full-Text: https://doi.org/10.1126/sciadv.abc0764

This brief review outlines the ways in which different types of mobile phone data can help to better target and design measures to contain and slow the spread of the COVID-19 pandemic.

Bi Q, Wu Y, Mei S, et al. **Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study**. Lancet Inf Dis. April 27, 2020. Full-Text: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30287-5/fulltext ● (IMPORTANT)

This important analysis of 391 early SARS-CoV-2 cases and their close contacts in Shenzhen, China, provides insight into the natural history and transmission. This work further supports a short incubation period (4–6 days). Notably, 5% took 14 days or more to develop symptoms. In multiple conditional logistic regression analysis of contact types, household contact (OR 6.3; 95% CI 1.5–26.3) and travelling together (OR 7.1; 1.4–34.9) were significantly associated with infection. The secondary attack rate was relatively low with 11·2% (95% CI 9·1–13·8) among household contacts and was similar across all age categories. However, this could be considered an underestimate, since transmission chains were cut short: index cases detected by symptom-based surveillance were rapidly isolated outside of the home.

Nie X, Fan L, Mu G, et al. **Epidemiological characteristics and incubation period of 7,015 confirmed cases with Coronavirus Disease 2019 outside Hubei Province in China**. J Inf Dis, 27 April 2020. Full-text: https://doi.org/10.1093/infdis/jiaa211

Huge study from China. Based on 2,907 confirmed cases, the median incubation period was 5 days, and more than 95% of cases had an incubation period of less than 13 days. From January 23, the incubation period among imported confirmed cases outside Hubei Province showed a gradual upward trend, but this trend was not obvious in non-imported cases.

Diagnostics

Altman DM, Douek DC, Boyton RJ. **What policy makers need to know about COVID-19 protective immunity**. Lancet April 27, 2020. Full-text: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30985-5/fulltext

The bottom line of this comment: we don't know enough. There is no certainty as to the immunological correlates of antiviral protection or the proportion of the population who must attain them, making it impossible to identify a point when this level of immunity has been reached.

Lipsitch M, Kahn R, Mina MJ. **Antibody testing will enhance the power and accuracy of COVID-19-prevention trials**. Nature Medicine 27 April 2020. Full-text: https://doi.org/10.1038/s41591-020-0887-3.

Many groups have initiated trials of prophylactic drugs and have envisioned efficacy trials of vaccine candidates. The authors argue for serological testing of trial participants at the start and end of these trials (and at intermediate points), in order to enhance the value and interpretability of these studies.

Virology

Chu H, Chan JF, Yuen TT, et al. **Comparative tropism, replication kinetics, and cell damage profiling of SARS-CoV-2 and SARS-CoV with implications for clinical manifestations, transmissibility, and laboratory studies of COVID-19: an observational study**. Lancet Microbe April 21, 2020. Full-text: https://doi.org/10.1016/S2666-5247(20)30004-5 ● (IMPORTANT)

An elegant study explaining distinct clinical features of COVID-19 and SARS. Authors investigated cell susceptibility, species tropism, replication kinetics, and virus-induced cell damage from both SARS-CoVs, using live infectious virus particles. SARS-CoV-2 replicated more efficiently in human pulmonary cells, indicating that SARS-CoV-2 has most likely adapted better to humans. SARS-CoV-2 replicated significantly less in intestinal cells (might explain lower diarrhea frequency compared to SARS) but better in neuronal cells, highlighting the potential for neurological manifestations.

Huang H, Koyuncu OO, Enquist LW. **Pseudorabies Virus Infection Accelerates Degradation of the Kinesin-3 Motor KIF1A**. J Virol. 2020 Apr 16;94(9). PubMed: https://pubmed.gov/32075931. Full-text: https://doi.org/10.1128/JVI.01934-19

Pseudorabies virus (PRV), an alphaherpesvirus, is sorted and transported in axons in the anterograde direction by the kinesin-3 motor KIF1A. Why is this of interest? Because it's currently (April 28, 2020, 7:15 a.m. CET) the headline article of the Journal of Virology, the Journal of the American Society of Microbiology (Impact Factor 4.3). No work, no link on COVID-19, nothing on their website. This journal aims for "reporting important new discoveries and pointing to new directions in research". Just saying.

Clinical

Gandhi RT, Lynch JB, del Rio C. **Mild or Moderate Covid-19**. NEJM April 24, 2020, Full-text: https://doi.org/10.1056/NEJMcp2009249.

Nice review on clinical manifestations, evaluation and management, but also on infection control and prevention efforts.

Lai J, Ma S, Wang Y, et al. **Factors Associated With Mental Health Outcomes Among Health Care Workers Exposed to Coronavirus Disease 2019**. JAMA Netw Open. 2020;3(3):e203976. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.3976.

Protecting health care workers is an important component of public health measure! This cross-sectional survey of 1257 health care workers in Chinese hospitals found considerable proportions of participants with symptoms of depression (50%), anxiety (47%), insomnia (34%), and distress (72%). Participants reported experiencing psychological burden, especially nurses, women, those in Wuhan, and frontline health care workers directly engaged in the care for patients with COVID-19.

Treatment

Strollo R, Pozzilli P. **DPP4 inhibition: preventing SARS-CoV-2 infection and/or progression of COVID-19**? Diabetes Metab Res Rev. 2020 Apr 26. PubMed: https://pubmed.gov/32336007. Full-text: https://doi.org/10.1002/dmrr.3330

The next new idea. Dipeptidyl peptidase 4 (DPP4) is a serine exopeptidase expressed ubiquitously in several tissues, including but not limited to lung, kidney, liver, gut, and immune cells. Some careful thoughts on whether DPP4 modulation or inhibition (by diabetes drugs such as gliptins) may prevent infection and/or progression of the COVID-19.

29 April

Epidemiology

Baggett TP, Keyes H, Sporn N, Gaeta JM. **Prevalence of SARS-CoV-2 Infection in Residents of a Large Homeless Shelter in Boston.** JAMA. 2020 Apr 27. PubMed: https://pubmed.gov/32338732. Full-text: https://doi.org/10.1001/jama.2020.6887

Between March 28, 2020, and April 1, 2020, authorities became aware of a few cases in a single large homeless shelter in Boston, prompting SARS-CoV-2 testing of all remaining shelter residents. In total, 147/408 (36%) were positive. Of note, 88% had no symptoms and no fever at the time of diagnosis.

Transmission

Liu Y, Ning Z, Chen Y, et al. **Aerodynamic analysis of SARS-CoV-2 in two Wuhan hospitals**. Nature. 2020 Apr 27. PubMed: https://pubmed.gov/32340022. Full-text: https://doi.org/10.1038/s41586-020-2271-3 ● (IMPORTANT)

Toilets are the hot spots! Important study, sampling airborne SARS-CoV-2 and its aerosol deposition at 30 sites in two designated hospitals and public areas in Wuhan in February/March. The concentration in isolation wards and ventilated patient rooms was very low, but it was elevated in the patients' toilet areas. Levels were undetectable in the majority of public areas outside the hospitals and was undetectable except in two areas prone to crowding. Room ventilation, open space, sanitization of protective apparel as well as proper use and disinfection of toilet areas can effectively limit the concentration of SARS-CoV-2 RNA in aerosols.

Ferrazzi E, Frigerio L, Savasi V, et al. **Vaginal delivery in SARS-CoV-2 infected pregnant women in Northern Italy: a retrospective analysis.** BJOG. 2020 Apr 27. PubMed: https://pubmed.gov/32339382. Full-text: https://doi.org/10.1111/1471-0528.16278

Vaginal delivery is associated with low risk of intrapartum infection. Of 42 women with COVID-19 (19 with pneumonia), 24 delivered vaginally. Only 1/24 new-born had a positive test. Two women transmitted the virus while breastfeeding without a mask.

Diagnostics

Long QX, Liu BZ, Deng HJ, et al. **Antibody responses to SARS-CoV-2 in patients with COVID-19.** Nat Med. 2020 Jun;26(6):845-848. PubMed: https://pubmed.gov/32350462. Full-text: https://doi.org/10.1038/s41591-020-0897-1 ●● (OUTSTANDING)

One of the largest studies to date, reporting on acute antibody responses (using magnetic chemiluminescence enzyme immunoassay) in 285 patients (mostly non-severe COVID-19, 39 treated at ICU). Within 19 days after symptom onset, 100% of patients tested positive for antiviral IgG. Seroconversion for IgG and IgM occurred simultaneously or sequentially. Both IgG and IgM titers plateaued within 6 days after seroconversion. The median day of seroconversion for both IgG and IgM was 13 days post-symptom onset. No association between plateau IgG levels and clinical characteristics of the patients was found.

Clinical

Oxley J, Mocco J, Majidi S, et al. **Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young**. N Engl J Med, April 28, 2020. Full-text: https://www.nejm.org/doi/full/10.1056/NEJMc2009787

Five cases of large-vessel stroke in younger patients (age 33-49, 2 without any risk factors) who presented in New York City. By comparison, every 2 weeks over the previous 12 months, on average 0.73 patients younger than 50 years of age with large-vessel stroke had been treated.

Connors JM, Levy JH. **COVID-19 and its implications for thrombosis and anticoagulation**. Blood. 2020 Apr 27. PubMed: https://pubmed.gov/32339221. Full-text: https://doi.org/10.1182/blood.2020006000 ● (IMPORTANT)

Excellent review of coagulation abnormalities that occur in association with COVID-19, and clinical management questions likely to arise. The initial coagulopathy of COVID-19 presents with prominent elevation of D-dimer and fibrin/fibrinogen degradation products, while abnormalities in prothrombin time, partial thromboplastin time, and platelet counts are relatively uncommon. Coagulation test screening, including the measurement of D-dimer and fibrinogen levels, is suggested. Current data do not suggest the use of full intensity anticoagulation doses unless otherwise clinically indicated.

Comorbidities

De Filippo O, D'Ascenzo F, Angelini F, et al. **Reduced Rate of Hospital Admissions for ACS during Covid-19 Outbreak in Northern Italy**. N Engl J Med, April 28, 2020. Full-text: https://doi.org/10.1056/NEJMc2009166

The authors report a significant decrease in acute coronary syndrome-related hospitalization rates across several cardiovascular centers in northern Italy during the early days of the outbreak.

Castiglion V, Chiriacò M, Emdin M, et al. **Statin therapy in COVID-19 infection**. European Heart Journal Cardiovascular Pharmacotherapy, 2020, 29 April. Full-text: https://doi.org/10.1093/ehjcvp/pvaa042

Brief review: adjuvant treatment and continuation of pre-existing statin therapy could improve the clinical course of patients with COVID-19, either by their immunomodulatory action or by preventing cardiovascular damage.

Procedures

Feldman O, Meir M, Shavit D, Idelman R, Shavit I. **Exposure to a Surrogate Measure of Contamination From Simulated Patients by Emergency Department Personnel Wearing Personal Protective Equipment**. JAMA. 2020 Apr 27. PubMed: https://pubmed.gov/32338711. Full-text: https://doi.org/10.1001/jama.2020.6633

Interesting simulation experiment. The authors used adult and pediatric maniquins and a fluorescent marker to visualize deposition of simulated exhaled respiratory secretions and material onto HCWs performing or assisting in endotracheal intubation procedures. HCWs wore N95 respirators, eye protection, isolation gowns, and gloves. Fluorescent markers were found on the uncovered facial skin (7/8), hair, and shoes of the HCWs, suggesting that the current recommendations may not fully prevent exposures. Clothing that covers all skin may further diminish exposure risk.

Weissman DN, de Perio MA, Radonovich LJ Jr. **COVID-19 and Risks Posed to Personnel During Endotracheal Intubation**. JAMA. 2020 Apr 27. PubMed: https://pubmed.gov/32338710. Full-text: https://doi.org/10.1001/jama.2020.6627

Brief review on current knowledge on the risk during intubation, discussing the study above. Fundamental research is needed to better inform recommendations. A better understanding of the duration of infectivity and level of

risk posed by airborne SARS-CoV-2 would help to guide recommendations for respiratory protection.

30 April

Virology

Callaway E. **The race for coronavirus vaccines: a graphical guide, Eight ways in which scientists hope to provide immunity to SARS-CoV-2**. Nature 2020, 28 April 2020. 580, 576-577. https://doi.org/10.1038/d41586-020-01221-y

Fantastic graphical review on current vaccine development. Easy to understand, it explains different approaches such as virus, viral-vector, nucleic-acid and protein-based vaccines.

Clinical

Wadhera RK, Wadhera P, Gaba P, et al. **Variation in COVID-19 Hospitalizations and Deaths Across New York City Boroughs**. April 29, 2020. AMA. Published online April 29, 2020. Full-text: https://doi.org/10.1001/jama.2020.7197

By April 25, the Bronx (which has the highest proportion of racial/ethnic minorities, the most persons living in poverty, and the lowest levels of educational attainment) had higher rates (almost two-fold) of hospitalization and death related to COVID-19 than the other four New York City boroughs Brooklyn, Manhattan, Queens and Staten Island.

Comorbidities

Haberman R, Axelrad J, Chen A, et al. **Covid-19 in Immune-Mediated Inflammatory Diseases - Case Series from New York**. N Engl J Med. 2020 Apr 29. PubMed: https://pubmed.gov/32348641. Full-text: https://doi.org/10.1056/NEJMc2009567

Baseline use of biologics is not associated with worse COVID-19 outcomes. A case series of 86 patients with immune-mediated inflammatory disease (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis, inflammatory bowel disease, or related conditions) and symptomatic COVID-19, among them 62 (72%) receiving biologics or Janus kinase (JAK) inhibitors. The percentage of patients who were receiving biologics or JAK inhibitors at baseline was higher among the ambulatory patients than among the hospital-

ized patients. In contrast, hospitalization rates were higher in patients treated with oral glucocorticoids, hydroxychloroquine and methotrexate.

Rangé G, Hakim R, Motreff P. **Where have the STEMIs gone during COVID-19 lockdown**? European Heart Journal - Quality of Care and Clinical Outcomes, April 29, 2020. Full-text: https://doi.org/10.1093/ehjqcco/qcaa034

Best paper title of the day. Using a French Registry, the authors found a spectacular drop of 25% for admission due to STEMI between March 2019 and March 2020. The steep decline was found for both acute (< 24hrs) and late presentation (> 24 hrs) STEMI. But where did they go? According to the authors, explanations may be patients' fear of coming to the hospital or disturbing busy caregivers, especially in the case of mild STEMI clinical presentation. Other hypothetical reasons are reduced air pollution, better adherence to treatment, limited physical activity or absence of occupational stress during lockdown. When will we ever learn?

Baldi E, Sechi GM, Mare C, et al. **Out-of-Hospital Cardiac Arrest during the Covid-19 Outbreak in Italy**. N Engl J Med. 2020 Apr 29. PubMed: https://pubmed.gov/32348640. Full-text: https://doi.org/10.1056/NEJMc2010418

Avoiding hospitals, staying at home, dying of fear? Using data from the Lombardy Cardiac Arrest Registry for the provinces of Lodi, Cremona, Pavia, and Mantua during the first 40 days of the COVID-19 outbreak (February 21 through March 31, 2020), the authors found a 58% increase of out-of-hospital cardiac arrest compared to the same period in 2019.

Treatment

Ledford H. **Hopes rise on coronavirus drug remdesivir**. Nature Medicine 29 April 2020. Full-text: https://doi.org//10.1038/d41586-020-01295-8

The next example of "Fauci said". Anthony Fauci, director of the US National Institute of Allergy and Infectious Disease (NIAID) had announced that a clinical trial of "more than a thousand people showed that people taking remdesivir recovered in 11 days on average, compared to 15 days for those on a placebo". That's all. We believe that this is not an appropriate way to share data.

Wang Y, Zhang D, Du G, et al. **Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial.** Lancet. 2020 May 16;395(10236):1569-1578. PubMed: https://pubmed.gov/32423584. Full-text: https://doi.org/10.1016/S0140-6736(20)31022-9 ● (IMPORTANT)

And here it is, the first randomized, double-blind, placebo-controlled trial of remdesivir (and not the study Fauci was talking about)! This multicenter trial at ten hospitals in Hubei, China enrolled patients with severe COVID-19 to receive 10 days of single infusions or placebo. Clinical improvement up to day 28 was defined as the time (in days) to the point of a decline of two levels on a six-point ordinal scale of clinical status (from 1=discharged to 6=death) or discharged alive from hospital, whichever came first. In the 237 patients enrolled between Feb 6 and March 12, remdesivir use was not associated with a difference in time to clinical improvement (hazard ratio 1.23, 95% CI 0.87–1.75). Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early. The trial did not attain the predetermined sample size because the outbreak of COVID-19 was brought under control in China. Disappointing. More data are eagerly awaited.

Gates B. **Responding to Covid-19 — A Once-in-a-Century Pandemic**? NEJM April 30, 2020. N Engl J Med 2020; 382:1677-1679. Full-text: https://doi.org/10.1056/NEJMp2003762.

Bill Gates, talking about billions of dollars. He will donate some. According to this perspective, he has comitted “substantial resources”. Well done.

Severe COVID-19

Ziehr DR, Alladina J, Petri CR, et al. **Respiratory Pathophysiology of Mechanically Ventilated Patients with COVID-19: A Cohort Study.** Am J Respir Crit Care Med. 2020 Apr 29. PubMed: https://pubmed.gov/32348678. Full-text: https://doi.org/10.1164/rccm.202004-1163LE

Treat it like ARDS! The authors provide a pathophysiologic justification for the use of established ARDS therapies, including low tidal volume and early prone ventilation. In their retrospective cohort of 66 COVID-19 patients (median age 58 years) with respiratory failure, fatality was only 17%. The authors conclude that their patients exhibit similar gas exchange, respiratory system mechanics, and response to prone ventilation as prior large cohorts of patients with ARDS.

Procedures

Bertroche JT, Pipkorn P, Zolkind P, Buchman CA, Zevallos JP. **Negative-Pressure Aerosol Cover for COVID-19 Tracheostomy**. JAMA Otolaryngol Head Neck Surg. 2020 Apr 28. PubMed: https://pubmed.gov/32343299. Full-text: https://doi.org/10.1001/jamaoto.2020.1081

The authors present the creation of a novel negative-pressure aerosol cover made out of readily available operating room materials as an additional barrier to limit the spread of aerosols during tracheostomy. This cover was easy to create and deploy using readily available materials found in operating centers.

May 2020

1 May

Epidemiology

Jia JS, Lu X, Yuan Y. et al. **Population flow drives spatio-temporal distribution of COVID-19 in China**. Nature 2020. https://doi.org/10.1038/s41586-020-2284-y. Full-text: https://www.nature.com/articles/s41586-020-2284-y#citeas

When people move, they take contagious diseases with them. Using detailed mobile phone geolocation data to compute aggregate population movements, the authors tracked the transit of people from Wuhan to the rest of China. The geographic flow of people anticipated the subsequent location, intensity, and timing of outbreaks in the rest of China.

Virology, Immunology

Tang Y, Wu C, Li X**. On the origin and continuing evolution of SARS-CoV-2.** National Science Review 2020, March 03. https://doi.org/10.1093/nsr/nwaa036. Full-text: https://academic.oup.com/nsr/advance-article/doi/10.1093/nsr/nwaa036/5775463

Authors from China report on a SARS-CoV-2 subtype which seems to be more aggressive and to spread more quickly. This paper has gained much attraction in the media.

MacLean O, Orton RJ, Singer JB, et al. **No evidence for distinct types in the evolution of SARS-CoV-2**. Virus Evolution, veaa034, https://doi.org/10.1093/ve/veaa034. Full-text: https://academic.oup.com/ve/advance-article/doi/10.1093/ve/veaa034/5827470?searchresult=1

In this paper, Scottish researches now demonstrate very clearly that Tang et al. were wrong and that the major conclusions of that paper cannot be substantiated. Using examples from other viral outbreaks, the authors discuss the difficulty in demonstrating the existence or nature of a functional effect of a viral mutation, and advise against overinterpretation of genomic data during the pandemic. Although rapid publication is critical for unfolding dis-

ease outbreaks, thorough and independent peer review should not be bypassed to get results published quickly.

Tay MZ, Poh CM, Rénia L et al. **The trinity of COVID-19: immunity, inflammation and intervention**. Nat Rev Immunol (2020). https://doi.org/10.1038/s41577-020-0311-8. Full-text: https://www.nature.com/articles/s41577-020-0311-8#citeas

A brilliant overview of the pathophysiology of SARS-CoV-2 infection. How SARS-CoV-2 interacts with the immune system, how dysfunctional immune responses contribute to disease progression and how they could be treated.

Diagnostics

Yin L, Moi H, Shao J. **Correlation between Heart fatty acid binding protein and severe COVID-19: A case-control study**. PLOS One, 29 Apr 2020. https://doi.org/10.1371/journal.pone.0231687

Heart fatty acid-binding protein (HFABP), a serum biomarker for myocardial injury, is highly cardiac-specific. Elevated serum HFABP may be used as an indicator of severe COVID-19. This small retrospective analysis included 45 patients, in which HFABP was measured on the day of hospital admission. In the HFABP positive group (n = 15), severe illness was more common during hospitalization (87.5% vs 40%, p = 0.002).

Clinical

Zhang Y, Qin L, Zhao Y, et al. **Interferon-induced transmembrane protein-3 genetic variant rs12252-C is associated with disease severity in COVID-19**. J Infect Dis. 2020 Apr 29. PubMed: https://pubmed.gov/32348495. Full-text: https://doi.org/10.1093/infdis/jiaa224

The first study providing some evidence for a predisposition for severe disease. The authors analyzed a genetic variant of IFITM3. This gene encodes an immune effector protein critical to viral restriction and homozygosity for the C allele that has been associated with influenza severity. The CC genotype was found in 12/24 (50%) patients with severe COVID-19, compared to 16/56 (29%) with mild disease. After adjusting for age groups, the odds ratio for severe disease in patients with CC genotype was 6.3 (p < 0.001).

Meng Y, Wu P, Lu W, et al. **Sex-specific clinical characteristics and prognosis of coronavirus disease-19 infection in Wuhan, China: A retrospective study of 168 severe patients**. PLOS Pathogens 2020, April 28, 2020. https://doi.org/10.1371/journal.ppat.1008520.
https://doi.org/10.1371/journal.ppat.1008520

This retrospective cohort highlights sex-specific differences in clinical characteristics and prognosis. Older age and the presence of comorbidities were prognostic risk factors in 86 males but not in 82 females. Some laboratory parameters also showed significant differences.

Comorbidities

Stefanini GG, Montorfano M, Trabattoni D, et al. **ST-Elevation Myocardial Infarction in Patients with COVID-19: Clinical and Angiographic Outcomes**. Circulation. 2020 Apr 30. PubMed: https://pubmed.gov/32352306. Full-text: https://doi.org/10.1161/CIRCULATIONAHA.120.047525

STEMI may represent the first clinical manifestation of COVID-19. In 11 out of 28 patients (39%) with STEMI, a culprit lesion was not identifiable by coronary angiography. According to the authors, a dedicated diagnostic pathway should be delineated for COVID-19 patients with STEMI, aimed at minimizing patients' procedural risks and healthcare providers' risk of infection.

Yang G, Tan Z, Zhou L, et al. **Effects Of ARBs And ACEIs On Virus Infection, Inflammatory Status And Clinical Outcomes In COVID-19 Patients With Hypertension: A Single Center Retrospective Study**. Hypertension. 2020 Apr 29. PubMed: https://pubmed.gov/32348166. Full-text: https://doi.org/10.1161/HYPERTENSIONAHA.120.15143

The next retrospective study analysing COVID-19 patients with hypertension, argueing against deleterious effects of angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors. Patients on these drugs (n=43) had significantly lower concentrations of CRP ($p = 0.049$) and procalcitonin ($p = 0.008$) than patients on other antihypertensive drugs ($n = 83$). Furthermore, trends toward lower proportions of critical diseases (9.3% vs 22.9%; $p = 0.061$) and death rates (4.7% vs 13.3%; $p = 0.216$) were observed.

Treatment

Zeng QL, Yu ZJ, Gou JJ, et al. **Effect of Convalescent Plasma Therapy on Viral Shedding and Survival in COVID-19 Patients**. J Infect Dis. 2020 Apr 29. PubMed: https://pubmed.gov/32348485. Full-text: https://doi.org/10.1093/infdis/jiaa228

Don't be too late: Of 6 patients with respiratory failure receiving convalescent plasma at a median of 21 days after first detection of viral shedding, all tested RNA negative by 3 days after infusion. However, 5 died eventually.

2 May

Dermatology

This has been the week of the dermatologists: numerous studies reported on cutaneous manifestations seen in the context of COVID-19. The most prominent phenomenon, the so-called "COVID toes", are chilblain-like lesions which mainly occur at acral areas [chilblain: Frostbeule (de), engelure (fr), sabañón (es), gelone (it), frieira (pt), 冻疮 (cn)]. These lesions can be painful (sometimes itchy, sometimes asymptomatic) and may represent the only symptom or late manifestations of SARS-CoV-2 infection. Of note, in most patients with "COVID toes" the disease is only mild to moderate. It is speculated that the lesions are caused by inflammation in the walls of blood vessels, or by small micro-clots in the blood. However, whether "COVID toes" represent a coagulation disorder or a hypersensitivity reaction is still unknown. In addition, in many patients, SARS-CoV-2 PCR was negative (or not done) and serology tests (to prove the relationship) are still pending.

Fernandez-Nieto D, Jimenez-Cauhe J, Suarez-Valle A, et al. **Characterization of acute acro-ischemic lesions in non-hospitalized patients: a case series of 132 patients during the COVID-19 outbreak**. J Am Acad Dermatol. 2020 Apr 24. PubMed: https://pubmed.gov/32339703. Full-text: https://doi.org/10.1016/j.jaad.2020.04.093

Authors describe two different patterns of acute acro-ischemic lesions, which can overlap. The chilblain-like pattern was present in 95 patients (72.0%). It is characterized by red to violet macules, plaques and nodules, usually at the distal aspects of toes and fingers. The erythema multiforme-like pattern was present in 37 patients (28.0%).

Galvan Casas C, Catala A, Carretero Hernandez G, et al. **Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases**. Br J Dermatol. 2020 Apr 29. PubMed: https://pubmed.gov/32348545. Full-text: https://doi.org/10.1111/bjd.19163 ● (IMPORTANT)

The authors describe five clinical cutaneous manifestations of lesions: acral areas of erythema with vesicles or pustules (pseudo-chilblain) (19%), other vesicular eruptions (9%), urticarial lesions (19%), maculopapular eruptions (47%) and livedo or necrosis (6%). Vesicular eruptions appear early in the course of the disease (15% before other symptoms). The pseudo-chilblain pattern frequently appears late in the evolution of the COVID-19 disease (59% after other symptoms).

Piccolo V, Neri I, Filippeschi C, et al. **Chilblain-like lesions during COVID-19 epidemic: a preliminary study on 63 patients**. J Eur Acad Dermatol Venereol. 2020 Apr 24. PubMed: https://pubmed.gov/32330334. Full-text: https://doi.org/10.1111/jdv.16526

Preliminary results of a survey among Italian dermatologists and pediatrics, reporting on 63 cases (only a few patients with confirmed COVID-19).

Recalcati S, Barbagallo T, Frasin LA, et al. **Acral cutaneous lesions in the Time of COVID-19**. J Eur Acad Dermatol Venereol. 2020 Apr 24. PubMed: https://pubmed.gov/32330324. Full-text: https://doi.org/10.1111/jdv.16533

A dermatology unit in Italy reports on 14 cases including 11 children. Lesions were localized on the feet in 8 cases, on the hands in 4 cases, on both sites in 2.

Duong TA, Velter C, Rybojad M, et al. **Did Whatsapp reveal a new cutaneous COVID-19 manifestation?** J Eur Acad Dermatol Venereol. 2020 Apr 24. PubMed: https://pubmed.gov/32330322. Full-text: https://doi.org/10.1111/jdv.16534

In a Whatsapp group of 400 French dermatologists, a total of 295 atypical skin eruptions or lesions of suspected or confirmed COVID-19 patients were posted between March 14 and April 10. Chilblains or chilblain-like lesions represented 146 posts, and 149 posts included other suspected COVID-19-related skin eruption, e.g. urticaria, rash, chickenpox-like or pityriasis rosea.

Marzano AV, Genovese G, Fabbrocini G, et al. **Varicella-like exanthem as a specific COVID-19-associated skin manifestation: multicenter case series of 22 patients**. J Am Acad Dermatol. 2020 Apr 16. PubMed: https://pubmed.gov/32305439. Full-text: https://doi.org/10.1016/j.jaad.2020.04.044

Case series on 22 adult patients with varicella-like lesions. Typical features were constant trunk involvement, usually scattered distribution and mild/absent pruritus, the latter being in line with most viral exanthems but unlike true varicella. Lesions generally appeared 3 days after systemic symptoms and disappeared by 8 days.

Sanchez A, Sohier P, Benghanem S, et al. **Digitate Papulosquamous Eruption Associated With Severe Acute Respiratory Syndrome Coronavirus 2 Infection**. JAMA Dermatol. 2020 Apr 30. PubMed: https://pubmed.gov/32352486. Full-text: https://doi.org/10.1001/jamadermatol.2020.1704

Case report on digitate papulosquamous eruption in a patient with severe COVID-19. This paraviral dermatosis could be a secondary result of the immune response against the virus.

Diaz-Guimaraens B, Dominguez-Santas M, Suarez-Valle A, et al. **Petechial Skin Rash Associated With Severe Acute Respiratory Syndrome Coronavirus 2 Infection**. JAMA Dermatol. 2020 Apr 30. PubMed: https://pubmed.gov/32352487. Full-text: https://doi.org/10.1001/jamadermatol.2020.1741

And yes, of course, rash may also occur. A case report with petechial skin rash with striking absence of lesions in the crural folds.

Quintana-Castanedo L, Feito-Rodriguez M, Valero-Lopez I, Chiloeches-Fernandez C, Sendagorta-Cudos E, Herranz-Pinto P. **Urticarial exanthem as early diagnostic clue for COVID-19 infection**. JAAD Case Rep. 2020 Apr 29. PubMed: https://pubmed.gov/32352022. Full-text: https://doi.org/10.1016/j.jdcr.2020.04.026

Another patient with impressive rash (a 61-year-old Spanish medical doctor).

Madigan LM, Micheletti RG, Shinkai K. **How Dermatologists Can Learn and Contribute at the Leading Edge of the COVID-19 Global Pandemic**. JAMA Dermatol. 2020 Apr 30. PubMed: https://pubmed.gov/32352485. Full-text: https://doi.org/10.1001/jamadermatol.2020.1438

A word of caution. Not all rashes or cutaneous manifestations seen in patients with COVID-19 can be attributed to the virus. Coinfections or medical complications have to be considered. Comprehensive mucocutaneous examinations, analysis of other systemic clinical features or host characteristics, and histopathologic correlation, will be vital to understanding the pathophysiologic mechanisms of what we are seeing on the skin.

3 May

Epidemiology

Zhang J, Litvinova M, Liang Y, et al. **Changes in contact patterns shape the dynamics of the COVID-19 outbreak in China**. Science 29 Apr 2020: Full-text:
https://science.sciencemag.org/content/early/2020/04/28/science.abb8001

An elegant model demonstrating the impact of lockdown by using contact survey data for Wuhan and Shanghai before and during the outbreak. Daily contacts were reduced 7-8-fold during the social distancing period, with most interactions restricted to the household. Of note, children 0-14 years were less susceptible to infection than adults (however, numbers were low). Social distancing alone, as implemented during the outbreak, was sufficient to control COVID-19. While proactive school closures cannot interrupt transmission on their own, they can reduce peak incidence by 40-60% and delay the epidemic.

Lu J, du Plessis L, Liu Z. **Genomic Epidemiology of SARS-CoV-2 in Guangdong Province, China**. Cell April 30, 2020. Full-text: https://www.cell.com/cell/fulltext/S0092-8674(20)30486-4

A comprehensive study on genomic epidemiology of SARS-CoV-2 in Guangdong province. The authors generated 53 genomes from infected individuals in Guangdong and deduce that following the first COVID-19 case detected in early January, most infections were the result of virus importation from elsewhere, and that chains of local transmission were limited in size and duration.

Virology, Immunology

Gordon DE, Jang GM, Bouhaddou M, et al. **A SARS-CoV-2 protein interaction map reveals targets for drug repurposing**. Nature. 2020 Apr 30. PubMed: https://pubmed.gov/32353859. Full-text: https://doi.org/10.1038/s41586-020-2286-9

A blueprint for future therapies. This heroic work, emerging from a worldwide collaboration (> 100 co-authors!), systematically maps the interaction landscape between SARS-CoV-2 proteins and human proteins. The authors cloned, tagged and expressed 26 of the 29 SARS-CoV-2 proteins in human cells and analyzed the human proteins physically associated with each using affinity-purification mass spectrometry (AP-MS), identifying 332 high-confidence SARS-CoV-2-human protein-protein interactions (PPIs). In total 66 human proteins or host factors targeted by 69 compounds (29 FDA approved drugs, 12 drugs in clinical trials, and 28 preclinical compounds) were found. Screening a subset of these in multiple viral assays identified two sets of pharmacological agents that displayed antiviral activity: inhibitors of mRNA translation and predicted regulators of the Sigma1 and Sigma2 receptors.

Yin W, Mao C, Luan X. **Structural basis for inhibition of the RNA-dependent RNA polymerase from SARS-CoV-2 by Remdesivir**. Science 01 May 2020. Full-text: https://science.sciencemag.org/content/early/2020/04/30/science.abc1560
● (IMPORTANT)

Convincing data from clinical trials are still lacking (mostly rumours and press releases). However, this work shows how remdesivir inhibits the SARS-CoV-2 RdRp activity in theory. The authors describe the structure of the SARS-CoV-2 RdRp complex in the apo form and in the complex with a template-primer RNA and the active form of remdesivir. The cryo-EM structures reveal how the template-primer RNA is recognized by the enzyme and how chain elongation is inhibited by remdesivir (and why other nucleotides such as EIDD-2801 may be more potent).

Lamers MM, Beumer J, van der Vaart J, et al. **SARS-CoV-2 productively infects human gut enterocytes**. Science 01 May 2020. Full-text: https://science.sciencemag.org/content/early/2020/04/30/science.abc1669
● (IMPORTANT)

SARS-CoV and SARS-CoV-2 infected enterocyte lineage cells in a human intestinal organoid model. Similar infection rates of enterocyte-precursors and

enterocytes were observed and low levels of ACE2 may be sufficient for viral entry. This study explains why gastrointestinal symptoms are observed in a subset of patients and why viral RNA can be found in rectal swabs, even after nasopharyngeal testing has turned negative.

Diagnostics

Zhang K, Liu X, Shen J, et al. **Clinically Applicable AI System for Accurate Diagnosis, Quantitative Measurements and Prognosis of COVID-19 Pneumonia Using Computed Tomography**. Cell April 29. Full-text: https://www.cell.com/cell/fulltext/S0092-8674(20)30551-1

A CT-based artificial intelligence (AI) system was shown to have the potential to assist in the early diagnosis and monitoring of pneumonia. For the classification model, 361,221 CT images from 2,246 patients including 752 NCP, 797 common pneumonia patients and 697 normal control patients were used for training. In brief, the AI system performance was overall superior to that of junior radiologists and comparable to mid-senior radiologists.

Clinical

von der Thusen J, van der Eerden M. **Histopathology and genetic susceptibility in COVID-19 pneumonia**. Eur J Clin Invest. 2020 Apr 30. PubMed: https://pubmed.gov/32353898. Full-text: https://doi.org/10.1111/eci.13259

Brief review on the current knowledge on the remarkable heterogeneity of disease patterns from a clinical, radiological, and histopathological point of view. The idiosyncratic responses of individual patients may be in part related to underlying genetic variations.

Comorbidities

Zhu L, She ZG, Cheng X. **Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes**. Cell Metabolism, April 30, 2020. Full-text: https://www.cell.com/cell-metabolism/fulltext/S1550-4131(20)30238-2 ● (IMPORTANT)

Check your HbA1c! The hitherto largest retrospective study on the impact of type 2 diabetes (T2D) has carefully analyzed 7,337 cases of COVID-19 in Hubei Province, China, among them 952 with pre-existing T2D. The authors found that subjects with T2D required more medical interventions and had a significantly higher mortality (7.8% versus 2.7%; adjusted hazard ratio, 1.49) and multiple organ injury than the non-diabetic individuals. Well-controlled

blood glucose was associated with markedly lower mortality (in-hospital death rate 1.1% versus 11.0%) compared to individuals with poorly controlled BG.

Piccolo R, Bruzzese D, Mauro C, et al. **Population Trends in Rates of Percutaneous Coronary Revascularization for Acute Coronary Syndromes Associated with the COVID-19 Outbreak. Circulation**. 2020 Apr 30. PubMed: https://pubmed.gov/32352318. Full-text: https://doi.org/10.1161/CIRCULATIONAHA.120.047457

Collateral damage of the current pandemic: data from Italy providing evidence that the outbreak of COVID-19 was associated with a decline by 32% in the number of percutaneous coronary intervention for acute coronary syndromes.

Treatment

Bonam SR, Kaveri SV, Saluntabhai A, et al. **Adjunct immunotherapies for the management of severely ill COVID-19 patients**. Cell Rep Med April 29, 2020. DOI:https://doi.org/10.1016/j.xcrm.2020.100016. Full-text: https://www.cell.com/action/showPdf?pii=S2666-3791%2820%2930021-5

Comprehensive review on current immunotherapies which either neutralize cytokines, SARS-CoV-2 or exert immunomodulation. Immunotherapies may not only reduce inflammation, inflammation-associated lung damage, or viral load, but could also prevent intensive care unit hospitalization.

4 May

Top Ten Special on

ACE inhibitors/ARBs – continue them (or start them up again)!

There has hardly been a topic in the last weeks of this pandemic that has kept doctors (mainly internists) and their patients as busy as the question of whether ACE inhibitors or angiotensin-receptor blockers (ARBs) can cause harm to patients. Early observations of an increased risk for mortality or severe COVID-19 in patients with hypertension, cardiovascular diseases and diabetes (Guan 2020) raised concerns. These diseases share underlying renin-angiotensin-aldosterone system pathophysiology that may be clinically insightful. In particular, activity of the angiotensin-converting enzyme 2 (ACE2) is dysregulated (increased) in cardiovascular disease (Vaduganathan 2020). As

SARS-CoV-2 cell entry depends on ACE2 (Hoffmann 2020), increased ACE2 levels may increase the virulence of the virus within the lung and heart. ACE inhibitors or ARBs which are frequently used to treat cardiovascular diseases may alter ACE2 and variation in ACE2 expression may in part be responsible for disease virulence.

Although a recent review of 12 animal studies and 12 human studies overwhelmingly implies that administration of both drug classes does not increase ACE2 expression (Sriram 2020), some concerns on deleterious effects remain and some media sources and health systems have called for the discontinuation of these drugs.

However, some small retrospective studies from China have shown no negative effect (Meng 2020). In the largest study, 188 patients taking ACEIs/ARBs were compared with 940 patients who did not use them. Of note, unadjusted mortality rate was lower in the ACEI/ARB group (3.7% vs. 9.8%) and a lower risk was also found in a multivariate Cox model (Zhang 2020).

Last week, three studies were published in the NEJM that will hopefully put an end to this discussion. Although all three were observational studies with the possibility of confounding, their message was consistent — none of the three studies showed any evidence of harm (Jarcho 2020).

The first study analyzed a total of 8,910 COVID-19 patients (from 169 hospitals located in 11 countries) for whom discharge status was availably by March 29 (Mehra 2020). A total of 515 (5.8%) died in the hospital. Factors independently associated with an increased risk of in-hospital death were an age greater than 65 years (odds ratio, 1.93), coronary artery disease (2.70), heart failure (2.48; 95% CI, 1.62 to 3.79), cardiac arrhythmia (1.95; 95% CI, 1.33 to 2.86), chronic obstructive pulmonary disease (2.96; 95% CI, 2.00 to 4.40), and current smoking (1.79; 95% CI, 1.29 to 2.47). No increased risk was found for the use of ACE inhibitors (0.33; 95% CI, 0.20 to 0.54) or the use of ARBs (1.23; 95% CI, 0.87 to 1.74). Of note, use of either ACE inhibitors or statins was associated with better survival. However, these associations should be considered with extreme caution as the study design cannot exclude the possibility of confounding.

The second study analyzed 2,573 COVID-19 patients with hypertension from New York City (Reynolds 2020). In total, 634 (24.6%) had severe disease, as indicated by ICU admission, mechanical ventilation, or death by April 15, 2020. After looking at different classes of antihypertensive medication — ACE inhibitors, ARBs, beta-blockers, calcium-channel blockers, and thiazide diuretics, the authors ruled out any substantial difference in the likelihood of severe COVID-19, with at least 97.5% certainty for all medication classes.

The third study looked at a possible independent relationship between RAAS blockers and the susceptibility to COVID-19 (Mancia 2020). The authors matched 6,272 Italian cases (positive for SARS-CoV-2) with 30,759 beneficiaries of the Regional Health Service (controls) according to sex, age, and municipality of residence. There was no evidence that ACE inhibitors or ARBs modify susceptibility to COVID-19. The results applied to both sexes as well as to younger and older persons.

We think that's it. Take your ACE inhibitors or ARBs. We do not agree with the NEJM editorial that "one or more randomized trials will be needed to answer definitively the question of whether ACE inhibitors or ARBs pose a harm to patients with COVID-19" (Jarcho 2020). Let's not waste time and/or resources. We have bigger fish to fry.

Top 10 references

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Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. **Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19**. N Engl J Med. 2020 May 1. PubMed: https://pubmed.gov/32356626. Full-text: https://doi.org/10.1056/NEJMoa2007621

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Sriram K, Insel PA. **Risks of ACE inhibitor and ARB usage in COVID-19: evaluating the evidence**. Clin Pharmacol Ther. 2020 Apr 22. PubMed: https://pubmed.gov/32320478. Full-text: https://doi.org/10.1002/cpt.1863

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5 May

Get it done!

On remdesivir, rumors of recovery, rolling reviews, and random noise

"That's very exciting. Get it done, Daniel." If you want to get an idea about the incredible pressure on and expectations from researchers, then please read the protocol from the White House (Trump 2020). NIAID's Anthony Fauci and Gilead's CEO Daniel O'Day make heroic attempts to explain the situation to decision makers. This pressure has its consequences. What we've seen during the last few days has probably never happened during the last 500 years on this planet: a drug the authorities (read: FDA) give "Emergency Use Authorization", two days after the first randomized trial practically shows ineffectiveness. Crazy times. What is whispered at press conferences counts more than peer-reviewed scientific evidence. Because the window for learning is so short, the need to balance scientific rigor against speed seems inevitable. But should that really be the case? Last Friday, a smart comment in SCIENCE argued "against pandemic research exceptionalism". Even in such a crisis, the rules of good science should not be thrown overboard. Releasing the full data is essential to allow scientists to understand studies (London 2020).

Let's take a closer look on the scarce data we have on remdesivir:

1. Compassionate Use Program: this was a fragmentary case series (Grein 2020) on some patients (only 53/61 patients were analyzed) with varying disease severity. Some improved, some didn't: random noise. We believe, for a number of reasons, this case series published in the New England Journal of Medicine is a cautionary tale for "science in a hurry", arousing false expectations. It might have been preferable to postpone the publication. However, Daniel O'Day, Gilead's CEO, wrote the same day that "the majority" of patients "demonstrated clinical improvement".

2. NCT04257656: This multicentre trial, funded by the Chinese Ministry of Science and Technology, was conducted between Feb 6 and March 12 at ten hospitals in Hubei (Wang 2020). A total of 237 patients with pneumonia confirmed by chest imaging, oxygen saturation of 94% or lower on room air and within 12 days of symptom onset were randomized to receive 10 days of single infusions or placebo. Clinical improvement was defined as the days to the point of a decline of two levels on a six-point clinical scale (from 1=discharged to 6=death) or discharged alive from hospital, whichever came first. Patients were 65 years old (IQR 56–71), 56% male, many were co-treated with lopinavir (28%) and corticosteroids. The trial did not attain the predetermined full sample size because the outbreak was brought under control in China. However, from the analyzable data, remdesivir was not associated with a difference in time to clinical improvement (hazard ratio 1.23, 95% CI 0.87–1.75). Clinical improvement rates were 27% versus 23% at day 14 and 65% versus 58% at day 28. Day 28 mortality was 14% versus 13%. Of note, the viral load decreased similarly in both groups. Some patients with remdesivir had dosing prematurely stopped due to adverse events (12% versus 5%, mainly gastrointestinal symptoms and increases of liver enzymes). But let's think positive: Time to recovery was "numerically" shorter in the remdesivir group than the control group, particularly in those treated within 10 days of symptom onset.

3. SIMPLE 1: This Phase III trial evaluated 5-day and 10-day dosing durations in 397 hospitalized patients with severe COVID-19. On April 29, Gilead announced that no difference was seen in clinical improvement (odds ratio: 0.75, 95% CI 0.51 – 1.12] on day 14. The most common adverse events were nausea (9.5 %) and acute respiratory failure (8.3%). Grade 3 or higher liver enzyme elevations occurred in 7.3%, with 3.0 % discontinuing remdesivir. Gilead plans to submit the full data for publication in a peer-reviewed journal "in the coming weeks". An expansion phase will enrol an additional 5,600 (!) patients around the world.

4. ACTT (Adaptive COVID-19 Treatment Trial): Sponsored by NIH, this was the first phase III study launched in the United States. ACTT began on February 21 (the first participant was repatriated after being quarantined on the

Diamond Princess) and enrolled 1,063 hospitalized patients with advanced COVID-19 and lung involvement. The design was "adaptive" to incorporate additional investigative treatments (and, surprisingly, to adapt new response criteria, see below). A total of 68 sites participated, among them 47 in the US and 21 in Europe and Asia. On April 16, it was decided to modify the primary endpoint (from mortality to time of recovery), facing "evolving clinical data". Only 11 days later, an independent DSMB noted that remdesivir was better than placebo with regard to the new primary endpoint, time to recovery (defined as being well enough for hospital discharge or returning to normal activity level). With the drug, recovery was 31% faster (11 versus 15 days, p<0.001). For the initial primary endpoint, mortality, results suggested an only marginal benefit (8.0% versus 11.6%, p=0.059). "Whenever you have clear-cut evidence a drug works, you have an ethical obligation to immediately let the people in the placebo group know so they can have access to it", said Anthony Fauci. Fine. But now we have waited another week. So where is the data? It will be probably not that easy to explain why such a major trial switched the key outcome measure only a few days before the interim analysis was done. At that time, they were still blinded for the results, correct? There is no doubt that this paper will have a complex and interesting discussion.

In the meantime, both the optimists and the pessimists can hold onto their opinions (see table).

What comes next?

Several additional trials are ongoing. Some have been suspended such as **NCT04252664**, a trial in adults with mild and moderate COVID-19, because during the last few weeks no eligible patients could be recruited. The second SIMPLE trial, **NCT04292730 (GS-US-540-5774)** is probably the most interesting study, evaluating the efficacy of two remdesivir regimens compared to standard of care in 600 patients with moderate COVID-19, with respect to clinical status assessed by a 7-point ordinal scale on day 11. Estimated study completion date is May 2020. INSERM in France has initiated a study evaluating remdesivir and other potential treatments, using a master protocol (**SOLIDARITY**) developed by WHO. This study (**NCT04315948**) is a multi-centre, adaptive, randomized, open clinical trial of the safety and efficacy of treatments of COVID-19 in hospitalized adults. Adults hospitalized for severe COVID-19 will be randomized to one of 4 treatment arms, including standard of care, remdesivir, lopinavir/r plus interferon ß-1a and hydroxychloroquine.

Table 1. Remdesivir, optimistic and pessimistic view

Study	Optimistic view	Pessimistic view
Compassionate Use	Encouraging, the majority demon-strated clinical improvement	No control group, fragmentary data without any message
SIMPLE	Similar efficacy with 5- and 10-day dosing, no new safety signals	No control group. Placebo for 5 vs 10 days would've produced the same results
NCT04257656	Time to recovery numerically shorter	No effect on mortality, no effect on viral load, some side effects
ACTT	Faster time to recovery, strong trend towards lower mortality (8 versus 12%)	No significant effect on mortality in >1,000 patients, and is 4 days of "faster recovery" relevant?

In the meantime, EMA's human medicines committee (CHMP) has started a 'rolling review' of data. This speeds up the assessment of a promising investigational medicine during a public health emergency but does not imply that its benefits outweigh its risks. We'll see what happens. By the way, the EUA allows for the distribution and emergency use of remdesivir only for the treatment of COVID-19; remdesivir remains an investigational drug and has not been approved anywhere. The fact sheet for health care providers is found here: FDA 2020.

Yes, very exciting.

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Grein J, Ohmagari N, Shin D, et al. **Compassionate Use of Remdesivir for Patients with Severe Covid-19**. N Engl J Med. 2020 Apr 10. PubMed: https://pubmed.gov/32275812. Full-text: https://doi.org/10.1056/NEJMoa2007016

London AJ, Kimmelman J. **Against pandemic research exceptionalism**. Science. 2020 May 1;368(6490):476-477. PubMed: https://pubmed.gov/32327600. Full-text: https://doi.org/10.1126/science.abc1731

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Wang Y, Zhang D, Du G, et al. **Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial**. April 29, 2020. Fulltext PDF: https://doi.org/10.1016/S0140-6736(20)31022-9. Full-text web page: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31022-9/fulltext

6 May

Epidemiology

Chou R, Dana T, Buckley DI, Selph S, Fu R, Totten AM. **Epidemiology of and Risk Factors for Coronavirus Infection in Health Care Workers: A Living Rapid Review.** Ann Intern Med. 2020 May 5. PubMed: https://pubmed.gov/32369541. Full-text: https://doi.org/10.7326/M20-1632

This review summarizes the risk factors for coronavirus infections in HCWs. There was evidence that more consistent and full use of recommended PPE measures was associated with decreased risk for infection, suggesting a dose–response relationship. This association was most consistent for masks but was also observed for gloves, gowns, and eye protection, as well as handwashing. Some evidence was found that N95 masks might be associated with decreased risk for infection versus surgical masks. Evidence also indicated an association between certain exposures (such as involvement in intubations, direct contact with infected patients, or contact with bodily secretions).

Lai S, Ruktanonchai NW, Zhou L, et al. **Effect of non-pharmaceutical interventions to contain COVID-19 in China**. Nature. 2020 May 4. PubMed: https://pubmed.gov/32365354. Full-text: https://doi.org/10.1038/s41586-020-2293-x

Another study on the impact of non-pharmaceutical interventions (NPIs) in China. Without NPIs, the COVID-19 cases would likely have shown a 67-fold increase (interquartile range 44-94) by February 29. Early detection and isolation of cases was estimated to have prevented more infections than travel restrictions and contact reductions, but combined NPIs achieved the strongest and most rapid effect. The lifting of travel restrictions does not appear to lead to an increase in cases if social distancing interventions are maintained.

Virology

Thao TTN, Labroussaa F, Ebert N, et al. **Rapid reconstruction of SARS-CoV-2 using a synthetic genomics platform**. Nature. 2020 May 4. PubMed: https://pubmed.gov/32365353. Full-text: https://doi.org/10.1038/s41586-020-2294-9

An important technical advance, enabling the rapid generation and functional characterization of evolving RNA virus variants. The authors show the functionality of a yeast-based synthetic genomics platform to genetically reconstruct diverse RNA viruses (which are cumbersome to clone and manipulate due to size and instability). They were able to engineer and resurrect chemically-synthetized clones of SARS-CoV-2 in only a week after receipt of the synthetic DNA fragments.

Cyranoski D. **Profile of a killer: the complex biology powering the coronavirus pandemic**. Nature. 2020, 581, 22-26. Full-text: https://www.nature.com/articles/d41586-020-01315-7

Fantastic, a thrilling feature on what we know about how the virus operates, where it came from and what it might do next. Leading scientists are asked about their hypotheses and current research projects on the origin and on the heterogeneity of the clinical course of COVID-19.

Lau SY, Wang P, Mok BW, et al. **Attenuated SARS-CoV-2 variants with deletions at the S1/S2 junction**. Emerg Microbes Infect. 2020 Dec;9(1):837-842. PubMed: https://pubmed.gov/32301390. Full-text: https://doi.org/10.1080/22221751.2020.1756700

Viral variants which contain 15-30-bp deletions (Del-mut) or point mutations respectively at the S1/S2 junction are described. Some of them were less pathogenic in a hamster model. It would be interesting to see the prevalence of these variants in asymptomatic infected cases. The potential of the Del-mut variants as an attenuated vaccine or laboratory tool should also be evaluated.

Clinical

Hu L, Chen S, Fu Y, et al. **Risk Factors Associated with Clinical Outcomes in 323 COVID-19 Hospitalized Patients in Wuhan, China**. Clin Infect Dis. 2020 May 3. PubMed: https://pubmed.gov/32361738. Full-text: https://doi.org/10.1093/cid/ciaa539

In multivariate regression, age > 65 years, smoking, critical disease status, diabetes, high hypersensitive troponin I (>0.04 pg/mL), leukocytosis (>10 x 10^9/L) and neutrophilia (>75 x 10^9/L) predicted unfavorable clinical outcomes. Of note, the administration of hypnotics was significantly associated with favorable outcomes (p<0.001). Dexzopiclone, a drug for insomnia, was administered at a dose of 1.0 mg per day to 82 patients for the duration of their hospitalization. Overall, favorable outcomes were recorded for these patients, including a better survival rate. Hypnotics may be an effective ancillary treatment for COVID-19.

Du RH, Liang LR, Yang CQ, et al. **Predictors of Mortality for Patients with COVID-19 Pneumonia Caused by SARS-CoV-2: A Prospective Cohort Study**. Eur Respir J. 2020 Apr 8. PubMed: https://pubmed.gov/32269088. Full-text: https://doi.org/10.1183/13993003.00524-2020

Among their 179 COVID-19 patients, the authors identified four risk factors, age ≥65 years, pre-existing concurrent cardiovascular or cerebrovascular diseases, CD3+CD8+ T cells ≤75 cell·μL-1, and cardiac troponin I ≥0.05 ng·mL-1. Especially the latter two factors were predictors for mortality. Two predictive models for in-hospital mortality are presented.

Menter T, Haslbauer JD, Nienhold R, et al. **Post-mortem examination of COVID19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings of lungs and other organs suggesting vascular dysfunction**. Histopathology. 2020 May 4. PubMed: https://pubmed.gov/32364264. Full-text: https://doi.org/10.1111/his.14134

Post-mortem examination of 21 COVID-19 cases, indicating a strong virus-induced vascular dysfunction. Interesting co-finding: 65% of the deceased

patients had blood group A. Coincidence? Probably not. Blood group A may be associated with the failure of pulmonary microcirculation and coagulopathies in COVID-1. Another explanation could be the direct interaction between antigen A and the viral S protein, thus facilitating virus entry via ACE2.

Bowles L, Platton S, Yartey N, et al. **Lupus Anticoagulant and Abnormal Coagulation Tests in Patients with Covid-19**. NEJM May 5, 2020. Full-text: https://www.nejm.org/doi/full/10.1056/NEJMc2013656?query=featured_home

Of 216 patients with SARS-CoV-2, 44 (20%) were found to have a prolonged aPTT. After excluding 9 patients, 31/34 (91%) had positive lupus anticoagulant assays. As this is not associated with a bleeding tendency, authors recommend that prolonged aPTT should not be a barrier to the use of anticoagulation therapies in the prevention and treatment of venous thrombosis.

Pediatrics

Parri N, Lenge M, Buonsenso D. **Children with Covid-19 in Pediatric Emergency Departments in Italy**. N Engl J Med. 2020 May 1. PubMed: https://pubmed.gov/32356945. Full-text: https://doi.org/10.1056/NEJMc2007617

Among a total of 100 children with SARS-CoV-2 from Italy, 21% were asymptomatic, 58% had mild disease, 19% had moderate disease, 1% had severe disease, and 1% were in critical condition.

7 May

Epidemiology

Persad G, Emanuel EJ. **The Ethics of COVID-19 Immunity-Based Licenses ("Immunity Passports")**. JAMA. Published online May 6, 2020. Full-text: https://jamanetwork.com/journals/jama/fullarticle/2765836

Chile, Germany and the UK, among others, have indicated they will implement certifications that a person has contracted and recovered from COVID-19. According to the authors, immunity-based licenses require careful implementation to be ethical in practice. These "licenses" may allow immune people to engage in economic activity and safer care for vulnerable populations. However, major concerns remain as community licensing could stigmatize people, undermining the value of equal treatment. Businesses may use un-

regulated evidence of immunity, such as test results, or use assumptions about immunity or vulnerability that are likely to be arbitrary and biased.

Virology

Watanabe Y, Allen JD, Wrapp D, McLellan JS, Crispin M. **Site-specific glycan analysis of the SARS-CoV-2 spike**. Science. 2020 May 4. PubMed: https://pubmed.gov/32366695. Full-text: https://doi.org/10.1126/science.abb9983

The surface of the envelope spike is dominated by host-derived glycans. These glycans facilitate immune evasion by shielding specific epitopes from antibody neutralization. The SARS-CoV-2 S gene encodes 22 N-linked glycan sequons per protomer. Using a site-specific mass spectrometric approach, authors reveal these glycan structures on a recombinant SARS-CoV-2 S immunogen.

Transmission

Liao L, Xiao W, Zhao M, et al. **Can N95 Respirators Be Reused after Disinfection? How Many Times?** ACS Nano. 2020 May 5. PubMed: https://pubmed.gov/32368894. Full-text: https://doi.org/10.1021/acsnano.0c03597

How can we re-use N95 respirators? Heat is better than sun or vapors. At 85°C, 50 cycles of heat treatment did not significantly change filtration efficiency. At low humidity and temperatures up to 100 degrees, 20 cycles were possible. Ultraviolet irradiation was a secondary choice, which was able to withstand 10 cycles of treatment and showed small degradation by 20 cycles. However, UV can potentially impact the material strength. Treatments involving liquids and vapors require caution, as steam, alcohol, and household bleach all may lead to degradation of the filtration efficiency.

Diagnostics

Sethuraman N, Jeremiah SS, Akihide Ryo A, et al. **Interpreting Diagnostic Tests for SARS-CoV-2**. JAMA May 6, 2020. Full-text: https://jamanetwork.com/journals/jama/fullarticle/2765837

Using available evidence, a clinically useful timeline of diagnostic markers for detection of COVID-19 is devised.

Clinical

Middeldorp S, Coppens M, van Haaps TF, et al. **Incidence of venous thromboembolism in hospitalized patients with COVID-19**. J Thromb Haemost. 2020 May 5. PubMed: https://pubmed.gov/32369666. Full-text: https://doi.org/10.1111/jth.14888 ● (IMPORTANT)

The next study reporting on an incredibly high number of venous thromboembolism (VTE). In this single-center study from Amsterdam on 198 hospitalized cases, the cumulative incidence of VTE at 7, 14, and 21 days were 16%, 33% and 42%. In 74 ICU Patients, cumulative incidence was 59% at 21 days, despite thrombosis prophylaxis. The authors have changed their practice during the follow-up period by performing screening compression ultrasound in the ICU every 5 days.

Helms J, Tacquard C, Severac F, et al. **High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study**. Intensive Care Med. 2020 May 4. PubMed: https://pubmed.gov/32367170. Full-text: https://doi.org/10.1007/s00134-020-06062-x

Same idea: In this prospective study from France, 64/150 (43%) patients were diagnosed with clinically relevant thrombotic complications. Authors argue for higher anticoagulation targets in critically ill patients.

Ahmed MZ, Khakwani M, Venkatadasari I, et al. **Thrombocytopenia as an initial manifestation of Covid-19; Case Series and Literature review**. Br J Haematol. 2020 May 5. PubMed: https://pubmed.gov/32369609. Full-text: https://doi.org/10.1111/bjh.16769

Three patients, two of them with hemorrhagic manifestation and severe thrombocytopenia responded to IVIG fairly quickly with a sustained response over weeks.

Martin Carreras-Presas C, Amaro Sanchez J, Lopez-Sanchez AF, Jane-Salas E, Somacarrera Perez ML. **Oral vesiculobullous lesions associated with SARS-CoV-2 infection**. Oral Dis. 2020 May 5. PubMed: https://pubmed.gov/32369674. Full-text: https://doi.org/10.1111/odi.13382

Three cases of COVID-19-associated ulcers in the oral cavity, with pain, desquamative gingivitis, and blisters.

Treatment

Wang C, Li W, Drabek D, et al. **A human monoclonal antibody blocking SARS-CoV-2 infection**. Nat Commun. 2020 May 4;11(1):2251. PubMed: https://pubmed.gov/32366817. Full-text: https://doi.org/10.1038/s41467-020-16256-y ●● (Outstanding)

The first report of a human monoclonal antibody that neutralizes SARS-CoV-2. 47D11 binds a conserved epitope on the spike RBD explaining its ability to cross-neutralize SARS-CoV and SARS-CoV-2, using a mechanism that is independent of receptor-binding inhibition. This antibody could be useful for development of antigen detection tests and serological assays targeting SARS-CoV-2.

Cao B, Zhang D, Wang C. **A Trial of Lopinavir-Ritonavir in Covid-19. Reply.** N Engl J Med. 2020 May 5;382(21). PubMed: https://pubmed.gov/32369286. Full-text: https://doi.org/10.1056/NEJMc2008043#sa6

Interesting discussion about the results of the large open-label randomized trial which was published in March. In this trial, administration of lopinavir/r did not result in a shorter time until clinical improvement compared to placebo. Bottom line of most comments: "absence of evidence is not evidence of absence". Lopinavir/r may still be a potential therapeutic agent against COVID-19, especially when given earlier.

8 May

Epidemiology

Wallace M, Hagan L, Curran KG, et al. **COVID-19 in Correctional and Detention Facilities — United States, February–April 2020**. MMWR Early Release, May 6, 2020. https://www.cdc.gov/mmwr/volumes/69/wr/mm6919e1.htm

First documentation of the epidemic in correctional and detention facilities. Aggregated data on COVID-19 cases reported to CDC by 37 of 54 state and territorial health department jurisdictions in the US. Prison bars do not work: As of April 21, 2020, 4,893 cases and 88 deaths among incarcerated and detained persons and 2,778 cases and 15 deaths among staff members have been reported.

Wells CR, Stearns JK, Lutumba P, Galvani AP. **COVID-19 on the African continent**. Lancet Infect Dis May 06, 2020. Full-text: https://doi.org/10.1016/S1473-3099(20)30374-1

Brief review. The transmissibility of SARS-CoV-2, combined with the scarcity of crucial health equipment and the challenges of implementing widespread physical distancing and case isolation, poses a grave threat to the African continent.

Fusaroli P, Balena S, Lisotti A. **On the death of 100+ Italian doctors from COVID-19**. Infection 2020. https://doi.org/10.1007/s15010-020-01436-1. Full-text: https://link.springer.com/article/10.1007/s15010-020-01436-1.

Authors speculate on the reasons why 95/100 of deceased Italian doctors were men. Could different habits between men and women have played a role too? According to some research, women are supposedly more scrupulous in performing hand hygiene than men.

Virology

Bao L, Deng W, Huang B, et al. **The pathogenicity of SARS-CoV-2 in hACE2 transgenic mice**. Nature. 2020 May 7. PubMed: https://pubmed.gov/32380511. Full-text: https://doi.org/10.1038/s41586-020-2312-y

In transgenic mice bearing human ACE2 and infected with SARS-CoV-2, pathogenicity of the virus was demonstrated. This mouse model will be valuable for evaluating antiviral therapeutics and vaccines as well as understanding the pathogenesis of COVID-19.

Xiao K, Zhai J, Feng Y, et al. **Isolation of SARS-CoV-2-related coronavirus from Malayan pangolins**. Nature. 2020 May 7. PubMed: https://pubmed.gov/32380510. Full-text: https://doi.org/10.1038/s41586-020-2313-x ● (IMPORTANT)

In a wildlife rescue center, authors found coronavirus in 25 Malayan pangolins (some of whom were very sick), showing 90-100% amino acid identity with SARS-CoV-2 in different genes. Comparative genomic analysis suggested that SARS-CoV-2 might have originated from the recombination of a Pangolin-CoV-like virus with a Bat-CoV-RaTG13-like virus. As the RBD of Pangolin-CoV is virtually identical to that of SARS-CoV-2, the virus in pangolins presents a potential future threat to public health. Pangolins and bats are both nocturnal animals, eat insects, and share overlapping ecological niches,

which make pangolins the ideal intermediate host. Stop illegal pangolin trade!

Clinical

Jiang M, Guo Y, Luo Q, et al. **T cell subset counts in peripheral blood can be used as discriminatory biomarkers for diagnosis and severity prediction of COVID-19**. J Infect Dis. 2020 May 7. PubMed: https://pubmed.gov/32379887. Full-text: https://doi.org/10.1093/infdis/jiaa252

CD3+, CD4+ and CD8+T cells but also NK cells were significantly decreased in COVID-19 patients and related to the severity of the disease. Thresholds of CD8+T and CD4+T used for distinguishing between COVID-19 patients and healthy controls were 285.5/µl and 386.0/µl. According to the authors, CD8+T and CD4+T cell counts can be used as diagnostic markers of COVID-19 and predictors of disease severity.

Metlay JP, Waterer GW. **Treatment of Community-Acquired Pneumonia During the Coronavirus Disease 2019 (COVID-19) Pandemic**. Ann Intern Med. 2020 May 7. PubMed: https://pubmed.gov/32379883. Full-text: https://doi.org/10.7326/M20-2189

Some ideas on how to treat community-acquired pneumonia (CAP) during these days and how to interpret CAP guidelines.

Thornton J. **Covid-19: the challenge of patient rehabilitation after intensive care**. BMJ. 2020 May 6;369:m1787. PubMed: https://pubmed.gov/32376670. Full-text: https://doi.org/10.1136/bmj.m1787

Discharge from ICU is not the end. Challenges remain for appropriate rehabilitation—physical, cognitive, and psychological. And whether this will be available for the huge numbers of people who will need to deal with the enormous impact of a stay in critical care.

Treatment

Geleris J, Sun Y, Platt J, et al. **Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19**. N Engl J Med. 2020 May 7. PubMed: https://pubmed.gov/32379955. Full-text: https://doi.org/10.1056/NEJMoa2012410 ● (IMPORTANT)

The end of hydroxychloroquine (HCQ)? Incredible large observational study from New York City. Of 1,376 consecutive hospitalized patients, 811 (59%) received HCQ (600 mg BID day 1, then 400 mg QD, 60% also received azithromycin). The decision to prescribe the drugs was "left to the discretion of the treating team for each individual patient". HCQ-treated patients were more severely ill at baseline. Authors adjusted for likely confounders, including age, race and ethnic group, body-mass index, diabetes, underlying kidney or lung disease, hypertension, baseline vital signs, Pao2:Fio2, and inflammatory markers of the severity of illness. There was no significant association between HCQ use and intubation or death. However, despite this extensive adjustment, it is still possible that some amount of unmeasured confounding remains. According to the authors, the study should not be taken to rule out either benefit or harm of HCQ but the results do not support the use of HCQ outside randomized clinical trials.

Hanley B, Roufosse CA, Osborn M, Naresh KN. **Convalescent donor SARS-COV-2-specific cytotoxic T lymphocyte infusion as a possible treatment option for COVID-19 patients with severe disease - has not received enough attention till date**. Br J Haematol. 2020 May 5. PubMed: https://pubmed.gov/32369628. Full-text: https://doi.org/10.1111/bjh.16780

Authors argue that therapeutic off-the-shelf SARS-COV-2-specific HLA-matched cytotoxic T cells prepared from convalescent COVID-19 patients is the most pressing need. It remains unclear why.

9 May

Top 10 Special on

Kawasaki-like syndrome in children (March/April 2020)

A new twist in this new pandemic: at the end of March 2020, Jones et al. described the case of a six-month-old baby girl with fever, rash and swelling characteristic of a rare pediatric inflammatory condition, Kawasaki syndrome (Jones 2020). The child is treated according to treatment guidelines with a single dose of 2g/kg intravenous immunoglobulin and high dose acetylsalicylic 20mg/kg four times daily. The fever breaks within hours.

A month later, on 27 April, the National Health Service (NHS) sends an email alert to members of the British Paediatric Critical Care Society (PICS) highlighting "a small rise in the number of cases of critically ill children presenting with an unusual clinical picture." Many of these children have tested pos-

itive for COVID-19, while some had not. The alert indicates that "the cases have in common overlapping features of toxic shock syndrome and atypical Kawasaki disease with blood parameters consistent with severe COVID-19 in children. Abdominal pain and gastrointestinal symptoms have been a common feature as has cardiac inflammation", (see the PICS statement).

A few days later, Sylvain Renolleau, head of the intensive care unit at Necker hospital, Paris, reports more than 20 children and adolescents 3 to 17 years old hospitalized in intensive care. The first cases were seen around 15 April. Symptoms included abdominal pain, diarrhea and vomiting, sometimes fever, myocarditis, and a strong inflammatory syndrome. Although not all children tested positive for SARS-CoV-2, all seem to have been in contact with the virus. No deaths have been reported so far. At the end of April, nearly 100 cases had been found in children in France, Great Britain, Italy, Spain, Switzerland and the United States.

On 1 May 2020, the Royal College of Paediatrics and Child Health released guidance describing a systemic inflammatory response sharing "common features with other pediatric inflammatory conditions including: Kawasaki disease, staphylococcal and streptococcal toxic shock syndromes, bacterial sepsis, and macrophage activation syndromes (Royal College of Paediatrics and Child Health 2020)." On 4 May, New York City's Department of Health issued a similar alert (NYC Health 2020). Two days later, 64 cases were reported from New York (New York Department of Health 2020).

Kawasaki Disease

Kawasaki disease (KD) is an acute-onset systemic vasculitis of medium-sized vessels that mostly affects infants and toddlers (Hedrich 2017).

The first English-language report of 50 patients goes back to Tomisaku Kawasaki in 1974 (Kawaski 1974, Burns 2000). The KD incidence is much higher in Northeast Asian countries including Japan, South Korea, China, and Taiwan, 10–30 times higher than that of KD in North America and Europe (see the world map in Kim GB 2019).

More than 90% of children were less than 5 years old in a study from Inner Mongolia (Zhu 2015). Untreated, KD leads to coronary artery aneurysms in around 25% of cases (**don't miss this paper: McCrindle 2017**). The diagnosis of "classic KD" is based on the presence of ≥5 days of fever plus four out of five diagnostic criteria including erythema of the lips or mouth, trunk rash, swelling or erythema of the hands or feet, conjunctivitis, and lymph node swelling (see the detailed discussion in McCrindle 2017).

Prompt diagnosis is essential, immune globulin being the mainstay of initial treatment. Even in these COVID-19 times, physicians should keep an eye out for KD in all children with prolonged fever, especially in those younger than 1 year (Harasheh 2020).

The cause of KD remains unknown. Some lines of evidence point to a post-infectious trigger causing hyperreaction of the immune system (Dietz 2017) and an association between viral respiratory infections and KD (Jordan-Villegas 2010, Kim JH 2012, Turnier 2015). The primarily winter-spring KD seasonality and well-documented Japanese epidemics with wave-like spread also support an infectious trigger (Rowley 2018).

The Future

It is still unknown if there is a correlation between the cases described above and COVID-19. If there is a correlation, it is unclear whether COVID-19-associated inflammatory disorder and Kawasaki disease are identical (COVID-19-associated cases seem to have more severe abdominal pain, nausea and vomiting; those with severe shock are often older than the typical Kawasaki patients; and in Kawasaki cases, heart vessels seem to be more involved).

Summary

- A new Kawasaki-like syndrome may be emerging in children of all ages.
- The syndrome is rare.
- This syndrome may be related to SARS-CoV-2 but could as well be related to a different infectious pathogen with similar characteristics.
- So far, little is known about the new syndrome.
- To be remembered: serious COVID-19 complications are **very rare** among children. Throughout Europe, SARS-CoV-2 has caused very few victims among children. In Britain, only 9 children aged 0 to 19 have died after testing positive for coronavirus (0.05% of the 21,678 deaths recorded at the end of April).

See also selected press articles from France (Le Monde, Libération), UK (The Guardian), Spain (El País), Italy (Corriere della Sera) and Germany (FAZ).

References

Burns JC, Kushner HI, Bastian JF, et al. **Kawasaki disease: A brief history.** Pediatrics. 2000 Aug;106(2):E27. PubMed: https://pubmed.gov/10920183. Full-text: https://pediatrics.aappublications.org/content/106/2/e27

Dietz SM, van Stijn D, Burgner D, et al. **Dissecting Kawasaki disease: a state-of-the-art review.** Eur J Pediatr. 2017 Aug;176(8):995-1009. PubMed: https://pubmed.gov/28656474. Full-text: https://doi.org/10.1007/s00431-017-2937-5

Harahsheh AS, Dahdah N, Newburger JW, et al. **Missed or Delayed Diagnosis of Kawasaki Disease During the 2019 Novel Coronavirus Disease (COVID-19) Pandemic.** J Pediatr. 2020 Apr 23. PubMed: https://pubmed.gov/32370951. Full-text: https://doi.org/10.1016/j.jpeds.2020.04.052

Hedrich CM, Schnabel A, Hospach T. **Kawasaki Disease.** Front Pediatr. 2018 Jul 10;6:198. PubMed: https://pubmed.gov/30042935. Full-text: https://doi.org/10.3389/fped.2018.00198

Jones VG, Mills M, Suarez D, et al. **COVID-19 and Kawasaki Disease: Novel Virus and Novel Case.** Hosp Pediatr. 2020 Apr 7. PubMed: https://pubmed.gov/32265235. Full-text: https://doi.org/10.1542/hpeds.2020-0123 ● (IMPORTANT) – This is the first report about Kawasaki disease and concurrent SARS-CoV-2 infection. The authors describe the case of a a six-month-old baby girl with fever, rash and swelling characteristic of Kawasaki syndrom. The child had minimal respiratory symptoms. She was treated with a single dose of 2g/kg intravenous immunoglobulin (IVIG) and high dose acetylsalicylic acid (ASA 20mg/kg four times daily) according to treatment guidelines.

Jordan-Villegas A, Chang ML, Ramilo O, Mejias A. **Concomitant respiratory viral infections in children with Kawasaki disease.** Pediatr Infect Dis J. 2010 Aug;29(8):770-2. PubMed: https://pubmed.gov/20354462. Full-text: https://doi.org/10.1097/INF.0b013e3181dba70b

Kawaski T, Kosaki F, Okawa S, et al (1974) **A new infantile acute febrile mucocutaneous lymph node syndrome (MCLS) prevailing in Japan.** Pediatrics 54:271–276. Full-text: https://pediatrics.aappublications.org/content/pediatrics/54/3/271.full-text.pdf

Kim JH, Yu JJ, Lee J, et al. **Detection rate and clinical impact of respiratory viruses in children with Kawasaki disease.** Korean J Pediatr. 2012 Dec;55(12):470-3. PubMed: https://pubmed.gov/23300502. Full-text: https://doi.org/10.3345/kjp.2012.55.12.470

Kim GB. **Reality of Kawasaki disease epidemiology.** Korean J Pediatr. 2019 Aug;62(8):292-296. PubMed: https://pubmed.gov/31319643. Full-text: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6702118/

McCrindle BW, Rowley AH, Newburger JW, et al. **Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association.** Circulation. 2017 Apr 25;135(17):e927-e999. PubMed: https://pubmed.gov/28356445. Full-text: https://doi.org/10.1161/CIR.0000000000000484

New York City's Department of Health. **2020 Health Alert #13: Pediatric Multi-System Inflammatory Syndrome Potentially Associated with COVID-19.** 4 May 2020 (accessed 6 May 2020). Document: https://www1.nyc.gov/assets/doh/downloads/pdf/han/alert/2020/covid-19-pediatric-multi-system-inflammatory-syndrome.pdf

New York Departement of Health. **Healthadvisory: pediatric multi-system inflammatory syndrome potentially associated with coronavirus disease (covid-19) in children.** 6 May 2020 (accessed 9 May 2020). Document: http://dmna.ny.gov/covid19/docs/all/DOH_COVID19_PediatricInflammatorySyndrome_050620.pdf

Paediatric Critical Care Society. **PICS Statement: Increased number of reported cases of novel presentation of multi-system inflammatory disease.** 27 April 2020 (accessed 7 May 2020). Document: https://picsociety.uk/wp-content/uploads/2020/04/PICS-statement-re-novel-KD-C19-presentation-v2-27042020.pdf

Rowley AH, Shulman ST. **The Epidemiology and Pathogenesis of Kawasaki Disease.** Front Pediatr. 2018 Dec 11;6:374. PubMed: https://pubmed.gov/30619784. Full-text: https://doi.org/10.3389/fped.2018.00374

Royal College of Paediatrics and Child Health. **Paediatric multisystem inflammatory syndrome temporally associated with COVID-19.** 1 May 2020 (accessed 4 May). Document:

https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19

Turnier JL, Anderson MS, Heizer HR, Jone PN, Glode MP, Dominguez SR. **Concurrent Respiratory Viruses and Kawasaki Disease.** Pediatrics. 2015 Sep;136(3):e609-14. PubMed: https://pubmed.gov/26304824. Full-text: https://doi.org/10.1542/peds.2015-0950

Zhu H, Yu SF, Bai YX, Liang YY, Su XW, Pan JY. **Kawasaki disease in children: Epidemiology, clinical symptoms and diagnostics of 231 cases in 10 years.** Exp Ther Med. 2015 Jul;10(1):357-361. PubMed: https://pubmed.gov/26170962. Full-text: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4486877/

10 May

Epidemiology

Weitz JS, Beckett SJ, Coenen AR, et al. **Modeling shield immunity to reduce COVID-19 epidemic spread.** Nat Med. 2020 May 7. PubMed: https://pubmed.gov/32382154. Full-text: https://doi.org/10.1038/s41591-020-0895-3

The authors propose an approach to limit transmission, which is both complementary to and intended to lessen the multifaceted costs of mitigation and suppression. The core idea is to leverage a mechanism of 'interaction substitution' by identifying recovered individuals who have protective antibodies and deploying them back into the community. The intention is to develop population-level 'shield immunity' by amplifying the proportion of interactions with recovered individuals relative to those of individuals of unknown status.

Immunology

Vabret N, Britton GJ, Gruber C, et al. **Immunology of COVID-19: Current State of the Science.** Immunity. 2020 Jun 16;52(6):910-941. PubMed: https://pubmed.gov/32505227. Full-text: https://doi.org/10.1016/j.immuni.2020.05.002 ●● (OUTSTANDING)

Brilliant review on the current knowledge of innate and adaptive immune responses elicited by SARS-CoV-2 infection and the immunological pathways that likely contribute to disease severity and death.

Ni L, Ye F, Cheng ML, et al. **Detection of SARS-CoV-2-specific humoral and cellular immunity in COVID-19 convalescent individuals**. Immunity 2020, May 03. Full-text: https://www.cell.com/action/showPdf?pii=S1074-7613%2820%2930181-3 ● (IMPORTANT)

SARS-CoV-2-specific humoral and cellular immunity was characterized in 14 recovered patients. Of these, 13 displayed serum neutralizing activities in a pseudotype entry assay. Notably, there was a strong correlation between neutralization antibody titers and the numbers of virus-specific T cells. These findings suggest that both B and T cells participate in immune-mediated protection.

Diagnostics

Cai XF, Chen J, Hu JL, et al. **A Peptide-based Magnetic Chemiluminescence Enzyme Immunoassay for Serological Diagnosis of Coronavirus Disease 2019 (COVID-19).** J Infect Dis. 2020 May 8. PubMed: https://pubmed.gov/32382737. Full-text: https://doi.org/10.1093/infdis/jiaa243

A new antibody assay, based on a peptide from the S protein, which was screened out from 20 candidate peptides deduced from the genomic sequence. Using a synthetic peptide may enhance the stability and repeatability of the assay, and theoretically would be more specific. A high specificity was shown. Sensitivity was lower: in 276 infection-confirmed patients, IgG was detected in 71.4% and was higher than the detection rate of IgM (57.2%).

Comorbidities

Chung SC, Providencia R, Sofat R, et al. **Association between Angiotensin Blockade and Incidence of Influenza in the United Kingdom**. NEJM May 8, 2020. Full-text: https://www.nejm.org/doi/full/10.1056/NEJMc2005396

Like SARS-CoV-2, influenza A viruses have been shown to use the ACE2 receptor. Using the linked electronic health care records of 5.6 million persons in the United Kingdom, authors have investigated the incidence of influenza among adults who received a prescription for an ACE inhibitor from 1998 through 2016. Main results: the use of ACE inhibitors and ARBs was associated with either no effect on the incidence of influenza or a lower incidence.

Clinical

Creel-Bulos C, Hockstein M, Amin N, Melhem S, Truong A, Sharifpour M. **Acute Cor Pulmonale in Critically Ill Patients with Covid-19**. N Engl J Med. 2020 May 6. PubMed: https://pubmed.gov/32374956. Full-text: https://doi.org/10.1056/NEJMc2010459

Five patients from Atlanta, USA, with profound hemodynamic instability due to the development of acute cor pulmonale. Although acute pulmonary thromboembolism was the most likely cause of right ventricular failure in these patients (4/5 were younger than 65 years of age), this was not definitively confirmed in all cases.

Wichmann D, Sperhake JP, Lutgehetmann M, et al. **Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study**. Ann Intern Med. 2020 May 6. PubMed: https://pubmed.gov/32374815. Full-text: https://doi.org/10.7326/M20-2003 ● (IMPORTANT)

Autopsy findings from 12 COVID-19 patients who died in Hamburg, Germany. Seven of the twelve had deep vein thrombosis, and pulmonary embolism was the direct cause of death in four cases. Of note, viremia was found in 6 of 10 patients tested and 5/12 patients demonstrated high viral RNA titers in the liver, kidney, or heart.

Ong SW, Young BE, Leo YS. **Association of higher body mass index (BMI) with severe coronavirus disease 2019 (COVID-19) in younger patients**. Clinical Infectious Diseases 2020, May 8. Full-text: https://doi.org/10.1093/cid/ciaa548

Retrospective analysis of 182 patients from Singapore. Among those aged <60 years, a BMI ≥25 was significantly associated with pneumonia on chest radiograph on admission (p value = 0.017), requiring low-flow supplemental oxygen (OR 6.32, 95% CI 1.23 – 32.34) and mechanical ventilation (OR 1.16, 95% CI 1.00 – 1.34).

Treatment

Cohen J. **The race is on for antibodies that stop the new coronavirus**. Science 08 May 2020: Vol. 368, Issue 6491, pp. 564-565. https://science.sciencemag.org/content/368/6491/564 ● (IMPORTANT)

Great overview about antibodies as a potential treatment. Many researchers are optimistic that these antibodies will, relatively quickly, prove their worth as a preventive or as a remedy that buys the world some time until a vaccine arrives (if it does). The main questions will be the capacity to manufacture at scale, distribute, and the cost.

Wrapp D, De Vlieger D, Corbett KS, et al. **Structural Basis for Potent Neutralization of Betacoronaviruses by Single-Domain Camelid Antibodies**. Cell. 2020 Apr 29. PubMed: https://pubmed.gov/32375025. Full-text: https://doi.org/10.1016/j.cell.2020.04.031

Here is one. In addition to conventional antibodies, camelids also produce heavy-chain-only antibodies (HCAbs), which contain a single variable domain (VHH) instead of two variable domains (VH and VL) that make up the equivalent antigen-binding fragment (Fab) of conventional immunoglobulin G (IgG) antibodies. These so-called 'nanobodies' have several potential therapeutic advantages, including increased stability and ease of production. Using llamas immunized with prefusion-stabilized betacoronavirus spike proteins, the authors identified neutralizing cross-reactive VHH camelid antibodies, which may serve as potential therapeutic candidates. Crystal structures further reveal how these antibodies bind to spike proteins to prevent viral entry into cells.

11 May

Epidemiology

Tian H, Liu Y, Li Y, et al. **An investigation of transmission control measures during the first 50 days of the COVID-19 epidemic in China**. Science. 2020 May 8;368(6491):638-642. PubMed: https://pubmed.gov/32234804. Full-text: https://doi.org/10.1126/science.abb6105

Quantitative analysis of the impact of control measures between 31 December 2019 and 19 February 2020. Travel restrictions in and out of Wuhan were too late to prevent the spread of the virus. However, measures such as closing citywide public transport and entertainment venues and banning public gatherings combined to avert hundreds of thousands of cases of infection.

Virology

Yuan M, Wu NC, Zhu X, et al. **A highly conserved cryptic epitope in the receptor binding domains of SARS-CoV-2 and SARS-CoV**. Science. 2020 May 8;368(6491):630-633. PubMed: https://pubmed.gov/32245784. Full-text: https://doi.org/10.1126/science.abb7269

Molecular insights into how SARS-CoV-2 can be targeted by the humoral immune response. The authors determined the crystal structure of CR3022, a neutralizing antibody previously isolated from a convalescent SARS patient,

in complex with the receptor binding domain of the SARS-CoV-2 spike protein.

Zhou H, Chen X, Hu T. **A novel bat coronavirus closely related to SARS-CoV-2 contains natural insertions at the S1/S2 cleavage site of the spike protein**. Current Biology 2020, May 10. Full-text: https://doi.org/10.1016/j.cub.2020.05.023

A novel bat-derived coronavirus was identified from a metagenomics analysis of samples from 227 bats collected from Yunnan Province between May and October 2019. Notably, RmYN02 shares 93.3% nucleotide identity with SARS-CoV-2 at the scale of the complete genome and 97.2% identity in the 1ab gene, in which it is the closest relative of SARS-CoV-2 reported to date. However, RmYN02 showed low sequence identity (61.3%) in the receptor binding domain and might not bind to ACE2.

Enserink M, Cohen J. **Fact-checking Judy Mikovits, the controversial virologist attacking Anthony Fauci in a viral conspiracy video**. Science 2020, May 8. Full-text: https://www.sciencemag.org/news/2020/05/fact-checking-judy-mikovits-controversial-virologist-attacking-anthony-fauci-viral

The pandemic has resulted in numerous conspiracy theories and misinformation, mainly spread through social media. WHO has declared an "infodemic" of incorrect information about the virus, which poses risks to global health. In a video that has exploded on social media in the past few days, virologist Judy Mikovits claims the virus is being wrongly blamed for many deaths. Fortunately, there are intelligent science journalists who take the time to refute this crap.

Diagnostics

Sama IE, Ravera A, Santema BT, et al. **Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin–angiotensin–aldosterone inhibitors**. European Heart Journal 2020, May 10. Full-text: https://doi.org/10.1093/eurheartj/ehaa373

The first substantial study to examine the association between plasma ACE2 concentrations and the use of RAAS blockers in patients with cardiovascular disease. Authors measured ACE2 concentrations in 1485 men and 537 women with heart failure (index cohort, 11 European countries). Results were validated in 1123 men and 575 women (validation cohort from Scotland). In both cohorts, plasma concentrations of ACE2 were markedly higher in men than in

women, but not the use of either an ACE inhibitor or an ARB. Data might explain the higher fatality rate of COVID-19 in men, but do not support the hypothesis that RAAS blockers increase the vulnerability for COVID-19.

Clinical

Parohan M, Yaghoubi S, Seraj A. **Liver injury is associated with severe Coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of retrospective studies**. Hepatol Res. 2020 May 9. PubMed: https://pubmed.gov/32386449. Full-text: https://doi.org/10.1111/hepr.13510

Meta-analysis of 20 retrospective studies with 3,428 COVID-19 infected patients (1,455 severe cases and 1,973 mild cases). Higher serum levels of ALT, AST, bilirubin and lower serum levels of albumin were associated with a significant increase in the severity of COVID-19.

Draulans D. **Scientist who fought Ebola and HIV reflects on facing death from COVID-19**. Sciencemag 2020, May 8. Full-text: https://www.sciencemag.org/news/2020/05/finally-virus-got-me-scientist-who-fought-ebola-and-hiv-reflects-facing-death-covid-19

Peter Piot, 71, one of the discoverers of the Ebola virus in 1976, former UNAIDS director and coronavirus adviser to European Commission President Ursula von der Leyen, discusses a severe case of COVID-19 occurring in March: his own. Interesting reflections on the disease and on death.

Comorbidities

Härter G, Spinner CD, Roider J, at al. **COVID-19 in people living with human immunodeficiency virus: a case series of 33 patients**. Infection 2020, May 11. https://doi.org/10.1007/s15010-020-01438-z. Full-text https://link.springer.com/article/10.1007/s15010-020-01438-z. ● (IMPORTANT)

The first larger case series in HIV-infected patients. No excess morbidity and mortality was found among symptomatic COVID-19 cases. As the majority (22/33) was treated with tenofovir, including those developing severe or critical disease, data indicate no or only minimal clinical effect of tenofovir against SARS-CoV-2. Four patients also were on darunavir when they developed COVID-19 symptoms.

Xiong F, Tang H, Liu L, et al. **Clinical Characteristics of and Medical Interventions for COVID-19 in Hemodialysis Patients in Wuhan, China**. J Am Soc Nephrol. 2020 May 8. PubMed: https://pubmed.gov/32385130. Full-text: https://doi.org/10.1681/ASN.2020030354

First large (multicenter retrospective) study about epidemiologic and clinical characteristics of patients undergoing hemodialysis with COVID-19. There were 101 mild/moderate and 30 severe/critical cases. Of note, 28 (21%) were asymptomatic over the whole course of the disease and were diagnosed only by universal screening. Morbidity was around 2% and only 52% of patients experienced fever.

Treatment

Spinelli FR, Conti F, Gadina M. HiJAKing SARS-CoV-2? **The potential role of JAK inhibitors in the management of COVID-19**. Sci Immunol. 2020 May 8;5(47). PubMed: https://pubmed.gov/32385052. Full-text: https://doi.org/10.1126/sciimmunol.abc5367

Targeting IL-6 and other cytokines with JAK-dependent signaling is one way to restrain the excessive level of cytokine signaling. JAK kinase inhibitors are being investigated as a way of managing the cytokine storm in severe COVID-19 patients. However, this well-balanced review also discusses potential concerns on side effects, such as the reduction of NK cells or thromboembolic risks seen with baricitinib and tofacitinib treatment.

Mojoli F, Mongodi S, Orlando A, et al. **Our recommendations for acute management of COVID-19**. Crit Care. 2020 May 8;24(1):207. PubMed: https://pubmed.gov/32384909. Full-text: https://doi.org/10.1186/s13054-020-02930-6

Some helpful (and very practical) clinical management suggestions, derived from the direct experience of Italian physicians.

12 May

Virology

Hui KPY, Cheung MC, Perera RAPM, et al. **Tropism, replication competence, and innate immune responses of the coronavirus SARS-CoV-2 in human respiratory tract and conjunctiva: an analysis in ex-vivo and in-vitro cultures**. Lancet Respir Med. 2020 May 7. PubMed:

https://pubmed.gov/32386571. Full-text: https://doi.org/10.1016/S2213-2600(20)30193-4 ● (IMPORTANT)

More insights into transmissibility and pathogenesis. Using ex-vivo cultures, authors evaluated tissue and cellular tropism of SARS-CoV-2 in the human respiratory tract and conjunctiva in comparison with other coronaviruses. In the bronchus and in the conjunctiva, SARS-CoV-2 replication competence was higher than SARS-CoV. In the lung, it was similar to SARS-CoV but lower than MERS-CoV.

Corey L, Mascola JR, Fauci AS, Collins FS. **A strategic approach to COVID-19 vaccine R&D**. Science Policy Forum, May 11, 2020. Full-text https://science.sciencemag.org/content/early/2020/05/08/science.abc5312

The full development pathway for an effective vaccine for SARS-CoV-2 will require that industry, government, and academia collaborate in unprecedented ways, each adding their individual strengths. Authors discuss one such collaborative program that has recently emerged: the ACTIV (Accelerating COVID-19 Therapeutic Interventions and Vaccines) public-private partnership.

Bost P, Giladi A, Liu Y, et al. **Host-viral infection maps reveal signatures of severe COVID-19 patients**. Cell May 07, 2020. Full-text: https://doi.org/10.1016/j.cell.2020.05.006

A computational method is proposed that globally scans unmapped scRNA-seq data for the presence of viral RNA, enabling transcriptional cell sorting of infected versus bystander cells. It is shown how SARS-CoV-2 infects epithelial cells and alters the immune landscape in patients with severe disease.

Li H, Liu L, Zhang D, et al. **SARS-CoV-2 and viral sepsis: observations and hypotheses**. Lancet. 2020 May 9;395(10235):1517-1520. PubMed: https://pubmed.gov/32311318. Full-text: https://doi.org/10.1016/S0140-6736(20)30920-X

Brief but nice review and several hypotheses about SARS-CoV-2 pathogenesis. What happens during the second week - when resident macrophages initiating lung inflammatory responses are unable to contain SARS-CoV-2 infection and when both innate and adaptive immune responses are insufficient to curb the viral replication and the patient doesn't recover quickly.

Clinical

Menni, C., Valdes, A.M., Freidin, M.B. et al. **Real-time tracking of self-reported symptoms to predict potential COVID-19**. Nat Med 2020, May 11. https://doi.org/10.1038/s41591-020-0916-2

A total of 18,401 participants from US/UK reported potential symptoms on a smartphone app and underwent a SARS-CoV-2 test. The proportion of participants who reported loss of smell and taste was higher in those with a positive test result (65% vs 22%). A combination of symptoms, including anosmia, fatigue, persistent cough and loss of appetite was appropriate to identify individuals with COVID-19.

Teufel M, Schweda A, Dörrie N. **Not all world leaders use Twitter in response to the COVID-19 pandemic: impact of the way of Angela Merkel on psychological distress, behaviour and risk perception**. Journal of Public Health May 12, 2020. Full-text: https://academic.oup.com/jpubhealth/advance-article/doi/10.1093/pubmed/fdaa060/5835923

By no doubt the weirdest paper title of the day. In a large online survey, the authors determined the levels of COVID-19 fear, anxiety and depression in 12,244 respondents during two weeks in March. Concurrent with Angela Merkel's speech on March 16, a reduction of anxiety and depression was noticeable in the German population.

Diagnostics

Kandemirli SG, Dogan L, Sarikaya ZT, et al. **Brain MRI Findings in Patients in the Intensive Care Unit with COVID-19 Infection**. Radiology. 2020 May 8:201697. PubMed: https://pubmed.gov/32384020. Full-text: https://doi.org/10.1148/radiol.2020201697

A brain MRI was performed in 27/50 patients with neurologic symptoms. The most common imaging finding was cortical signal abnormalities on FLAIR images (10/27, 37%), accompanied by cortical diffusion restriction or leptomeningeal enhancement. However, the complex clinical course including comorbidities, long ICU stay with multidrug regimens, and respiratory distress with hypoxia episodes can all act as confounding factors - a clear cause-effect relationship between COVID-19 infection and MRI findings will be hard to establish.

Treatment

Hung FN, Lung KC, Tso EY, et al. **Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial**. Lancet May 08, 2020. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31042-4/fulltext ● (IMPORTANT)

Some evidence that interferon may be helpful, when given during the first week: this Phase II, multicentre, open-label trial from Hong Kong randomized 127 patients with mild-to-moderate COVID-19 (median 5 days from symptom onset) to receive lopinavir/r only or a triple combination. Triple therapy was given only to patients with less than 7 days from symptom onset and consisted of lopinavir/r, ribavirin (400 mg BID), and interferon beta-1b (1-3 doses of 8 Mio IE per week). Combination therapy led to a significantly shorter median time to negative results in nasopharyngeal swab (7 versus 12 days, p=0.001) and other specimens. Clinical improvement was significantly better, with a shorter time to complete alleviation of symptoms and a shorter hospital stay. Of note, all differences were driven by the 76 patients who started treatment less than 7 days after onset of symptoms.

Martin-Blondel G, Ruiz S, Murris M, et al. **Hydroxychloroquine in COVID-19 patients: what still needs to be known about the kinetics**. Clin Infect Dis. 2020 May 11. PubMed: https://pubmed.gov/32392332. Full-text: https://doi.org/10.1093/cid/ciaa558

Different dosage regimens of hydroxychloroquine are currently used to manage COVID-19. The concentrations measured in 57 patients showed that hydroxychloroquine exposure was relatively low and in most instances lower than the values reported in systemic lupus erythematosus patients, in particular for the standard regimen of 200 mg TID. A full hydroxychloroquine kinetic exploration is needed.

Pediatrics

Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. **Hyperinflammatory shock in children during COVID-19 pandemic**. Lancet. 2020 May 7. PubMed: https://pubmed.gov/32386565. Full-text: https://doi.org/10.1016/S0140-6736(20)31094-1 ● (IMPORTANT)

Unprecedented cluster of eight children (all previously fit and well) with hyperinflammatory shock, showing features similar to atypical Kawasaki dis-

ease, Kawasaki disease shock syndrome, or toxic shock syndrome. Two children (one died) were positive for SARS-CoV-2 and four children had a known family exposure to COVID-19. This case cluster formed the basis of a national alert.

13 May

Transmission

Wu J, Huang Y, Tu C, et al. **Household Transmission of SARS-CoV-2, Zhuhai, China, 2020**. Clin Infect Dis. 2020 May 11. PubMed: https://pubmed.gov/32392331. Full-text: https://doi.org/10.1093/cid/ciaa557

The next study on a relatively low transmission rate among household contacts. A total of 35 index cases from Zhuhai, China and their 148 household contacts were carefully analyzed, using questionnaires, active symptom monitoring and nasopharyngeal swabs. The second infection rate in the household context was 32% (95% CI 22-44%). Multivariate analysis showed that household contacts with underlying medical conditions, a history of direct exposure to Wuhan, and shared vehicle with an index patient were associated with higher susceptibility.

Hijnen D, Marzano AV, Eyerich K, et al. **SARS-CoV-2 Transmission from Presymptomatic Meeting Attendee, Germany**. Emerg Infect Dis. 2020 May 11;26(8). PubMed: https://pubmed.gov/32392125. Full-text: https://doi.org/10.3201/eid2608.201235 ● (IMPORTANT)

Wanna make sure that SARS-CoV-2 is transmitted with almost 100% efficacy? Then use advisory boards or comparable settings: Eight dermatologists and 6 scientists from the same company attended a meeting at a hotel in Munich. The meeting was held in a room (≈70 m2) with conventional radiators; a U-shaped set-up of tables were separated by a central aisle >1 m wide. Refreshments were served buffet style in the same room 4 times during the day. After the 9.5 hours of discussions, participants had dinner in a nearby restaurant. Additional direct contacts were handshakes during welcome and farewells with a few short hugs without kisses and a 45 min. taxi ride with 3 participants. Results: The asymptomatic (!) index patient managed to infect at least 11/13 (!) participants. Note: The meeting was held on February 20; the country had <20 diagnosed cases at the time.

Comorbidities

Alqahtani JS, Oyelade T, Aldhahir AM, et al. **Prevalence, Severity and Mortality associated with COPD and Smoking in patients with COVID-19: A Rapid Systematic Review and Meta-Analysis**. PLoS One. 2020 May 11;15(5):e0233147. PubMed: https://pubmed.gov/32392262. Full-text: https://doi.org/10.1371/journal.pone.0233147

Time to quit smoking. Meta-analysis of 15 studies, including a total of 2,473 confirmed cases. COPD patients were at a higher risk of more severe disease (calculated RR 1.88). Current smokers were 1.45 times more likely to have severe complications compared to former and never smokers. Current smokers also had a higher mortality rate of 39%.

Paul S, Rausch CR, Jain N, et al. **Treating Leukemia in the Time of COVID-19**. Acta Haematol. 2020 May 11:1-13. PubMed: https://pubmed.gov/32392559. Full-text: https://doi.org/10.1159/000508199

This paper offers some recommendations on the optimization of leukemia management during high-risk COVID-19 periods. Instead of reducing patient access to specialized cancer centers and modifying therapies to ones with unproven curative benefit, there is more rationale for less intensive yet effective therapies that may require fewer visits to the clinic or hospitalizations.

Diagnostics

Kirkcaldy RD, King BA, Brooks JT. **COVID-19 and Postinfection Immunity: Limited Evidence, Many Remaining Questions**. JAMA. 2020 May 11. PubMed: https://pubmed.gov/32391855. Full-text: https://doi.org/10.1001/jama.2020.7869

After reading this viewpoint on the knowledge gaps on post-infection immunity, you will realize that any "COVID pass" would be about as accurate as issuing a certificate that she or he is "a kind person". ☺

Fraser B. **Chile plans controversial COVID-19 certificates.** Lancet. 2020 May 9;395(10235):1473. PubMed: https://pubmed.gov/32386581. Full-text: https://doi.org/10.1016/S0140-6736(20)31096-5

However, Chile is poised to become the first country to provide COVID passes to people who have recovered from the infection. We'll see how this works.

Treatment

Rodel F, Arenas M, Ott OJ, et al. **Low-dose radiation therapy for COVID-19 pneumopathy: what is the evidence**? Strahlenther Onkol. 2020 May 9. PubMed: https://pubmed.gov/32388805. Full-text: https://doi.org/10.1007/s00066-020-01635-7

Given the lack of effective pharmacological concepts, this review (re)considers historical reports on low-dose radiation therapy for pneumonia. Although these reports are of low-level evidence, they indicate effectiveness in the dose range between 0.3 and 1Gy, similar to more recent dose concepts in the treatment of inflammatory/degenerative benign diseases with, e.g., a single dose per fraction of 0.5Gy. The authors (known experts in the field) critically review the evidence for low-dose radiation treatment of COVID-19 pneumopathy and discuss whether it is worth investigating (answer: yes).

Rosenberg ES, Dufort EM, Udo T, et al. **Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State**. JAMA. 2020 May 11. PubMed: https://pubmed.gov/32392282. Full-text: https://doi.org/10.1001/jama.2020.8630

The next large retrospective cohort study of 1,438 patients from a random sample of all admitted patients with COVID-19 in 25 hospitals in the New York metropolitan region between March 15 and 28. In adjusted Cox models, compared with patients receiving neither drug, there were no significant differences in mortality for patients receiving hydroxychloroquine (HCQ) + azithromycin, HCQ alone, or azithromycin alone. In logistic models, cardiac arrest was significantly more likely in patients receiving HCQ + azithromycin (adjusted OR 2.13). The main limitation was the observational design. HCQ patients were more sick and had more comorbidities – the key (and unresolved) question is whether adjustment was sufficient.

Pediatrics

Shekerdemian LS, Mahmood NR, Wolfe KK, et al. **Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units**. JAMA Pediatr. 2020 May 11. PubMed: https://pubmed.gov/32392288. Full-text: https://doi.org/10.1001/jamapediatrics.2020.1948

Cross-sectional study including 48 children with COVID-19 (median age 13 years) admitted to 46 North American pediatric ICUs between March 14 and

April 3, 2020. Forty patients (83%) had significant preexisting comorbidities and 18 (38%) required invasive ventilation. Targeted therapies were used in 28 patients (61%, mainly HCQ). Two patients (4%) died and 15 (31%) were still hospitalized, with 3 still requiring ventilatory support and 1 receiving extracorporeal membrane oxygenation.

Andina D, Noguera-Morel L, Bascuas-Arribas M, et al. **Chilblains in children in the setting of COVID-19 pandemic**. Pediatr Dermatol. 2020 May 9. PubMed: https://pubmed.gov/32386460. Full-text: https://doi.org/10.1111/pde.14215

Retrospective review (from Spain) of 22 children and adolescents with acute chilblain-like lesions [chilblain: Frostbeule (de), engelure (fr), sabañón (es), gelone (it), frieira (pt), 冻疮 (cn)]. All patients had lesions clinically consistent with chilblains of the toes or feet, with 3 also having lesions of the fingers. Pruritus and mild pain were the only skin symptoms elicited. All cases showed spontaneous marked improvement or complete healing.

14 May

Epidemiology

Salje J, Kiem CT, Lefrancq N, et al. **Estimating the burden of SARS-CoV-2 in France.** Science 13 May 2020. Full-text: https://doi.org/10.1126/science.abc3517

A suite of modeling analyses was used to characterize the dynamics of SARS-CoV-2 transmission in France and the impact of the lockdown on these dynamics. The authors estimated that 3.6% of infected individuals were hospitalized and 0.7% died. The lockdown reduced the reproductive number from 2.90 to 0.67. By 11 May 2020, authors project 2.8 million infections in France (or 4.4% of the population (range: 2.8–7.2)). Population immunity appeared to be insufficient to avoid a second wave.

Transmission

Halfmann PJ, Hatta M, Chiba S, et al. **Transmission of SARS-CoV-2 in Domestic Cats.** N Engl J Med. 2020 May 13. PubMed: https://pubmed.gov/32402157. Full-text: https://doi.org/10.1056/NEJMc2013400

Three domestic cats were inoculated with SARS-CoV-2. One day later, an uninfected cat was co-housed with each of the inoculated cats. All six cats became infected but none showed any symptoms. All cats had developed anti-

body titers on day 24. Are cats potential intermediate hosts in chains of human–cat–human transmission?

Hamiel U, Kozer E, Youngster I. **SARS-CoV-2 Rates in BCG-Vaccinated and Unvaccinated Young Adults.** JAMA. 2020 May 13. PubMed: https://pubmed.gov/32401274. Full-text: https://doi.org/10.1001/jama.2020.8189

Could it be possible that a BCG vaccination is protective? No. In this very large cohort of Israeli adults aged 35 to 41 years, BCG vaccination in childhood was associated with a very similar rate of positive test results for SARS-CoV-2 compared with no vaccination.

Diagnostics

Amanat F, Stadlbauer D, Strohmeier S, et al. **A serological assay to detect SARS-CoV-2 seroconversion in humans.** Nat Med. 2020 May 12. PubMed: https://pubmed.gov/32398876. Full-text: https://doi.org/10.1038/s41591-020-0913-5

A simple solution is the use of a binding assay, e.g. an enzyme-linked immunosorbent assay (ELISA), with recombinant antigen as substrate, especially if ELISA results correlate with neutralization assay results. The authors report the development of such an assay and provide a protocol for both recombinant antigen production as well as the ELISA methodology. The method is based on reactivity to the immunogenic S protein of the virus, is relatively simple and quick in its execution and can be performed at biosafety level 2 as it does not involve live virus.

Clinical

Puelles VG, Lütgehetmann M, Lindenmeyer MT, et al. **Multiorgan and Renal Tropism of SARS-CoV-2.** NEJM May 13, 2020. Full-text: https://www.nejm.org/doi/full/10.1056/NEJMc2011400

SARS-CoV-2 viral load was quantified in autopsy tissue samples obtained from 22 deceased patients. The highest levels were detected in the respiratory tract, but lower levels were also detected in the kidneys, liver, heart, brain, and blood, indicating a broad organotropism of SARS-CoV-2.

Zhou J, Li C, Liu X et al. **Infection of bat and human intestinal organoids by SARS-CoV-2.** Nat Medicine 2020. https://doi.org/10.1038/s41591-020-0912-6

Authors demonstrate active replication of SARS-CoV-2 in human intestinal organoids and isolation of infectious virus from the stool specimen of a patient with diarrheal COVID-19. They also established the first expandable organoid culture system of bat intestinal epithelium and present evidence that SARS-CoV-2 can infect bat intestinal cells.

Liang W, Liang H, Ou L, et al. **Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19.** JAMA Intern Med. 2020 May 12. PubMed: https://pubmed.gov/32396163. Full-text: https://doi.org/10.1001/jamainternmed.2020.2033

Using a development cohort of 1590 patients and a validation cohort of 710 patients, a risk score was developed (COVID-GRAM) to predict development of critical illness. The risk factors used in the score were: chest radiography abnormality, age, hemoptysis, dyspnea, unconsciousness, number of comorbidities, cancer history, neutrophil-to-lymphocyte ratio, lactate dehydrogenase, and direct bilirubin. The score has been translated into an online risk calculator that is freely available to the public (http://118.126.104.170/)

Comorbidities

Latif F, Farr MA, Clerkin KJ, et al. **Characteristics and Outcomes of Recipients of Heart Transplant With Coronavirus Disease 2019.** JAMA Cardiol. 2020 May 13. PubMed: https://pubmed.gov/32402056. Full-text: https://doi.org/10.1001/jamacardio.2020.2159

Is there a higher mortality risk in heart transplanted patients? Probably yes. In this case series of 28 patients who had received a heart transplant in a large academic center (New York), 22 patients (79%) were hospitalized. At the end of the follow-up, 4 remained hospitalized and 7 (25%) had died.

Treatment

Wu Y, Wang F, Shen C, et al. **A noncompeting pair of human neutralizing antibodies block COVID-19 virus binding to its receptor ACE2.** Science. 2020 Jun 12;368(6496):1274-1278. PubMed: https://pubmed.gov/32404477. Full-text: https://doi.org/10.1126/science.abc2241 ● (IMPORTANT)

Neutralizing antibodies are promising candidates for prophylactic and therapeutic treatment against COVID-19 virus. Four human-origin monoclonal antibodies were isolated from a convalescent patient, all of which displayed neutralization abilities. B38 and H4 block the binding between virus S protein RBD and cellular receptor ACE2. A competition assay indicates their different epitopes on the RBD. In a mouse model, both antibodies reduced virus titers in infected lungs. The RBD-B38 complex structure revealed that most residues on the epitope overlap with the RBD-ACE2 binding interface, explaining the blocking effect and neutralizing capacity.

Pediatrics

Mehta NS, Mytton OT, Mullins EWS, et al. **SARS-CoV-2 (COVID-19): What do we know about children? A systematic review.** Clin Infect Dis. 2020 May 11. PubMed: https://pubmed.gov/32392337. Full-text: https://doi.org/10.1093/cid/ciaa556

According to this review of 24 studies, children appear to be less affected by COVID-19 than adults by observed rate of cases in large epidemiological studies. Limited data on attack rate indicate that children are just as susceptible to infection. Data on clinical outcomes are scarce but include several reports of asymptomatic infection and a milder course of disease in young children, though radiological abnormalities have been noted.

15 May

Immunology

Grifoni A, Weiskopf D, Ramirez SI, et al. **Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals.** Cell. 2020 Jun 25;181(7):1489-1501.e15. PubMed: https://pubmed.gov/32473127. Full-text: https://doi.org/10.1016/j.cell.2020.05.015 ●● (Outstanding)

Cellular response is a major knowledge gap. This important study identified circulating SARS-CoV-2–specific CD8 and CD4 T cells in around 70 and 100% of 20 COVID-19 convalescent patients, respectively. CD4 T cell responses to the spike protein were robust and correlated with the magnitude of IgG titers. Of note, the authors detected SARS-CoV-2–reactive CD4 T cells in 40-60% of unexposed individuals, suggesting cross-reactive T cell recognition between circulating seasonal coronaviruses and SARS-CoV-2.

Bordoni V, Sacchi A, Cimini E, et al. **An inflammatory profile correlates with decreased frequency of cytotoxic cells in COVID-19.** Clin Infect Dis. 2020 May 1. PubMed: https://pubmed.gov/32407466. Full-text: https://doi.org/10.1093/cid/ciaa577

The increase in inflammatory mediators is correlated with a reduction of innate and adaptive cytotoxic antiviral function. Authors found a lower perforin+ NK cell number in 7 intensive care unit (ICU) patients compared to 41 non-ICU patients, suggesting an impairment of the immune cytotoxic arm as a pathogenic mechanism.

Diagnostics

Kucirka LM, Lauer SA, Laeyendecker O, et al. **Variation in False-Negative Rate of Reverse Transcriptase Polymerase Chain Reaction–Based SARS-CoV-2 Tests by Time Since Exposure**. Annals Int Med 2020, May 13. https://doi.org/10.7326/M20-1495. Full-text: https://www.acpjournals.org/doi/10.7326/M20-1495 ● (IMPORTANT)

The authors estimated the false-negative rate by day since infection, reviewing 7 studies with a total of 1,330 respiratory samples analyzed by RT-PCR. Over the 4 days before symptom onset, the rate decreased from 100% to 67%. On the day of symptom onset (day 5), the rate was 38%, decreased to 20% (day 8) and then began to increase again, from 21% (day 9) to 66% (day 21). If clinical suspicion is high, infection should not be ruled out on the basis of RT-PCR alone. The false-negative rate is lowest 3 days after onset of symptoms, or approximately 8 days after exposure.

Mathur F, Mathur S. **Antibody Testing For Covid-19: Can It Be Used As A Screening Tool In Areas With Low Prevalence**? American Journal of Clinical Pathology 2020, May 15. Full-text: https://academic.oup.com/ajcp/advance-article/doi/10.1093/ajcp/aqaa082/5837473

Answer is: probably no, because specificity is not 100%. Average sensitivity and specificity of FDA-approved antibody tests is 84.9% and 98.6%, respectively. Given the variable prevalence of COVID-19 (1%-15%) in different places, the positive predictive value can be statistically as low as 30% to 50% in areas with low prevalence.

Clinical

Marinho PM, Marcos AAA, Romano AC, Nascimento H, Belfort R Jr. **Retinal findings in patients with COVID-19**. Lancet. 2020 May 12PubMed: https://pubmed.gov/32405105. Full-text: https://doi.org/10.1016/S0140-6736(20)31014-X

COVID-19 and the eye: Using optical coherence tomography (OCT) as a non-invasive imaging technique that is useful for demonstrating subclinical retinal changes, the authors describe their experience in 12 adult patients (9 were physicians). All patients showed hyper-reflective lesions at the level of the ganglion cell and the inner plexiform layers more prominently at the papillomacular bundle in both eyes.

Treatment

Amir Qaseem A, Yost J, Etxeandia-Ikobaltzeta I, et al. **Should Clinicians Use Chloroquine or Hydroxychloroquine Alone or in Combination With Azithromycin for the Prophylaxis or Treatment of COVID-19**? Annals Internal Medicine May 13, 2020. Full-text: https://www.acpjournals.org/doi/10.7326/M20-1998

The answer is: no. These "Living Practice Points" From the American College of Physicians (based on an evidence review conducted on 17 April 2020) very clearly say that both drugs should not be used as prophylaxis or treatment of patients with COVID-19. In light of known harms and very uncertain evidence of benefit in patients with COVID-19, however, clinicians may treat hospitalized COVID-19–positive patients in the context of a clinical trial.

Schoergenhofer C, Jilma B, Stimpfl T, et al. **Pharmacokinetics of Lopinavir and Ritonavir in Patients Hospitalized With Coronavirus Disease 2019 (COVID-19)**. Annals of Internal Medicine 12 May 2020. Full-text: https://www.acpjournals.org/doi/10.7326/M20-1550

Although lopinavir trough levels were approximately 2-fold higher in 8 COVID-19 patients than in HIV infected patients receiving the same dose, levels may be too low for COVID-19. Approximately 60- to 120-fold higher concentrations are required to reach the assumed EC50 at trough levels, making effective treatment of COVID-19 with lopinavir/r at the currently used dose unlikely.

Wang X, Cao R, Zhang H, et al. **The anti-influenza virus drug, arbidol is an efficient inhibitor of SARS-CoV-2 in vitro**. Cell Discov. 2020 May 2;6:28. PubMed: https://pubmed.gov/32373347. Full-text: https://doi.org/10.1038/s41421-020-0169-8

Among six anti-influenza drugs, only arbidol efficiently inhibited SARS-CoV-2 infection in cell experiments. Functionally, arbidol appeared to block virus entry by impeding viral attachment and release from the endolysosomes. However, higher dosages may be required to achieve therapeutic efficacy (800 mg?) than the current dose (200 mg, 3 times/day) as recommended by the Chinese Guidelines.

Li Y, Xie Z, Lin W, et al. **Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: an exploratory randomized controlled trial**. Med (Cell Press) 2020. Full-text: https://doi.org/10.1016/j.medj.2020.04.001

This study randomized a total of 86 patients with mild to moderate COVID-19 to receive lopinavir/r, arbidol (200 mg TID) or no antiviral medication (control). The primary endpoint, the rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid, was similar between groups. There were no differences between groups in the secondary endpoints, the rates of antipyresis, cough alleviation, or improvement of chest CT at days 7 or 14. Again, dosage of arbidol may have been too low.

Pediatric

DeBiasi RL, Song X, Delaney M, et al. **Severe COVID-19 in Children and Young Adults in the Washington, DC Metropolitan Region**. J Pediatr. 2020 May 13. PubMed: https://pubmed.gov/32405091. Full-text: https://doi.org/10.1016/j.jpeds.2020.05.007

From 177 infected pediatric patients, 44 were hospitalized and 9 were critically ill. Of these, 6/9 were adolescents and young adults > 15 years of age. Although asthma was the most prevalent underlying condition overall, it was not more common among patients with severe disease. There were no significant differences in the presence of underlying conditions overall or any specific underlying diagnosis. Asthma exacerbation is not the primary determinant of more severe disease.

16 May

Epidemiology

Dehning K, Zierenberg , Spitzner FP. **Inferring change points in the spread of COVID-19 reveals the effectiveness of interventions**. Science 15 May 2020. Full-text: https://doi.org/10.1126/science.abb9789

Focusing on the COVID-19 spread in Germany, these elegant models detected three change points in the effective growth rate that correlated well with interventions. First, the spreading rate decreased from 0.43 to 0.25, the decrease initiating around March 7 (cancellation of large public events, such as trade fairs and soccer matches). Second, the rate decreased further to 0.15 (around March 16, closure of schools, childcare facilities, non-essential stores). Third, the spreading rate decreased further to 0.09 (initiated around March 24, strict contact ban). While the first two change points were not sufficient to trigger a shift from the growth of novel cases to a decline, the third brought this crucial reversal. This model can be used for future scenarios – the code is freely available and can be readily adapted to any country. The paper also highlights the impact of time: delaying restrictions by only 5 days may have an incredible impact on case numbers. Sleep well, Boris, Jair, Mark etc.

Transmission

Zheng L, Wang X, Zhou C, et al. **Analysis of the infection status of the health care workers in Wuhan during the COVID-19 outbreak: A cross-sectional study**. Clinical Infectious Diseases 2020, May 15. Full-text: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa588/5837357

By now, the most comprehensive data on infections among HCW. Among 2,457 infected HCW in Wuhan, China, 52% were nurses, 34% were doctors and 14% were medical staff. Case infection rate of nurses (2.22%) was higher than that of doctors (1.92%). The majority (89%) came from general hospitals. The case infection rate of HCW (2.10%) was dramatically higher than that of non-HCW (0.43%). The case fatality rate of was significantly lower (0.69% versus 5.30%).

Diagnostics

Joung J, Ladha A, Saito M, et al. **Point-of-care testing for COVID-19 using SHERLOCK diagnostics**. Full-text: https://doi.org/10.1101/2020.05.04.20091231.

Point-of-care testing is based on easy-to-use devices to facilitate testing outside laboratory settings. They are eagerly awaited. On May 6, the FDA granted an emergency use authorization for a clustered regularly interspaced short palindromic repeats (CRISPR)-based SARS-CoV-2 fluorescent assay marketed by Sherlock Biosciences. This method gives results in an hour and has successfully diagnosed 12 positive and 5 negative COVID-19 patients, with at least 2 of 3 replicates scoring positive in infected persons. However, use still remains limited to laboratories certified to perform high-complexity tests. On May 6, FDA also authorized Quidel's Sofia 2 SARS Antigen Fluorescent Immunoassay. The test must be read on a dedicated analyser and detects SARS-CoV-2 nucleocapsid protein from nasopharyngeal swabs in 15 min. According to the manufacturer, the assay demonstrated acceptable clinical sensitivity and detected 47/59 infections (80%). Unfortunately, no peer-reviewed papers have been published to date.

Comorbidities

Mackey K, King VJ, Gurley S. **Risks and Impact of Angiotensin-Converting Enzyme Inhibitors or Angiotensin-Receptor Blockers on SARS-CoV-2 Infection in Adults. A Living Systematic Review**. Annals Internal Medicine 2020, May 15. Full-text: https://www.acpjournals.org/doi/10.7326/M20-1515

According to this review (data cut on May 4), evidence is of moderate certainty that ACEI and ARB use is not associated with a higher likelihood of receiving a positive SARS-CoV-2 test result. Evidence is of high certainty (14 observational studies, involving 23,565 adults) that neither medication is associated with more severe COVID-19 illness. Four registered randomized trials plan to evaluate ACEIs and ARBs for treatment of COVID-19. For more information, see our special from May 4: https://covidreference.com/top-10-may-4.

Severe COVID-19

Berlin DA, Gulick RM, Martinez FJ. **Severe Covid-19**. May 15, 2020. Full-text: https://www.nejm.org/doi/full/10.1056/NEJMcp2009575 ● (IMPORTANT)

Comprehensive overview about current knowledge (and knowledge gaps) about treatment of patients who develop severe disease. Basics of respiratory

care, ventilation management and supportive care. Areas of uncertainties are also discussed.

Lax SF, Skok K, Zechner P. **Pulmonary Arterial Thrombosis in COVID-19 With Fatal Outcome: Results From a Prospective, Single-Center, Clinicopathologic Case Series**. Annals Int Med 2020, May 14. Full-text: https://www.acpjournals.org/doi/10.7326/M20-2566

The next autopsy study on 11 deceased patients with COVID-19 (10 selected randomly). Death may be caused by the thrombosis observed in segmental and subsegmental pulmonary arterial vessels despite the use of prophylactic anticoagulation.

Deshpande C. **Thromboembolic Findings in COVID-19 Autopsies: Pulmonary Thrombosis or Embolism?** Annals Int Med 2020, May 15. Full-text: https://doi.org/10.7326/M20-3255.

Well-balanced editorial, condensing current knowledge on the contributions of pulmonary thrombosis, embolism, or their combination to deaths of patients with COVID-19. Some studies have found pulmonary embolism with or without deep venous thrombosis, as well as presence of recent thrombi in prostatic venous plexus, in patients with no history of VTE, suggesting de novo coagulopathy in these patients with COVID-19. Others have highlighted changes consistent with thrombosis occurring within the pulmonary arterial circulation, in the absence of apparent embolism.

Treatment

Grein J, Ohmagari N, Shin D, et al. **Compassionate Use of Remdesivir for Patients with Severe Covid-19**. N Engl J Med. 2020 Apr 10. PubMed: https://pubmed.gov/32275812. To the editor: https://www.nejm.org/doi/10.1056/NEJMc2015312#sa1

Four letters, making critical comments on the NEJM paper about the remdesivir compassionate use program. We have discussed many of these issues on April 16, see here: https://covidreference.com/remdesivir

Cavalli G, De Luca G, Campochiaro C, et al. **Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyper-inflammation: a retrospective cohort study**. Lancet Rheumatol 2020. Full-text:

https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30127-2/fulltext

This retrospective cohort study at the San Raffaele Hospital in Milan, Italy, included patients with moderate-to-severe ARDS and hyperinflammation (serum C-reactive protein, CRP ≥100 mg/L) who were managed with non-invasive ventilation and HCQ and lopinavir/r. At 21 days, treatment with high-dose anakinra was associated with reductions in CRP and progressive improvements in respiratory function in 21/29 (72%) patients.

Dimopoulos G, de Mast Q, Markou N, et al. **Favorable anakinra responses in severe COVID-19 patients with secondary hemophagocytic lymphohistiocytosis**. Cell Host and Microbe 2020, May 14. Full-text: https://doi.org/10.1016/j.chom.2020.05.007

Another small case series of critically ill patients with secondary hemophagocytic lymphohistocytosis (sHLH) characterized by pancytopenia, hypercoagulation, acute kidney injury and hepatobiliary dysfunction. At the end of treatment, ICU patients had less need for vasopressors and significantly improved respiratory function. Although 3/8 patients died, the mortality was lower than historical series of patients with sHLH in sepsis.

17 May

Epidemiology

Banerjee A, Pasea L, Harris S, et al. **Estimating excess 1-year mortality associated with the COVID-19 pandemic according to underlying conditions and age: a population-based cohort study**. Lancet. 2020 May 12. PubMed: https://pubmed.gov/32405103. Full-text: https://doi.org/10.1016/S0140-6736(20)30854-0 - OurRisk.CoV (online tool): http://covid19-phenomics.org/PrototypeOurRiskCoV.html

The authors provide a simple model and an online tool for understanding excess mortality over 1 year from the COVID-19 pandemic, based on age, sex, and underlying condition-specific estimates. For the UK, 293,991 deaths would be expected in a "do-nothing scenario". With mitigation (ie, less rigorous and voluntary measures), authors predict between 18,000 and 37,000 deaths.

Virology

Gao Y, Yan L, Huang Y, et al. **Structure of the RNA-dependent RNA polymerase from COVID-19 virus**. Science 15 May 2020: Vol. 368, Issue 6492, pp. 779-782. Full-text: https://doi.org/10.1126/science.abb7498

Another study analyzing the RNA synthesizing machine. Using cryoelectron microscopy, the authors determined a 2.9 angstrom resolution structure of the RNA-dependent RNA polymerase (also known as nsp12), which catalyzes the synthesis of viral RNA, in complex with two cofactors, nsp7 and nsp8.

Immunology

Blanco-Melo D, Nilsson-Payant BE, Liu WC, et al. **Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19.** Cell. 2020 May 28;181(5):1036-1045.e9. PubMed: https://pubmed.gov/32416070. Full-text: https://doi.org/10.1016/j.cell.2020.04.026 ●● (OUTSTANDING)

Incredible in-depth analysis of host response to SARS-CoV-2 and other human respiratory viruses in cell lines, primary cell cultures, ferrets, and COVID-19 patients. Data consistently revealed a unique and inappropriate inflammatory response to SARS-CoV-2 which is imbalanced with regard to controlling virus replication versus activation of the adaptive immune response. It is defined by low levels of type I and III interferons juxtaposed to elevated chemokines and high expression of IL-6. The authors propose that reduced innate antiviral defenses coupled with exuberant inflammatory cytokine production are the defining and driving features of COVID-19. Given this dynamic, treatments for COVID-19 have less to do with the IFN response and more to do with controlling inflammation.

Transmission

Böhmer MM, Buchholz U, Corman VM. **Investigation of a COVID-19 outbreak in Germany resulting from a single travel-associated primary case: a case series**. Lancet Infect Dis 2020, May 15. Full-text: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30314-5/fulltext

The German patient zero was a Chinese person who visited Germany for professional reasons. Sixteen persons became infected. This thorough description of transmission dynamics revealed that attack rates were 75% among members of a household cluster in common isolation, 10% among household contacts only together until isolation of case, and 5% among non-household high-risk contacts. Although most patients presented with only mild and non-

specific symptoms, infectiousness before or on the day of symptom onset was substantial. Additionally, the incubation period was often very short and false-negative tests occurred.

Hamner L, Dubbel P, Capron I, et al. **High SARS-CoV-2 Attack Rate Following Exposure at a Choir Practice - Skagit County, Washington, March 2020**. MMWR Morb Mortal Wkly Rep. 2020 May 15;69(19):606-610. PubMed: https://pubmed.gov/32407303. Full-text: https://doi.org/10.15585/mmwr.mm6919e6 ● (IMPORTANT)

What a disaster! Among 61 persons who attended a March 10 choir practice, 32 confirmed and 20 probable secondary COVID-19 cases occurred. Three were hospitalized (5.7%), and two died (3.7%). The 2.5 hour singing practice provided several opportunities for droplet and fomite transmission, including members sitting close to one another, sharing snacks, and stacking chairs at the end of the practice. Chairs were arranged in six rows of 20 chairs each, spaced 6–10 inches apart with a center aisle dividing left and right stages. Most choir members sat in their usual rehearsal seats (see full paper for more details). The act of singing itself might have contributed to transmission through emission of aerosols, which is affected by the loudness of vocalization.

Clinical

New York City Department of Health and Mental Hygiene (DOHMH) COVID-19 Response Team. **Preliminary Estimate of Excess Mortality During the COVID-19 Outbreak — New York City, March 11–May 2, 2020**. Morb Mortal Wkly Rep 2020; 69:603-605. Full-text: http://dx.doi.org/10.15585/mmwr.mm6919e5

Anybody out there still doubting excess mortality? Please show them this paper, including the most impressive figure of the day. It depicts the total excess all-cause deaths in New York, calculated as observed deaths minus expected deaths as determined by a seasonal regression model using mortality data from the period January 1, 2015–May 2, 2020.

Smith JC, Sauswille EL, Girish V, et al. **Cigarette smoke exposure and inflammatory signaling increase the expression of the SARS-CoV-2 receptor ACE2 in the respiratory tract**. Development Cell, May 16, 2020. Full-text: https://doi.org/10.1016/j.devcel.2020.05.012

Quit smoking, immediately! Lung ACE2 levels do not vary by age or sex, but smokers exhibit upregulated ACE2. Cigarette smoke triggers an increase in ACE2+ cells by driving secretory cell expansion. The overabundance of ACE2 in the lungs of smokers may partially explain why smokers are significantly more likely to develop severe COVID-19.

Lusignan S, Dorward J, Correa A, et al. **Risk factors for SARS-CoV-2 among patients in the Oxford Royal College of General Practitioners Research and Surveillance Centre primary care network: a cross-sectional study**. Lancet Inf Dis 2020, May 15. Full-text: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30371-6/fulltext - PDF: https://doi.org/10.1016/S1473-3099(20)30371-6

Well, it's not that easy (quitting smoking and finding clinical correlations to cell experiments). Within a surveillance centre primary care sentinel network, multivariable logistic regression models were used to identify risk factors for positive SARS-CoV-2 tests. Of note, active smoking was associated with decreased odds (yes, decreased: adjusted OR 0.49, 95% CI 0.34–0.71). According to the authors, their findings should not be used to conclude that smoking prevents SARS-CoV-2 infection, or to encourage ongoing smoking. Several explanations are given, such as selection bias (smokers are more likely to have a cough, more frequent testing could increase the proportion of smokers with negative results). Active smoking might also affect RT-PCR test sensitivity.

Severe COVID-19

Elharrar X, Trigui Y, Dols AM, et al. **Use of Prone Positioning in Nonintubated Patients With COVID-19 and Hypoxemic Acute Respiratory Failure**. JAMA. May 15, 2020. Full-text: https://jamanetwork.com/journals/jama/fullarticle/2766292

This prospective, before-after study was conducted in Aix-en-Provence (France) among 24 awake, non-intubated, spontaneously breathing patients with COVID-19 and hypoxemic acute respiratory failure requiring oxygen supplementation. Efficacy of prone positioning was only moderate. Only 63% were able to tolerate PP for more than 3 hours. Oxygenation increased in only 25% and was not sustained in half of those after resupination. However, prone sessions were short, partly because of limited patient tolerance.

Telias I, Katira BH, Brochard L, et al. **Is the Prone Position Helpful During Spontaneous Breathing in Patients With COVID-19?** JAMA. Published online May 15, 2020. Full-text: https://doi.org/10.1001/jama.2020.8539 ● (IMPORTANT)

This editorial summarizes current knowledge on prone position. PP during spontaneous and assisted breathing may become a therapeutic intervention. Tolerance may be a limitation of the technique and the benefits of short sessions remain to be seen. Several larger trials are ongoing, addressing the question whether PP prevents intubation.

18 May

Virology

Munster VJ, Feldmann F, Williamson BN, et al. **Respiratory disease in rhesus macaques inoculated with SARS-CoV-2.** Nature 2020. https://doi.org/10.1038/s41586-020-2324-7 ● (IMPORTANT)

SARS-CoV-2 caused respiratory disease in 8 infected rhesus macaques, lasting 8-16 days. Pulmonary infiltrates were visible in lung radiographs. High viral loads were detected in swabs as well as in bronchoalveolar lavages. Taken together, this rhesus macaque "model" recapitulates COVID-19, with regard to virus replication and shedding, the presence of pulmonary infiltrates, histological lesions and seroconversion.

Sia SF, Yan L, Chin AWH. et al. **Pathogenesis and transmission of SARS-CoV-2 in golden hamsters**. Nature 2020. https://doi.org/10.1038/s41586-020-2342-5

In most cases, you don't need monkeys. Golden Syrian hamsters may also work as an animal model. SARS-CoV-2 transmitted efficiently from inoculated hamsters to naïve hamsters by direct contact and via aerosols. Transmission via fomites in soiled cages was less efficient. Inoculated and naturally-infected hamsters showed apparent weight loss, and all animals recovered with the detection of neutralizing antibodies.

Immunology

Bojkova D, Klann K, Koch B et al. **Proteomics of SARS-CoV-2-infected host cells reveals therapy targets**. Nature 2020, May 14. https://doi.org/10.1038/s41586-020-2332-7

The authors describe a SARS-CoV-2 cell infection system to determine changes in host-cell pathways upon infection, resulting from host-cell (antiviral) responses or viral effector proteins, and assess some potential inhibitors.

Transmission

Sit TH, Brackman CJ, Ip SM et al. **Infection of dogs with SARS-CoV-2.** Nature 2020. https://doi.org/10.1038/s41586-020-2334-5. Full-text: https://www.nature.com/articles/s41586-020-2334-5#citeas

Two out of fifteen dogs (one Pomeranian and one German Shepherd) from households with confirmed human cases of COVID-19 in Hong Kong were found to be infected. Both dogs remained asymptomatic but later developed antibody responses detected using plaque reduction neutralization assays. Genetic analysis suggested that the dogs caught the virus from their owners. It still remains unclear whether infected dogs can transmit the virus to other animals or back to humans.

Seyer A, Sanlidag T. **Solar ultraviolet radiation sensitivity of SARS-CoV-2**. Lancet Microbe 2020, 1:e8-e9, May, 2020. Full-text: https://doi.org/10.1016/S2666-5247(20)30013-6

Sunlight reaching the ground lacks germicidal ultraviolet C radiation. According to the authors, scientists should avoid voicing assumptions on the effect of sunlight on viral transmission.

Clinical

Bolay H, Gul A, Baykan B. **COVID-19 is a Real Headache!** Headache 2020 May 15. PubMed: https://pubmed.gov/32412101. Full-text: https://doi.org/10.1111/head.13856

Nice overview on a symptom which is frequently overlooked in clinical practice. Headache was observed in 11-34% of hospitalized patients (in 6-10% as presenting symptom). Significant features are moderate to severe, bilateral headache with pulsating or pressing quality in the temporo-parietal, forehead or periorbital region. The most striking features are sudden to gradual onset and poor response to common analgesics. Possible pathophysiological mech-

anisms include activation of peripheral trigeminal nerve endings by SARS-CoV2 directly or through vasculopathy and/or increased circulating pro-inflammatory cytokines and hypoxia.

Comorbidities

Tschopp J, L´Huillier AG, Mombelli M, et al. **First experience of SARS-CoV-2 infections in solid organ transplant recipients in the Swiss Transplant Cohort Study**. Am J Transplant 2020 May 15. PubMed: https://pubmed.gov/32412159. Full-text: https://doi.org/10.1111/ajt.16062

Data from Switzerland. Overall, 21 patients were included with a median age of 56 years (10 kidney, 5 liver, 1 pancreas, 1 lung, 1 heart and 3 combined transplantations). Ninety-five percent and 24% of patients required hospitalization and ICU admission, respectively. After a median of 33 days of follow-up, 16 patients were discharged, 3 were still hospitalized and 2 patients died.

Treatment

Cao Y, Sui B, Guo X, et al. **Potent neutralizing antibodies against SARS-CoV-2 identified by high-throughput single-cell sequencing of convalescent patients' B cells**. Cell 2020, May 17, 2020. Full-text: https://doi.org/10.1016/j.cell.2020.05.025

Fantastic work, identifying 14 potent neutralizing antibodies by high-throughput single B-cell RNA- sequencing from 60 convalescent patients. The most potent one, BD-368-2, exhibited an IC50 of 15 ng/mL against SARS-CoV-2. This antibody displayed strong therapeutic and prophylactic efficacy in mice, the epitope overlaps with the ACE2 binding site. Time to go into the clinic!

Pawlotsky JM. **SARS-CoV-2 pandemic : Time to revive the cyclophilin inhibitor alisporivir**. Clin Infect Dis 2020 May 15. PubMed: https://pubmed.gov/32409832. Full-text: https://doi.org/10.1093/cid/ciaa587

Some arguments supporting the use of alisporivir, a non-immunosuppressive analogue of cyclosporine A developed by Novartis. Arguments include the cyclophilin-dependency of the lifecycle of many coronaviruses and preclinical data on antiviral and cytoprotective properties.

Pediatrics

Garazzino S, Montagnani C, Dona D, et al. **Multicentre Italian study of SARS-CoV-2 infection in children and adolescents, preliminary data as at 10 April 2020.** Euro Surveill. 2020 May;25(18). PubMed: https://pubmed.gov/32400362. Full-text: https://doi.org/10.2807/1560-7917.ES.2020.25.18.2000600

The largest cohort of European children and adolescents, comprising 168 patients with laboratory-confirmed COVID-19. Nearly 40% were under 1 year of age and the majority of them were hospitalized. However, all patients, including those with comorbidities, recovered fully, and no sequelae were reported at the last follow-up.

19 May

Diagnostics

Krammer F, Simon V. **Serology assays to manage COVID-19**. Science 15 May 2020. Full-text: https://doi.org/10.1126/science.abc1227

Nice overview on different platforms, including binding assays such as enzyme-linked immunosorbent assays (ELISAs), lateral flow assays, or Western blot–based assays. In addition, functional assays that test for virus neutralization, enzyme inhibition, or bactericidal assays can also inform on antibody-mediated immune responses. Many caveats and open questions with regard to antibody testing are also discussed.

Teng J, Dai J, Su Y, et al. **Detection of IgM and IgG antibodies against SARS-CoV-2 in patients with autoimmune diseases**. Lancet Rheumatology 2020, May 18. Full-text: https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30128-4/fulltext.

No cross-reactivity between autoantibodies and SARS-CoV-2 antibodies: in 290 older serum samples from patients with rheumatoid arthritis, systemic lupus erythematosus, and Sjogren's syndrome, no IgG and IgM antibodies against SARS-CoV-2 were detected.

Lv H, Wu, NC, Tsang OT, et al. **Cross-reactive antibody response between SARS-CoV-2 and SARS-CoV infections**. Open Access Published: May 17, 2020. Full-text: https://doi.org/10.1016/j.celrep.2020.107725

While cross-reactivity in antibody binding to the spike protein is common, cross-neutralization of the two live SARS viruses may be rare, indicating the presence of a non-neutralizing antibody response to conserved epitopes in the spike.

Gupta S, Parker J, Smits S, Underwood J, Dolwani S. **Persistent viral shedding of SARS-CoV-2 in faeces - a rapid review**. Colorectal Dis. 2020 May 17. PubMed: https://pubmed.gov/32418307. Full-text: https://doi.org/10.1111/codi.15138

Combining study results of 26 studies, 54% of those patients tested for fecal RNA were positive. Duration of fecal viral shedding ranged from 1 to 33 days after a negative nasopharyngeal swab. Evidence is still insufficient to suggest that COVID-19 is transmitted via fecally shed virus.

Clinical

Caussy C, Pattou RF, Wallet F, et al. **Prevalence of obesity among adult inpatients with COVID-19 in France**. Lancet Diabetes Endocrinology 2020, May 18. Full-text: https://www.thelancet.com/journals/landia/article/PIIS2213-8587(20)30160-1/fulltext

Analysis of 340 hospitalized patients in Lyon with information on BMI. In multivariable analyses, odds of critical COVID-19 versus non-critical COVID-19 were higher in patients with obesity than in patients without obesity when adjusted for age and sex. The association remained significant after adjustment for the other potential specific risk factors, with age-sex-adjusted ORs ranging between 1·80 and 2·03.

Rogers JP, Chesney E, Oliver D, et al. **Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic**. Lancet Psychiatry 2020, May 18. Full-text: https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(20)30203-0/fulltext

It's time to talk about possible psychiatric and neuropsychiatric implications of the current pandemic. According to this systematic review, preliminary data suggest that patients with COVID-19 might experience delirium, confusion, agitation, and altered consciousness, as well as symptoms of depression, anxiety, and insomnia. High-quality peer-reviewed research into psychiatric

symptoms as well as into potential mitigating factors and interventions is needed.

Piccininni M, Rohmann JL, Foresti L, et al. **Use of all cause mortality to quantify the consequences of covid-19 in Nembro, Lombardy: descriptive study**. BMJ 2020, May 14. Full-text: https://doi.org/10.1136/bmj.m1835 ● (IMPORTANT)

One common argument in the current discussion is that some of the people who died "with" COVID-19 did not actually die "from" it. This would overestimate the "real" mortality. This is probably true. However, the opposite is also true – that many who died from the infection without testing positive never contribute to the official death toll. In the small town of Nembro (around 11,500 residents) that was among the first Italian cities hit by COVID-19, monthly all-cause mortality between 2012 and February 2020 fluctuated around 10 per 1000 person years, with a maximum of 21.5. In March 2020, mortality reached a peak of 154.4 (driven by older men) and decreased to 23.0 in early April. From the outbreak onset until 11 April 2020, only half (85/166) of deaths had a confirmed COVID-19 diagnosis. The full implications of this crisis can only be completely understood if all-cause mortality in a given region and time frame is considered.

Severe COVID-19

Heman-Ackah SM, Su YS, Spadola M, MD. **Neurologically Devastating Intraparenchymal Hemorrhage in COVID-19 Patients on Extracorporeal Membrane Oxygenation: A Case Series**. Neurosurgery 2020. Full-text: https://doi.org/10.1093/neuros/nyaa198

Two patients required ECMO for refractory hypoxia secondary to COVID-19 and developed neurologically devastating intra-parenchymal hemorrhage despite lacking the classical risk factors. Authors recommend CT screening to identify brain injury that would otherwise go undetected due to the poor reliability of classic coagulation markers as accurate clinical predictors of hemorrhage in this cohort, as well as the inability to perform neurological assessments in the setting of paralysis, sedation, and proning.

Comorbidities

Arjomandi Rad A, Vardanyan R, Tas NR. **Ibuprofen and thromboembolism in SARS-COV2**. J Thromb Haemost. 2020 May 16. PubMed: https://pubmed.gov/32415902. Full-text: https://doi.org/10.1111/jth.14901

Review of the literature on thromboembolic events (TE) associated with COVID-19. The causation between the effects of ibuprofen and TE remains speculative. The role of ibuprofen on a vascular level remains unclear as well as whether ibuprofen is able to interact with SARS-CoV-2 through some mechanism. However, the authors recommend careful consideration to avoiding a high dosage of ibuprofen in subjects at particular risk of thromboembolic events.

Treatment

Coomes EA, Haghbayan H. **Favipiravir, an antiviral for COVID-19**? J Antimicrob Chemother. 2020 May 17. PubMed: https://pubmed.gov/32417899. Full-text: https://doi.org/10.1093/jac/dkaa171

Why not favipiravir for COVID-19? This purine nucleoside analogue acts as a competitive inhibitor of RNA-dependent RNA polymerase and can be given orally (in contrast to remdesivir, another RdRp inhibitor). Authors give a brief overview on clinical studies. The results of several ongoing randomized controlled trials are eagerly awaited. 20 May

20 May

Transmission

Ortega R, Gonzalez M, Nozari A, et al. **Personal Protective Equipment and Covid-19**. NEJM 2020, May 19. Full-text: https://doi.org/1056/NEJMvcm2014809

Prevention works only through training and demonstrated competency in putting on and removing personal protective equipment (PPE). This video demonstrates a procedure for "donning and doffing" PPE.

James A, Eagle L, Phillips C. **High COVID-19 Attack Rate Among Attendees at Events at a Church — Arkansas, March 2020**. MMWR 2020, May 19. Full-text: http://dx.doi.org/10.15585/mmwr.mm6920e2

High transmission rates of SARS-CoV-2 have been reported from hospitals, long-term care facilities, family gatherings, choir practice. This report de-

scribes church events. In total, 35 confirmed COVID-19 cases occurred among 92 attendees at church events during March 6–11; estimated attack rates ranged from 38% to 78%. Of note, a higher proportion of adults aged 19–64 years and ≥65 years received positive test results than did younger persons.

Hastie CE, Mackay DF, Ho F, et al. **Vitamin D Concentrations and COVID-19 Infection in UK Biobank**. Diabetes Metab Syndr 2020 May 7;14(4):561-565. Full-text: https://doi.org/10.1016/j.dsx.2020.04.050

No link between vitamin D and infection risk. Of 348,598 UK biobank participants, 449 had confirmed COVID-19 infection. Ethnicity was associated with COVID-19 infection (blacks versus whites OR = 5.32, South Asians versus whites OR = 2.65). Vitamin D was not associated with COVID-19 infection, after adjustment for confounders. Vitamin D did not explain ethnic differences.

Diagnostics

Li Y, Zhao K, Wei H, et al. **Dynamic Relationship Between D-dimer and COVID-19 Severity**. Br J Haematol 2020 May 18. Full-text: https://doi.org/10.1111/bjh.16811

Testing coagulation profile for ten consecutive days since admission in 279 COVID-19 patients, this study gives some insights into the dynamic changes of D-dimer level that are of prognostic value.

Clinical

Michelozzi Paola, de'Donato Francesca, Scortichini Matteo, et al. **Mortality impacts of the coronavirus disease (COVID-19) outbreak by sex and age: rapid mortality surveillance system, Italy, 1 February to 18 April 2020**. Euro Surveill. 2020;25(19). Full-text: https://doi.org/10.2807/1560-7917.ES.2020.25.19.2000620

Old white men. From the start of the epidemic until 18 April, an overall 4,805 (+45%) excess deaths were observed in Italian cities, with a significantly higher excess in the north (+76%, +4,295 deaths) compared with the center and the south (+10%, +510 deaths). Overall, the excess in mortality was higher among men than among women in cities in the north vs the center and the south (men: +87% and +70% and women: +17% and +9%, respectively), with an increase in the trend by age. The greatest excess in the north was among elderly men (+76% in 65–74 year-olds, +89% in 75–84 year-olds and +102% in those 85 years and older). In central and southern Italy, the excess in mortality

among men was lower, with a statistically significant excess only among elderly men: +13% and +28%, respectively, in the 75–84 years and ≥85 years age group.

Zhang L, Feng X, Zhang D, et al. **Deep Vein Thrombosis in Hospitalized Patients With Coronavirus Disease 2019 (COVID-19) in Wuhan, China: Prevalence, Risk Factors, and Outcome**. Circulation 2020 May 18. Full-text: https://doi.org/10.1161/CIRCULATIONAHA.120.046702

The next study emphasizes the high thrombosis risk. Of 143 patients hospitalized with COVID-19 (aged 63 ± 14 years; 52% men), 66 patients developed lower extremity Deep Vein Thrombosis (DVT) (46.1%), among them 23 with proximal DVT. Compared with patients without DVT, patients were older and had a lower oxygenation index, a higher rate of cardiac injury, and worse prognosis. Multivariate analysis found CURB-65 score 3-5 (OR = 6.122), Padua prediction score ≥4 (OR = 4.016), and D-dimer >1.0 μg/ml (OR = 5.818) to be associated with DVT.

Comorbidities

Brenner Ej, Ungaro RC, Gearry RB, et al. **Corticosteroids, but Not TNF Antagonists, Are Associated With Adverse COVID-19 Outcomes in Patients With Inflammatory Bowel Diseases: Results From an International Registry**. Gastroenterology 2020 May 18. Full-text: https://doi.org/10.1053/j.gastro.2020.05.032

An important and large study, analysing 525 patients with IBD from 33 countries. Thirty-seven patients (7%) had severe COVID-19, and 16 patients died (3% case fatality rate). Risk factors for severe COVID-19 among IBD patients included increasing age, ≥2 comorbidities, systemic corticosteroids (aOR 6.9, 95% CI 2.3-20.5), and sulfasalazine or 5-aminosalicylate use (aOR 3.1, 95% CI 1.3-7.7). Maintaining remission with steroid-sparing treatments will be important in managing patients with IBD through this pandemic. However, a causal relationship cannot be definitively established. Notably, TNF antagonist treatment was not associated with severe COVID-19.

Solomon MD, McNulty EJ, Rana JS, et al. **The Covid-19 Pandemic and the Incidence of Acute Myocardial Infarction**. NEJM 2020, May 19. Full-text: HTTPS://DOI.ORG/10.1056/NEJMc2015630

In a large diverse community setting in California, the incidence of hospitalization for acute myocardial infarction declined after March 4 by up to 48%

more than would be expected on the basis of typical seasonal variation alone. Similar findings have been noted in northern Italy.

Severe COVID-19

George PM, Wells AU, Jenkins RG. **Pulmonary Fibrosis and COVID-19: The Potential Role for Antifibrotic Therapy**. Lancet Respir Med 2020 May 15; S2213-2600(20)30225-3. https://doi.org10.1016/S2213-2600(20)30225-3. Full-text: https://linkinghub.elsevier.com/retrieve/pii/S2213260020302253 ● (IMPORTANT)

This brilliant article gives an overview on the (potentially high) burden of fibrotic lung disease following SARS-CoV-2 infection. Post-viral fibrosis may lead to severe physiological impairment. Available antifibrotic therapies such as pirfenidone (a pyridone with a poorly understood mechanism of action) and the thyrosine kinase inhibitor nintedanib have broad antifibrotic activity regardless of etiology, and these drugs might have a role in attenuating profibrotic pathways in SARS-CoV-2 infection. Current knowledge and future strategies are discussed.

Treatment

Pinto D, Park YJ, Beltramello M, et al. **Cross-neutralization of SARS-CoV-2 by a Human Monoclonal SARS-CoV Antibody**. Nature 2020 May 18. Full-text: https://doi.org/10.1038/s41586-020-2349-y

The next interesting antibody study. The authors describe multiple monoclonal antibodies targeting SARS-CoV-2 spike identified from memory B cells of an individual who was infected with SARS-CoV in 2003. One antibody, named S309, potently neutralizes SARS-CoV-2 by engaging the S receptor-binding domain. Using cryo-electron microscopy and binding assays, authors show that S309 recognizes a glycan-containing epitope that is conserved within the sarbecovirus subgenus, without competing with receptor attachment.

Procedures

McGrath BA, Brenner MJ, Warrillow SJ, et al. **Tracheostomy in the COVID-19 Era: Global and Multidisciplinary Guidance**. Lancet Respir Med 2020 May 15. Full-text: https://doi.org/10.1016/S2213-2600(20)30230-7

This article provide detailed consensus guidelines and recommendations on the conduct and management of tracheostomy during the pandemic. All important issues such as timing of tracheostomy (delayed until at least day 10 of

mechanical ventilation and considered only when patients are showing signs of clinical improvement), optimal setting (hierarchic approach to operative location, enhanced PPE), optimal procedure as well as management after tracheostomy are discussed.

21 May

A Top 10 Speciel

An update on HIV infection in the current crisis

HIV infection is of particular interest in the current crisis. First, many patients take antiretroviral therapies that are thought to have some effects against SARS-CoV-2. Second, HIV serves as a model of cellular immune deficiency. Third and by the far most important point, the collateral damage caused by COVID-19 in the HIV population may be much higher than that of COVID-19 itself.

Inexplicably, information on the HIV population is still scarce. However, preliminary data suggest no elevated incidence of COVID-19. In 5,700 patients from New York, only 43 (0.8%) were found to be HIV-positive (Richardson 2020). Similar findings were reported from Chicago (Ridgeway 2020). In Barcelona where a local protocol included HIV serology for all hospitalized COVID-19 patients, 32/2102 (1.5%) were HIV-infected, among them only one single new HIV diagnosis (Miro 2020). Given the fact that HIV+ patients may be at higher risk for other infectious diseases such as STDs, these percentages were so low that some experts have already speculated on potential "protective" factors (i.e., antiviral therapies or immune activation). Moreover, a defective cellular immunity could paradoxically be protective for severe cytokine dysregulation, preventing the cytokine storm seen in severe COVID-19 cases.

Appropriately powered and designed studies that are needed to draw conclusions on the effect of COVID-19 are still lacking. However, our own retrospective analysis of 33 confirmed SARS-CoV-2 infections between March 11 and April 17 in 12 participating German HIV centers revealed no excess morbidity or mortality (Haerter 2020). The clinical case definition was mild in 25/33 cases (76%), severe in 2/33 cases (6%), and critical in 6/33 cases (18%). At the last follow up, 29/32 of patients with documented outcome (90%) had recovered. Three out of 32 patients had died. One patient was 82 years old, one had a CD4 T-cell count of 69/µl and one suffered from several comorbidities. A similar observation was made in Milan, Italy, where 45/47 patients with HIV and COVID-19 (only 28 with confirmed SARS-CoV-2 infection) recovered

(Gervasoni 2020). In this study, as in our cohort, severe immune deficiency was rare. The last median CD4 count was 670/µl (range, 69 to 1715) and in 30/32 cases in our cohort, the latest HIV RNA was below 50 copies/mL (Härter 2020). It remains to be seen whether HIV patients with uncontrolled viremia and/or low CD4 cells are at higher risk for severe disease. It is also unclear whether immunity after infection remains impaired. However, there are case reports on delayed antibody response in HIV patients (Zhao 2020).

Another issue making HIV patients an interesting population is a potential effect of antiretroviral therapies against SARS-CoV-2. For lopinavir/r, some reports on beneficial effects in patients with SARS, MERS and COVID-19 exist, but the evidence remains poor. Several studies on lopinavir are still underway (see Treatment chapter). According to both the US DHHS and EACS statement, an ART regimen should not be changed to include a PI to prevent or treat COVID-19 (EACS 2020, US 2020). In our cohort, 4/33 (12%) patients were on darunavir when they developed COVID-19 symptoms. In the Milan Cohort, the rate of patients on a PI was 11% (Gervasoni 2020). Both studies indicate that PIs do not protect from SARS-CoV-2 infection. Beside the PI, we did not find any clear evidence for a protective effect of tenofovir. Tenofovir alafenamide has some chemical similarities to remdesivir and has been shown to bind to SARS-CoV-2 RNA polymerase (RdRp) with binding energies comparable to those of native nucleotides and to a similar extent as remdesivir. Consequently, tenofovir has recently been suggested as a potential treatment for COVID-19 (Elfiky 2020). In Spain, a large randomized Phase III placebo-controlled study (EPICOS, NCT04334928) compares the use of tenofovir disoproxil fumarate/emtricitabine, hydroxychloroquine or the combination of both versus placebo as prophylaxis for COVID-19 in healthcare workers. Our observation that the majority (22/33) of HIV+ patients with COVID-19 were treated with tenofovir, including those developing severe or critical disease, indicate no or only minimal clinical effect against SARS-CoV-2 (Härter 2020). In Milan, 42% were receiving a tenofovir-based regimen (Gervasoni 2020).

The most serious concern regarding HIV, however, is the collateral damage induced by COVID-19. In Western countries, only few HIV+ patients had problems in gaining access to their HIV medications or had trouble taking them due to COVID-19 or the plans to manage it (Sanchez 2020). In contrast, disruption to delivery of health care in sub-Saharan African settings could well lead to adverse consequences beyond those from COVID-19 itself. Lockdown, transport restrictions and fear of coronavirus infection have already led to a dramatic drop in HIV and TB patients collecting medication in several African countries (Adepoju 2020). Using five different existing mathematical models

of HIV epidemiology and intervention programmes in sub-Saharan Africa, investigations have already estimated the impact of different disruptions to HIV prevention and treatment services. Predicted average relative excess in HIV-related deaths and new HIV infections (caused by unsuppressed HIV RNA during treatment interruptions) per year over 2020-2024 in countries in sub-Saharan Africa that would result from 3 months of disruption of specific HIV services, were 1.20-1.27 for death and 1.02-1.33 for new infections, respectively. A 6-month interruption of ART would result in over 500,000 excess HIV deaths in sub-Saharan Africa (range of estimates 471,000 - 673,000). Disrupted services could also reverse gains made in preventing mother-to-child transmission. According to WHO, there is a clear need for urgent efforts to ensure HIV service continuity and preventing treatment interruptions due to COVID-19 restrictions in sub-Saharan Africa.

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Härter G, Spinner CD, Roider J, at al. **COVID-19 in people living with human immunodeficiency virus: a case series of 33 patients**. Infection 2020, May 11. https://doi.org/10.1007/s15010-020-01438-z. Full-text: https://link.springer.com/article/10.1007/s15010-020-01438-z

Jewell B, Mudimu E, Stover J, et al. **Potential effects of disruption to HIV programmes in sub-Saharan Africa caused by COVID-19: results from multiple models**. Pre-print, https://doi.org/10.6084/m9.figshare.12279914.v1 + https://doi.org/10.6084/m9.figshare.12279932.v1

Miró JM, Ambrosioni J, Blanco JL. **COVID-19 in patients with HIV - Authors' reply**. Lancet HIV. 2020 May 14:S2352-3018(20)30140-5. PubMed: https://pubmed.gov/32416770. Full-text: https://doi.org/10.1016/S2352-3018(20)30140-5

Richardson S, Hirsch JS, Narasimhan M, et al. **Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area**. JAMA. 2020 Apr 22:e206775. PubMed: https://pubmed.gov/32320003. Full-text: https://doi.org/10.1001/jama.2020.6775

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Zhao J, Liao X, Wang H, et al. **Early virus clearance and delayed antibody response in a case of COVID-19 with a history of co-infection with HIV-1 and HCV**. Clin Infect Dis. 2020 Apr 9:ciaa408. PubMed: https://pubmed.gov/32270178. Full-text: https://doi.org/10.1093/cid/ciaa408

22 May

Epidemiology

Lyu W, Wehby GL. **Comparison of Estimated Rates of Coronavirus Disease 2019 (COVID-19) in Border Counties in Iowa Without a Stay-at-Home Order and Border Counties in Illinois With a Stay-at-Home Order**. JAMA Netw Open. 2020 May 1;3(5):e2011102. PubMed: https://pubmed.gov/32413112. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.11102 ● (IMPORTANT)

Is it necessary to stay home during the epidemic's peak? Probably, yes. This well-conducted study focused on the effects of a general stay-at-home-order. On March 21, Illinois did so while Iowa didn't. Authors compared daily incidence in 8 Iowa counties bordering Illinois with those in the 7 Illinois counties bordering Iowa. Within a month after the stay-at-home order, the curves started to diverge considerably. Cases increased more quickly in Iowa and more slowly in Illinois, leading to an excess of about 30 % in Iowa counties. Sensitivity analyses addressing differences in timing of closing schools and nonessential businesses and differences in population density and poverty rates between the two states supported these findings.

Sood N, Simon P, Ebner P, et al. **Seroprevalence of SARS-CoV-2–Specific Antibodies Among Adults in Los Angeles County, California, on April 10-11, 2020**. JAMA. Published online May 18, 2020. Full-text: https://doi.org/10.1001/jama.2020.8279

No herd immunity in LA. Participants were offered testing at 6 study sites or at home in mid-April. Among 865 cases, the prevalence of antibodies was 4.65%. However, even this low number may be biased due to nonresponse or due to the fact that symptomatic persons may have been more likely to participate.

Virology

Chandrashekar A, Liu J, Martinot AJ, et al. **SARS-CoV-2 infection protects against rechallenge in rhesus macaques**. Science. 2020 May 20:eabc4776. PubMed: https://pubmed.gov/32434946. Full-text: https://doi.org/10.1126/science.abc4776 ● (IMPORTANT)

No re-infection in macaques. Following initial viral clearance and on day 35 following initial viral infection, 9 rhesus macaques were re-challenged with the same doses of virus that were utilized for the primary infection. Very limited viral RNA was observed in bronchoalveolar lavage on day 1, with no viral RNA detected at subsequent timepoints. These data show that SARS-CoV-2 infection induced protective immunity against re-exposure in non-human primates.

Transmission

Guasp M, Laredo C, Urra X. **Higher solar irradiance is associated with a lower incidence of COVID-19**. Clin Infect Dis. 2020 May 19:ciaa575. PubMed: https://pubmed.gov/32426805. Full-text: https://doi.org/10.1093/cid/ciaa575

Increasing sunlight exposure in the upcoming weeks may help flatten the curve! UVB radiation from sunlight (the primary source of UV radiation) is the principal environmentally effective virucide, probably much more relevant than temperature and humidity. Authors studied the relationship between the incidence of COVID-19, demographic, and climatologic measurements in different regions across the world. They show a significant association of the incidence of COVID-19 and both reduced solar irradiance and increased population density, highlighting the sterilizing properties of UV radiation.

Ratnesar-Shumate S, Williams G, Green B, et al. **Simulated Sunlight Rapidly Inactivates SARS-CoV-2 on Surfaces**. J Infect Dis. 2020 May 20:jiaa274. PubMed: https://pubmed.gov/32432672. Full-text: https://doi.org/10.1093/infdis/jiaa274 ● (IMPORTANT)

This lab data supports the above observation of inactivation. Store your masks in the sun! Simulated sunlight rapidly inactivated SARS-CoV-2 suspended in either simulated saliva or culture media and dried on stainless steel plates. Ninety percent of infectious virus was inactivated every 6.8 minutes in simulated saliva and every 14.3 minutes in culture media when exposed to simulated sunlight representative of the sun on a clear summer day. No significant decay was observed in darkness over 60 minutes.

Bunyavanich S, Do A, Vicencio A. **Nasal Gene Expression of Angiotensin-Converting Enzyme 2 in Children and Adults.** JAMA. 2020 May 20. PubMed: https://pubmed.gov/32432657. Full-text: https://doi.org/10.1001/jama.2020.8707

Is this the reason for lower infection rates in children? As the nasal epithelium is one of the first sites of infection, investigators evaluated the expression of ACE in nasal epithelial samples collected 2015-2018 as part of an asthma study. Among a cohort of 305 patients, all age groups had higher expression of ACE2 in the nasal epithelium compared with younger children (4-9 years old). ACE2 expression was age-dependent and higher with each subsequent age group after adjusting for sex and asthma. A good argument for opening a day care center for children.

Diagnostics

Tom MR, Mina MJ. **To Interpret the SARS-CoV-2 Test, Consider the Cycle Threshold Value**. Clin Infect Dis. 2020 May 21:ciaa619. PubMed: https://pubmed.gov/32435816. Full-text: https://doi.org/10.1093/cid/ciaa619 ● (Important)

A positive RT-qPCR result may not necessarily mean the person is still infectious or that they still have any meaningful disease. The RNA could be from nonviable virus and/or the amount of live virus may be too low for transmission. RT-qPCR provides quantification by first reverse transcribing RNA into DNA, and then performing qPCR where a fluorescence signal increases proportionally to the amount of amplified nucleic acid. The test is positive if the fluorescence reaches a specified threshold within a certain number of PCR cycles (Ct value, inversely related to the viral load). Many qPCR assays use a Ct cut-off of 40, allowing detection of very few starting RNA molecules. The authors suggest to use this Ct value or to calculate viral load which can help to refine decision-making (re: shorter isolation etc.).

Severe COVID-19

Ackermann M, Verleden SE, Kuehnel M, et al. **Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19**. N Engl J Med. 2020 May 21. PubMed: https://pubmed.gov/32437596. Full-text: https://doi.org/10.1056/NEJMoa2015432 ● (Important)

It's not influenza. The authors carefully examined lungs from 7 deceased COVID-19 patients with lungs from 7 patients who died from ARDS secondary

to influenza A and 10 age-matched, uninfected control lungs. In COVID-19 or influenza, the histologic pattern was diffuse alveolar damage with perivascular T-cell infiltration. However, the COVID-19 lungs showed distinctive vascular features, consisting of severe endothelial injury associated with the presence of intracellular virus and disrupted cell membranes. Histologic analysis of pulmonary vessels showed widespread thrombosis with microangiopathy. Alveolar capillary microthrombi and the amount of vessel growth were 9 and almost 3 times as prevalent as in influenza, respectively.

Treatment

Fan J, Zhang X, Liu J, et al. **Connecting hydroxychloroquine in vitro antiviral activity to in vivo concentration for prediction of antiviral effect: a critical step in treating COVID-19 patients**. Clin Infect Dis. 2020 May 21:ciaa623. PubMed: https://pubmed.gov/32435791. Full-text: https://doi.org/10.1093/cid/ciaa623

The price for the most cryptic abstract of the day goes to this FDA group. "Translation of *in vitro* antiviral activity to the *in vivo* setting is crucial to identify potentially effective dosing regimens of hydroxychloroquine. *In vitro* EC50/EC90 values for hydroxychloroquine should be compared to the *in vivo* free extracellular tissue concentration, which is similar to the free plasma hydroxychloroquine concentration." Did they not dare to tell the truth? Their (important, yet cryptic) message was: HCQ doses tolerable for humans are too low to have any antiviral effect.

Parang K, El-Sayed NS, Kazeminy AJ, Tiwari RK. **Comparative Antiviral Activity of Remdesivir and Anti-HIV Nucleoside Analogs Against Human Coronavirus 229E (HCoV-229E)**. Molecules. 2020 May 17;25(10):E2343. PubMed: https://pubmed.gov/32429580. Full-text: https://doi.org/10.3390/molecules25102343.

Most almost-misleading title of the day: Compara***tive***, not compara***ble***. A series of anti-HIV nucleosides were compared with remdesivir for antiviral activity against seasonal HCoV-229E in MRC-5 cells. Remdesivir was found to be potent, with an EC50 value of 0.07 μM. Only emtricitabine (FTC) showed modest activity, with an EC50 value of 82 μM. Other NRTIs did not show compar***able*** activity. But it was compar***ative***, yes.

23 May

Epidemiology

Kofler N, Baylis F. **Ten reasons why immunity passports are a bad idea**. Nature 2020, 581, 379-381. Full-text: https://doi.org/10.1038/d41586-020-01451-0

Forget the COVID pass! During the past weeks, we have shared several reasons why immunity passports are a bad idea. This commentary provides 10 more reasons. Restricting liberty on the basis of biology threatens freedom, fairness and public health.

Haushofer J, Metcalf JE. **Which interventions work best in a pandemic**? Science 21 May 2020: eabb6144. Full-text: https://doi.org/10.1126/science.abb6144

Randomized controlled trials can be used for non-pharmaceutical interventions. Surprisingly they have received little attention in the current pandemic, despite a long history in epidemiology and social science. In this interesting commentary, authors describe how RCTs can be practically and ethically implemented in a pandemic, how compartmental models from infectious disease epidemiology can be used to minimize measurement requirements, and how to control for spillover effects and harness their benefits.

Virology

Hillen HS, Kokic G, Farnung L et al. **Structure of replicating SARS-CoV-2 polymerase**. Nature 2020. Full-text: https://doi.org/10.1038/s41586-020-2368-8.

The cryo-electron microscopic structure of the SARS-CoV-2 RdRp in its active form, mimicking the replicating enzyme. Long helical extensions in nsp8 protrude along exiting RNA, forming positively charged 'sliding poles'. These sliding poles can account for the known processivity of the RdRp that is required for replicating the long coronavirus genome. A nice video provides an animation of the replication machine.

Zhang X, Tan Y, Ling Y, et al. **Viral and host factors related to the clinical outcome of COVID-19.** Nature. 2020 May 20. PubMed: https://pubmed.gov/32434211. Full-text: https://doi.org/10.1038/s41586-020-2355-0 ●● (OUTSTANDING)

Viral variants do not affect outcome. This important study on 326 cases found at least two major lineages with differential exposure history during the early phase of the outbreak in Wuhan. Patients infected with these different clades did not exhibit significant difference in clinical features, mutation rate or transmissibility. Lymphocytopenia, especially a reduced CD4+ and CD8+ T cell counts upon admission, was predictive of disease progression. High levels of IL-6 and IL-8 during treatment were observed in patients with severe or critical disease and correlated with decreased lymphocyte count. The determinants of disease severity seemed to stem mostly from host factors such as age, lymphocytopenia, and its associated cytokine storm.

Yu , Tostanoski LH, Peter L, et al. **DNA vaccine protection against SARS-CoV-2 in rhesus macaques**. Science 20 May 2020. Full-text: https://doi.org/10.1126/science.abc6284

A series of different DNA vaccine candidates expressing different forms of the spike protein were evaluated in 35 rhesus macaques. Vaccinated animals (especially those receiving a vaccine encoding the full-length spike protein) developed humoral and cellular immune responses, including neutralizing antibody titers comparable to those found in convalescent humans. Protection was likely not sterilizing but instead appeared to be mediated by rapid immunologic control following challenge.

Transmission

Bao L, Gao H, Deng W, et al. **Transmission of SARS-CoV-2 via close contact and respiratory droplets among hACE2 mice**. J Inf Dis 2020, May 23. Full-text: https://doi.org/10.1093/infdis/jiaa281

Using ACE2 mice, authors simulated different transmission modes. Close contact and droplets worked better than aerosol exposition. Animals could not be experimentally infected via aerosol inoculation until continuous exposition for up to 25 min even with high virus concentrations.

Clinical

Docherty AB, Harrison EM, Green CA, et al. **Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study.** BMJ. 2020 May 22;369:m1985. PubMed: https://pubmed.gov/32444460. Full-text: https://doi.org/10.1136/bmj.m1985 ●● (OUTSTANDING)

Clinical data from 20,133 patients, admitted to (or diagnosed in) 208 acute care hospitals in the UK until April 19. Median age was 73 years (interquartile range 58-82) and 60% were men. Comorbidities were common, namely chronic cardiac disease (31%), diabetes (21%), non-asthmatic chronic pulmonary disease (18%). Overall, 41% of patients were discharged alive, 26% died, and 34% continued to receive care. 17% required admission to high dependency or intensive care units; of these, 28% were discharged alive, 32% died, and 41% continued to receive care. Of those receiving mechanical ventilation, 17% were discharged alive, 37% died, and 46% remained in hospital. Increasing age, male sex, and comorbidities including chronic cardiac disease, non-asthmatic chronic pulmonary disease, chronic kidney disease, liver disease and obesity were associated with higher mortality in hospital.

Severe COVID-19

Bhatraju PK, Ghassemieh BJ, Nichols M, et al. **Covid-19 in Critically Ill Patients in the Seattle Region — Case Series**. N Engl J Med 2020, May 21; 382:2012-2022. Full-text: https://doi.org/10.1056/NEJMoa2004500

This report describes clinical characteristics, imaging findings, and outcomes among 24 critically ill COVID-19 patients who presented with acute hypoxemic respiratory failure in the Seattle metropolitan area. Mortality was high (at least 50%, three patients still intubated at last follow-up).

Treatment

Beigel JH. Tomashek KM, Dodd LE. **Remdesivir for the Treatment of Covid-19 — Preliminary Report**. NEJM 2020, May 22. Full-text: https://doi.org/10.1056/NEJMoa2007764 ● (IMPORTANT)

It took almost a month to publish this eagerly awaited paper: does remdesivir work? Yes, in some patients. The conclusion of this double-blinded study that randomized 1,063 COVID-19 patients throughout the world to the drug or to placebo, was remarkably short: “Remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with COVID-19 and evidence of lower respiratory tract infection”. Median recovery time was 11 versus 15 days. The benefit was most apparent in patients with a baseline ordinal score of 5 (requiring oxygen but no high-flow oxygen). In patients requiring mechanical ventilation or ECMO, there was no effect at all (although the numbers were low). Gender, ethnicity, age or symptom duration had no impact. The Kaplan-Meier estimates of mortality at 14 days were 7.1% and somewhat (not significantly) lower with remdesivir compared to 11.9% with placebo

(hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04). This is, however, preliminary. The full analysis of the entire trial population will occur soon, although more comparative data may be hard to find as all patients were rolled over to the active agent at this point in the study."

Liu Y, Pang Y, Hu Z, et al. **Thymosin alpha 1 (Tα1) reduces the mortality of severe COVID-19 by restoration of lymphocytopenia and reversion of exhausted T cells**. Clinical Infectious Diseases 2020, May 22. Full-text: https://doi.org/10.1093/cid/ciaa630

In this study of 76 patients with severe COVID-19, Tα1 supplement (subcutaneous injections of 10 mg) appeared to reduce mortality, especially in those with low CD4 and CD8 cell counts. This immunomodulating thymic peptide reversed T cell exhaustion and recovers immune reconstitution through promoting thymus output during SARS-CoV-2 infection. However, this is uncontrolled retrospective data and results should be interpreted with caution.

24 May

Epidemiology

Le Quéré C, Jackson RB, Jones MW et al. **Temporary reduction in daily global CO2 emissions during the COVID-19 forced confinement**. Nat Clim Chang 2020. Full-text: https://doi.org/10.1038/s41558-020-0797-x

The global CO2 emissions have decreased by 17% by early April 2020 compared with the mean 2019 levels, just under half from changes in surface transport (cars, truck, buses). More than one billion tons of carbon emissions less. At their peak, emissions in individual countries decreased by an average of 26%, admittedly extreme and probably unseen before, but just to the level of emissions in 2006. The impact on 2020 annual emissions will depend on the duration of the confinement, with a low estimate of −4% if pre-pandemic conditions return by mid-June, and a high estimate of −7% if some restrictions remain worldwide until the end of 2020. These figures are comparable to the rates of decrease needed year-on-year over the next decades to limit climate change to a 1.5 °C warming.

Memish ZA, Aljerian N, Ebrahim SH. **Tale of three seeding patterns of SARS-CoV-2 in Saudi Arabia. Lancet Infect Dis**. 2020 May 19:S1473-3099(20)30425-4. PubMed: https://pubmed.gov/32442522. Full-text: https://doi.org/10.1016/S1473-3099(20)30425-4

With regard to case numbers, Saudi Arabia already ranks #15 in the world. Beside routine travel, authors describe two factors driving the epidemic. First, each month about 1 million incoming pilgrims from 180 countries merge with about 1 million Saudi national Sunni pilgrims at Saudi Arabia's two holy sites. Second is the returning Shiite Saudi national pilgrims (4·9 million Shiite population in Saudi Arabia) who travel to Iran for pilgrimage. Of note, men and woman older than 60 years are overrepresented among pilgrims. Bad prospects.

Vaccine

Zhu FC, Li YH, Guan XH, et al. **Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial.** Lancet. 2020 Jun 13;395(10240):1845-1854. PubMed: https://pubmed.gov/32450106. Full-text: https://doi.org/10.1016/S0140-6736(20)31208-3 ● (IMPORTANT)

Open-label Phase I trial of an Ad5 vectored COVID-19 vaccine, using the full-length spike glycoprotein. A total of 108 healthy adults aged between 18 and 60 years from Wuhan, China, were given three different doses. ELISA antibodies and neutralising antibodies increased significantly and peaked 28 days post-vaccination. Specific T cell response peaked at day 14 post-vaccination. Follow-up is still short and the authors are going to follow up the vaccine recipients for at least 6 months, so more data will be obtained. Of note, adverse events were relatively frequent, encompassing pain at injection sites (54%), fever (46%), fatigue (44%) and headache (39%). Phase II studies are underway.

Transmission

Marjolein F. Q. Kluytmans-van den Bergh MF, Buiting AG, Pas SD, et al. **Prevalence and Clinical Presentation of Health Care Workers With Symptoms of Coronavirus Disease 2019 in 2 Dutch Hospitals During an Early Phase of the Pandemic**. JAMA Netw Open. 2020;3(5):e209673. https://doi.org/10.1001/jamanetworkopen.2020.9673

Of 9,705 HCWs from the Netherlands, 1353 (14%) reported fever or respiratory symptoms and were tested. Of those, 86 HCWs (6%) were infected. Hospital acquisition was unlikely to explain the vast majority of cases. Of note, 54 HCWs (63%) mentioned having worked while being symptomatic.

Lai X, Wang M, Quin C, et al. **Coronavirus Disease 2019 (COVID-2019) Infection Among Health Care Workers and Implications for Prevention Measures in a Tertiary Hospital in Wuhan, China**. JAMA Netw Open May 21, 2020;3(5):e209666. Full-text: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2766227

Overall, 110 of 9,684 HCWs in Tongji Hospital tested positive, with an infection rate of 1.1%. Most infections occurred at the early stage of the epidemic (before January 25), before protective measures were taken. Of those who worked in fever clinics or wards, 17/3110 were infected, indicating an infection rate of 0.5% among first-line HCWs. Of note, a higher rate of infection was found in non-first-line HCW (93/6.574, 1.4%). Authors speculate that this was due to insufficient protective measures available in clinical departments other than fever clinics and wards.

Clase CM, Fu EL, Joseph M, et al. **Cloth Masks May Prevent Transmission of COVID-19: An Evidence-Based, Risk-Based Approach**. Ann Int Med 2020, May 22. Full-text: https://www.acpjournals.org/doi/10.7326/M20-2567

According to the authors, there is high-quality, consistent evidence that many (but not all) cloth masks reduce droplet and aerosol transmission and may be effective in reducing contamination of the environment. No direct evidence indicates that public mask wearing protects either the wearer or others. However, the possible benefit of a modest reduction in transmission likely outweighs the possibility of harm.

Severe COVID-19

Cummings MJ, Baldwin MR, Abrams D, et al. **Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study**. Lancet. 2020 May 19:S0140-6736(20)31189-2. PubMed: https://pubmed.gov/32442528. Full-text: https://doi.org/10.1016/S0140-6736(20)31189-2● (IMPORTANT)

More on critically ill patients. Among 1,150 adults who were admitted to two NYC hospitals with COVID-19 in March, 257 (22%) were critically ill. The median age of patients was 62 years (IQR 51-72), 67% were men and 82% patients had at least one chronic illness. As of the end of April, 101 (39%) patients had died and 94 (37%) remained hospitalised. 203 (79%) patients received invasive mechanical ventilation for a median of 18 days, 66% received vasopressors and 31% received renal replacement therapy. In the multivariable Cox model, older age, chronic cardiac disease (adjusted HR 1.76), chronic pulmonary dis-

ease (2.94) were independently associated with in-hospital mortality. This was also seen for higher concentrations of interleukin-6 and D-dimer, highlighting the role of systemic inflammation and endothelial-vascular damage in the development of organ dysfunction. Studies on immunomodulating and anticoagulant drugs are urgently needed.

Varga Z, Flammer AJ, Steiger P, et al. **Electron microscopy of SARS-CoV-2: a challenging task - Authors' reply**. Lancet. 2020 May 19:S0140-6736(20)31185-5. PubMed: https://pubmed.gov/32442527. Full-text: https://doi.org/10.1016/S0140-6736(20)31185-5

Endothelial cell dysfunction may explain the vascular microcirculatory complications seen in different organs in patients with COVID-19. The authors discuss the framework of endotheliitis, providing explanation for the unique predilection of SARS-CoV-2 in those individuals with hypertension, diabetes, or established cardiovascular disease, groups known to have pre-existing endothelial dysfunction.

Schünemann HJ, Khabsa J, Solo K, et al. **Ventilation Techniques and Risk for Transmission of Coronavirus Disease, Including COVID-19. A Living Systematic Review of Multiple Streams of Evidence**. Ann Int Med 2020, May 22. Full-text: https://www.acpjournals.org/doi/10.7326/M20-2306 ● (IMPORTANT)

The authors reviewed evidence regarding the benefits and harms of ventilation techniques. Indirect and low-certainty evidence suggests that use of noninvasive ventilation, similar to invasive mechanical ventilation, probably reduces mortality but may increase the risk for transmission of COVID-19 to health care workers.

Treatment

Mehra MR, Desai SS, Ruschitzka F, Patel AM. **Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis**. Lancet May 22, 2020 Full-text: https://doi.org/10.1016/S0140-6736(20)31180-6

Probably the end of chloroquine. And the end of hydroxychloroquine. And the end of chloroquine plus azithromycin or clarithromycin. And, yes, the end of hydroxychloroquine plus azithromycin or clarithromycin. **We should no longer use these four drug regimens** as COVID-19 treatments! In this incredible large multinational registry, analysis from 671 hospitals in six con-

tinents, 14,888 patients treated with these regimens were compared with 81,444 control patients. Each drug regimen was associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias. However, the study (including a 20-page supplement) is too complex to be discussed here in a few words. We will come back to this soon.

25 May

A brief (and probably the last) review on hydroxychloroquine and chloroquine

A few months ago, lab experiments suggested that hydroxychloroquine (HCQ) and chloroquine (CQ) might have some antiviral effects against SARS-CoV-2 due to an increase in the endosomal pH value which disrupts the virus-cell fusion and some post-entry steps (Wang 2020, Yao 2020). An early enthusiastic mini-review stated "results from more than 100 patients" showed that chloroquine phosphate would be able to alleviate the course of the disease (Gao 2020). Other experts, however, dampened the enthusiasm, pointing out that a benefit of chloroquine would be the first positive signal, after decades of unsuccessful studies conducted in a huge number of acute viral diseases (Touret 2020). On March 17, a preliminary report from Marseille/France appeared to show some benefit in a small non-randomized study on 36 patients (Gautret 2020). Although this work lacked essential standards of data generation and interpretation (Kim 2020), someone's swanky tweet claiming on March 21 that the combination of HCQ and azithromycin has "a real chance to be one of the biggest game changers in the history of medicine", attracted world-wide attention and led to tens of thousands of uncontrolled treatments. Moreover, many patients decided against clinical trials of other therapies that would require them to give up chloroquine treatments. This has already prompted serious delays in trial enrolment, muddled efforts to interpret data and endangered clinical research (Ledford 2020). Some countries have stockpiled CQ and HCQ, resulting in a shortage of these medications for those that need them for approved clinical indications.

Only a few weeks later, we are now facing an overwhelming amount of data strongly arguing against any use of both HCQ and CQ.

- The by-far most convincing data were published last Friday, May 22 (Mehra 2020). In this extraordinary multinational registry analysis from 671 hospitals on six continents, 14,888 patients (1,868 received CQ; 3,783 received CQ with azithromycin or clarithromycin; 3,016 received HCQ; and 6,221 received HCQ with a macrolide) were compared to 81,144 control pa-

tients who did not receive these drugs. Mortality was higher in all treatment groups than in the controls (18.0-23.8% versus 9.3%) and each treatment regimen was independently associated with an increased risk of in-hospital mortality and with *de novo* ventricular arrhythmia, especially in the combination groups (4.3-8.1 versus 0.3%). Adjustment for multiple confounding factors, a propensity score matching analysis and a tipping-point analysis (an analysis that shows the effect size and prevalence of an unmeasured confounder that could shift the upper boundary of the CI towards null) did not affect the results. Although the authors concluded that a cause-and-effect relationship between drug therapy and survival should not be inferred and that their data do not apply to the use of any treatment regimen used in the ambulatory, out-of-hospital setting, it is hard to find any argument for any of these strategies. Data do not support the use of these regimens outside randomized clinical trials (RCTs). Researchers who conduct and supervise RCTs should consider whether ongoing recruitment is necessary.

Other key studies arguing against HCQ in recent weeks

1. In an observational study from New York City of 1,376 consecutive hospitalized patients, 811 received HCQ (60% received also azithromycin) (Geleris 2020). After adjusting for several confounders (HCQ patients were more severely ill at baseline), hydroxychloroquine administration was not associated with either a greatly lowered or an increased risk of the composite end point of intubation or death.
2. Another retrospective cohort of 1,438 patients from 25 hospitals in the New York metropolitan region looked at 1,438 patients (Rosenberg 2020). In adjusted Cox models, compared with patients receiving neither drug, there were no significant differences in mortality for patients receiving HCQ + azithromycin, HCQ alone, or azithromycin alone. Cardiac arrest was significantly more likely with HCQ + azithromycin (adjusted OR 2.13).
3. A randomized, Phase IIb clinical trial in Brazil allocated severe COVID-19 patients to receive high-dose CQ (600 mg BID for 10 days) or low-dose CQ (450 mg BID on day 1, QD for 4 days). The DSMB terminated the trial after 81/440 individuals were enrolled (Borba 2020). By day 13 of enrolment, 6/40 patients (15%) in the low-dose group had died, compared with 16/41 (39%) in the high-dose group. Viral RNA was detected in 78% and 76%, respectively.

4. In a retrospective study of 251 patients receiving HCQ plus azithromycin, extreme new QTc prolongation to >500 ms, a known marker of high risk for torsade de pointes, had developed in 23% (Chorin 2020).
5. HCQ does not work as prophylaxis. A case series described 17 lupus patients with COVID-19, among them several severe cases (Mathian 2020).
6. Free plasma HCQ concentration achieved with HCQ doses tolerable for humans are probably too low to have any antiviral effects (Fan 2020).

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Chorin E, Wadhwani L, Magnani S, et al. **QT Interval Prolongation and Torsade De Pointes in Patients with COVID-19 treated with Hydroxychloroquine/Azithromycin**. Heart Rhythm. 2020 May 11:S1547-5271(20)30435-5. PubMed: https://pubmed.gov/32407884. Full-text: https://doi.org/10.1016/j.hrthm.2020.05.014 ● (IMPORTANT)

Fan J, Zhang X, Liu J, et al. **Connecting hydroxychloroquine in vitro antiviral activity to in vivo concentration for prediction of antiviral effect: a critical step in treating COVID-19 patients**. Clin Infect Dis. 2020 May 21:ciaa623. PubMed: https://pubmed.gov/32435791. Full-text: https://doi.org/10.1093/cid/ciaa623

Gao J, Tian Z, Yang X. **Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies**. Biosci Trends. 2020 Mar 16;14(1):72-73. PubMed: https://pubmed.gov/32074550. Full-text: https://doi.org/10.5582/bst.2020.01047

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Geleris J, Sun Y, Platt J, et al. **Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19**. N Engl J Med. 2020 May 7. PubMed:

https://pubmed.gov/32379955. Full-text: https://doi.org/10.1056/NEJMoa2012410 ● (IMPORTANT)

Kim AH, Sparks JA, Liew JW. **A Rush to Judgment? Rapid Reporting and Dissemination of Results and Its Consequences Regarding the Use of Hydroxychloroquine for COVID-19**. Ann Intern Med 2020. Full-text: https://doi.org/10.7326/M20-1223

Ledford H. **Chloroquine hype is derailing the search for coronavirus treatments**. Nature Medicine, 24 April 2020. Full-text: https://www.nature.com/articles/d41586-020-01165-3

Mathian A, Mahevas M, Rohmer J, et al. **Clinical course of coronavirus disease 2019 (COVID-19) in a series of 17 patients with systemic lupus erythematosus under long-term treatment with hydroxychloroquine**. Ann Rheum Dis. 2020 Apr 24. PubMed: https://pubmed.gov/32332072. Full-text: https://doi.org/10.1136/annrheumdis-2020-217566

Mehra MR, Desai SS, Ruschitzka F, Patel AM. **Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis**. Lancet May 22, 2020 Full-text: https://doi.org/10.1016/S0140-6736(20)31180-6

Rosenberg ES, Dufort EM, Udo T, et al. **Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State**. JAMA. 2020 May 11. https://pubmed.gov/32392282. Full-text: https://doi.org/10.1001/jama.2020.8630 ● (IMPORTANT)

Touret F, de Lamballerie X. **Of chloroquine and COVID-19**. Antiviral Res. 2020 Mar 5;177:104762. PubMed: https://pubmed.gov/32147496. Full-text: https://doi.org/10.1016/j.antiviral.2020.104762

Wang M, Cao R, Zhang L, et al. **Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro**. Cell Res. 2020 Mar;30(3):269-271. PubMed: https://pubmed.gov/32020029. Full-text: https://doi.org/10.1038/s41422-020-0282-0

Yao X, Ye F, Zhang M, et al. **In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)**. Clin Infect Dis. 2020 Mar 9. PubMed: https://pubmed.gov/32150618. Full-text: https://doi.org/10.1093/cid/ciaa237

26 May

Epidemiology

Peak CM, Kahn R, Grad YH, et al. **Individual quarantine versus active monitoring of contacts for the mitigation of COVID-19: a modelling study**. Lancet Infect Dis. 2020 May 20. PubMed: https://pubmed.gov/32445710. Full-text: https://doi.org/10.1016/S1473-3099(20)30361-3

Complex models, comparing individual quarantine (separation from others of an individual who is believed to be exposed to the disease but not currently showing symptoms) with active monitoring targeted by contact tracing (assessing for symptoms at regular intervals such as twice-daily visits by HCW or phone-based self-monitoring, and if symptoms are detected, the individual is promptly isolated). Bottom line: It depends. It depends on the assumptions regarding the serial interval, the amount of transmission that occurs before symptom onset, and the feasibility setting. With a short mean serial interval of 4.8 days and hence substantial pre-symptomatic infectiousness, individual quarantine was considerably more effective than active monitoring at reducing onward transmission. With longer serial intervals both active monitoring and individual quarantine effectively reduce transmission.

Liotta G, Marazzi MC, Orlando S. **Is social connectedness a risk factor for the spreading of COVID-19 among older adults**? The Italian paradox. PLOS May 21, 2020. Full-text:

One hypothesis about the fatal spread of SARS-CoV-2 in Italy is that the supposed closeness between younger and older generations in Italian families may have played a major role. In this study, this was not confirmed. Paradoxically, it seemed that the variables associated with social isolation were risk factors for higher rates among the elderly. Social relationships may be protective against increased mortality rates during a crisis impacting the frailest populations. Instead, availability of beds in nursing homes were one of the determinants of infection rate among individuals aged >80.

Transmission

Nordling L. **Study tells 'remarkable story' about COVID-19's deadly rampage through a South African hospital.** May 25, 2020. Full-text: https://www.sciencemag.org/news/2020/05/study-tells-remarkable-story-about-covid-19-s-deadly-rampage-through-south-african

Screen the staff! Incredible story about a man who sought help for coronavirus symptoms on March 9, spending only a few hours at the emergency department of a hospital in Durban, South Africa. He was kept separate in a triage area, but that room was reached through the main resuscitation bay, where a stroke patient occupied a bed. Both patients were seen by the same doctor. After likely transmitting the virus to the stroke patient, the results, eight weeks later were: 39 patients and 80 staff linked to the hospital had been infected, and 15/39 patients had died. Lesson learnt: Nosocomial outbreaks may be a major amplifier of COVID-19 transmission.

Groß R, Conzelmann C, Müller JA, et al. **Detection of SARS-CoV-2 in human breastmilk**. Lancet. 2020 May 21:S0140-6736(20)31181-8. PubMed: https://pubmed.gov/32446324. Full-text: https://doi.org/10.1016/S0140-6736(20)31181-8

SARSCoV2 RNA in milk samples from an infected mother (two mothers were examined) was found on 4 consecutive days. Detection of viral RNA in milk coincided with mild COVID19 symptoms and a SARSCoV2 positive diagnostic test of the newborn.

Diagnostics

Han MS, Byun JH, Cho Y, Rim JH. **RT-PCR for SARS-CoV-2: quantitative versus qualitative**. Lancet Infect Dis. 2020 May 20:S1473-3099(20)30424-2. PubMed: https://pubmed.gov/32445709. Full-text: https://doi.org/10.1016/S1473-3099(20)30424-2

Should we measure the "viral load"? Unfortunately, there is wide heterogeneity and inconsistency of the standard curves calculated from studies that provided Ct values from serial dilution samples and the estimated viral loads. According to the authors, precautions are needed when interpreting the Ct values of SARS-CoV-2 RT-PCR results shown in COVID-19 publications to avoid misunderstanding of viral load kinetics for comparison across different studies.

Luo X, Zhou W, Yan X, et al. **Prognostic value of C-reactive protein in patients with COVID-19**. Clin Infect Dis. 2020 May 23:ciaa641. PubMed: https://pubmed.gov/32445579. Full-text: https://doi.org/10.1093/cid/ciaa641

In 359 patients, CRP performed better than other parameters (age, neutrophil count, platelet count) in predicting adverse outcome. Besides, admission serum CRP level was identified as a moderate discriminator of disease severity.

Clinical

Petrilli CM, Jones SA, Yang J, et al. **Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study**. BMJ. 2020 May 22;369:m1966. PubMed: https://pubmed.gov/32444366. Full-text: https://doi.org/10.1136/bmj.m1966

Of 5,279 cases confirmed in a large medical center in New York, 52% were admitted to hospital, of whom 1,904 (69.5%) were discharged alive without hospice care and 665 (24.3%) were discharged to hospice care or died. Of 647 (23.6%) patients requiring mechanical ventilation, 391 (60.4%) died and 170 (26.2%) were extubated or discharged. The strongest risk for hospital admission was associated with age with an odds ratio of 37.9 for ages 75 years and older. Other risks were heart failure (OR 4.4), male sex (2.8), chronic kidney disease (2.6), and BMI >40 (2.5). Admission oxygen saturation of <88% (3.7), troponin level >1 (4.8), CRP >200 (5.1), and D dimer level >2500 (3.9) were more strongly associated with critical illness than age or comorbidities. Risk of critical illness decreased significantly over the study period. Similar associations were found for mortality alone.

Cormorbidities

Valente S, AnselmiF, Cameli M. **Acute coronary syndromes during COVID-19. European Heart Journal**, 2020, May 25. Full-text: https://doi.org/10.1093/eurheartj/ehaa457.

Brief guide for clinicians for managing different cases of STEMI/NSTEMI ACS with potential or known COVID-19 infection, based on recent worldwide evidence and standardization protocols.

Treatment

Remy KE, Brakenridge SC, Francois B, et al. **Immunotherapies for COVID-19: lessons learned from sepsis**. Lancet Respir Med. 2020 Apr 28. PubMed: https://pubmed.gov/32444269. Full-text: https://doi.org/10.1016/S2213-2600(20)30217-4

The hypothesis that quelling the cytokine storm with anti-inflammatory therapies directed at reducing interleukin-6 (IL-6), IL-1, or even tumour necrosis factor α (TNFα) might be beneficial has led to several ongoing trials. The authors are less enthusiastic and urge caution. Past attempts to block the cytokine storm associated with other microbial infections and with sepsis have not been successful and, in some cases, have worsened outcomes. Moreover, there is concern that suppressing the innate and adaptive immune system to address increased cytokine concentrations, could enable unfettered viral replication, suppress adaptive immunity, and delay recovery processes. There is growing recognition that potent immunosuppressive mechanisms are also prevalent in such patients. Giving immunosuppressive agents seems not to be a good idea.

Gregoire M, Le Turnier P, Gaborit BJ, et al. **Lopinavir pharmacokinetics in COVID-19 patients**. J Antimicrob Chemother. 2020 May 22. PubMed: https://pubmed.gov/32443151. Full-text: https://doi.org/10.1093/jac/dkaa195

Lopinavir concentrations in 12 COVID-19 patients at the Nantes University Hospital, France, were extremely high compared with those usually observed in HIV-infected patients (trough: 18,000 ng/mL versus 5365 ng/mL with 400/100 mg q12h).

27 May

Epidemiology

Randolph HE, Barreiro LB. **Herd Immunity: Understanding COVID-19**. Immunity Volume 52, ISSUE 5, P737-741, 2020. Full-text: https://doi.org/10.1016/j.immuni.2020.04.012

Overview on the basic concepts of herd immunity and its implications. There is no straightforward, ethical path to reach herd immunity, as the societal consequences of achieving it are devastating. Instead, an emphasis should be placed on policies that protect the most vulnerable groups in the hopes that

herd immunity will eventually be achieved as a "byproduct" of such measures, although not the primary objective itself.

Honigsbaum M. **Revisiting the 1957 and 1968 influenza pandemics**. Lancet May 25, 2020. Full-text: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31201-0/fulltext

Were people really more stoic in 1918, 1957, and 1968? Or were there other factors that might account for the dampened social and emotional responses to these pandemics? And what should historians make of functionalist and, arguably, selective readings of history that seek to draw moral lessons from the past? This intelligent article has some interesting thoughts on these issues.

Transmission

Hou YJ, Okuda K, Edwards CE, et al. **SARS-CoV-2 Reverse Genetics Reveals a Variable Infection Gradient in the Respiratory Tract**. Cell, May 26, 2020. Full-text: https://doi.org/10.1016/j.cell.2020.05.042

This study quantitated differences in ACE2 receptor expression and SARS-CoV-2 infectivity in the nose (high) vs the peripheral lung (low). If the nasal cavity is the initial site mediating seeding of the lung via aspiration, these studies argue for the widespread use of masks to prevent aerosol, large droplet, and/or mechanical exposure to the nasal passages.

Diagnostics

Wu J, Liu X, Liu J, et al. **Coronavirus Disease 2019 Test Results After Clinical Recovery and Hospital Discharge Among Patients in China**. JAMA Netw Open. 2020;3(5):e209759. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.9759

In this cross-sectional study, 10 of 60 patients previously diagnosed with and treated for COVID-19 had RT-PCR test results positive for SARS-CoV-2 from 4 to 24 days after index hospital discharge. In total, 6/10 patients had positive anal swab results. However, the infectivity remains unclear, as infectious viruses have not been isolated from stool samples. Positive results were presumed to be persistent viral shedding rather than reinfection.

Clinical

Lechien JR, Chiesa-Estomba CM, Hans S, et al. **Loss of Smell and Taste in 2013 European Patients With Mild to Moderate COVID-19**. Annals Int Med 2020, May 26. Full-text: https://doi.org/10.7326/M20-2428

The largest study to date, analysing these important symptoms. Of 2,013 patients, 1,754 patients (87%) reported loss of smell, whereas 1,136 (56%) reported taste dysfunction. Most patients had loss of smell after other general and otolaryngologic symptoms. Mean duration of olfactory dysfunction was 8.4 days. The prevalence of self-reported smell and taste dysfunction was higher than previously reported and may be characterized by different clinical forms. Anosmia may not be related to nasal obstruction or inflammation. Of note, only two thirds of patients reporting olfactory symptoms and who had objective olfactory testing had abnormal results.

Kuo CL, Pilling LC, Atkins JL, et al. **APOE e4 genotype predicts severe COVID-19 in the UK Biobank community cohort**. The Journals of Gerontology: May 26, 2020. Full-text: https://doi.org/10.1093/gerona/glaa131

The authors investigated the association between different ApoEe4 alleles and COVID-19 severity, using the UK Biobank data. ApoEe4e4 homozygotes were more likely to be COVID-19 test positives (OR = 2.31, 95% CI: 1.65 to 3.24) compared to e3e3 homozygotes. The ApoEe4e4 allele increased risks of severe COVID-19 infection, independent of pre-existing dementia, cardiovascular disease, and type 2 diabetes. This interesting observation needs to be confirmed (and explained).

Comorbidities

Lupo-Stanghellini MT, Messina C, Marktel S, et al. **Following-up allogeneic transplantation recipients during the COVID-19 pandemic**. Lancet Haematol. 2020 May 22:S2352-3026(20)30176-9. PubMed: https://pubmed.gov/32450053. Full-text: https://doi.org/10.1016/S2352-3026(20)30176-9

The authors describe their way of taking care of the most vulnerable patient groups using telemedicine. They contacted 236/465 adult patients who received an allogeneic transplantation. Physicians felt confident about the management of patients using teleconsultations, and patients—reassured that they were not left alone while in quarantine—provided positive feedback on this approach.

Gartshteyn Y, Askanase AD, Schmidt NM, et al. **COVID-19 and systemic lupus erythematosus: a case series**. Published: May 26, 2020. Full-text: https://doi.org/10.1016/S2665-9913(20)30161-2

Of 18 SLE patients with COVID-19, most recovered. Previous intake of immunosuppressants before admission to hospital did not seem to influence the severity of infection.

Junejo M, Girometti N, McOwan A. **HIV postexposure prophylaxis during COVID-19**. May 25, 2020. Full-text: https://doi.org/10.1016/S2352-3018(20)30146-6

Weekly prescriptions of PEP at a large center in London dropped from a peak of 54 (from Feb 17–23, 2020) to four (from March 30–April 5, 2020) during lockdown. The most obvious explanation for this decline is that individuals are engaging in less condomless sex during lockdown. However, this might also reflect people's reluctance to travel during this period, which would mean that individuals are not accessing the PEP they require.

Comment of the copy-editor: “And might also mean, that if they have less desire to travel, are hooking up less, and perhaps less sex is happening.”

Treatment

Ju B, Zhang Q, Ge J, et al. **Human neutralizing antibodies elicited by SARS-CoV-2 infection**. Nature. 2020 May 26. PubMed: https://pubmed.gov/32454513. Full-text: https://doi.org/10.1038/s41586-020-2380-z

As long as all other therapies fail or have only modest effects, antibodies are the hope for the near future. Isolation and characterization of 206 RBD-specific monoclonal antibodies were derived from single B cells of eight SARS-CoV-2 infected individuals. Some antibodies showed potent anti-SARS-CoV-2 neutralization activity that correlates with their competitive capacity with ACE2 for RBD binding. Surprisingly, neither the anti-SARS-CoV-2 antibodies nor the infected plasma cross-reacted with SARS-CoV or MERS-CoV RBDs, although substantial plasma cross-reactivity to their trimeric Spike proteins was found.

28 May

Epidemiology

Larochelle MR. **"Is It Safe for Me to Go to Work?" Risk Stratification for Workers during the Covid-19 Pandemic**. N Engl J Med. 2020 May 26. PubMed: https://pubmed.gov/32453518. Full-text: https://doi.org/10.1056/NEJMp2013413

A simple framework to help clinicians counsel patients about continuing to work in the midst of the pandemic based on their occupational risk of contracting SARS-CoV-2 and their risk of death if they are infected.

Campbell KH, Tornatore JM, Lawrence KE, et al. **Prevalence of SARS-CoV-2 Among Patients Admitted for Childbirth in Southern Connecticut**. JAMA. 2020 May 26. PubMed: https://pubmed.gov/32453390. Full-text: https://doi.org/10.1001/jama.2020.8904

From April 2, 2020, to April 29, 2020, screening and testing of patients admitted for childbirth was initiated at 3 Yale New Haven Health hospitals in southern Connecticut. Of 770 patients, 30 (3.9%) tested positive for SARS-CoV-2, of whom 22 (73%) were asymptomatic.

Transmission

Prather KA, Wang CC, Schooley RT. **Reducing transmission of SARS-CoV-2.** Science. 2020 Jun 26;368(6498):1422-1424. PubMed: https://pubmed.gov/32461212. Full-text: https://doi.org/10.1126/science.abc6197

This perspective clearly shows that masks and testing are necessary and essential to combat asymptomatic spread in aerosols and droplets. It cannot be repeated often enough: infectious aerosol particles can be released during breathing and speaking by asymptomatic infected individuals. No masking maximizes exposure, whereas universal masking results in the least exposure.

Zhang Y, Li Y, Wang L, Li M, Zhou X. **Evaluating Transmission Heterogeneity and Super-Spreading Event of COVID-19 in a Metropolis of China**. Int J Environ Res Public Health. 2020 May 24;17(10):E3705. PubMed: https://pubmed.gov/32456346. Full-text: https://doi.org/10.3390/ijerph17103705

Over the last few weeks, it has become very clear that some individuals spread to a disproportionate number of individuals, compared to most individuals who infect a few or no-one. This important paper looked at transmission heterogeneity and the emergence of these super-spreading events (SSEs). In total, 135 cases from official public sources in Tianjin, China were grouped into 43 transmission chains. The reproductive number R and the dispersion parameter k (lower value indicating higher heterogeneity) were estimated to be 0.67 (95% CI: 0.54-0.84) and 0.25 (95% CI: 0.13-0.88), respectively. Transmission was very heterogeneous and one SSE was identified. Transmission characteristics of COVID-19 need more exploration and investigation on a large scale.

Zhang W, Cheng W, Luo L, et al. **Secondary Transmission of Coronavirus Disease from Presymptomatic Persons, China**. Emerg Infect Dis. 2020 May 26;26(8). PubMed: https://pubmed.gov/32453686. Full-text: https://doi.org/10.3201/eid2608.201142

Contact-tracing surveillance data collected in Guangzhou, China during January 28 – March 15, 2020, to explore the secondary attack rate from different types of contact with 38 pre-symptomatic patients. The secondary attack rates (SAR) among household contacts was 16.1% and was 1.1% for social contacts, and 0 for workplace contacts. Older close contacts had the highest SAR compared to other age groups.

Comorbidities

Yahalom J, Dabaja BS, Ricardi U. **ILROG emergency guidelines for radiation therapy of hematological malignancies during the COVID-19 pandemic**. Blood 2020, 135 (21): 1829–1832. https://doi.org/10.1182/blood.2020006028

Realizing the need to reduce the exposure of patients and staff to potential infection with COVID-19, a task force makes recommendations for alternative radiation treatment schemes. The emphasis is on maintaining clinical efficacy and safety by increasing the dose per fraction while reducing the number of daily treatments.

Treatment

Goldman JD, Lye DC, Hui DS, et al. **Remdesivir for 5 or 10 Days in Patients with Severe Covid-19**. May 27, 2020. https://www.nejm.org/doi/full/10.1056/NEJMoa2015301?query=featured_home

In this randomized, open-label, Phase III trial in 397 hospitalized patients with severe COVID-19 and not requiring IMV, clinical improvement at day 14 was 64% with 5 days remdesivir and 54% with 10 days. After adjustment for (significant) baseline imbalances in disease severity, outcomes were similar. The most common adverse events were nausea (9%), worsening respiratory failure (8%), elevated ALT level (7%), and constipation (7%). Because the trial lacked a placebo control, it was not a test of efficacy for remdesivir.

Shi R, Shan C, Duan X, et al. **A human neutralizing antibody targets the receptor binding site of SARS-CoV-2**. Nature. 2020 May 26. PubMed: https://pubmed.gov/32454512. Full-text: https://doi.org/10.1038/s41586-020-2381-y

Another interesting specific human monoclonal antibody (MAb) from a convalescent patient. CB6 demonstrated potent neutralization activity *in vitro* against SARS-CoV-2 and worked in 6 rhesus monkeys at both prophylactic and treatment settings. This MAb recognizes an epitope that overlaps with ACE2 binding sites in SARS-CoV-2 receptor binding domain (RBD), thereby interfering with the virus/receptor interactions by both steric hindrance and direct interface-residue competition.

Treon SP, Castillo JJ, Skarbnik AP, et al. **The BTK inhibitor ibrutinib may protect against pulmonary injury in COVID-19–infected patients**. Blood 2020, 135: 1912–1915. https://doi.org/10.1182/blood.2020006288

Five Waldenstroem macroglobulinemia patients on Bruton tyrosine kinase (BTK) inhibitor ibrutinib, 420 mg/d, did not require hospitalization. Their course was marked by steady improvement, and resolution or near resolution of COVID-19 symptoms during the follow-up period. Clinical trials examining the benefit of BTK inhibitors to abrogate lung injury are being initiated.

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Epidemiology

Ball P, Maxmen A. **The epic battle against coronavirus misinformation and conspiracy theories.** Nature 2020, 581, 371-374. Full-text: https://doi.org/10.1038/d41586-020-01452-z

This article shows how analysts and researchers have been scrambling to track and analyse the disparate falsehoods floating around — both 'misinformation', which is wrong but not deliberately misleading, and 'disinformation',

which refers to organized falsehoods that are intended to deceive. Inaccurate information doesn't only mislead, but could be a matter of life and death if people start taking unproven drugs, ignoring public-health advice, or refusing a coronavirus vaccine if one becomes available.

Lam TT. **Tracking the genomic footprints of SARS-CoV-2 transmission**. Trends in Genetics 2020. Full-text: https://doi.org/10.1016/j.tig.2020.05.009

Analysis of SARS-CoV-2 genomes provides insights into the origin, transmission, spread and evolution. Brief review on current knowledge and research.

Virology, Immunology

Shen B, Yi X, Sun Y, et al. **Proteomic and Metabolomic Characterization of COVID-19 Patient Sera**. Cell May 27, 2020. Full-text: https://www.sciencedirect.com/science/article/pii/S0092867420306279 ● (IMPORTANT)

Molecular insights into the pathogenesis of SARS-CoV-2 infection. Authors applied proteomic and metabolomic technologies to analyze the proteome and metabolome of sera from COVID-19 patients and several control groups. Pathway analyses and network enrichment analyses of the 93 differentially expressed proteins showed that 50 of these proteins belong to three major pathways, namely activation of the complement system, macrophage function and platelet degranulation. It was found that 80 significantly changed metabolites were also involved in the three biological processes revealed in the proteomic analysis.

Park A, Iwasaki A. **Type I and Type III Interferons - Induction, Signaling, Evasion, and Application to Combat COVID-19.** Cell Host Microbe. 2020 Jun 10;27(6):870-878. PubMed: https://pubmed.gov/32464097. Full-text: https://doi.org/10.1016/j.chom.2020.05.008 ● (IMPORTANT)

The interferon (IFN) response constitutes the major first line of defense against viruses. This complex host defense strategy can, with accurate understanding of its biology, be translated into safe and effective antiviral therapies. In their comprehensive review, authors describe the recent progress in our understanding of both type I and type III IFN-mediated innate antiviral responses against human coronaviruses and discuss the potential use of IFNs as a treatment strategy.

Transmission

On Kwok K, Hin Chan HH, Huang Y, et al. **Inferring super-spreading from transmission clusters of COVID-19 in Hong Kong, Japan and Singapore**. J Hosp Infect. 2020 May 21:S0195-6701(20)30258-9. PubMed: https://pubmed.gov/32446721. Full-text: https://doi.org/10.1016/j.jhin.2020.05.027 ● (IMPORTANT)

Super-spreading events in an outbreak can change the nature of an epidemic. Therefore, it is useful for public health teams to determine if an ongoing outbreak has any contribution from such events, which may be amenable to interventions. The dispersion factor (k) from empirical data on clusters of epidemiologically-linked COVID-19 cases in Hong Kong, Japan and Singapore was relatively high, indicating that large cluster sizes, compatible with super-spreading, were unlikely.

Comorbidities

Kuderer NM, Choueiri TK, Shah DP. **Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study**. Lancet May 28, 2020. Full-text: https://doi.org/10.1016/S0140-6736(20)31187-9

Cohort study from the USA, Canada, and Spain, analysing 928 cancer patients with COVID-19. Median age was 66 years (IQR 57–76) and the most prevalent malignancies were breast (21%) and prostate (16%). In total 121 (13%) patients had died. Beside general risk factors (age, male sex etc), independent factors associated with increased mortality were an ECOG status of 2 or higher and "active" cancer.

Vizcarra P, Pérez-Elías M, Quereda C, et al. **Description of COVID-19 in HIV-infected individuals: a single-centre, prospective cohort**. Lancet HIV. Published: May 28, 2020. Full-text: https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(20)30164-8/fulltext ● (IMPORTANT)

Single center study from Madrid, comparing 51 HIV+ patients with COVID-19 (35 confirmed cases) with 1,288 HIV patients without COVID-19. Six patients were critically ill and two died. There was no evidence that any specific antiretroviral drug (such as tenofovir or PIs) affected COVID-19 susceptibility or severity.

Geerts H, van der Graaf PH. **Salvaging CNS Clinical Trials halted due to COVID-19**. CPT Pharmacometrics Syst Pharmacol. 2020 May 28. PubMed: https://pubmed.gov/32468710. Full-text: https://doi.org/10.1002/psp4.12535

COVID-19 has halted many ongoing CNS clinical trials, especially in Alzheimer's disease. While some of these trials will need to restart, others can re-start at different points with substantial protocol amendments. Authors propose the concept of mechanistic modeling-based virtual twin patients as a possible solution to harmonize the readouts from these complex and fragmented clinical datasets in a biologically relevant way.

Severe COVID-19

Maatman TK, Jalali F, Feizpour C, et al. **Routine Venous Thromboembolism Prophylaxis May Be Inadequate in the Hypercoagulable State of Severe Coronavirus Disease 2019**. Critical Care Medicine May 27, 2020. Full-text: https://doi.org/10.1097/CCM.0000000000004466 ● (IMPORTANT)

240 consecutive patients with confirmed SARS-CoV-2 were admitted to one of three US hospitals and 109 were critically ill. Venous thromboembolism was diagnosed in 31 patients (28%) 8 ± 7 days after hospital admission. Authors conclude that routine chemical venous thromboembolism prophylaxis may be inadequate in preventing venous thromboembolism in severe COVID-19.

Treatment

Hernandez AV, Roman YM, Pasupuleti V, et al. **Hydroxychloroquine or Chloroquine for Treatment or Prophylaxis of COVID-19: A Living Systematic Review**. Annals of Internal Medicine 27 May 2020. Full-text: https://doi.org/10.7326/M20-2496.

The main conclusion of this review is that there is insufficient and often conflicting evidence on the benefits and harms of using hydroxychloroquine or chloroquine to treat COVID-19. As such, it is impossible to determine the balance of benefits to harms. There are no assessments of hydroxychloroquine or chloroquine for prophylaxis against COVID-19.

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Epidemiology

Gonzalez-ReicheAS, Hernandez MM, Sullivan MJ, et al. **Introductions and early spread of SARS-CoV-2 in the New York City area**. Science 29 May 2020: eabc1917. Full-text: https://doi.org/10.1126/science.abc1917

A first analysis of the SARS-CoV-2 viral genotypes collected from patients seeking medical care in the New York City metropolitan area. Main message: The NYC epidemic has been mainly sourced from untracked transmission between the US and Europe, with limited evidence of direct introductions from China where the virus originated. Isolates were distributed throughout the phylogenetic tree; consistent with multiple independent introductions.

Sen S, Karaca-Mandic P, Georgiou A. **Association of Stay-at-Home Orders With COVID-19 Hospitalizations in 4 States**. JAMA May 27, 2020. Full-text: https://10.1001/jama.2020.9176

Staying at home works. In 4 US states (Colorado, Minnesota, Ohio, and Virginia) with stay-at-home orders, cumulative hospitalizations for COVID-19 deviated from projected best-fit exponential growth rates after these orders became effective. The deviation started 2 to 4 days sooner than the median effective date of each state's order and may reflect the use of a median incubation period for symptom onset and time to hospitalization to establish this date.

Virology

Peng Q, Peng R, Yuan B, et al. **Structural and biochemical characterization of nsp12-nsp7-nsp8 core polymerase complex from SARS-CoV-2**. Cell Reports. May 30, 2020. Full-text: https://10.1016/j.celrep.2020.107774

The replication of coronavirus is operated by a set of non-structural proteins (nsps) encoded by the open-reading frame 1a (ORF1a) and ORF1ab in its genome, which are initially translated as polyproteins followed by proteolysis cleavage for maturation. These proteins assemble into a multi-subunit polymerase complex to mediate the transcription and replication of viral genome. Among them, nsp12 is the catalytic subunit with RNA-dependent RNA polymerase (RdRp) activity. The nsp12 itself is capable of conducting polymerase reaction with extremely low efficiency, whereas the presence of nsp7 and nsp8 cofactors remarkably stimulates its polymerase activity. Using cryo-EM,

near-atomic resolution structure of SARS-CoV-2 nsp12-nsp7-nsp8 core polymerase complex is described.

Clinical

Price-Haywood EG, Burton J, Fort D, Seoane L. **Hospitalization and Mortality among Black Patients and White Patients with Covid-19**. N Engl J Med. 2020 May 27. PubMed: https://pubmed.gov/32459916. Full-text: https://doi.org/10.1056/NEJMsa2011686

It's poverty and obesity, but not race. In a large cohort of 3,481 patients in Louisiana, 76.9% of the patients who were hospitalized with COVID-19 and 70.6% of those who died were black, whereas blacks comprise only 31% of the population. Of note, black race was not associated with higher in-hospital mortality than white race, after adjustment for differences in sociodemographic and clinical characteristics on admission.

Zubair AS, McAlpine LS, Gardin T, et al. **Neuropathogenesis and Neurologic Manifestations of the Coronaviruses in the Age of Coronavirus Disease 2019: A Review**. JAMA Neurology May 29, 2020. Full-text: https://10.1001/jamaneurol.2020.2065 ● (IMPORTANT)

Viral neuro-invasion may be achieved by several routes, including transsynaptic transfer across infected neurons, entry via the olfactory nerve, infection of vascular endothelium, or leukocyte migration across the blood-brain barrier. This review summarizes available information regarding coronaviruses in the nervous system, identify the potential tissue targets and routes of entry of SARS-CoV-2 into the central nervous system.

Politi LS, Salsano E, Grimaldi M. **Magnetic Resonance Imaging Alteration of the Brain in a Patient With Coronavirus Disease 2019 (COVID-19) and Anosmia**. JAMA Neurology May 29, 2020. Full-text: https://10.1001/jamaneurol.2020.2125

Interesting case report, describing *in vivo* brain alteration during COVID-19. A patient with COVID-19 showed a signal alteration compatible with viral brain invasion in a cortical region (ie, posterior gyrus rectus). Slight and reversible olfactory bulb changes were also seen.

Yang R, Gui X, Xiong Y, et al. **Comparison of Clinical Characteristics of Patients with Asymptomatic vs Symptomatic Coronavirus Disease 2019 in Wuhan, China**. JAMA Netw Open, May 27 2020. Full-text: https://10.1001/jamanetworkopen.2020.10182i ● (IMPORTANT)

Case series, including carefully selected data for 78 patients (33 asymptomatic) from 26 cluster cases of exposure to the Hunan seafood market or close contact with other patients with COVID. Asymptomatic patients were younger and had a median shorter duration of viral shedding from nasopharynx swabs (median duration, 8 days vs 19 days)

Comorbidities

Tian J, Yuan X, Xiao J, et al. **Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study**. Lancet Oncology 2020, May 29. Full-text: https://10.1016/S1470-2045(20)30309-0

232 COVID-19 patients with cancer and were compared with 519 matched patients without cancer. Patients with cancer were more likely to have severe COVID-19 (64% versus 32%). Risk factors (of those well-known) for severe disease were advanced tumour stage (OR 2.60), elevated tumour necrosis factor α (1.22), elevated N-terminal pro-B-type natriuretic peptide (1.65).

COVIDSurg Collaborative. **Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study**. Lancet May 29, 2020. Full-text: https://doi.org/10.1016/S0140-6736(20)31182-X ● (IMPORTANT)

This large cohort includes 1128 patients who had surgery between Jan 1 and March 31, 2020, among them 835 (74%) emergency surgery and 280 (25%) elective surgery. SARS-CoV-2 infection was confirmed preoperatively in 294 (26%) patients. 30-day mortality was 24% and pulmonary complications occurred in 577 (51%). In adjusted analyses, 30-day mortality was associated with male sex (Odds Ratio 1.75), age 70 years or older (2.30), ASA grades 3–5 versus grades 1–2 (2.35), malignant versus benign (1.55), emergency versus elective surgery (1.67), and major versus minor surgery (1.52).

Treatment

Huet T, Beaussier H, Voisin O, et al. **Anakinra for severe forms of COVID-19: a cohort study**.Lancet Rheumatol 2020, May 29, 2020. https://doi.org/10.1016/S2665-9913(20)30164-8

This study from Paris compared 52 consecutive patients treated with anakinra with 44 historical patients. Admission to the ICU for invasive mechanical ventilation or death occurred in 25% patients in the anakinra group and 73% patients in the historical group. Treatment effect of anakinra remained significant in the multivariate analysis. Controlled trials are needed.

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Epidemiology

Jorden MA, Rudman SL, et al. **Evidence for Limited Early Spread of COVID-19 Within the United States, January–February 2020**. MMWR Morb Mortal Wkly Rep. 29 May 2020. Full-text: http://dx.doi.org/10.15585/mmwr.mm6922e1

Information from diverse data sources suggests that limited community transmission of SARS-CoV-2 in the United States occurred between the latter half of January and the beginning of February, following an importation from China. This importation initiated a lineage, the Washington State clade, which subsequently spread throughout the Seattle metropolitan area and possibly elsewhere. Several importations of SARS-CoV-2 from Europe followed in February and March. Of note, overall disease incidence before February 28 was too low to be detected through emergency department syndromic surveillance data.

Sehra ST, Salciccioli JD, Wiebe DJ, Fundin S, Baker JF. **Maximum Daily Temperature, Precipitation, Ultra-Violet Light and Rates of Transmission of SARS-Cov-2 in the United States**. Clin Infect Dis. 2020 May 30. PubMed: https://pubmed.gov/32472936. Full-text: https://doi.org/10.1093/cid/ciaa681

Transmission is likely to remain high at warmer temperatures. Using negative binomial regression modelling, authors investigated whether daily maximum temperature, precipitation and UV index were related to COVID-19 incidence. Incidence declined with increasing temperature up to 52°F and was somewhat lower at warmer versus cooler temperatures. However, the association between temperature and transmission was small.

Transmission

Chan JF, Yuan S, Zhang AJ, et al. **Surgical mask partition reduces the risk of non-contact transmission in a golden Syrian hamster model for Coronavirus Disease 2019 (COVID-19)**. Clin Infect Dis. 2020 May 30. PubMed: https://pubmed.gov/32472679. Full-text: https://doi.org/10.1093/cid/ciaa644

They work! Even in a hamster model. Surgical mask partition for challenged index or naïve hamsters significantly reduced transmission.

Diagnostics

Traugott M, Aberle SW, Aberle JH, et al. **Performance of SARS-CoV-2 antibody assays in different stages of the infection: Comparison of commercial ELISA and rapid tests**. J Infect Dis. 2020 May. PubMed: https://pubmed.gov/32473021. Full-text: https://doi.org/10.1093/infdis/jiaa305

Four commercial ELISAs and two rapid tests performed well in 77 patients with PCR-confirmed SARS-CoV-2 infection, grouped by intervals from symptom onset. While test sensitivities were low (<40%) within the first 5 days post disease onset, IgM-, IgA- and total antibody-ELISAs increased in sensitivity to >80% between the 6th and 10th day post-symptom onset. The evaluated tests (including IgG and rapid tests) provided positive results in all patients at or after the 11th day post-onset of disease.

Clinical

Phipps MM, Barraza LH, LaSota ED, et al. **Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large US Cohort**. Hepatology. 2020 May 30. PubMed: https://pubmed.gov/32473607. Full-text: https://doi.org/10.1002/hep.31404

One of the largest studies evaluating liver injury. Among 2,273 patients who tested positive, 45% had mild, 21% moderate, and 6.4% severe liver injury. In multivariate analysis, severe acute liver injury was significantly associated with elevated inflammatory markers including ferritin and IL-6. Peak ALT was significantly associated with death or discharge to hospice (OR 1.14, p = 0.044), controlling for age, body mass index, diabetes, hypertension, intubation, and renal replacement therapy.

Marijon E, Karam N, Jost D, et al. **Out-of-hospital cardiac arrest during the COVID-19 pandemic in Paris, France: a population-based, observational study**. Lancet Public Health. 2020 May 27:S2468-2667(20)30117-1. PubMed: https://pubmed.gov/32473113. Full-text: https://doi.org/10.1016/S2468-2667(20)30117-1

Staying at home is not always the best decision. During the COVID-19 pandemic in the Paris area, authors observed a significant (two-fold) and transient increase in the incidence of out-of-hospital cardiac arrest (OHCA), coupled with a major reduction in survival at hospital admission. Although this finding might be partly related to direct COVID-19 deaths, indirect effects related to lockdown and reorganisation of healthcare systems may account for a substantial part.

Lansbury L, Lim B, Baskaran V, Lim WS. **Co-infections in people with COVID-19: a systematic review and meta-analysis**. J Infect. 2020 May 27:S0163-4453(20)30323-6. PubMed: https://pubmed.gov/32473235. Full-text: https://doi.org/10.1016/j.jinf.2020.05.046

According to this review, low proportions of COVID-19 patients have a bacterial co-infection, less than in previous influenza pandemics. These findings do not support the routine use of antibiotics in the management of confirmed COVID-19 infection.

Treatment

Kupferschmidt K. **Scientists put survivors' blood plasma to the test**. Science 29 May 2020: Vol. 368, Issue 6494, pp. 922-923. Full-text: https://doi.org/10.1126/science.368.6494.922

Nice article describing convalescent plasma as a promising new strategy. However, controlled clinical data are still lacking. Other issues such as supply (may become a challenge), consistency (concentration differs) and risks (transfusion-related acute lung injury, in which transferred antibodies damage pulmonary blood vessels, or transfusion-associated circulatory overload) are also discussed.

Salazar E, Perez KK, Ashraf M, et al. **Treatment of COVID-19 Patients with Convalescent Plasma**. Am J Pathol. 2020 May 27. PubMed: https://pubmed.gov/32473109. Full-text: https://doi.org/10.1016/j.ajpath.2020.05.014

Some more clinical data on this strategy. In 25 patients with severe and/or life-threatening COVID-19 disease enrolled at a Houston hospital, convalescent plasma was safe. By day 14 post-transfusion, 19 (76%) patients had at least a 1-point improvement in clinical status and 11 were discharged.

June 2020

1 June

Epidemiology

Dora AV, Winnett A, Jatt LP, et al. **Universal and Serial Laboratory Testing for SARS-CoV-2 at a Long-Term Care Skilled Nursing Facility for Veterans - Los Angeles, California, 2020**. MMWR Morb Mortal Wkly Rep. 2020 May 29;69(21):651-655. PubMed: https://pubmed.gov/32463809. Full-text: https://doi.org/10.15585/mmwr.mm6921e1

Again and again: Test them all, immediately. On March 28, 2020, two residents of a long-term care skilled nursing facility in Los Angeles had positive test results. From March 29-April 23, all residents, regardless of symptoms, underwent serial (approximately weekly) nasopharyngeal PCR testing. 19/99 (19%) residents and 8/136 (6%) staff members had positive test results. 14/19 residents were asymptomatic at the time of testing. Among these, eight developed symptoms 1-5 days after specimen collection and were later classified as presymptomatic.

Looi MK. **Covid-19: Japan ends state of emergency but warns of "new normal"**. BMJ. 2020 May 26;369:m2100. PubMed: https://pubmed.gov/32457055. Full-text: https://doi.org/10.1136/bmj.m2100

Japan has done a good job. This article explains why. Public adherence to the rules, along with cluster tracing and a ban on mass gatherings, seems to have achieved success in bringing the outbreak under control, alongside widespread mask use and hygiene being a normal part of Japanese etiquette. Japan has ended its state of emergency a week after its new infections fell below 50 a day.

Transmission

Somsen GA, van Rijn C, Kooij S, Bem RA, Bonn D. **Small droplet aerosols in poorly ventilated spaces and SARS-CoV-2 transmission**. Lancet Respir Med. 2020 May 27. PubMed: https://pubmed.gov/32473123. Full-text: https://doi.org/10.1016/S2213-2600(20)30245-9 ●● (Outstanding)

Doors and windows open! Important study, analyzing droplet production due to coughs and speech by measuring the droplet size distribution, travel dis-

tance and velocity, and the airborne time in relation to the level of air ventilation (no ventilation, mechanical ventilation only, and mechanical ventilation supported by the opening of an entrance door and a small window). In the best ventilated room, after 30 s the number of droplets had halved, whereas with no ventilation this took about 5 min!

Tam PCK, Ly KM, Kernich ML, et al. **Detectable severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in human breast milk of a mildly symptomatic patient with coronavirus disease 2019 (COVID-19)**. Clin Infect Dis. 2020 May 30:ciaa673. PubMed: https://pubmed.gov/32472683. Full-text: https://doi.org/10.1093/cid/ciaa673

A second case of detectable SARS-CoV-2 RNA from human milk in a patient with COVID-19. Despite mild clinical symptoms, the patient had detectable virus in human milk in two separate samples taken ten days apart but interspersed with a number of negative results.

Clinical

Argenziano MG, Bruce SL, Slater CL, et al. **Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series**. BMJ. 2020 May 29. PubMed: https://pubmed.gov/32471884. Full-text: https://doi.org/10.1136/bmj.m1996

Characterization of the first 1000 consecutive patients with COVID-19 who received care at the emergency department in NYC hospital. Rates of renal complications were high: 33.9% of all patients and 78% of patients in intensive care units developed acute kidney injury. Concomitantly, 13.8% of all patients and 35.2% of patients in intensive care units required in-patient dialysis, leading to a shortage of equipment for dialysis and continuous renal replacement therapy.

Szekely Y, Lichter Y, Taieb P, et al. **The Spectrum of Cardiac Manifestations in Coronavirus Disease 2019 (COVID-19) - a Systematic Echocardiographic Study**. Circulation. 2020 May 29. PubMed: https://pubmed.gov/32469253. Full-text: https://doi.org/10.1161/CIRCULATIONAHA.120.047971

100 consecutive patients diagnosed with COVID-19 infection underwent complete echocardiographic evaluation within 24 hours of admission and were compared to reference values. Thirty two patients (32%) had a normal echocardiogram at baseline. The most common cardiac pathology was RV right ventricular (RV) dilatation and dysfunction (observed in 39% of patients),

followed by LV diastolic dysfunction (16%) and LV systolic dysfunction (10%). The authors concluded that LV systolic function is preserved in the majority of patients, but LV diastolic and RV function are impaired.

Severe COVID-19

Tremblay D, van Gerwen M, Alsen M, et al. **Impact of anticoagulation prior to COVID-19 infection: a propensity score-matched cohort study**. Blood. 2020 May 27. PubMed: https://pubmed.gov/32462179. Full-text: https://doi.org/10.1182/blood.2020006941 ● (IMPORTANT)

Empiric therapeutic anti-coagulation (AC) is now being employed in clinical practice in many centers, and will be evaluated in randomized clinical trials. To adjust for bias due to non-random allocation of potential covariates among COVID-19 patients, the authors applied propensity score matching methods. Among > 3000 patients, propensity matching yielded 139 patients who received AC and 417 patients who did not receive treatment with balanced variables between the groups. Results suggest that AC alone is unlikely to be protective for COVID-19-related morbidity and mortality.

Comorbidities

Shalev N, Scherer M, LaSota ED, et al. **Clinical characteristics and outcomes in people living with HIV hospitalized for COVID-19.** Clin Inf Dis 2020, May 30. Full-text: https://doi.org/10.1093/cid/ciaa635

31 people living with HIV (PLWH) were hospitalized for COVID-19. All patients were on antiretroviral therapy and virologically suppressed at the time of admission. One was mild (3%), 2 moderate (6.5%), 21 severe (60%) and 7 were critical (23%). At the time of analysis, 8 (25.8%) patients had died, 21 (67.7%) were alive and discharged and 2 (6.5%) were alive and hospitalized. Four deaths occurred in subjects over 65 years of age and 4 in patients between 50 and 65 years of age.

Treatment

Mahase E. Covid-19: **WHO halts hydroxychloroquine trial to review links with increased mortality risk**. BMJ. 2020 May 28. PubMed: https://pubmed.gov/32467095. Full-text: https://doi.org/10.1136/bmj.m2126

The World Health Organization has halted the hydroxychloroquine arm of the SOLIDARITY trial after a large registry study found that the drug was linked

with an increased risk of mortality and heart arrhythmias. The registry data are discussed.

Ektorp E**. Death threats after a trial on chloroquine for COVID-19**. Lancet Infect Dis. 2020 Jun;20(6):661. PubMed: https://pubmed.gov/32473139. Full-text: https://doi.org/10.1016/S1473-3099(20)30383-2

Whether or not to adopt HCQ to treat COVID-19 has turned into a political dispute that seems to benefit no one. This article describes how unfavorable outcomes have provoked animosity. Brazilian authors of the important JAMA study showing that higher doses are associated with higher mortality (the trial was discontinued) received death threats through social media and had to request police protection, which was kept for more than 2 weeks. The Brazilian president's son Eduardo Bolsonaro (who has 2 million Twitter followers) had called it "a fake study aimed at demonizing the drug".

2 June

Epidemiology

Lee H, Lee H, Song KH, et al. **Impact of Public Health Interventions on Seasonal Influenza Activity During the SARS-CoV-2 Outbreak in Korea**. Clin Infect Dis. 2020. PubMed: https://pubmed.gov/32472687. Full-text: https://doi.org/10.1093/cid/ciaa672

Efforts to activate high level national response not only led to a decrease in COVID-19, but also a substantial decrease in seasonal influenza activity. During the period of enforced social distancing from week 9 to 17 of 2020 in Korea, influenza hospitalization cases were 11.9-26.9-fold lower compared with previous seasons. This is good news, because nobody needs influenza.

Transmission

Ragan I, Hartson L, Pidcoke H, Bowen R, Goodrich R. **Pathogen reduction of SARS-CoV-2 virus in plasma and whole blood using riboflavin and UV light**. PLoS One. 2020 May 29;15(5. PubMed: https://pubmed.gov/32470046. Full-text: https://doi.org/10.1371/journal.pone.0233947. eCollection 2020

Plasma and whole blood units infected with SARS-CoV-2 underwent treatment with riboflavin and UV light. Riboflavin and UV light effectively reduced the titer of SARS-CoV-2 to the limit of detection in human plasma and by 3.30 ± 0.26 on average in whole blood. This is good news, because these

treatments may reduce blood-borne pathogens in high-risk settings while maintaining blood product quality.

Nagano T, Arii J, Nishimura M, et al. **Diligent medical activities of a publicly designated medical institution for infectious diseases pave the way for overcoming COVID-19: A positive message to people working at the cutting edge**. Clin Infect Dis. 2020 May 31. PubMed: https://pubmed.gov/32474577. Full-text: https://doi.org/10.1093/cid/ciaa694

Of 509 medical staff members working to treat COVID-19 patients at the Hyogo Prefectural Kakogawa Medical Center, a large medical institution for infectious diseases in Japan (mean number of hospitalized COVID-19 patients was 20), none had IgG antibodies for SARS-CoV-2 on May 1-8. This is good news, because results show that standard preventive measures against infectious diseases can prevent SARS-CoV-2 exposure in medical staff.

Diagnostics

Bullard J, Dust K, Funk D, et al. **Predicting infectious SARS-CoV-2 from diagnostic samples**. Clinical Infectious Diseases 2020, May 22 2020. Full-text: https://doi.org/10.1093/cid/ciaa638

This retrospective cross-sectional study determined PCR positive samples for their ability to infect cell lines. Of 90 samples, only 29% demonstrated viral growth. There was no growth in samples with a Ct > 24 (the lower the cycle threshold, the higher the viral load) or duration of symptoms > 8 days. This is very good news, because positive PCR does not mean infectivity. And infectivity duration is short.

Hao S, Lian J, Lu Y, et al. **Decreased B cells on admission was associated with prolonged viral RNA shedding from respiratory tract in Coronavirus Disease 2019: a case control study**. J Infect Dis. 2020 May 31. PubMed: https://pubmed.gov/32474608. Full-text: https://doi.org/10.1093/infdis/jiaa311

In 104 patients, a decrease in B cells was independently associated with prolonged viral RNA shedding. The viral RNA shedding from respiratory tract in patients with normal B cell count was significantly shorter than patients with decreased B cell on admission (median 11 vs 16 days). This is good news, because these observations may help to individualize monitoring of COVID-19 patients.

Ojha V, Mani A, Pandey NN, Sharma S, Kumar S. **CT in coronavirus disease 2019 (COVID-19): a systematic review of chest CT findings in 4410 adult patients**. Eur Radiol. 2020 May 30. PubMed: https://pubmed.gov/32474632. Full-text: https://doi.org/10.1007/s00330-020-06975-7

A total of 45 studies comprising 4,410 (!) patients were included in this review. Ground glass opacities (GGOs), whether isolated (50%) or coexisting with consolidations (44%) in bilateral and subpleural distribution, were the most prevalent chest CT findings in adult COVID-19 patients. Follow-up CT shows a progression of GGOs into a mixed pattern, reaching a peak at 10-11 days, before gradually resolving or persisting as patchy fibrosis. Younger people tend to have more GGOs. Older or sicker people tend to have more extensive involvement with consolidations. This is good news, because it's good to see that there are nerds out there (like us) who have nothing better to do than look through 4,410 CT scans.

Basu A, Zinger T, Inglima K, et al. **Performance of Abbott ID NOW COVID-19 rapid nucleic acid amplification test in nasopharyngeal swabs transported in viral media and dry nasal swabs, in a New York City academic institution**. J Clin Microbiol. 2020 May 29. PubMed: https://pubmed.gov/32471894. Full-text: https://doi.org/10.1128/JCM.01136-20

The authors evaluated the recently released Abbott ID NOW COVID-19 assay (uses isothermal nucleic acid amplification of the RdRp viral target) which is capable of producing positive results in as little as 5 minutes. Results were compared with RT-PCR Cepheid Xpert Xpress SARS-CoV-2 using nasopharyngeal swabs. Regardless of method of collection and sample type, the rapid test had negative results in a third of the samples that tested positive by PCR when using nasopharyngeal swabs in viral transport media and 45% when using dry nasal swabs. This is good news, well, because this is the-good-news-day. However, these rapid tests (if further improved) may find their role in clinical settings such as emergency departments where rapid diagnosis is crucial.

Comorbidties

Gianfrancesco M, Hyrich KL, Al-Adely S, et al. **Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry**. Ann Rheum Dis. 2020 May 29. PubMed:

https://pubmed.gov/32471903. Full-text: https://doi.org/10.1136/annrheumdis-2020-217871

Case series of 600 COVID-19 patients with rheumatic diseases from 40 countries. Nearly half of the cases were hospitalized (277 or 46%) and 55 (9%) died. In multivariable-adjusted models, prednisone dose ≥10 mg/day was associated with higher odds of hospitalization but not the use of conventional disease-modifying anti-rheumatic drug (DMARD) alone or in combination with biologics, the Janus Kinase inhibitors. This is good news because only high glucocorticoid exposure (which has well-known side effects anyway) is associated with a higher odds of hospitalization but not either DMARDs or NSAIDs.

Treatment

Irie K, Nakagawa A, Fujita H, et al. **Pharmacokinetics of Favipiravir in Critically Ill Patients with COVID-19.** Clin Transl Sci. 2020 May 31. PubMed: https://pubmed.gov/32475019. Full-text: https://doi.org/10.1111/cts.12827

In 7 patients with severe COVID-19 who were admitted to the intensive care unit and placed on mechanical ventilation, the favipiravir trough concentration was much lower than that of healthy subjects in a previous clinical trial. This is, however, good news, because this will lead to further PK studies that will help to optimize dosage and formulation – and improve efficacy of this drug.

Freedberg DE, Conigliaro J, Wang TC, et al. **Famotidine Use is Associated with Improved Clinical Outcomes in Hospitalized COVID-19 Patients: A Propensity Score Matched Retrospective Cohort Study**. Gastroenterology. 2020 May 21. PubMed: https://pubmed.gov/32446698. Full-text: https://doi.org/10.1053/j.gastro.2020.05.053

Famotidine is a histamine-2 receptor antagonist that suppresses gastric acid production. It is thought to inhibit the 3-chymotrypsin-like protease (3CLpro) and/or to act via its antagonism or inverse-agonism of histamine signalling. This retrospective study looked at 1,620 patients, including 84 patients (5.1%) who received different doses of famotidine within 24 hours of hospital admission. After adjusting for baseline patient characteristics, use of famotidine remained independently associated with a reduced risk for death or intubation (adjusted hazard ratio 0.42, 95% CI 0.21-0.85) and this remained unchanged after careful propensity score matching to further balance the covariables. Of note, there was no protective effect associated with use of PPIs. The maximum plasma ferritin value during hospitalization was lower with

famotidine, indicating that the drug blocks viral replication and reduces the cytokine storm. RCTs are underway, keep an eye on this! This is damned good news!

4 June

Epidemiology

Davies NG, Kucharski ADJ, Eggo RM, et al. **Effects of non-pharmaceutical interventions on COVID-19 cases, deaths, and demand for hospital services in the UK: a modelling study**. Lancet, June 02, 2020. Full-text: https://doi.org/10.1016/S2468-2667(20)30133-X

Herd immunity? Forget it. Using a stochastic age-structured transmission model to explore a range of intervention scenarios, tracking 66 million people in England, Wales, Scotland, and Northern Ireland, the authors projected a median unmitigated burden of 23 million (95% prediction interval 13–30) clinical cases and 350,000 deaths (170,000–480, 000) due to COVID-19 in the UK by December, 2021. Bad news because extreme measures are probably required to bring the epidemic under control.

Virology

Jamrozik E, Selgelid MJ. **COVID-19 human challenge studies: ethical issues**. Lancet Infect Dis. 2020 May 29:S1473-3099(20)30438-2. PubMed: https://pubmed.gov/32479747. Full-text: https://doi.org/10.1016/S1473-3099(20)30438-2

Human challenge studies could accelerate vaccine development, helping to test multiple candidate vaccines. This personal view on ethical issues explains why this will be difficult. This is bad news. However, this is also somewhat good news (exception today!), as the authors argue that human challenge studies can "reasonably be considered ethically acceptable insofar as such studies are accepted internationally and by the communities in which they are done, can realistically be expected to accelerate or improve vaccine development, have considerable potential to directly benefit participants, are designed to limit and minimise risks to participants, and are done with strict infection control measures to limit and reduce third-party risks."

Transmission

Eskew EA, Carlson CJ. **Overselling wildlife trade bans will not bolster conservation or pandemic preparedness**. Lancet Planetary Health, June 01, 2020. Full-text: https://doi.org/10.1016/S2542-5196(20)30123-6

Nice comment about a wildlife trade ban. Many (including us) have been quick to advocate for complete restriction of commercial trade, particularly in wet markets (like Wuhan) given their potential role as hotspots of cross-species viral transmission. This collective rhetoric suggests that eliminating wildlife trade is a simple, effective defense against zoonotic pandemics. According to the authors, stopping pandemics is not as simple as stopping wildlife trade. The bad news is that even with extensive wildlife trade bans, crippling zoonotic disease burden remains a near certainty.

Baer S, Kim MC, Kim JY. **Notice of Retraction: Effectiveness of Surgical and Cotton Masks in Blocking SARS-CoV-2**. Annals Int Med 2020, June 2. https://doi.org/10.7326/L20-0745

Come on, guys. "We are retracting our article....we had not fully recognized the concept of limit of detection (LOD) of the in-house RT-PCR used in the study (2.63 log copies/mL), and we regret our failure to express the values below LOD as "<LOD (value)." The LOD is a statistical measure of the lowest quantity of the analyte that can be distinguished from the absence of that analyte. Therefore, values below the LOD are unreliable and our findings are uninterpretable." We regret, too.

Baer S, Kim MC, Kim JY, et al. **Effectiveness of Surgical and Cotton Masks in Blocking SARS-CoV-2: A Controlled Comparison in 4 Patients**. Ann Intern Med. 2020 Apr 6. PubMed: https://pubmed.gov/32251511. Full-text: https://doi.org/10.7326/M20-1342

This was our comment on this study in April: "Very small study, but both surgical and cotton masks appeared to be ineffective in preventing the virus dissemination from the coughs of patients with COVID-19 to the environment and external mask surface."

Nardell EA, Nathavitharana RR. **Airborne Spread of SARS-CoV-2 and a Potential Role for Air Disinfection**. JAMA. 2020 Jun 1. PubMed: https://pubmed.gov/32478797. Full-text: https://doi.org/10.1001/jama.2020.7603

We will have to deal with upper-room germicidal UV filters (GUV). According to the authors, preparation for future respiratory viral pathogens should include consideration of the use of upper-room GUV to help mitigate airborne transmission. Sounds complicated, expensive. Bad news.

Diagnostics

Tang MS, Hocl KG, Logsdon NM, et al. **Clinical Performance of the Roche SARS-CoV-2 Serologic Assay**. Clinical Chemistry, June 2, 2020. hvaa132, https://doi.org/10.1093/clinchem/hvaa132.

The authors compared the clinical performance of several serologic assays (Abbott, EUROIMMUN and the Roche Elecsys assay). The Abbott assay demonstrated the fewest false negative results > 14d post-symptom onset and the fewest false positive results. While the Roche assay detected more positive results earlier after onset of symptoms, none of the assays demonstrated high enough clinical sensitivity before day 14 from symptom onset to diagnose acute infection. This is bad news because we still have to rely on PCR during the first two weeks.

Clinical

Kola L. **Global mental health and COVID-19**. Lancet Psychiatry June 02, 2020. Full-text: https://doi.org/10.1016/S2215-0366(20)30235-2

Intelligent comment. The psychosocial burden of COVID-19 will become increasingly evident in the coming months as the effects of social measures such as physical distancing, loneliness, death of friends and family members, and job losses manifest. Bad news, no good prospects (but the best author name of the month!).

Comorbidities

Rubin EJ. **Expression of Concern**: Mehra MR et al. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. N Engl J Med 2020, June 2. Full-text: https://doi.org/10.1056/NEJMoa2007621

Ooops. They don't trust their own authors (Mehra 2020). "Recently, substantive concerns have been raised about the quality of the information in that database", editor Eric Rubin writes, washing NEJM's hands in innocence. "We have asked the authors to provide evidence that the data are reliable. In the interim and for the benefit of our readers, we are publishing this Expression of Concern about the reliability of their conclusions." Ok. Let's wait and see

what happens. But bad news because even in a journal like NEJM, bad data quality is possible.

Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. **Cardiovascular disease, drug therapy, and mortality in Covid-19**. N Engl J Med. Full-text: https://doi.org/10.1056/NEJMoa2007621

This was the original work of concern. Bad news that we cannot trust it. This was our comment: "The first study analyzed a total of 8,910 COVID-19 patients (from 169 hospitals located in 11 countries) for whom discharge status was availably by March 29 (Mehra 2020). A total of 515 (5.8%) died in the hospital. Factors independently associated with an increased risk of in-hospital death were an age greater than 65 years (odds ratio, 1.93), coronary artery disease (2.70), heart failure (2.48; 95% CI, 1.62 to 3.79), cardiac arrhythmia (1.95; 95% CI, 1.33 to 2.86), chronic obstructive pulmonary disease (2.96; 95% CI, 2.00 to 4.40), and current smoking (1.79; 95% CI, 1.29 to 2.47). No increased risk was found for the use of ACE inhibitors (0.33; 95% CI, 0.20 to 0.54) or the use of ARBs (1.23; 95% CI, 0.87 to 1.74). Of note, use of either ACE inhibitors or statins was associated with better survival. However, these associations should be considered with extreme caution as the study design cannot exclude the possibility of confounding."

4 June

Treatment

Boulware DR, Pullen MF, Bangdiwala AS, et al. **A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19.** N Engl J Med. 2020 Jun 3:NEJMoa2016638. PubMed: https://pubmed.gov/32492293. Full-text: https://doi.org/10.1056/NEJMoa2016638 ●● (OUTSTANDING)

In total, 821 asymptomatic participants were randomized to receive hydroxychloroquine or placebo within 4 days after exposure (88% with a high-risk exposure). Incidence of confirmed SARS-CoV-2 was 11.8% with CQ and 14.3% with placebo. Side effects were more common with hydroxychloroquine than with placebo (40.1% vs. 16.8%), but no serious adverse reactions were reported.

This is bad news because after high-risk or moderate-risk exposure to Covid-19, HCQ did not prevent infection when used as postexposure prophylaxis within 4 days after exposure.

5 June

The Lancet and the NEJM: Retractions

We suspected it. Yesterday, two papers that were considered milestones in COVID-19 research (and were well-reviewed in our Top Ten section) were retracted by the authors.

Which papers are we talking about?

1. The first is a NEJM paper reporting that ACE inhibitors had proven to be harmless.

   ~~Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2007621.~~

   Mehra MR, Desai SS, Kuy SR, Henry TD, Patel AN. **Retraction: Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19**. N Engl J Med. June 4, 2020. https://doi.org/10.1056/NEJMc2021225

   "Because all the authors were not granted access to the raw data and the raw data could not be made available to a third-party auditor, we are unable to validate the primary data sources underlying our article, "Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19." We therefore request that the article be retracted. We apologize to the editors and to readers of the Journal for the difficulties that this has caused."

2. The second is a Lancet paper of the same group in which chloroquine-based therapies were more dangerous than effective.

   ~~Mehra MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet May 22, 2020~~

   Mehra MR, Ruschitzka F, Patel AN. **Retraction—Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis**. Lancet June 4, 2020. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31324-6/fulltext

   "After publication of our Lancet Article, several concerns were raised with respect to the veracity of the data and analyses conducted by Surgisphere Corporation and its founder and our co-author, Sapan Desai, in our publication. We launched an independent third-party peer review of Surgisphere...(they) informed us that Surgisphere

> would not transfer the full dataset." "We deeply apologize", and so on.

Apologize? This is inexcusable. Both papers are probably based on fake data. Gathered together and fantasized by a mailbox company. It is of concern to see how in the current situation the pressure on science is exploited by unscrupulous authors. And how such crooks will play into the hands of conspiracy theorists. But let's also hope that it be an incentive for these high-ranked medical journals to take a closer scrutiny of the submitted data in the future.

Scientific publishing is a fantastic business model and you're always surprised that everyone participates. Scientific authors write the manuscripts for free (they have to publish), according to rigorous instructions for authors, thick as a book. Reviewers read the submitted manuscripts within a few days, again, for free (they want to get their own papers peer-reviewed). There are many journals where authors are required to pay charges "to share in the high costs of production". Or supplemental data fees. Or reprints. They are all extra. On the other hand: readers pay. Subscribers pay, institutional subscribers pay (a lot). Pharmaceutical companies pay (a lot) for supported supplements. Conference organisations pay to get their abstract supplements published. In addition there is advertising revenue.

But where is the substantial contribution of the journals, apart from editing and layout? One has to take these cases as an opportunity to reflect on the practice of scientific publishers. It can't go on like this. Scientific journals must provide the resources for reviewing the data sets and basic information of their origin. They have enough money to do that. Simply publishing "Expressions of Concern" and then a "Retraction" without further comment of the editors is not enough. It's like playing Pontius Pilate, washing their hands of responsibility. We want to know how this could happen.

We have to postpone the fourth edition of COVID Reference another few days. Some parts need to be revised.

Fortunately, nothing has changed in the essential messages regarding the two topics of these fake papers. ACE inhibitors are probably not harmful in the current pandemic, and hydroxychloroquine and chloroquine are probably useless (Boulware 2020, Horby and Landray 2020).

References

Boulware DR, Pullen MF, Bangdiwala AS, et al. **A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19.** N Engl J Med 2020, June 3. Full-text: https://www.nejm.org/doi/full/10.1056/NEJMoa2016638

Horby P, Landray M. **Statement from the Chief Investigators of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial on hydroxychloroquine.** RECOVERY trial, 5 June 2020. Web: http://www.recoverytrial.net; PDF: https://www.recoverytrial.net/files/hcq-recovery-statement-050620-final-002.pdf

6 June

Virology

Sun SH, Chen Q, Gu HJ, et al. **A Mouse Model of SARS-CoV-2 Infection and Pathogenesis**. Cell Host Microbe. 2020 May 27:S1931-3128(20)30302-4. PubMed: https://pubmed.gov/32485164. Full-text: https://doi.org/10.1016/j.chom.2020.05.020

Human ACE2 knockin mice were generated by using CRISPR-Cas9 technology. Bottom line: SARS-CoV-2 led to robust replication in the lung, trachea, and brain. SARS-CoV-2 caused interstitial pneumonia and elevated cytokines. A high dose of virus could establish infection via an intragastric route.

Transmission

Chu DK, Akl EA, Duda S, Solo K, Yaacoub S, Schünemann HJ; **COVID-19 Systematic Urgent Review Group Effort (SURGE) study authors. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis**. Lancet. 2020 Jun 1. PubMed: https://pubmed.gov/32497510. Full-text: https://doi.org/10.1016/S0140-6736(20)31142-9 ● (IMPORTANT)

Nothing really new, but this incredible work had to be done. This systematic review identified 172 observational studies across 16 countries and six continents and 44 relevant comparative studies in health-care and non-health-care settings. Transmission of viruses was lower with physical distancing of 1 m or more, compared with a distance of less than 1 m (n=10,736, pooled adjusted odds ratio 0.18), protection was increased as distance was lengthened. Face mask use could result in a large reduction in risk of infection (n=2,647; AOR

0.15), stronger associations with N95 or similar respirators compared with disposable surgical masks or similar. Eye protection also was helpful (n=3,713; AOR 0.22). The findings support face masks, eye protection and physical distancing of 1 m or more.

Iannone P, Castellini G, Coclite D, et al. **The need of health policy perspective to protect Healthcare Workers during COVID-19 pandemic. A GRADE rapid review on the N95 respirators effectiveness**. PLoS One. 2020 Jun 3. PubMed: https://pubmed.gov/32492045. Full-text: https://doi.org/10.1371/journal.pone.0234025. eCollection 2020

Another review of N95 masks. Four RCTs involving 8,736 HCWs were included. There was no direct high quality evidence on whether N95 respirators are better than surgical masks for HCWs protection from SARS-CoV-2. However, wearing N95 respirators could prevent 73 more clinical respiratory infections per 1000 HCWs compared to surgical masks (low quality evidence).

Fischer RJ, Morris DH, van Doremalen N, et al. **Effectiveness of N95 Respirator Decontamination and Reuse against SARS-CoV-2 Virus**. Emerg Infect Dis. 2020 Jun 3;26(9). PubMed: https://pubmed.gov/32491983. Full-text: https://doi.org/10.3201/eid2609.201524

Recycle your masks 2-3 times but not more! Authors have analyzed 4 different decontamination methods – UV light (260–285 nm), 70ºC dry heat, 70% ethanol, and vaporized hydrogen peroxide (VHP), for their ability to reduce contamination with infectious SARS-CoV-2 and their effect on N95 respirator function. UV light inactivated virus rapidly from steel but more slowly on N95 fabric, probably because of its porous nature. Heat caused more rapid inactivation on N95 than on steel; inactivation rates on N95 were comparable to UV. In conclusion, N95 respirators can be decontaminated and reused up to 3 times by using UV light and VHP and 1–2 times by using dry heat. Subsequent rounds of decontamination caused sharp drops in filtration performance.

Diagnostics

Tu YP, Jennings R, Hart B, et al. **Swabs Collected by Patients or Health Care Workers for SARS-CoV-2 Testing**. N Engl J Med. 2020 Jun 3. PubMed: https://pubmed.gov/32492294. Full-text: https://doi.org/10.1056/NEJMc2016321 ● (Important)

Let the patients do their own swabs! A total of 530 patients with upper respiratory infection were provided with instructions and asked to collect tongue,

nasal, and mid-turbinate samples. A nasopharyngeal (NP) sample was then collected from the patient by a HCW. When this NP sample was used as the comparator, the estimated sensitivities of the tongue, nasal, and mid-turbinate samples collected by the patients were 89.8%, 94.0% and 96.2%, respectively. This study shows the clinical usefulness of these samples. This may reduce PPE use and provide a more comfortable patient experience.

Woloshin S, Patel N, Kesselheim AS. **False Negative Tests for SARS-CoV-2 Infection - Challenges and Implications.** N Engl J Med. 2020 Jun 5. PubMed: https://pubmed.gov/32502334. Full-text: https://doi.org/10.1056/NEJMp2015897

Important article on false negative tests (which are frequent), with several conclusions. According to the authors, FDA should ensure that manufacturers provide details of tests' clinical sensitivity and specificity at the time of market authorization. It will also be important to develop prediction rules for estimating the pre-test probability of infection (for asymptomatic and symptomatic people) to allow calculation of post-test probabilities after positive or negative results.

Clinical

Oran DP, Topol EJ. **Prevalence of Asymptomatic SARS-CoV-2 Infection: A Narrative Review**. Ann Intern Med. 2020 Jun 3. PubMed: https://pubmed.gov/32491919. Full-text: https://doi.org/10.7326/M20-3012

Review of the available evidence on asymptomatic SARS-CoV-2 infection. Asymptomatic persons seem to account for approximately 40-45% of infections, and they can transmit the virus to others for an extended period, perhaps longer than 14 days. The absence of COVID-19 symptoms might not necessarily imply an absence of harm as subclinical lung abnormalities are frequent.

Severe COVID-19

Al-Samkari H, Karp Leaf RS, Dzik WH, et al. **COVID and Coagulation: Bleeding and Thrombotic Manifestations of SARS-CoV2 Infection**. Blood. 2020 Jun 3:blood.2020006520. PubMed: https://pubmed.gov/32492712. Full-text: https://doi.org/10.1182/blood.2020006520

Retrospective study, describing the rate and severity of hemostatic and thrombotic complications of 400 hospital-admitted COVID-19 patients (144 critically ill), receiving standard-dose prophylactic anticoagulation. The

overall and major bleeding rates were 4.8% and 2.3%. RCTs are needed to determine any potential benefit of intensified anticoagulant prophylaxis in COVID-19 patients.

Treatment

Li L, Zhang W, Hu Y, et al. **Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial**. JAMA. 2020 Jun 3. PubMed: https://pubmed.gov/32492084. Full-text: https://doi.org/10.1001/jama.2020.10044 ● (IMPORTANT)

The first randomized trial of well-characterized plasma units with a high titer of antibody to SARS-CoV-2. Unfortunately, the study was terminated before it reached its targeted original sample size of 200 patients; only 103 were enrolled (when the epidemic was under control in China, no more patients could be recruited). Consequently, the study was underpowered. Of 103 patients who were randomized, clinical improvement (discharged alive or reduction of 2 points on a 6-point disease severity scale) occurred within 28 days in 52% vs 43%. There was no significant difference in 28-day mortality (16% vs 24%) or time from randomization to discharge. Of note, convalescent plasma treatment was associated with a negative conversion rate of viral PCR at 72 hours in 87% of the convalescent plasma group versus 38% (OR, 11.39). Main take-homes: convalescent plasma is not a silver bullet and antiviral efficacy does not necessarily lead to better survival.

Casadevall A, Joyner MJ, Pirofski LA. **A Randomized Trial of Convalescent Plasma for COVID-19-Potentially Hopeful Signals**. JAMA. 2020 Jun 3. PubMed: https://pubmed.gov/32492105. Full-text: https://doi.org/10.1001/jama.2020.10218

Careful discussion of the previous study. According to the authors, the study provides an important signal of possible benefit in the subgroup of severely ill patients and suggests that high titer antibody against SARS-CoV-2 may have antiviral efficacy. These results suggest that future studies should focus on determining efficacy in less severely ill patients.

7 June

Epidemiology

Li Z, Chen Q, Feng L, et al. **Active case finding with case management: the key to tackling the COVID-19 pandemic**. The Lancet, June 4, 2020. https://doi.org/10.1016/S0140-6736(20)31278-2

Learning from China. Case finding and management, with identification and quarantine of close contacts: the authors describe the next steps planned in China following the containment effort.

Virology

Cyranoski D. **The biggest mystery: what it will take to trace the coronavirus source**. Nature 2020, June 05. Full-text: https://www.nature.com/articles/d41586-020-01541-z

Elegant article summarizing the current (and limited) knowledge of the origin of SARS-CoV-2. Most researchers say the more likely explanation is that bats passed it to an intermediate animal, which then spread it to people. However, this finding will be tricky, as will calming speculations of a "lab escape". This would require a forensic investigation, looking for viruses that matched the genetic sequence of SARS-CoV-2 and. Authorities would need to take samples from the lab, interview staff, review lab books and records of safety incidents, and see what types of experiment researchers had done.

Transmission

Han MS, Seong MW, Kim N, et al. **Viral RNA Load in Mildly Symptomatic and Asymptomatic Children with COVID-19, Seoul**. Emerg Infect Dis. 2020 Jun 4;26(10). PubMed: https://pubmed.gov/32497001. Full-text: https://doi.org/10.3201/eid2610.202449

This study raises doubts on the hypothesis that children are less infectious. Of 12 children (median 6.5 years), 9 were mildly symptomatic and 3 were asymptomatic. Viral RNA load in the nasopharyngeal swabs (and saliva) peaked early at high levels, achieving a median of 7.56 (range 6.19–10.56) $\log_{10}$ copies/mL. Along with positive SARS-CoV-2 RNA in nasopharyngeal swabs, viral RNA was detectable at high concentration for > 3 weeks in fecal samples.

Diagnostics

Hung DL, Li X, Chiu KH, et al. **Early Morning Versus Spot Posterior Oropharyngeal Saliva for Diagnosis of SARS-CoV-2 Infection: Implication of Timing of Specimen Collection for Community-wide Screening**. Open Forum Infectious Diseases, June 7. Full-text: https://doi.org/10.1093/ofid/ofaa210

The cycle threshold (Ct) PCR values (low = more virus) were compared in posterior oropharyngeal saliva, collected at five different time points within the same day from 18 COVID-19 patients. There was an overall trend of lower Ct values from specimens collected in the early morning, with a gradual decrease of viral load towards night time. Eight out of 13 subjects had highest viral load in the early morning than the rest of the four time points. The results suggest a diurnal variation of viral shedding from the upper respiratory tract.

Comorbidities

Belli LC, Duvoux C, Karam V, et al. **COVID-19 in liver transplant recipients: preliminary data from the ELITA/ELTR registry**. Lancet Gastroenterology & Hepatology, June 4, 2020. Full-text: https://doi.org/10.1016/S2468-1253(20)30183-7

First large analysis on liver transplant recipients. At a median follow-up of 18 days, 16/100 died from COVID-19. Of note, mortality was observed only in patients aged 60 years or older (16/73) and was more common in male recipients than in female recipients. Although not statistically significant, more patients who were transplanted at least 2 years earlier died than did those who received their transplant within the past 2 years (15/82, 18% vs 1/21, 5%).

Severe COVID

Ferreyro BL, Angriman F, Munshi L, et al. **Association of Noninvasive Oxygenation Strategies With All-Cause Mortality in Adults With Acute Hypoxemic Respiratory Failure**. JAMA June 4, 2020. Full-text: https://doi.org/10.1001/jama.2020.9524

For this network meta-analysis of trials of adult patients with acute hypoxemic respiratory failure, the authors included 25 studies with 3,804 patients. Compared with standard oxygen therapy, helmet NIV (3 trials with 330 patients), face mask NIV (14 trials with 1725 patients) and HFNC (5 trials with 1479 patients) were associated with a lower risk of endotracheal intubation.

Both forms of NIV, helmet and face mask, were also associated with a lower risk of death.

Patel BK, Kress JP, Hall JB. **Alternatives to Invasive Ventilation in the COVID-19 Pandemic**. JAMA June 4, 2020. Full-text: https://doi.org/10.1001/jama.2020.9611

This article reviews the meta-analysis and describes how COVID-19 has accelerated the need to add clarity to the ongoing debate of whether to intubate early and, if not, which type of non-invasive support (NIV, HFNC, or standard oxygen therapy) is the most efficacious. Future clinical trials comparing these strategies should not focus on declaring a "winner" *per se* but rather on identifying the patient phenotypes that stand to benefit from each non-invasive oxygenation support method. According to the authors, a heterogeneous syndrome like AHRF requires multiple options.

Von Weyhern C, Kaufmann I, Neff F, Kremer M. **Early evidence of pronounced brain involvement in fatal COVID-19 outcomes**. The Lancet, June 4, 2020. Full-text: https://doi.org/10.1016/S0140-6736(20)31282-4

Autopsy findings of six patients (four men and two women, aged 58–82 years) who died from COVID-19 in April 2020. A pronounced CNS involvement with pan-encephalitis, meningitis, and brainstem neuronal cell damage were key events in all cases. In patients younger than 65 years, CNS hemorrhage was a fatal complication of COVID-19.

Treatment

Ucciferri C, Auricchio A, Di Nicola M, et al. **Canakinumab in a subgroup of patients with COVID-19**. Lancet Rheumatology, June 4, 2020. https://doi.org/10.1016/S2665-9913(20)30167-3

Canakinumab is human monoclonal antibody against IL-1 β, approved for treatment of juvenile rheumatoid arthritis and other chronic autoinflammatory syndromes. In a pilot trial, 10 patients with hyperinflammation (defined as CRP ≥ 50 mg/L) and respiratory failure showed a rapid improvement in serum inflammatory biomarkers and an improvement in oxygenation.

Pediatrics

Toubiana J, Poirault C, Corsia A, et al. **Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study**. BMJ. 2020 Jun 3;369:m2094. PubMed: https://pubmed.gov/32493739. Full-text: https://doi.org/10.1136/bmj.m2094

Of 21 children and adolescents (3.7-16.6 years, 19 with recent SARS-CoV-2 infection) with features of Kawasaki disease who were admitted between 27 April and 11 May 2020, 12 (57%) presented with Kawasaki disease shock syndrome and 16 (76%) with myocarditis. 17 (81%) required intensive care support. All 21 patients had noticeable gastrointestinal symptoms and high levels of inflammatory markers. All 21 patients received intravenous immunoglobulin and 10 (48%) also received corticosteroids. The clinical outcome was favourable in all patients.

8 June

Epidemiology

Xu X, Sun J, Nie S, et al. **Seroprevalence of immunoglobulin M and G antibodies against SARS-CoV-2 in China**. Nat Med. 2020 Jun 5. PubMed: https://pubmed.gov/32504052. Full-text: https://doi.org/10.1038/s41591-020-0949-6

To estimate the cumulative prevalence, authors evaluated IgM and IgG antibodies in 17,368 individuals from Wuhan, China. The seropositivity in Wuhan was low, varying between 3.2% and 3.8% in different sub-cohorts. As seen in other studies, an early and a higher level of IgG response was observed, compared to IgM.

Graham N, Junghans C, Downes R, et al. **SARS-CoV-2 infection, clinical features and outcome of COVID-19 in United Kingdom nursing homes**. J Infect. 2020 Jun 3:S0163-4453(20)30348-0. PubMed: https://pubmed.gov/32504743. Full-text: https://doi.org/10.1016/j.jinf.2020.05.073

Outbreak investigation involving 394 residents and 70 staff in 4 nursing homes in central London. Overall, 26% of residents died over a two-month period. Systematic testing identified 40% of residents as positive for SARS-CoV-2 and of these, 43% were asymptomatic and 18% had only atypical symptoms during the two weeks prior to testing. Of note, this was also true of

many residents in the days leading up to death indicating that even in severe COVID-19, fever and cough were commonly absent. 4% of asymptomatic staff also tested positive.

Immunology

Subbarao K, Mahanty S. **Respiratory Virus Infections: Understanding COVID-19**. Immunity. 2020 May 20:S1074-7613(20)30212-0. PubMed: https://pubmed.gov/32497522. Full-text: https://doi.org/10.1016/j.immuni.2020.05.004

Nice review about the immune response to respiratory viruses. What happens when the virus reaches the respiratory mucosa? What are the consequences of infection in the host?

Virology, Vaccine

Wang H, Zhang Y, Huang B, et al. **Development of an inactivated vaccine candidate, BBIBP-CorV, with potent protection against SARS-CoV-2**. Cell 2020, June 06. Full-text: https://doi.org/10.1016/j.cell.2020.06.008

Will this be the first vaccine? Compared with the adenovirus-vectored and the DNA vaccine, inactivated vaccine development and production is a conventional and mature technology (main pro: large amounts of vaccine doses can be easily manufactured, main con: safety issues, including an antibody-dependent worsening of the infection). BBIBP-CorV, an inactivated SARS-CoV-2 vaccine, induced high levels of neutralizing antibody in several animal models, including 8 rhesus macaques, protecting them against SARS-CoV-2 infection. There was no observable antibody-dependent infection enhancement or immunopathological exacerbation. A Phase I clinical trial of BBIBP-CorV is currently in progress and a Phase II clinical trial has recently been initiated.

Transmission

Newman A, Smith D, Ghai RR, et al. **First Reported Cases of SARS-CoV-2 Infection in Companion Animals - New York, March-April 2020.** MMWR Morb Mortal Wkly Rep. 2020 Jun 12;69(23):710-713. PubMed: https://pubmed.gov/32525853. Full-text: https://doi.org/10.15585/mmwr.mm6923e3

American cats are not protected: Two domestic cats with respiratory illnesses lasting 8 and 10 days were the first reported companion animals with SARS-

CoV-2 infection in the United States. Both cats were owned by persons with suspected or confirmed COVID-19. According to the authors, persons with COVID-19 should avoid contact with animals. Companion animals that test positive for SARS-CoV-2 should be monitored and separated from persons and other animals until they recover. Good news: both cats fully recovered.

Diagnostics

Cheng MP, Yansouni CP, Basta NE, et al. **Serodiagnostics for Severe Acute Respiratory Syndrome–Related Coronavirus-2**. Annals Int Med 2020, Jun 4. Full-text: https://doi.org/10.7326/M20-2854

For SARS-CoV-2, the accuracy of antibody test results and the appropriate test interpretation both depend on clinical context. This article discusses key use cases for SARS-CoV-2 antibody detection tests and their application to serologic studies, reviews currently available assays, highlights key areas of ongoing research, and proposes potential strategies for test implementation. This review also includes a decision tree for interpreting antibody test results.

Long DR, Gombar S, Hogan CA. **Occurrence and Timing of Subsequent SARS-CoV-2 RT-PCR Positivity Among Initially Negative Patients**. Clinical Infectious Diseases 2020, June 7. Full-text: https://doi.org/10.1093/cid/ciaa722

If the first PCR is negative, a second PCR only yields a small number of positive results. Using data for 20,912 patients, authors analyzed the frequency of SARS-CoV-2 RT-PCR test discordance among individuals initially testing negative by nasopharyngeal swab who were retested on clinical grounds within 7 days. The frequency of subsequent positivity within this window was only 3.5% and similar across institutions.

Treatment

Roschewski M, Lionakis MS, **Sharman JP, et al. Inhibition of Bruton tyrosine kinase in patients with severe COVID-19**. Science Immunology 05 Jun 2020: Vol. 5, Issue 48, eabd0110. Full-text: https://doi.org/10.1126/sciimmunol.abd0110

Ex vivo analysis revealed significantly elevated bruton tyrosine kinase (BTK, regulates macrophage signalling and activation) activity, as evidenced by autophosphorylation, and increased IL-6 production in blood monocytes from patients with severe COVID-19 compared with blood monocytes from healthy

volunteers. In a pilot study, 19 patients with severe COVID-19 received the BTK inhibitor acalabrutinib. Within 10-14 days, oxygenation improved "in a majority of patients", often within 1-3 days, and inflammation markers and lymphopenia normalized quickly in most patients. At the end of acalabrutinib treatment, 8/11 (72.7%) patients in the supplemental oxygen cohort had been discharged on room air. These results suggest that targeting excessive host inflammation with a BTK inhibitor is a therapeutic strategy. A confirmatory RCT is underway.

Pediatrics

Whittaker E, Bamford A, Kenny J, et al. **Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2**. JAMA. Published online June 8, 2020. Full-text: https://doi.org/10.1001/jama.2020.10369

This case series included 58 hospitalized children, meeting definitional criteria for (attention, a novel term/syndrome) "PIMS-TS", including fever, inflammation, and organ dysfunction. Of these children, all had fever and nonspecific symptoms, such as abdominal pain (53%), rash (52%), and conjunctival injection (45%); 50% developed shock and required inotropic support or fluid resuscitation; 22% met diagnostic criteria for Kawasaki disease; and 14% had coronary artery dilatation or aneurysms. Some clinical and laboratory characteristics had important differences compared with Kawasaki disease, Kawasaki disease shock syndrome, and toxic shock syndrome.

McCrindle BW, Manlhiot C. **SARS-CoV-2–Related Inflammatory Multisystem Syndrome in Children Different or Shared Etiology and Pathophysiology as Kawasaki Disease**? JAMA June 8, 2020. Full-text: https://doi.org/10.1001/jama.2020.10370

Nice editorial on current knowledge (and knowledge gaps) on PIMS-TS and Kawasaki Disease (KD), noting that the differences between PIMS-TS and Kawasaki Disease (KD) are just as interesting as the similarities. For PIMS-TS, SARS-CoV-2 may be acting either as the trigger or an immune-modulating factor. 9 June

9 June

Epidemiology

Flaxman S, Mishra S, Gandy A, et al. **Estimating the effects of non-pharmaceutical interventions on COVID-19 in Europe**. Nature. 2020 Jun 8. PubMed: https://pubmed.gov/32512579. Full-text: https://doi.org/10.1038/s41586-020-2405-7 ● (IMPORTANT)

This world-leading group of epidemiologists and statisticians estimated the total infection rates across 11 European countries. Main results: between 12 and 15 million individuals have been infected with SARS-CoV-2 up to May 4th, representing between 3.2% and 4.0% of the population. Percentages of total population infected were for Austria 0.76% (0.59% - 0.98%), Belgium 8.0 % (6.1% - 11%), Denmark 1.0% (0.81% - 1.4%), France 3.4% (2.7% - 4.3%), Germany 0.85% (0.66% - 1.1%), Italy 4.6% (3.6% - 5.8%), Norway 0.46% (0.34% - 0.61%), Spain 5.5% (4.4% - 7.0%), Sweden 3.7% (2.8% - 5.1%), Switzerland 1.9% (1.5% - 2.4%) and United Kingdom 5.1% (4.0% - 6.5%). Results also showed that major non-pharmaceutical interventions and lockdown in particular have had a large effect on reducing transmission.

Deng X, Gu W,Federman S, et al. **Genomic surveillance reveals multiple introductions of SARS-CoV-2 into Northern California**. Science 08 Jun 2020. Full-text: https://doi.org/10.1126/science.abb9263

Detective work, analysing the genomic epidemiology of SARS-CoV-2 in Northern California from late January to mid-March 2020, using samples from 36 patients spanning 9 counties and the Grand Princess cruise ship. Phylogenetic analyses revealed the cryptic introduction of at least 7 different SARS-CoV-2 lineages into California, including epidemic WA1 strains associated with Washington State, with a lack of predominant lineage, and limited transmission between communities.

Immunology

Suthar MS, Zimmerman MG, Kauffman RC, et al. **Rapid generation of neutralizing antibody responses in COVID-19 patients**. Cell Rep Med June 05, 2020. Full-text: https://doi.org/10.1016/j.xcrm.2020.100040

A robust humoral immune response occurs early during severe or moderate COVID-19 infections: in this cross-sectional study of 44 hospitalized COVID-19 patients, receptor-binding domain (RBD)-specific IgG responses became detectable in all patients 6 days after PCR confirmation. Neutralizing antibody

titers were detectable in 40/44 cases, mostly by 20 days of symptom onset. Of note, RBD-specific IgG titers seemed to correlate with the neutralizing potency, indicating that RBD-specific IgG titers could be used as a surrogate of neutralization activity against SARS-CoV-2 infection.

Seydoux E, Homad LJ, MacCamy AJ, et al. **Analysis of a SARS-CoV-2 infected individual reveals development of potent neutralizing antibodies to distinct epitopes with limited somatic mutation**. Immunity June 05, 2020. Full-text: https://doi.org/10.1016/j.immuni.2020.06.001

The authors isolated B cells specific for the SARS-CoV-2 envelope glycoprotein spike (S) from a COVID-19-infected subject. Main findings: The 45 S-specific monoclonal antibodies generated had undergone minimal somatic mutation, with limited clonal expansion. Most anti-S antibodies that were generated in this patient during the first weeks of COVID-19 infection were non-neutralizing and targeted epitopes outside the RBD. Neutralizing antibodies targeting the interaction of the S protein with ACE2 were minimally mutated.

Gutierrez L, Beckford J, Alachkar H. **Deciphering the TCR repertoire to solve the COVID-19 mystery**. Trends Pharmacol Sci. June 03, 2020. Full-text: https://www.cell.com/trends/pharmacological-sciences/fulltext/S0165-6147(20)30130-9

Outstanding article on unresolved questions. Why do some patients develop severe disease, while others do not; and what roles do genetic variabilities play in the individual immune response to this viral infection? The authors discuss the critical role T cells play in the orchestration of the antiviral response underlying the pathogenesis of COVID-19.

Transmission

Matson MJ, Yinda CK, Seifert SN, et al. **Effect of Environmental Conditions on SARS-CoV-2 Stability in Human Nasal Mucus and Sputum**. Emerg Infect Dis. 2020 Jun 8;26(9). PubMed: https://pubmed.gov/32511089. Full-text: https://wwwnc.cdc.gov/eid/article/26/9/20-2267_article

Environmental conditions affect the stability of the virus in nasal mucus and sputum. The virus is more stable at low temperature and low humidity conditions, whereas warmer temperatures and higher humidity shortened half-life. Although infectious virus was undetectable after 48 hours, viral RNA remained detectable for 7 days.

Diagnostics

Theel ES, Harring J, Hilgart H, Granger D. **Performance Characteristics of Four High-Throughput Immunoassays for Detection of IgG Antibodies against SARS-CoV-2.** J Clin Microbiol. 2020 Jun 8:JCM.01243-20. PubMed: https://pubmed.gov/32513859. Full-text: https://doi.org/10.1128/JCM.01243-20 ● (IMPORTANT)

Head-to-head comparison of four high-throughput, commercially available anti-SARS-CoV-2 IgG serologic tests from Abbott Laboratories, Epitope Diagnostics Inc, Euroimmun, and Ortho-Clinical Diagnostics, using serially collected acute and convalescent sera from both hospitalized patients and outpatients with RT-PCR confirmed COVID-19. All four immunoassays performed similarly with respect to sensitivity in COVID-19 hospitalized patients, and except for the Epitope assay, also in individuals with milder forms of the infection. The Abbott and Ortho-Clinical immunoassays provided the highest overall specificity, of over 99%.

Severe COVID-19

Carsana L, Sonzogni A, Nasr A, et al. **Pulmonary post-mortem findings in a series of COVID-19 cases.** Lancet 2020, June 08. Full-text: https://doi.org/10.1016/S1473-3099(20)30434-5

Lung tissue samples from 38 patients who died from COVID-19 in two hospitals in northern Italy were analyzed. The predominant pattern was diffuse alveolar damage, as described in patients infected with SARS and MERS. Hyaline membrane formation and pneumocyte atypical hyperplasia were frequent. However, the presence of platelet–fibrin thrombi in small arterial vessels was consistent with coagulopathy, which appears to be common in patients with COVID-19.

Treatment

Tonn T, Corman VM, Johnsen M, et al. **Stability and neutralising capacity of SARS-CoV-2-specific antibodies in convalescent plasma**. Lancet Microbe 2020. Full-text: https://doi.org/10.1016/S2666-5247(20)30037-9

How stable are antibodies that are found in convalescent plasma? Very stable. Pathogen inactivation (using psoralen and UV light) did not impair the stability and neutralising capacity of SARS-CoV-2-specific antibodies that was also

preserved at 100% when the plasma was shock frozen at -30°C after pathogen-inactivation or stored as liquid plasma for up to 9 days.

Magagnoli J, Narendran S, Pereira F, et al. **Outcomes of hydroxychloroquine usage in United States veterans hospitalized with COVID-19**. Med 2020, June 05, 2020. Full-text: https://doi.org/10.1016/j.medj.2020.06.001

A total of 807 COVID-19 patients hospitalized in US Veterans Administration medical centers in March and April were classified based on their exposure to HCQ or with azithromycin (HCQ+AZ) or no HCQ as treatments. Compared to the no-HCQ group, after propensity score adjustment for clinical characteristics, the risk of death from any cause was higher in the HCQ group (adjusted hazard ratio (1.83; 95% CI, 1.16 to 2.89) but not in the HCQ+AZ group (1.31, 95% CI, 0.80 to 2.15). Both the propensity score-adjusted risks of mechanical ventilation and death after mechanical ventilation were not significantly different in the two HCQ groups, compared to the no HCQ group.

10 June

Epidemiology

Payne DC, Smith-Jeffcoat SE, Nowak G, et al. **SARS-CoV-2 Infections and Serologic Responses from a Sample of U.S. Navy Service Members — USS Theodore Roosevelt, April 2020**. MMWR Morb Mortal Wkly Rep. ePub: 9 June 2020. Full-text: https://www.cdc.gov/mmwr/volumes/69/wr/mm6923e4.htm

In late March 2020, a large outbreak on the aircraft carrier USS Theodore Roosevelt was characterized by widespread transmission with relatively mild symptoms and asymptomatic infection among mostly young, healthy adults with close, congregate exposures. One fifth of infected participants reported no symptoms. Preventive measures, such as using face-coverings and observing social distancing, reduced risk for infection: among 382 service members, those who reported taking preventive measures had a lower infection rate than did those who did not report taking these measures (e.g., wearing a face-covering, 56% versus 81%; avoiding common areas, 54% versus 68%; and observing social distancing, 55% versus 70%, respectively).

Immunology

Wilk AJ, Rustagi A, Zhao NQ, et al. **A single-cell atlas of the peripheral immune response in patients with severe COVID-19**. Nat Med. 2020 Jun 8. PubMed: https://pubmed.gov/32514174. Full-text: https://doi.org/10.1038/s41591-020-0944-y ● (IMPORTANT)

Using single-cell RNA sequencing, the authors profiled peripheral blood mononuclear cells from seven patients hospitalized for COVID-19 and six healthy controls. The cell atlas of the peripheral immune response to severe COVID-19 included a heterogeneous interferon-stimulated gene signature, HLA class II down-regulation and a developing neutrophil population that appeared closely related to plasmablasts appearing in patients with acute respiratory failure requiring mechanical ventilation. Of note, peripheral monocytes and lymphocytes did not express substantial amounts of pro-inflammatory cytokines.

Transmission

El-Boghdadly K, Wong DJN, Owen R, et al**. Risks to healthcare workers following tracheal intubation of patients with COVID-19: a prospective international multicentre cohort study**. Anaesthesia. 2020 Jun 9. PubMed: https://pubmed.gov/32516833. Full-text: https://doi.org/10.1111/anae.15170

Around 1 in 10 HCW becomes infected: This prospective international multicentre cohort study recruited 1,718 healthcare workers participating in 5,148 tracheal intubation episodes of patients with suspected or confirmed COVID-19 from 503 hospitals in 17 countries. The overall incidence of the primary endpoint (lab-confirmed COVID-19 diagnosis or new symptoms requiring self-isolation or hospitalisation) was 10.7% over a median follow-up of 32 days. The cumulative incidence within 7, 14 and 21 days of the first tracheal intubation episode was 3.6%, 6.1%, and 8.5%, respectively. The risk varied by country and was higher in females, but was not associated with other factors.

Diagnostics

Grifoni E, Valoriani A, Cei F. **Interleukin-6 as prognosticator in patients with COVID-19**. J Infection 2020, June 8. Full-text: https://doi.org/10.1016/j.jinf.2020.06.008

According to this study analysing 77 patients, IL-6 levels at hospital admission seem to be a good ”prognosticator” for the combined endpoint progression to

severe disease and/or in-hospital mortality, and it seems to be the best prognosticator for negative outcome.

Clinical

Gervaise A, Bouzad C, Peroux E, Helissey C. **Acute pulmonary embolism in non-hospitalized COVID-19 patients referred to CTPA by emergency department**. Eur Radiol. 2020 Jun 9. PubMed: https://pubmed.gov/32518989. Full-text: https://doi.org/10.1007/s00330-020-06977-5

Acute pulmonary embolism (APE) is not limited to severe or critical COVID-19. Five of 13 (38%) patients with APE in this small study had a moderate clinical COVID-19 type.

Lala A, Johnson KW, Januzzi JL, et al. **Prevalence and Impact of Myocardial Injury in Patients Hospitalized with COVID-19 Infection**. J Am Coll Cardiol. 2020 Jun 5:S0735-1097(20)35552-2. PubMed: https://pubmed.gov/32517963. Full-text: https://doi.org/10.1016/j.jacc.2020.06.007

Myocardial injury is prevalent. Among 2,736 COVID-19 patients admitted to one of five Mount Sinai Health System hospitals in New York City who had troponin-I measured within 24 hours of admission, 985 (36%) patients had elevated troponin concentrations. After adjusting for disease severity and relevant clinical factors, even small amounts of myocardial injury (0.03-0.09 ng/mL) were significantly associated with death (adjusted HR: 1.75, 95% CI 1.37-2.24) while greater amounts (>0.09 ng/dL) were significantly associated with higher risk (adjusted HR 3.03, 95% CI 2.42-3.80).

Treatment

Williamson BNس, Feldmann F, Schwarz B, et al. **Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2**. Nature. 2020 Jun 9. PubMed: https://pubmed.gov/32516797. Full-text: https://doi.org/10.1038/s41586-020-2423-5

In macaques, remdesivir works, if given early. Twelve rhesus macaques were inoculated with SARS-CoV-2. Twelve hours later, six animals received 10mg/kg intravenous remdesivir and the other six an equal volume of vehicle solution (2ml/kg). In contrast to vehicle-treated animals, animals treated with remdesivir did not show signs of respiratory disease and had reduced pulmonary infiltrates and reduced virus titers in bronchoalveolar lavages. Virus shedding from the upper respiratory tract was not reduced. At necrop-

sy, lung viral loads of remdesivir-treated animals were lower and there was a reduction in damage to the lungs. According to the authors, treatment should be initiated as early as possible to achieve the maximum treatment effect. **But is this realistic in clinical practice?** We would need a new way of application, instead of the current infusions (i.e., tablets, inhalators).

La Rosée F, Bremer HC, Gehrke I, et al. **The Janus kinase 1/2 inhibitor ruxolitinib in COVID-19 with severe systemic hyperinflammation**. Leukemia. 2020 Jun 9. PubMed: https://pubmed.gov/32518419. Full-text: https://doi.org/10.1038/s41375-020-0891-0

In this retrospective study, 12/14 patients treated with the JAK inhibitor ruxolitinib achieved significant reduction of the newly developed "COVID-19 Inflammation Score" by ≥ 25% on day 7 with sustained clinical improvement in 11/14 patients without short-term red-flag warnings of Rux-induced toxicity. Rux treatment for COVID-19 in patients with hyperinflammation was safe with some signals of efficacy to prevent or overcome multi-organ failure. A multi-center Phase II clinical trial has been initiated (NCT04338958).

Pregnancy

Knight M, Bunch K, Vousden N, et al**. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study**. BMJ. 2020 Jun 8;369:m2107. PubMed: https://pubmed.gov/32513659. Full-text: https://doi.org/10.1136/bmj.m2107

Outcome of 427 pregnant women admitted to hospital with confirmed SARS-CoV-2 infection between 1 March 2020 and 14 April 2020: Most (but not all) outcomes were good, and transmission of SARS-CoV-2 to infants was uncommon. Of note, there were 233 (56%) women from black or other ethnic minority groups, 281 (69%) were overweight or obese, 175 (41%) were aged 35 or over, and 145 (34%) had pre-existing comorbidities. 266 (62%) women gave birth or had a pregnancy loss; 196 (73%) gave birth at term. Forty one (10%) women admitted to hospital needed respiratory support, and five (1%) women died. Twelve (5%) of 265 infants tested positive for SARS-CoV-2 RNA, six of them within the first 12 hours after birth.

Martínez-Perez O, Vouga M, Cruz Melguizo S, et al. **Association Between Mode of Delivery Among Pregnant Women With COVID-19 and Maternal and Neonatal Outcomes in Spain**. JAMA. 2020 Jun 8. PubMed: https://pubmed.gov/32511673. Full-text: https://doi.org/10.1001/jama.2020.10125

Of 82 pregnant patients, 4 presented with severe COVID-19 symptoms, including 1 with concomitant preeclampsia; all 4 underwent cesarean delivery and required ICU admission. Among patients with mild symptoms at presentation, all patients with a vaginal birth had excellent outcomes. In contrast, 13.5% of women undergoing cesarean delivery had severe maternal outcomes and 21.6% had clinical deterioration. Women undergoing cesarean delivery may have been at higher risk of adverse outcomes, but after adjusting for confounding factors, cesarean birth remained independently associated with an increased risk of clinical deterioration. The physiological stress induced by surgery is known to increase postpartum maternal complications

11 June

Epidemiology

ECDC Public Health Emergency Team, Danis K, Fonteneau L, et al. **High impact of COVID-19 in long-term care facilities, suggestion for monitoring in the EU/EEA**. May 2020. Eurosurveillance, Volume 25, Issue 22, 04/Jun/2020 Article. Full-text: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.22.2000956

Residents in long-term care facilities contribute 30–60% of all COVID-19 deaths in many European countries. This article provides an overview of the importance of surveillance and infection prevention and control measures, in order to identify clusters early, decrease the spread within and between facilities and reduce the size and severity of outbreaks.

Enserink M. **Coronavirus rips through Dutch mink farms, triggering culls to prevent human infections**. Science Mag 2020, June 9. Full-text: https://www.sciencemag.org/news/2020/06/coronavirus-rips-through-dutch-mink-farms-triggering-culls-prevent-human-infections

Sad story on several outbreaks at Dutch mink farms. That mink are susceptible wasn't a surprise, because they are closely related to ferrets. Once COVID-19 reaches a farm, the virus appears to spread like wildfire, even though the

animals are housed in separate cages. The government decided to cull thousands of animals because the problem could become bigger in the months ahead.

Transmission

Behrens GM, Cossmann A, Stankov MV. et al. **Perceived versus proven SARS-CoV-2-specific immune responses in health-care professionals**. Infection 2020. Full-text: https://www.springermedizin.de/perceived-versus-proven-sars-cov-2-specific-immune-responses-in-/18070162

The gap between perceived risk and evidence: Upon enrollment, HCW in Hannover, Germany, were asked to estimate their personal likelihood of having had a SARS-CoV-2 infection (How high do you rate the probability of having been infected so far? 0–100%). Of 201 study participants, 19% rated their probability greater than 50%. In contrast to the high percentage of self-perceived positive SARS-CoV-2 infection status, only two tested frontline HCPs showed a clearly positive reaction to the ELISA.

Diagnostics

Liu ZL, Liu Y, Wan LG, et al. **Antibody profiles in mild and severe cases of COVID-19**. Clinical Chemistry 10 June 2020. Full-text: https://doi.org/10.1093/clinchem/hvaa137

This study analysed antibody response in 192 RT-PCR confirmed COVID-19 patients, using two commercial microparticle chemiluminescence immunoassays (Wantai). Patients were stratified by disease severity. Severe cases had significantly higher IgM titers than mild cases after day 6 post-onset. Strikingly, 34% and 14% of mild patients were consistently serologically negative for IgM and total antibody, respectively.

Chew KL, Tan SS, Saw S, et al. **Clinical evaluation of serological IgG antibody response on the Abbott Architect for established SARS-CoV-2 infection**. Clin Microbiol June 09, 2020. Full-text: https://doi.org/10.1016/j.cmi.2020.05.036

Residual sera from 177 symptomatic COVID-19 patients, and 163 non-COVID-19 patients were tested for antibody with the Abbott SARS-CoV-2 IgG assay. Specificity of the assay was 100%. The clinical sensitivity varied depending on time from onset of symptoms, increasing with longer periods since onset of clinical illness. The clinical sensitivity at ≤ 6 days was 8.6%, 7-13 days: 43.6%, 14-20 days: 84.0%, and ≥ 21 days: 84.4%.

Wong MC, Huang J, Lai C, et al. **Detection of SARS-CoV-2 RNA in fecal specimens of patients with confirmed COVID-19: a meta-analysis**. J Infection, June 11, 2020. Full-text: https://doi.org/10.1016/j.jinf.2020.06.012

In this meta-analysis of 17 studies, the pooled detection rate of fecal SARS-CoV-2 RNA was 43.7% and 33.7% by patient and number of specimens, respectively. Female individuals (59.6% vs. 53.5%), those who presented with gastrointestinal symptoms (77.1% vs. 57.7%), and patients with more severe disease (68.3% vs. 34.6%) tended to have a higher detection rate.

Clinical

Covino M, De Matteis G, Santoro M, et al. **Clinical characteristics and prognostic factors in COVID-19 patients aged ≥80 years**. Geriatr Gerontol Int. 2020 Jun 9. PubMed: https://pubmed.gov/32516861. Full-text: https://doi.org/10.1111/ggi.13960

Of 69 patients aged 80-98 years who presented at a large center in Rome, Italy, 36% had a critical COVID-19 disease. Multivariate Cox regression analysis showed that, among other factors, severe dementia was an independent risk factor for death (Hazard Ratio 3.9, 95 % CI 1.2-12.2).

Treatment

Piller C. **Who's to blame? These three scientists are at the heart of the Surgisphere COVID-19 scandal**. Science Mag 2020, June 8. Full-text: https://www.sciencemag.org/news/2020/06/whos-blame-these-three-scientists-are-heart-surgisphere-covid-19-scandal

More insights into the research scandal about two fake COVID-19 treatment papers (published *in The Lancet* and the *NEJM*) that were retracted last week. There were several red flags that the studies warranted intensive scrutiny – scrutiny that the two journals unforgivably failed to provide. This scandal tells us a lot about scientific publishing. Answers, comments, explanations by the two journals are still pending.

Lim SY, Osuna CE, Best K, et al. **A direct-acting antiviral drug abrogates viremia in Zika virus–infected rhesus macaques**. Science Transl Med 10 Jun 2020, Vol. 12, Issue 547. Full-text: https://doi.org/10.1126/scitranslmed.aau9135

Galidesivir is a nucleoside RNA polymerase inhibitor with a broad-spectrum activity *in vitro* against more than 20 RNA viruses in nine different families, including coronaviruses and viral disease families that include filoviruses, togaviruses, bunyaviruses, arenaviruses, paramyxoviruses, and flaviviruses. A NIAID-funded, randomized, double-blind, placebo-controlled clinical trial to assess the safety, clinical impact and antiviral effects of galidesivir in patients with COVID-19 is underway. Of note, the drug also works against Zika: In the study presented here, galidesivir dosing in rhesus macaques was safe and offered postexposure protection against Zika virus infection.

Jácome R, Campillo-Balderas JA, Ponce de León S, Becerra A, Lazcano A. **Sofosbuvir as a potential alternative to treat the SARS-CoV-2 epidemic**. Sci Rep. 2020 Jun 9;10(1):9294. PubMed: https://pubmed.gov/32518317. Full-text: https://doi.org/10.1038/s41598-020-66440-9

Some thoughts about the possibility of using sofosbuvir against SARS-CoV-2, a nucleoside analog antiviral approved for hepatitis C virus infections. The structural superposition of the hepatitis C virus polymerase bound to sofosbuvir with the SARS-CoV polymerase shows that the residues that bind to the drug are present in the latter.

12 June

Epidemiology

Furuse Y, Sando E, Tsuchiya N, et al. **Clusters of Coronavirus Disease in Communities, Japan**. January-April 2020. Emerg Infect Dis. 2020 Jun 10;26(9). PubMed: https://pubmed.gov/32521222. Full-text: https://doi.org/10.3201/eid2609.202272

Bye, bye, karaoke. The Japanese authors defined a cluster as > 5 cases with primary exposure reported at a common event or venue, excluding within-household transmissions. In total, 61 COVID-19 clusters were found in various communities in the country: 18 (30%) in healthcare facilities; 10 (16%) in care facilities of other types, such as nursing homes and day care centers; 10 (16%) in restaurants or bars; 8 (13%) in workplaces; 7 (11%) in music-related events, such as live music concerts, chorus group rehearsals, and karaoke parties; 5

(8%) in gymnasiums; 2 (3%) in ceremonial functions; and 1 (2%) in transportation-related incident in an airplane. Of note, 41% of probable primary case-patients were pre-symptomatic or asymptomatic at the time of transmission. 45% had cough. Many clusters were associated with heavy breathing in close proximity.

Stringhini S, Wisniak A, Piumatti G, et al. The Lancet, June 11, 2020. **Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study**. **Full-text:** https://doi.org/10.1016/S0140-6736(20)31304-0

Geneva was a COVID-19 hot spot in Switzerland (5000 cases over < 2,5 months in half a million people). Authors performed 5 consecutive weekly serosurveys among 2,766 randomly selected participants from a previous population-representative survey, and 1,339 household members aged 5 years and older. Each participant was tested for anti-SARS-CoV-2-IgG antibodies. Seroprevalence increased from about 5% to about 11%. Of note, young children (5–9 years) and older people (≥ 65 years) had significantly lower seroprevalence than the other age groups. Authors estimated that there were 11 infections for every COVID-19 confirmed case.

Virology

Day T, Gandon S, Lion S, et al. **On the evolutionary epidemiology of SARS-CoV-2.** Curr Biol 2020, June 11. Full-text: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7287426 ●● (Outstanding)

Outstanding essay about what little is currently known about the evolution of SARS-CoV-2. At present, there is a lack of compelling evidence that any existing variants impact the progression, severity, or transmission of COVID-19 in an adaptive manner. The authors discuss the potential evolutionary routes that SARS-CoV-2 might take and dispel some of the current misinformation that is circulating in the media.

Gussow AB, Auslander N, Faure G, Wolf YI, Zhang F, Koonin EV. **Genomic determinants of pathogenicity in SARS-CoV-2 and other human coronaviruses.** Proc Natl Acad Sci U S A. 2020 Jun 30;117(26):15193-15199. PubMed: https://pubmed.gov/32522874. Full-text: https://doi.org/10.1073/pnas.2008176117

This in-depth molecular analysis reconstructs key genomic features that differentiate SARS-CoV-2, SARS-CoV and MERS-CoV from less pathogenic coronaviruses. Exploring the regions identified within the nucleocapsid that predict the high case fatality rate of coronaviruses, the authors found that these deletions and insertions result in substantial enhancement of motifs that determine nuclear localization. The deletions, insertions, and substitutions in the N proteins of the high-CFR coronaviruses map to two monopartite nuclear localization signals. These findings imply an important role of the subcellular localization of the nucleocapsid protein in coronavirus pathogenicity.

Immunology

Hassan AO, Case JB, Winkler ES, et al. **A SARS-CoV-2 infection model in mice demonstrates protection by neutralizing antibodies**. Cell 2020, June 10. Full-text: https://doi.org/10.1016/j.cell.2020.06.011

Most mice are not readily infected by SARS-CoV-2 because of species-specific differences in their ACE2 receptors. US researchers transduced replication-defective adenoviruses encoding human ACE2 via intranasal administration into BALB/c mice and established receptor expression in lung tissues. hACE2-transduced mice were productively infected with SARS-CoV-2, and this resulted in high viral titers in the lung and lung pathology. Neutralizing mAbs protect from SARS-CoV-2 induced lung infection, and inflammation. This accessible mouse model will expedite the testing and deployment of therapeutics and vaccines.

Sun J, Zhuang, Zheng J, et al. **Generation of a Broadly Useful Model for COVID-19 Pathogenesis Vaccination, and Treatment**. Cell 2020, June 10. **Full-text:** https://doi.org/10.1016/j.cell.2020.06.010

Another murine model, but from China. After exogenous delivery of human ACE2 with a replication-deficient adenovirus, Ad5-hACE2-sensitized mice developed pneumonia and high-titer virus replication in lungs. Type I interferon, T cells and, most importantly, signal transducer and activator of transcription 1 (STAT1) were critical for virus clearance and disease resolution. This murine model of broad and immediate utility will help to investigate COVID-19 pathogenesis, and to evaluate new therapies and vaccines.

Transmission

Liu M, Cheng SZ, Xu KW, et al. **Use of personal protective equipment against coronavirus disease 2019 by healthcare professionals in Wuhan, China: cross sectional study.** BMJ. 2020 Jun 10;369:m2195. PubMed: https://pubmed.gov/32522737. Full-text: https://doi.org/10.1136/bmj.m2195

PPE works well: This study analyzed 420 healthcare professionals (116 doctors and 304 nurses) who were deployed to Wuhan by two affiliated hospitals of Sun Yatsen University and Nanfang Hospital of Southern Medical University for 6-8 weeks from 24 January to 7 April 2020. All were provided with appropriate personal protective equipment to deliver healthcare to patients admitted to hospital with COVID-19. Although all were involved in aerosol generating procedures (high risk of exposure), no-one contracted infection.

Schuit M, Ratnesar-Shumate S, Yolitz J, et al. **Airborne SARS-CoV-2 is Rapidly Inactivated by Simulated Sunlight**. J Infect Dis. 2020 Jun 11:jiaa334. PubMed: https://pubmed.gov/32525979. Full-text: https://doi.org/10.1093/infdis/jiaa334 ● (IMPORTANT)

Again, it's sunlight! This study examined the effect of simulated sunlight and relative humidity on the stability of SARS-CoV-2 in aerosols. A 90% loss of virus in simulated saliva was 19 minutes under simulated sunlight levels representative of late winter/early fall, 6 minutes of summer levels and 125 minutes without simulated sunlight across all relative humidity levels. Aerosol transmission of SARS-CoV-2 may be dependent on environmental conditions, particularly sunlight.

Clinical

Destras G, Bal A, Excuret V, et al. **Systematic SARS-CoV-2 screening in cerebrospinal fluid during the COVID-19 pandemic**. The Lancet Microbe June 11, 2020. Full-text: https://doi.org/10.1016/S2666-5247(20)30066-5

Among 578 CSF samples analyzed at the virology laboratory of Lyon University Hospital during the COVID-19 epidemic (Feb 1 to May 11, 2020), all were negative, except for two samples that were slightly positive for SARS-CoV-2 corresponding to post-mortem samples from two adults with confirmed COVID-19. Importantly, the other 21 CSF samples from patients with confirmed COVID-19 were negative. These data suggest that, although SARS-CoV-2 is able to replicate in neuronal cells *in vitro*, SARS-CoV-2 testing in CSF is not relevant in the general population.

Comorbidities

Pinto BGG, Oliveira AER, Singh Y, et al. **ACE2 Expression is Increased in the Lungs of Patients with Comorbidities Associated with Severe COVID-19**. J Infect Dis. 2020 Jun 11:jiaa332. PubMed: https://pubmed.gov/32526012. Full-text: https://doi.org/10.1093/infdis/jiaa332

The authors analyzed over 700 lung transcriptome samples of patients with comorbidities associated with severe COVID-19 and found that ACE2 was highly expressed in these patients, compared to control individuals. Findings suggest that the higher expression of ACE2 in the lungs is associated with higher chances of developing a severe form of COVID-19, by facilitating SARS-CoV-2 entry into lung cells during the infection.

13 June

Epidemiology

Walker PG, Whittaker C, Watson OJ, et al. **The impact of COVID-19 and strategies for mitigation and suppression in low- and middle-income countries.** Science 12 Jun 2020. Full-text: https://DOI.ORG/10.1126/science.abc0035

An in-depth analysis of the potential impact of the pandemic in low- and middle-income countries (LMIC). The analysis gives insight into how differences in demography, social structure and health care availability and quality combine and potentially influence the impact of measures that can help reduce the spread of the virus. However, the bottom line is: We don't know yet. On one hand, we have an overall younger population and a shorter time for lockdown measures to be in place in LMIC. On the other hand, there is a higher burden of infectious diseases such as AIDS and TB already, and of poverty-related determinants of poorer health outcomes such as malnutrition. There is also a more persistent spread to older age categories (higher levels of household-based transmissions) and poorer quality health care and lack of health care capacity.

Oreshkova N, Molenar RJ, Vremen S. **SARS-CoV-2 infection in farmed minks, the Netherlands, April and May 2020**. Eurosurveillance 2020, June 11. Volume 25, Issue 23. Full-text: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.23.2001005

Despite a law approved by the Dutch parliament in 2012 that will ban mink farming as of 2024 for ethical reasons, there are still around 125 mink farms in the Netherlands, with an average of 5,000 female breeding animals. In 2019, 4 million minks were "produced". This article describes several outbreaks on these farms. Detection of viral RNA in the airborne inhalable dust clearly suggests dust and/or droplets as means of transmission between the minks and occupational risk of exposure for the workers on the farms. On 3 June, the Dutch Ministry of Agriculture decided to cull all minks of SARS-CoV-2-infected farms, starting on 5 June. This may be the right time to speed up the final ban.

Immunology

Major J, Crotta S, Llorian M, et al. **Type I and III interferons disrupt lung epithelial repair during recovery from viral infection.** Science. 2020 Jun 11:eabc2061. PubMed: https://pubmed.gov/32527928. Full-text: https://doi.org/10.1126/science.abc2061 ●● (OUTSTANDING)

Key message: Interferon may be helpful during early infection and harmful at later stages. IFN-λ mainly signals in epithelia, inducing localized antiviral immunity, and has a key role in the reduction of epithelial proliferation and differentiation during lung repair. In animal and cell experiments, the authors show that IFN-induced p53 directly reduces epithelial proliferation and differentiation, increasing disease severity and susceptibility to bacterial superinfections. Excessive or prolonged IFN production may aggravate viral infection by impairing lung epithelial regeneration.

Broggi A, Ghosh S, Sposito B, et al. **Type III interferons disrupt the lung epithelial barrier upon viral recognition**. Science 11 Jun 2020. Full-text: https://DOI.ORG/10.1126/science.abc3545 ● (IMPORTANT)

Same direction as above: Detrimental activities of IFN-λ only occur upon chronic exposure and in the presence of tissue damage. In mice, IFN-λ produced by lung dendritic cells in response to a synthetic viral RNA-induced barrier damage, causing susceptibility to lethal bacterial superinfections.

Diagnostics

Caini S, Bellerba F, Corso F, et al. **Meta-analysis of diagnostic performance of serological tests for SARS-CoV-2 antibodies up to 25 April 2020 and public health implications**. Eurosurveillance 2020, June 11. Volume 25, Issue 23. Full-text: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.23.2000980 ● (IMPORTANT)

This review of the diagnostic accuracy of SARS-CoV-2 serological tests includes 9 studies, using different test kits. Random-effects models yielded a summary sensitivity of 82% for IgM, and 85% for IgG and total antibodies. For specificity, the pooled estimates were 98% for IgM and 99% for IgG and total antibodies. In populations with ≤ 5% of seroconverted individuals, the positive predictive value would be ≤ 88%. According to the authors, serological tests should be used for prevalence surveys only in hard-hit areas.

Hung IF, Cheng VC, Li X. **SARS-CoV-2 shedding and seroconversion among passengers quarantined after disembarking a cruise ship: a case series**. Lancet Inf Dis, June 12, 2020. Full-text: https://doi.org/10.1016/S1473-3099(20)30364-9

Among 215 adult (≥ 18 years) passengers from Hong Kong who had been on board the Diamond Princess cruise ship and who had been found to be PCR-negative before disembarking, 9 became positive during quarantine. Those with evidence of pneumonia on imaging tended to have an increased antibody response. However, positive IgG or IgM confirmed infection of COVID-19 in both symptomatic and asymptomatic patients.

Clinical

Sakurai A, Sasaki T, Kato S, et al. **Natural History of Asymptomatic SARS-CoV-2 Infection**. NEJM June 12, 2020. Full-text: https://DOI.ORG/10.1056/NEJMc2013020

More on asymptomatic infection: The authors followed 90 persons from the cruise ship Diamond Princess who were asymptomatic at the time of the positive PCR test and remained so until the resolution of infection (as determined by two consecutive negative PCR tests). 27% had coexisting medical conditions. The median time between the first positive PCR test result (either on the ship or at the hospital) and the first of the two serial negative PCR results was 9 days (range, 3 to 21), and the cumulative percentages of persons with resolution of infection 8 and 15 days after the first positive PCR were 48% and 90%, respectively.

Tabata S, Imai K, Kawano S, et al. **Clinical characteristics of COVID-19 in 104 people with SARS-CoV-2 infection on the Diamond Princess cruise ship: a retrospective analysis**. Lancet Inf Dis 2020, June 12. Full-text: https://doi.org/10.1016/S1473-3099(20)30482-5.

Among 104 people from the Diamond Princess cruise ship who were admitted to a Tokyo hospital, 33 (32%) participants were confirmed as being asymptomatic, 43 (41%) as having mild COVID-19, and 28 (27%) as having severe COVID-19. Serum lactate hydrogenase concentrations were significantly higher in the ten participants who were asymptomatic on admission but developed symptomatic COVID-19 compared with the 33 participants who remained asymptomatic throughout the observation period.

Solomon IH, Normandin E, Bhattacharyya B, et al. **Neuropathological Features of Covid-19.** NEJM June 12, 2020. Full-text: https://DOI.ORG/10.1056/NEJMc2019373

Histopathological examination of brain specimens obtained from 18 patients who died 0 to 32 days after the onset of symptoms showed only hypoxic changes and did not show encephalitis or other specific brain changes referable to the virus. The virus was detected at low levels in 6 brain sections obtained from 5 patients; it remains to be seen whether this was due to *in situ* virions or viral RNA from blood.

Wright Hr KP, Linton SK, Withrow D. **Sleep in University Students Prior to and During COVID-19 Stay-at-Home Orders**. Current Biology, June 10, 2020 Full-text: https://doi.org/10.1016/j.cub.2020.06.022

Good to know: during lockdown, they sleep better. This ground-breaking study investigated sleep behaviors prior to and during Stay-at-Home orders in 139 university students. During Stay-at-Home, nightly time in bed devoted to sleep increased by 30 min during weekdays and by 24 mins on weekends and regularity of sleep timing improved by 12 min. Sleep timing became later by 50 min during weekdays and 25 min on weekends, and thus the difference between weekend and weekday sleep timing decreased—hence reducing the amount of social jetlag. A subsequent study on changes in breakfast behaviors is eagerly awaited (proposed hypothesis: less coffee, more jam).

14 June

Health Care Workers

Heath C, Sommerfield A, von Ungern-Sternberg BS. **Resilience strategies to manage psychological distress amongst healthcare workers during the COVID-19 pandemic: a narrative review**. Anaesthesia. 2020 Jun 13. PubMed: https://pubmed.gov/32534465. Full-text: https://doi.org/10.1111/anae.15180

This article summarises the available management strategies to increase resilience in healthcare workers during the COVID-19 pandemic and beyond. According to the authors, some of the strategies require substantial lead time and will potentially challenge negotiations with organisational stakeholders. This might require increasing the number of or reallocation of support staff; reallocating how revenue is distributed throughout the organisation; ensuring physicians feel valued and heard; and changing reimbursement and compensation models. However, in the current crisis, some strategies can be implemented quickly and easily such as: mindfulness interventions; Battle Buddies (a rapidly-deployable psychological resilience intervention based on the "Battle Buddy" system of the US army); and staff feedback sessions.

Kiser SB, Bernaci RE. **When the Dust Settles: Preventing a Mental Health Crisis in COVID-19 Clinicians**. Annals Int Med 2020, June 9. Full-text: https://doi.org/10.7326/M20-3738

Touching article about an emergency room physician who took her own life, after spending weeks caring for COVID-19 patients in New York City. Considering the profound effects of the crisis on clinicians' mental health, leaders must protect their clinicians by carefully considering appropriate time off in scheduling and ensuring that colleagues, superiors, and trainees use this time.

Behaviour

Muto K, Yamamoto I, Nahasu M, et al. **Japanese citizens' behavioral changes and preparedness against COVID-19: An online survey during the early phase of the pandemic**. PLOS ONE, 11 Jun 2020. Full-text: https://doi.org/10.1371/journal.pone.0234292

20% - young male trolls. This cross-sectional study investigated how and from when Japanese citizens changed their precautionary behavior under circumstances in which the government simply requested their cooperation. For the 11,332 participants, the most important event influencing precautionary ac-

tions (frequent hand washing, social distancing etc) was the infection aboard the Diamond Princess. However, about 20% of the participants were reluctant to implement proper prevention measures. Typical characteristics were male, younger (under 30 years old), unmarried, from lower-income households, a drinking or smoking habit, and a higher extraversion score.

Garbe L, Rau R, Toppe T. **Influence of perceived threat of Covid-19 and HEXACO personality traits on toilet paper stockpiling**. PLOS 2020, June 12. Full-text: https://doi.org/10.1371/journal.pone.0234232

Probably the most burning issue in the current health crisis: Who hoards toilet paper? This article wins our new award for the best introduction ("empirical studies on the psychological underpinnings of toilet paper stockpiling are still scarce"). In an online survey across 22 countries among the 996 (!) respondents, those who felt more threatened and who had a predisposition towards emotionality and high conscientiousness, stockpiled more toilet paper. But of course, many open questions remain, and according to the authors, "experimental studies would be required in order to explicitly test the directionality implied in (their) investigation of indirect effects".

Psychological impact

Dubey S, Biswas P, Ghosh R, et al**. Psychosocial impact of COVID**-19. Diabetes Metab Syndr. 2020 May 27;14(5):779-788. PubMed: https://pubmed.gov/32526627. Full-text: https://doi.org/10.1016/j.dsx.2020.05.035

Apart from its physical burden on patients and health-care services, COVID-19 has enormous psychosocial impact. This comprehensive article reviews "coronaphobia", a plethora of psychiatric manifestations across the different strata of society. But why is this in a diabetes journal?

Lockdown effects

Drake TM, Docherty AB, Weiser TG, et al. **The effects of physical distancing on population mobility during the COVID-19 pandemic in the UK**. Lancet 2020, June 12. Full-text: https://doi.org/10.1016/S2589-7500(20)30134-5

This work used Google mobility data to map spatial and temporal changes in mobility across the UK in six areas during lockdown: residential areas; supermarkets, grocery shops, and pharmacies; workplaces; retail and recreational areas; transit stations (subway, bus, and train stations); and parks. The authors saw a 63% overall reduction in movement, with retail and recreation-

al areas (decreased by 85%; not surprising given restrictions imposed on this sector) and transit stations (decreased by 75%) showing the largest reductions. Good news: "park use initially decreased but has now increased to levels seen before the lockdown restrictions, perhaps because of good weather or people adapting their exercise requirements".

Warburton E, Raniolo G. **Domestic Abuse during COVID-19: What about the boys?** Psychiatry Research. Volume 291, September 2020, 113155. Full-text: https://doi.org/10.1016/j.psychres.2020.113155

Harsh criticism on a previous article, summarizing that, during the COVID-19 pandemic, domestic abuse experienced by men is of 'lower severity'. The authors want to steer the domestic abuse conversation away from a gender divide and open up the discussion to promote zero tolerance of domestic abuse towards both men and women. They propose that "domestic abuse towards men, although less frequent, is of equal severity to the domestic abuse suffered by women". Best conclusion of the day: "Abuse is abuse."

Blume C, Schmidt MH, Cajochen. **Effects of the COVID-19 lockdown on human sleep and rest-activity rhythms**. Current Biology 2020, June 10. Full-text: https://doi.org/10.1016/j.cub.2020.06.021

Yesterday we learned that US students slept better during lockdown. In Europe, however, things went differently. According to this study on 435 (!) people in 3 countries, the lockdown led to an improved individual sleep-wake timing and overall, yes, more sleep. At the same time, however, many people suffered a decrease in sleep quality in this exceptional situation. Well. Data from other continents pending.

Other issues

Muller JJ, Nathan DG. **COVID-19, nuclear war, and global warming: lessons for our vulnerable world**. Lancet June 12, 2020. Full-text: https://doi.org/10.1016/S0140-6736(20)31379-9

Prize for the most megalomaniac paper title of the day. According to the authors of this Lancet letter, the origins and solutions of all three threats "are remarkably similar": "First, each threat must be recognised. Second, political leaders must respect truth and defer to expertise. Third, the threats are global and require global cooperation. Fourth, we all have to focus on our collective survival, and that includes care for the least privileged". Well then, if that's the case, let's get to work!

McManus S, D'Ardenne J, Wessely S. **Covid Conspiracies: Misleading Evidence Can Be More Damaging Than No Evidence at All**. Psychol Med, June 2020. Full-text: https://doi.org/10.1017/S0033291720002184

Well-written commentary on the myriad of articles publishing on the incredible number of people believing in conspiracy theories. Many of these studies suffer from serious methodological problems and severely overestimate the prevalence of conspiracy thinking, trying to attract media attention. Headlines like "One fifth of English people blamed Jews or Muslims for COVID-19" are nonsense and dangerous. See paper title, maybe "can be" should be "are".

15 June

Epidemiology

Mubarak N, Zin CS. **Religious tourism and mass religious gatherings - The potential link in the spread of COVID-19. Current perspective and future implications**. Travel Med Infect Dis. 2020 Jun 9;36:101786. PubMed: https://pubmed.gov/32531422. Full-text: https://doi.org/10.1016/j.tmaid.2020.101786

Important comment on mass religious gatherings. The authors recommend restrictions on the entry of Hajj pilgrims who are from epicentres and hotspots, from countries with suboptimal disease surveillance systems or with inadequate quarantine and diagnostic infrastructure for returning pilgrims who are over 50 years old or suffer from chronic disease, ie patients with diabetes and cardiovascular complications. Saudi Arabia needs to deploy a pre-emptive approach. We'll see whether this is feasible.

Habib H. **Has Sweden's controversial covid-19 strategy been successful?** BMJ 2020; 369. Full-text: https://doi.org/10.1136/bmj.m2376

Probably not. Some thoughts on Sweden's controversial decision not to lock down the country. They are still far away from herd immunity (an ongoing nationwide study on 20 May found that just 7.3% of Stockholm residents had developed antibodies) and the death toll is immense.

Okell LC, Verity R, Watson OJ, et al. **Have deaths from COVID-19 in Europe plateaued due to herd immunity**? Lancet. 2020 Jun 11:S0140-6736(20)31357-X. PubMed: https://pubmed.gov/32534627. Full-text: https://doi.org/10.1016/S0140-6736(20)31357-X

No. Epidemiological data suggest that no country has yet seen infection rates sufficient to prevent a second wave of transmission, should controls or behavioural precautions be relaxed without compensatory measures in place.

Transmission

Rempel D, Members of the N95DECON Consortium. **Scientific Collaboration During the COVID-19 Pandemic: N95DECON.org**. Annals of Work Exposures and Health 2020, June 13. Full-text: https://doi.org/10.1093/annweh/wxaa057

This commentary describes the spontaneous formation of an international team of 115 researchers who summarized the literature on safe methods for decontaminating N95 filtering facepiece respirators in response to the supply crisis. The summary reports and fact sheets on the www.n95decon.org website are frequently being updated with new research findings and have had more than 200,000 visits.

Diagnostics

Kam KG, Yung CF, Maiwald M, et al. **Clinical Utility of Buccal Swabs for Severe Acute Respiratory Syndrome Coronavirus 2 Detection in Coronavirus Disease 2019–Infected Children**. J Ped Inf Dis 2020, Jun 13. Full-text: https://doi.org/10.1093/jpids/piaa068

Best conclusion of the day: "Buccal swabs are not good" as COVID-19 screening specimens in children. In 11 children positive via nasopharyngeal swabs, 2 remained negative using buccal swabs. There was a general trend for buccal specimens to contain lower SARS-CoV-2 viral loads (higher Ct values) compared with nasopharyngeal specimens. The sensitivity of buccal swabs compared with nasopharyngeal swabs ranged from 25% to 71.4% on different days of collection during the first week of illness/diagnosis. Buccal SARS-CoV-2 was undetectable by day 8 of admission/diagnosis, although the nasopharyngeal SARS-CoV-2 was still detectable.

Lamb LE, Bartolone SN, Ward E, Chancellor MB. **Rapid detection of novel coronavirus/Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by reverse transcription-loop-mediated isothermal amplification.** PLoS One. 2020 Jun 12;15(6):e0234682. PubMed: https://pubmed.gov/32530929. Full-text: https://doi.org/10.1371/journal.pone.0234682. eCollection 2020

The authors describe a "fast and robust assay for detection of SARS-CoV-2 in 30–45 minutes". This simple assay (Reverse Transcription Loop-Mediated Isothermal Amplification, RT-LAMP) could be used outside of a central laboratory on various types of biological samples. This assay can be completed by individuals without specialty training or equipment and may provide a new diagnostic strategy for combatting the spread of SARS-CoV-2 at the point-of-risk. However, numbers of tested samples were low. Sensitivity and specificity have to be tested in larger populations.

Chia WN, Tan CW, Foo R, et al. **Serological differentiation between COVID-19 and SARS infections**. Emerg Microbes Infect. 2020 Jun 12:1-23. PubMed: https://pubmed.gov/32529906. Full-text: https://doi.org/10.1080/22221751.2020.1780951

The authors examined the performance of N, S1 and RBD proteins from SARS-CoV-2 and SARS-CoV in four different test platforms. Results show that the RBD protein provides the best specificity, whereas the N protein of either virus is not suitable to detect virus-specific antibodies due to a very high level of cross-reactivity.

Severe COVID-19

Endeman H, van der Zee P, van Genderen ME, van den Akker JPC, Gommers D. **Progressive respiratory failure in COVID-19: a hypothesis.** Lancet Infect Dis. 2020 Apr 29:S1473-3099(20)30366-2. PubMed: https://pubmed.gov/32530428. Full-text: https://doi.org/10.1016/S1473-3099(20)30366-2

Of 90 patients with severe COVID-19, 17 deteriorated within 2 weeks and no longer responded to prone positioning. All (!) of these patients had major pulmonary embolism established by lung CT or cardiac ultrasound. A plasma D-dimer concentration greater than 4 µg/mL, combined with increasing inflammatory markers such as interleukin-6 (the authors recommend to measure it regularly), and loss of response to prone positioning might be useful parameters to identify patients at risk of pulmonary embolism.

Gabarre P, Dumas G, Dupont T, Darmon M, Azoulay E, Zafrani L. **Acute kidney injury in critically ill patients with COVID-19**. Intensive Care Med. 2020 Jun 12. PubMed: https://pubmed.gov/32533197. Full-text: https://doi.org/10.1007/s00134-020-06153-9

One of the best reviews on this topic to date. AKI is prevalent in critically ill COVID-19 patients. Several mechanisms are possibly involved, including direct invasion of SARS-CoV-2 into the renal parenchyma, an imbalanced RAAS and microthrombosis, but also kidney injury secondary to hemodynamic instability, inflammatory cytokines and the consequences of therapeutics that are used in ICU (nephrotoxic drugs, mechanical ventilation).

Comorbidities

Doglietto F, Vezzoli M, Gheza F, et al. **Factors Associated With Surgical Mortality and Complications Among Patients With and Without Coronavirus Disease 2019 (COVID-19) in Italy**. JAMA Surg. 2020 Jun 12. PubMed: https://pubmed.gov/32530453. Full-text: https://doi.org/10.1001/jamasurg.2020.2713

There is no good time for surgery: In this cohort study of 41 surgical patients with COVID-19 and 82 tightly matched control patients, significant differences were documented regarding rates of early mortality and complications (odds ratios 9.5 and 5.0, respectively), mainly pneumonia and thrombotic complications, were significantly associated with COVID-19, and different models identified COVID-19 as the first variable associated with surgical complications. These data suggest that, whenever possible, surgery should be postponed in patients with COVID-19.

16 June

Epidemiology

Stoke EK, Zambrano LD, Anderson KN. **Coronavirus Disease 2019 Case Surveillance — United States, January 22–May 30, 2020**. MMWR June 15, 2020. Full-text: https://www.cdc.gov/mmwr/volumes/69/wr/mm6924e2.htm

A detailed picture of the epidemic in the US. This report describes demographic characteristics, underlying health conditions, symptoms, and outcomes among 1,320,488 laboratory-confirmed COVID-19 cases individually

reported to CDC during January 22–May 30, 2020. Some key messages: Overall, 14% of patients were hospitalized, 2% were admitted to an intensive care unit (ICU), and 5% died. Among cases with known race and ethnicity, 33% of persons were Hispanic, 22% were black, and 1.3% were non-Hispanic American Indian or Alaska Native. These findings suggest that persons in these groups, who account for 18%, 13%, and 0.7% of the U.S. population, respectively, are disproportionately affected by the COVID-19 pandemic.

Thornton J. **Covid-19: Africa's case numbers are rising rapidly, WHO warns**. BMJ 2020; 369. Full-text: https://doi.org/10.1136/bmj.m2394

A brief but concerning review on the situation in Africa. Since the virus was first detected in Egypt on 14 February, it took 98 days to reach 100,000 cases and only 18 days to move to 200,000 cases on the continent. More than 5,600 people have died from the illness, 70% of whom were in just five countries: Algeria, Egypt, Nigeria, South Africa, and Sudan.

Transmission

Cox RJ, Brokstadt KA, Krammer F, et al. **Seroconversion in household members of COVID-19 outpatients.** Lancet June 15, 2020. Full-text: https://doi.org/10.1016/S1473-3099(20)30466-7

This study from Norway shows that detection of seroconversion might provide a more accurate picture of attack rates in households than intermittent RT-PCR testing. Of 158 cases, 125 (79%) tested positive for antibodies and 12 (8%) were defined as borderline. In 77 household members, 24 (31%) tested positive and two (3%) were borderline.

Comorbidities

Furfaro F, Vuitton L, Fiorino G, et al. **SFED recommendations for IBD endoscopy during COVID-19 pandemic: Italian and French experience.** Nat Rev Gastroenterol Hepatol. 2020 Jun 11:1-10. PubMed: https://pubmed.gov/32528139. Full-text: https://doi.org/10.1038/s41575-020-0319-3

This perspective aims to provide a guide based on the Italian and French experience to better face the difficulties encountered by endoscopists during this pandemic. Some helpful recommendations regarding the use of personal protective equipment (both for patients and HCW) are proposed and different

scenarios in endoscopic IBD management are evaluated to suggest when endoscopy could be rescheduled and replaced by alternative biomarkers.

Treatment

Marovich M, Mascola JR, Cohen MS. **Monoclonal Antibodies for Prevention and Treatment of COVID-19.** JAMA June 15, 2020. Full-text: https://doi.org/10.1001/jama.2020.10245 ● (IMPORTANT)

Neutralizing monoclonal antibodies to SARS-CoV-2 have the potential for both therapeutic and prophylactic applications (probably more than all antiviral drugs that are currently being tested). This viewpoint summarizes current knowledge. Several mAbs are poised to enter clinical trials during the summer of 2020. Trials will include treatment of patients with SARS-CoV-2 infection, with varying degrees of illness, to block disease progression. Given the long half-life of most mABs (approximately 3 weeks for IgG1), a single infusion should be sufficient.

Baum A, Fulton BO, Wloga E, et al. **Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies.** Science 15 Jun 2020: eabd0831. Full-text: https://doi.org/10.1126/science.abd0831 ● (IMPORTANT)

Elegant cell experiments, showing that a combination of antibodies may provide a powerful way to minimize mutational escape by SARS-CoV-2; in particular, two antibodies were chosen so as to bind to distinct and non-overlapping regions of the viral target (in this case, the RBD of the spike protein), in order to thus require the unlikely occurrence of simultaneous mutations at two distinct genetic sites for viral escape.

Rogers TF, Zhao F, Huang D, et al. **Isolation of potent SARS-CoV-2 neutralizing antibodies and protection from disease in a small animal model.** Science 15 Jun 2020: eabc7520. Full-text: https://doi.org/10.1126/science.abc7520

Using a high-throughput rapid system for antibody discovery, the authors isolated more than 1000 mAbs from 3 convalescent donors by memory B cell selection using SARS-CoV-2 S or RBD (receptor-binding domain) recombinant proteins. Of note, only a small fraction of these Abs was neutralizing, highlighting the value of deep mining of responses to access the most potent Abs. RBD-nAbs that directly compete with ACE2 are clearly the most preferred for prophylactic and therapeutic applications, and as reagents to define nAb

epitopes for vaccine. With these nABs, Syrian hamsters were protected from weight loss. However, animals that received higher doses also showed body weight loss, possibly indicating antibody-mediated enhanced disease.

Brouwer PJ, Caniels TG, van der Straten K, et al. **Potent neutralizing antibodies from COVID-19 patients define multiple targets of vulnerability.** Science 15 Jun 2020: eabc5902. Full-text: https://doi.org/10.1126/science.abc5902

Antibodies from convalescent COVID-19 patients had low levels of somatic hypermutation and showed a strong enrichment in VH1-69, VH3-30-3 and VH1-24 gene usage. A subset of the antibodies were able to potently inhibit authentic SARS-CoV-2 infection as low as 0.007 μg/mL. Competition and electron microscopy studies illustrate that the SARS-CoV-2 spike protein contains multiple distinct antigenic sites. The authors isolated 19 neutralizing antibodies that target a diverse range of antigenic sites on the S protein, of which two showed picomolar (very strong!) neutralizing activities.

Tedder RS, Semple MG. **Appropriate selection of convalescent plasma donors for COVID-19**. Lancet Inf Dis June 15, 2020. Full-text: https://doi.org/10.1016/S1473-3099(20)30470-9

The authors report on unpublished data (their own), indicating that quantification of specific antibody to the receptor-binding domain (RBD) will indicate levels of neutralising antibodies. This may help to find the best plasma donors. So why don't they publish their data?

Pediatrics

Stewart DJ, Hartley JC, Johnson M, et al. **Renal dysfunction in hospitalised children with COVID-19**. Lancet Child Adol Health. June 15, 2020. Full-text: https://doi.org/10.1016/S2352-4642(20)30178-4

Of 52 hospitalized children, 24 (46%) had elevated serum creatinine, and 15 (29%) met the diagnostic criteria for acute kidney injury (AKI). Most AKI cases occurred in those admitted to the pediatric ICU (93%), and in those with pediatric inflammatory multisystem syndrome temporarily associated with SARS-CoV-2 (PIMS-TS; 73%). This underlines the importance of renal function surveillance in all hospitalised pediatric cases of COVID-19, while simultaneously avoiding factors that exacerbate kidney injury, such as hypovolemia and the use of nephrotoxic drugs. According to the authors, standard care should in-

volve screening for nephritis and follow-up for long-term sequelae of acute kidney injury, such as hypertension and proteinuria.

17 June

Epidemiology

Davies NG, Klepac P, Liu Y et al. **Age-dependent effects in the transmission and control of COVID-19 epidemics**. Nat Med 2020, June 16. https://doi.org/10.1038/s41591-020-0962-9 ● (IMPORTANT)

Do children have a lower susceptibility to infection? Probably yes. The authors used epidemic data from Canada, China, Italy, Japan, Singapore, and South Korea to determine the level of susceptibility and clinical symptoms in various age groups. Susceptibility to infection in individuals under 20 years of age was approximately half that of adults aged over 20 years, and clinical symptoms manifest in 21% (95% confidence interval: 12–31%) of infections in 10- to-19-year-olds, rising to 69% (57–82%) of infections in people aged over 70 years. These estimates have implications for the expected global burden of COVID-19, as a result of demographic differences across settings.

Kucharski AJ, Klepac P, Conlan AJ, et al. **Effectiveness of isolation, testing, contact tracing, and physical distancing on reducing transmission of SARS-CoV-2 in different settings: a mathematical modelling study**. The Lancet Infectious Diseases 2020 Published: June 16, 2020. Full-text: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30457-6/fulltext

Another mathematical modelling study, using pandemic data from 40,162 UK participants and simulating the effect of a range of different testing, isolation, tracing, and physical distancing scenarios. If combined with moderate physical distancing measures, self-isolation and contact tracing would be more likely to achieve control of SARS-CoV- 2 transmission.

Prevention

Cai C, Floyd EL. **Effects of Sterilization With Hydrogen Peroxide and Chlorine Dioxide on the Filtration Efficiency of N95, KN95, and Surgical Face Masks**. JAMA Netw Open. 2020 Jun 1;3(6):e2012099. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.12099

This quality improvement study found that the sterilization process had different effects on the filtration efficiencies of different masks. Sterilization with H_2O_2 had fewer negative effects than ClO_2.

Diagnostics

Patel MR, Carroll D, Ussery E, et al. **Performance of oropharyngeal swab testing compared to nasopharyngeal swab testing for diagnosis of COVID-19 -United States, January-February 2020**. Clin Infect Dis. 2020 Jun 16:ciaa759. PubMed: https://pubmed.gov/32548635. Full-text: https://doi.org/10.1093/cid/ciaa759

Among persons with specimens collected early in the course of illness, SARS-CoV-2 RNA diagnostic results were highly concordant between OP and NP swabs (95.2%). However, NP swab Ct values were lower (indicating more virus) in 66.7% of concordant-positive pairs, suggesting NP swabs may more accurately detect SARS-CoV-2.

Transmission

Steensels D, Oris E, Coninx L, et al. **Hospital-Wide SARS-CoV-2 Antibody Screening in 3056 Staff in a Tertiary Center in Belgium**. JAMA. 2020 Jun 15. PubMed: https://pubmed.gov/32539107. Full-text: https://doi.org/10.1001/jama.2020.11160

In this large, hospital-wide screening study for SARS-CoV-2 antibodies among hospital staff in a Belgian tertiary care center, neither direct involvement in clinical care nor working in a COVID-19 unit increased the odds of being seropositive, while having a suspected COVID-19 household contact did. Overall, 197 staff (6.4%, 95% CI, 5.5%-7.3%) had IgG antibodies for SARS-CoV-2.

Clinical

Suleyman G, Fadel RA, Malette KM, et al. **Clinical Characteristics and Morbidity Associated With Coronavirus Disease 2019 in a Series of Patients in Metropolitan Detroit**. JAMA Netw Open. 2020 Jun 1;3(6):e2012270. PubMed: https://pubmed.gov/32543702. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.12270-

Case series of 463 consecutive patients with COVID-19 (72.1% African American), evaluated at Henry Ford Health System in metropolitan Detroit, Michigan. Most patients (94%) had at least 1 comorbidity, including hypertension (64%), chronic kidney disease (39.3%), and diabetes (38%). 355 patients (77%)

were hospitalized; 141 (40%) required intensive care unit management and 114 (81%) of those patients required invasive mechanical ventilation. Male sex (OR, 1.8) and age older than 60 years (OR 5.3) were significantly associated with mortality, whereas African American race was not.

Patel MC, Chaisson LH, Borgetti S, et al. **Asymptomatic SARS-CoV-2 infection and COVID-19 mortality during an outbreak investigation in a skilled nursing facility**. Clin Infect Dis. 2020 Jun 16:ciaa763. PubMed: https://pubmed.gov/32548628. Full-text: https://doi.org/10.1093/cid/ciaa763

Of 126 residents tested at a skilled nursing facility in Illinois, 33 had confirmed SARS-CoV-2. Nineteen (58%) had symptoms at the time of testing, 1 (3%) developed symptoms over follow-up, and 13 (39%) remained asymptomatic. Thirty-five residents who tested negative on March 15 developed symptoms over follow-up; of these, 3 were re-tested and 2 were positive. The 30-day probability of death among cases was 29%.

Comorbidities

Piccolo R, Bruzzese D, Mauro C, et al. **Population Trends in Rates of Percutaneous Coronary Revascularization for Acute Coronary Syndromes Associated With the COVID-19 Outbreak**. Circulation. 2020 Jun 16; 141(24): 2035–2037. Full-text: https://doi.org/10.1161/CIRCULATIONAHA.120.047457

This study investigated the association between the outbreak of COVID-19 and PCI rates for ACS (Acute Coronary Syndromes) in the Campania region, which, with 5.8 million residents, represents ≈10% of the Italian population. The outbreak was associated with a decline in the number of PCIs for ACS by 32%. In the last 2 weeks of the observational period, PCIs for ACS were reduced by 50%. In comparison with PCI volumes for the same time in 2019, the decline in PCI rates was of a similar magnitude (between 36% and 38%).

Garassino MC, Whisenant JG, Huang LC, et al. **COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study**. Lancet Oncol. 2020 Jun 12:S1470-2045(20)30314-4. PubMed: https://pubmed.gov/32539942. Full-text: https://doi.org/10.1016/S1470-2045(20)30314-4

Of 200 patients with COVID-19 and thoracic cancers (76% NSCLC) from eight countries were identified and included in the TERAVOLT registry, 152 (76%) were hospitalised and 66 (33%) died. Of note, in a multivariable analysis, only

smoking history (OR 3.18, 95% CI 1.11-9.06) was associated with increased risk of death.

Treatment

Luo W, Li YX, Jiang LJ. **Targeting JAK-STAT Signaling to Control Cytokine Release Syndrome in COVID-19**. Trends Pharmacol Science June 17, 2020. Full-text: https://doi.org/10.1016/j.tips.2020.06.007

Several inflammatory cytokines that correlate with adverse clinical outcomes in COVID-19 employ a distinct intracellular signalling pathway mediated by Janus kinases (JAKs). JAK-STAT signalling may be an excellent therapeutic target. This article reviews the possibilities and challenges of targeting this pathway in COVID-19.

18 June

Epidemiology

Soriano V, Meiriño R, Corral O, Guallar MP. **SARS-CoV-2 antibodies in adults in Madrid, Spain.** Clin Infect Dis. 2020 Jun 16:ciaa769. PubMed: https://pubmed.gov/32544951. Full-text: https://doi.org/10.1093/cid/ciaa769

Madrid has been the most deeply hit region by COVID-19 in Spain, with 65,000 confirmed cases and 9,000 deaths up to May 10th, eight weeks after the country's lockdown had been implemented on March 14th. The authors found that roughly 10.9% of adults in Madrid (excluding those living in communities of 10 to 25 persons) had SARS-CoV-2 antibodies at the time of lockdown release on May 10th.

Transmission

Jing JQ, Liu MJ, Yuan J. **Household secondary attack rate of COVID-19 and associated determinants in Guangzhou, China: a retrospective cohort study**. Lancet Infect Dis. 2020; (published online June 17.) https://doi.org/10.1016/S1473-3099(20)30471-0

Are children less susceptible? Using a comprehensive contact tracing dataset, the authors estimated secondary attack rate among household contacts to be 12.4% (95% CI 9.8–15.4) when household contacts were defined on the basis of close relatives, and 17.1% (13.3–21.8) when household contacts were defined on the basis of residential address. Compared with the oldest age group (≥ 60

years), the risk of household infection was lower in the youngest age group (< 20 years; odds ratio 0.23) and among adults aged 20–59 years (OR 0.64).

Du W, Yu J, Liu X, Chen H, Lin L, Li Q. **Persistence of SARS-CoV-2 virus RNA in feces: A case series of children**. J Infect Public Health. 2020 Jun 7. PubMed: https://pubmed.gov/32546439. Full-text: https://doi.org/10.1016/j.jiph.2020.05.025

During follow-up examination after discharge, seven out of ten children contained SARS-CoV-2 virus RNA in their fecal specimens, despite all patients showing negative results in respiratory tract specimens. One out of those seven patients relapsed. The median time from onset to being negative in respiratory tract and fecal specimens was 9 days and 34.43 days, respectively.

Dhand R, Li J. **Coughs and Sneezes: Their Role in Transmission of Respiratory Viral Infections, Including SARS-CoV-2**. Am J Respir Crit Care Med. 2020 Jun 16. PubMed: https://pubmed.gov/32543913. Full-text: https://doi.org/10.1164/rccm.202004-1263PP ● (IMPORTANT)

Everything you always wanted to know about... coughs and sneezes. A total of 79 references are used to explain how larger droplets produced by coughing and sneezing settle quickly, and the force with which they are expelled determines how far they are dispersed. Nice visuals in the supplement at the end of the paper.

Prevention

Lyu W, Wehby GL. **Community Use Of Face Masks And COVID-19: Evidence From A Natural Experiment Of State Mandates In The US**. Health Aff (Millwood). 2020 Jun 16. PubMed: https://pubmed.gov/32543923. Full-text: https://doi.org/10.1377/hlthaff.2020.00818

Masks, masks, masks. This study provides evidence from a natural experiment on the effects of state government mandates in the US for face mask use in public issued by 15 states plus DC between April 8 and May 15. Mandating face mask use in public was associated with a decline in the daily COVID-19 growth rate by 0.9, 1.1, 1.4, 1.7, and 2.0 percentage-points in 1–5, 6–10, 11–15, 16–20, and 21+ days after implementation, respectively. Estimates suggest as many as 230,000–450,000 COVID-19 cases possibly averted by May 22, 2020 due to these mandates.

Clinical

Elinghaus D, Degenhardt F, Bujanda L, et al. **Genomewide Association Study of Severe Covid-19 with Respiratory Failure**. NEJM, June 17, 2020. Full-text: https://doi.org/10.1056/NEJMoa2020283 ● (IMPORTANT)

The authors identified a 3p21.31 gene cluster as a genetic susceptibility locus in patients with COVID-19 with respiratory failure and confirmed a potential involvement of the ABO blood-group system. A blood-group–specific analysis showed a higher risk in blood group A than in other blood groups (odds ratio, 1.45; 95% CI, 1.20 to 1.75) and a protective effect in blood group O as compared with other blood groups (odds ratio, 0.65; 95% CI, 0.53 to 0.79). However, please don't measure the blood groups of your patients now. The risk elevations are low (male gender possibly, see below). These results are much more relevant with regard to the underlying pathophysiology (the locus also contains genes encoding chemokine receptors).

Clark A, Jit M, Warren-Gash C, et al. **Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health conditions in 2020: a modelling study**. The Lancet Global Health June 15, 2020. Full-text: https://doi.org/10.1016/S2214-109X(20)30264-3

No good prospects. Analyzing data from 188 nations, the team estimates that 1.7 billion people worldwide have an elevated risk of 'severe' illness. The researchers also estimate that 349 million (186–787) people (4% of the global population) are at high risk of severe COVID-19 and would require hospital admission if infected (ranging from < 1% of those younger than 20 years to approximately 20% of those aged 70 years or older). In total, 6% of males were found to be at high risk compared with 3% of females.

Severe COVID-19

Thompson AE, Ranard BL, Wei Y. **Prone Positioning in Awake, Nonintubated Patients With COVID-19 Hypoxemic Respiratory Failure**. JAMA Intern Med June 17, 2020. Full-text: https://doi.org/10.1001/jamainternmed.2020.3030

The next study on proning. In this small single-center cohort study, use of the prone position for 25 awake, spontaneously breathing patients with COVID-19 was associated with improved oxygenation. In addition, patients with an Spo2 of 95% or greater after 1 hour of the prone position was associated with a lower rate of intubation. Unfortunately, there was no control group and the

sample size was very small. Ongoing clinical trials of prone positioning in non–mechanically ventilated patients (NCT04383613, NCT04359797) will hopefully help clarify the role of this simple, low-cost approach for patients with acute hypoxemic respiratory failure.

Treatment

De Luca G, Cavalli G, Campochiaro C, et al. **GM-CSF blockade with mavrilimumab in severe COVID-19 pneumonia and systemic hyperinflammation: a single-centre, prospective cohort study**. Lancet Rheumatology 2020, June 16. Full-text: https://doi.org/10.1016/S2665-9913(20)30170-3

Mavrilimumab, an anti-granulocyte macrophage colony stimulating factor receptor-α monoclonal antibody, was added as a single intravenous dose to standard management in 13 patients with severe COVID-19 pneumonia, hypoxia, and systemic hyperinflammation (26 patients with "contemporaneous patients with similar baseline characteristics" were used a control group. During the 28-day follow-up, no patients in the mavrilimumab group died, and seven (27%) patients in the control group died (p=0.086). At day 28, all patients in the mavrilimumab group and 17 (65%) patients in the control group showed clinical improvement (p=0.030), with earlier improvement in the mavrilimumab than in the control group. Comment: Interesting, but larger trials are needed. Small sample size, an absence of randomisation, and a short follow-up period may reduce the full generalisability.

Mehta P, Porter JC, Manson JJ, et al. **Therapeutic blockade of granulocyte macrophage colony-stimulating factor in COVID-19-associated hyperinflammation: challenges and opportunities**. Lancet Respiratory Medicine June 16, 2020. Full-text: https://doi.org/10.1016/S2213-2600(20)30267-8

Granulocyte macrophage colony-stimulating factor (GM-CSF) is an immunoregulatory cytokine with a pivotal role in initiation and perpetuation of inflammatory diseases. In this nice review, the authors consider the scientific rationale and potential risks for therapeutic targeting of GM-CSF in COVID-19-associated hyperinflammation.

19 June

Epidemiology

Emeruwa UN, Ona S, Shaman JL, et al. **Associations Between Built Environment, Neighborhood Socioeconomic Status, and SARS-CoV-2 Infection Among Pregnant Women in New York City**. JAMA 2020, June 18, 2020. Full-text: https://doi.org/10.1001/jama.2020.11370

This cross-sectional study of 396 pregnant New York City residents delivering at New York hospitals showed that the likelihood of SARS-CoV-2 varied substantially across measures of built environment and neighborhood socioeconomic status. Large household membership, household crowding, and low socioeconomic status were associated with a 2-3 fold higher risk of infection.

Devi S. **COVID-19 resurgence in Iran**. Lancet 2020, June 20, 2020. Full-text: https://doi.org/10.1016/S0140-6736(20)31407-0

Brief overview. Iran was one of the first countries to experience a COVID-19 epidemic, and began relaxing restrictions in April. Cases dropped, with fewer than 1000 new cases per day by the start of May, but daily cases have since increased, with the Iranian Health Ministry reporting 2,410 new cases on June 13.

Clapham H, Hay J, Routledge I, et al. **Seroepidemiologic Study Designs for Determining SARS-COV-2 Transmission and Immunity**. Emerg Infect Dis. 2020 Jun 16;26(9). PubMed: https://pubmed.gov/32544053. Full-text: https://doi.org/10.3201/eid2609.201840

Numerous challenges exist in terms of sample collection, what the presence of antibodies actually means, and appropriate analysis and interpretation to account for test accuracy and sampling biases. The authors review strengths and limitations of different assay types and study designs, and discuss methods for rapid sharing and analysis of serologic data.

Transmission

Xu XK, Liu XF, Wu Y, et al. **Reconstruction of Transmission Pairs for novel Coronavirus Disease 2019 (COVID-19) in mainland China: Estimation of Super-spreading Events, Serial Interval, and Hazard of Infection**. Clinical Infectious Diseases 2020. Full-text: https://doi.org/10.1093/cid/ciaa790

The virus is so fast: This database with detailed demographic characteristics, travel history, social relationships, and epidemiological timelines for 1,407

transmission pairs that formed 643 transmission clusters in mainland China used statistical model fittings to identify the super-spreaders and estimate serial interval distributions. There were 34 primary cases identified as super-spreaders, with 5 super-spreading events occurring within households. Serial intervals were short and were estimated as 5.0 (95% CI: 4.4-5.5) and 5.2 (95% CI: 4.9- 5.7) days for household transmissions and 5.2 (95% CI: 4.6-5.8) and 5.3 (95% CrI: 4.9-5.7) days for non-household transmissions, respectively.

Mani NS, Budak JZ, Lan KF, et al. **Prevalence of COVID-19 Infection and Outcomes Among Symptomatic Healthcare Workers in Seattle, Washington**. Clin Infect Dis. 2020 Jun 16:ciaa761. PubMed: https://pubmed.gov/32548613. Full-text: https://doi.org/10.1093/cid/ciaa761

The authors have stablished two high-throughput employee testing centers in Seattle, Washington with drive-through and walk-through options for symptomatic employees at the University of Washington Medicine system and its affiliated organizations. Between March 12 and April 23, a total of 3,477 symptomatic employees were tested; 185 (5.3%) employees tested positive for COVID-19. The prevalence of SARS-CoV-2 was similar when comparing frontline HCWs (5.2%) to non-frontline staff (5.5%).

Diagnostics

Long Q, Tang X, Shi Q et al. **Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections**. Nat Med 2020. Full-text: https://doi.org/10.1038/s41591-020-0965-6 ● (IMPORTANT)

"COVID-19 passes" will last a few weeks, at least in patients with mild symptoms: Compared to symptomatic patients, 37 asymptomatic patients had a significantly longer duration of viral shedding. The virus-specific IgG levels were significantly lower in the acute phase. IgG levels and neutralizing antibodies started to decrease within 2–3 months after infection. Of note, 40% became seronegative (13% of the symptomatic group) for IgG in the early convalescent phase.

Clinical

Tan T, Khoo B, Mills EG, et al. **Association between high serum total cortisol concentrations and mortality from COVID-19**. Lancet Diabetes and Endocrinology 2020, June 18. Full-text: https://doi.org/10.1016/S2213-8587(20)30216-3

In 535 patients, multivariable analysis showed that a doubling of cortisol concentration was associated with a significant 42% increase in the hazard of mortality, after adjustment for age, the presence of comorbidities, and laboratory tests. Cortisol seemed to be a better independent predictor than other laboratory markers associated with COVID-19, such as CRP, D-dimer, and neutrophil to leukocyte ratio.

Hubiche T, Le Duff F, Chiverini C, et al. **Negative SARS-CoV-2 PCR in patients with chilblain-like lesions**. Lancet Inf Dis 2020, Published: June 18, 2020. Full-text: https://doi.org/10.1016/S1473-3099(20)30518-1 ● (IMPORTANT)

Among 40 young patients with chilblain lesions and with suspected SARS-CoV-2 infection, COVID-19 serology was positive in 12 (30%) patients. All had negative PCR results at the time of presentation, suggesting that in young patients SARS-CoV-2 is completely suppressed before a humoral immune response is induced.

Comorbidities

Arlet JB, de Luna G, Khimoud D, et al. **Prognosis of patients with sickle cell disease and COVID-19: a French experience**. Lancet Hematology 2020, June 18. Full-text: https://doi.org/10.1016/S2352-3026(20)30204-0

Results of this French cohort of 83 patients suggest that COVID-19, even if potentially severe, does not seem to carry an increased risk of morbidity or mortality in patients with sickle cell disease, as most patients worldwide have the SS/Sβ0 genotype and are younger than 45 years.

Zeidan AM, Poddu P, Patniak MM, et al. **Special considerations in the management of adult patients with acute leukaemias and myeloid neoplasms in the COVID-19 era: recommendations from a panel of international experts**. Lancet Hematology 2020, June 18. Full-text: https://doi.org/10.1016/S2352-3026(20)30205-2

This article summarise key changes related to service allocation, clinical and supportive care, clinical trial participation, and ethical considerations regarding the use of lifesaving measures for these patients. It also offers a consensus on clinical practice guidance for optimal care in both the university and community health-care settings.

Treatment

Dao W, Zhang W, Zhang B. **Structure-based design of antiviral drug candidates targeting the SARS-CoV-2 main protease**. Science 19 Jun 2020. Vol. 368, Issue 6497, pp. 1331-1335. Full-text: https://doi.org/10.1126/science.abb4489 ● (IMPORTANT)

HIV protease inhibitors (PIs) such as darunavir or lopinavir probably don't work. These authors have developed better ones, based on analyzing the structure of the Mpro active site. Both PIs strongly inhibited the activity of Mpro and showed good antiviral activity in cell culture. Compound 11a had good pharmacokinetic properties and low toxicity when tested in mice and beagle dogs, suggesting that it is a promising drug candidate.

20 June

Epidemiology

Truelove S, Abrahim O, Altare C, et al. **The potential impact of COVID-19 in refugee camps in Bangladesh and beyond: A modeling study**. PLoS Med 2020 Jun 16;17(6):e1003144. PubMed: https://pubmed.gov/32544156. Full-text: https://doi.org/10.1371/journal.pmed.1003144

Bangladesh hosts almost 1 million Rohingya refugees from Myanmar, with 600,000 concentrated in the Kutupalong-Balukhali Expansion Site. Using different transmission models and considering the age distribution in the camp, the authors expect 2,040-2,880 deaths (assuming that age was the primary determinant of infection severity and hospitalization). They also expect that comorbidities, limited hospitalization, and intensive care capacity may increase this risk.

Vaccine

Fuller DH, Berglund P. **Amplifying RNA Vaccine Development**. NEJM, June 18, 2020. N Engl J Med 2020; 382:2469-2471. Full-text: https://doi.org/10.1056/NEJMcibr2009737

Recent interest in messenger RNA (mRNA) vaccines has been fueled by methods that increase mRNA stability and protein production and improve delivery. The mRNA vaccines do not need to enter the nucleus to express the antigen. Avoidance of the risk of integration into the host genome is thus considered a comparative advantage. The authors describe new techniques in this field. The most promising seems to be a strategy that is based on two RNA

vectors — one retaining the replicase-encoding gene and the other encoding the antigen.

Huo J, Zhao Y, Ren J, et al. **Neutralisation of SARS-CoV-2 by destruction of the prefusion Spike**. Cell Host Microbe June 19, 2020. Full-text: https://doi.org/10.1016/j.chom.2020.06.010

The monoclonal antibody CR3022 tightly binds the receptor binding domain (RBD) and neutralizes SARS-CoV-2. The highly conserved, structure-stabilising, CR3022 epitope is inaccessible in the prefusion Spike, suggesting that CR3022 binding facilitates conversion to the fusion-incompetent post-fusion state. The mechanism of neutralisation is new and was not seen before for coronaviruses, suggesting that the CR3022 epitope should be a major target for therapeutic antibodies.

Clinical

Sardanelli D, Cozzi A, Monfardini L, et al. **Association of mediastinal lymphadenopathy with COVID-19 prognosis**. Lancet Inf Dis June 19, 2020. Full-text: https://doi.org/10.1016/S1473-3099(20)30521-1

Among 410 patients with COVID-19 who underwent CT at emergency department admission in three hospitals in Lombardy, Italy, 76 (19%) patients had mediastinal lymphadenopathies (ie, lymph nodes with a short-axis diameter > 1 cm). Data suggest that lymphadenopathy may be considered a predictor of a worse outcome. The pathophysiological meaning of this finding remains to be investigated.

Comorbidities

Fosbøl EL, Butt JH, Østergaard L, et al. **Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With COVID-19 Diagnosis and Mortality**. JAMA June 19, 2020. Full-text: https://doi.org/10.1001/jama.2020.11301

ACE inhibitors are not harmful, even in Denmark (one of the countries with the best epidemiological data). In a retrospective cohort study of 4,480 (!) patients diagnosed as having COVID-19, prior ACEI/ARB use, compared with no use, was not significantly associated with mortality (adjusted hazard ratio, 0.83). In a nested case-control study of a cohort of 494,170 patients with hypertension, use of ACEI/ARB, compared with use of other antihypertensive medications, was not significantly associated with COVID-19 diagnosis (adjusted hazard ratio, 1.05).

Lai PH, Lancet EA, Weiden MD. **Characteristics Associated With Out-of-Hospital Cardiac Arrests and Resuscitations During the Novel Coronavirus Disease 2019 Pandemic in New York City**. JAMA Cardiol. Published online June 19, 2020. Full-text: https://doi.org/10.1001/jamacardio.2020.2488

In this population-based cross-sectional study of 5,325 patients with out-of-hospital cardiac arrests in New York City, the number undergoing resuscitation was 3-fold higher during the COVID-19 period compared with the similar period in 2019. The authors report 2,653 excess out-of-hospital cardiac arrests (90% of these excess cases resulted in out-of-hospital deaths).

Koopmann A, Ekaterini G, Falk K, et al. **Did the General Population in Germany Drink More Alcohol during the COVID-19 Pandemic Lockdown**? Alcohol and Alcoholism, June 19 20020. Full-text: https://doi.org/10.1093/alcalc/agaa058

Question of the day. Answer: Some did so, yes. Out of the 2,102 participants of this survey, 34.7% reported drinking "more or much more" alcohol since the begin of the lockdown. Binary logistic regression analyses showed that especially low educated subjects and subjects with higher levels of perceived stress due to the lockdown were at risk of consuming more alcohol during the lockdown.

Cappo A, Bellani G, Wintertin D, et al**. Feasibility and physiological effects of prone positioning in non-intubated patients with acute respiratory failure due to COVID-19 (PRON-COVID): a prospective cohort study**. Lancet Resp Med June 19, 2020. Full-text: https://doi.org/10.1016/S2213-2600(20)30268-X

This prospective cohort study enrolled 56 patients with COVID-19-related pneumonia receiving supplemental oxygen or non-invasive continuous positive airway pressure. Prone positioning was feasible in most patients and effective in rapidly ameliorating blood oxygenation. The effect was maintained after resupination in half of the patients.

Treatment

Robbiani DF, Gaebler C, Muecksch F et al. **Convergent antibody responses to SARS-CoV-2 in convalescent individuals**. Nature 2020. https://doi.org/10.1038/s41586-020-2456-9 ● (IMPORTANT)

This may help to explain why convalescent plasma does not work in all patients. In plasma from 149 patients collected an average of 39 days after the onset of symptoms, neutralizing titres were extremely variable. Most plasmas did not contain high levels of neutralizing activity. Nevertheless, rare but recurring RBD-specific antibodies with potent antiviral activity were found in all individuals tested, suggesting that a vaccine designed to elicit such antibodies could be broadly effective.

Clementi N, Ferrarese R, Criscuolo E, et al. **Interferon-β 1a inhibits SARS-CoV-2 in vitro when administered after virus infection**. J Inf Dis, June 19 2020. Full-text: https://doi.org/10.1093/infdis/jiaa350

IFN may work, when given early. Several clinical trials into the administration of IFN to COVID-19 patients are currently ongoing. These *in vitro* observations shed light for the first time on antiviral activity of IFN-β1a against SARS-CoV-2 when administered after the infection of cells, highlighting its possible efficacy in an early therapeutic setting.

21 June

Epidemiology

Twahirwa Rwema JO, Diouf D, Phaswana-Mafuya N, et al. **COVID-19 Across Africa: Epidemiologic Heterogeneity and Necessity of Contextually Relevant Transmission Models and Intervention Strategies**. Ann Intern Med. 2020 Jun 18. PubMed: https://pubmed.gov/32551812. Full-text: https://doi.org/10.7326/M20-2628

Brief overview on the burden and outcomes associated with COVID-19 in Africa, showing substantial variations across countries. Some explanations why many multiple mathematical models have failed to project the epidemic on the continent.

Han X, Wei X, Alwalid O, et al. **Severe Acute Respiratory Syndrome Coronavirus 2 among Asymptomatic Workers Screened for Work Resumption, China**. Emerg Infect Dis. 2020 Jun 17;26(9). PubMed: https://pubmed.gov/32553070. Full-text: https://doi.org/10.3201/eid2609.201848

It's not completely gone. After the outbreak in Wuhan, China, the authors assessed 29,299 workers screened with PCR during March 13–April 25, 2020. They noted 18 (0.06%) cases of asymptomatic infection; 13 turned negative within 8.0 days, and 41 close contacts tested negative. Of 22,633 persons tested for SARS-CoV-2 antibodies, 617 (2.7%) cases had positive IgG but negative IgM; 196 (0.87%) cases had positive IgG and IgM; and 40 (0.18%) cases had negative IgG but positive IgM.

Czeisler MÉ, Tynan MA, Howard ME, et al. **Public Attitudes, Behaviors, and Beliefs Related to COVID-19, Stay-at-Home Orders, Nonessential Business Closures, and Public Health Guidance - United States, New York City, and Los Angeles, May 5-12, 2020**. MMWR Morb Mortal Wkly Rep. 2020 Jun 19;69(24):751-758. PubMed: https://pubmed.gov/32555138. Full-text: https://doi.org/10.15585/mmwr.mm6924e1

Most people agree: during the week of May 5–12, 2020, a survey among 2,402 adults in New York City and Los Angeles and broadly across the United States found widespread support of stay-at-home orders and nonessential business closures and high degree of adherence to COVID-19 mitigation guidelines. 74-82% reported they would not feel safe if these restrictions were lifted nationwide at the time the survey was conducted. In addition, among those who reported that they would not feel safe, some indicated that they would nonetheless want community mitigation strategies lifted and would accept associated risks (13-17%, respectively).

Virology

Wu KE, Fazal FM, Parker KR, et al. **RNA-GPS Predicts SARS-CoV-2 RNA Residency to Host Mitochondria and Nucleolus**. Cell Systems, June 20, 2020. Full-text: https://doi.org/10.1016/j.cels.2020.06.008

SARS-CoV-2 genomic and subgenomic RNA (sgRNA) transcripts hijack the host cell's machinery. But where is the viral RNA localized in the cell? Computational modeling of SARS-CoV-2 viral RNA subcellular residency across eight subcellular neighborhoods, predicted the SARS-CoV-2 RNA genome and sgRNAs to be enriched towards the host mitochondrial matrix and nucleolus.

The authors interpret the mitochondrial residency signal as an indicator of intracellular RNA trafficking with respect to double-membrane vesicles, a critical stage in the coronavirus life cycle.

Clinical

Berzuini A, Bianco C, Paccapelo C, et al. **Red cell bound antibodies and transfusion requirements in hospitalized patients with COVID-19**. Blood. 2020 Jun 19:. PubMed: https://pubmed.gov/32559762. Full-text: https://doi.org/10.1182/blood.2020006695

The direct antiglobulin test (DAT) detects immunoglobulin or complement bound *in vivo* to red blood cells (RBC), and is widely used to diagnose immune mediated hemolytic anemias. A positive DAT was found in 52 of 113 COVID-19 patients (46%) using the microcolumn screening assay. Thus, anti-RBC antibodies were detectable in almost half of the patients. Although the serologic features of DAT reactivity in COVID-19 patients were somewhat different from those generally observed in autoimmune hemolytic anemia, DAT positivity was associated with increasing frequency of anemia and greater transfusion requirements.

Severe COVID

Colling ME, Kanthi Y. **COVID-19-associated coagulopathy: An exploration of mechanisms**. Vasc Med. 2020 Jun 19:1358863X20932640. PubMed: https://pubmed.gov/32558620. Full-text: https://doi.org/10.1177/1358863X20932640 ● (IMPORTANT)

Nice review of the laboratory and clinical findings of patients with COVID-19-associated coagulopathy. The authors hypothesize that an imbalance between coagulation and inflammation may result in a hypercoagulable state. Although thrombosis initiated by the innate immune system is hypothesized to limit SARS-CoV-2 dissemination, aberrant activation of this system can cause endothelial injury resulting in loss of thromboprotective mechanisms, excess thrombin generation, and dysregulation of fibrinolysis and thrombosis.

Treatment

Stader F, Khoo S, Stoeckle M, et al. **Stopping lopinavir/ritonavir in COVID-19 patients: duration of the drug interacting effect**. J Antimicrob Chemother. 2020 Jun 17. PubMed: https://pubmed.gov/32556272. Full-text: https://doi.org/10.1093/jac/dkaa253

The duration of cytochrome P-450 (CYP) 3A inhibition after stopping lopinavir/r treatment is not well understood, leading to some uncertainty as to how long to maintain adjusted doses of co-medications or when to restart drug therapies against comorbidities. The authors investigated the duration of hepatic and intestinal CYP3A inhibition after stopping lopinavir/r treatment by a verified modelling approach. In all age groups, there was more than 80% disappearance of CYP3A inhibition 5 days after stopping lopinavir/r under the consideration of population variability. Complete disappearance of CYP3A inhibition, however, took 21 days in all simulated age groups.

Hegerova L, Gooley T, Sweerus KA, et al. **Use of Convalescent Plasma in Hospitalized Patients with Covid-19 - Case Series**. Blood. 2020 Jun 19. PubMed: https://pubmed.gov/32559767. Full-text: https://doi.org/10.1182/blood.2020006964

The next case series on early clinical experience of 20 hospitalized patients treated with CP. Compared to 20 matched controls with severe or life-threatening COVID-19 infection, laboratory and respiratory parameters were improved in patients following CP infusion. The 7- and 14-day case fatality rate in CP patients compared favorably to that in controls. However, sample size was small and the study was not randomized. Larger trials are eagerly awaited.

Pediatrics

Otto WR, Geoghegan S, Posch LC, et al. **The Epidemiology of SARS-CoV-2 in a Pediatric Healthcare Network in the United States**. J Pediatric Infect Dis Soc. 2020 Jun 19. PubMed: https://pubmed.gov/32559282. Full-text: https://doi.org/10.1093/jpids/piaa074

Huge numbers, giving a clearer picture of what happens in children: Of 7,256 children tested for SARS-CoV-2, 424 (6%) tested positive. By race, 10% of black children tested positive vs. 3% of white children. Of the 424 patients who tested positive for SARS-CoV-2, 77 (18%) were hospitalized, of which 24 required respiratory support. Twelve (2.8%) SARS-CoV-2 positive patients developed critical illness requiring mechanical ventilation and 2 patients required ECMO. Two patients died.

22 June

Epidemiology

Percivalle E, Cambiè G, Cassaniti I, et al. **Prevalence of SARS-CoV-2 specific neutralising antibodies in blood donors from the Lodi Red Zone in Lombardy, Italy, as at 06 April 2020**. Euro Surveill. 2020;25(24. Full-text: https://doi.org/10.2807/1560-7917.ES.2020.25.24.2001031

This study evaluated SARS-CoV-2 RNA and neutralizing antibodies in blood donors (BD) residing in the highly affected "Lodi Red Zone", Italy (an area of 169 km^2, including 10 municipalities and 51,500 inhabitants, which went into lockdown in February 2020). Of 390 BDs recruited after 20 February – when the first COVID-19 case in Lombardy was identified, 91 (23%) aged 19–70 years were antibody positive.

Savulescu J, Cameron J. **Why lockdown of the elderly is not ageist and why levelling down equality is wrong**. J Med Ethics. 2020 Jun 19:medethics-2020-106336. PubMed: https://pubmed.gov/32561661. Full-text: https://doi.org/10.1136/medethics-2020-106336

Some intelligent thoughts on a "partial" lockdown for the elderly. The authors think that ethically, selective isolation is permissible. It is not unjust discrimination. It is analogous to only screening women for breast cancer: selecting those at a higher probability of suffering from a disease. Even if it were unjust discrimination, it would be proportionate because it brings benefits to the elderly and is necessary given the grave risks to the economy and subsequent well-being of the larger population of an indiscriminate lockdown. To oppose selective isolation of the elderly is to engage in a levelling down of equality which is itself morally questionable. There is no Hollywood happy ending here where everyone is a winner. Everything has its upsides and its downsides.

Transmission

Rickman HM, Rampling T, Shaw K, et al. **Nosocomial transmission of COVID-19: a retrospective study of 66 hospital-acquired cases in a London teaching hospital**. Clin Infect Dis. 2020 Jun 20. PubMed: https://pubmed.gov/32562422. Full-text: https://doi.org/10.1093/cid/ciaa816

A good example for working up a catastrophy, learning from mistakes. Of 435 cases of PCR-positive inpatients in a London hospital, 47 (11%) met the definition for definite hospital acquisition, with a further 19 (4%) probable hospital-

acquired. Symptom onset for these 66 hospital acquired cases was a median of 26 days (IQR 13-55) from admission. 24 (36%) patients died. Evidence of patient-to-patient transmission through contact in the same hospital bay was found in 55%.

Diagnostics

Münchhoff M, Mairhofer H, Nitschko H, et al. **Multicentre comparison of quantitative PCR-based assays to detect SARS-CoV-2, Germany, March 2020**. Eurosurveillance 2020, June 18. 25(24). Full-text: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.24.2001057

The authors compared 11 different RT-PCR test systems used in seven diagnostic laboratories in Germany in March 2020. The majority of RT-PCR assays detected ca 5 RNA copies per reaction, reflecting a high sensitivity and their suitability for screening purposes worldwide. A reduced sensitivity was noted for the original Charité RdRp gene confirmatory protocol, which may have impacted the confirmation of some cases in the early weeks of the pandemic. The CDC N1 primer/probe set was sensitive and robust for detection of SARS-CoV-2 in nucleic acid extracts from respiratory material, stool and serum from COVID-19 patients.

Chi Y, Ge Y, Wu B, et al. **Serum Cytokine and Chemokine profile in Relation to the Severity of Coronavirus disease 2019 (COVID-19) in China**. J Infect Dis. 2020 Jun 21:jiaa363. PubMed: https://pubmed.gov/32563194. Full-text: https://doi.org/10.1093/infdis/jiaa363

In this study, the authors detected the serum levels of 48 cytokines and chemokines (!) in a cohort of 74 patients including asymptomatic, mild, moderate and severe cases with laboratory confirmed COVID-19 in Jiangsu, China. IL-6, IL-7, IL-10, IL-18, G-CSF, M-CSF, MCP-1, MCP-3, IP-10, MIG, and MIP-1α were found to be associated with the severity of COVID-19. Some cytokines were significantly higher in men and many were elevated in asymptomatic patients.

Clinical

Bangalore S, Sharma A, Slotwiner A. **ST-Segment Elevation in Patients with Covid-19 — A Case Series.** N Engl J Med June 18, 2020; 382:2478-2480. Full-text: https://doi.org/10.1056/NEJMc2009020

Among 18 patients with COVID-19 who had ST-segment elevation indicating potential acute myocardial infarction 6/9 patients who underwent coronary angiography had obstructive disease. However, prognosis was dismal: A total of 13 patients (72%) died in the hospital (4 with myocardial infarction and 9 with noncoronary myocardial injury).

Ghannam M, Alshaer Q, Al-Chalabi M, Zakarna L, Robertson J, Manousakis G. **Neurological involvement of coronavirus disease 2019: a systematic review**. J Neurol. 2020 Jun 19. PubMed: https://pubmed.gov/32561990. Full-text: https://doi.org/10.1007/s00415-020-09990-2

In a systematic review of the literature, 82 cases of COVID-19 with neurological complications were identified. Conclusion: Neurological manifestations of COVID-19 are not rare, especially large vessel stroke, Guillain–Barré syndrome, and meningoencephalitis.

Schaefer IM, Padera RF, Solomon IH, et al. **In situ detection of SARS-CoV-2 in lungs and airways of patients with COVID-19**. Mod Pathol. 2020 Jun 19. PubMed: https://pubmed.gov/32561849. Full-text: https://doi.org/10.1038/s41379-020-0595-z

In 5/5 patients with acute phase DAD (≤ 7 days from onset of respiratory failure), SARS-CoV-2 was detected in pulmonary pneumocytes and ciliated airway cells, and in 2/5 in upper airway epithelium. In two patients with organizing DAD (> 14 days from onset of respiratory failure), no virus was detected in the lungs or airways. No endothelial cell infection was observed. The findings suggest that the virus is absent in the organizing phase.

Comorbidities

El-Sharkawi D, Iyengar S. **Haematological Cancers and the risk of severe COVID-19: Exploration and critical evaluation of the evidence to date**. Br J Haematol. 2020 Jun 19. PubMed: https://pubmed.gov/32559308. Full-text: https://doi.org/10.1111/bjh.16956

The authors review the evidence to date to see whether a history of hematological malignancy is associated with increased risk of COVID-19. Results: Multivariable analysis does indicate that patients with hematological malignancy, especially those diagnosed recently, are at increased risk of death with COVID-19 compared to the general population. The evidence that this risk is higher than for those with solid malignancies is conflicting. There is suggestive evidence from smaller cohort studies that those with myeloid malignan-

cy may be at increased risk within the blood cancer population, but this needs to be confirmed through larger studies.

Ibáñez-Samaniego L, Bighelli F, Usón C, et al. **Elevation of liver fibrosis index FIB-4 is associated with poor clinical outcomes in patients with COVID-19**. J Infect Dis. 2020 Jun 21:jiaa355. PubMed: https://pubmed.gov/32563190. Full-text: https://doi.org/10.1093/infdis/jiaa355

In middle-aged patients with COVID-19, the FIB-4 index may have a relevant prognostic role. In a multivariate analysis, among other risk factors, a FIB-4 > 2.67 increased the risk of ICU admission significantly (OR 3.41; 95% CI 1.30-8.92).

23 June

Immunology

Yang D, Chu H, Hou Y, et al. **Attenuated interferon and pro-inflammatory response in SARS-CoV-2-infected human dendritic cells is associated with viral antagonism of STAT1 phosphorylation**. J Infect Dis. 2020 Jun 21:jiaa356. PubMed: https://pubmed.gov/32563187. Full-text: https://doi.org/10.1093/infdis/jiaa356

Some novel insights into pathogenesis: Dendritic cells (DCs) and macrophages are sentinel cells for innate and adaptive immunity. The authors demonstrate that these cells were permissive to SARS-CoV-2 infection but did not support productive virus replication. SARS-CoV-2 launched an attenuated interferon response in both cell types and an attenuated immune response in DCs. The latter was associated with viral antagonism of STAT1 phosphorylation (STAT1 plays a critical role in the innate immune response in the clearance of SARS-CoV).

Diagnostics

Jääskeläinen AJ, Kuivanen S, Kekäläinen E, et al. **Performance of six SARS-CoV-2 immunoassays in comparison with microneutralisation**. J Clin Virol. 2020 Jun 15;129:104512. PubMed: https://pubmed.gov/32563180. Full-text: https://doi.org/10.1016/j.jcv.2020.104512

"Variable" performance means that some performed badly: Among 62 COVID-19 patients with neutralising antibodies, the specificity and sensitivity values

of the commercial antibody tests were as follows: 95%/81% (Abbott Architect), 95%/44% (Diasorin Liaison), 68%/88% (Euroimmun IgA), 87%/71% (Euroimmun IgG), 74%/56% (Acro IgG), 70%/46% (Acro 2019 IgM), 98%/72% (Xiamen IgG), and 89%/81% (Xiamen IgM). The variable performance highlights the need for laboratories to carefully consider their testing process in order to optimize the overall performance of SARS-CoV-2 serodiagnostics.

Atum M, Boz AAE, Çakır B, et al. **Evaluation of Conjunctival Swab PCR Results in Patients with SARS-CoV-2 Infection**. Ocul Immunol Inflamm. 2020 Jun 22:1-4. PubMed: https://pubmed.gov/32569495. Full-text: https://doi.org/10.1080/09273948.2020.1775261

Don't use conjunctival swabs, even in patients with conjunctivitis. Among 40 patients (10 with conjunctivitis) who tested positive by RT-PCR of nasopharyngeal and oropharyngeal swabs, conjunctival swab rRT-PCR was positive for 3 patients (one with conjunctivitis).

Clinical

Kronbichler A, Kresse D, Yoon S, Lee KH, Effenberger M, Shin JI. **Asymptomatic patients as a source of COVID-19 infections: A systematic review and meta-analysis**. Int J Infect Dis. 2020 Jun 17:S1201-9712(20)30487-2. PubMed: https://pubmed.gov/32562846. Full-text: https://doi.org/10.1016/j.ijid.2020.06.052

In total, 506 patients from 34 studies (68 single cases and 438 from case series) with an asymptomatic course were identified. Main findings: Asymptomatic patients tend to be younger and may be more socially active. Laboratory findings in most asymptomatic cases were unremarkable. However, 62% had lung opacities, most frequently ground glass opacities.

Lee YH, Hong CM, Kim DH, Lee TH, Lee J. **Clinical Course of Asymptomatic and Mildly Symptomatic Patients with Coronavirus Disease Admitted to Community Treatment Centers, South Korea**. Emerg Infect Dis. 2020 Jun 22;26(10). PubMed: https://pubmed.gov/32568662. Full-text: https://doi.org/10.3201/eid2610.201620

Of 632 asymptomatic and mildly symptomatic patients admitted to community treatment centers for isolation in South Korea, 75 (12%) had symptoms at admission, 186 (29%) were asymptomatic at admission but developed symptoms during their stay, and 371 (59%) remained asymptomatic during their entire clinical course. The mean virologic remission period was 20.1 days (SD

+ 7.7 days). The virologic remission period was longer in symptomatic patients than in asymptomatic patients. In mildly symptomatic patients, the mean duration from symptom onset to virologic remission was 11.7 days (SD + 8.2 days).

Comorbidities

Lange SJ, Ritchey MD, Goodman AB, et al. **Potential Indirect Effects of the COVID-19 Pandemic on Use of Emergency Departments for Acute Life-Threatening Conditions — United States, January–May 2020**. MMWR Morb Mortal Wkly Rep. ePub: 22 June 2020. Full-text: https://www.cdc.gov/mmwr/volumes/69/wr/mm6925e2.htm

National syndromic surveillance data has found that emergency department (ED) visits declined 42% during the early months of the pandemic. This report describes trends in ED visits for three acute life-threatening health conditions, immediately before and after declaration of the COVID-19 pandemic as a national emergency: in the 10 weeks following the declaration, ED visits declined 23% for heart attack, 20% for stroke, and 10% for hyperglycemic crisis. The substantial reduction might be explained by many pandemic-related factors including fear of exposure to COVID-19, unintended consequences of public health recommendations to minimize non-urgent health care, stay-at-home orders, or other reasons.

Severe COVID-19

Pfeifer M, Ewig S, Voshaar T, et al. **Position Paper for the State-of-the-Art Application of Respiratory Support in Patients with COVID-19**. Respiration. 2020 Jun 19:1-21. PubMed: https://pubmed.gov/32564028. Full-text: https://doi.org/10.1159/000509104 ●● (Outstanding)

Important statements including observations about the pathophysiology of acute respiratory failure (ARF). Pulmonary damage in advanced COVID-19 often differs from acute respiratory distress syndrome (ARDS). Two types (type L and type H) are differentiated, corresponding to early- and late-stage lung damage. This differentiation should be taken into consideration in respiratory support. Based on current knowledge, inhalation therapy, nasal high-flow therapy (NHF), continuous positive airway pressure (CPAP), or non-invasive ventilation (NIV) can be performed without an increased risk of infection to staff if PPE is provided. In ARF, NIV should be carried out in an intensive care unit or a comparable setting by experienced staff. If the ARF pro-

gresses under CPAP/NIV, intubation should be implemented without delay in patients who do not have a "do not intubate".

Treatment

Chi X, Yan R, Zhang J, et al. **A neutralizing human antibody binds to the N-terminal domain of the Spike protein of SARS-CoV-2**. Science 22 Jun 2020. Full-text: https://doi.org/10.1126/science.abc6952

The authors isolated and characterized monoclonal antibodies (mAbs) from ten convalescent COVID-19 patients, among them the most interesting mAb, named 4A8. Of note, 4A8 exhibited high neutralization potency but did not bind the RBD (like most other mABs). Cryo-EM revealed that the epitope of 4A8 seems to be the N terminal domain (NTD) of the S protein.

Contini C, Enrica Gallenga C, Neri G, Maritati M, Conti P. **A new pharmacological approach based on remdesivir aerosolized administration on SARS-CoV-2 pulmonary inflammation: A possible and rational therapeutic application**. Med Hypotheses. 2020 May 24;144:109876. PubMed: https://pubmed.gov/32562915. Full-text: https://doi.org/10.1016/j.mehy.2020.109876

Some ideas on remdesivir as an inhalation therapy. Local instillation or aerosol in the first phase of infection, both in asymptomatic but nasopharyngeal swab positive patients, together with antiseptic-antiviral oral gargles and povidone-iodine eye drops for conjunctiva would attack the virus directly through the receptors to which it binds, significantly decreasing viral replication and risk of severe COVID-19. Gilead is working on this (knowing that "early intravenous infusions" are not feasible).

Rojas-Marte GR, Khalid M, Mukhtar O, et al. **Outcomes in Patients with Severe COVID-19 Disease Treated with Tocilizumab - A Case- Controlled Study.** QJM. 2020 Jun 22:hcaa206. PubMed: https://pubmed.gov/32569363. Full-text: https://doi.org/10.1093/qjmed/hcaa206

Large retrospective, case-control, single-center study in patients with severe to critical COVID-19 disease. In total, 96 patients received tocilizumab, while 97 served as control group. There was a non-statistically significant lower mortality in the treatment group (52% versus 62%). When excluding intubated patients, there was statistically significant lower mortality in patients treated with tocilizumab (6% vs. 27%, $p = 0.024$). Bacteremia was more common in the control group, while fungemia was similar.

24 June

Epidemiology

Britton T, Ball F, Trapman P. **A mathematical model reveals the influence of population heterogeneity on herd immunity to SARS-CoV-2**. Science 23 Jun 2020. Full-text: https://doi.org/10.1126/science.abc6810

43%, not 60%: Disease-induced herd immunity may be achieved at a substantially lower percentage than the classical herd immunity level derived from mathematical models assuming homogeneous immunization. The model indicates a reduction of herd immunity from 60% under homogeneous immunization down to 43% (assuming R0 = 2.5) in a structured population, **but this should be interpreted as an illustration, rather than an exact value or even a best estimate**.

Immunology

Barnes CO, West Jr AP, Huey-Tubman KE. **Structures of human antibodies bound to SARS-CoV-2 spike reveal common epitopes and recurrent features of antibodies**. Cell June 23, 2020. Full-text: https://doi.org/10.1016/j.cell.2020.06.025

Incredible work, providing a glimpse (67 pages!) into diverse antibody responses in neutralizing plasmas from donors who recovered from COVID-19. Polyclonal plasma IgGs exhibited different degrees of cross-reactive binding between S proteins from SARS-CoV-2, SARS-CoV, and MERS-CoV and showed that the plasma IgGs also included non-cross-reactive antibodies against common cold virus RBDs. By mapping SARS-CoV-2 S epitopes targeted by convalescent plasma IgGs, the authors not only observed the expected targeting of the S protein RBD, but also discovered an S1A epitope outside of the RBD, which may represent an alternative binding site for neutralizing antibodies.

Transmission

Jayaweera M, Perera H, Gunawardana B, Manatunge J. **Transmission of COVID-19 virus by droplets and aerosols: A critical review on the unresolved dichotomy**. Environ Res. 2020 Jun 13;188:109819. PubMed: https://pubmed.gov/32569870. Full-text: https://doi.org/10.1016/j.envres.2020.109819 ● (IMPORTANT)

This review paper "intends to outline the literature" (no doubt they've done it, 139 references!) concerning the transmission of virus-laden droplets and

aerosols in different environmental settings. Nice pictures, demonstrating the behavior of droplets and aerosols resulting from a cough-jet of an infected person in various confined spaces.

Rafferty M, Nihtianova S, Amirian ES. **COVID-19 Safety Grades for Businesses—A Possible Mitigation Tool**. JAMA Health Forum June 22, 2020. Full-text: https://jamanetwork.com/channels/health-forum/fullarticle/2767689

The average customer has no reliable way of knowing whether those in a restaurant kitchen or in employee-only areas are following good hygiene, wearing facial coverings, and observing social distancing. Many jurisdictions are relying on public health recommendations for businesses, which depend on cooperation and are legally unenforceable. The authors propose a tactic that could provide some of the requisite knowledge individuals need to make more informed decisions.

Carraturo F, Del Giudice C, Morelli M, et al. **Persistence of SARS-CoV-2 in the environment and COVID-19 transmission risk from environmental matrices and surfaces**. Environ Pollut. 2020 Jun 9;265(Pt B):115010. PubMed: https://pubmed.gov/32570023. Full-text: https://doi.org/10.1016/j.envpol.2020.115010

Reviewing the current literature, these authors come to the conclusion that COVID-19 airborne spread via particulates is not a major transmission route. Virus persistance in water, wastewater, and sludge is very low at more than 20 °C.

Wang Y, Wu W, Cheng Z, et al. **Super-factors associated with transmission of occupational COVID-2019 infection among healthcare staff in Wuhan , China**. J Hosp Infect. 2020 Jun 20:S0195-6701(20)30308-X. PubMed: https://pubmed.gov/32574702. Full-text: https://doi.org/10.1016/j.jhin.2020.06.023

Don't touch your nose: This cross-sectional study was conducted among 92 frontline members of medical staff. The main factor that contributed to COVID-19 infections was touching the cheek, nose and mouth while working, emphasizing the need to strengthen hand, oral and nasal hygiene practices. Wearing the right type or size of PPE every time as required and following the operation specifications and operation instructions improved self-protection.

Diagnostics

Lerner AM, Eisinger RW, Lowy DR et al. **The COVID-19 Serology Studies Workshop: Recommendations and Challenges**. Immunity June 23, 2020. Full-text: https://doi.org/10.1016/j.immuni.2020.06.012

Summary of a virtual workshop convened on May 7, 2020 by leading US experts (from NIAID and CDC) in the field. Recommendations for advancing serology assays and conducting crucial serology field studies to advance our understanding of immunity to SARS-CoV-2 will lead to protection and duration of protection, including the correlation between serological test results and risk of reinfection.

Hu X, Zhang R, An T, et al. **Impact of Heat-Inactivation on the detection of SARS-CoV-2 IgM and IgG Antibody by ELISA**. Clin Chim Acta. 2020 Jun 19:S0009-8981(20)30294-1. PubMed: https://pubmed.gov/32569631. Full-text: https://doi.org/10.1016/j.cca.2020.06.032

Sera inactivated by heating may minimize the risk of virus contamination of laboratory staff. In this study in 62 patients, heat-activation at 56°C for 30 minutes did not impair the diagnostic efficacy of SARS-CoV-2 IgM or IgG antibodies (ELISA-immunoassay).

Clinical

Grant MC, Geoghegan L, Arbyn M, et al. **The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): A systematic review and meta-analysis of 148 studies from 9 countries**. PLoS One. 2020 Jun 23;15(6. PubMed: https://pubmed.gov/32574165. Full-text: https://doi.org/10.1371/journal.pone.0234765 ● (IMPORTANT)

What hard work. Of 851 unique citations, 148 articles were included which comprised 24,410 adults with confirmed COVID-19 from 9 countries. The most prevalent symptoms were fever (78%), cough (57%) and fatigue (31%). Overall, 19% of hospitalized patients required non-invasive ventilation (44 studies, 6,513 patients), 17% required intensive care (33 studies, 7504 patients), 9% required invasive ventilation (45 studies, 6933 patients) and 2% required ECMO (12 studies, 1,486 patients).

Comorbidities

Kent DG, Knapp DJ, Kannan N. **Survey Says: "COVID-19 Lockdown Hits Young Faculty and Clinical Trials"**. Stem Cells Rep June 22, 2020. Full-text: https://doi.org/10.1016/j.stemcr.2020.06.010

The survey was conducted from 6 to 15 April, 2020 and filled out by 762 researchers from 52 countries. It captured opinions from across all career stages on how COVID-19 has severely impacted laboratory research (i.e., 65% of laboratories were mostly or completely shut). From the crippling of ongoing and planned clinical trials across the full breadth of stem cell research to the devastating loss of productivity for those researchers near career transitions, the survey revealed some of the bleak truths on the impact of COVID-19 in the stem cell community.

25 June

Epidemiology

Lewis M, Sanchez R, Auerbach S, et al. **COVID-19 Outbreak Among College Students After a Spring Break Trip to Mexico — Austin, Texas, March 26–April 5, 2020**. MMWR Morb Mortal Wkly Rep. ePub: 24 June 2020. Full-text: http://dx.doi.org/10.15585/mmwr.mm6926e1

A college spring break trip mid-March led to 64 cases (14 asymptomatic and 50 symptomatic at the time of testing), including 60 among 183 vacation travelers, one among 13 household contacts, and three among 35 community contacts. Asymptomatic persons or those with mild symptoms likely played an important role in sustaining transmission. Prompt epidemiologic investigation contributed to outbreak control.

Immunology/Pathogenesis

Song JW, Lam SM, Fan X, et al. **Omics-driven systems interrogation of metabolic dysregulation in COVID-19 pathogenesis**. Cell Metabolism June 24, 2020. Full-text: https://doi.org/10.1016/j.cmet.2020.06.016

To date, the largest quantitative repository on the plasma lipidome and metabolome distinctly associated with COVID-19. Evaluation of metabolic pathway alterations based on differential correlation network analyses, highlighting two lipid modules possibly implicated in COVID-19 pathogenesis.

Tong M, Jiang Y, Xia D, et al. **Elevated Serum Endothelial Cell Adhesion Molecules Expression in COVID-19 Patients**. J Inf Dis, 25 June 2020. Full-text: https://doi.org/10.1093/infdis/jiaa349

A small but important retrospective study of 39 COVID-19 patients and 32 control participants, examining the expression of endothelial cell adhesion molecules by enzyme-linked immunosorbent assays (ELISA). Serum levels of fractalkine, vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and vascular adhesion protein-1 were elevated in mild patients, elevated dramatically in severe cases, while decreased in the convalescence phase. The increased expression may contribute to coagulation dysfunction.

Transmission

Chou R, Dana R, Jungbauer R, et al. **Masks for Prevention of Respiratory Virus Infections, Including SARS-CoV-2, in Health Care and Community Settings**. Ann Int Med 24 Jun 2020. Full-text: https://doi.org/10.7326/M20-3213

According to this "living rapid" review of 39 studies (18 randomized controlled trials and 21 observational studies; 33,867 participants), evidence on mask effectiveness for respiratory infection prevention is stronger in health care than community settings. N95 respirators might reduce SARS-CoV-1 risk versus surgical masks in health care settings, but applicability to SARS-CoV-2 is uncertain.

Clinical

Borras-Bermejo B, Martínez-Gómez X, Gutierrez-San Miguel M, et al. **Asymptomatic SARS-CoV-2 infection in nursing homes, Barcelona, Spain, April 2020**. Emerg Infect Dis. 2020 Sep [June 23, 2020]. https://doi.org/10.3201/eid2609.202603

High number of asymptomatic patients: the authors obtained a total of 5,869 samples, 3,214 from residents and 2,655 from facility staff in 69 nursing homes. Overall, 768 (23.9%) residents and 403 (15.2%) staff members tested positive for SARS-CoV-2. The presence of fever or respiratory symptoms during the preceding 14 days was recorded in 2,624 residents (81.6%) and 1,772 staff members (66.7%). Among those testing positive with information about symptoms, 69.7% of the residents and 55.8% of staff were asymptomatic. However, the ascertainment process could lead to misclassification due to atypical symptoms in the elderly. Moreover, cross-sectional symptom as-

sessment did not allow the authors to differentiate between presymptomatic and asymptomatic cases.

Comorbidities

Zhang XJ, Quin JJ, Cheng X, et al. **In-hospital Use of Statins is Associated with a Reduced Risk of Mortality among Individuals with COVID-19**. Cell Metabolism June 24, 2020. Full-text: https://doi.org/10.1016/j.cmet.2020.06.015

Retrospective study on 13,981 patients in Hubei Province, China, among which 1,219 received statins. Based on a Cox model with time-varying exposure and after propensity score-matching, 28-day all-cause mortality was 5.2% and 9.4% in the matched statin and non-statin groups, respectively. Randomized controlled trials involving statin treatment for COVID-19 are needed.

Robilotti EV, Babady NE, Mead PA, et al. **Determinants of COVID-19 disease severity in patients with cancer**. Nat Med June 24, 2020. Full-text: https://doi.org/10.1038/s41591-020-0979-0

Among 423 cases of symptomatic COVID-19 who were diagnosed at Memorial Sloan Kettering Cancer Center, 40% were hospitalized for COVID-19 and 12% died within 30 days. Age older than 65 years and treatment with immune checkpoint inhibitors (ICIs) were predictors for hospitalization and severe disease, whereas receipt of chemotherapy and major surgery were not.

Treatment

Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. **Tocilizumab in patients with severe COVID-19: a retrospective cohort study**. Lancet Rheumatology. June 24, 2020. Full-text: https://doi.org/10.1016/S2665-9913(20)30173-9 ● (IMPORTANT)

The largest retrospective, observational cohort study (from Italy) to date, reporting on IL-6 receptor blocker tocilizumab which was given either intravenously or subcutaneously. 57 (16%) of 365 patients in the standard of care (SOC) group needed mechanical ventilation, compared with 33 (18%) of 179 patients treated with tocilizumab (88 patients treated intravenously). 73 (20%) patients in the SOC group died, compared with 13 (7%; p<0·0001) patients treated with tocilizumab. After adjustment for sex, age, duration of symptoms, and SOFA (Sequential Organ Failure Assessment) score, tocilizumab treatment was associated with a reduced risk of invasive mechanical

ventilation or death (adjusted hazard ratio 0.61, 95% CI 0.40–0.92). However, the precise group of patients who might benefit from tocilizumab and the optimal biomarkers for identifying the cytokine storm in the setting of COVID-19 remain unknown.

Deftereos SG, Giannopoulos G, Vrachatis DA, et al. **Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019The GRECCO-19 Randomized Clinical Trial**. JAMA Netw Open June 24, 2020;3(6. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.13136

In this prospective, open-label, randomized clinical trial, 105 patients hospitalized with COVID-19 in Greece were randomized to either standard medical treatment or colchicine plus standard medical treatment. Participants who received colchicine had statistically "significantly improved time to clinical deterioration". However, there were no significant differences in biomarkers and the observed difference was based on a narrow margin of clinical significance; according to the authors their observations "should be considered hypothesis generating" and "be interpreted with caution".

Sarpatwari A, Kaltenboeck A, Kesselheim AS, et al. **Missed Opportunities on Emergency Remdesivir Use**. JAMA. June 24, 2020 Full-text: https://doi.org/10.1001/jama.2020.11932

Important viewpoint on monitoring remdesivir use, pricing, and drug supply. Gilead has yet to comment what the bounds of a reasonable price could be. According to the authors, the FDA should revise its current EUA for remdesivir to require the creation of a patient registry that includes information on patient demographics, treatment dose and duration, and safety outcomes.

26 June

Virology

Barr IG, Rynehart C, Whitney P, et al. **SARS-CoV-2 does not replicate in embryonated hen's eggs or in MDCK cell lines**. Eurosurveillance Volume 25, Issue 25, 25/Jun/2020. Full-text: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.25.2001122

This study showed that even if a clinical sample, containing both human influenza and SARS-CoV-2, was inoculated into substrates used to prepare seeds for influenza vaccine production (embryonated chicken eggs or MDCK-based cell lines), SARS-CoV-2 would be unlikely to be propagated and would be undetectable after a small number of passages. This finding reassures influenza vaccine production staff and laboratory scientists who might be concerned about potential exposure to SARS-CoV-2 and also suggests that loss of potentially important influenza candidate vaccine viruses or final vaccine lots due to SARS-CoV-2 contamination is unlikely.

Immunology

Sokolowska M, Lukasik Z, Agache I, et al. **Immunology of COVID-19: mechanisms, clinical outcome, diagnostics and perspectives - a report of the European Academy of Allergy and Clinical Immunology (EAACI)**. Allergy. 2020 Jun 25. PubMed: https://pubmed.gov/32584441. Full-text: https://doi.org/10.1111/all.14462

Experts in basic and clinical immunology have joined forces to provide a consensus report on the basic molecular and immune mechanisms associated with susceptibility, clinical presentations and severity of COVID-19. This report summarizes current immunological data, including the differences between adequate innate and adaptive immune response in mild disease and the deep immune dysfunction in the more severe multi-organ disease.

Clinical

Roca-Ginés J, Torres-Navarro I, Sánchez-Arráez J, et al. **Assessment of Acute Acral Lesions in a Case Series of Children and Adolescents During the COVID-19 Pandemic**. JAMA Dermatol. 2020 Jun 25. PubMed: https://pubmed.gov/32584397. Full-text: https://doi.org/10.1001/jamadermatol.2020.2340 ● (IMPORTANT)

In this case series from Valencia following 20 patients aged 1 to 18 years with new-onset acral inflammatory lesions, all lacked systemic manifestations of COVID-19. Surprisingly, both PCR and serologic test results were negative for SARS-CoV-2, questioning an association between acral skin disease and COVID-19.

Herman A, Peeters C, Verroken A, et al. **Evaluation of Chilblains as a Manifestation of the COVID-19 Pandemic**. JAMA Dermatol. 2020 Jun 25. PubMed: https://pubmed.gov/32584377. Full-text: https://doi.org/10.1001/jamadermatol.2020.2368

Same in Belgium. Of 31 patients (mostly teenagers) who had recently developed chilblains, histopathologic analysis of skin biopsy specimens (22 patients) confirmed the diagnosis of chilblains and showed occasional lymphocytic or microthrombotic phenomena. In all patients, PCR and serology remained negative. Chilblains appeared not to be directly associated with COVID-19 in this case series. According to the authors, lifestyle changes associated with community containment and lockdown measures are a possible explanation for these lesions.

Varatharaj A, Thomas N, Ellul MA, et al. **Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study**. Lancet Psychiatry June 25, 2020. Full-text: https://doi.org/10.1016/S2215-0366(20)30287-X

Online network study from the UK, including 125 patients with data and with neurologic/neuropsychiatric complications. Of these, 77 (62%) presented with a cerebrovascular event, of whom 57 (74%) had an ischemic stroke, nine (12%) an intracerebral hemorrhage, and one (1%) CNS vasculitis. Altered mental status was the second most common presentation (31%), comprising encephalopathy or encephalitis and primary psychiatric diagnoses, often occurring in younger patients.

Maugeri G, Castrogiovanni P, Battaglia G. **The impact of physical activity on psychological health during Covid-19 pandemic in Italy**. Heliyon June 24, 2020. Full-text: https://doi.org/10.1016/j.heliyon.2020.e04315

Maintain your exercise routine! Among 2524 subjects completing an online survey, total physical activity significantly decreased between before and during the COVID-19 pandemic. A significant positive correlation was found between the variation of physical activity and mental well-being, suggesting that the reduction of total physical activity had a profoundly negative impact on psychological health and well-being of population.

Mallapaty S. **Mounting clues suggest the coronavirus might trigger diabetes**. Nature 2020, June 24. Full-text: https://www.nature.com/articles/d41586-020-01891-8

Does COVID-19 lead to diabetes? Some comments on preprint papers indicating growing evidence from tissue studies and some clinical cases that the virus damages insulin-producing cells. It remains to be seen how relevant this problem is.

Comorbidities

Meca-Lallana V, Aguirre C, Beatrizdel Río, Cardeñoso L, Alarcon T, Vivancos J. **COVID-19 in 7 multiple sclerosis patients in treatment with ANTI-CD20 therapies**. Mult Scler Relat Disord. 2020 Jun 15;44:102306. PubMed: https://pubmed.gov/32585617. Full-text: https://doi.org/10.1016/j.msard.2020.102306

A small case series on patients with MS and COVID-19, treated with the anti-CD20 monoclonal antibodies (mAbs) ocrelizumab and rituximab. Although the severity of the clinical picture varied, patients' development was good, indicating that B cells and immunoglobulin may not be absolutely necessary for viral elimination. Not all patients developed antibodies against SARS-CoV-2.

Sivaloganathan H, Ladikou EE, Chevassut T. **COVID-19 mortality in patients on anticoagulants and antiplatelet agents**. Br J Haematol. 2020 Jun 25. PubMed: https://pubmed.gov/32584423. Full-text: https://doi.org/10.1111/bjh.16968

Anticoagulants, or other antithrombotic agents such as antiplatelet drugs, might counteract the coagulopathic effects of COVID-19 resulting in improved outcomes. This small, matched-control study shows that this is probably not the case. Patients on aspirin (n=18), on clopidogrel (n=8), apixaban (n=12), warfarin (n=7) and some other drugs did not have a significantly different mortality risk to patients not taking these drugs. According to the authors, this could suggest these agents negate any potential increased mortality risk attributable to whichever disease the drugs had been prescribed, but further data on comorbidities is required to confirm this assertion.

Treatment

Yeleswaram S, Smith P, Burn T, et al. **Inhibition of cytokine signaling by ruxolitinib and implications for COVID-19 treatment**. Clin Immunol. 2020 Jun 22:108517. PubMed: https://pubmed.gov/32585295. Full-text: https://doi.org/10.1016/j.clim.2020.108517

Comprehensive review on ruxolitinib. As many of the elevated cytokines signal through Janus kinase (JAK)1/JAK2, inhibition of these pathways with rux-

olitinib has the potential to mitigate the COVID-19-associated cytokine storm and reduce mortality. This is supported by preclinical and clinical data from other diseases with hyperinflammatory states, where ruxolitinib has been shown to reduce cytokine levels and improve outcomes. However, it is important to consider that this work was supported by Incyte, a manufacturer of the drug.

Pediatrics

Götzinger F, Santiago-García B, Noguera-Julián A, et al. **COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study**. Lancet Child Adol Health June 25, 2020. Full-text: https://doi.org/10.1016/S2352-4642(20)30177-2

One of the largest registries to date, confirming that COVID-19 is generally a mild disease in children. Of 582 children and adolescents (median age 5.0 years, 25% with pre-existing conditions) with PCR-confirmed SARS-CoV-2 infection, 363 (62%) were admitted to hospital and 48 (8%) individuals required ICU admission. Significant risk factors for requiring ICU admission in multivariate analyses were being younger than 1 month (odds ratio 5.1), male sex (2.1) and pre-existing medical conditions (3.3). Four children died.

27 June

Epidemiology

Horton R. **Offline: The second wave**. Lancet 2020, June 27, 395, ISSUE 10242, P1960. Full-text: https://doi.org/10.1016/S0140-6736(20)31451-3

Not in a good mood today? Then don't read this important comment on what will likely happen during the next months. The first wave of the 1918 influenza pandemic took place between March and July. It proved relatively mild. The second wave arrived in August. It was much worse. Most of the 50–100 million deaths caused by influenza took place during 13 weeks between September and December, 1918. In many countries, the test, trace, and isolate system is still not fully functional and we have angry debates about whether physical distancing should be 1 m or 2 m. Scientists predict that a second wave will arrive in September, peaking by the end of 2020. Just sayin'.

Transmission

Ortega R, Gonzalez M, Nozari A, et al. **Personal Protective Equipment and Covid-19**. N Engl J Med 2020; June 25. Full-text: https://doi.org/10.1056/NEJMvcm2014809

Helpful video, demonstrating the complex procedure for putting on and removing PPE that has been recommended by the CDC to minimize the risk of exposure to infectious material during the care of patients with COVID-19.

Prather KA, Wang CC, Schooley RT. **Reducing transmission of SARS-CoV-2**. Science 26 Jun 2020: Vol. 368, Issue 6498, pp. 1422-1424. Full-text: https://doi.org/10.1126/science.abc6197

Aerosol transmission of viruses must be acknowledged as a key factor leading to the spread of infectious respiratory diseases. This viewpoint summarizes current research that is already leading to a better understanding of the importance of airborne transmission.

Diagnostics

Mak GC, Cheng PK, Lau SS, et al. **Evaluation of rapid antigen test for detection of SARS-CoV-2 virus**. J Clin Virol. 2020 Jun 8;129:104500. PubMed: https://pubmed.gov/32585619. Full-text: https://doi.org/10.1016/j.jcv.2020.104500

Bad performance of the commercially available rapid BIOCREDIT COVID-19 antigen test. This test was 10,000 fold less sensitive than RT-PCR and detected between 11.1 % and 45.7 % of RT-PCR-positive samples from COVID-19 patients. It serves only as adjunct to RT-PCR test because of the potential for false-negative results.

Ben-Ami R, Klochendler A, Seidel M, et al. **Large-scale implementation of pooled RNA extraction and RT-PCR for SARS-CoV-2 detection**. Clin Microbiol Infect. 2020 Jun 22:S1198-743X(20)30349-9. PubMed: https://pubmed.gov/32585353. Full-text: https://doi.org/10.1016/j.cmi.2020.06.009

Due to the overwhelming use of SARS-CoV-2 RT-PCR tests worldwide, availability of test kits has become a major bottleneck. The authors show how to overcome these challenges by pooling samples, performing RNA extraction and RT-PCR in pools. A comparison of 184 samples tested individually and in pools of 8 samples, showed that test results were not significantly affected.

Amanat F, White KM, Miorin L, et al. **An In Vitro Microneutralization Assay for SARS-CoV-2 Serology and Drug Screening**. Curr Protoc Microbiol. 2020 Sep;58(1):e108. PubMed: https://pubmed.gov/32585083. Full-text: https://doi.org/10.1002/cpmc.108

A new microneutralization assay is described in detail. This assay can be used to assess in a quantitative manner if antibodies or drugs can block entry and/or replication of SARS-CoV-2 in vitro. Compared to the most common neutralization assay, the plaque reduction neutralization test (PRNT), more samples can be analyzed. Compared to RBD-ACE2 inhibition assays, the test will also detect neutralizing antibodies binding to epitopes outside of the RBD. Different virus isolates can be used, and the assay can likely be adapted for staining antibodies other than mAbs (e.g., polyclonal sera, antibodies targeting S or M, etc.).

Deeks JJ, Dinnes J, Takwoingi Y, et al. **Antibody tests for identification of current and past infection with SARS-CoV-2**. Cochrane Database Syst Rev. 2020 Jun 25;6:CD013652. PubMed: https://pubmed.gov/32584464. Full-text: https://doi.org/10.1002/14651858.CD013652

This Cochrane analysis on 57 publications with 15,976 samples says that the sensitivity of antibody tests is too low in the first week from symptom onset to have a primary role in the diagnosis of COVID-19. However, these tests may still have a role complementing other testing in individuals presenting later, when RT-PCR tests are negative, or are not done. Antibody tests are likely to have a useful role for detecting previous SARS-CoV-2 infection if used 15 or more days after the onset of symptoms. Data beyond 35 days post-symptom onset is scarce. According to the authors, studies of the accuracy of COVID-19 tests require considerable improvement. Studies must report data on sensitivity disaggregated by time from onset of symptoms. Updates of this living systematic review are planned.

Clinical

Lockhart SM, O'Rahilly S. **When two pandemics meet: Why is obesity associated with increased COVID-19 mortality**? Med 2020,June 25. Full-text: https://doi.org/10.1016/j.medj.2020.06.005 ● (IMPORTANT)

What a nice understatement. The authors describe "some hypotheses regarding the deleterious impact of obesity on the course of COVID-19". This brilliant overview summarizes current knowledge on the underlying mecha-

nisms. These are: 1. Increased inflammatory cytokines (potentiate the inflammatory response), 2. reduction in adiponectin secretion (abundant in the pulmonary endothelium), 3. increases in circulating complement components, 4. systemic insulin resistance (associated with endothelial dysfunction and with increased plasminogen activator inhibitor-1), and 5. ectopic lipid deposited in type 2 pneumocytes (pre-disposing to lung injury).

Comorbidities

Louapre C, Collongues N, Stankoff B, et al. **Clinical Characteristics and Outcomes in Patients With Coronavirus Disease 2019 and Multiple Sclerosis**. JAMA Neurol 2020, June 26. Full-text: https://doi.org/10.1001/jamaneurol.2020.2581

This registry-based cohort study from France has included 347 patients with MS with a confirmed or highly suspected diagnosis of COVID-19. In total, 73 patients (21.0%) had a COVID-19 severity score of 3 or more, and 12 patients (3.5%) died. Age, Expanded Disability Severity Scale score (EDSS; ranging from 0 to 10, with cutoffs at 3 and 6), and obesity were independent risk factors for severe COVID-19; there was no association found between exposure to disease-modifying therapies and severity.

Treatment

Li S, Hu Z, Song X. **High-dose but not low-dose corticosteroids potentially delay viral shedding of patients with COVID-19**. Clinical Infectious Diseases 2020, June 26. Full-text: https://doi.org/10.1093/cid/ciaa829

This study with 206 patients suggests that the effect of corticosteroids on viral shedding may be in a dose-response manner. High-dose (80 mg/d) but not low-dose corticosteroids (40 mg/d) delayed viral shedding of patients with COVID-19.

28 June

Anything goes

Here we present the best or weirdest (depending on your point of view) case reports on COVID-19 published in the first 6 months. Focus of this first issue will be gastrointestinal manifestations...

Prince G, Sergel M. **Persistent hiccups as an atypical presenting complaint of COVID-19**. Am J Emerg Med. 2020 Apr 18:S0735-6757(20)30274-6. PubMed:

https://pubmed.gov/32345563. Full-text: https://doi.org/10.1016/j.ajem.2020.04.045

Believe it or not: COVID-19 may atypically present as persistent hiccups for four days (62 year old man, Chicago).

Abdalhadi A, Alkhatib M, Mismar AY, Awouda W, Albarqouni L. **Can COVID 19 present like appendicitis**? Version 2. IDCases. 2020 Jun 2;21:e00860. PubMed: https://pubmed.gov/32523872. Full-text: https://doi.org/10.1016/j.idcr.2020.e00860. eCollection 2020

And yes, of course, as appendicitis, the abdominal chameleon (40 year old woman, Quatar).

Gulen M, Satar S. **Uncommon presentation of COVID-19: Gastrointestinal bleeding**. Clin Res Hepatol Gastroenterol. 2020 May 21:S2210-7401(20)30139-X. PubMed: https://pubmed.gov/32505730. Full-text: https://doi.org/10.1016/j.clinre.2020.05.001

In the case of epigastric tenderness in the abdominal examination and if melena is present at the rectal examination, consider also COVID-19-associated gastrointestinal bleeding (53-year-old male from Adana, Turkey).

Zhai LL, Xiang F, Wang W, et al. **Atypical presentations of coronavirus disease 2019 in a patient with acute obstructive suppurative cholangitis**. Clin Res Hepatol Gastroenterol. 2020 May 21:S2210-7401(20)30141-8. PubMed: https://pubmed.gov/32482542. Full-text: https://doi.org/10.1016/j.clinre.2020.05.003

Or an obstructive suppurative cholangitis (71-year-old woman with a one-week history of yellow skin, Wuhan, China).

Meireles PA, Bessa F, Gaspar P, et al. **Acalculous Acute Pancreatitis in a COVID-19 Patient**. Eur J Case Rep Intern Med. 2020 May 13;7(6):001710. PubMed: https://pubmed.gov/32523925. Full-text: https://doi.org/10.12890/2020_001710. eCollection 2020

But, attention! If amylase and lipase levels increase to 6-700 U/l, it may be also be acalculous pancreatitis (36-year-old woman, Lisbon, Portugal).

Schepis T, Larghi A, Papa A, et al. **SARS-CoV2 RNA detection in a pancreatic pseudocyst sample**. Pancreatology. 2020 May 28:S1424-3903(20)30185-X. PubMed: https://pubmed.gov/32498972. Full-text: https://doi.org/10.1016/j.pan.2020.05.016

A pancreatic pseudocyst in which the virus can be detected and which can be successfully treated with endoscopic ultrasound-guided transgastric drainage using AXIOS™ Stent and Electrocautery Enhanced Delivery System (67-year-old woman, Rome, Italy).

Damiani GR, Biffi A, Del Boca G, Arezzo F. **Abdominal pregnancy during the COVID-19 pandemic**. Int J Gynaecol Obstet. 2020 Jun 10. PubMed: https://pubmed.gov/32524618. Full-text: https://doi.org/10.1002/ijgo.13271

Or, of course, in the case of a female patient of child-bearing age, an abdominal pregnancy has to be considered (33-year-old primigravida from Bari, Italy, presenting at 14 weeks of pregnancy with persistent abdominal pain lasting 15 days). But, please, be prepared when reading this report: worrying photos of the fetus located behind the posterior wall of the uterus, close to the rectosigmoid junction.

Rabice SR, Altshuler PC, Bovet C, Sullivan C, Gagnon AJ. **COVID-19 infection presenting as pancreatitis in a pregnant woman: A case report**. Case Rep Womens Health. 2020 Jul;27:e00228. PubMed: https://pubmed.gov/32537425. Full-text: https://doi.org/10.1016/j.crwh.2020.e00228

Or consider both. Pregnancy AND pancreatitis (36-year-old woman, G4P2, at 33 weeks of gestation, from Denver, CO).

Kim J, Thomsen T, Sell N, Goldsmith AJ. **Abdominal and testicular pain: An atypical presentation of COVID-19**. Am J Emerg Med. 2020 Mar 31:S0735-6757(20)30194-7. PubMed: https://pubmed.gov/32273141. Full-text: https://doi.org/10.1016/j.ajem.2020.03.052

But be careful: in male patients, it may be wiser to consider the testicles (42-year-old male with 8 days of abdominal, testicular, and back pain who had been, it's worth mentioning, seated in the ED waiting room for 2 h prior to being roomed).

Yoneoka Y, Aizawa N, Nonomura Y, Ogi M, Seki Y, Akiyama K. **Traumatic non-missile penetrating transnasal anterior skull-base fracture and brain injury with cerebrospinal fluid leak: intraoperative leak detection and an effective reconstruction procedure for a localized skull base defect especially after COVID-19 outbreak**. World Neurosurg. 2020 Jun 1:S1878-8750(20)31207-9. PubMed: https://pubmed.gov/32497852. Full-text: https://doi.org/10.1016/j.wneu.2020.05.236

And please, finally, be also very careful these days while beekeeping, especially if you fall down on the ground near your bee hives (65-year-old male from Niigata, Japan). A garden pole may poke directly into your right nostril, leading to serous rhinorrhea. Not in all cases your CSF leakage will be caulked by endonasal endoscopic using an FFG plug which, according to the authors, is useful, "in particular for the post-COVID-19 era, because it is simple, low-cost, and timesaving: requiring no special skills or no sophisticated instruments, thus reducing infection risks during the surgery". ☺

29 June

Epidemiology

Nagler AR, Goldberg ER, Aguero-Rosenfeld ME, et al. **Early Results from SARS-CoV-2 PCR testing of Healthcare Workers at an Academic Medical Center in New York City**. Clin Inf Dis, June 28, 2020. Full-text: https://doi.org/10.1093/cid/ciaa867

Widespread testing of HCW offers valuable information for hospital workflow and workforce amid an epidemic that threatened to overwhelm the healthcare system. Over eight weeks, 14,764 employees were tested: 33% of employees were symptomatic, 8% of asymptomatic employees reported COVID-19 exposure, 3% of employees returning to work were antibody-positive. Positivity rates declined over time.

Hong LX, Lin A, He ZB, et al. **Mask wearing in pre-symptomatic patients prevents SARS-CoV-2 transmission: An epidemiological analysis**. Travel Med Infect Dis. 2020 Jun 24;36:101803. PubMed: https://pubmed.gov/32592903. Full-text: https://doi.org/10.1016/j.tmaid.2020.101803

The incidence of COVID-19 doubled (19.0% vs. 8.1%) for local residents who had close contact with people returning from Wuhan, who did not wear masks and turned out to be pre-symptomatic COVID-19 patients. In this

study, a cluster of 21 local COVID-19 patients originated from a couple returning from Wuhan who played cards sequentially in a space-limited Chess and Card Room or who were living together over a longer-term with pre-symptomatic or asymptomatic relatives. No bridge for grandma during these days.

Transmission

Maltezou HC, Dedoukou X, Tseroni M, et al. **SARS-CoV-2 infection in healthcare personnel with high-risk occupational exposure: evaluation of seven-day exclusion from work policy**. Clin Inf Dis June 29, 2020. Full-text: https://doi.org/10.1093/cid/ciaa888

In this study, 3,398 occupationally-exposed HCW were followed prospectively, among them 1,599 (47.1%) with low-risk, 765 (22.5%) with moderate-risk, and 1,031 (30.4%) with high-risk exposures. Of the 66 HCW with COVID-19, 46, 7, and 13 had a history of high-, moderate- or low-risk exposure. Male gender, administrative personnel, underlying disease and high-risk exposure were significantly associated with an increased risk for the onset of COVID-19. HCW with high-risk occupational exposure to COVID-19 had increased probability of serious morbidity, healthcare seeking, hospitalization and absenteeism.

Shrestha NK, Canosa FM, Nowacki AS, et al. **Distribution of Transmission Potential during Non-Severe COVID-19 Illness**. Clin Inf Dis 29 June 2020. Full-text: https://doi.org/10.1093/cid/ciaa886

Infectivity lasts ten days. In 230 HCW with non-severe COVID-19, viral loads declined by orders of magnitude within a few days of symptom onset. Of the area under the curve (the distribution of transmission potential over time during the course of illness) spanning symptom onset to 30 days, 86.3% lay within the first 5 days, 96.9% within the first 7 days, and 99.7% within the first 10 days. The only variable significantly associated with viral load was time from onset of symptoms.

Pastorino B, Touret F, Gilles M, de Lamballerie X, Charrel RN. **Prolonged infectivity of SARS-CoV-2 in fomites.** Emerg Infect Dis. 2020 Sep [date cited]. Full-text: https://doi.org/10.3201/eid2609.201788

Clean surfaces! The authors observed a steady infectivity (< 1 $\log_{10}$ drop) on plastic, a 3.5 $\log_{10}$ decrease on glass, and a 6 $\log_{10}$ drop on aluminum within 96 hours. Data showed that SARS-CoV-2 infectivity was remarkably preserved in

the presence of proteins (bovine serum albumin), regardless of the type of surface.

Diagnostics

Pinninti S, Trieu C, Pati SK; et al**. Comparing Nasopharyngeal and Mid-Turbinate Nasal Swab Testing for the Identification of SARS-CoV-2**. Clin Inf Dis 29 June 2020. Full-text: https://doi.org/10.1093/cid/ciaa882

Mid-turbinate nasal swab is not sufficient. Testing of paired MT nasal and nasopharyngeal (NP) swabs, collected by trained personnel from 40 patients with COVID-19 showed more NP (76/95, 80%) than MT swabs tested positive (61/95, 64%; p=0.02). Among samples collected a week after study enrollment, fewer MT than NP samples were positive (45% vs 76%; p=0.001). Patients whose NP swabs are PCR-positive but have a lower viral load as suggested by high CT values (> 30), may often test negative by MT swab.

Nicol T, Lefeuvre C, Serri O, et al. **Assessment of SARS-CoV-2 serological tests for the diagnosis of COVID-19 through the evaluation of three immunoassays: Two automated immunoassays (Euroimmun and Abbott) and one rapid lateral flow immunoassay (NG Biotech)**. J Clin Virol. 2020 Jun 15;129:104511. PubMed: https://pubmed.gov/32593133. Full-text: https://doi.org/10.1016/j.jcv.2020.104511

Lateral flow immunoassay (LFIA) can be used easily as point of care tests or in the laboratory, with a result in less than 15 min. In this study, a LFIA (NG-Test®) was reliable and accurate. The authors compared LFIA and two immunoassays (Abbott CLIA and Euroimmun ELISA) in 293 specimens. Overall sensitivity for IgG was equivalent (around 80%) among all tests and reached 100% > 14 days after onset of symptoms. Overall specificity for IgG was greater for CLIA and LFIA (more than 98%) compared to ELISA (95.8%). Specificity was significantly different between IgA ELISA (78.9%) and IgM LFIA (95.8%) ($p < 0.05$).

Clinical

Price-Haywood EG, Burton J, Fort D, et al. **Hospitalization and Mortality among Black Patients and White Patients with Covid-19**. N Engl J Med 2020; June 25, 382:2534-2543. Full-text: https://doi.org/10.1056/NEJMsa2011686

It's not ethnicity. Of a total of 3,481 COVID-19 patients, seen within an integrated-delivery health system in Louisiana, 70.4% were black non-Hispanic. Although black patients represent 31% of the patients routinely cared for in the system, they made up 76.9% of hospitalized COVID-19 patients. Black patients had higher prevalences of obesity, diabetes, hypertension, and chronic kidney disease than white patients. However, black race was NOT associated with higher in-hospital mortality than white race, after adjustment for sociodemographic and clinical differences on admission. Of note, there were racial differences in several laboratory results, indicating a longer wait to access care among black patients, resulting in more severe illness on presentation to health care facilities.

Bielecki M, Züst R, Siegrist D, et al. **Social distancing alters the clinical course of COVID-19 in young adults: A comparative cohort study**. Clin Inf Dis, June 29, 2020. Full-text: https://doi.org/10.1093/cid/ciaa889 ● (IMPORTANT)

Important finding that was long suspected: viral inoculum during infection or mode of transmission may be key factors determining the clinical course of COVID-19. The authors prospectively studied an outbreak in Switzerland among a population of 508 predominantly male soldiers with a median age of 21 years. Infections were followed in two spatially separated cohorts with almost identical baseline characteristics - before and after implementation of stringent social distancing. Results: of 354 soldiers infected prior to the implementation of social distancing, 30% fell ill. In contrast, none out of 154 soldiers in which infections (confirmed by NP swabs or serology) appeared after implementation of social distancing developed COVID-19.

Treatment

Leegwater E, Strik A, Wilms EB, et al. **Drug-induced liver injury in a COVID-19 patient: potential interaction of remdesivir with P-glycoprotein inhibitors**. Clin Inf Dis, 28 June 2020. Full-text: https://doi.org/10.1093/cid/ciaa883

Acute hepatotoxicity related to remdesivir (now sold under the brand name Veklury®), with probable interaction of P-glycoprotein (P-gp) inhibitors. Five days after start of remdesivir, a patient developed an acute increase in ALT (1305 IU/L) and AST (1461 U/L). Total bilirubin was 8 μmol/ L. The pati
treated with the P-gp inhibitors chloroquine (last administration nine days before remdesivir, with a half-life of two weeks) and amiodarone (concomitantly with remdesivir). Authors recommend physicians to be cautious with the prescription of P-gp inhibitors in patients receiving remdesivir therapy.

30 June

Epidemiology

Njuguna H, Wallace M, Simonson S, et al. **Serial Laboratory Testing for SARS-CoV-2 Infection Among Incarcerated and Detained Persons in a Correctional and Detention Facility — Louisiana, April–May 2020**. MMWR Morb Mortal Wkly Rep. ePub: 29 June 2020. Full-text: http://dx.doi.org/10.15585/mmwr.mm6926e2

High COVID-19 attack rates can occur in correctional and detention facilities. During May 7–21, among 98 incarcerated and detained persons in Louisiana who were quarantined because of virus exposure, 71 (72%) had lab-confirmed SARS-CoV-2 infection identified through serial testing, among them 45% without any symptoms at the time of testing. These findings suggest ongoing transmission among quarantined persons living in close settings; therefore, serial testing of contacts of persons with COVID-19 in correctional and detention facilities can identify asymptomatic and presymptomatic persons who would be missed through symptom screening alone.

Brown NE, Bryant-Genevier J, Bandy U, Browning CA, Berns AL, Dott M, et al. **Antibody responses after classroom exposure to teacher with coronavirus disease, March 2020**. Emerg Infect Dis. 2020 Sep [date cited]. https://doi.org/10.3201/eid2609.201802

No big surprise: classroom interaction between an infected teacher and students might result in virus transmission. After returning from Europe to the United States on March 1, 2020, a symptomatic teacher received positive test results. In total 2/21 students exposed to the teacher in the classroom had positive serologic results.

Pulla P. **'The epidemic is growing very rapidly': Indian government adviser fears coronavirus crisis will worsen**. Nature 2020, June 26. Full-text: https://www.nature.com/articles/d41586-020-01865-w

Interview with Jayaprakash Muliyil, an epidemiologist and advisor of the Indian government, providing insight into the epidemic in India where the virus seems to spread much faster and the infection rates are higher. A discussion on why officials in some badly affected cities seem reluctant to say that outbreaks are being driven by community transmission — where cases cannot be linked to known sources.

Immunology, Vaccine

Cohen J. **The line is forming for a COVID-19 vaccine. Who should be at the front?** Science Mag 2020, June 29. Full-text: https://www.sciencemag.org/news/2020/06/line-forming-covid-19-vaccine-who-should-be-front

Even if the optimists are right and a COVID-19 vaccine is approved for widespread use as early as this fall, it is likely to be in short supply at first. This article summarizes WHO's and CDC's plans to deal with this problem. For the US, a top tier includes 12 million people referred to as "critical health care and other workers," with the first doses going to a subset of these people who are the "highest risk medical, national security, and other essential workers". Tiers two and three would include 110 million people who also work in health care and other essential jobs, or are in these groups: 65 and older, living in long-term care facilities, or those with medical conditions known to increase the risk of developing severe COVID-19. And then everyone else.

Transmission

Dau NQ, Lau H, Skinner C. **Why N95 Should Be the Standard for All COVID-19 Inpatient Care**. Ann Int Med 2020, Jun 29. Full-text: https://doi.org/10.7326/M20-2623

Important viewpoint emphasizing that N95 respirators achieve better filtration of airborne particles than medical masks if used properly and continuously. According to the authors, guideline recommendations that do not support N95 use for all inpatient COVID-19 management should consider reevaluating existing data or at least acknowledge the issues raised.

Oosterhoff B, Palmer CA. **Attitudes and Psychological Factors Associated With News Monitoring, Social Distancing, Disinfecting, and Hoarding Behaviors Among US Adolescents During the Coronavirus Disease 2019 Pandemic**. JAMA Pediatr. Published online June 29, 2020. Full-text: https://doi.org/10.1001/jamapediatrics.2020.1876

Interesting survey on 770 adolescents' beliefs about COVID-19 and community attachment as well as attitudes and psychological factors that inform their response to the pandemic. Many teens reported not engaging in pure social distancing (69%), but they were monitoring the news (89%) and disinfecting daily (88%). Some teens reported hoarding (20%). Greater social responsibility was associated with more disinfecting and news monitoring and less hoard-

ing. Greater self-interest values were associated with less social distancing and more hoarding.

Diagnostics

Choe PG, Kang CK, Suh HJ, Jung J, Kang EK, Lee SY, et al. **Antibody responses to SARS-CoV-2 at 8 weeks postinfection in asymptomatic patients**. Emerg Infect Dis. 2020 Sep [date cited]. Full-text: https://doi.org/10.3201/eid2610.202211

The authors compared levels of SARS-CoV-2 neutralizing antibodies in recovery plasma from 7 completely asymptomatic patients with those in symptomatic patients in South Korea. Serologic diagnostic testing was positive for 71% (5/7) of completely asymptomatic patients, but neutralizing antibody response occurred in all 7 patients.

Comorbidities

Tison GH, Avram R, Kuhar P, et al. **Worldwide Effect of COVID-19 on Physical Activity: A Descriptive Study**. Ann Int Med 2020, June 29. Full-text: https://doi.org/10.7326/M20-2665

Big data: Using data from a popular health and wellness smartphone app (Argus), a rapid worldwide step count decrease was seen during the COVID-19 pandemic, with regional variability. Samples from different countries varied widely in the number of days after pandemic declaration that a 15% step count decrease was seen: Italy (5 days), Spain (9 days), France (12 days), India (14 days), the United States (15 days), the United Kingdom (17 days), Australia (19 days), and Japan (24 days).

Severe COVID-19

McGonagle D, O'Donnell JS, Sharif K. **Pulmonary intravascular coagulopathy in COVID-19 pneumonia** – Authors' reply. Lancet June 29, 2020. Full-text: https://doi.org/10.1016/S2665-9913(20)30174-0

Interesting discussion about the diffuse, alveolar-centred inflammation that triggers immunothrombosis in the lung microvasculature of patients with COVID-19 pneumonia. It seems highly probable that multiple mechanisms contribute to the pulmonary intravascular coagulopathy.

Mangalmurti N, Hunter CA. **Cytokine Storms: Understanding COVID-19**. Immunity June 28, 2020. Full-text: https://doi.org/10.1016/j.immuni.2020.06.017 ● (IMPORTANT)

Facing the storm: In their nice overview, the authors explain the protective function of cytokines in "ideal" responses; the multi-factorial origins that can drive these responses to become pathological; and how this ultimately leads to vascular damage, immunopathology, and worsening clinical outcomes. Of note, not all cytokine storms are the same, and there are many variables—the nature of the insult, host immune status, tissue affected, crosstalk with immune thrombosis, and complement activation—that influence the magnitude and kinetics of these responses and thus the clinical manifestations.

Pediatrics

Feldstein LR, Rose EB, Horwitz SM, et al. **Multisystem Inflammatory Syndrome in U.S. Children and Adolescents**. NEJM June 29, 2020. Full-text: https://doi.org/10.1056/NEJMoa2021680 ● (IMPORTANT)

The largest study on multisystem inflammatory syndrome in children (MIS-C) to date. The authors report on 186 patients with MIS-C in 26 states. The median age was 8.3 years, 115 patients (62%) were male, 135 (73%) had previously been healthy, 131 (70%) were positive for SARS-CoV-2 by RT-PCR or antibody testing. Detailed analysis of clinical manifestation revealed the gastrointestinal system (92%), cardiovascular (80%), hematologic (76%), mucocutaneous (74%), and respiratory involvement (70%). In total 148 patients (80%) received intensive care, 37 (20%) received mechanical ventilation, and 4 (2%) died. Coronary-artery aneurysms were documented in 15 patients (8%), and Kawasaki's disease–like features were documented in 74 (40%).

July 2020

1 July

Epidemiology

Tenforde MW, Billig Rose E, Lindsell CJ, et al. **Characteristics of Adult Outpatients and Inpatients with COVID-19 - 11 Academic Medical Centers, United States, March-May 2020.** MMWR Morb Mortal Wkly Rep. 2020 Jul 3;69(26):841-846. PubMed: https://pubmed.gov/32614810. Full-text: https://doi.org/10.15585/mmwr.mm6926e3

Telephone interviews in a random sample of 350 adults aged ≥ 18 years who had positive RT-PCR in outpatient and inpatient settings at 11 U.S. academic medical centers in nine states revealed that only 46% were aware of recent close contact with someone with COVID-19, highlighting a need for increased screening, case investigation, contact tracing, and isolation of infected persons during periods of community transmission. Of note, approximately one third of symptomatic outpatients reported that they had not returned to baseline health by the interview date 14–21 days after testing positive.

Vaccine

Dai L, Zheng T, Xu K, et al. **A universal design of betacoronavirus vaccines against COVID-19, MERS and SARS**. Cell June 28, 2020. Full-text: https://doi.org/10.1016/j.cell.2020.06.035

The CoV spike receptor-binding domain (RBD) is an attractive vaccine target but is undermined by limited immunogenicity. The authors identified a dimeric form of MERS-CoV RBD that overcomes this limitation and significantly increased the immunogenicity. The RBD-dimer significantly increased neutralizing antibody (NAb) titers compared to conventional monomeric form and protected mice against MERS-CoV infection. This can be a generalizable strategy for beta-CoV vaccine design.

Pathogenesis

Bouhaddou M, Memon D, Meyer B, et al. **The Global Phosphorylation Landscape of SARS-CoV-2 Infection.** Cell. 2020 Jun 28:S0092-8674(20)30811-4. PubMed: https://pubmed.gov/32645325. Full-text: https://doi.org/10.1016/j.cell.2020.06.034 ●● (OUTSTANDING)

Nothing to do next weekend? Then read this incredible work of 66 pages (> 400 references!). In brief: proteomics approaches that globally quantify changes in protein abundance and phosphorylation represent a powerful tool to elucidate mechanisms of viral pathogenesis by providing a snapshot of how cellular pathways and processes are rewired upon infection. Using a quantitative mass spectrometry-based phosphoproteomics survey of SARS-CoV-2 infection in Vero E6 cells, the 78 (!) authors present the global phosphorylation and protein abundance landscape of SARS-CoV-2 infection, map phosphorylation changes to disrupted kinases and pathways, and use these profiles to find drugs with the potential to treat SARS-CoV-2 infection. In total, 87 compounds (10 FDA-approved drugs) were identified.

Transmission

Abbas M, Pittet D. **Surfing the COVID-19 scientific wave**. Lancet June 30, 2020. Full-text: https://doi.org/10.1016/S1473-3099(20)30558-2

Harsh, relentless (maybe justified?) critical letter on the methodological flaws of the experiment of visualizing speech-generated oral fluid droplets (see below). The authors are "surprised that experiments in one person were published in a leading scientific journal" and state that the experiment had "more to do with sialoquence (spraying saliva when speaking) than with SARS-CoV-2".

Anfinrud P, Stadnytskyi V, Bax CE, Bax A. **Visualizing speech-generated oral fluid droplets with laser light scattering**. N Engl J Med. 2020; 382: 2061-2063. Full-text: https://www.nejm.org/doi/full/10.1056/nejmc2007800

Clinical

Lavezzo E, Franchin E, Ciavarella C et al. **Suppression of a SARS-CoV-2 outbreak in the Italian municipality of Vo'**. Nature 2020, June 30. Full-text: https://doi.org/10.1038/s41586-020-2488-1

On the 21st of February 2020 a resident of the municipality of Vo', a small town near Padua, Italy, died of pneumonia due to SARS-CoV-2 infection. At the start and the end of the lockdown, NP swabs were performed for 85.9% and 71.5% of the population (n=2,812), yielding to a prevalence of infection of 2.6% (95% CI 2.1-3.3%) and 1.2% (95% CI 0.8-1.8%), respectively. Of note, 42.5% of the confirmed SARS-CoV-2 infections detected across the two surveys were asymptomatic. Viral load of symptomatic versus asymptomatic infections did not differ.

Hewitt J, Carter B, Vilches-Moraga A, et al. **The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study**. Lancet June 30, 2020. Full-text: https://doi.org/10.1016/S2468-2667(20)30146-8

Using the clinical frailty scale (CFS), 1,564 patients from the UK and Italy were grouped according to their score (1–2=fit; 3–4=vulnerable, but not frail; 5–6=initial signs of frailty but with some degree of independence; and 7–9=severe or very severe frailty). Not very surprising: Compared with CFS 1–2, the adjusted hazard ratios for time from hospital admission to death were 1.55 for CFS 3–4, 1.83 for CFS 5–6, and 2.39 for CFS 7–9. Of note, disease outcomes were better predicted by frailty than either age or comorbidity.

Severe COVID-19

Goshua G, Pine AB, Meizlish ML, et al. **Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study**. Lancet June 30, 2020. Full-text: https://doi.org/10.1016/S2352-3026(20)30216-7

In 68 COVID-19 patients, the authors assessed several markers of endothelial cell and platelet activation, including von Willebrand Factor (VWF) antigen, soluble thrombomodulin, soluble P-selectin, and soluble CD40 ligand, as well as coagulation factors, endogenous anticoagulants, and fibrinolytic enzymes. Markers of endothelial cell and platelet activation were significantly elevated in ICU patients compared with non-ICU patients, including VWF antigen and soluble P-selectin. Some were of prognostic value, indicating that endotheliopathy is present in COVID-19 and is likely to be associated with critical illness and death.

Comorbidities

Del Amo J, Polo R, Moreno S, et al. **Incidence and Severity of COVID-19 in HIV-Positive Persons Receiving Antiretroviral Therapy - A Cohort Study**. Annals Int Med 2020, June 26. Full-text: https://doi.org/10.7326/M20-3689

Is there an effect of TDF? Of 77,590 HIV-positive persons receiving ART, 236 were diagnosed with COVID-19, 151 were hospitalized, 15 were admitted to the ICU, and 20 died. The risk for COVID-19 hospitalization was 20.3 (95% CI, 15.2 to 26.7) among patients receiving TAF/FTC, 10.5 (CI, 5.6 to 17.9) among those receiving TDF/FTC, 23.4 (CI, 17.2 to 31.1) among those receiving ABC/3TC, and 20.0 (CI, 14.2 to 27.3) for those receiving other regimens. How-

ever, residual confounding by comorbid conditions cannot be completely excluded.

Treatment

Tempestilli M, Caputi P, Avataneo V, et al. **Pharmacokinetics of remdesivir and GS-441524 in two critically ill patients who recovered from COVID-19**. J Antimicr Chemoth, July 1, 2020. Full-text: https://doi.org/10.1093/jac/dkaa239

Small PK pilot study on remdesivir (Veklury®) and the nucleoside analog GS-441524 (of which remdesivir is a prodrug). After intravenous administration, in both patients remdesivir showed a peak at the end of infusion and a half-life of 1 h, while GS-441524 reached a peak 1 h after infusion and then remained detectable until the next remdesivir administration. GS-441524 plasma concentrations were higher in the patient with renal impairment, indicating that renal excretion was a major route of elimination.

Pediatrics

L'Huillier AG, Torriani G, Pigny F, et al. **Culture-Competent SARS-CoV-2 in Nasopharynx of Symptomatic Neonates, Children, and Adolescents**. Emerg Infect Dis 2020, Pub June 29, 2020. Full-text: https://doi.org/10.3201/eid2610.202403

No differences between adults and children. The authors isolated culture-competent virus in vitro from 12 (52%) of 23 SARS-CoV-2–infected children; the youngest was 7 days old. SARS-CoV-2 viral load and shedding patterns of culture-competent virus in the 12 symptomatic children resembled those in adults. Therefore, transmission of SARS-CoV-2 from children is plausible.

2 July

Immunity

Schultheiß C, Paschold L, Simnica D, et al. **Next Generation Sequencing of T and B cell receptor repertoires from COVID-19 patients showed signatures associated with severity of disease**. Cell June 29, 2020. Full-text: https://doi.org/10.1016/j.immuni.2020.06.024 ● (IMPORTANT)

Insights on adaptive immunity. The authors analyzed COVID-19 patients with active, severe infection (n=20) or after recovery of mild disease (n=19) and created a repository of currently > 14 million B and T cell receptor (BCR, TCR)

sequences from the blood of these patients. The B cell response showed converging IGHV3-driven BCR clusters closely associated with SARS-CoV-2 antibodies. The T cell pools of patients with active disease were considerably diminished and showed shifts towards CD4+ and expanded T_{reg} cells. Clonality and skewing of TCR repertoires was associated with interferon type I and III responses and early CD4+ and CD8+ T cell activation.

Vaccine

Deming ME, Michael NL, Robb M, et al. **Accelerating Development of SARS-CoV-2 Vaccines — The Role for Controlled Human Infection Models**. NEJM July 1, 2020. Full-text: https://doi.org/10.1056/NEJMp2020076. Full-text: https://www.nejm.org/doi/full/10.1056/NEJMp2020076

The authors review practical considerations relevant to the development of a SARS-CoV-2 controlled human infection models (CHIMs) and the prerequisites for using such a model. Large, randomized, controlled trials of SARS-CoV-2 vaccines are still the most efficient, generalizable, and scientifically robust path to establishing vaccine efficacy. However, SARS-CoV-2 CHIM development might be able to accelerate the development of later rounds of vaccine candidates.

Diagnostics

Paden CR, Tao Y, Queen K, et al. **Rapid, sensitive, full-genome sequencing of severe acute respiratory syndrome coronavirus 2**. Emerg Infect Dis. 2020, Jul 1, 2020. https://doi.org/10.3201/eid2610.201800

Validated protocols are described for generating high-quality, full-length genomes from primary samples. One protocol uses multiplex reverse transcription PCR, followed by MinION or MiSeq sequencing; the other uses singleplex, nested reverse transcription PCR and Sanger sequencing. These protocols enable sensitive virus sequencing in different laboratory environments.

Clinical

Ikeuchi K, Saito M, Yamamoto S, Nagai H, Adachi E. **Relative bradycardia in patients with mild-to-moderate coronavirus disease, Japan**. Emerg Infect Dis 2020, July 1. Full-text: https://doi.org/10.3201/eid2610.202648

Relative bradycardia is a characteristic physical finding in some intracellular bacterial infections, viral infections, and non-infectious diseases. In this case

series of 54 patients with mild-to-moderate COVID-19 in Japan, it was also a common finding. This clinical sign could help clinicians to diagnose this disease. Only body temperature was independently associated with pulse rate by multivariate analysis. The predicted change in pulse rate was 7.37 beats/min for each 1°C increase in body temperature.

Weinberger DM, Chen J, Cohen T, et al. **Estimation of Excess Deaths Associated With the COVID-19 Pandemic in the United States, March to May 2020**. JAMA Intern Med July 1, 2020. Full-text: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2767980

There were approximately 781,000 deaths in the US from March 1 to May 30, 2020, representing 122,300 (95% prediction interval, 116,800 - 127,000) more deaths than would typically be expected. The number of excess all-cause deaths was 28% higher than the official tally of COVID-19–reported deaths during that period. There was substantial variability between states in the difference between official COVID-19 deaths and the estimated burden of excess deaths.

Woolf SH, Chapman DA, Sabo RT. **Excess Deaths From COVID-19 and Other Causes, March-April 2020**. JAMA July 1, 2020. Full-text: https://jamanetwork.com/journals/jama/fullarticle/2768086

Same idea: the weekly death data for the 50 US states and the District of Columbia were obtained from the National Center for Health Statistics for January through April 2020 and the preceding 6 years. The authors provide state-by-state estimates of excess deaths and a more detailed account of the 5 states most affected by COVID-19. It was estimated that the number of COVID-19 deaths reported in the first weeks of the pandemic captured only two-thirds of excess deaths in the US.

Severe COVID-19

Sinha P, Matthay MA, Calfee CS. **Is a "Cytokine Storm" Relevant to COVID-19?** JAMA Intern Med June 30, 2020. Full-text: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2767939 ● (IMPORTANT)

"Cytokine storm" has no definition. Broadly speaking, it denotes a hyperactive immune response characterized by the release of interferons, interleukins, tumor necrosis factors, chemokines, and several other mediators. In this

editorial, a critical evaluation of the term cytokine storm and its relevance is given. The authors point out that although the term "cytokine storm" conjures up dramatic imagery and has captured the attention of the mainstream and scientific media, the current data do not support its use. Until new data establish otherwise, the linkage of cytokine storm to COVID-19 may be nothing more than a tempest in a teapot.

Comorbidities

Armeni E, Aziz U, Qamar S, et al. **Protracted ketonaemia in hyperglycaemic emergencies in COVID-19: a retrospective case series**. Lancet Diabetol Endocrinol July 01, 2020. Full-text: https://doi.org/10.1016/S2213-8587(20)30221-7

COVID-19 is associated with hyperglycemic emergencies in COVID-19. In this case series of 35 patients from three hospitals in north London, UK, March 1–30, 2020, an over-representation of type 2 diabetes in patients presenting with diabetic ketoacidosis and long-lasting ketosis was observed. Findings suggest acute insulinopenia in patients with COVID-19 and with type 2 diabetes, which persisted up until the time of discharge in 30% of patients previously not insulin-treated. Moreover, the study sample, with almost half of patients of African background, had protracted ketonemia and ketoacidosis.

Pediatrics

Dufort EM, Koumans EH, Chow EJ, et al. **Multisystem Inflammatory Syndrome in Children in New York State**. NEJM June 29, 2020. Full-text: Full-text: https://www.nejm.org/doi/full/10.1056/NEJMoa2021756

Another large cohort of 95 patients with a multi-system inflammatory syndrome in children (MIS-C), reported to the New York State Department of Health. Detailed analysis of the characteristics: Elevated levels of C-reactive protein, d-dimer, and troponin were found in 100%, 91%, and 71% of the patients, respectively; 53% had evidence of myocarditis, 80% were admitted to an intensive care unit, and 2 died.

Abdel-Mannan O, Eyre M, Löbel U. **Neurologic and Radiographic Findings Associated With COVID-19 Infection in Children**. JAMA Neurol July 1, 2020. Full-text:
https://jamanetwork.com/journals/jamaneurology/fullarticle/2767979

A case series of 4 children with COVID-19 and neurological symptoms is described. Symptoms included encephalopathy, headaches, brainstem and cere-

bellar signs, muscle weakness, and reduced reflexes. All 4 patients had signal changes in the splenium of the corpus callosum on neuroimaging and required intensive care admission for the treatment of COVID-19 pediatric multisystem inflammatory syndrome.

3 July

Epidemiology

Cheng SY, Wang J, Shen AC, et al. **How to Safely Reopen Colleges and Universities During COVID-19: Experiences From Taiwan**. Ann Int Med 2020, Jul 2. Full-text: https://doi.org/10.7326/M20-2927

Reopening colleges and universities poses a special challenge worldwide. Taiwan is one of the few countries where schools are functioning normally. To secure the safety of students and staff, the Ministry of Education in Taiwan established general guidelines, including a combination of strategies such as – our future? - active campus-based screening and access control; school-based screening and quarantine protocols; student and faculty quarantine when warranted; mobilization of administrative and health center staff; regulation of dormitories and cafeterias; and reinforcement of personal hygiene, environmental sanitation, and indoor air ventilation practices. Somewhat depressing, but necessary?

Callaghan AW, Chard AN, Arnold P, et al. **Screening for SARS-CoV-2 Infection Within a Psychiatric Hospital and Considerations for Limiting Transmission Within Residential Psychiatric Facilities - Wyoming, 2020**. MMWR Morb Mortal Wkly Rep. 2020 Jul 3;69(26):825-829. PubMed: https://pubmed.gov/32614815. Full-text: https://doi.org/10.15585/mmwr.mm6926a4

Following admission of two patients with SARS-CoV-2 infection on April 13, 2020, in the absence of specific guidance on prevention and management of COVID-19 in psychiatric facilities, the state hospital implemented expanded admission screening and infection prevention and control procedures. The results of the point prevalence survey, indicating no further transmission among patients and HCW almost 3 weeks after admission of the two SARS-CoV-2-positive patients, suggested that the expanded procedures might have been effective.

Virology

Korber B, Fischer WM, Gnanakaran S, et al. **Tracking changes in SARS-CoV-2 Spike: evidence that D614G increases infectivity of the COVID-19 virus**. Cell July 02, 2020. Full-text: https://doi.org/10.1016/j.cell.2020.06.043 ● (IMPORTANT)

Based on 28,576 sequences until May 29, 2020, the authors show that a SARS-CoV-2 variant carrying the Spike protein amino acid change D614G (caused by an A-to-G nucleotide mutation at position 23,403 in the Wuhan reference strain) has become the most prevalent form in the global pandemic within a month. G614 has replaced D614 as the dominant pandemic form and the consistent increase of G614 at regional levels may indicate a fitness advantage. Moreover, G614 is associated with lower RT-PCR CT in the upper respiratory tract, suggestive of higher viral loads in patients. The G614 variant also grows to higher titers as pseudotyped virions. However, there was no association between G614 and disease severity.

Grubaugh ND, Hanage WP, Rasmussen AL. **Making sense of mutation: what D614G means for the COVID-19 pandemic remains unclear**. Cell July 02, 2020. Full-text: https://doi.org/10.1016/j.cell.2020.06.040

Comment on the above work. Main message = title. While clinical and in vitro data suggest that D614G changes the virus phenotype, the impact of the mutation on transmission, disease, vaccine and therapeutic development are largely unknown. As these forces can work in tandem, it's often hard to differentiate when a virus mutation becomes common through fitness or by chance. It is even harder to determine if a single mutation will change the outcome of an infection, or a pandemic.

Transmission

Guo L, Zhao S, Li W, et al. **Absence of SARS-CoV-2 in Semen of a COVID-19 Patient Cohort**. Andrology. 2020 Jun 29. PubMed: https://pubmed.gov/32598557. Full-text: https://doi.org/10.1111/andr.12848

No virus in the semen: all of 23 brave patients with SARS-CoV-2 infections (12 of them still positive in sputum and fecal specimens) tested negative for SARS-CoV-2 RNA in semen specimens.

Bastug A, Hanifehnezhad A, Tayman C, et al. **Virolactia in an Asymptomatic Mother with COVID-19**. Breastfeed Med. 2020 Jul 1. PubMed: https://pubmed.gov/32614251. Full-text: https://doi.org/10.1089/bfm.2020.0161

Another case report of a pregnant woman with subclinical COVID-19 whose breast milk sample obtained after delivery tested positive for SARS-CoV-2 by RT-PCR. In addition, although an initial nasopharyngeal swab (NPS) sample from the neonate resulted negative, neonatal NPS, stool, and blood samples obtained after breastfeeding were all positive in real-time RT-PCR assay.

Diagnostics

Magleby R, Westblade LF, Trzebucki A, et al**. Impact of SARS-CoV-2 Viral Load on Risk of Intubation and Mortality Among Hospitalized Patients with Coronavirus Disease 2019**. Clin Infect Dis. 2020 Jun 30:ciaa851. PubMed: https://pubmed.gov/32603425. Full-text: https://doi.org/10.1093/cid/ciaa851 ● (IMPORTANT)

Viral load matters: admission SARS-CoV-2 viral load among hospitalized patients with COVID-19 independently correlated with the risk of intubation and in-hospital mortality. In 678 patients with COVID-19, higher viral load was associated with increased age, comorbidities, smoking status, and recent chemotherapy. In-hospital mortality was 35.0% with a high viral load (Ct < 25; n = 220), 17.6% with a medium viral load (Ct 25-30; n=216), and 6.2% with a low viral load (Ct > 30; n = 242; P < 0.001). The risk of intubation was also higher in patients with a high viral load (29.1%), compared to those with a medium (20.8%) or low viral load (14.9%; P < 0.001). High viral load was independently associated with mortality (adjusted odds ratio 6.05; 95% CI: 2.92-12.52) and intubation (aOR 2.73; 95% CI: 1.68-4.44) in multivariate models.

Clinical

Baqui P, Bica I, Marra V, et al. **Ethnic and regional variations in hospital mortality from COVID-19 in Brazil: a cross-sectional observational study**. Lancet Global Health 2020, July 2. Full-text: https://doi.org/10.1016/S2214-109X(20)30285-0

The most extensive study (cross-sectional observational) of COVID-19 hospital survival in Brazil ranks second worldwide in total number of COVID-19 cases and deaths. Survivors were more likely to be younger, be women, and have fewer comorbidities, keeping with worldwide findings. In addition, Pardo ethnicity (mixed race) was the second most important risk factor (after age)

for death. The ethnicity effect might be related to differences in susceptibility to COVID-19 and access to health care (including intensive care) across ethnicities.

Feaster M, Goh Y-Y. **High proportion of asymptomatic SARS-CoV-2 infections in 9 long-term care facilities, Pasadena, California, USA, April 2020**. Emerg Infect Dis 2020, Jul 2. Full-text: https://doi.org/10.3201/eid2610.202694

SARS-CoV-2 prevalence in 9 long-term care facilities demonstrated a high proportion (40.7%, 257/631) of asymptomatic infections among residents and staff members. The prevalence of asymptomatic infection differed markedly between facilities: among staff members from 17.4% to 30.6%, among residents from 19.0% to 85.7%.

Treatment

Kupferschmidt K. **One U.K. trial is transforming COVID-19 treatment. Why haven't others delivered more results?** Science Jul. 2, 2020. Full-text: https://doi.org/10.1126/science.abd6417

Where are the results of the hundreds of clinical trials conducted during the last months? This article describes the challenges that clinical trials are facing world-wide. Some details on WHO's SOLIDARITY are given. With recruitment running at about 500 patients per week now, SOLIDARITY's three remaining treatment arms are likely to yield answers "soon" (whatever that means), raising the question of what drugs to test afterward. Some repurposed drugs such as camostat mesylate or favipiravir are still being discussed, but increasingly the attention is turning to monoclonal antibodies, designed to target the virus.

4 July

Epidemiology

Yu X, Wei D, Chen Y, et al. **Retrospective detection of SARS-CoV-2 in hospitalized patients with influenza-like illness**. Emerging Microbes & Infections 2020, Full-text: https://doi.org/10.1080/22221751.2020.1785952

No cryptic transmission before early officially confirmed cases. In this retrospective screening for SARS-CoV-2 RNA in 1,271 nasopharyngeal swab samples, as well as the prevalence of IgM, IgG, and total antibodies against SARS-CoV-2 in 357 matched serum samples collected from hospitalized patients

with influenza-like illness between December 1, 2018 and March 31, 2020 in Shanghai Ruijin Hospital, the onset date of the earliest COVID-19 case was January 25.

Immunology, vaccine

Deng W, Bao L, Liu J, et al. **Primary exposure to SARS-CoV-2 protects against reinfection in rhesus macaques**. Science 02 Jul 2020. Full-text: https://doi.org/10.1126/science.abc5343

Four rhesus macaques were re-challenged intratracheally with the same dose of the SARS-CoV-2 strain at 28 days post-initial challenge with the identical SARS-CoV-2 strain. Animals did not show detectable viral dissemination, clinical manifestations of viral disease, or histopathological changes. Comparing the humoral and cellular immunity between primary infection and rechallenge revealed notably enhanced neutralizing antibody and immune responses.

Transmission

Aboubakr HA, Sharafeldin TA, Goyal SM. **Stability of SARS-CoV-2 and other coronaviruses in the environment and on common touch surfaces and the influence of climatic conditions: a review**. Transbound Emerg Dis. 2020 Jun 30. PubMed: https://pubmed.gov/32603505. Full-text: https://doi.org/10.1111/tbed.13707

A comprehensive review of the available data (by May 21, 2020) on the stability of coronaviruses, including SARS-CoV-2, from previous reports, to help understand its environmental survival.

Edwards SJL, Santini JM. **Anthroponotic risk of SARS-CoV-2, precautionary mitigation, and outbreak management**. Lancet Microbe, July 02, 2020. Full-text: https://doi.org/10.1016/S2666-5247(20)30086-0

Important comment on the evidence of infection of animals with SARS-CoV-2 that has been shown experimentally both *in vivo* and *in vitro* for mammals including monkeys, cats, ferrets, rabbits, foxes, and hamsters, while bioinformatic studies also predict infectivity of pigs and wild boar among other mammals. According to the authors, we should also consider the potential for transmissibility, not just infection.

Sikkema RS, Niewenhuijse DF, O'Toole A, et al. **COVID-19 in health-care workers in three hospitals in the south of the Netherlands: a cross-sectional study**. Lancet Inf Dis, July 02, 2020. Full-text: https://doi.org/10.1016/S1473-3099(20)30527-2

Social events outside the hospital. In this cross-sectional study at three hospitals located in the south of the Netherlands, from 50 HCWs (and ten patients), complete and near-complete genome sequences were analyzed. Most sequences were grouped into three clusters, with two clusters showing local circulation within the region. The genomic diversity recorded was consistent with multiple introductions through community-acquired infections, and some local amplification related to specific social events in the community, rather than widespread within-hospital transmission. Thus, data do not support widespread nosocomial transmission as the source of infection in patients or health-care workers.

Diagnostics

Tollånes MC, Bakken Kran AM, Abildsnes E, Jenum PA, Breivik AC, Sandberg S. **Evaluation of eleven rapid tests for detection of antibodies against SARS-CoV-2**. Clin Chem Lab Med. 2020 Jun 29. PubMed: https://pubmed.gov/32598303. ● (IMPORTANT)

Sensitivity of rapid tests is at best moderate: the authors evaluated diagnostic performance of eleven rapid tests for detection of antibodies to SARS-CoV-2 in 20 hospitalized patients with PCR-confirmed COVID-19, 23 recovered outpatients with former PCR-confirmed COVID-19, and 49 participants with suspected COVID-19 presenting at a primary care emergency room. All eleven tests detected antibodies in hospitalized COVID-19 patients, though with varying sensitivities. In former outpatients recovered from COVID-19, there were differences between tests in the immunoglobulin type G (IgG) sensitivity, with five tests having a sensitivity below 65%. In participants with suspected COVID-19 infection, the rapid tests had very low sensitivities.

Clinical

Vestergaard LS, Nielsen J, Richter L, et al. **Excess all-cause mortality during the COVID-19 pandemic in Europe – preliminary pooled estimates from the EuroMOMO network, March to April 2020**. Euro Surveill. 2020;25(26). Full-text: https://doi.org/10.2807/1560-7917.ES.2020.25.26.2001214

The authors present preliminary pooled estimates of all-cause mortality for 24 European countries/federal states participating in the European monitor-

ing of excess mortality for public health action (EuroMOMO) network, for the period March–April 2020. Excess mortality particularly affected ≥ 65-year-olds (91% of all excess deaths), to a lesser extent those 45–64 (8%) and 15–44-year-olds (1%). The cumulative excess mortality from week 1 to week 18, 2020 reached a total of 185,287 deaths, including 24,438 (13%) in persons aged 65–74 years, 55,226 (30%) in persons aged 75–84 years, and 88,598 (48%) in persons aged ≥ 85 years.

Shi D, Wu W, Wang Q, et al. **Clinical characteristics and factors associated with long-term viral excretion in patients with SARS-CoV-2 infection: a single center 28-day study**. J Inf Dis, 02 July 2020. Full-text: https://doi.org/10.1093/infdis/jiaa388

SARS-CoV-2 RNA clearance time was associated with sex, disease severity and lymphocyte function. Among 99 patients, 61 patients had SARS-CoV-2 clearance (virus-negative group), but 38 patients had sustained positive results (virus-positive group). Male sex (HR, 0.58), immunoglobulin use (0.42), APACHE II score (0.89), and lymphocyte count (1.81) were independent factors associated with a prolonged duration of SARS-CoV-2 shedding. Antiviral therapy and corticosteroid treatment were not independent factors.

Boscolo-Rizzo P, Borsetto D, Fabbris C, et al. **Evolution of Altered Sense of Smell or Taste in Patients With Mildly Symptomatic COVID-19**. JAMA Otolaryngol Head Neck Surg. 2020 Jul 2. PubMed: https://pubmed.gov/32614442. Full-text: https://doi.org/10.1001/jamaoto.2020.1379

At 4 weeks from onset, most patients experience complete resolution or even improvement of altered sense of smell or taste. Of 202 patients completing the survey at baseline, 187 (92.6%) also completed the follow-up survey. The evaluation of 113 patients reporting sudden onset of these symptoms at baseline showed that 55 patients (49%) reported complete resolution of smell or taste impairment, 46 (41%) reported an improvement in the severity, and only 12 (11%) reported the symptom was unchanged or worse. Persistent loss of smell or taste was not associated with persistent SARS-CoV-2 infection.

Treatment

Gendelman O, Amital H, Bragazzi NL, Watad A, Chodick G. **Continuous hydroxychloroquine or colchicine therapy does not prevent infection with SARS-CoV-2: Insights from a large healthcare database analysis**. Auto-

immun Rev 2020 Jul;19(7):102566. PubMed: https://pubmed.gov/32380315. Full-text: https://doi.org/10.1016/j.autrev.2020.102566

No protection with HCQ and colchicine. An overall sample of 14,520 subjects from Israel were screened for SARS-CoV-2 infection and 1317 resulted positive. No significant difference was found in terms of rates of usage of hydroxychloroquine or colchicine between those who were found positive for SARS-CoV-2 and those who were found negative (0.23% versus 0.25% for hydroxychloroquine, and 0.53% versus 0.48% for colchicine, respectively).

5 July

Epidemiology

Petersen E, Koopmans M, Go U, et al. **Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics**. Lancet Inf Dis 2020, July 03, 2020. Full-text: https://doi.org/10.1016/S1473-3099(20)30484-9

The basic reproductive rate (R0) for SARS-CoV-2 is estimated to be 2·5 (range 1·8–3·6) compared with 2·0–3·0 for SARS-CoV and the 1918 influenza pandemic, 0·9 for MERS-CoV, and 1·5 for the 2009 influenza pandemic. In their viewpoint, the authors postulate that historical evidence from prior influenza pandemics indicates that pandemics tend to come in waves over the first 2–5 years as population immunity builds-up (naturally or through vaccination) and that this is the most likely trajectory for SARS-CoV-2. A combination of physical distancing, enhanced testing, quarantine, and contact tracing will be needed for a long time.

Transmission

Goldman E. **Exaggerated risk of transmission of COVID-19 by fomites**. Lancet Inf Dis July 03, 2020. Full-text: https://doi.org/10.1016/S1473-3099(20)30561-2

A note of caution, to curb excesses that become counterproductive. According to the author, the chance of transmission through inanimate surfaces is very small, and only in instances where an infected person coughs or sneezes on the surface, and someone else touches that surface soon after the cough or sneeze (within 1–2 h). Although periodically disinfecting surfaces and use of gloves are reasonable precautions especially in hospitals, he believes that fomites that have not been in contact with an infected carrier for many hours do not pose a measurable risk of transmission.

Prevention

Patrício Silva AL, Prata JC, Walker TR, et al. **Rethinking and optimising plastic waste management under COVID-19 pandemic: Policy solutions based on redesign and reduction of single-use plastics and personal protective equipment**. Sci Total Environ. 2020 Jun 30;742:140565. PubMed: https://pubmed.gov/32622168. Full-text: https://doi.org/10.1016/j.scitotenv.2020.140565

The amount of waste generated due to COVID-19 indeed threatens the existing waste management streams, meaning that plastic leakage/pollution may impose severe risks to both environmental and human health. Thus, it is imperative to increase monitoring (aquatic, terrestrial and aerial surveys) of plastic waste under post-COVID-19, around the world. This paper provides an overview of plastic policies and discusses the readjustments of these policies during the COVID-19 pandemic along with their potential environmental implications. Policy recommendations and future research directions are also discussed.

Diagnostics

Bastos ML, Tavaziva G, Abidi SK, et al. **Diagnostic accuracy of serological tests for covid-19: systematic review and meta-analysis**. BMJ July 1, 2020; 370. Full-text: https://doi.org/10.1136/bmj.m2516 ● (IMPORTANT)

Systematic review of 40 studies on sensitivity and specificity, stratified by method of serological testing (enzyme linked immunosorbent assays, ELISAs), lateral flow immunoassays (LFIAs), or chemiluminescent immunoassays, CLIAs). The pooled sensitivity of ELISAs measuring IgG or IgM was 84.3% (95% confidence interval 75.6% to 90.9%), of LFIAs was 66.0% (49.3% to 79.3%), and of CLIAs was 97.8% (46.2% to 100%). According to the authors, higher quality clinical studies assessing the diagnostic accuracy of serological tests for COVID-19 are urgently needed. Currently, available evidence does not support the continued use of existing point-of-care serological tests.

Shi J, Han D, Zhang R, et al. **Molecular and Serological Assays for SARS-CoV-2: Insights from Genome and Clinical Characteristics**. Clinical Chemistry Jul 5, 2020. Full-text: https://doi.org/10.1093/clinchem/hvaa122

This comprehensive review summarizes the principles and related details of PCR and serological assays for SARS-CoV-2 as well as the quality assurance measures for these assays.

Guo X, Jie Y, Chen P, et al. **Upper Respiratory Tract Viral RNA Load at Hospital Admission is Associated with COVID-19 Disease Severity**. Open Forum Infectious Diseases Jul 5, 2020. Full-text: https://doi.org/10.1093/ofid/ofaa282

The next study reporting that initial viral load is positive correlated to illness severity. Among 195 patients, the two conversely correlated indexes for initial viral load, $\log_{10}$ (copies/mL) and Ct value, were found to be respective significantly positive and negative correlated to severity.

Dong Y, Chi X, Hai H, et al. **Antibodies in the breast milk of a maternal woman with COVID-19**. Emerg Microbes Infect. 2020 Dec;9(1):1467-1469. PubMed: https://pubmed.gov/32552365. Full-text: https://doi.org/10.1080/22221751.2020.1780952

Case report of an infected mother, in which IgG and IgA antibodies were detected in breast milk, indicating the potential immune protection for the neonates. The infant negative for SARS-CoV-2 at birth had elevated IgG in serum but it quickly decayed.

Clinical

Hoxha A, Wyndham-Thomas C, Klamer S, et al. **Asymptomatic SARS-CoV-2 infection in Belgian long-term care facilities**. Lancet Inf Dis July 03, 2020. Full-text: https://doi.org/10.1016/S1473-3099(20)30560-0

Following a mass testing campaign in long-term care facilities in Belgium, no symptoms were reported for 2,185 (74.0%) staff and 4,059 (75.3%) residents. Given the cross-sectional nature of this analysis, however, it was not possible to determine whether any of the asymptomatic individuals went on to develop symptoms. If pre-symptomatic or asymptomatic: risk of under-ascertainment of symptoms, although mitigated by medical assessment, persists.

Comorbidities

Stanworth SJ, New HV, Apelseth TO, et al. **Effects of the COVID-19 pandemic on supply and use of blood for transfusion**. Lancet Hematology, July 03, 2020. Full-text: https://doi.org/10.1016/S2352-3026(20)30186-1

The pandemic has major implications for blood transfusion. There are uncertain patterns of demand, and transfusion institutions need to plan for reduc-

tions in donations and loss of crucial staff because of sickness and public health restrictions. This article provides a synthesis of the published literature and guidance during times of potential or actual shortage. However, a reduction in donor numbers has largely been matched by reductions in demand for transfusion.

Zhong J, Shen G, Yang H, et al. **COVID-19 in patients with rheumatic disease in Hubei province, China: a multicentre retrospective observational study**. Lancet Rheumatology July 03, 2020. Full-text: https://doi.org/10.1016/S2665-9913(20)30227-7

Patients with autoimmune rheumatic disease might be more susceptible. Within 42 families with at least one member suffering from a rheumatic disease, COVID-19 was diagnosed in 27 (63%) of 43 patients with a rheumatic disease and in 28 (34%) of 83 of their family members with no rheumatic disease (adjusted odds ratio 2.68, 95% CI 1.14–6.27). Patients with rheumatic disease who were taking hydroxychloroquine had a lower risk of COVID-19 infection than patients taking other disease-modifying anti-rheumatic drugs (OR 0.09, 0.01–0.94).

6 July

Epidemiology

Adam D. **A guide to R — the pandemic's misunderstood metric**. Nature News. 03 July 2020. Full-text: https://www.nature.com/articles/d41586-020-02009-w

Nice article about what R, the reproduction number, can and can't tell us about managing COVID-19. Politicians seem to have embraced R with enthusiasm but it's far more important to watch for clusters of cases and to set up comprehensive systems to test people, trace their contacts and isolate those infected, than to look at R.

Pollán M, Pérez-Gómez B, Pastor-Barriuso R, et al. **Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study**. The Lancet 2020, July 06, 2020. Full-text: https://doi.org/10.1016/S0140-6736(20)31483-5

The vast majority (95%) of the Spanish population is seronegative, even in hotspot areas. In this nationwide, representative study, 61,075 participants were tested. Seroprevalence was 5·0% (95% CI 4.7–5.4) by the point-of-care

test and 4.6% (4.3–5.0) by immunoassay, with a lower seroprevalence in children younger than 10 years (< 3.1% by the point-of-care test). There was high geographical variability, with higher prevalence around Madrid (> 10%) and lower in coastal areas (< 3%).

Eckerle I, Meyer B. **SARS-CoV-2 seroprevalence in COVID-19 hotspots**. The Lancet July 06, 2020. Full-text: https://doi.org/10.1016/S0140-6736(20)31482-3

Comment on these findings. Most of the population appears to have remained unexposed to SARS-CoV-2, even in areas with widespread virus circulation. Any proposed approach to achieve herd immunity through natural infection is not only highly unethical, but also unachievable. With a large majority of the population being infection-naïve, virus circulation can quickly return to early pandemic dimensions in a second wave once measures are lifted.

Diagnostics

Schmidt M, Hoehl S, Berger A, et al. **Novel multiple swab method enables high efficiency in SARS-CoV-2 screenings without loss of sensitivity for screening of a complete population**. Transfusion. 2020 Jul 6. PubMed: https://pubmed.gov/32627200. Full-text: https://doi.org/10.1111/trf.15973

The authors present a novel alternate multiple swab protocol that is based on incubation of a respiratory swab first in a single-sample tube, and then again in a multiple-sample tube. No significant difference in the amount of virus was detected by NAT in the single-sample or multiple-swab tube. The novel protocol was able to reduce the total number of required NAT tests by up to 80%, without loss of diagnostic sensitivity.

Comorbidities

Tadic M, Cuspidi C, Grassi G, Mancia G. **COVID-19 and arterial hypertension: Hypothesis or evidence? J Clin Hypertens (Greenwich)**. 2020 Jul 6. PubMed: https://pubmed.gov/32627330. Full-text: https://doi.org/10.1111/jch.13925

Hypertension has been proven to be more prevalent in patients with an adverse outcome. So far, there is no study that demonstrates the independent predictive value of hypertension on mortality in COVID-19 patients. This review summarizes the current knowledge about the relationship between hypertension and COVID-19 and the role of hypertension on outcome in these patients.

Severe COVID-19

Kollias A, Kyriakoulis KG, Stergiou GS, Syrigos K. **Heterogeneity in reporting venous thromboembolic phenotypes in COVID-19: Methodological issues and clinical implications**. Br J Haematol. 2020 Jul 4. PubMed: https://pubmed.gov/32621757. Full-text: https://doi.org/10.1111/bjh.16993

Some thoughts about the heterogeneity in the reported VTE risk as well as in the thromboembolic phenotypes of COVID-19 patients (isolated DVT, isolated pulmonary embolism/thrombosis, concurrent DVT and pulmonary embolism/thrombosis). It might be suggested that variation in VTE accounts for this heterogeneity: characteristics of the patients include well-established risk factors for VTE, hospitalization conditions and interventions as well as SARS-CoV-2 specific factors.

Nightingale R, Nwosu N, Kutubudin F, et al. **Is continuous positive airway pressure (CPAP) a new standard of care for type 1 respiratory failure in COVID-19 patients? A retrospective observational study of a dedicated COVID-19 CPAP service**. BMJ Open Respir Res. 2020 Jul;7(1):e000639. PubMed: https://pubmed.gov/32624495. Full-text: https://doi.org/10.1136/bmjresp-2020-000639

Small retrospective study of 24 patients. According to the authors, with careful patient selection and close monitoring, CPAP can be a successful treatment strategy in critically ill patients with type 1 respiratory failure in COVID-19, and that it can be safely deployed outside the critical care environment.

Treatment

Li L, Tong X, Chen H, et al. **Characteristics and serological patterns of COVID-19 convalescent plasma donors: optimal donors and timing of donation**. Transfusion. 2020 Jul 6. PubMed: https://pubmed.gov/32627216. Full-text: https://doi.org/10.1111/trf.15918

When is the best time to donate plasma? In 49 donors, S-RBD-specific and N-specific IgG antibodies increased after 4 weeks from the onset of symptoms, with no significant correlation to age, sex, or ABO blood type. Donors with disease presentation of fever exceeding 38.5°C or lasting longer than 3 days exhibited higher levels of S-RBD-specific IgG antibodies at the time of donation. The authors recommend the following selection criteria for optimal donation of COVID-19 convalescent plasma: 28 days after the onset of symptoms

and with a disease presentation of fever lasting longer than 3 days or a body temperature exceeding 38.5°C. Selection based on these criteria can ensure a high likelihood of achieving sufficiently high S-RBD-specific IgG titers.

Della-Torre E, Campochiaro C, Cavalli G, et al. **Interleukin-6 blockade with sarilumab in severe COVID-19 pneumonia with systemic hyperinflammation: an open-label cohort study**. Ann Rheum Dis. 2020 Jul 3. PubMed: https://pubmed.gov/32620597. Full-text: https://doi.org/10.1136/annrheumdis-2020-218122

Open-label study of sarilumab (a recombinant human IL-6Rα antagonist) in severe COVID-19 pneumonia with hyperinflammation. Sarilumab 400 mg was administered intravenously in addition to standard of care to 28 patients and results were compared with 28 contemporary matched patients treated with standard of care alone. At day 28, 61% of patients treated with sarilumab experienced clinical improvement and 7% died. These findings were not significantly different from the comparison group. However, sarilumab was associated with faster recovery in a subset of patients showing minor lung consolidation at baseline.

Pediatrics

Gao J, Li W, Hu X, et al. **Disappearance of SARS-CoV-2 Antibodies in Infants Born to Women with COVID-19, Wuhan, China**. Emerg Infect Dis. 2020 Jul 3;26(10). PubMed: https://pubmed.gov/32620180. Full-text: https://doi.org/10.3201/eid2610.202328

First study on detection and decline over time of antibodies in infants born to women with COVID-19. Among the 24 infants born to women with COVID-19, 15 (62.5%) had detectable IgG and 6 (25.0%) had detectable IgM; nucleic acid test results were all negative. Among 11 infants tested at birth, all had detectable IgG and 5 had detectable IgM. IgG titers with positive IgM declined more slowly than those without.

7 July

Immunology

O'Callaghan KP, Blatz AM, Offit PA. **Developing a SARS-CoV-2 Vaccine at Warp Speed**. JAMA, July 6, 2020. Full-text: https://doi.org/10.1001/jama.2020.12190

In this Viewpoint, the authors describe the the five currently leading vaccine candidates, all of which are aimed at inducing antibodies directed against the receptor-binding domain of the surface spike S protein of SARS-CoV-2. These vaccine candidates are messenger RNA-based (Moderna, Pfizer), recombinant vesicular stomatitis virus vectored (MSD) and adenovirus replication-defective vectored (Johnson & Johnson, AstraZeneca). All 5 candidates are undergoing rigorous investigation of their safety profile, including unintended adverse events.

Case JB, Rothlauf PW, Chen RE, et al. **Neutralizing antibody and soluble ACE2 inhibition of a replication-competent VSV-SARS-CoV-2 and a clinical isolate of SARS-CoV-2**. Cell Host Microbe July 01, 2020. Full-text: https://doi.org/10.1016/j.chom.2020.06.021

Using an infectious molecular clone of vesicular stomatitis virus (VSV), researchers replaced the glycoprotein gene (G) with the spike protein of SARS-CoV-2 (VSV-eGFP-SARS-CoV-2) and developed a high-throughput imaging-based neutralization assay at biosafety level 2. This provides a tool for testing inhibitors of SARS-CoV-2 mediated entry under reduced biosafety containment.

Dieterle EM, Haslwater D, Bortz RH, et al. **A replication-competent vesicular stomatitis virus for studies of SARS-CoV-2 spike-mediated cell entry and its inhibition**. Cell July 01, 2020. Full-text: https://doi.org/10.1016/j.chom.2020.06.020

Same direction. This group from the Albert Einstein College in New York have also generated a highly infectious recombinant VSV bearing the SARS-CoV-2 spike glycoprotein S as its sole entry glycoprotein and show that this recombinant virus, rVSV-SARS-CoV-2 S, closely resembles SARS-CoV-2 in its entry-related properties. Another step towards robust, scalable, and readily deployable surrogate viral assays to screen antiviral humoral responses, define correlates of immune protection, and down-select candidate antivirals.

Transmission

Morawska L, Milton DK. **It is Time to Address Airborne Transmission of COVID-19**. Clinical Infectious Diseases, July 6, 2020. Full-text: https://doi.org/10.1093/cid/ciaa939 ● (IMPORTANT)

In their comment, the authors appeal to the medical community and to all relevant national and international bodies to recognize the potential for air-

borne spread of COVID-19. Given the significant potential for inhalation exposure to viruses in microscopic respiratory droplets (microdroplets) at short to medium distances (up to several meters, or room scale), the authors are advocating for the use of preventive measures. This includes sufficient and effective ventilation (supply clean outdoor air, minimize recirculating air) particularly in public buildings, workplace environments, schools, hospitals, and aged care homes, but also supplement general ventilation with airborne infection control (such as local exhaust, high efficiency air filtration, and germicidal ultraviolet lights). Third, overcrowding has to be avoided, particularly in public transport and public buildings

Stubblefield WB, Talbot HK, Feldstein L, et al. **Seroprevalence of SARS-CoV-2 Among Frontline Healthcare Personnel During the First Month of Caring for COVID-19 Patients - Nashville, Tennessee**. Clin Infect Dis. 2020 Jul 6. PubMed: https://pubmed.gov/32628750. Full-text: https://doi.org/10.1093/cid/ciaa936

Among 249 HCW who worked in hospital units with COVID-19 patients for one month, 19 (7.6%) tested positive for SARS-CoV-2 antibodies. Only 11/19 (57.9%) reported symptoms of a prior illness, suggesting asymptomatic HCW could be an important source of SARS-CoV-2 transmission.

Diagnostics

Mei Q, Li J, Du R, et al. **Assessment of patients who tested positive for COVID-19 after recovery**. Lancet Inf Dis 2020, July 06, 2020. Full-text: https://doi.org/10.1016/S1473-3099(20)30433-3

In this study, 23 (3%) of 651 patients tested positive on a retest for SARS-CoV-2 by RT-qPCR assay in a routine health check. Of note, 52% had IgG anti-viral antibodies and 30% had IgM antibodies, indicating partial immune system recognition of SARS-CoV-2. Of note, 35% of patients had one or more COVID-19-related symptoms, questioning the usefulness of viral antibodies in COVID-19 clearance.

Clinical

Merkler ASE, Parikh NS, Mir S, et al. **Risk of Ischemic Stroke in Patients With Coronavirus Disease 2019 (COVID-19) vs Patients With Influenza**. JAMA Neurol. Published online July 2, 2020. Full-text: https://doi.org/10.1001/jamaneurol.2020.2730

Again, it's NOT a flu. In this retrospective cohort study, 1,916 COVID-19 patients and 1,486 influenza patients (with emergency department visits or hospitalizations) were compared. There were 31 (1.6%; 95% CI, 1.1% - 2.3%) acute ischemic strokes with COVID-19, compared to 3 with influenza (0.2%; 95% CI, 0.0% - 0.6%). After adjustment for age, sex, and race, the likelihood of stroke was almost 8-fold higher with COVID-19 (odds ratio, 7.6; 95% CI, 2.3 - 25.2).

Goyal P, Ringel JB, Rajan M, et al. **Obesity and COVID-19 in New York City: A Retrospective Cohort Study**. Ann Int Med 6 Jul 2020. Full-text: https://www.acpjournals.org/doi/10.7326/M20-2730

More on obesity. In this study of 1,687 adults hospitalized with COVID-19 in New York City, obesity was an independent risk factor for respiratory failure but not for in-hospital mortality. These findings explain the extensive use of invasive mechanical ventilation reported in the US, where the prevalence of obesity exceeds 40%. The risk conferred by obesity was similar across age, sex, and race.

Severe COVID-19

Fan E, Beitler JR, Brochard L, et al. **COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted**? Lancet Respir Med July 06, 2020. Full-text: https://doi.org/10.1016/S2213-2600(20)30304-0 ● (IMPORTANT)

In their Viewpoint, the authors address ventilation strategies in the context of recent discussions on phenotypic heterogeneity in patients with COVID-19-associated ARDS. Although early reports suggested distinctive features that set it apart from historical ARDS, emerging evidence indicates that the respiratory system mechanics are broadly similar. In the absence of evidence to support a shift away from the current paradigm of ventilatory management, we strongly recommend adherence to evidence-based management, informed by bedside physiology, as resources permit.

Treatment

Wang J, Xing S, Ding L, et al. **Human IgG neutralizing monoclonal antibodies block SARS-CoV-2 infection**. Cell July 01, 2020. Full-text: https://doi.org/10.1016/j.celrep.2020.107918 ● (IMPORTANT)

Forget HCQ, lopinavir, etc. Over the last months, it has become increasingly clear that monoclonal antibodies will be the most promising therapeutic can-

didates for COVID-19. The authors identified 178 S1 and RBD binding human monoclonal antibodies from the memory B cells of 11 recently recovered patients. Of 8 antibodies showing robust authentic viral neutralizing activities, the best one, 414-1, showed neutralizing IC50 at 1.75 nM. Epitope mapping revealed that the antibodies bound to 3 different RBD epitopes, and epitope B antibody 553-15 could substantially enhance neutralizing abilities of most other neutralizing antibodies.

8 July

Epidemiology

Kang CR, Lee JY, Park Y, Huh IS, Ham HJ, Han JK, et al**. Coronavirus disease exposure and spread from nightclubs, South Korea**. Emerg Infect Dis. 2020 Sep. Full-text: https://doi.org/10.3201/eid2610.202573 ● (IMPORTANT)

Despite low incidence, superspreading related to visiting nightclubs has the potential to spark a resurgence of cases. This article describes large-scale testing for active case-finding among persons who visited 5 Itaewon nightclubs in downtown Seoul, South Korea. Nightclubs had reopened ahead of the April 30–May 5 Golden Week holiday. Among the 41,612 total tests (!) conducted by May 25, positive results were found in 0.19% (67/35,827) of nightclub visitors, 0.88% (51/5,785) of their contacts, and 0.06% (1/1,627) of anonymously tested persons. 246 COVID-19 cases were associated with the reopening of nightclubs in Seoul. Hooray for the Asian thoroughness and some strong arguments against reopening nightclubs...

Yehya N, Venkataramani A, Harhay MO. **Statewide Interventions and Covid-19 Mortality in the United States: An Observational Study**. Clin Infect Dis. 2020 Jul 8. PubMed: https://pubmed.gov/32634828. Full-text: https://doi.org/10.1093/cid/ciaa923

Every day counts. In this large, nationwide study, later statewide emergency declarations and school closures were associated with higher COVID-19 mortality. Each day of delay increased mortality risk by 5 to 6%.

Waltenburg MA, Victoroff T, Rose CE, et al. **Update: COVID-19 Among Workers in Meat and Poultry Processing Facilities – United States, April–May 2020**. MMWR Morb Mortal Wkly Rep. ePub: 7 July 2020. Full-text: https://www.cdc.gov/mmwr/volumes/69/wr/mm6927e2.htm

One more reason to go veg. Overall, 239 facilities reported 16,233 COVID-19 cases and 86 COVID-19–related deaths among workers. The percentage of workers with COVID-19 ranged from 3.1% to 24.5% per facility. Among seven facilities that implemented facility-wide testing, the crude prevalence of asymptomatic or presymptomatic infections among 5,572 workers who had positive SARS-CoV-2 test results was 14.4%.

Virology

Sharma A, Garcia G, Arumugaswami V, Svendsen CN. **Human iPSC-Derived Cardiomyocytes are Susceptible to SARS-CoV-2 Infection.** bioRxiv. 2020 Apr 21:2020.04.21.051912. PubMed: https://pubmed.gov/32511402. Full-text: https://doi.org/10.1101/2020.04.21.051912

In this study, human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) were used as a model to examine the mechanisms of cardiomyocyte-specific infection by SARS-CoV-2. Microscopy and RNA-sequencing demonstrated that SARS-CoV-2 can enter hiPSC-CMs via ACE2. Viral replication and cytopathic effect induce hiPSC-CM apoptosis and cessation of beating after 72 hours of infection.

Qian Q, Fan L, Liu W, et al. **Direct evidence of active SARS-CoV-2 replication in the intestine**. Clin Inf Dis 2020, July 8. Full-text: https://doi.org/10.1093/cid/ciaa925

The virus is not only in the heart but also in the rectum. In this case report, quantitative RT-PCR was performed on rectal tissue specimens obtained from surgical resection in a COVID-19 patient with rectal adenocarcinoma. RNA of SARS-CoV-2 was detected in surgically resected rectal specimens, but not in samples collected 37 days after discharge. Notably, coinciding with rectal tissues of surgical specimens nucleic acid positive for SARS-CoV-2, typical coronavirus virions in rectal tissue were observed under electron microscopy. Moreover, abundant lymphocytes and macrophages (some are SARS-CoV-2 positive) infiltrating the lamina propria were found with no significant mucosal damage.

Transmission

Zhou J, Otter JA, Price JR, et al. **Investigating SARS-CoV-2 surface and air contamination in an acute healthcare setting during the peak of the COVID-19 pandemic in London.** Clin Infect Dis. 2020 Jul 8:ciaa905. PubMed: https://pubmed.gov/32634826. Full-text: https://doi.org/10.1093/cid/ciaa905

Cross-sectional observational study in a multi-site London hospital. Air and surface samples were collected from several areas. Viral RNA was detected on 114/218 (52.3%) of surfaces and 14/31 (38.7%) air samples but no virus was cultured. Viral RNA was more likely to be found in areas immediately occupied by COVID-19 patients than in other areas. The high PCR Ct value for all samples (> 30) indicated that the virus would not be culturable.

Schlottau K, Rissmann M, Graaf A, et al. **SARS-CoV-2 in fruit bats, ferrets, pigs, and chickens: an experimental transmission study**. Lancet Microbe July 07, 2020. Full-text: https://doi.org/10.1016/S2666-5247(20)30089-6

Lucky pigs. The authors intranasally inoculated twelve fruit bats (Rousettus aegyptiacus), 12 ferrets (Mustela putorius), pigs (Sus scrofa domesticus), and 20 chickens (Gallus gallus domesticus) with TCID50 of a SARS-CoV-2 isolate per animal. Pigs and chickens could not be infected intranasally or oculo-oronasally by SARS-CoV-2, whereas fruit bats showed characteristics of a reservoir host. Virus replication in ferrets resembled a subclinical human infection with efficient spread.

Diagnostics

Dharavath B, Yadav N, Desai N, et al. **A one-step, one-tube real-time RT-PCR based assay with an automated analysis for detection of SARS-CoV-2**. Heliyon. July 07, 2020. Full-text: https://doi.org/10.1016/j.heliyon.2020.e04405

The authors present a rapid, easy-to-implement real-time PCR based assay with automated analysis using a novel COVID qPCR Analyzer tool with graphical user interface to analyze the raw qRT-PCR data in an unbiased manner at a cost of less than $3 per reaction and turn-around time of less than 2h, to enable in-house SARS-CoV-2 testing across laboratories.

Wang Y, Zhang L, Sang L, et al. **Kinetics of viral load and antibody response in relation to COVID-19 severity**. J Clin Invest. 2020 Jul 7:138759. PubMed: https://pubmed.gov/32634129. Full-text: https://doi.org/10.1172/JCI138759

In 8/12 patients with severe COVID-19, viral shedding was shown in a variety of tissues for 20~40 days post-onset of disease; in contrast 9/11 patients with mild disease had viral shedding restricted to the respiratory tract and had no detectable virus RNA after 10 days post-onset.

Treatment

Gladstone DE, Kim BS, Mooney K, et al. **Regulatory T Cells for Treating Patients With COVID-19 and Acute Respiratory Distress Syndrome: Two Case Reports.** Ann Int Med 2020, Jul 6. Full-text: https://www.acpjournals.org/doi/10.7326/L20-0681

Regulatory T cells (also known as T_{regs}) migrate into inflamed tissues, dampening inflammatory responses and hastening tissue repair. Two patients who became critically ill despite receiving tocilizumab were treated with T_{regs} and recovered. Infusions were rapidly followed by decreases in interleukin-6, tumor necrosis factor-α, and interferon-γ.

9 July

Epidemiology

Saloner B, Parish K, Ward JA. **COVID-19 Cases and Deaths in Federal and State Prisons.** JAMA July 8, 2020. Full-text: https://doi.org/10.1001/jama.2020.12528

By June 6, 2020, there had been 42,107 cases of COVID-19 and 510 deaths among 1.3 million prisoners in the US. The case rate was initially lower in prisons but surpassed the US population on April 14, 2020. The mean daily case growth rate was 8.3% per day in prisons and 3.4% per day in the US population.

Maxmen A. **California's San Quentin prison declined free coronavirus tests and urgent advice — now it has a massive outbreak.** Nature NEWS 07 July 2020. Full-text: https://doi.org/10.1038/d41586-020-02042-9

And this is a story behind the numbers. San Quentin Prison, which got through most of May without a single reported case among inmates, is now dealing with the third-largest coronavirus outbreak in the US. More than one-third of the inmates and staff (1,600 people) have tested positive. Six have died. Researchers fear that other institutions are at risk.

Transmission

Chen J, He H, Cheng W, et al. **Potential transmission of SARS-CoV-2 on a flight from Singapore to Hanghzou, China: An epidemiological investigation.** J Trav Med 2020, Jul 6, 2020. Full-text: https://doi.org/10.1016/j.tmaid.2020.101816

Among 335 passengers on a flight from Singapore to Hangzhou in China (a Boeing 787, 5-hour flight, seat occupancy 89%), a total of 16 COVID-19 patients were diagnosed among all passengers, yielding an attack rate of 4.8%. However, after careful investigation, only one case was identified who appears to have become infected during the flight. He was seated near four infected passengers from Wuhan for approximately an hour (he had moved a seat) and did not wear his facemask correctly during the flight. The sources of infection in the other 15 passengers were complex and the passengers could have acquired their infections in Wuhan before the tour, or during the group tour before boarding.

Clinical

Williamson EJ, Walker AJ, Bhaskaran K et al. **OpenSAFELY: factors associated with COVID-19 death in 17 million patients**. Nature 08 July 2020 (2020). Full-text: https://doi.org/10.1038/s41586-020-2521-4 ● (IMPORTANT)

Using a secure health analytics platform covering 40% of all patients in England, primary care records of 17,278,392 adults were pseudonymously linked to 10,926 COVID-19-related deaths. COVID-19-related death was associated with being male (hazard ratio 1.59, 95% CI 1.53–1.65); older age and deprivation, ie marginalized, (both with a strong gradient); diabetes; severe asthma; and various other medical conditions. Compared with people with white ethnicity, Black and South Asian people were at higher risk even after adjustment for other factors (HR 1.48 and 1.44, respectively).

Patterson RW, Brown RL, Benjamin L, et al. **The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings**. Brain 08 July 2020. Full-text: https://doi.org/10.1093/brain/awaa240

A broad spectrum of neurological complications: among 43 patients (29 with confirmed diagnosis) admitted to a London hospital, five major categories emerged: 1. Encephalopathies (n = 10) with delirium/psychosis and no distinct MRI or CSF abnormalities 2. Inflammatory CNS syndromes (n = 12) including encephalitis 3. Ischemic strokes (n = 8) 4. Peripheral neurological disorders (n = 8), seven with Guillain-Barré syndrome. 5. Miscellaneous central disorders (n = 5) who did not fit these categories.

Liu YC, Ang M, Ong HS, et al. **SARS-CoV-2 infection in conjunctival tissue**. Lancet Resp Med July, 2020. Full-text: https://doi.org/10.1016/S2213-2600(20)30272-1

Is the conjunctival epithelium a potential portal of infection? These authors doubt it. A brief review on current knowledge is given.

Severe COVID-19

Ackermann M, Verlden SE, Kuehnel M, et al. **Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19**. NEJM July 9, 2020; 383:120-128. Full-text: https://doi.org/10.1056/NEJMoa2015432 ● (IMPORTANT)

This study examined the morphologic and molecular features of seven lungs obtained during autopsy from COVID-19 patients and found three distinctive angiocentric features: 1. Severe endothelial injury associated with intracellular virus and disrupted endothelial cell membranes. 2. Widespread vascular thrombosis with microangiopathy and occlusion of alveolar capillaries (9 times as prevalent as in patients with influenza). 3. significant new vessel growth through a mechanism of intussusceptive angiogenesis (2.7 x higher).

Comorbidities

Panepinto JA, Brandow A, Mucalo L, et al. **Coronavirus disease among persons with sickle cell disease, United States, March 20–May 21, 2020**. Emerg Infect Dis. 2020 Oct. Full-text: https://doi.org/10.3201/eid2610.202792

Sickle cell disease (SCD) disproportionately affects Black or African-American persons in the United States and can cause multisystem organ damage and reduced lifespan. Among 178 persons with SCD in the US who were reported to an SCD–coronavirus disease case registry, 122 (69%) were hospitalized and 13 (7%) died. According to the authors, this is alarming, given that the mean patient age was < 40 years. However, there may be bias toward more severe cases in this registry.

Treatment

Wadman M. **Can boosting interferons, the body's frontline virus fighters, beat COVID-19?** Science News Jul 8, 2020. Full-text: https://doi.org/10.1126/science.abd7137

Brief overview on current trials evaluating synthetic interferons given before or soon after infection, in order to tame the virus before it causes serious disease. Controlled clinical trials are eagerly awaited.

Pediatrics

Parri N, Lenge M, Buonsenso D, et al. **Children with Covid-19 in Pediatric Emergency Departments in Italy**. N Engl J Med 2020; 383:187-190, July 9, 2020. Full-text: https://doi.org/10.1056/NEJMc2007617

Of 100 children (median age 3 years), 21% were asymptomatic, 58% had mild disease, 19% had moderate disease, 1% had severe disease, and 1% were in critical condition. The incidence of transmission through apparent exposure to a family cluster was lower than that in other cohorts, possibly because of the late lockdown in Italy.

10 July

Epidemiology

Houlihan CF, Vora N, Byrne T, et al. **Pandemic peak SARS-CoV-2 infection and seroconversion rates in London frontline health-care workers**. Lancet July 09, 2020. Full-text: https://doi.org/10.1016/S0140-6736(20)31484-7

A total of 200 high-risk frontline HCWs were enrolled between March 26 and April 8 in a prospective cohort study in an acute National Health Service hospital trust in London. 25% of HCWs were already seropositive at enrolment and a further 20% became seropositive within the first month of follow-up. Most infections occurred between March 30 and April 5, the week with the highest number of new cases in London.

The Lancet. **COVID-19: the worst may be yet to come**. Lancet July 11, 2020. Full-text: https://doi.org/10.1016/S0140-6736(20)31517-8

What a depressing editorial. Don't read this if you're in a bad mood. Five months after WHO declared the SARS-CoV-2 outbreak a global health emergency, the virus continues to beat a concerning and complex path. For much of the globe, the worst may be yet to come.

Watsa M. **Rigorous wildlife disease surveillance**. Science 10 Jul 2020, 369: 145-147. Full-text: https://doi.org/10.1126/science.abc0017

There are no international or national conventions on pathogen screening associated with animals, animal products or their movements. Capacity for emerging infectious disease (EID) diagnostics is limited along much of the human-wildlife interface. EID risks associated with the wildlife trade remain the largest unmet challenge of current disease surveillance efforts. According

to this comment, an internationally recognized standard for managing wildlife trade on the basis of known disease risks should be established.

Immunology

Zost SJ, Gilchuk P, Chen RE et al. **Rapid isolation and profiling of a diverse panel of human monoclonal antibodies targeting the SARS-CoV-2 spike protein**. Nat Med Jul 10, 2020. Full-text: https://doi.org/10.1038/s41591-020-0998-x

Using a rapid antibody discovery platform, the authors isolated hundreds of human monoclonal antibodies (mAbs) against the SARS-CoV-2 spike protein. Antibodies could be grouped into five binding patterns on the basis of domain recognition and cross-reactivity. There were 178 mAbs that recognized the RBD domain and 43 that recognized the NTD domain. Most of the neutralizing antibodies (67/70) mapped to the RBD, revealing the RBD to be the principal site of vulnerability for SARS-CoV-2 neutralization.

Transmission

Rockett RJ, Arnott A, Lam C, et al. **Revealing COVID-19 transmission in Australia by SARS-CoV-2 genome sequencing and agent-based modeling**. Nat Med 2020 Jul 9. PubMed: https://pubmed.gov/32647358. Full-text: https://doi.org/10.1038/s41591-020-1000-7

These researchers examined the added value of near real-time genome sequencing of SARS-CoV-2 in a subpopulation of infected patients during the first 10 weeks of COVID-19 containment in Australia. Genomic evidence was used to cluster 38.7% (81 out of 209) of cases for which the available epidemiological data could not identify direct links. This included clustering 12.4% (26 out of 209) of cases with a history of recent arrival from overseas with other cases without a travel history and 5.3% (11/209) of locally acquired cases with unknown epidemiological links. Twenty-two (10.5%) of the 209 cases were epidemiologically classified as 'locally acquired—contact not identified'.

Mueller AV, Eden MJ, Oakes JM, et al. **Quantitative Method for Comparative Assessment of Particle Removal Efficiency of Fabric Masks as Alternatives to Standard Surgical Masks for PPE**. Matter July 09, 2020. Full-text: https://doi.org/10.1016/j.matt.2020.07.006

The effectiveness of masks to protect wearers from airborne particles is known to be a function of both materials and fit. The authors present a rapid testing protocol for evaluation of loose-fitting type masks to provide quanti-

tative, intercomparable data for particle removal efficacy of masks made with different types of fabrics and with different designs/fits, independently providing an assessment of the quality of the mask fit and the material used. Commercial surgical masks marketed for medical use had mean particle removal efficiencies from 50-75% when worn as designed but up to 90% when close fitting to the face under a nylon layer. Cloth masks tested had widely varying mean particle removal efficiencies (< 30% to near 90%), with some cloth masks achieving similar particle removal efficiencies as commercial surgical masks.

Diagnostics

Mathers AJ. **The practical challenges of making clinical use of the quantitative value for SARS-CoV-2 viral load across several dynamics.** Clin Infect Dis. 2020 Jul 10:ciaa958. Full-text: https://doi.org/10.1093/cid/ciaa958

Review of several hurdles and nuances which need to be addressed to deploy Ct value as a meaningful clinical metric. Facing the variability of specimen collection and different diagnostic platforms with varying sensitivity, laboratory professionals will need to develop a standard equivalency across their own diagnostic platforms and specimen types.

Clinical

Gupta A, Madhavan MV, Sehgal K. et al. **Extrapulmonary manifestations of COVID-19.** Nat Med Jul 10, 2020. https://doi.org/10.1038/s41591-020-0968-3 ● (IMPORTANT)

This article reviews the extrapulmonary organ-specific pathophysiology, presentations and management considerations for patients with COVID-19 (248 references!). These conditions include thrombotic complications, myocardial dysfunction and arrhythmia, acute coronary syndromes, acute kidney injury, gastrointestinal symptoms, hepatocellular injury, hyperglycemia and ketosis, neurologic illnesses, ocular symptoms, and dermatologic complications.

Faghy MA, Ashton RE, Maden-Wilkinson TM, et al. **Integrated sports and respiratory medicine in the aftermath of COVID-19**. Lancet Resp Med July 09, 2020. Full-text: https://doi.org/10.1016/S2213-2600(20)30307-6

The long-term effects on recovering patients remains unknown. According to this commentary, we must marshal our resources and develop strong collaborative approaches that combine clinical and sports medicine disciplines.

Pediatrics

Davies P, Evans C, Kanthimathinathan HK. **Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study**. Lancet Child Adolesc Health July 09, 2020. Full-text: https://doi.org/10.1016/S2352-4642(20)30215-7

In 78 cases of PIMS-TS reported by 21 of 23 centres in the UK, male patients (67%) and those from ethnic minority backgrounds (78%) were overrepresented. In total, 36 (46%) were invasively ventilated and 28 (36%) had evidence of coronary artery abnormalities (18 aneurysms and ten echogenicity). Three children needed ECMO and two children died.

11 July

Epidemiology

Torres JP, Piñera C, De La Maza V, et al. **SARS-CoV-2 antibody prevalence in blood in a large school community subject to a Covid-19 outbreak: a cross-sectional study**. Clin Infect Dis. 2020 Jul 10:ciaa955. PubMed: https://pubmed.gov/32649743. Full-text: https://doi.org/10.1093/cid/ciaa955

In this school-based outbreak in Santiago, Chile identified on March 12, affecting nearly 50 people among school and household members, antibody positivity rates based on a self-administered test were 9.9% for 1,009 students and 16.6% for 235 staff. Among students, positivity was associated with younger age ($p = 0.01$), lower grade level ($p = 0.05$), prior RT-PCR positivity ($p = 0.03$), and history of contact with a confirmed case ($p < 0.001$). Among staff, positivity was higher in teachers ($p = 0.01$) and in those previously RT-PCR positive ($p < 0.001$). Teachers were more affected during the outbreak and younger children were at higher infection risk, likely because index case(s) were teachers and/or parents from preschool. Reopening schools should focus on avoiding new cases among teachers.

Virology

Wong YC, Lau SY, Wang KK, et al. **Natural transmission of bat-like SARS-CoV-2ΔPRRA variants in COVID-19 patients**. Clin Infect Dis July 10, 2020. Full-text: https://doi.org/10.1093/cid/ciaa953

SARS-CoV-2 contains the furin cleavage PRRA motif in the S1/S2 region, which enhances viral pathogenicity but is absent in closely related bat and pangolin coronaviruses. It remains unknown if bat-like coronaviral variants without PRRA (ΔPRRA) can establish natural infection in humans. In this study, these variants were readily detected among acute patients, including a family cluster showing that these variants exist naturally and are currently transmitting in COVID-19 patients. Although these variants only consisted of a very small fraction in the wild type viral challenge stock, they were also consistently detected in intranasally inoculated hamsters.

Immunology

Lee JS, Park S, Jeong W, et al. **Immunophenotyping of COVID-19 and influenza highlights the role of type I interferons in development of severe COVID-19**. Science Immunology 10 Jul 2020: Vol. 5, Issue 49. Full-text: https://doi.org/10.1126/sciimmunol.abd1554

Delayed IFN-I response contributes to pathological inflammation whereas early IFN-I response controls viral replication. The authors performed single-cell RNA-seq using tens of thousands of peripheral blood mononuclear cells (PBMCs) obtained from 4 healthy donors, 8 patients with mild or severe COVID-19, and 5 patients with severe influenza. Patients with COVID-19 exhibited hyper-inflammatory signatures across all types of cells among PBMCs, particularly up-regulation of the TNF/IL-1β-driven inflammatory response as compared to severe influenza. The IFN-I response might contribute to the hyper-inflammatory response by potentiating TNF/IL-1β-driven inflammation in severe progression of COVID-19.

Transmission

Dorfman D, Raz M. **Mask Exemptions During the COVID-19 Pandemic—A New Frontier for Clinicians**. JAMA Health Forum July 10, 2020. Full-text: https://jamanetwork.com/channels/health-forum/fullarticle/2768376

While masking remains contentious, there is bipartisan agreement among policy makers that medical exemptions for masking are necessary and appropriate. Yet there is a dearth of guidance for clinicians on how to approach a request for an exemption. The authors analyze the medical and legal standards to guide this debate. In this evidence-free zone, clinicians must make individual determinations as to whether a patient should be exempt from mask wearing. There is no obligation to provide a mask exemption to patients if it is not medically warranted.

Clinical

Carfi A, Bernabei R, Landi F. **Persistent Symptoms in Patients After Acute COVID-19**. JAMA July 9, 2020. Full-text: https://doi.org/10.1001/jama.2020.12603 ● (IMPORTANT)

Long time to recover: 143 patients discharged from the hospital after recovery from COVID-19 were assessed for follow-up post–acute care after a mean of 60 days after onset of the first COVID-19 symptom. Only 18 (12.6%) were completely free of any COVID-19 related symptom, while 32% had 1 or 2 symptoms and 55% had 3 or more. None of the patients had fever or any signs or symptoms of acute illness. Worsened quality of life was observed among 44.1% of patients. Many patients still reported fatigue (53%), dyspnea (43%), joint pain (27%) and chest pain (28%).

Severe COVID

Liao D, Zhou F, Luo L, et al. **Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study**. Lancet Hematology July 10, 2020. Full-text: https://doi.org/10.1016/S2352-3026(20)30217-9

This retrospective cohort study focussed on hematological and coagulation parameters in patients with moderate, severe, and critical COVID-19, along with specific analyses of coagulopathy in non-survivors. Among 380 patients, thrombocytopenia was more frequent in patients with critical disease (49%) than in those with severe (14%) or moderate (6%). In multivariate analyses, death was associated with increased neutrophil to lymphocyte ratio (odds ratio 5.39), thrombocytopenia (OR 8.33), prolonged prothrombin time (OR 4.94), and increased D-dimer (OR 4.41). The onset of sepsis-induced coagulopathy was typically before overt disseminated intravascular coagulation.

Kander T. **Coagulation disorder in COVID-19**. Lancet Hematology July 10, 2020. Full-text: https://doi.org/10.1016/S2352-3026(20)30218-0

Careful comment on these findings. According to the author, the study is a valuable contribution to the knowledge of the coagulation profile of patients with COVID-19 and highlights the established role of routine coagulation tests as predictive variables for mortality and morbidity. However, the question of whether the observed changes in routine coagulation tests are just markers of the severity of illness or whether they show a significant and specific pathophysiology that drives morbidity and mortality in itself is still unanswered.

Moezinia CH, Ji-Xu A, Azari A, et al. **Iloprost for COVID-19-related vasculopathy**. Lancet Rheumatology July 10, 2020. Full-text: https://doi.org/10.1016/S2665-9913(20)30232-0

Interesting new finding: iloprost as a therapy to mitigate the pathological effects of COVID-19. Iloprost is a prostacyclin receptor agonist that promotes vasodilation of circulatory beds with minimal impact on hemodynamic parameters. It is licensed for the treatment of pulmonary arterial hypertension and is widely used for the management of peripheral vascular disease and digital vasculopathy, including digital ulcers and critical digital ischemia in systemic sclerosis. The authors describe three morbidly obese patients with severe COVID-19 and systemic microvasculopathy who obviously benefitted from its use. Its potential ability to reduce endothelial dysfunction and systemic inflammation could make iloprost a key player in management of COVID-19 vasculopathy.

Comorbidities

Ikematsu H, Hayden FG, Kawaguchi K, et al. **Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts**. NEJM July 8, 2020. Full-text: https://doi.org/10.1056/NEJMoa1915341

How will we deal with influenza next winter? Baloxavir marboxil (baloxavir) is a prodrug of the cap-dependent endonuclease inhibitor baloxavir acid and was approved as a single-dose treatment for uncomplicated influenza A and B in Japan and in the US in 2018. Among 752 household contacts of 545 index patients (96% influenza A) virus infection, the percentage in whom clinical influenza developed was significantly lower in the baloxavir group than in the placebo group (1.9% vs. 13.6%).

Uyeki TM. **Baloxavir for Postexposure Prophylaxis against Influenza in Households**. NEJM July 8, 2020. Full-text: https://doi.org/10.1056/NEJMe2022702

This editorial discusses some caveats of the above trial, including resistance issues. Moreover, 73% of the household contacts received baloxavir or placebo rapidly - within 24 hours after the onset of illness. Last but not least, clinicians are reminded that the primary prevention of influenza is through annual influenza vaccination. We have to be prepared next winter.

12 July

Epidemiology

Verdery AM, Smith-Greenaway E, Margolis R, Daw J. **Tracking the reach of COVID-19 kin loss with a bereavement multiplier applied to the United States**. Proc Natl Acad Sci U S A. 2020 Jul 10:202007476. PubMed: https://pubmed.gov/32651279. Full-text: https://doi.org/10.1073/pnas.2007476117

Multiply deaths by nine. These authors created a “bereavement multiplier", an indicator that clarifies the downstream impact of COVID-19 mortality and can be applied to different epidemiological projections of death counts: how many people are at risk for losing a grandparent, parent, sibling, spouse, or child for each COVID-19 death. In the US, every death from COVID-19 will leave approximately nine bereaved.

Fenton MB. **Bats navigate with cognitive maps**. Science 10 Jul 2020: Vol. 369, Issue 6500, pp. 142. Full-text: https://doi.org/10.1126/science.abd1213

Interested in bats these days? They are smart. And they know where they are. This article summarizes current research on the path-finding strategies of fruit bats. Bats do not systematically follow known routes, nor do they directly sense cues such as landmarks or beacons: they rely on a cognitive map frame of reference for their current positions in relation to a goal that they had not yet detected.

Clinical

Wortham JM, Lee JT, Althomsons S, et al. **Characteristics of Persons Who Died with COVID-19 — United States, February 12–May 18, 2020**. MMWR Morb Mortal Wkly Rep. ePub: 10 July 2020. Full-text: http://dx.doi.org/10.15585/mmwr.mm6928e1

Using national case-based surveillance and supplementary data reported from 16 jurisdictions, detailed characteristics of 10,647 COVID-19 deaths that occurred during February 12–April 24, 2020 are described. More than one third of Hispanic decedents (34.9%) and nearly one third (29.5%) of non-white decedents were aged < 65 years, but only 13.2% of white decedents were aged < 65 years. Most decedents had one or more underlying medical conditions reported (76.4%) or were aged ≥ 65 years (74.8%). Among reported underlying medical conditions, cardiovascular disease and diabetes were the most common.

Kirschenbaum D, Imbach LL, Ulrich S, et al. **Inflammatory olfactory neuropathy in two patients with COVID-19**. Lancet July 10, 2020. Full-text: https://doi.org/10.1016/S0140-6736(20)31525-7

Post-mortem histological analysis of the olfactory epithelium in two COVID-19 patients showed prominent leukocytic infiltrates in the lamina propria and focal atrophy of the mucosa. However, it is unclear whether the observed inflammatory neuropathy is a result of direct viral damage or is mediated by damage to supporting non-neural cells.

Hengeveld PJ, Omar Khader A, de Bruin LHA, et al. **Blood cell counts and lymphocyte subsets of patients admitted during the COVID-19 pandemic: a prospective cohort study**. Br J Haematol. 2020 Jul 11. PubMed: https://pubmed.gov/32652585. Full-text: https://doi.org/10.1111/bjh.16983

Based on ICU admission or death during hospital admission, 197 COVID-19 patients were compared with 354 patients in whom COVID-19 was ruled out (controls). At admission, anemia, leukocytosis and neutrophilia were more prevalent in controls than in COVID-19 patients. In agreement with recent reports, thrombocyte counts were lower in COVID-19 patients, and thrombocytopenia was associated with an increased risk of in-hospital mortality.

Diagnostics

Fung B, Gopez A, Servellita V, et al. **Direct Comparison of SARS-CoV-2 Analytical Limits of Detection across Seven Molecular Assays**. J Clin Microbiol. 2020 Jul 10:JCM.01535-20. PubMed: https://pubmed.gov/32651238. Full-text: https://jcm.asm.org/content/early/2020/07/09/JCM.01535-20

The authors have determined analytical limits of detection for seven SARS-CoV-2 assays using serial dilutions of pooled patient material quantified with droplet digital PCR. Limits of detection ranged from ≤ 10-74 copies/mL for commercial high-throughput laboratory analyzers (Roche Cobas, Abbott m2000, Hologic Panther Fusion) and 167-511 copies/mL for sample to answer (Diasorin Simplexa, Genmark ePlex) and point-of-care instruments (Abbott ID NOW). The CDC assay yielded limits of detection ranging from 85-499 copies/mL, depending on the extraction method and thermocycler used.

Treatment

Beigel JH, Tomashek KM, Dodd LE, et al. **Remdesivir for the Treatment of Covid-19 - Preliminary Report. Reply**. N Engl J Med 2020 Jul 10;383. Full-text: https://doi.org/10.1056/NEJMc2022236

Discussion about the preliminary report on the large Phase III US trial of remdesivir (remember the Fauci press conference). Several letters elucidate the challenges arising from the dissemination of early results. The authors promise solemly that they have begun to analyze the final data and will revise the report after that analysis is complete, including a more detailed analyses of the duration of illness and its relationship to baseline disease severity and outcomes, as well as concomitant medications during the trial. Why this seemingly takes months (perceived years), remains unclear. We are very curious.

Somers EC, Eschenauer GA, Troost JP, et al. **Tocilizumab for treatment of mechanically ventilated patients with COVID-19**. Clin Infect Dis. 2020 Jul 11. PubMed: https://pubmed.gov/32651997. Full-text: https://doi.org/10.1093/cid/ciaa954

Comparison of 78 patients who received tocilizumab (TCZ) and 76 who did not. TCZ-treated patients were younger, less likely to have chronic pulmonary disease, and had lower D-dimer values at time of intubation. In IPTW-adjusted models, tocilizumab was associated with a 45% reduction in hazard of death and improved status on the ordinal outcome scale. Though tocilizumab was associated with an increased proportion of patients with superinfections (54% vs. 26%, mainly S. aureus), there was no difference in 28-day case fatality rate among TCZ-treated patients with versus without superinfection. We urgently need adequately powered RCT.

Wise J, Coombes R. Covid-19: **The inside story of the RECOVERY trial**. BMJ 2020; 370 Full-text: https://doi.org/10.1136/bmj.m2670

The UK's flagship COVID-19 clinical trial may help in this regard. Patients enrolled in the open label RECOVERY trial are randomised to standard care or to one of six treatment arms: hydroxychloroquine (now closed), dexamethasone (also closed, press release June 16), lopinavir/ritonavir, azithromycin, convalescent plasma, and, in a second randomisation for patients who deteriorate, the anti-inflammatory drug tocilizumab. The authors unpack the criticisms that still surround this mammoth task, of mounting a large scale trial amid the first major pandemic in 100 years in record time.

Pregnancy

Khalil A, von Dadelszen P, Draycott T, et al. **Change in the Incidence of Stillbirth and Preterm Delivery During the COVID-19 Pandemic**. JAMA July 10, 2020. Full-text: https://doi.org/10.1001/jama.2020.12746

Pregnancy outcomes at St George's University Hospital, London, were evaluated in two periods: from October 2019 to January 2020 and from February to June 2020. The incidence of stillbirth was significantly higher during the pandemic period (9.31 per 1000) than during the pre-pandemic period (2.38 per 1000). Of note, the increase in stillbirths may have also resulted from indirect effects such as reluctance to attend hospital when needed, fear of contracting infection, or not wanting to add to the National Health Service burden. Changes in obstetric services may have played a role secondary to staff shortages or reduced antenatal visits, ultrasound scans, and/or screening.

13 July

Virology

Chan KH, Sridhar S, Zhang RR, et al. **Factors affecting stability and infectivity of SARS-CoV-2**. J Hosp Infect. 2020 Jul 8. PubMed: https://pubmed.gov/32652214. Full-text: https://doi.org/10.1016/j.jhin.2020.07.009

Dry heat is bad, damp cold is good (for the virus). Dried SARS-CoV-2 virus on glass retained viability for over 3-4 days at room temperature and for 14 days at 4°C, but lost viability rapidly (within one day) at 37°C. SARS-CoV-2 in solution remained viable for much longer under the same different temperature conditions. Commonly used fixatives, nucleic acid extraction methods and heat inactivation were found to significantly reduce viral infectivity.

Wang X, Xu W, Hu G, et al. **Retraction Note to: SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion**. Cell Mol Immunol (2020). Full-text: https://doi.org/10.1038/s41423-020-0498-4

The authors have retracted this article (which has been discussed in the Virology chapter of the 4th issue of covidreference.com) after it came to the authors' attention that in order to support the conclusions of the study, the authors should have used primary T cells instead of T cell lines. In addition, there were concerns that the flow cytometry methodology applied here was

flawed. These points resulted in the conclusions being considered invalid. The question remains why the reviewers (a highly ranked Cell journal would have at least 2-4 for each paper) did not see this. But again, good news: bad science will not stand the test of time.

Abritis A, Marcus A, Oransky I. **An 'alarming' and 'exceptionally high' rate of COVID-19 retractions?** Account Res. 2020 Jul 7. PubMed: https://pubmed.gov/32634321. Full-text: https://doi.org/10.1080/08989621.2020.1793675

While we're at it: See the title. The authors say no. It should also be noted that COVID-19 papers are being subjected to a high rate of scrutiny, which means that flaws are being detected more frequently than they might otherwise.

Transmission

Xie W, Campbell S, Zhang W. **Working memory capacity predicts individual differences in social-distancing compliance during the COVID-19 pandemic in the United States**. Proc Natl Acad Sci U S A. 2020 Jul 10:202008868. PubMed: https://pubmed.gov/32651280. Full-text: https://doi.org/10.1073/pnas.2008868117

Among 850 US residents participating in a survey, the authors found that social distancing compliance could be predicted by individual differences in working memory (WM) capacity. WM retains a limited amount of information over a short period of time at the service of other ongoing mental activities. Its limited capacity constrains our mental functions, such that higher WM capacity is often associated with better cognitive and affective outcomes. Of note, the unique contribution of WM capacity to the individual differences in social distancing compliance could not be explained by other psychological and socioeconomic factors (e.g., moods, personality, education, and income levels). The message that the authors hide using scientific language can be said more clearly: if you see a guy sitting in the bus not wearing a mask: poor idiot, don't get closer. His WM capacity is poor.

Clinical

Smithgall MC, Dowlatshahi M, Spitalnik SL. **Types of Assays for SARS-CoV-2 Testing: A Review** Laboratory Medicine, 2020, Jul 13. Full-text: https://doi.org/10.1093/labmed/lmaa039

Comprehensive review of multiple novel assays for SARS-CoV-2 diagnosis, including molecular and serologic-based tests, some with point-of-care testing capabilities.

Prevention

Rodriguez-Martinez CE, Sossa-Briceño MP, Cortés-Luna JA. **Decontamination and reuse of N95 filtering facemask respirators: a systematic review of the literature**. Am J Infect Control. 2020 Jul 8:S0196-6553(20)30690-8. PubMed: https://pubmed.gov/32652253. Full-text: https://doi.org/10.1016/j.ajic.2020.07.004

Again, put your masks in the sun. But not too often as at higher UV dosages and cycles, strengths of the material can be reduced. The maximum number of cycles under different conditions is still unclear. However, among 14 studies reporting on the different decontamination methods that might allow disposable N95 FFRs to be reused, ultraviolet germicidal irradiation (UVGI) and vaporized hydrogen peroxide (VHP) seem to be the most promising decontamination methods for N95 FFRs. This is based on their biocidal efficacy, filtration performance, fitting characteristics, and residual chemical toxicity, as well as other practical aspects such as the equipment required for their implementation and the maximum number of decontamination cycles.

Clinical

Shafi AMA, Shaikh SA, Shirke MM, Iddawela S, Harky A. **Cardiac manifestations in COVID-19 patients-A systematic review**. J Card Surg. 2020 Jul 11. PubMed: https://pubmed.gov/32652713. Full-text: https://doi.org/10.1111/jocs.14808

This literature review includes 61 articles on a wide array of cardiovascular manifestations (including heart failure, cardiogenic shock, arrhythmia, and myocarditis among others) and cardiac-specific biomarkers (including CK-MB, CK, myoglobin, troponin, and NT-proBNP) as prognostic tools. But who did review this review? In the methods, there is no date re: when this analysis was performed.

Naeini AS, Karimi-Galougahi M, Raad N, et al. **Paranasal sinuses computed tomography findings in anosmia of COVID-19**. Am J Otolaryngol. 2020 Jul 3;41(6):102636. PubMed: https://pubmed.gov/32652405. Full-text: https://doi.org/10.1016/j.amjoto.2020.102636

Interesting finding: among 49 confirmed COVID-19 patients with anosmia, there were no significant pathological changes in the paranasal sinuses on CT scans. Olfactory cleft and ethmoid sinuses appeared normal while in other sinuses, partial opacification was detected only in some cases. Conductive causes of anosmia (i.e., mucosal disease) do not seem play a significant role.

Nemati M, Ansary J, Nemati N. **Machine Learning Approaches in COVID-19 Survival Analysis and Discharge Time Likelihood Prediction using Clinical Data**. Pattern July 10, 2020. Full-text: https://doi.org/10.1016/j.patter.2020.100074

How many patients stay how long in which hospital unit? This work introduces statistical models and machine learning (ML)-based approaches that can be directly applied to real-world COVID-19 data to predict the patient discharge time from hospital and evaluate how the patient clinical information could have an impact on the length of stay in hospital. These estimations are important for decision-makers for efficient allocation of equipment and managing hospital overload.

Treatment

Davis MR, McCreary EK, Pogue JM. **That Escalated Quickly: Remdesivir's Place in Therapy for COVID-19**. Infect Dis Ther. 2020 Jul 10. PubMed: https://pubmed.gov/32651941. Full-text: https://doi.org/10.1007/s40121-020-00318-1

After reviewing all remdesivir studies until May 31, the authors make some recommendations on use. Remdesivir (5 days) should be prioritized for hospitalized patients requiring low-flow supplemental oxygen as it appears these patients derive the most benefit. The data also support some benefit in hospitalized patients breathing ambient air (if there is adequate drug supply). Current data do NOT suggest benefit for those requiring high-flow oxygen or either non-invasive or invasive mechanical ventilation. While it appears that progression of disease plays an important role in the efficacy of remdesivir, the amount of time from onset of symptoms does not.

14 July

Epidemiology

Rincón A, Moreso F, López-Herradón A. **The keys to control a coronavirus disease 2019 outbreak in a haemodialysis unit**. Clinical Kidney Journal, 13 July 2020. Full-text: https://doi.org/10.1093/ckj/sfaa119

Outbreak in an hemodialysis unit in Barcelona, involving 18% of patients receiving treatment in this facility. In total, 22 symptomatic and 14 of the 170 asymptomatic patients became infected. The main risk factors for SARS-CoV-2 infection were sharing health-care transportation, living in a nursing home and having been admitted to the reference hospital within the previous 2 weeks.

Virology

Pollock DD, Castoe TA, Perry BW, et al. **Viral CpG deficiency provides no evidence that dogs were intermediate hosts for SARS-CoV-2**. Mol Biol Evol. 2020 Jul 13. PubMed: https://pubmed.gov/32658964 . Full-text: https://doi.org/10.1093/molbev/msaa178

No, dogs are not intermediate hosts. The authors clearly refute the conclusions of another group that dogs are a likely intermediate host of a SARS-CoV-2 ancestor, highlighting major flaws in the inference process and analysis.

Immunology

Hadjadj J, Yatim N, Barnabei L. **Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients**. Science 13 Jul 2020. Full-text: https://doi.org/10.1126/science.abc6027

Not the first, but the largest study to date, analyzing the integrated immune analysis on a cohort of 50 COVID-19 patients with various disease severity. The picture is clearer now: SARS-CoV-2 infection is characterized by an absence of circulating IFN-β with all disease-severity grades. In addition, most severe COVID-19 patients display impaired IFN-α production that is associated with lower viral clearance and an exacerbated inflammatory response. Inflammation is partially driven by the transcriptional factor NF-κB and characterized by increased tumor necrosis factor (TNF)-α and interleukin (IL)-6 production and signaling.

Ovsyannikova IG, Haralambieva IH, Crooke SN, Poland GA, Kennedy RB. **The role of host genetics in the immune response to SARS-CoV-2 and COVID-19 susceptibility and severity**. Immunol Rev. 2020 Jul 13. PubMed: https://pubmed.gov/32658335 . Full-text: https://doi.org/10.1111/imr.12897

Individuals in the population harbor single nucleotide polymorphisms (SNPs) across a variety of genes (eg, ACE2, TMPRSS2, HLA, CD147, MIF, IFNG, IL6) that have been implicated in the pathology and immunology of SARS-CoV-2 and other pathogenic coronaviruses. This well-written review gives an overview on current knowledge on host factors involved in coronavirus infections and proposes a large research agenda.

Yuan M, Liu H, Wu NC, et al. **Structural basis of a shared antibody response to SARS-CoV-2**. Science 13 Jul 2020. Full-text: https://doi.org/10.1126/science.abd2321

Among 294 anti-SARS-CoV-2 antibodies, IGHV3-53 was the most frequently used IGHV gene for targeting the receptor-binding domain (RBD) of the spike protein. Co-crystal structures of two IGHV3-53 neutralizing antibodies with RBD revealed that the germline-encoded residues dominate recognition of the ACE2 binding site. These IGHV3-53 antibodies show minimal affinity for maturation and high potency, which is promising for vaccine design.

Diagnostics

Mallapaty S. **The mathematical strategy that could transform coronavirus testing**. Nature 10 July 2020. Full-text: https://www.nature.com/articles/d41586-020-02053-6

If you are interested in math, then this article is for you (everyone else should avoid it). Beautiful mental exercise about how to best pool samples from as many people as possible, in order to save time and/or resources. It's not that trivial. Some sophisticated strategies are discussed.

Clinical

Fauvel C, Weizman O, Trimaille A. **Pulmonary embolism in COVID-19 patients: a French multicentre cohort study**. European Heart Journal, 13 July 2020. Full-text: https://doi.org/10.1093/eurheartj/ehaa500

In this retrospective multicentre study, 103/1,240 (8.3%) consecutive patients hospitalized for COVID-19 (patients who were directly admitted to an ICU were excluded) had evidence for PE. In a multivariable analysis, male gender,

anticoagulation with a prophylactic or therapeutic dose, elevated C-reactive protein, and time from symptom onset to hospitalization were associated with PE risk. PE risk factors in the COVID-19 context do not include traditional thromboembolic risk factors but rather independent clinical and biological findings at admission, including a major contribution of inflammation.

Bäuerle A, Teufel N, Musche V. **Increased generalized anxiety, depression and distress during the COVID-19 pandemic: a cross-sectional study in Germany**. Journal of Public Health, 13 July 2020. Full-text: https://doi.org/10.1093/pubmed/fdaa106

The more you know, the more afraid you'll be of COVID-19. In this cross-sectional study on 15,704 German residents, trust in governmental actions to face COVID-19 and the subjective level of information regarding COVID-19 were negatively associated with mental health burden. However, the subjective level of information regarding COVID-19 was positively associated with increased COVID-19-related fear.

Comorbidities

Hogan AB, Jewel BL, Sherrard-Smith E, et al. **Potential impact of the COVID-19 pandemic on HIV, tuberculosis, and malaria in low-income and middle-income countries: a modelling study**. Lancet July 13, 2020. Full-text: https://doi.org/10.1016/S2214-109X(20)30288-6

The collateral damage is just as great. Using established transmission models, data indicate that in countries with a high burden of malaria, HIV and tuberculosis, COVID-19 related disruptions in care could lead to a loss of life-years of over 5 years, that is of the same order of magnitude as the direct impact from COVID-19. The authors estimate that deaths due to HIV, tuberculosis, and malaria over 5 years could increase by up to 10% due to HIV (mainly due to treatment interruptions), 20% to TB (less timely diagnosis and treatment of new cases), and 36% to malaria (interruption of planned net campaigns), respectively.

Treatment

Mak YM, Chan FK, Ng SC. **Probiotics and COVID-19 – Authors' reply**. Lancet Gastroenterology Hepatology Volume 5, ISSUE 8, P722-723, August 01, 2020. Full-text: https://doi.org/10.1016/S2468-1253(20)30197-7

COVID-19 patients have an altered gut microbiome. Well, okay, but who doesn't? Several letters discuss whether probiotics represent a complemen-

tary approach for the prevention and restoration of SARS-CoV-2-induced mucosal damage or inflammation through the modulation of gut microbiota. Some groups are optimistic, others aren't.

15 July

Today, 15 July 2020, there will be no Top 10, but the **Top 1,000**:

COVID Reference Top 10 - Daily Science (390 pages, download)

Here we publish in a single PDF our daily Top 10 papers we have presented ever since COVID Reference's first edition on 29 March 2020. There is no secret to our procedure: the daily scanning of the literature helps us to stay afloat in the never-ending waves of new publications about SARS-CoV-2 and COVID-19. Many papers discussed in the Top 10 will eventually make it into subsequent editions of COVID Reference.

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Christian Hoffmann & Bernd Sebastian Kamps

P. S.

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P. P. S.

We have also updated the Transmission chapter in order to reflect the latest WHO statement on aerosol transmission:

"There have been reported outbreaks of COVID-19 in some closed settings, such as restaurants, nightclubs, places of worship or places of work where people may be shouting, talking, or singing. In these outbreaks, aerosol transmission, particularly in these indoor locations where there are crowded and inadequately ventilated spaces where infected persons spend long periods of time with others, cannot be ruled out."

16 July

Epidemiology

Islam N, Sharp SJ, Chowell G, et al. **Physical distancing interventions and incidence of coronavirus disease 2019: natural experiment in 149 countries**. BMJ. 2020 Jul 15;370:m2743. PubMed: https://pubmed.gov/32669358. Full-text: https://doi.org/10.1136/bmj.m2743

Be fast - but don't close the metro. In this large empirical study, data from 149 countries were pooled, in order to estimate the relative effectiveness of different policy interventions within each country. Implementation of any physical distancing intervention was associated with an overall incidence reduction of 13% (IRR 0.87). Closure of public transport was not associated with any additional reduction when the other four physical distancing interventions were in place. Data from 11 countries also suggested similar overall effectiveness (IRR 0.85) when school closures, workplace closures, and restrictions on mass gatherings were in place. Earlier implementation of lockdown was associated with a larger reduction (IRR 0.86) compared with a delayed implementation of lockdown after other physical distancing interventions were in place (IRR 0.90).

Vaccine, Immunology

Jackson LA, Anderson EJ, Rouphael NG, et al. **An mRNA Vaccine against SARS-CoV-2 - Preliminary Report**. N Engl J Med. 2020 Jul 14. PubMed: https://pubmed.gov/32663912. Full-text: https://doi.org/10.1056/NEJMoa2022483

This study conducted in Washington and Atlanta evaluated the candidate vaccine mRNA-1273 that encodes the stabilized prefusion SARS-CoV-2 spike protein. In a Phase I open label trial, 45 healthy adults received two vaccinations, 28 days apart, at three different doses. Antibody responses were higher with a higher dose and further increased after the second vaccination, leading to serum-neutralizing activity in all participants. Values were similar to those in the upper half of the distribution of a panel of control convalescent serum specimens. Solicited adverse events that occurred in > 50% included fatigue, chills, headache, myalgia, and pain at the injection site.

Arnold C. **How computational immunology changed the face of COVID-19 vaccine development**. Nat Med. 2020 Jul 15. PubMed:

https://pubmed.gov/32669667. Full-text: https://doi.org/10.1038/d41591-020-00027-9

After more than two decades of work, computational immunology now enables the development of a candidate vaccine in just a few hours. However, no *in silico* analysis, no matter how high-quality the input and how exacting the computational algorithms, will ever be a substitute for experimental data.

Mathew D, Giles JR, Baxter AE, et al. **Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications**. Science 2020 Jul 15. PubMed: https://pubmed.gov/32669297. Full-text: https://doi.org/10.1126/science.abc8511

Patients differ: Analysing 125 COVID-19 patients, the authors identified three "immunotypes" associated with poorer clinical trajectories versus improving health. A subgroup of patients had T cell activation characteristic of acute viral infection and plasmablast responses reaching > 30% of circulating B cells. However, another subgroup had lymphocyte activation comparable to uninfected subjects. Stable versus dynamic immunological signatures were identified and linked to trajectories of disease severity change. This study provides a compendium of immune response data and also an integrated framework as a "map" for connecting immune features to disease. By localizing patients on an immune topology map built on this dataset, we can begin to infer which types of therapeutic interventions may be most useful in specific patients.

Le Bert N, Tan AT, Kunasegaran K, et al. **SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls**. Nature. 2020 Jul 15. PubMed: https://pubmed.gov/32668444. Full-text: https://doi.org/10.1038/s41586-020-2550-z

Is there a natural immunity? In this study, T cell responses to structural (nucleocapsid protein, NP) and non-structural (NSP-7 and NSP13 of ORF1) regions of SARS-CoV-2 were analyzed in 36 COVID-19 convalescents. In all of them, CD4 and CD8 T cells recognizing multiple regions of the NP protein were found. Surprisingly, the authors also frequently detected SARS-CoV-2 specific T cells in 37 individuals with no history of SARS, COVID-19 or contact with SARS/COVID-19 patients. These T cells exhibited a different pattern of immunodominance, frequently targeting the ORF-1-coded proteins NSP7 and 13 as well as the NP structural protein. Epitope characterization of NSP7-specific T cells showed recognition of protein fragments with low homology to "common cold" human coronaviruses but conserved amongst animal be-

tacoronaviruses. Thus, infection with betacoronaviruses induces multispecific and long-lasting T cell immunity to the structural protein NP.

Transmission

Vivanti AJ, Vauloup-Fellous C, Prevot S, et al. Transplacental transmission of SARS-CoV-2 infection. Nat Commun2020. Full-text: https://doi.org/10.1038/s41467-020-17436-6

Maybe the first documented case of transplacental transmission. French doctors report on a 23-year-old COVID-19 patient who gave birth by cesarean section to a baby found to have the infection. The viral load was much higher in the placental tissue than in the amniotic fluid or maternal blood: this suggests the presence of the virus in placental cells, which is consistent with findings of inflammation seen at histological examination. Good news: baby is fine.

Clinical

Yadav DK, Singh A, Zhang Q, et al. **Involvement of liver in COVID-19: systematic review and meta-analysis**. Gut. 2020 Jul 15:gutjnl-2020-322072. PubMed: https://pubmed.gov/32669289. Full-text: https://doi.org/10.1136/gutjnl-2020-322072

In this meta-analysis of 9 studies with a total of 2115 patients, patients with COVID-19 with liver injury were at an increased risk of severity (OR 2.57) and mortality (1.66). Thus, special attention should be given to any liver dysfunction while treating patients with COVID-19.

Belanger MJ, Hill MA, Angelidi AM, Dalamaga M, Sowers JR, Mantzoros CS. **Covid-19 and Disparities in Nutrition and Obesity**. N Engl J Med. 2020 Jul 15. PubMed: https://pubmed.gov/32668105. Full-text: https://doi.org/10.1056/NEJMp2021264

Nice perspective. Though the factors underlying racial and ethnic disparities in COVID-19 in the United States are multifaceted and complex, long-standing disparities in nutrition and obesity play a crucial role in the health inequities unfolding during the pandemic.

Zhang AJ, Lee AC, Chu H, et al. **SARS-CoV-2 infects and damages the mature and immature olfactory sensory neurons of hamsters**. Clin Infect Dis. 2020

Jul 15. PubMed: https://pubmed.gov/32667973. Full-text: https://doi.org/10.1093/cid/ciaa99532667967

Poor golden Syrian hamsters. But, this probably explains what happens in your nose. After intranasal inoculation with SARS-CoV-2, inflammatory cell infiltration and proinflammatory cytokine/chemokine responses were detected in the nasal turbinate tissues peaking between 2 to 4 days post-infection with the highest viral load detected at day 2 post-infection.

Treatment

Okafor EC, Pastick KA, Rajasingham R. **Hydroxychloroquine as Postexposure Prophylaxis for Covid-19**. Reply. N Engl J Med. 2020 Jul 15. PubMed: https://pubmed.gov/32668109. Full-text: https://doi.org/10.1056/NEJMc2023617

Some discussion on this trial in which HCQ did not work as a COVID-19 PEP. Main messages: absence of evidence is not evidence of absence. It is argued that the PEP was started too late, the trial too small and that testing capacity was limited.

17 July

Immunology

Lynch KL, Whitman JD, Lacanienta NP, et al. **Magnitude and kinetics of anti-SARS-CoV-2 antibody responses and their relationship to disease severity**. Clin Infect Dis. 2020 Jul 14. PubMed: https://pubmed.gov/32663256. Full-text: https://doi.org/10.1093/cid/ciaa979

Using a high-throughput quantitative IgM and IgG assay that detects antibodies to the spike protein receptor binding domain and nucleocapsid protein, the authors evaluated antibody kinetics and correlation between magnitude of the response and disease severity in a total of 533 sera samples from 94 acute and 59 convalescent COVID-19 patients. Compared to those with milder disease, peak measurements were significantly higher for patients admitted to the ICU for all time intervals between days 6 and 20 for IgM, and all intervals after 5 days for IgG.

Akbar AN, Gilroy DW. **Aging immunity may exacerbate COVID-19**. Science 17 Jul 2020: Vol. 369, Issue 6501, pp. 256-257. Full-text: https://doi.org/10.1126/science.abb0762

Nice brief overview on how "inflammaging", a common denominator of age-associated frailty, may contribute to the severe COVID-19 course in older people. One hypothesis is that pre-existing inflammatory cells, including senescent populations and adipocytes, create the inflammaging phenotype that amplifies subsequent inflammatory events. Nevertheless, high amounts of inflammation alone do not explain the devastating tissue destruction and it may be that age-associated changes in T cells have a role in the immunopathology.

Transmission

Hendrix MJ, Walde C, Findley K, Trotman R. **Absence of Apparent Transmission of SARS-CoV-2 from Two Stylists After Exposure at a Hair Salon with a Universal Face Covering Policy — Springfield, Missouri, May 2020**. MMWR Morb Mortal Wkly Rep. 14 July 2020. Full-text: http://dx.doi.org/10.15585/mmwr.mm6928e2

Have we ever mentioned masks? Among 139 clients exposed to two symptomatic hair stylists with confirmed COVID-19 while both the stylists and the clients wore face masks, not a single symptomatic secondary case was observed; among 67 clients tested for SARS-CoV-2, all tests were negative. At least one hair stylist was infectious: all four close household contacts (presumably without masks) became ill.

Wang X, Ferro EG, Zhou G, Hashimoto D, Bhatt DL. **Association Between Universal Masking in a Health Care System and SARS-CoV-2 Positivity Among Health Care Workers**. JAMA. 2020 Jul 14. PubMed: https://pubmed.gov/32663246. Full-text: https://doi.org/10.1001/jama.2020.12897

Again, universal masking: in March 2020, the Mass General Brigham, the largest health care system in Massachusetts (12 hospitals, > 75,000 employees), implemented universal masking of all HCWs and patients with surgical masks. During the preintervention period, the SARS-CoV-2 positivity rate increased exponentially, with a case doubling time of 3.6 days. During the intervention period, the positivity rate decreased linearly from 14.65% to 11.46%, with a weighted mean decline of 0.49% per day and a net slope change of 1.65% additional decline per day compared with the preintervention period.

Contejean A, Leporrier J, Canouï E, et al. **Comparing dynamics and determinants of SARS-CoV-2 transmissions among health care workers of adult**

and pediatric settings in central Paris. Clin Infect Dis. 2020 Jul 15:ciaa977. PubMed: https://pubmed.gov/32663849. Full-text: https://doi.org/10.1093/cid/ciaa977

This prospective study compared a 1,500-bed adult and a 600-bed pediatric setting of a university hospital located in central Paris. From February 24th until April 10th, 2020, all symptomatic HCW were screened. Attack rates were of 3.2% and 2.3% in the adult and pediatric setting, respectively (p = 0.0022). In the adult setting, HCW more frequently reported exposure to COVID-19 patients without PPE (25% versus 15%, p = 0.046). The total number of HCW cases peaked on March 23rd, then decreased slowly, concomitantly with a continuous increase in preventive measures (including universal medical masking and PPE). Residual transmissions were related to exposures with undiagnosed patients or colleagues but not to contacts with children attending out-of-home care facilities.

Brooks JT, Butler JC, Redfield RR. **Universal Masking to Prevent SARS-CoV-2 Transmission—The Time Is Now**. JAMA July 14, 2020. Full-text: https://doi.org/10.1001/jama.2020.13107

See title. Data is clear now. First, public health officials need to ensure that the public understands clearly when and how to wear cloth face coverings properly. Second, innovation is needed to extend physical comfort and ease of use. Third, the public needs consistent, clear, and appealing messaging that normalizes community masking. According to the authors, broad adoption of cloth face coverings is a civic duty, a small adaption in our daily lives reliant on a highly effective low-tech solution that can help turn the tide.

Clinical

Perez-Saez J, Lauer SA, Kaiser L. **Serology-informed estimates of SARS-CoV-2 infection fatality risk in Geneva, Switzerland**. Lancet July 14, 2020. Full-text: https://doi.org/10.1016/S1473-3099(20)30584-3

This important study has estimated age-specific infection fatality risks (IFRs) for Geneva, Switzerland, using population-based seroprevalences. After accounting for demography and age-specific seroprevalence, the population-wide IFR was 0.64% (0.38–0.98). Check your age: IFR differed markedly between the age groups. IFR was only 0.0092% (95% between 0.0042–0.016) for individuals aged 20–49 years, 0.14% (0.096–0.19) for those aged 50–64 years but 5.6% (4.3–7.4) for those aged 65 years and older.

Buscarini E, Manfredi G, Brambilla G, et al. **GI symptoms as early signs of COVID-19 in hospitalised Italian patients**. Gut. 2020 Aug;69(8):1547-1548. PubMed: https://pubmed.gov/32409587 . Full-text: https://doi.org/10.1136/gutjnl-2020-321434

Among 411 consecutive COVID-19 patients, 42 (10.2%) reported GI symptoms including nausea (4.3%), vomiting (3.8%), diarrhea (3.6%) or abdominal pain (1.2%). GI symptoms had a mean onset of 4.9 ± 4.4 days before admission. Absence of cough was reported in 35/42 (83%) patients with GI symptoms. According to the authors, their findings of these 10% of COVID-19 patients confirms that the prevalence of GI symptoms at onset "is not negligible". That's probably why this was published in *Gut*.

Severe COVID-19

Grasselli G, Greco M, Zanella A, et al. **Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy**. JAMA Intern Med July 15, 2020. Full-text: https://doi.org/10.1001/jamainternmed.2020.3539

If you are in the ICU, it's 50/50. In this large cohort study of 3,988 critically ill patients, most required invasive mechanical ventilation, and mortality rate was high. In the subgroup of the first 1715 patients, 915 patients died in the hospital for an overall hospital mortality of (53.4%).

Gupta S, Hayek SS, Wang W, et al. **Factors Associated With Death in Critically Ill Patients With Coronavirus Disease 2019 in the US**. JAMA Intern Med July 15, 2020. –Full-text: https://doi.org/10.1001/jamainternmed.2020.3596

But it depends where you are. In this US cohort of 2,215 adults with COVID-19 who were admitted to ICUs at 65 sites, 784 (35.4%) died within 28 days. However, mortality showed an extremely wide variation among hospitals (range, 6.6%-80.8%). Factors associated with death included older age, male sex, obesity, coronary artery disease, cancer, acute organ dysfunction, and, importantly, admission to a hospital with fewer intensive care unit beds. Patients admitted to hospitals with fewer than 50 ICU beds versus at least 100 ICU beds had a higher risk of death (OR 3.28; 95% CI, 2.16-4.99).

18 July

Virology

Thoms M, Buschauer R, Ameismeier M, et al. **Structural basis for translational shutdown and immune evasion by the Nsp1 protein of SARS-CoV-2.** Science 17 Jul 2020: eabc8665. Full-text: https://doi.org/10.1126/science.abc8665

A major virulence factor of SARS-CoV is the non-structural protein 1 (Nsp1) which suppresses host gene expression by ribosome association. Using cryo-electron microscopy, these researchers from Munich have characterized the interaction of Nsp1 of SARS-CoV-2 with the human translation machinery. Nsp1 effectively blocks innate immune responses that would otherwise facilitate clearance of the infection. The next step (and probably the next *Science* paper) is the structural characterization of the inhibitory mechanisms.

Immunology

Li Q, Wu J, Nie J, et al. **The impact of mutations in SARS-CoV-2 spike on viral infectivity and antigenicity**. Cell July 17, 2020 Full-text: https://doi.org/10.1016/j.cell.2020.07.012

This work may be of high relevance for antibody and vaccine development. The authors investigated 80 variants and 26 glycosylation site modifications of the spike protein of SARS-CoV-2 for the infectivity and reactivity to a panel of neutralizing antibodies and sera from convalescent patients. D614G, along with several variants containing both D614G and another amino acid change, were significantly more infectious. Most variants and the majority of glycosylation deletions were less infectious. However, some variants and N234Q glycosylation were markedly resistant to neutralizing antibodies.

Codo AC, Davanzo GG, de Brito Monteiro L, et al. **Elevated glucose levels favor SARS-CoV-2 infection and monocyte response through a HIF-1α/glycolysis dependent** axis. Cell Metabolism July 17, 2020. Full-text: https://doi.org/10.1016/j.cmet.2020.07.007

Why diabetes is bad (if uncontrolled). Elevated glucose levels directly induce viral replication and pro-inflammatory cytokine expression. Glycolytic flux is required for CoV-2 replication. Virus-induced mtROS production stabilizes HIF-1α, which in turn upregulates glycolytic genes and IL-1β expression. These data may explain why uncontrolled diabetes is a risk factor for severe COVID-19. The mtROS/HIF-1α/glycolysis-axis could be a treatment target.

Sariol A, Perlman S. **Lessons for COVID-19 immunity from other coronavirus infections**. Immunity July 14, 2020. Full-text: https://doi.org/10.1016/j.immuni.2020.07.005

In this comprehensive review, these two researchers describe the immune responses to other coronaviruses and discuss their relevance to the SARS-CoV-2 immune response. They also address crucial questions for COVID-19 immunity.

Diagnostics

Collier Dam Assennato SM, Warne B, et al. **Point of care nucleic acid testing for SARS-CoV-2 in hospitalised patients: a clinical validation trial and implementation study**. Cell Rep Med 2020, July 15, 2020. Full-text: https://doi.org/10.1016/j.xcrm.2020.100062

This will be the future (at least in hospitals). A point of care (POC) nucleic acid amplification testing (NAAT) was evaluated in 149 participants with parallel combined nasal/throat swabbing for POC versus standard time to result was 2.6 versus 26.4 hours. In an implementation study, POC testing increases isolation room availability, avoids bed closures, allows discharge to care homes and expedites access to hospital procedures.

Clinical

Pham TD, Huang CH, Wirz OF, et al. SARS-CoV-2 **RNAemia in a Healthy Blood Donor 40 Days After Respiratory Illness Resolution**. Ann Int Med Jul 17, 2020. Full-text: https://doi.org/10.7326/L20-0725

What happened here? The authors describe a case of donor RNAemia more than one month after symptom resolution. Plasma viral RNA was reproducibly detected at a time point that exceeded recommendations for deferral based on time since symptom resolution (14 days). Given the low viral load, however, these data suggest that this donor posed a limited but uncertain risk to the safety of the blood supply.

Treatment

The RECOVERY Collaborative Group. **Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report**. NEJM July 17, 2020. Full-text: https://doi.org/10.1056/NEJMoa2021436

Applause to these UK researchers! These first peer-reviewed results of the incredibly huge RECOVERY trial show that dexamethasone works in critically

ill patients. In this open-label trial (comparing a range of treatments), hospitalized patients were randomized to receive oral or intravenous dexa (at a dose of 6 mg once daily) for up to 10 days or to receive usual care alone. Overall, 482 patients (22.9%) in the dexa group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (age-adjusted rate ratio, 0.83). Death rate was lower among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%) but not among those who were receiving no respiratory support (17.8% vs. 14.0%).

Skipper CP, Pastick KA, Engen NW, et al. **Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19**. Ann Int Med, Jul 16. Full-text: https://doi.org/10.7326/M20-4207

The last piece of the puzzle that HCQ doesn't work, even when given early. Symptomatic, nonhospitalized adults with lab-confirmed or probable COVID-19 and high-risk exposure were randomized within 4 days of symptom onset to HCQ (800 mg once, followed by 600 mg at 6 to 8 hours, then 600 mg daily for 4 more days) or masked placebo. Among 423 patients, change in symptom severity over 14 days did not differ. At 14 days, 24% receiving HCQ had ongoing symptoms compared with 30% receiving placebo (p = 0.21). Adverse events occurred in 43% versus 22%. Although many letters can be expected (dosage wrong, too low, too high, too late, too early, wrong patients, too many unconfirmed patients etc), the lesson is learned: HCQ does NOT substantially reduce symptom severity in outpatients with early, mild COVID-19. Please, let's forget it. Completely.

Schluger NW. **The Saga of Hydroxychloroquine and COVID-19: A Cautionary Tale**. Ann Int Med 2020, Jul 6. Full-text: https://doi.org/10.7326/M20-5041

Editorial, commenting on the above data. The saga of hydroxychloroquine and COVID-19 will likely reach its sad end. Many good ideas in medicine do not work. Some thoughts on how this HCQ hype could have happened.

Pruijssers AJ, George AS, Schäfer A, et al. **Remdesivir Inhibits SARS-CoV-2 in Human Lung Cells and Chimeric SARS-CoV Expressing the SARS-CoV-2 RNA Polymerase in Mice**. Cell Reports, July 14, 2020. Full-text: https://doi.org/10.1016/j.celrep.2020.107940

Good to know that remdesivir works in cells. It potently inhibits SARS-CoV-2 replication in human lung cells and primary human airway epithelial cultures. In mice infected (with a chimeric virus), remdesivir diminished lung viral load and improved pulmonary function.

19 July

A kind request to all authors of scientific papers: to everyone in the scientific community currently working on a scientific paper on COVID-19, brooding over introductions. It is no longer necessary to emphasize that the "COVID-19 pandemic has to date caused > 7 million infections resulting in over 400,000 deaths" and that "following infection with SARS-CoV-2, COVID-19 patients can experience mild or even asymptomatic disease, or can present with severe disease requiring hospitalization and mechanical ventilation" (*Science*, July 15). And please, don't start your paper or your abstract with the COVID-19 pandemic as "a major threat to global health for which there are limited medical countermeasures" (*Nature*, July 15). Other hot-off-the-press findings you don't need to repeat? "The severe acute respiratory syndrome coronavirus 2 emerged in late 2019 and spread globally, prompting an international effort to accelerate development of a vaccine" (*NEJM*, July 15).

Are you kidding? We know it. We all know it! We know it all! On July 16th, pubmed.gov listed more than 31,000 COVID-19 papers. Almost every paper is (fortunately) freely accessible. We are faced with dozens of important scientific papers every day and our time is limited. So get down to business, folks. Straight to the point, no elaborations. Save yourself cumbersome or scrambled introductions.

Be brief. We all thank you!

Rob Camp, Christian Hoffmann, Bernd Sebastian Kamps

20 July

Epidemiology

Ruktanonchai NW, Floyd JR, Lai S, et al. **Assessing the impact of coordinated COVID-19 exit strategies across Europe.** Science. 2020 Jul 17:eabc5096. PubMed: https://pubmed.gov/32680881. Full-text: https://doi.org/10.1126/science.abc5096

Collaboration is better than unilateralism (some people should have thought about that before voting pro-Brexit). Using mobile phone and case data to quantify how coordinated exit strategies can delay European resurgence of COVID-19, the authors conclude that synchronizing intermittent lockdowns would reduce the number of total lockdown periods. It doesn't escape their notice that the implications of their study extend well beyond Europe and COVID-19.

Transmission and Prevention

Park YJ, Choe YJ, Park O, et al. **Contact Tracing during Coronavirus Disease Outbreak, South Korea, 2020.** Emerg Infect Dis October 2020. Full-text: https://wwwnc.cdc.gov/eid/article/26/10/20-1315_article

The authors analyzed 59,073 contacts of 5,706 COVID-19 index patients. Of 10,592 household contacts, 11.8% had COVID-19; rates were higher for contacts of children than adults. Of 48,481 non-household contacts, 1.9% had COVID-19. Interestingly, the highest COVID-19 rate (18.6%) was found for household contacts of school-aged children and the lowest (5.3%) for household contacts of children 0–9 years in the middle of school closure.

Vaccine

Folegatti PM, Ewer KJ, Aley PK, et al. **Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial.** Lancet, 20 July 2020. Full-text: https://www.thelancet.com/lancet/article/s0140-6736(20)31604-4

Andrew Pollard and colleagues report their Phase 1/2 randomized trial of a chimpanzee adenovirus-vector vaccine (ChAdOx1 nCoV-19) expressing the SARS-CoV-2 spike protein. Study participants received either ChAdOx1 nCoV-19 (n = 543) or a meningococcal conjugate vaccine (MenACWY) as control (n = 534). In ChAdOx1 vaccinees, T cell responses peaked on day 14, anti-spike IgG responses rose by day 28, and neutralizing antibody responses against SARS-CoV-2 were detected in > 90% (find more details in the paper, especially about results after a booster dose). Adverse events such as fatigue, headache, and local tenderness commonly occurred. There were no serious adverse events.

Zhu FC, Guan XH, Li YH, et al. **Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2**

trial. Lancet, 20 July 2020. Full-text: https://www.thelancet.com/lancet/article/s0140-6736(20)31605-6

Wei Chen and colleagues report results from a randomized Phase 2 trial of an Ad5-vector COVID-19 vaccine from a single center in Wuhan. More than 90% of participants had T cell responses, seroconversion of binding antibody occurred in more than 96%, and neutralizing antibodies were seen in about 85%. The authors found that compared with the younger population, older people had a significantly lower immune response, but higher tolerability, to the Ad5-vector COVID-19 vaccine. In a Phase 2b trial, an additional dose might therefore be needed to induce a better immune response in the older population. Adverse events such as fever, fatigue, headache, or local site pain were comparable to the ChAdOx1 study above.

Bar-Zeev N, Moss WJ. **Encouraging results from phase 1/2 COVID-19 vaccine trials.** Lancet, 20 July 2020. Full-text: https://www.thelancet.com/lancet/article/s0140-6736(20)31611-1

A comment on the two papers above as well as a list of questions to be addressed by the coming Phase 3 trials:

- Will a single dose be sufficient in older adults, or is a booster dose required?
- Does longevity of response or rates of waning differ with a two-dose regimen, and does longevity of clinical protection require cell-mediated responses?
- Are there host-specific differences in immunogenicity by age, sex, or ethnicity?
- Do T cell responses correlate with protection irrespective of humoral titers?
- Are there specific adverse events in pregnant women?

Immunology

Zhu L, Yang P, Zhao Y, et al. **Single-cell sequencing of peripheral blood mononuclear cells reveals distinct immune response landscapes of COVID-19 and influenza patients.** Immunity, published July 19, 2020. Web: https://www.cell.com/immunity/fulltext/S1074-7613(20)30316-2. Full-text: https://doi.org/10.1016/j.immuni.2020.07.009

The authors report the single-cell transcriptional landscape of longitudinally collected peripheral blood mononuclear cells (PBMCs) in both COVID-19 and

influenza A virus (IAV)-infected patients. COVID-19 (STAT1 and IRF3) and IAV (STAT3 and NF κB) activate distinct signaling.

Fischer B, Knabbe C, Vollmer T. **SARS-CoV-2 IgG seroprevalence in blood donors located in three different federal states, Germany, March to June 2020.** Euro Surveill. 2020;25(28), published 16 July 2020. Full-text: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.28.2001285

Bad news for German herd immunity. In 3,186 regular blood donors in three German federal states, the seroprevalence of IgG SARS-CoV-2 antibodies was 0.91% overall, ranging from 0.66% in Hesse to 1.22% in Lower-Saxony. 99% of Germans have no specific immunity against SARS-CoV-2 infection.

Comorbidities

Tan M, He FJ, MacGregor GA. **Obesity and covid-19: the role of the food industry.** BMJ. 2020 Jun 10;369:m2237. PubMed: https://pubmed.gov/32522740. Full-text: https://doi.org/10.1136/bmj.m2237

Sorry for being 40 days late to present this article published in June. As obesity is recognized as an independent risk factor for severe illness and death with COVID-19, a reminder of the players involved in the obesity pandemic is always helpful. The authors have a concise message: "Food industries around the world must immediately stop promoting, and governments must force reformulation of, unhealthy foods and drinks." As food industries won't stop promoting, governments must regulate them.

Apicella M, Campopiano MC, Mantuano M, et al. **COVID-19 in people with diabetes: understanding the reasons for worse outcomes.** Lancet Diabetes Endocrinol, 17 July 2020. Full-text: https://doi.org/10.1016/S2213-8587(20)30238-2

This review provides an assessment of prognostic factors in patients with diabetes and COVID-19. A poorer prognosis would be the consequence of the syndromic nature of diabetes: hyperglycemia, older age, comorbidities, and in particular hypertension, obesity, and cardiovascular disease. All would contribute to an increased risk.

Pediatrics

Derespina KR, Kaushik S, Plichta A, et al. **Clinical Manifestations and Outcomes of Critically Ill Children and Adolescents with COVID-19 in New York City.** J Pediatr. 2020 Jul 15:S0022-3476(20)30888-X. PubMed: https://pubmed.gov/32681989. Full-text: https://doi.org/10.1016/j.jpeds.2020.07.039

Retrospective observational study of 70 children who were admitted between mid-March and the beginning of May to 9 New York City pediatric intensive care units. About 75% presented with fever and cough, the most common presenting symptoms. Find out how many patients met severe sepsis criteria, required vasopressor support, developed ARDS, met acute kidney injury criteria, etc.

21 July

4th Turkish Edition

Today, **Zekeriya Temircan, Füsun Ferda Erdoğan, Türev Demirtaş and Dilara Güngör** have published the 4th Turkish edition of COVID Reference (PDF, 362 pages).

Transmission and Prevention

Stewart CL, Thornblade LW, Diamond DJ, Fong Y, Melstrom LG. **Personal Protective Equipment and COVID-19: A Review for Surgeons.** Ann Surg. 2020 Aug;272(2):e132-e138. PubMed: https://pubmed.gov/32675516. Full-text: https://doi.org/10.1097/SLA.0000000000003991

Are you a surgeon? Then your particular medical association has been using personal protective equipment (PPE) for more than a century. This review addresses both the mechanism of SARS-CoV-2 transmission and the capabilities of PPE in the perioperative COVID-19 setting.

Plautz J. **Is it safe to strike up the band in a time of coronavirus?** Science, 17 July 2020. Full-text: https://www.sciencemag.org/news/2020/07/it-safe-strike-band-time-coronavirus

Is keeping 2 meters away enough to stay safe from a trumpet at full blast? Try it, find out! Introduce five student musicians – a soprano singer and clarinet, flute, French horn, and trumpet players — in a clean room one at a time and let them perform a short solo piece.

Comorbidities

Mato AR, Roeker LE, Lamanna N, et al. **Outcomes of COVID-19 in Patients with CLL: A Multicenter, International Experience.** Blood. 2020 Jul 20:blood.2020006965. PubMed: https://pubmed.gov/32688395. Full-text: https://doi.org/10.1182/blood.2020006965

CLL patients have impaired humoral and cellular immune function. The authors describe the first large, disease-specific series in a defined cohort of hematologic cancer patients from 43 international centers. Of 198 CLL patients diagnosed with symptomatic COVID-19, 39% were treatment-naïve ("watch and wait") while 61% received at least one CLL therapy. At a median follow-up of 16 days, the overall case fatality rate was 33%, while another 25% were still in hospital. Discover differences between "Watch and wait" and treated cohorts with regard to ICU admission, intubation, and mortality. CLL patients are at high risk of death.

Bilaloglu S, Aphinyanaphongs Y, Jones S, et al. **Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System.** JAMA. Published online July 20, 2020. Full-text: https://doi.org/10.1001/jama.2020.13372

The authors assessed the incidence of, and risk factors for, venous and arterial thrombotic events in patients with COVID-19 in 4 hospitals in New York City. Among 3334 consecutive patients, a thrombotic event occurred in 16.0%. 207 (6.2%) were venous (3.2% PE and 3.9% DVT) and 365 (11.1%) were arterial (1.6% ischemic stroke, 8.9% MI, and 1.0% systemic thromboembolism). All-cause mortality was 24.5% and was higher in those with thrombotic events (43.2% vs 21.0%). D-dimer level at presentation was independently associated with thrombotic events, consistent with early coagulopathy.

Collateral Effects

Maringe C, Spicer J, Morris M, et al. **The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study.** Lancet Oncology, published: July 20, 2020. Full-text: https://doi.org/10.1016/S1470-2045(20)30388-0

During the UK COVID lockdown, cancer screening was suspended, routine diagnostic work deferred, and only urgent symptomatic cases were prioritized for diagnostic intervention. The authors estimate the impact of diagnostic delays over a 12-month period from the commencement of physical distancing measures, on March 16, 2020, up to 1, 3, and 5 years after diagnosis.

They expect an increase in the number of avoidable cancer as a result of the COVID-19 pandemic:

Breast cancer: 281–344 additional deaths (increase: 7.9–9.6%)

Colorectal cancer: 1445–1563 additional deaths (15.3–16.6%)

Lung cancer: 1235–1372 additional deaths (4.8–5.3%)

Esophageal cancer: 330–342 additional deaths (5.8–6.0%)

See also the comment by Hamilton W: **Cancer diagnostic delay in the COVID-19 era: what happens next?** Lancet Oncology, published: July 20, 2020. Full-text: https://doi.org/10.1016/S1470-2045(20)30391-0

Kamrath C, Mönkemöller K, Biester T, et al. **Ketoacidosis in Children and Adolescents With Newly Diagnosed Type 1 Diabetes During the COVID-19 Pandemic in Germany.** JAMA. Published online July 20, 2020. Full-text: https://doi.org/10.1001/jama.2020.13445

The COVID pandemic has caused people to delay medical care, even for life-threatening conditions. The authors analyzed data of 532 children and adolescents with newly diagnosed type 1 diabetes from 216 German diabetes centers (median age: 9.9 years). Diabetic ketoacidosis was present in 238 patients (44.7%) and severe ketoacidosis in 103 patients (19.4%). During the same periods in 2019 and 2018, the frequency of diabetic ketoacidosis was significantly lower (2019: 24.5%; 2018: 24.1%). The incidence of **severe** diabetic ketoacidosis was also significantly lower (2019: 13.9%; 2018: 12.3% in 2018). Children younger than 6 years had the highest risk.

Pediatrics

Abbas K, Procter SR, van Zandvoort K, et al. **Routine childhood immunisation during the COVID-19 pandemic in Africa: a benefit–risk analysis of health benefits versus excess risk of SARS-CoV-2 infection.** Lancet Global Health, published 17 July. Web: https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30308-9/fulltext. Full-text: https://doi.org/10.1016/S2214-109X(20)30308-9

National immunization programs are at risk of suspension during the COVID-19 pandemic. This benefit–risk analysis estimates that routine childhood immunization in Africa outweighs the excess risk of COVID-19 deaths which might be associated with clinic visits for vaccinations.

Journal Feature

Guglielmi G. **The explosion of new coronavirus tests that could help to end the pandemic.** Nature. 2020 Jul;583(7817):506-509. PubMed: https://pubmed.gov/32681157. Full-text: https://doi.org/10.1038/d41586-020-02140-8

Mass testing for SARS-CoV-2 — millions of tests per country per week — is one of the ways out of the COVID-19 crisis. It allows you to isolate those who test positive, limit the spread of disease and help to determine when it is safe to relax restrictions. Faster, simpler and cheaper methods of testing — Giorgia Guglielmi shows the way.

22 July

Epidemiology

Ali ST, Wang L, Lau EHY, et al. **Serial interval of SARS-CoV-2 was shortened over time by nonpharmaceutical interventions.** Science 21 Jul 2020. Full-text: https://doi.org/10.1126/science.abc9004

The *serial interval* is the time between illness onset in successive cases in a transmission chain. The authors show that during the early epidemic in China, the mean serial intervals of SARS-CoV-2 infection shortened from 7.8 days to 2.6 days between January 9 and February 13. This reduction was driven by intensive non-pharmaceutical interventions, particularly, reduction of the isolation delay period. Isolation of an infector one day earlier is expected to reduce the mean serial interval by 0.7 days.

Virology

Cai Y, Zhang J, Xiao T, et al. **Distinct conformational states of SARS-CoV-2 spike protein.** Science 21 Jul 2020. Full-text: https://doi.org/10.1126/science.abd4251

The authors report two cryo-EM structures, derived from a preparation of the full-length S protein, representing its pre-fusion (2.9Å resolution) and post-fusion (3.0Å resolution) conformations, respectively, and identify a structure near the fusion peptide – the fusion peptide proximal region (FPPR), which may play a critical role in the fusogenic structural rearrangements of S protein. Discover why the study raises potential concerns about current vaccine strategies.

Prevention

Sehgal AR, Himmelstein DU, Woolhandler S. **Feasibility of Separate Rooms for Home Isolation and Quarantine for COVID-19 in the United States.** Ann Intern Med. 2020 Jul 21. PubMed: https://pubmed.gov/32692931. Full-text: https://doi.org/10.7326/M20-4331

SARS-CoV-2-infected and -exposed persons are instructed to separate themselves from others to limit further spread through droplets and aerosol produced by coughs, sneezes, singing or even talking. But what if separate bedrooms and bathrooms are unavailable? The sober finding of the authors: more than 80 million persons in the US (about 1 in 5) live in places that are not suitable for isolation or quarantine.

Clinical

Walker A, Potting G, Scott A, Hopkins C. **Anosmia and loss of smell in the era of covid-19.** BMJ 2020;370:m2808. Full-text: https://doi.org/10.1136/bmj.m2808 (Published 21 July 2020)

The BMJ *10-Minute Consultation* summarizes in four points what you need to do:

1. Half of patients with COVID-19 may lose their sense of smell; guidance states that a new change or loss in sense of smell should prompt a period of self-isolation
2. Nine in 10 patients can expect substantial improvement in their sense of smell within four weeks
3. Most patients with loss of smell do not require further investigations or referral, although their COVID-19 status should be established if possible
4. Treatment involves reassurance, olfactory training, safety advice, and topical corticosteroids—but oral prednisolone should be avoided where acute COVID-19 infection is suspected

Covid-19: What do we know about "long covid"? BMJ 2020;370:m2815. Full-text: https://doi.org/10.1136/bmj.m2815

A reminder of "long COVID-19". In particular, re-read Paul Garner's experience: **For 7 weeks I have been through a roller coaster of ill health, extreme emotions, and utter exhaustion.** The BMJ Opinion, 5 May 2020. Full-text: https://blogs.bmj.com/bmj/2020/05/05/paul-garner-people-who-have-

a-more-protracted-illness-need-help-to-understand-and-cope-with-the-constantly-shifting-bizarre-symptoms/ (accessed 16 May 2020)

Hadjieconomou S, Hughes J. **Covid-19 associated chilblain-like lesions in an asymptomatic doctor.** BMJ 2020;370:m2245. Full-text. https://doi.org/10.1136/bmj.m2245 (Published 22 July 2020)

A reminder of chilblain with two photos.

Treatment

Ramiro S, Mostard RLM, Magro-Checa C, et al. **Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome: results of the CHIC study.** Ann Rheum Dis, 2020;0:1–9. Full-text: http://dx.doi.org/10.1136/annrheumdis-2020-218479

86 patients with COVID-19-associated cytokine storm syndrome received high-dose intravenous methylprednisolone for 5 consecutive days (250 mg on day 1 followed by 80 mg on days 2 – 5). If the respiratory condition did not improve sufficiently (in 43%), tocilizumab (8 mg/kg body weight, single infusion) was added on or after day 2. Compared to retrospectively matched patients (sex and age), treated patients had a 79% higher likelihood on reaching the primary outcome (defined as ≥ 2 stages of improvement on a 7-item WHO-endorsed scale for trials in patients with severe influenza pneumonia, or discharge from the hospital) (7 days earlier), 65% less mortality and 71% less invasive mechanical ventilation. Also, see the comment in BMJ.

Comorbidities

Yao Z, Chen J, Wang Q, et al. **Three Patients with COVID-19 and Pulmonary Tuberculosis, Wuhan, China, January-February 2020.** Emerg Infect Dis. 2020 Jul 15;26(11). PubMed: https://pubmed.gov/32667282. Full-text: https://doi.org/10.3201/eid2611.201536

Tham SM, Lim WY, Lee CK, et al. **Four Patients with COVID-19 and Tuberculosis, Singapore, April-May 2020.** Emerg Infect Dis. 2020 Jul 15;26(11). PubMed: https://pubmed.gov/32667283. Full-text: https://doi.org/10.3201/eid2611.202752

Two papers about three patients with COVID-19 and tuberculosis in Wuhan and four patients in Singapore. Clinicians treating at-risk populations should

be aware of possible co-infection with *M. tuberculosis* and SARS-CoV-2 in patients with atypical radiographic features of COVID-19.

Journal Feature

Dance A. **Coronavirus vaccines get a biotech boost.** Nature, published 21 July 2020. Full-text: https://www.nature.com/articles/d41586-020-02154-2

'Platform technologies', 'plug-and-play', ChAdOx1 – take a reconnaissance flight over the new Vaccine World. Read also *Coronavirus vaccines leap through safety trials — but which will work is anybody's guess*, by Ewen Callayway, Nature.

Sweet Article!

Bohn AJ, Kenworthy MA, Ginski C, et al. **Two Directly Imaged, Wide-orbit Giant Planets around the Young, Solar Analog TYC 8998-760-1.** Astrophys J Lett, volume 898, Number 19. Published 2020 July 22. Article: https://iopscience.iop.org/article/10.3847/2041-8213/aba27e + comment in Science by Daniel Clery.

Just to remember that science is spinning fast in other research areas, too.

23 July

Epidemiology

Sudharsanan N, Didzun O, Bärnighausen T Geldsetzer P. **The Contribution of the Age Distribution of Cases to COVID-19 Case Fatality Across Countries - A 9-Country Demographic Study.** Ann Intern Med 2020, published 22 July. Full-text: https://doi.org/10.7326/M20-2973

The overall observed case-fatality rates (CFR) vary widely, with the highest rates in Italy (9.3%) and the Netherlands (7.4%) and the lowest rates in South Korea (1.6%) and Germany (0.7%). This cross-sectional study of population-based data from China, France, Germany, Italy, the Netherlands, South Korea, Spain, Switzerland, and the US finds that age distribution of cases explains 66% of the variation of across countries, with a resulting age-standardized median CFR of 1.9%. See also the editorial by David N. Fisman, Amy L. Greer, and Ashleigh R. Tuite: **Age Is Just a Number: A Critically Important Number for COVID-19 Case Fatality**; full-text: https://doi.org/10.7326/M20-4048.

Fisman DN, Bogoch I, Lapointe-Shaw L, et al. **Risk Factors Associated With Mortality Among Residents With Coronavirus Disease 2019 (COVID-19) in Long-term Care Facilities in Ontario, Canada.** JAMA, published July 22, Full-text: https://doi.org/10.1001/jamanetworkopen.2020.15957

The authors compare the risk of death from coronavirus disease 2019 (COVID-19) among residents of long-term care (LTC) homes with that among the general population in long-term care facilities in Ontario, Canada. In the LTC facility setting, the incidence of mortality was more than 13 times greater than that seen in community-living adults older than 69 years during a similar period. Infection among LTC staff was associated with death among residents with a 6-day lag.

Immunology

Liu L, Wang P, Nair MS, et al. **Potent neutralizing antibodies directed to multiple epitopes on SARS-CoV-2 spike.** *Nature* (2020). Published: 22 July. Full-text: https://doi.org/10.1038/s41586-020-2571-7

A group of researchers including Yaoxing Huang, Lawrence Shapiro and David D. Ho report the isolation of 61 SARS-CoV-2-neutralizing monoclonal antibodies from 5 infected patients hospitalized with severe disease. Among these are 19 antibodies that potently neutralized the authentic SARS-CoV-2 *in vitro*, 9 of which exhibited exquisite potency, with 50% virus-inhibitory concentrations of 0.7 to 9 ng/mL. The list of findings grows. A must-read!

(David H. Ho will remind senior scientists of studies published in the 90's about HIV and AIDS (see pubmed.gov/10341272, pubmed.gov/10577640, pubmed.gov/11018071, pubmed.gov/15781098, pubmed.gov/16890836, among several hundred other publications). In 2001, he was presented with the Presidential Citizens Medal by President Clinton.)

Li J, Guo M, Tian X et al. **Virus-host interactome and proteomic survey of PBMCs from COVID-19 patients reveal potential virulence factors influencing SARS-CoV-2 pathogenesis.** Cell Med, published July 21, 2020. Full-text: https://doi.org/10.1016/j.medj.2020.07.002

The highlights:

1. Genome-wide screens identify 58 binary interactions between 29 SARS-CoV-2 proteins
2. Virus-host interactome identifies 286 host targets for SARS-CoV-2 proteins

3. Quantitative analysis depicts the overall proteome signature in COVID-19 PBMCs
4. Nsp10 targets NKRF to facilitate IL-8 induction

Diagnostics

McCulloch DJ, Kim AE, Wilcox NC. **Collected Nasopharyngeal Swabs for Detection of SARS-CoV-2 Infection.** JAMA 2020;3(7):e2016382. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.16382

Home self-collected swabs may increase testing access while minimizing exposure risk to health care workers and depletion of personal protective equipment, allowing for early community detection of COVID-19. The authors provided participants with test kits for unsupervised home self-collection of a mid-nasal swab. Home swab performance was compared with clinician-collected nasopharyngeal swabs collected by medical assistants and nurses. Compared with clinician swabs, sensitivity and specificity of home swabs was 80.0% and 97.9%, respectively. Unsupervised home mid-nasal swab collection was comparable to clinician-collected nasopharyngeal swab collection for detection of SARS-CoV-2 in symptomatic patients, particularly those with higher viral loads.

Tromberg, BJ, Schwetz TA, Pérez-Stable EJ, et al. **Rapid Scaling Up of Covid-19 Diagnostic Testing in the United States — The NIH RADx Initiative.** N Engl J Med 2020, published July 22. Full-text: https://doi.org/10.1056/NEJMsr2022263

Earlier in 2020, the COVID-19 epidemic in the US was fueled by a severe (scandalous?) lack of testing capacity. The authors describe the role of the NIH in the effort to increase the range and availability of diagnostic SARS-CoV-2 tests.

Treatment

Wang N, Zhan Y, Zhu L, et al. **Retrospective Multicenter Cohort Study Shows Early Interferon Therapy Is Associated with Favorable Clinical Responses in COVID-19 Patients.** Cell Host Microb, published July 22. Full-text: https://doi.org/10.1016/j.chom.2020.07.005

A retrospective multicenter cohort study of 446 COVID-19 patients, taking advantage of drug stock disparities between two medical centers in Hubei during the peak of the Chinese COVID-19 outbreak. **Early administration** (≤

5 days after admission) of IFN-α2b was associated with **reduced** in-hospital **mortality** in comparison with no admission of IFN-α2b, whereas **late administration** of IFN-α2b was associated with **increased mortality**. IFN therapy was not associated with recovery time for COVID-19.

Severe COVID

Kon ZN, Smith DE, Chang SH, et al. **Extracorporeal Membrane Oxygenation Support in Severe COVID-19.** Ann Thorac Surg. 2020 Jul 17:S0003-4975(20)31152-8. PubMed: https://pubmed.gov/32687823. Full-text: https://doi.org/10.1016/j.athoracsur.2020.07.002

The authors describe their institutional practice regarding ECMO support for 27 patients with COVID-19. At the time of paper submission, survival was 96.3% (one death) in over 350 days of total ECMO support. Thirteen patients (48.1%) remained on ECMO support, while 13 patients (48.1%) were successfully decannulated. Seven patients (25.9%) were discharged from the hospital while six patients (22.2%) remained in the hospital, of which four were on (unmodified) room air. The authors rightly conclude that the judicious use of ECMO support may be clinically beneficial.

Collateral Effects

Kansagra AP, Goyal MS, Hamilton S, Albers GW. **Collateral Effect of Covid-19 on Stroke Evaluation in the United States.** N Engl J Med 2020; 383:400-401. Full-text: https://doi.org/10.1056/NEJMc2014816

Any decrease in care for patients with ischemic stroke may be consequential because timely treatment may decrease the incidence of disability. The authors compare the mean daily counts per hospital of patients in the pre-pandemic 29-day epoch from February 1, 2020, through February 29, 2020, with the mean daily counts per hospital of patients in a 14-day period during the early pandemic, from March 26, 2020, through April 8, 2020. They found a decrease of approximately 39% in the numbers of patients who received evaluations for acute stroke between two recent periods in U.S. hospitals. The decrease in the use of stroke imaging from the pre-pandemic epoch to the early-pandemic period was seen across all ages, sexes, and stroke severity subgroups.

Education

Stone JR, Tran KM, Conklin J, Mino-Kenudson M. **Case 23-2020: A 76-Year-Old Woman Who Died from Covid-19.** N Engl J Med 2020; 383:380-387. Full-text: https://doi.org/10.1056/NEJMcpc2004974

A 76-year-old woman was admitted to the Massachusetts General Hospital because of confusion and hypoxemia (O_2 saturation at 87% while breathing ambient air).

Rubin EJ, Baden LR, Morrissey S. **Dexamethasone and Covid-19.** Audio interview (19:56). N Engl J Med 2020; 383:e52. Access: https://doi.org/10.1056/NEJMe2025927

The editors discuss the dexamethasone study by The RECOVERY Collaborative Group (Full-text: https://doi.org/10.1056/NEJMoa2021436) and the implications of corticosteroid use in patients with COVID-19.

Society

Egede LE, Walker RJ. **Structural Racism, Social Risk Factors, and Covid-19 — A Dangerous Convergence for Black Americans.** N Engl J Med 2020, published 22 July. Full-text: https://doi.org/10.1056/NEJMp2023616

Laurencin CT, Walker JM. **A Pandemic on a Pandemic: Racism and COVID-19 in Blacks.** Cell Systems 2020, published 22 July. Full-text: https://doi.org/10.1016/j.cels.2020.07.002

Racism and COVID-19 represent a pandemic on top of a pandemic for Blacks. Recommended action items for mitigating structural racism proposed by Egede & Walker:

1. Change policies that keep structural racism in place.
2. Break down silos and create cross-sector partnerships.
3. Institute policies to increase economic empowerment.
4. Fund community programs that enhance neighborhood stability.
5. Be consistent in efforts by health systems to build trust in vulnerable communities.
6. Test and deploy targeted interventions that address social risk factors.

Beyond COVID-19

Sherwood S, Webb JM, Annan JD, et al. **An assessment of Earth's climate sensitivity using multiple lines of evidence.** Reviews of Geophysics 2020. Full-text: https://climateextremes.org.au/wp-content/uploads/2020/07/WCRP_ECS_Final_manuscript_2019RG000678R_FINAL_200720.pdf (166 pages)

By doubling atmospheric carbon dioxide (CO_2) from preindustrial levels, planet Earth will eventually warm up to between 2.6°C and 3.9°C. This new estimate by 25 scientists is based on three strands of evidence:

1. Trends indicated by contemporary warming
2. The latest understanding of the feedback effects that can slow or accelerate climate change
3. Lessons from ancient climates

Read also the comment by Paul Voosen, published in Science: **After 40 years, researchers finally see Earth's climate destiny more clearly.** Full-text: https://doi.org/10.1126/science.abd9184

24 July

Epidemiology

Candido DS, Claro M, de Jesus JG, et al. **Evolution and epidemic spread of SARS-CoV-2 in Brazil.** Science 23 Jul 2020:eabd2161. Full-text: https://doi.org/10.1126/science.abd2161

Using a mobility-driven transmission model, the authors show that non-pharmaceutical interventions (lockdowns, etc) reduced the reproduction number from > 3 to 1 – 1.6 in São Paulo and Rio de Janeiro. In addition, after sequencing hundreds of genomes, they identified > 100 international virus introductions in Brazil with 76% of Brazilian strains falling into three clades that were introduced from Europe between 22 February and 11 March 2020. Finally, the study provides evidence that the current interventions (in an insalubrious political environment - *note of the CR editor*) remain insufficient to keep virus transmission under control in Brazil.

Havers FP, Reed C, Lim T, et al. **Seroprevalence of Antibodies to SARS-CoV-2 in 10 Sites in the United States, March 23-May 12, 2020.** JAMA Intern Med. 2020 Jul 21. PubMed: https://pubmed.gov/32692365. Full-text: https://doi.org/10.1001/jamainternmed.2020.4130

This cross-sectional study reports the presence of antibodies to SARS-CoV-2 spike protein in samples collected from March 23 through May 12, 2020, in 12 US sites from San Francisco to New York City. Adjusted estimates of the proportion of seropositive persons ranged from 1.0% in the San Francisco Bay area (collected April 23-27) to 6.9% of persons in New York City (collected March 23-April 1). The estimated number of SARS-CoV-2 infections is around 10 times the number of reported cases.

Transmission

Günther T, Czech-Sioli M, Indenbirken D, et al. **Investigation of a super-spreading event preceding the largest meat processing.** Pre-print available at https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3654517

In June, more than 1,400 employees at a meat-processing plant (MPP) in Germany were infected with SARS-CoV-2. Now a research group led by virologist Melanie Brinkmann (Helmholtz Center for Infection Research, Braunschweig) reconstructed how the virus was transmitted in the company. The first employees who became infected worked the early shift (147 workers), mostly in a fixed position on the conveyor belt. The evaluation of these positions showed that the risk of infection was greatest within a distance of eight meters from the first infected individual. In order words: a distance of 1.5 or two meters, which is currently thought (and instituted!) as relatively safe in most situations, was far from sufficient. The authors conclude that climate conditions (10° C ambient air temperature) and airflow are important factors that can promote spread of SARS-CoV-2 via distances of more than 8 meters. These findings may have far-reaching implications for pandemic mitigation strategies in industrial workplace settings.

Yamagishi T, Ohnishi M, Matsunaga N, et al. **Environmental sampling for severe acute respiratory syndrome coronavirus 2 during COVID-19 outbreak in the Diamond Princess cruise ship.** J Infect Dis. 2020 Jul 21:jiaa437. PubMed: https://pubmed.gov/32691828. Full-text: https://doi.org/10.1093/infdis/jiaa437

In the early epidemic in Japan, many infections occurred among the passengers and crew members on board the *Diamond Princess* cruise ship in Febru-

ary, 2020. By March 1, 2020, there were approximately 700 individuals with laboratory-detected SARS-CoV-2 infection (see the previous articles by Russell et al., Yamagishi et al. and Tabata et al.). The authors performed environmental sampling on the Diamond Princess cruise ship on 22-23 February 2020 (prior to disinfection of the vessel and while some passengers and crew members remained aboard) and obtained specimens from cabins in which confirmed COVID-19 cases stayed (case cabins), cabins with no confirmed case at any point (non-case cabins), and common areas. SARS-CoV-2 RNA was detected from 58 out of 601 samples (10%) from case cabins 1-17 days after the cabins were vacated, but not from non-case cabins. There was no difference in the detection proportion between cabins for symptomatic (15%, 28/189) and asymptomatic cases (21%, 28/131). No SARS-CoV-2 virus was isolated from any of the samples. The authors conclude that transmission risk of SARS-CoV-2 from symptomatic and asymptomatic patients may be similar and environmental surfaces could be involved in viral transmission.

Immunology

Hsieh CL, Goldsmith JA, Schaub M, et al. **Structure-based design of prefusion-stabilized SARS-CoV-2 spikes.** Science, 23 Jul 2020. Full-text: https://doi.org/10.1126/science.abd0826

High-yield production of a stabilized prefusion spike protein will accelerate the development of vaccines and serological diagnostics for SARS-CoV-2. After characterizing 100 structure-guided spike designs and 26 individual substitutions that increased protein yields and stability, the authors identified a promising variant, HexaPro, which contained four beneficial proline substitutions (F817P, A892P, A899P, A942P) as well as the two proline substitutions of previously described prefusion spikes. HexaPro had the ability to withstand heat stress, storage at room temperature, and three freeze-thaw cycles. The authors anticipate that "the high yield and enhanced stability of HexaPro should enable industrial production of subunit vaccines and could also improve DNA or mRNA-based vaccines by producing more antigen per nucleic acid molecule, thus improving efficacy at the same dose or maintaining efficacy at lower doses."

Lv Z, Deng YQ, Ye Q, et al. **Structural basis for neutralization of SARS-CoV-2 and SARS-CoV by a potent therapeutic antibody.** Science 23 Jul 2020: eabc5881. Full-text: Full-text: https://doi.org/10.1126/science.abc5881

The authors report a humanized monoclonal antibody, H014, which neutralizes SARS-CoV-2 and SARS-CoV pseudoviruses as well as authentic SARS-CoV-

2 at nanomolar level by engaging the S receptor binding domain. In the hACE2 mouse model, H014 reduced SARS-CoV-2 titers in the infected lungs and prevented pulmonary pathology. H014 seems to prevent attachment of SARS-CoV-2 to its host cell receptors. The authors are hopeful that antibody-based therapeutic interventions might play a key role in the treatment of COVID-19.

Horton R. **Offline: Preparing for a vaccine against COVID-19.** Lancet, July 25, 2020. Full-text: https://doi.org/10.1016/S0140-6736(20)31636-6

The British ChAdOx1 nCoV-19, the Chinese adenovirus type-5-vector vaccine and the American mRNA-1273 "give great encouragement to the view" that a vaccine can be produced within the next 18 months. But there are reasons for anxiety. Richard Horton takes you on a 3-minute tour.

Diagnostics

Mallapaty S. **The mathematical strategy that could transform coronavirus testing.** Nature. 2020 Jul;583(7817):504-505. PubMed: https://pubmed.gov/32651561. Full-text: https://doi.org/10.1038/d41586-020-02053-6

Widespread testing is needed to get SARS-CoV-2 outbreaks under control but in many regions, there's a shortage of the chemicals needed to run diagnostics. The solution: pooling samples from many people to save time and resources.

Clinical

Mackey K, Kansagara D, Vela K. **Update Alert 2: Risks and Impact of Angiotensin-Converting Enzyme Inhibitors or Angiotensin-Receptor Blockers on SARS-CoV-2 Infection in Adults.** Ann Intern Med. 2020 Jul 23. PubMed: https://pubmed.gov/32701362. Full-text: https://doi.org/10.7326/L20-0969

In this second monthly update of a living review (Medline), inclusion of three new meta-analyses and five new observational studies did not change the certainty of evidence rating reported in the original manuscript: there is high-certainty evidence that ACEI or ARB use is not associated with more severe COVID-19 disease.

Journal Feature

Arnold C. **How computational immunology changed the face of COVID-19 vaccine development.** Nature Med 2020, 15 July. Full-text: https://www.nature.com/articles/d41591-020-00027-9

When it comes to designing vaccines and antibody therapies, building a viable candidate can take years and cost tens of millions of dollars. By developing and investing in advanced computational tools, this process can be compressed into hours instead of years.

Beyond plate borders

Micheletti SJ, Bryc K, Ancona Esselmann SG, et al. **Genetic Consequences of the Transatlantic Slave Trade in the Americas.** Am J Hum Genet 2020, July 23. Full-text: https://doi.org/10.1016/j.ajhg.2020.06.012

This investigation of the transatlantic slave trade establishes genetic links between individuals in the Americas and populations across Africa, yielding a more comprehensive understanding of the African roots of peoples in the Americas.

25 July

Epidemiology

Liang L, Tseng Cl Ho HJ, et al. **Covid-19 mortality is negatively associated with test number and government effectiveness.** Sci Rep 10, 12567 (2020). Full-text: https://doi.org/10.1038/s41598-020-68862-x

In this worldwide cross-sectional study, the authors find that COVID-19 mortality is

- Negatively associated with
    - Test number per 100 people
    - Government effectiveness score
    - Number of hospital beds
- Positively associated with
    - Proportion of population aged 65 or older
    - Transport infrastructure quality score

Remember: Government effectiveness!

Virology

Viswanathan T, Arya S, Chan SH, et al. **Structural basis of RNA cap modification by SARS-CoV-2.** Nat Commun 11, 3718 (2020). Full-text: https://doi.org/10.1038/s41467-020-17496-8

Does SARS-CoV-2 use an alarm code to enter cells without bells going off? That's the proposal by Yogesh K. Gupta and colleagues who explain that the virus possesses the code to waltz right in. The authors report the high-resolution structure of a ternary complex of SARS-CoV-2 nsp16 and nsp10 (nps = nonstructural protein) in the presence of cognate RNA substrate analogue and methyl donor, S-adenosyl methionine. The nsp16/nsp10 heterodimer is captured in the act of 2′-O methylation of the ribose sugar of the first nucleotide of SARS-CoV-2 mRNA. A perfect camouflage: SARS-CoV-2 avoids the induction of the innate immune response mediated by interferon stimulated genes. As a result of these modifications, viral messenger RNA is considered as part of the cell's own code and not foreign. As genetic disruption of SARS-CoV *nsp16* markedly reduces (by 10-fold) the synthesis of viral RNA, the authors speculate that the ablation of nsp16 activity should trigger an immune response to SARS-CoV-2 infection and limit pathogenesis. They go on to describe a distantly located ligand-binding site in nsp16/10 capable of accommodating small molecules outside of the catalytic pocket. A new class of antiviral drugs on the horizon? Remember that these developments take years.

Transmission

Fennelly KP. **Particle sizes of infectious aerosols: implications for infection control.** Lancet Respir Med, July 24, 2020. Full-text: https://doi.org/10.1016/S2213-2600(20)30323-4

Is there really evidence that some pathogens are carried *only in large droplets*? Or would cough aerosols and exhaled breath from patients with various respiratory infections show striking similarities in aerosol size distributions? In case of doubt, how would you protect your family and yourself?

Stein-Zamir C, Abramson N, Shoob H, et al. **A large COVID-19 outbreak in a high school 10 days after schools' reopening, Israel, May 2020 separator commenting unavailable.** Eurosurveill 2020, Volume 25, Issue 29, 23 July. Full-text: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.29.2001352

After two months of lockdown, schools in Israel re-opened on 17 May. Ten days later, two cases of SARS-CoV-2 infection were diagnosed in a high school in Jerusalem; the two cases were epidemiologically not linked. Testing of the school community revealed 153 students (attack rate: 13.2%) and 25 staff members (16.6%) who were SARS-CoV-2 positive. Overall, some 260 persons were infected (students, staff members, relatives and friends).

As September approaches, health authorities in other countries should take note. In the present study, the mass COVID-19 transmission occurred when teenage students returned to their regular classes after a 2-month closure. An extreme heatwave (on 19 May) with temperatures rising to 40 °C and above led to an exemption from facemasks for three days (19–21 May) and continuous air-conditioning. Classes in the first affected school had more than 30 students.

The authors remind us that COVID-19 prevention in schools involves

- Studying in small groups
- Minimizing student mixing in activities and transportation
- The wearing of facemasks by teachers and parents
- Keeping physical distance and practicing hand hygiene
- Avoiding school attendance at any sign of illness
- Learning from home if possible to reduce the need for class attendance
- Organize outdoors classes in selected cases

Remember the 'three Cs': closed spaces with poor ventilation, crowded places and close-contact settings.

Immunology

Yang L, Liu S, Liu J, et al. **COVID-19: immunopathogenesis and Immunotherapeutics.** Sig Transduct Target Ther 5, 128 (2020). Full-text: https://doi.org/10.1038/s41392-020-00243-2

Six pages and 79 references – the ideal weekend read. Zhang and colleagues try and elucidate the mechanisms underlying immune abnormalities in patients with COVID-19. In addition to using *potent* antiviral drugs (which are still beyond the horizon), the successful management of clinical COVID-19 will include enhancing anti-viral immunity and inhibiting systemic inflammation.

Diagnostics

Tan CW, Chia WN, Qin X, et al. **A SARS-CoV-2 surrogate virus neutralization test based on antibody-mediated blockage of ACE2–spike protein–protein interaction.** Nat Biotechnol (2020). Full-text: https://doi.org/10.1038/s41587-020-0631-z

"A robust serological test to detect **neutralizing antibodies** to SARS-CoV-2 is urgently needed to determine not only the infection rate, herd immunity and predicted humoral protection, but also vaccine efficacy during clinical trials and after large-scale vaccination." To avoid neutralization tests that require live pathogen and a biosafety level 3 laboratory (BSL3), the authors propose a test based on antibody-mediated blockage of the interaction between the angiotensin-converting enzyme 2 (ACE2) receptor protein and the receptor-binding domain. The test achieved 99.93% specificity and 95–100% sensitivity. Time to completion: 1–2 h. Lab requirement: BSL2.

Genetics

van der Made CI, Simons A, Schuurs-Hoeijmakers J, et al. **Presence of Genetic Variants Among Young Men With Severe COVID-19.** JAMA. Published online July 24, 2020. Full-text: https://doi.org/10.1001/jama.2020.13719

When young patients died of COVID-19, we suspected the existence of genetic factors. Here, van der Made and colleagues describe two male brother pairs, 21 and 32 years old, with no history of major chronic disease. They were healthy before developing respiratory insufficiency due to severe COVID-19, requiring mechanical ventilation in the ICU. The mean duration of ventilatory support was 10 days (range, 9-11); the mean duration of ICU stay was 13 days (range, 10-16). One patient died. The authors describe "two families with rare germline variants in an innate immune-sensing gene, toll-like receptor 7 (*TLR7*), that leads to severe disease in males who inherit the mutated gene on a single copy of their X chromosome. The study implicates TLR7 as a critical node in recognizing SARS-CoV-2 and initiating an early immune response to clear the virus and prevent the development of COVID-19" (Plenge RM. **Molecular Underpinnings of Severe Coronavirus Disease 2019.** JAMA. Published online July 24, 2020. https://doi.org/10.1001/jama.2020.14015).

Toyoshima Y, Nemoto K, Matsumoto S, et al. **SARS-CoV-2 genomic variations associated with mortality rate of COVID-19.** J Hum Genet (2020). Full-text: https://doi.org/10.1038/s10038-020-0808-9

The authors analyzed 12,343 SARS-CoV-2 genome sequences isolated from patients/individuals in six geographic areas and identified a total of 1234 mutations compared to the reference SARS-CoV-2 sequence. They suggest that SARS-CoV-2 mutations as well as BCG-vaccination status and a host genetic factor, *HLA* genotypes might affect the susceptibility to SARS-CoV-2 infection or severity of COVID-19.

Treatment

Riva L, Yuan S, Yin X, et al. **Discovery of SARS-CoV-2 antiviral drugs through large-scale compound repurposing.** Nature (2020). Full-text: https://doi.org/10.1038/s41586-020-2577-1

After profiling a library of known drugs encompassing approximately 12,000 clinical-stage or FDA-approved small molecules, the authors identified 100 molecules that inhibit viral replication. Thirteen were found to be able to achieve therapeutic doses in patients, including the PIKfyve kinase inhibitor apilimod and several cysteine protease inhibitors. The known pharmacological and human safety profiles of these compounds might enable accelerated preclinical and clinical evaluation of these drugs for the treatment of COVID-19.

Pediatrics

Salvatore CM, Han JY, Acker KP, et al. **Neonatal management and outcomes during the COVID-19 pandemic: an observation cohort study.** Lancet Child Adolesc Health, July 23, 2020. Full-text: https://doi.org/10.1016/S2352-4642(20)30235-2

Transmission of COVID-19 is unlikely to occur if correct hygiene precautions are undertaken. This recommendation is confirmed via an observational cohort study in neonates born at three hospitals in New York City to mothers positive for SARS-CoV-2 at delivery. Of a total of 1481 deliveries, 116 (8%) mothers tested positive for SARS-CoV-2; 120 neonates were identified. All neonates were tested at 24 h of life and none were positive for SARS-CoV-2. All mothers were allowed to breastfeed. Of the neonates who completed follow-up at day 5–7 and day 14 of life, none was infected. The message: allowing neonates to room in with their mothers and direct breastfeeding are safe procedures when paired with effective parental education of infant protective strategies.

Journal Feature

Spinney L. **Smallpox and other viruses plagued humans much earlier than suspected.** Nature Med 2020, 23 July. Full-text: https://www.nature.com/articles/d41586-020-02083-0

When did humans first die of smallpox? When did the measles virus jump to people? When were the first humans infected by *M. tuberculosis*? If you like these questions, the News Feature by Laura Spinney is for you.

26 July

Today, review what you have learned over the past months and find a summary of articles about **clinical manifestations**, **co-morbidities** and **severe COVID-19** since the beginning:

https://covidreference.com/daily-science-clinical

27 July

Epidemiology

Jingwen Li, Chengbi Wu, Xing Zhang, Lan Chen, Xinyi Wang, Xiuli Guan, Jinghong Li, Zhicheng Lin, Nian Xiong. **Post-pandemic testing of SARS-CoV-2 in Huanan Seafood Market area in Wuhan, China.** Clinical Infectious Diseases 2020, published 25 July 2020. Full-text: https://doi.org/10.1093/cid/ciaa1043

The Wuhan lockdown lasted 76 days, from 23 January to 8 April, 2020. Two and a half weeks later, the number of both hospitalized COVID-19 patients and daily new cases in Wuhan decreased to zero. When sporadic cases were reported after May 11th, the Chinese authorities started a citywide mass nucleic acid testing of SARS-CoV-2 for all citizens in Wuhan city (14 May to 1 June 2020). Now Nian Xiong and colleagues report the results from 107,662 residents around the Huanan Seafood Market. Six (6) persons tested positive for SARS-CoV-2, accounting for 0.006%, the equivalent of 60 cases per million.

Transmission

Patterson EI, Elia G, Grassi A, et al. **Evidence of exposure to SARS-CoV-2 in cats and dogs from households in Italy.** bioRxiv 23 July 2020. Full-text: https://doi.org/10.1101/2020.07.21.214346

Nicola Decaro and colleagues assess SARS-CoV-2 infection in 817 companion animals in northern Italy at the height of the spring 2020 epidemic. Although no animals tested PCR positive, 3.4% of dogs and 3.9% of cats had measurable SARS-CoV-2 neutralizing antibody titers, with dogs from COVID-19 positive households being significantly more likely to test positive than those from COVID-19 negative households. From their experience, the authors conclude that it is unlikely that infected pets play an active role in SARS-CoV-2 transmission to humans. Only under special circumstances, such as the high animal population densities encountered on infected mink farms, animal-to-human transmission might be likely.

Prevention

Gallagher J, Johnson I, Verbeek J et al. **Relevance and paucity of evidence: a dental perspective on personal protective equipment during the COVID-19 pandemic.** Br Dent J 229, 121–124 (2020). Full-text: https://doi.org/10.1038/s41415-020-1843-9

Dentists and their staff are among the most exposed health care professionals to SARS-CoV-2 infection. The authors apply a recently updated Cochrane review (see below, Verbeek et al.) of personal protective equipment (PPE) and examine evidence on which type of full body PPE and what methods of putting on or taking off full body PPE are most effective.

Verbeek JH, Rajamaki B, Ijaz S, et al. **Personal protective equipment for preventing highly infectious diseases due to exposure to contaminated body fluids in healthcare staff.** Cochrane Database Syst Rev. 2020 May 15;5:CD011621. PubMed: https://pubmed.gov/32412096. Full-text: https://doi.org/10.1002/14651858.CD011621.pub5

Parker S, Mahomed O. **Hypoxia and Thrombosis in COVID-19: New Considerations for Air Passengers.** Journal of Travel Medicine 2020, published 25 July. Full-text: https://doi.org/10.1093/jtm/taaa122

The authors recommend pre-boarding as well as on-board pulse oximetry screening for early detection of silent hypoxia, especially in unwell passengers boarding long-haul commercial flights.

Immunology

Simon D, Tascilar K, Krönke G, et al**Patients with immune-mediated inflammatory diseases receiving cytokine inhibitors have low prevalence of SARS-CoV-2 seroconversion.** Nat Commun 11, 3774 (2020). Full-text: https://doi.org/10.1038/s41467-020-17703-6

Might cytokine inhibitors be partially protective against the effects of SARS-CoV-2 infection? That's what Georg Schett and colleagues from the University of Erlangen, Germany, are suggesting. They analyzed 534 patients who received continuous cytokine blockade for immune-mediated inflammatory diseases (IMIDs) of the joints, gut and skin (i.e., rheumatoid arthritis, spondyloarthritis, inflammatory bowel disease, psoriasis); 259 patients with IMIDs receiving no cytokine inhibition (n = 259); 2
involved in the treatment of these patients; and 971 healthy controls from the same region. The authors conclude that patients with IMIDs receiving cytokine inhibitors may have a lower risk for SARS-CoV-2 infection than IMID patients not receiving such drugs or the general community.

	n	SARS-CoV-2 IgG+ (n)	SARS-CoV-2 IgG+ [95% CI]
Control group	971	22	2.27% [1.42–3.43]
Healthcare professionals	285	12	4.21% [2.18–7.35]
IMID*, no cytokine blockade	259	8	3.09% [1.33–6.09]
IMID*, continuous cytokine blockade	534	4	0.75% [0.20–1.92]

* Immune-mediated inflammatory diseases of the joints, gut and skin (i.e., rheumatoid arthritis, spondyloarthritis, inflammatory bowel disease, psoriasis)

Vaccine

Zhang NN, Li XF, Deng YQ. **A thermostable mRNA vaccine against COVID-19.** Cell 2020, ublished: July 23. Abstract: https://www.cell.com/cell/fulltext/S0092-8674(20)30932-6. Full-text: https://doi.org/10.1016/j.cell.2020.07.024

The authors describe the development of an LNP-encapsulated mRNA vaccine (termed "ARCoV") which targets the RBD of SARS-CoV-2. The vaccine induces neutralizing antibodies and T cell immunity in mice and non-human pri-

mates. Two doses of ARCoV immunization in mice conferred complete protection against the challenge of a SARS-CoV-2 mouse adapted strain. Phase 1.

Clinical

Tenforde MW, Kim SS, Lindsell CJ, et al. **Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network — United States, March–June 2020.** MMWR Morb Mortal Wkly Rep. ePub: 24 July 2020. Full-text: http://dx.doi.org/10.15585/mmwr.mm6930e1

What is the clinical course of COVID-19 and how long does it take for persons with milder illness to return to baseline health? Mark W. Tenforde and colleagues provide us with a treasure of data. They conducted telephone interviews with a random sample of adults aged ≥ 18 years who were tested SARS-CoV-2 positive at an outpatient visit at one of 14 US academic health care systems. Interviews were conducted 14 – 21 days after the test date. 274 persons reported one or more symptoms at testing and were included in this analysis. The median age of symptomatic respondents was 42.5 years Overall, 141 of 264 (53%) with available data reported one or more chronic medical conditions. Among the 270 of 274 interviewees with available data on return to usual health, 175 (65%) reported that they returned to their usual state of health a median of 7 days (IQR = 5–12 days) from the date of testing. Ninety-five (35%) reported that they had not returned to their usual state of health at the time of interview. The proportion who had not returned to their usual state of health differed across age groups: 26% of interviewees aged 18 – 34 years, 32% aged 35 – 49 years, and 47% aged ≥ 50 years reported not having returned to their usual state of health (p = 0.010) within 14–21 days after receiving a positive test result.

Comorbidities

Karim QA, Karim SSA. **COVID-19 affects HIV and tuberculosis care.** Science 24 Jul 2020:Vol. 369, Issue 6502, pp. 366-368. Full-text: https://science.sciencemag.org/content/369/6502/366

Key resources that had been extensively built up over decades for the control of HIV and TB are now being redirected to control COVID-19 in various countries in Africa, particularly South Africa. Find out how HIV and TB prevention and treatment have been affected by the SARS-CoV-2 pandemic.

Léger D, Beck F, Fressard L, Verger P, Peretti-Watel P, COCONEL Group. **Poor sleep associated with overuse of media during the COVID-19 lockdown.** Sleep 2020, published 25 July. Full-text: https://doi.org/10.1093/sleep/zsaa125

This COCONEL survey was based on a permanent panel of 750,000 French individuals, authorized by the French National Agency for Data Protection (*CNIL*). Here, 1005 panelists answered the survey out of the 25,800 invitations mailed out in mid-April of 2020. Damien Leger and colleagues report that the prevalence of sleep problems during the lockdown was notably higher (73%) than that reported among the general population in France in 2017 (49%). Their comment: "Physicians usually recommend coping with sleep disorders by exercising, going outside, avoiding screen time, and having a regular schedule — all recommendations difficult to apply during lockdown." A concise two-page read.

Society

Khoury P, Azar E, Hitti E. **COVID-19 Response in Lebanon: Current Experience and Challenges in a Low-Resource Setting.** JAMA. Published online July 23, 2020. Full-text: https://doi.org/10.1001/jama.2020.12695

COVID-19 is a challenge in a densely populated country like Lebanon, with 6.9 million residents—87.2% of whom live in urban areas—including 2 million displaced persons and 500,000 migrant workers, all within 10,452 km^2 (approximately the size of Kosovo or the state of Connecticut, US). It is even more of a challenge in a country that has been suffering, since autumn 2019, an unprecedented economic crisis (see Le Monde, 26 June 2020). Petra Khoury, Eid Azar, and Eveline Hitti report their experiences.

28 July

Epidemiology

Vahidy FS, Bernard DW, Boom ML, et al. **Prevalence of SARS-CoV-2 Infection Among Asymptomatic Health Care Workers in the Greater Houston, Texas, Area.** JAMA Netw Open 2020;3(7):e2016451. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.16451

Facing patients or not facing patients, that's the question. Roberta L. Schwartz and colleagues from the Houston Methodist Academic Institute, US, report a 4.8% difference between COVID-19–facing (5.4%) and non–COVID-19–facing (0.6%) HCWs. The cross-sectional study presents data on SARS-CoV-2

seropositivity in 2872 self-reported *asymptomatic individuals*, including 2787 HCWs and 85 community residents. In all, 3.9% tested positive for SARS-CoV-2. Among clinical HCWs, 5.4% from COVID-19 units and 0.6% from non–COVID-19 units had a positive RT-PCR test. None of the non-clinical HCWs or community residents tested positive.

Among 1992 HCWs in units caring for patients with COVID-19, the rate of SARS-CoV-2 positivity ranged between 3.6% for support staff to 6.5% for allied health and 6.5% for administrative staff. However, the proportions of participants with positive results for SARS-CoV-2 were not significantly different across five job categories of COVID-19–facing HCWs.

Transmission

Riediker M, Tsai D. **Estimation of Viral Aerosol Emissions From Simulated Individuals With Asymptomatic to Moderate Coronavirus Disease 2019.** JAMA Netw Open 2020;3(7):e2013807. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.13807

In this modeling study, Michael Riediker from the Swiss Centre for Occupational and Environmental Health in Winterthur and Dai-Hua Tsai from the University Hospital of Psychiatry in Zurich, Switzerland, it is estimated that viral load concentrations in a room with an individual who was coughing frequently were very high, with a maximum of 7.44 million copies/m^3 from an individual who was a high emitter. However, regular breathing from an individual who was a high emitter was modeled to result in lower room concentrations of up to 1248 copies/m^3. They conclude that the estimated infectious risk posed by a person with typical viral load who breathes normally was low and that only a few people with very high viral load posed an infection risk in the poorly ventilated closed environment simulated in this study.

Vaccine

Graham SP, McLean RK, Spencer AJ et al. **Evaluation of the immunogenicity of prime-boost vaccination with the replication-deficient viral vectored COVID-19 vaccine candidate ChAdOx1 nCoV-19.** npj Vaccines **5,** 69 (2020). Full-text: https://doi.org/10.1038/s41541-020-00221-3

Simon P. Graham, Teresa Lambe and colleagues compare the immunogenicity of one or two doses of ChAdOx1 nCoV-19 in both mice and pigs. Whilst a single dose induced antigen-specific antibody and T cell responses, a booster immunization enhanced antibody responses, particularly in pigs, with a significant increase in SARS-CoV-2 neutralizing titers. See also the ChAdOx1

Phase 1/2 randomized trial of a chimpanzee adenovirus-vector vaccine (nCoV-19) published a week ago: https://covidreference.com/top-10-july-20.

Martin C, Lowery D. **mRNA vaccines: intellectual property landscape.** Nat Rev Drug Discov 2020, 27 July. Full-text: https://www.nature.com/articles/d41573-020-00119-8

Cecilia Martin and Drew Lowery generate an intellectual property landscape surrounding mRNA vaccine development. Overall filing activity aims at protecting methods to improve mRNA delivery efficiency as well as pharmacological modifications to reduce mRNA instability and innate immunogenicity. Moderna, CureVac, BioNTech and GSK own nearly half of the mRNA vaccine patent applications.

Immunology

Lucas C, Wong P, Klein J, et al. **Longitudinal analyses reveal immunological misfiring in severe COVID-19.** Nature. 2020 Jul 27. PubMed: https://pubmed.gov/32717743. Full-text: https://doi.org/10.1038/s41586-020-2588-y

Akiko Iwasaki and colleagues serially analyzed the immune responses in 113 COVID-19 patients with moderate (non-ICU) and severe (ICU) disease. Following an early increase in cytokines, COVID-19 patients with moderate disease displayed a progressive reduction in type 1 (antiviral) and type 3 (antifungal) responses. In contrast, patients with severe disease maintained these elevated responses throughout the course of disease. Moreover, severe disease was accompanied by an increase in multiple type 2 (anti-helminths) effectors including, IL-5, IL-13, IgE and eosinophils. The authors identified four immune signatures, representing

a. growth factors
b. type 2/3 cytokines
c. mixed type 1/2/3 cytokines
d. chemokines

which correlated with three distinct disease trajectories in patients. These differences in the expression of inflammatory markers along disease progression between patients who exhibit moderate vs. severe COVID-19 symptoms may provide opportunities for targeted treatment.

Weisblum Y, Schmidt F, Zhang F, et al. **Escape from neutralizing antibodies by SARS-CoV-2 spike protein variants.** bioRxiv 2020, posted 22 July. Full-text: https://doi.org/10.1101/2020.07.21.214759 | *Not yet peer reviewed.*

Will SARS-CoV-2 adapt over time and evade neutralizing antibodies? Theodora Hatziioannou, Paul Bieniasz and colleagues at Rockefeller University made an animal virus produce the SARS-CoV-2 spike protein. When grown in the presence of neutralizing antibodies, functional SARS-CoV-2 spike protein variants with mutations in the receptor binding domain (RBD) and N-terminal domain that conferred resistance to monoclonal antibodies or convalescent plasma could be readily selected. Monoclonal antibodies, if one day used as treatment for COVID-19, will probably need to be designed as cocktails of multiple neutralizing antibodies which target distinct neutralizing epitopes.

Comorbidities

Puntmann VO, Carerj ML, Wieters I, et al. **Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19).** JAMA Cardiol 2020, published online July 27. Full-text: https://doi.org/10.1001/jamacardio.2020.3557

Are COVID-19 patients at risk of heart problems after surviving an illness? In a prospective observational cohort study, Eike Nagel and colleagues from the University of Frankfurt, Germany, evaluated cardiovascular magnetic resonance (CMR) images of 100 patients who were recovering from COVID-19 disease. A total of 78 patients (78%) had abnormal CMR findings, including raised myocardial native T1 (n = 73), raised myocardial late gadolinium enhancement (n = 32), and pericardial effusion (n = 22). Endomyocardial biopsy in patients with severe findings revealed active lymphocytic inflammation. At the time of CMR, high-sensitivity troponin T was detectable (3 pg/mL or greater) in 71 patients recently recovered from COVID-19 (71%) and significantly elevated (13.9 pg/mL or greater) in 5 patients (5%). Of note, the median time interval between COVID-19 diagnosis and CMR was 71 (IQR: 64-92) days. The authors stress the need for ongoing investigation of the long-term cardiovascular consequences of COVID-19.

Read also the editorial by Clyde W. Yancy and Gregg C. Fonarow: **Coronavirus Disease 2019 (COVID-19) and the Heart—Is Heart Failure the Next Chapter?** JAMA Cardiol 2020, published online July 27. Full-text: https://doi.org/doi:10.1001/jamacardio.2020.3575

Lindner D, Fitzek A, Bräuninger H, et al. **Association of Cardiac Infection With SARS-CoV-2 in Confirmed COVID-19 Autopsy Cases.** JAMA Cardiol 2020, published online July 27. Full-text: https://doi.org/10.1001/jamacardio.2020.3551

How much is COVID-19 associated with myocardial injury, possibly as the result of viral infection of the heart? Dirk Westermann and colleagues from the University Heart and Vascular Center in Hamburg, Germany, report on a series of 39 autopsies of patients with COVID-19 in whom pneumonia was the clinical cause of death in 35 of 39. SARS-CoV-2 was documented in 24 of 39 patients (61.5%) and viral load above 1000 copies per μg RNA in 1 tients (41.0%). A cytokine response panel consisting of 6 proinflammatory genes was increased in those 16 patients compared with 15 patients without any SARS-CoV-2 in the heart. *In situ* hybridization suggested that the most likely localization of SARS-CoV-2 was not in the cardiomyocytes but in interstitial cells or macrophages invading the myocardial tissue.

Read also the editorial by Clyde W. Yancy and Gregg C. Fonarow: **Coronavirus Disease 2019 (COVID-19) and the Heart—Is Heart Failure the Next Chapter?** JAMA Cardiol 2020, published online July 27. Full-text: https://doi.org/doi:10.1001/jamacardio.2020.3575

Pediatrics

Bonnet M, Champagnac A, Lantelme P, Harbaoui B. **Endomyocardial biopsy findings in Kawasaki-like disease associated with SARS-CoV-2.** European Heart Journal 2020, published 25 July. Full-text: https://doi.org/10.1093/eurheartj/ehaa588

Beyond your plate borders

Witze A. **How space missions snatch pieces of other worlds and bring them back to Earth.** Nature 2020, published 27 July. Full-text: https://www.nature.com/articles/d41586-020-02185-9

NASA is going to launch a spacecraft to collect samples from Mars. Andrea Witze looks back at missions that have grabbed extraterrestrial material. Visit the Moon, asteroids, a comet, solar wind and Mars.

29 July

Epidemiology

McNeil Jr DG. **A Viral Epidemic Splintering Into Deadly Pieces.** The New York Times, 29 July 2020. Full-text: https://www.nytimes.com/2020/07/29/health/coronavirus-future-america.html

This is not a scientific paper, but it is better than two thirds of published and pre-published articles about COVID-19 epidemiology. More than 4,000 words thoughtfully put down by Donald G. McNeil Jr. If you don't read it now, read it on the weekend.

Virology

Chen J, Malone B, Llewellyn E, et al. **Structural basis for helicase-polymerase coupling in the SARS-CoV-2 replication-transcription complex.** Cell 2020, 27 July, 2020. Full-text: https://doi.org/10.1016/j.cell.2020.07.033

The SARS-CoV-2 genome is replicated and transcribed by the RNA-dependent RNA polymerase holoenzyme (subunits nsp7/nsp8$_2$/nsp12) along with accessory factors such as the nsp13 helicase. Elizabeth A. Campbell, Seth A. Darst and colleagues now present a cryo-electron microscopic structure of the SARS-CoV-2 holo-RdRp with an RNA template-product with two molecules of the nsp13 helicase and identify a new potential target for future antiviral drugs.

Transmission

Sekizuka T, Itokawa K, Kageyama T, et al. **Haplotype networks of SARS-CoV-2 infections in the Diamond Princess cruise ship outbreak.** PNAS 2020, published 28 July. Full-text: https://doi.org/10.1073/pnas.2006824117

We remember the *Diamond Princess*: a cruise ship put under quarantine off of Yokohama, Japan, in early February. Of around 3,700 people on board, more than 700 people became infected with SARS-CoV-2 and seven patients died. Now, after whole-genome sequencing of SARS-CoV-2 and a network/phylogeny analysis of the outbreak, Makoto Kuroda and colleagues conclude that there was a single introduction of SARS-CoV-2, which disseminated among passengers on the ship through possible mass-gathering events in the recreational areas where people dance, sing, watch performances, or shop.

Immunology

Braun J, Loyal L, Frentsch M, et al. **SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19.** Nature 2020, published 29 July. Full-text: https://doi.org/10.1038/s41586-020-2598-9

Induction of SARS-CoV-2-specific $CD4_+$ T cells is likely to be critical in the instruction of potentially protective antibody responses. Andreas Thiel, Leif-Erik Sander, Claudia Giesecke-Thiel and colleagues therefore investigated SARS-CoV-2 spike glycoprotein (S)-reactive $CD4^+$ T cells in peripheral blood of patients with COVID-19 and SARS-CoV-2-unexposed healthy donors (HD). Surprise: they detected SARS-CoV-2 S-reactive $CD4^+$ T cells in 83% of patients with COVID-19 but also in 35% of unexposed HD. These data raise the intriguing possibility that pre-SARS-CoV-2 S-reactive T cells represent cross-reactive clones, probably acquired during previous infections with endemic human coronaviruses (HCoVs) such as 229E and OC43. The biological role of such pre-existing S-cross-reactive $CD4_+$ T cells in 35% of HD still remains unclear. However, assuming that these cells have a protective role in SARS-CoV-2 infection, they may contribute to divergent manifestations of COVID-19 and explain the resilience of children and young adults to symptomatic SARS-CoV-2 infection (more frequent social contacts than people from older age groups and thus a higher HCoV prevalence). This hypothesis remains to be validated in larger cohorts. The authors don't forget to underline that the presence of S-cross-reactive T cells in a sizable fraction of the general population may have important implications for the design and analysis of upcoming COVID-19 vaccine trials.

Chen Z, John Wherry E. **T cell responses in patients with COVID-19.** Nat Rev Immunol 2020, published 29 July. Full-text: https://doi.org/10.1038/s41577-020-0402-6

Will T cells provide long-term protection from reinfection with SARS-CoV-2? Nobody knows yet. Now Zeyu Chen and E. John Wherry from Philadelphia review recent studies which have shed light on T cell responses to SARS-CoV-2 infection. Accumulating evidence supports a role for T cells in COVID-19 and probably in the immunological memory after SARS-CoV-2 infection. Multiple distinct patterns of T cell response may exist in different patients and the authors suggest that the possibility of distinct clinical approaches may one day be tailored to the particular immunotype of a specific patient.

Vaccine

Corbett KS, Flynn B, Foulds KE, et al. **Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates.** N Engl J Med 2020, published 28 July. Full-text: https://doi.org/10.1056/NEJMoa2024671

Vaccination of non-human primates with mRNA-1273 induces robust SARS-CoV-2 neutralizing activity, rapid protection in the upper and lower airways, and no pathologic changes in the lung. For this important vaccine trial, Barney S. Graham, Robert A. Seder and colleagues divided 12 female and 12 male Indian-origin rhesus macaques into groups of three and vaccinated them intramuscularly at week 0 and at week 4 with either 10 or 100 μg of mRNA-1273 or placebo. At week 8 (4 weeks after the second vaccination), all animals were challenged with SARS-CoV-2. mRNA-1273 induced antibody levels exceeding those found in human convalescent phase serum. Vaccination also induced type 1 helper T cell (Th1)–biased CD4 T cell responses and low or undetectable Th2 or CD8 T cell responses.

No viral replication was detectable in the nose of any of the eight animals in the 100 μg dose group by day 2 after challenge (8 weeks after the first vaccination). The ability to limit viral replication in both the lower and the upper airways will have important implications for vaccine-induced prevention of both SARS-CoV-2 disease and transmission.

Liu G, Carter B, Bricken T, Jain S, Viard M, Carrington M, Gifford DK. **Computationally Optimized SARS-CoV-2 MHC Class I and II Vaccine Formulations Predicted to Target Human Haplotype Distributions.** Cell Systems 2020, published 27 July. Full-text: https://www.cell.com/cell-systems/fulltext/S2405-4712(20)30238-6

Do you want to optimize peptide vaccine formulations for SARS-CoV-2? David K. Gifford and colleagues from MIT now give you a combinatorial machine learning method. They also encourage the early publication of vaccine designs to enable collaboration and rapid progress toward safe and effective vaccines for COVID-19. Consequently, they provide an open-source implementation of their design methods (OptiVax), vaccine evaluation tool (EvalVax), as well as the data used in their design efforts: https://github.com/gifford-lab/optivax.

Clinical

Karagiannidis C, Mostert C, Hentschker C, et al. **Case characteristics, resource use, and outcomes of 10 -02 patients with COVID 920 German hospitals: an observational study.** Lancet Respir Med 2020, published 28 July. Full-text: https://doi.org/10.1016/S2213-2600(20)30316-7

In this observational study, Christian Karagiannidis and colleagues report on 10,021 adult patients with a confirmed COVID-19 diagnosis, who were admitted to 920 hospitals in Germany between 26 February and 19 April 2020. The median age was 72 years. 1727 patients (17%) needed mechanical ventilation. The main findings:

- Patients on mechanical ventilation had more comorbidities than patients without mechanical ventilation
- Mortality was 53% in patients being mechanically ventilated, reaching 63% in patients aged 70–79 years and 72% in patients aged 80 years and older
- Mortality was 73% in patients requiring both ventilation and dialysis

Table 1. Mortality in patients of the German AOK study.

	Mortality
No ventilation	16% (1323/8294)
With ventilation	53% (906/1727)
With ventilation + dialysis	78% (324/469)

Comorbidities

Nishiga M, Wang DW, Han Y et al. **COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives.** Nat Rev Cardiol 2020, published 20 July. Full-text: https://doi.org/10.1038/s41569-020-0413-9

Pre-existing cardiovascular disease is linked with higher morbidity and mortality in patients with COVID-19, whereas COVID-19 itself can induce myocardial injury, arrhythmia, acute coronary syndrome and venous thromboembolism. In this review, Masataka Nishiga, Joseph C. Wu and colleagues summarize the current understanding of the interaction between COVID-19 and the cardiovascular system.

Society

Kupferschmidt K. **'Vaccine nationalism' threatens global plan to distribute COVID-19 shots fairly.** Science 2020, 28 July. Full-text: https://www.sciencemag.org/news/2020/07/vaccine-nationalism-threatens-global-plan-distribute-covid-19-shots-fairly

'We will not sell it at cost." (We will sell it for profit.) That was the statement, a few days ago, of a company that is receiving almost 1,000,000,000 dollars from US tax payers for the development of a COVID-19 vaccine. Fortunately, other companies, too, are producing vaccines and good old WHO and other international organizations have set up a system to accelerate and equitably distribute vaccines, the COVID-19 Vaccines Global Access (**COVAX**) Facility. Kai Kupferschmidt summarizes the current state-of-affairs.

Beyond plate borders

Stone R. **Siberia's 'gateway to the underworld' grows as record heat wave thaws permafrost.** Science 2020, 28 July. Full-text: https://www.sciencemag.org/news/2020/07/siberia-s-gateway-underworld-grows-record-heat-wave-thaws-permafrost

Global warming is inflicting wounds across Siberia. Outbursts of pent-up methane gas in thawing permafrost have pocked Russia's desolate Yamal and Gydan peninsulas with holes tens of meters across. Apartment buildings are listing and collapsing on the unsteady ground, causing about $2 billion of damage per year to the Russian economy. Follow Richard Stone on a trip through climate-changed Siberia.

30 July

Epidemiology

Dawood FS, Ricks P, Njie GJ, et al. **Observations of the global epidemiology of COVID-19 from the prepandemic period using web-based surveillance: a cross-sectional analysis.** Lancet Infect Dis 2020, published 29 July. Full-text: https://doi.org/10.1016/S1473-3099(20)30581-8

Fatimah Dawood and colleagues describe the global spread of SARS-CoV-2 and characteristics of COVID-19 cases and clusters *before* WHO declared COVID-19 as a pandemic on 11 March 2020 (i.e., pre-pandemic). They identified cases of COVID-19 from official websites, press releases, press conference transcripts, and social media feeds of national ministries of health or other government

agencies. Cases with travel links to China, Italy, or Iran accounted for almost two-thirds of the first reported COVID-19 cases from affected countries. There were many clusters of household transmission among early cases; however, clusters in occupational or community settings tended to be larger. This is good news for future pandemic waves. *Keep your distance* and slow the spread of SARS-CoV-2.

Virology

Shin D, Mukherjee R, Grewe D et al. **Papain-like protease regulates SARS-CoV-2 viral spread and innate immunity.** Nature 2020, published 29 July. Full-text: https://doi.org/10.1038/s41586-020-2601-5

The papain-like protease PLpro, an essential coronavirus enzyme required for generating a functional replicase complex, is also implicated in evasion mechanisms against host anti-viral immune responses. Now Ivan Dikic and colleagues from Frankfurt Goethe University show that SCoV2-PLpro attenuates type I interferon responses and that inhibition of SCoV2-PLpro with the naphthalene-based inhibitor GRL-0617 impairs virus-induced cytopathogenic effects, fosters the anti-viral interferon pathway and reduces viral replication in infected cells. The authors conclude that targeting of SCoV2-PLpro could suppress SARS-CoV-2 infection and promote anti-viral immunity.

Transmission

Chen Y, Qin G, Chen J, et al. **Comparison of Face-Touching Behaviors Before and During the Coronavirus Disease 2019 Pandemic.** JAMA Netw Open 2020;3(7):e2016924. https://doi.org/10.1001/jamanetworkopen.2020.16924

Is wearing face masks really associated with reduced face-touching behaviors? To answer the question, Xing Li and colleagues from Sun Yat-sen University, Guangzhou, China, used videos recorded in public transportation stations, streets, and parks among the general population in China, Japan, South Korea, Western Europe (ie, England, France, Germany, Spain, and Italy), and the US to analyze mask-wearing and face-touching behavior in public areas. The authors found that mask wearing was associated with reduced face-touching behavior, especially touching of the eyes, nose, and mouth. They conclude that the reduction of face-touching behaviors by mask wearing could contribute to curbing the COVID-19 pandemic. Excellent news for the coming months.

Santarpia JL, Rivera DN, Herrera VL et al. **Aerosol and surface contamination of SARS-CoV-2 observed in quarantine and isolation care.** Sci Rep 10, 12732 (2020). Full-text: https://doi.org/10.1038/s41598-020-69286-3

After evacuation from the Diamond Princess cruise ship in March 2020, 11 were admitted to a hospital in Nebraska, two in a biocontainment unit and 9 in a quarantine unit. Key features of both units included: (1) individual rooms with private bathrooms; (2) negative-pressure rooms (> 12 ACH) and negative-pressure hallways; (3) key-card access control; (4) unit-specific infection prevention and control (IPC) protocols including hand hygiene and changing of gloves between rooms; and (5) personal protective equipment (PPE) for staff that included contact and aerosol protection. Joshua Santarpia and colleagues collected air and surface samples to examine viral shedding from isolated individuals and detected viral contamination among all samples. Their data suggest that SARS-CoV-2 environmental contamination around COVID-19 patients is extensive, and hospital IPC procedures should account for the risk of fomite, and potentially airborne, transmission of the virus.

Vaccine

van Doremalen N, Lambe T, Spencer A, et al. **ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques.** Nature 2020, published 30 July. Full-text: https://doi.org/10.1038/s41586-020-2608-y

The good news first or the bad news first? OK, the good news: Vincent Munster, Sarah Gilbert and colleagues showed that vaccination with the adenovirus-vectored ChAdOx1 vaccine (see the July 20 Top 10) induced a balanced Th1/Th2 humoral and cellular immune response in rhesus macaques. The authors observed a significantly reduced viral load in bronchoalveolar lavage fluid and lower respiratory tract tissue, and no pneumonia was observed in vaccinated animals. The bad news (for prevention policies in general and for anti-vaxxers in particular): there was no difference in nasal shedding between vaccinated and control animals. Back to the good news: there was no evidence of immune-enhanced disease following viral challenge in vaccinated animals.

Mercado NB, Zahn R, Wegmann F et al. **Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques.** Nature 2020, published 30 July. Full-text: https://doi.org/10.1038/s41586-020-2607-z

For global deployment and pandemic control, a vaccine that requires only a single immunization would be optimal. Hanneke Schuitemaker, Dan Barouch and colleagues developed a series of adenovirus serotype 26 (Ad26) vectors

encoding different variants of the SARS-CoV-2 spike (S) protein and showed the immunogenicity and protective efficacy of a single dose of Ad26 vector-based vaccines in 52 rhesus macaques. The optimal Ad26 vaccine induced robust neutralizing antibody responses and provided complete or near-complete protection in bronchoalveolar lavage and nasal swabs following SARS-CoV-2 challenge.

Yang J, Wang W, Chen Z et al. **A vaccine targeting the RBD of the S protein of SARS-CoV-2 induces protective immunity.** Nature 2020, published 29 July. Full-text: https://doi.org/10.1038/s41586-020-2599-8

The authors show that a recombinant vaccine comprising residues 319-545 of the Spike protein receptor-binding domain (S-RBD) can induce a potent functional antibody response in mice, rabbits and non-human primates as early as 7 or 14 days after a single dose injection. Antibodies shared common binding epitopes from infected patients, neutralizing activity was strong, and a simple adjuvant like Alum could further enhance the immune response. Even one dose of the vaccine generated viral neutralizing activity. The vaccine protected non-human primates from live SARS-CoV-2 challenge 28 days after the first vaccination.

Rubin EJ, Baden LR, Morrissey S. **New SARS-CoV-2 Vaccine Results**. N Engl J Med 2020; 383:e57. Access: https://www.nejm.org/doi/full/10.1056/NEJMe2026514

Audio interview (19:56) with Peter Piot who talks about his own experience with COVID-19, as well as recent developments in SARS-CoV-2 vaccines.

Education

Newton-Cheh C, Zlotoff DA, Hung J, Rupasov A, Crowley JC, and Funamoto M. **Case 24-2020: A 44-Year-Old Woman with Chest Pain, Dyspnea, and Shock.** N Engl J Med 2020; 383:475-484, published 30 July. Full-text: https://doi.org/10.1056/NEJMcpc2004975

Eight days before admission — and 3 days after her husband had begun to have fatigue, a non-productive cough, and fever — the patient started to have chills, a sore throat, a non-productive cough, and myalgias.

Sharma A, Eisen JE, Shepard JAO, Bernheim A, and Little BP. **Case 25-2020: A 47-Year-Old Woman with a Lung Mass.** N Engl J Med 2020, published 29 July. Full-text: https://doi.org/10.1056/NEJMcpc2004977

The patient had been well until 2 months before this evaluation, when intermittent non-productive cough and wheezing developed. She had no fever, chills, or shortness of breath. Two days before this evaluation, the cough worsened in frequency and severity and new shortness of breath developed.

Society

Adhikari S, Pantaleo NP, Feldman JM, Ogedegbe O, Thorpe L, Troxel AB. **Assessment of Community-Level Disparities in Coronavirus Disease 2019 (COVID-19) Infections and Deaths in Large US Metropolitan Areas.** JAMA Netw Open 2020;3(7):e2016938. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.16938

Urban counties in large metropolitan areas in the United States are among the most affected by the pandemic. In this cross-sectional study, Adhikari Samrachana and colleagues examined the association of neighborhood race/ethnicity and poverty with COVID-19 infections and related deaths. In poorer counties (median income: $60,240), those with substantially non-white populations had an infection rate nearly 8 times that of counties with substantially white populations and a death rate more than 9 times higher. Racial and ethnic disparities in COVID-19 infections and deaths existe even beyond those explained by differences in income.

Beyond your plate borders

Pennisi E. **Scientists pull living microbes, possibly 100 million years old, from beneath the sea.** Science 2020, published 28 July. Full-text: https://www.sciencemag.org/news/2020/07/scientists-pull-living-microbes-100-million-years-beneath-sea

If you bring back to the lab microbes buried beneath the sea floor, will they start to multiply? Life is persistent, here on Earth and perhaps elsewhere.

31 July

Prevention

National Academies of Sciences, Engineering, and Medicine. **Reopening K-12 Schools During the COVID-19 Pandemic: Prioritizing Health, Equity, and Communities.** The National Academies Press 2020. Washington, DC (accessed 31 July 2020). Full-text (download free PDF as guest): https://doi.org/10.17226/25858

How will schools reopen in the context of rapidly changing patterns of community SARS-CoV-2 spread (Dibner 2020)? Now the US National Academies of Sciences, Engineering, and Medicine provide a series of recommendations aimed at helping states and school districts determine both whether to open school buildings for in-person learning and, if so, how to reduce risk in the process of reopening (*Reopening K-12 Schools During the COVID-19 Pandemic: Prioritizing Health, Equity, and Communities*). Read also the comment by Dibner KA, Schweingruber HA and Christiakis DA. **Reopening K-12 Schools During the COVID-19 Pandemic.** JAMA 2020, published 29 July. Full-text: https://doi.org/10.1001/jama.2020.14745

Auger KA, Shah SS, Richardson T, et al. **Association Between Statewide School Closure and COVID-19 Incidence and Mortality in the US.** JAMA. 2020 Sep 1;324(9):859-870. PubMed: https://pubmed.gov/32745200. Full-text: https://doi.org/10.1001/jama.2020.14348

Was the closure of primary and secondary schools in the US associated with a decreased incidence and mortality of COVID-19? According to Katherine Auger and colleagues, it was: COVID-19 62% lower; deaths 58% lower. States that closed schools earlier, when cumulative incidence of COVID-19 was low, had the largest relative reduction in incidence and mortality. The authors caution that some of the reduction may have been related to other concurrent nonpharmaceutical interventions. See also the comment by Donohue JM, Miller E. **COVID-19 and School Closures.** JAMA 2020, published online July 29. Full-text: https://doi.org/10.1001/jama.2020.13092

Immunology

Lei X, Dong X, Ma R, et al. **Activation and evasion of type I interferon responses by SARS-CoV-2.** Nat Commun 11, 3810 (2020). Full-text: https://doi.org/10.1038/s41467-020-17665-9

The interplay and antagonism between SARS-CoV-2 and host innate immunity determine the clinical outcome of COVID-19. Now Jiang Wei and colleagues show that SARS-CoV-2 perturbs the host innate immune response both via its structural and nonstructural proteins. They reveal that SARS-CoV-2 induces an aberrant type I IFN response in cultured cells, with expressions of IFN-β and ISG56 being barely induced early during viral infection, and suggest that this delayed antiviral response might provide a window for virus replication. They also found that IFN-β treatment effectively blocks SARS-CoV-2 replication.

Diagnostics

Tu YP, Jennings R, Hart B, et al. **Swabs Collected by Patients or Health Care Workers for SARS-CoV-2 Testing.** N Engl J Med. 2020 Jul 30;383(5):494-496. PubMed: https://pubmed.gov/32492294. Full-text: https://doi.org/10.1056/NEJMc2016321

Ethan Berke et al. show the clinical usefulness of tongue, nasal, or midturbinate samples collected by patients as compared with nasopharyngeal samples collected by health care workers for the diagnosis of COVID-19. When a nasopharyngeal sample collected by a health care worker was used as the comparator, the estimated sensitivities of the tongue, nasal, and midturbinate samples collected by the patients were 89.8% (one-sided 97.5% confidence interval [CI], 78.2 to 100.0), 94.0% (97.5% CI, 83.8 to 100.0), and 96.2% (97.5% CI, 87.0 to 100.0), respectively. Adoption of patient sampling techniques may reduce use of personal protective equipment and provide a more comfortable patient experience.

Clinical

Anderson MR, Geleris J, Anderson DR, et al. **Body Mass Index and Risk for Intubation or Death in SARS-CoV-2 Infection.** Ann Intern Med 2020, published 29 July. Full-text: https://www.acpjournals.org/doi/10.7326/M20-3214

Should obesity be associated with increased risk for intubation or death from COVID-19 in adults younger than 65 years, but not in adults aged 65 years or older? That's the suggestion of a large multi-ethnic cohort study by Michaela Anderson and colleagues who looked at 2466 adults hospitalized with SARS-CoV-2 infection in a quaternary academic medical center and community hospital in New York City. Compared with overweight patients, patients with obesity had higher risk for intubation or death, with the highest risk among those with class 3 obesity (hazard ratio, 1.6 [95% CI, 1.1 to 2.1]). Interestingly,

this association was primarily observed among patients who were younger than 65 years, but not in older patients (p for interaction by age = 0.042). Body mass index was not associated with admission levels of biomarkers of inflammation, cardiac injury, or fibrinolysis.

Discover multiple potential mechanisms that may underlie the observed association of obesity with acute respiratory failure and death from SARS-CoV-2 infection.

Severe COVID

Bartoletti M, Pascale R, Cricca M, et al. **Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated patients: a prospective study.** Clin Inf Dis 2020, published 28 July. Full-text: https://doi.org/10.1093/cid/ciaa1065

Michele Bartoletti and colleagues enrolled 108 patients in a prospective, multicenter study to evaluate the incidence of invasive pulmonary aspergillosis among intubated patients with critical COVID-19. Coronavirus associated pulmonary aspergillosis (CAPA) was diagnosed in 30 patients (27.7%) after a median of 4 (2-8) days from intensive care unit (ICU) admission. Kaplan-Meier curves showed a significant higher 30-day mortality rate from ICU admission among patients with either CAPA (44% vs 19%, p = 0.002) or PIPA (74% vs 26%, p < 0.001) when compared with patients not fulfilling criteria for aspergillosis.

Comorbidities

Steardo L Jr, Steardo L, Verkhratsky A. **Psychiatric face of COVID-19.** Transl Psychiatry 2020;10,261. Full-text: https://doi.org/10.1038/s41398-020-00949-5

Your weekend review – 8 pages and 176 references? Father and son Steardo and Alexei Verkhratsky from Catanzaro, Benevento and Manchester/Bilbao/Moscow, respectively, outline possible neuropsychiatric complications of COVID-19: depression, bipolar disorders, reactive psychosis, obsessive-compulsive disorder, epilepsy, post-traumatic stress disorder. The authors predict an increased incidence of mental pathologies as a result of widespread SARS-CoV-2 infection.

Society

Cousins S. **COVID-19 has "devastating" effect on women and girls.** Lancet 2020; 396: P301-302, 1 August. Full-text: https://doi.org/10.1016/S0140-6736(20)31679-2

Fears are increasing that the COVID-19 pandemic will interfere with women's and girls' sexual and reproductive health and their access to care. In March, WHO issued interim guidance for maintaining essential services during an outbreak, which included advice to avert maternal and child mortality and morbidity. Will the deep existing inequalities COVID-19 has brought to the foreground encourage more action in the future?

Beyond plate borders

Cantwell M. **This tiny camera can show the world from a bug's point of view.** Science 2020, published 27 July. Short comment: https://www.sciencemag.org/news/2020/07/watch-tiny-camera-show-world-bug-s-point-view | YouTube video: https://youtu.be/VwiHf2T9bLU

Strap a 248 mg camera onto a beetle's back and stream video in almost real time. In the future, scientists could use these tiny cams to gain insight into the habits of insects outside the lab.

August 2020

1 August

Today, revise what you have read and learned over the past months. A summary of articles about Immunology and Vaccines from the beginning:

https://covidreference.com/daily-science-immunology

2 August

Epidemiology

Nguyen LH, Drew DA, Graham MS, et al. **Risk of COVID-19 among front-line health-care workers and the general community: a prospective cohort study.** Lancet Public Health. 2020 Sep;5(9):e475-e483. PubMed: https://pubmed.gov/32745512. Full-text: https://doi.org/10.1016/S2468-2667(20)30164-X

Front-line health care workers are at increased risk of SARS-CoV-2 infection. In a prospective, observational cohort study in the UK and the USA of the general community, including front-line health care workers, Andrew Chan and colleagues found that compared with the general community, front-line health care workers were at increased risk for reporting a positive COVID-19 test (adjusted HR 11·61, 95% CI 10·93–12·33). An increased risk (adjusted HR 3·40, 95% CI 3·37–3·43) was even found after accounting for differences in testing frequency between front-line health care workers and the general community. Post-hoc analyses showed that Black, Asian, and minority ethnic health care workers are at especially high risk of SARS-CoV-2 infection, with at least a fivefold (!) increased risk of COVID-19 compared with the non-Hispanic white general community.

de Souza WM, Buss LF, Candido DDS, et al. **Epidemiological and clinical characteristics of the COVID-19 epidemic in Brazil.** Nat Hum Behav. 2020 Jul 31. PubMed: https://pubmed.gov/32737472. Full-text: https://doi.org/10.1038/s41562-020-0928-4

Nuno Rodrigues Faria, Julio Croda and colleagues contextualize epidemiological, demographic and clinical findings for Brazilian COVID-19 cases in March, April and May 2020. By 31 May 2020, 514,200 COVID-19 cases and almost

30,000 deaths had been reported. They estimated a somewhat higher median transmission potential (R_0) of SARS-CoV-2 of 3.1 (2.4–5.5) in Brazil compared with Italy, the United Kingdom, France, and Spain. As expected, more populated and better-connected municipalities were affected earlier, and less populated municipalities at a later stage of the epidemic.

Virology

Xiong X, Qu K, Ciazynska KA, et al. **A thermostable, closed SARS-CoV-2 spike protein trimer.** Nat Struct Mol Biol. 2020 Jul 31. PubMed: https://pubmed.gov/32737467. Full-text: https://doi.org/10.1038/s41594-020-0478-5

The spike (S) protein which mediates receptor binding and cell entry exhibits substantial conformational flexibility. It transitions from closed to open conformations to expose its receptor-binding site and, subsequently, from pre-fusion to post-fusion conformations to mediate fusion of viral and cellular membranes. John Briggs, Xiaoli Xiong and colleagues now design mutations in the spike protein to allow the production of thermostable, disulfide-bonded S-protein trimers that are trapped in the closed, pre-fusion state. Furthermore, they demonstrate that the designed, thermostable, closed S trimer can be used in serological assays. They anticipate a wide array of potential applications as a reagent for serology, virology and as an immunogen.

Vaccine

Gu H, Chen Q, Yang G, et al. **Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy.** Science 2020 Jul 30:eabc4730. PubMed: https://pubmed.gov/32732280. Full-text: https://doi.org/10.1126/science.abc4730

First, adapt a clinical isolate of SARS-CoV-2 by serial passaging in the respiratory tract of aged BALB/c mice. When the mouse-adapted strain shows increased infectivity in mouse lung after 6 passages, leading to interstitial pneumonia and inflammatory responses following intranasal inoculation, sequence the virus genome and look for adaptive mutations which might be associated with the increased virulence. That's what Yusen Zhou, Cheng-Feng Qin, Shihui Sun, Shibo Jiang and colleagues did. They found an N501Y mutation located at the receptor binding domain (RBD) of the spike protein. They also showed the protective efficacy of a recombinant RBD vaccine candidate. They conclude that this MASCp6 could be of value in evaluating vaccines and antivirals against SARS-CoV-2.

Pathogenesis

Matheson NJ, Lehner PJ. **How does SARS-CoV-2 cause COVID-19?** Science 2020; 369:510-511. Full-text: https://doi.org/10.1126/science.abc6156

If you still have doubts about how SARS-CoV-2 enters human cells, read these two pages by Nicholas J. Matheson and Paul J. Lehner from Cambridge, UK. Find out what is so special about ACE2, what might cause the clinical deterioration that leads to severe systemic COVID-19 and how SARS-CoV-2 and our adaptive immune system, either antibodies or T cells, play together. The authors point out how essential it is to identify individuals with early SARS-CoV-2 infection who are at high risk of progression to severe disease. They recommend that treatment with future antiviral drugs should not be delayed until patients are hospitalized with severe lung injury.

Comorbidities

Rugge M, Zorzi M, Guzzinati S. **SARS-CoV-2 infection in the Italian Veneto region: adverse outcomes in patients with cancer.** Nat Cancer 2020, published 31 July. Full-text: https://doi.org/10.1038/s43018-020-0104-9

Massimo Rugge, Manuel Zorzi and Stefano Guzzinati describe 9,275 patients with SARS-CoV-2 infection (CV2+ve), 723 of whom (7.8%) had a cancer diagnosis. The proportion of patients hospitalized was higher among patients with cancer (56.6% versus 34.4% among other patients), and so was the proportion of deaths (14.7% versus 4.5%). The risk of adverse outcomes of SARS-CoV-2 infection was significantly higher for patients with cancer versus those without, particularly for males and older people. Breast cancer and hematological cancers were associated with a higher risk of both hospitalization and death. Lung cancer was associated with a fourfold risk of death due to SARS-CoV-2 infection. The authors insist that the clinical importance of these results warrants further investigation.

Books

Gellin B. **Why vaccine rumours stick—and getting them unstuck.** Lancet 2020, published 1 August. Full-text: https://doi.org/10.1016/S0140-6736(20)31640-8

We will be living with the COVID-19 pandemic's social and economic disruption until we are able to deploy effective vaccines globally. Unfortunately, vaccination policies have been and will be subject to political and ideological

debate. Bruce Gellin presents Heidi Larson's book *How Vaccine Rumors Start—and Why They Don't Go Away* which looks at the vaccine debate through the lens of an anthropologist who has been studying vaccine confidence for decades.

3 August

Epidemiology

Pham QT, Rabaa MA, Duong HL, et al. **The first 100 days of SARS-CoV-2 control in Vietnam**. Clin Infect Dis 2020, published 1 August. Full-text: https://doi.org/10.1093/cid/ciaa1130

One hundred days after the first SARS-CoV-2 case was reported in Vietnam on January 23rd, 270 cases were confirmed, with no deaths. Duc Anh Dang and colleagues describe the national control measures and conclude that Vietnam controlled SARS-CoV-2 spread through the early introduction of mass communication, meticulous contact-tracing with strict quarantine, and international travel restrictions. The value of these interventions is supported by the high proportion of asymptomatic and imported cases, and evidence for substantial pre-symptomatic transmission. A lesson for the world.

Transmission

Szablewski CM, Chang KT, Brown MM, et al. **SARS-CoV-2 Transmission and Infection Among Attendees of an Overnight Camp — Georgia, June 2020.** MMWR Morb Mortal Wkly Rep. ePub: 31 July 2020. Full-text: http://dx.doi.org/10.15585/mmwr.mm6931e1

Mid-June 2020. An overnight camp in Georgia (camp A) with trainees, staff members and campers. Wearing cloth masks for campers and opening windows and doors for increased ventilation in buildings were not required. (Cloth masks were required only for staff members.) Camp attendees engaged in a variety of indoor and outdoor activities, including daily vigorous singing and cheering. Of a total of 597 Georgia residents attendending camp A, test results were available for 344 (58%) attendees; among these 260 (76%) were positive. The overall attack rate was 44% (260 of 597), 51% among those aged 6–10 years, 44% among those aged 11–17 years, and 33% among those aged 18–21 years. Attack rates increased with increasing length of time spent at the camp, with staff members having the highest attack rate (56%).

Immunology

Atyeo C, Fischinger S, Zohar T, et al. **Distinct early serological signatures track with SARS-CoV-2 survival.** Immunity 2020, published 30 July. Abstract: https://www.cell.com/immunity/fulltext/S1074-7613(20)30327-7. **Full-text**: https://doi.org/10.1016/j.immuni.2020.07.020 | See also the **graphical abstract**: https://marlin-prod.literatumonline.com/cms/attachment/81258201-9c39-4b95-8a3d-bcb279d1e8c2/fx1.jpg

It still remains unclear why some individuals recover from infection while others rapidly progress and die. In order to investigate whether early SARS-CoV-2-specific humoral immune responses differ across individuals that ultimately recover or die from infection, Galit Alter, Helen Chu and colleagues profiled SARS-CoV-2–specific humoral responses on a small cohort of 22 hospitalized individuals and found that a combination of five SARS-CoV-2-specific antibody measurements were sufficient to distinguish individuals with different disease trajectories, including antibody measurements to S and N. In particular, spike–specific humoral responses were enriched among convalescent individuals, whereas functional antibody responses to the nucleocapsid were elevated in deceased individuals. This immunodominant S-specific antibody profile in convalescents was confirmed in a larger validation cohort. The authors suggest the potential of functional antigen-specific humoral immunity to guide patient care and vaccine development.

Pathogenesis

Ramlall V, Thangaraj PM, Meydan C et al. **Immune complement and coagulation dysfunction in adverse outcomes of SARS-CoV-2 infection.** Nat Med, published 3 August. Full-text: https://www.nature.com/articles/s41591-020-1021-2

Mortality of severe COVID-19 is driven by viral replication and comorbidities that influence immune-mediated pathology. As the complement system is a critical defense against pathogens that, when dysregulated, can contribute to inflammation-mediated pathologies, Sagi Shapira, Nicholas Tatonetti and colleagues explored the role of complement or coagulatory function in SARS-CoV-2 infection and clinical outcome. In a retrospective observational study of 11,116 patients who presented to New York-Presbyterian/Columbia University Irving Medical Center with suspected SARS-CoV-2 infection, they found that history of macular degeneration (a proxy for complement activation disorders) and history of coagulation disorders (thrombocytopenia, thrombosis and hemorrhage) are risk factors for morbidity and mortality in

SARS-CoV-2-infected patients. Moreover, patients with AMD succumbed to disease more rapidly than others. The authors also found that transcriptional profiling of nasopharyngeal swabs from 650 control and SARS-CoV-2-infected patients demonstrate that infection results in robust engagement and activation of complement and coagulation pathways.

Diagnostics

Lai CKC, Chen Z, Lui G, et al. **Prospective study comparing deep-throat saliva with other respiratory tract specimens in the diagnosis of novel coronavirus disease (COVID-19).** J Infect Dis 2020, published 1 August. Full-text: https://doi.org/10.1093/infdis/jiaa487

Self-collected specimens for SARS-CoV-2 diagnosis could one day avoid infectious exposure to healthcare workers. Now Paul Chan and colleagues perform a prospective study in two regional hospitals in Hong Kong, examining 563 serial samples collected during the viral shedding period of 50 patients: 150 deep throat saliva (DTS), 309 pooled-nasopharyngeal (NP) and throat swabs, and 104 sputum. (Instructions for deap throat saliva: first clear your throat by gargling with your own saliva, and then spit out the DTS into a sterile bottle.) Deep throat saliva produced the lowest viral RNA concentration and RT-PCR positive rate compared to conventional respiratory specimens.

Treatment

Malhotra A, Hepokoski M, McCowen KC, Shyy JYJ. **ACE2, Metformin, and COVID-19.** iScience 2020, pulished 30 July. Summary: https://www.cell.com/iscience/fulltext/S2589-0042(20)30615-5. Full-text: https://doi.org/10.1016/j.isci.2020.101425

Angiotensin converting enzyme 2 (ACE2) is essential to COVID-19 pathogenesis. Preclinical data suggest that ACE2 may be downregulated after SARS-CoV-2 binding, and treatments which increase ACE2 might prevent cardiopulmonary injury. Now Atul Malhotra, John Shyy and colleagues hypothesize that patients with COVID-19 taking metformin might have higher circulating ACE2 levels, and lower morbidity and mortality. They propose to test this hypothesis through a combination of retrospective cohort studies, and prospective translational studies evaluating the ACE2 axis in COVID-19 patients. The authors also cite an observational study from Wuhan, China, which showed that in-hospital mortality was significantly lower in a metformin group than in a control group (3/104 (2.9%) versus 22/179 (12.3%), p = 0.01; Luo P, Qiu L, Liu Y, et al. **Metformin Treatment Was Associated with Decreased Mortality in**

COVID-19 Patients with Diabetes in a Retrospective Analysis. Am J Trop Med Hyg 2020;103(1):69-72. PubMed: https://pubmed.gov/32446312. Full-text: https://doi.org/10.4269/ajtmh.20-0375).

Cheng GS, Hill JA. **To Toci or Not to Toci for COVID-19: Is That Still the Question?** Clin Infect Dis. 2020 Jul 31:ciaa1133. PubMed: https://pubmed.gov/32735642. Full-text: https://doi.org/10.1093/cid/ciaa1133

Joshua Hill and Guang-Shing Cheng first narrate the story of tocilizumab and the IL-6 receptor in such a way that you understand the impetus to use tocilizumab in hospitalized patients with COVID-19, despite the lack of data from controlled trials. They then go on to comment the study by Somers et al., *Tocilizumab for treatment of mechanically ventilated patients with COVID-19*, we presented on 12 July (https://covidreference.com/top-10-July-12). Excellent summary.

Collateral effects

Mekaoui N, Razine R, Bassat Q, et al. **The Effect of COVID-19 on Paediatric Emergencies and Admissions in Morocco: Cannot See the Forest for the Trees?** J Trop Pediatr 2020, published 1 August. Full-text: https://doi.org/10.1093/tropej/fmaa046

Where are the sick Moroccan children normally brought to the emergency department? When Nour Mekaoui and colleagues from the Rabat Children's Hospital, Morocco, compared the number of pediatric consultations (< 16 years) in the number of consultations of the same period in the preceding year, they discovered that the number of overall consultations decreased by 74% between the two periods (4232 vs. 1110; $p < 0.005$). Even the the number of hospitalizations declined (811 in 2019 vs. 471 in 2020, a 41.9% reduction, $p < 0.005$; see figure). The authors are worried: Where did these severely ill patients go? Might we anticipate a new wave of serious non-COVID-19 pediatric admissions?

4 August

Epidemiology

Kolthur-Seetharam U, Shah D, Shastri J, Juneja S, Kang G, Malani A, Mohanan M, Lobo GN, Velhal G, Gomare M. **SARS-CoV2 Serological Survey in Mumbai by NITI-BMC-TIFR.** Tata Institute of Fundamental Research (TIFR) 2020, published 29 June. Full-text: https://www.tifr.res.in/TSN/article/Mumbai-Serosurvey%20Technical%20report-NITI.pdf

We usually prefer peer-reviewed studies and seldom present pre-published papers. We are even less readily inclined to present a PDF with just the technical details of an unpublished study. Today we make an exception. In a cross-sectional survey in Mumbai, India, Ullas Kolthur-Seetharam and colleagues estimated the prevalence of SARS-CoV-2 infection in three areas in Mumbai (called 'wards') in July 2020. The authors found, on average, a prevalence of around 57% in the slum areas of Chembur, Matunga and Dahisar, and 16% in neighboring non-slums. If these data are confirmed, some Mumbai areas would soon reach herd immunity and could return to a pre-COVID way of life. For many countries in the world, this would be the best piece of news since the beginning of the pandemic.

Virology

Huang Y, Yang C, Xu X *et al.* **Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19.** Acta Pharmacol Sin 2020, published 3 August. Full-text: https://www.nature.com/articles/s41401-020-0485-4

The spike protein of SARS-CoV-2 plays a key role in the receptor recognition and cell membrane fusion process. In this review, Shu-wen Liu, Wei Xu and colleagues from Southern Medical University, Guangzhou, China, highlight recent research advances in the structure, function and development of antiviral drugs targeting the S protein. Six pages, 86 references.

Prevention

Krueger A, Gunn JK, Watson J, et al. **Characteristics and Outcomes of Contacts of COVID-19 Patients Monitored Using an Automated Symptom Monitoring Tool — Maine, May–June 2020.** MMWR Morb Mortal Wkly Rep 2020, published 3 August. Full-text: http://dx.doi.org/10.15585/mmwr.mm6931e2

A prompt case investigation can rapidly identify contacts and recommend quarantine, reducing additional exposures and transmission. Here Anna Krueger and colleagues present 1,622 contacts of 614 COVID-19 patients who were enrolled in an automated symptom monitoring system in May and June 2020. 190 (11.7%) eventually developed COVID-19. The authors conclude that using digital tools in support of a comprehensive contact tracing strategy can make the contact tracing and monitoring process faster and more efficient.

Immunology

Mateus J, Grifoni A, Tarke A, et al. **Selective and cross-reactive SARS-CoV-2 T cell epitopes in unexposed humans.** Science 2020, published 4 August. Full-text: https://science.sciencemag.org/content/early/2020/08/03/science.abd3871

SARS-CoV-2 reactive $CD4^+$ T cells have been reported in unexposed individuals, suggesting pre-existing cross-reactive T cell memory in 20-50% of people (see, for example, *SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19*, presented here on 29 July). To investigate this exciting topic, Daniela Weiskopf, Alessandro Sette and colleagues utilized PBMC samples from subjects collected between March 2015 and March 2018. They demonstrate a range of pre-existing memory $CD4^+$ T cells that are cross-reactive with comparable affinity to SARS-CoV-2 and the common cold coronaviruses HCoV-OC43, HCoV-229E, HCoV-NL63, or HCoV-HKU1. Based on these data, the authors find plausible to hypothesize that pre-existing cross-reactive HCoV $CD4^+$ T cell memory could explain different COVID-19 clinical outcomes and influence epidemiological models of herd immunity. However, their last sentence includes a warning: it's still highly speculative.

Pathogenesis

Zhang B, Chu H, Han S et al. **SARS-CoV-2 infects human neural progenitor cells and brain organoids.** Cell Res 2020, published 4 August. Full-text: https://doi.org/10.1038/s41422-020-0390-x

Jian-Dong Huang and colleagues assessed SARS-CoV-2 infection in induced pluripotent stem cells (iPSCs)-derived human neural progenitor cells (hNPCs), neurospheres, and brain organoids. They detected extensive viral protein expression and infectious viral particles in neurospheres and brain organoids infected with SARS-CoV-2, suggesting that SARS-CoV-2 can productively infect the human brain. In particular, they demonstrated that SARS-CoV-2 could also target the neuronal progenitor cell populations. Chronic or long-

term consequences of SARS-CoV-2 infection in the CNS should be closely monitored.

Treatment

Touret F, Gilles M, Barral K et al. **In vitro screening of a FDA approved chemical library reveals potential inhibitors of SARS-CoV-2 replication.** Sci Rep 2020; 10**,** 13093. Full-text: https://doi.org/10.1038/s41598-020-70143-6

Do you remember Franck Touret? On 5 March, he published *Of chloroquine and COVID-19* (Touret F, de Lamballerie X. **Of chloroquine and COVID-19.** Antiviral Res. 2020 May;177:104762. PubMed: https://pubmed.gov/32147496. Full-text: https://doi.org/10.1016/j.antiviral.2020.104762), a brilliant summary of chloroquine's repeated failures in treating acute human viral diseases over the last decades. Now, Franck Touret, Bruno Coutard and colleagues screened 1,520 approved and off-patent drugs of the Prestwick Chemical Library in an infected cell-based assay. Eleven compounds such as macrolides antibiotics, proton pump inhibitors (omeprazole and vonoprazan), antiarrhythmic agents or CNS drugs emerged that show an antiviral potency with 2 of them $\mu M EC50 \leq 20$

Chan KK, Dorosky D, Sharma P, et al. **Engineering human ACE2 to optimize binding to the spike protein of SARS coronavirus 2.** Science 2020, published 4 August. Full-text: https://science.sciencemag.org/content/early/2020/08/03/science.abc0870

Soluble ACE2 (sACE2) has been proposed as a therapeutic candidate that neutralizes infection by acting as a decoy. Now Eric Procko and colleagues describe mutations in ACE2 that increase S binding across the interaction surface, in the N90 glycosylation motif and at buried sites. A stable dimeric sACE2 variant with improved properties for binding viral spike showed potent SARS-CoV-2 and -1 neutralization *in vitro*. The authors conclude that exceptional affinity for protein S can be engineered into the natural receptor for the virus, while also providing insights into the molecular basis for initial virus-host interactions.

Co-morbidities

Velez JCQ, Caza T, Larsen CP. **COVAN is the new HIVAN: the re-emergence of collapsing glomerulopathy with COVID-19.** Nat Rev Nephrol2020, published 4 August. Full-text: https://doi.org/10.1038/s41581-020-0332-3

Is COVAN the new HIVAN? Collapsing glomerulopathy was first characterized in the setting of HIV infection and termed HIV-associated nephropathy (HIVAN). In recent months, five case reports of collapsing glomerulopathy akin to those seen during the HIV epidemic have been published describing cases of collapsing glomerulopathy in association with SARS-CoV-2 infection. All of these cases were in patients of African ethnicity. Juan Carlos Velez and co-authors propose the term COVID-19-associated nephropathy (COVAN) to be used to describe this specific entity.

5 August

Epidemiology

Sabbadini LL, Romano MC, et al. [**First results of the seroprevalence survey about SARS-CoV-2**] (*Primi risultati dell'indagine di sieroprevalenza sul SARS-CoV-2*). Italian Health Ministery and National Statistics Institute 2020, published 3 August. Full-text (Italian): https://www.istat.it/it/files//2020/08/ReportPrimiRisultatiIndagineSiero.pdf

According to a representative study by the Italian Ministry of Health (64,000 participants), 1.5 million people (2.5% of the population) had SARS-CoV-2 antibodies during the study period from May 25 to July 15. This figure is higher than the currently reported 250,000 cases, but far less than an estimate by the UK Imperial College which projected the number of infected people in Italy to be 6 million on 28 March (95% credible interval: 1,932,800 - 15,704,000; see the full-text, published on 30 March). Perhaps to beware of Imperial College projections. The more important message of the Italian study: if these figures are true, the *infection fatality rate* (IFR, the proportion of deaths among all the infected individuals) in Italy would be 2.3% (35,000 deaths/1,500,000 infections). This is higher than in other European countries and needs to be addressed in future studies.

Panovska-Griffiths J, Kerr CC, Stuart RM, et al. **Determining the optimal strategy for reopening schools, the impact of test and trace interventions, and the risk of occurrence of a second COVID-19 epidemic wave in the UK: a modelling study**. Lancet Child Adolesc Health 2020, August 03, 2020. Full-text: https://doi.org/10.1016/S2352-4642(20)30250-9

Does anyone doubt this? To prevent a second wave, relaxation of physical distancing, including reopening of schools, must be accompanied by large-

scale, population-wide testing of symptomatic individuals and effective tracing of their contacts, followed by isolation of diagnosed individuals. The authors estimate for the UK that without these levels of testing and contact tracing, reopening of schools together with gradual relaxing of the lockdown measures are likely to induce a second wave that would peak in December 2020 (if schools open full-time in September), having 2.0 – 2.3 times the size of the original COVID-19 wave.

Transmission

Macartney K, Quinn HE, Pillbury AJ. **Transmission of SARS-CoV-2 in Australian educational settings: a prospective cohort study**. Lancet Child Adolesc Health, August 03, 2020. Full-text: https://doi.org/10.1016/S2352-4642(20)30251-0

Transmission in schools may be less frequent than expected. This group has analyzed 15 schools and ten ECEC (early childhood education and care) settings which had children (n=12) or adults (n=15) attending while infectious, with 1,448 contacts monitored. Of these, 633 (44%) had nucleic acid testing or antibody testing, with 18 secondary cases identified (attack rate 1.2%). Five secondary cases (three children; two adults) were identified (attack rate 0.5%; 5/914) in three schools. No secondary transmission occurred in nine of ten ECEC settings among 497 contacts. However, one outbreak in an ECEC setting involved transmission to six adults and seven children (attack rate 35%; 13/37).

Valentine R, Valentine D, Valentine JL. **Relationship of George Floyd protests to increases in COVID-19 cases using event study methodology**. Journal of Public Health, August 5, 2020. Full-text: https://doi.org/10.1093/pubmed/fdaa127

Best author list of the day. Randall, Dawn and Jimmie L. Valentine (from different institutions) show that in 6/8 US cities in which protestors in the tens of thousands were reported, infection rate growth was positive and significant. The Valentines argue that to slow the spread of COVID-19, CDC guidelines must be followed in protest situations. Well, it's not that easy when you are angry.

Immunology

Zhou R, Wang KK, Wong YC, et al. **Acute SARS-CoV-2 infection impairs dendritic cell and T cell responses**. Immunology August 03, 2020. Full-text: https://doi.org/10.1016/j.immuni.2020.07.026

More insights on T cell immunity. By investigating 17 acute and 24 convalescent patients, the authors found that acute infection resulted in broad immune cell reduction including T, NK, monocyte and dendritic cells (DC). DCs were significantly reduced with functional impairment. Neutralizing antibodies were rapidly and abundantly generated in patients, there were delayed receptor binding domain (RBD)- and nucleocapsid protein (NP)-specific T cell responses during the first 3 weeks post symptom onset. These findings provide evidence that impaired DCs, together with timely inverted strong antibody but weak CD8 T cell responses, may contribute to acute COVID-19 pathogenesis.

Clinical

Califf RM, Hernandez AF, Landray M, et al. **Weighing the Benefits and Risks of Proliferating Observational Treatment Assessments: Observational cacophony, randomized harmony.** JAMA. Published online July 31, 2020. Full-text: https://doi.org/10.1001/jama.2020.13319

The authors provide some thoughts on how hundreds of observational studies that have added nothing more than noise, confusion, and false confidence when their findings were widely disseminated by the lay media.

Zhao J, Yang Y, Huang H, et al. **Relationship between the ABO Blood Group and the COVID-19 Susceptibility**. Clinical Infectious Diseases, August 4, 2020, ciaa1150, https://doi.org/10.1093/cid/ciaa1150.

Among 3700 patients from Wuhan, the risk for infection significantly increased for blood group A (OR 1.3, 95% CI1.1-1.4) and decreased for blood group O (OR 0.7, 95% CI 0.6-0.8). Blood group O was associated with a lower risk of death compared with non-O groups, with an OR of 0.7 (95% CI 0.5-0.9). On the other hand, blood group A was associated with a higher risk of death compared with non-A groups, with an OR of 1.5 (95% CI 1.1-2.0). However, many open questions remain and the authors conclude that it would be premature to use this study to guide clinical practice at this time.

Treatment

Fajgenbaum DC, Rader DJ. **Teaching Old Drugs New Tricks: Statins for COVID-19?** Cell Metabolism August 4, 2020, 32: 145-147. Full-text: https://doi.org/10.1016/j.cmet.2020.07.006

The authors review the literature and argue that, given the association between statin use and improved outcomes in a large observational study of hospitalized COVID-19 patients, but also given the widespread availability, low cost, and safety of statins, this drug class should be further investigated in randomized controlled trials.

Robson F, Khan KS, Le TK, et al. **Coronavirus RNA proofreading: molecular basis and therapeutic targeting**. Molecular Cell. August 04, 2020. Full-text: https://doi.org/10.1016/j.molcel.2020.07.027

These authors review the molecular basis of the CoV proofreading complex and evaluate its potential as a drug target. They also consider existing nucleoside analogues and novel genomic techniques as potential anti-CoV therapeutics that could be used individually or in combination to target the proofreading mechanism.

Clark KE, Collas O, Lachmann H, et al. **Safety of intravenous Anakinra in COVID-19 with evidence of hyperinflammation, a case series**. Rheumatol Adv Pract, August 4, 2020. Full-text: https://doi.org/10.1093/rap/rkaa040

Some more data on anakinra. Four patients with severe COVID-19 infection requiring intensive care admission and ventilatory support are described. Upon commencement of intravenous anakinra, there was subsequent improvement in the patients clinically with reduced ventilatory support and inotropic support, and biochemically, with rapid improvement in inflammatory markers. But again, think about the earlier JAMA comment above (Califf RM et al.)

6 August

Transmission

Hu M, Lin H, Wang J, et al. **The risk of COVID-19 transmission in train passengers: an epidemiological and modelling study.** Clin Infect Dis 2020, published 29 July. Full-text: https://doi.org/10.1093/cid/ciaa1057

How risky is train traveling in the COVID-19 era? To answer this question, analyze passengers in Chinese high-speed trains. Jinfeng Wang and colleagues quantified the transmission risk using data from 2,334 index patients and 72,093 close contacts who had co-travel times of 0–8 hours from 19 December 2019 through 6 March 2020. Unsurprisingly, travelers adjacent to an index patient had the highest attack rate (3.5%) and the attack rate **de**creased with increasing distance, but **in**creased with increasing co-travel time. The overall attack rate of passengers with close contact with index patients was 0.32%. The author's conclusion: during COVID outbreaks, when travelling on public transportation in confined spaces such as trains, increase seat distance and reduce passenger density.

Prevention

Aleta A, Martín-Corral D, Pastore y Piontti A, et al. **Modelling the impact of testing, contact tracing and household quarantine on second waves of COVID-19.** Nat Hum Behav 2020. Published 5 August. Full-text: https://doi.org/10.1038/s41562-020-0931-9

Some countries are currently facing second-wave scenarios. To understand the challenges ahead, Yamir Moreno, Esteban Moro, Alessandro Vespignani and colleagues integrated anonymized and privacy-enhanced data from mobile devices and census data and built a detailed agent-based model of SARS-CoV-2 transmission in the Boston metropolitan area. They found that a period of strict social distancing followed by a robust level of testing, contact-tracing and household quarantine could keep COVID-19 within the capacity of the healthcare system while enabling the reopening of economic activities.

Vaccine

Corbett KS, Edwards DK, Leist SR et al. **SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness.** Nature 2020, published 5 August. Full-text: https://doi.org/10.1038/s41586-020-2622-0

Barney Graham, Andrea Carfi and colleagues show that mRNA-1273, a vaccine currently tested in Phase 3 trials, protects mice against SARS-CoV-2 infection in the lungs and noses without evidence of immunopathology. The vaccine induced both potent neutralizing antibody responses to wild-type (D614) and D614G mutant[2] SARS-CoV-2 and CD8 T cell responses. The authors are prolific – a week ago, they evaluated the same vaccine in non-human primates and published their paper in the N Engl J Med (see Corbett et al., Top 10 July 29).

Read also the last paragraph of this week's paper where Corbett et al. describe a new paradigm for rapid vaccine development.

See also a Nat Biomed Eng editorial: **Fast-and-fit vaccines.** Published 10 August 2020. Full-text: https://doi.org/10.1038/s41551-020-00605-9

Treatment

Baum A, Copin R, Ajithdoss D, et al. **REGN-COV2 antibody cocktail prevents and treats SARS-CoV-2 infection in rhesus macaques and hamsters.** bioRxiv 2020, pre-published 3 August. Full-text: https://doi.org/10.1101/2020.08.02.233320

In this pre-print paper, Christos Kyratsous and colleagues report the *in vivo* efficacy in both rhesus macaques and golden hamsters of a cocktail of two neutralizing antibodies targeting non-overlapping epitopes on the SARS-CoV-2 spike protein. The animals were first dosed with the cocktail and challenged three days later with $1x10^5$ PFU of virus through intranasal and intratracheal routes. The cocktail, termed 'REGN-COV-2', greatly reduced viral load in the lower and the upper airways; it also decreased virus induced pathological sequalae when administered prophylactically or therapeutically. The paper has not yet been peer reviewed.

Harrison C. **Focus shifts to antibody cocktails for COVID-19 cytokine storm.** Nat Biotechnol 2020; 38:905–908. Full-text: https://doi.org/10.1038/s41587-020-0634-9

Combining agents targeting different cytokines may one day be used in supportive care for COVID-19 patients with acute respiratory distress syndrome. Charlotte Harrison takes you on a tour around Roche's **Actemra** (tocilizumab, a mAb targeting IL-6R), Russian Biocad's **Ilsira** (levilimab), Bermuda-based Kiniksa Pharmaceuticals' **mavrilimumab** (a human IgG4 mAb targeting GM-CSF), R-Pharm's **olokizumab**, a humanized anti-IL-6 mAb, **Sylvant** (siltuximab), an anti-IL-6 chimeric IgG1 mAb from EUSA Pharma and BeiGene, and many more.

Collateral Effects

Kaufman HW, Chen Z, Niles J, Fesko Y. **Changes in the Number of US Patients with Newly Identified Cancer Before and During the Coronavirus Disease 2019 (COVID-19) Pandemic.** JAMA Netw Open 2020;3(8):e2017267. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.17267

During and after lockdowns, people go into hibernation mode, but cancer does not. Now Harwey Kaufman and colleagues report a cross-sectional study about patients across the United States who received clinical laboratory testing related to any of 6 cancer types (i.e., **breast, colorectal, lung, pancreatic, gastric, and esophageal**). Each patient was counted once, at the first instance of a cancer-related ICD-10 code. The authors compared 258,598 patients from the **baseline period** (January 6, 2019, to February 29, 2020) with 20,180 patients from the **COVID-19 period** (March 1 to April 18, 2020). During the pandemic, the weekly number of newly identified patients **fell 46.4%** (from 4310 to 2310) for the 6 cancers combined, with significant declines in all cancer types, ranging from 24.7% for pancreatic cancer (from 271 to 204; $p = 0.07$) to 51.8% for breast ca ($p < 0.001$). The authors anticipate that a delay in diagnosis will likely lead to presentation at more advanced stages and poorer clinical outcomes.

Matsuo T, Kobayashi D, Taki F, et al. **Prevalence of Health Care Worker Burnout During the Coronavirus Disease 2019 (COVID-19) Pandemic in Japan.** JAMA Netw Open 2020; 3(8):e2017271. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.17271

How prevalent is burnout among frontline health care workers (HCWs) during the COVID-19 pandemic? Takahiro Matsuo and colleagues conducted an online cross-sectional survey among HCWs at a tertiary hospital in Tokyo which had among the highest numbers of patients with COVID-19 in Japan. Among the final sample of 312 HCW's, the burnout prevalence was 31.4% (98 of 312). Nurses: 59/126 (46.8%); radiological technologists: 8/22 (36.4%); pharmacists: 7/19 (36.8%). Find more details (i.e., burnout was more prevalent in participants with fewer years of experience) in the paper.

Society

Leonhardt D. **The Unique U.S. Failure to Control the Virus.** The New York Times 2020, published 6 August. Article: https://www.nytimes.com/2020/08/06/us/united-states-failure-coronavirus.html | Graphics: Lauren Leatherby

One country stands alone, as the only affluent nation to have suffered a severe, sustained outbreak for more than four months: the United States.

Education

Rubin EJ, Baden LR, Morrissey S. **The Impact of Covid-19 on Patients with Other Diseases, with Arnold Epstein**. N Engl J Med 2020; 383:e62. Access: https://www.nejm.org/doi/full/10.1056/NEJMe2027046

Audio interview (22:08) with Arnold Epstein who talks about the collateral impact of COVID-19 on the care of patients with other diseases and on the U.S. health care system itself.

Journal Feature

Scudellari M. **How the pandemic might play out in 2021 and beyond.** Nature 2020, published 5 August. Full-text: https://www.nature.com/articles/d41586-020-02278-5

In this *Nature* news feature, Megan Scudellari reports what scientists predict for the next months and years.

Beyond plate borders

Gibb R, Redding DW, Chin KQ et al. **Zoonotic host diversity increases in human-dominated ecosystems.** Nature 2020, published 5 August. Full-text: https://doi.org/10.1038/s41586-020-2562-8

Are changes in the way and intensity we use land creating hazardous interfaces between people, livestock and wildlife reservoirs of zoonotic disease? Kate Jones and colleagues provide important evidence for this claim. They analyzed 6,801 ecological assemblages and 376 host species worldwide and found that wildlife hosts of human-shared pathogens and parasites comprised a greater proportion of local species richness (18–72% higher) and total abundance (21–144% higher) in places dominated by humans (secondary, agricultural and urban ecosystems) compared with nearby undisturbed habitats.

Read also the discussion by Richard S. Ostfeld and Felicia Keesing: **Species that can make us ill thrive in human habitats.** Does the conversion of natural habitats to human use favour animals that harbour agents causing human disease? Nature 2020, published 5 August. Full-text: https://www.nature.com/articles/d41586-020-02189-5

7 August

Epidemiology

To KK, Chan WM, Ip JD, et al**. Unique SARS-CoV-2 clusters causing a large COVID-19 outbreak in Hong Kong**. Clin Infect Dis. 2020 Aug 5:ciaa1119. PubMed: https://pubmed.gov/32756996. Full-text: https://doi.org/10.1093/cid/ciaa1119

With a total of 617 locally acquired laboratory-confirmed cases reported between July 5 and 21, Hong Kong has experienced the largest local COVID-19 outbreak since the beginning of the pandemic. This phylogenetic study by Kwok-Yung Yuen, Kelvin Kai-Wang To and colleagues shows that this outbreak was related to imported cases and not to silent carriers from previous waves. Two unique SARS-CoV-2 clusters were identified.

Transmission

Klompas M, Baker MA, Rhee C. **Airborne Transmission of SARS-CoV-2: Theoretical Considerations and Available Evidence**. JAMA. 2020 Aug 4;324(5):441-442. PubMed: https://pubmed.gov/32749495 . Full-text: https://doi.org/10.1001/jama.2020.12458

Brief review. It is impossible to conclude that aerosol-based transmission never occurs, write Michael Klompas and colleagues, but the balance of currently available evidence suggests that long-range aerosol-based transmission is not the dominant mode of SARS-CoV-2 transmission.

Joonaki E, Hassanpouryouzband A, Heldt Cl, et al. **Surface Chemistry Can Unlock Drivers of Surface Stability of SARS-CoV-2 in Variety of Environmental Conditions**. Chem, August 06, 2020. Full-text: https://doi.org/10.1016/j.chempr.2020.08.001

Nice overview of existing knowledge concerning viral spread, molecular structure of SARS-CoV-2, and the stability of the virus surface. Edris Joonaki and colleagues discuss potential drivers of the SARS-CoV-2 surface adsorption and stability in various environmental conditions.

Immunology

Rodriguez, L, Pekkarinen, PT, Lakshmikanth, T, et al. **Systems-level immunomonitoring from acute to recovery phase of severe COVID-19.** Cell Rep Med 2020, published 5 August. Full-text: https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(20)30099-9

To treat hyperinflammation in severe COVID-19 we need to better understand which cells are involved, how they interact and which protein mediators they use to orchestrate their responses. To this end, Petter Brodin and colleagues followed 37 adult patients diagnosed with COVID-19 from the acute to the recovery phases of the disease and performed longitudinal systems-level blood immunomonitoring. They describe an IFNγ – eosinophil axis activated prior to lung hyperinflammation and changes in cell-cell coregulation during different stages of the disease.

Schulte-Schrepping J, Reusch N, Paclik D, et al. **Severe COVID-19 is marked by a dysregulated myeloid cell compartment**. Cell August 05, 2020. Full-text: https://doi.org/10.1016/j.cell.2020.08.001

This German study revealed profound alterations in the myeloid cell compartment associated with severe COVID-19. By combining single-cell RNA-sequencing and single-cell proteomics of whole blood and peripheral blood mononuclear cells, Joachim Schultze and colleagues determined changes in immune cell composition and activation in mild versus severe COVID-19 cases (n = 109) over time. HLA-DRhiCD11chi inflammatory monocytes with an interferon-stimulated gene signature were elevated in mild COVID-19. Severe COVID-19 was marked by occurrence of neutrophil precursors, as evidence of emergency myelopoiesis, dysfunctional mature neutrophils, and HLA-DRlo monocytes.

Silvin A, Chapuis N, Dunsmore G, et al. **Elevated calprotectin and abnormal myeloid cell subsets discriminate severe from mild COVID-19**. Published: August 05, 2020. Full-text: https://doi.org/10.1016/j.cell.2020.08.002

Performing high dimensional flow cytometry and single cell RNA sequencing of COVID-19 patients, Eric Solary, Michaela Fontenay, Florent Ginhoux and colleagues found that severe COVID-19 was associated with a burst of circulating calprotectin that preceded cytokine release syndrome, low levels of non-classical monocytes in the peripheral blood, and an emergency myelopoiesis that releases immature and dysplastic myeloid cells with an immune suppres-

sive phenotype. This work provides further rationale for the testing of several clinical strategies, including blocking emergency myelopoiesis.

Clinical

Pujadas E, Chaudry F, McBride R, et al. **SARS-CoV-2 viral load predicts COVID-19 mortality**. Lancet Respir Med August 06, 2020. Full-text: https://doi.org/10.1016/S2213-2600(20)30354-4

In this large cohort (n=1145) of hospitalized, symptomatic patients from New York, viral loads were measured. In a Cox proportional hazards model adjusting for several confounders, Carlos Cordon-Cardo and colleagues found a significant independent association between viral load and mortality (hazard ratio 1.07, 95% CI 1.03–1.11, p = 0.0014), with a 7% increase in hazard for each log transformed copy / mL.

Treatment

Hodge C, Marra F, Marzolini C, et al. **Drug interactions: a review of the unseen danger of experimental COVID-19 therapie**s. J Antimicrob Chemother. 2020 Aug 4:dkaa340. PubMed: https://pubmed.gov/32750131 . Full-text: https://doi.org/10.1093/jac/dkaa340

Experimental COVID-19 therapies carry significant risk for drug-drug interactions (DDIs), especially the HIV protease inhibitor lopinavir/ritonavir, chloroquine, hydroxychloroquine and ruxolitinib. In contrast, anakinra, baricitinib, favipiravir, interferon-b, nitazoxanide, ribavirin, remdesivir, sarilumab and tocilizumab have lower propensity for drug interactions. In March 2020, this group from Liverpool (famous for their HIV interaction website) published a DDI resource for experimental COVID therapies (www.covid19-druginteractions.org). Here Saye Khoo and colleagues summarize the methodology and processes undertaken to establish this resource.

Moorlag SJ, van Deuren RX, van Werkhoven CH, et al. **Safety and COVID-19 symptoms in individuals recently vaccinated with BCG: a retrospective cohort study**. Cell Rep Med August 05, 2020. Full-text: https://www.sciencedirect.com/science/article/pii/S2666379120300938

Mihai Netea and colleagues retrospectively assessed COVID-19 related symptoms in three cohorts of healthy volunteers who either received BCG in the last five years (n = 266) or not (n = 164). BCG vaccination was not associated with increased incidence of symptoms and might be associated with a decrease in the incidence of sickness during the COVID-19 pandemic, and lower

incidence of extreme fatigue. However, caution is warranted in interpreting these findings: limitations include the retrospective nature of the study in two relatively small groups of volunteers, and the potential for selection bias.

Education

Parker-Pope T. **The Many Symptoms of Covid-19.** The New York Times 2020, published 5 August. Full-text: https://www.nytimes.com/2020/08/05/well/live/coronavirus-covid-symptoms.html

"From a sniffle or cough that feels like allergies to severe body aches and crippling fatigue, the symptoms of coronavirus can be unpredictable from head to toe." Plain English for all of us.

8 August

Prevention

Budd J, Miller BS, Manning EM, et al. **Digital technologies in the public-health response to COVID-19.** Nat Med 2020, published 7 August. Full-text: https://doi.org/10.1038/s41591-020-1011-4

Your review for the weekend - seven pages and 151 references will give you a glimpse of how the digital world might fight back to SARS-CoV-2. Rachel McKendry and colleagues critically review how billions of mobile phones, low-cost computing resources and advances in machine learning and natural language processing are being recruited into a gigantic antiviral network.

Firth JA, Hellewell J, Klepac P, et al. **Using a real-world network to model localized COVID-19 control strategies.** Nat Med 2020, published 7 August. Full-text: https://doi.org/10.1038/s41591-020-1036-8

Lewis Spurgin and colleagues simulate control strategies for SARS-CoV-2 transmission in a real-world social network generated from high-resolution GPS data that were gathered in the course of a citizen-science experiment. They find that tracing the *contacts of contacts* reduces the size of simulated outbreaks more than tracing of only contacts and suggest that contact tracing and quarantine might be most effective as 'local lockdown' strategies when contact rates are high.

Schilling K, Gentner DR, Wilen L, et al. **An accessible method for screening aerosol filtration identifies poor-performing commercial masks and respirators.** J Expo Sci Environ Epidemiol 2020, published 7 August. Full-text: https://doi.org/10.1038/s41370-020-0258-7

During the initial phases of the COVID-19 pandemic the shortage of regulation-tested masks contributed to the rapid spread of SARS-CoV-2 in healthcare settings. Here Lisa Lattanza and colleagues present experimental methods to evaluate mask filtration and breathability via cost-effective approaches that could be easily replicated in communities without extensive infrastructure.

Immunology

Cohen J. **Designer antibodies could battle COVID-19 before vaccines arrive.** Science 2020, published 4 August. Full-text: https://www.sciencemag.org/news/2020/08/designer-antibodies-could-battle-covid-19-vaccines-arrive

Science writer Jon Cohen describes how the competition is heating up to produce targeted monoclonal antibodies which could both prevent and treat COVID-19. Read about treatment and prevention trials, antibody cocktails and the role monoclonal antibodies might play even after the general availability of effective vaccines. Read also about the final problem of monoclonal antibodies: their cost, especially for the higher doses needed for treatment. Don't expect monoclonals to be affordable globally. Rather, they might split the world into the haves and have-nots, like many previous drugs. That's another reason why accessible vaccines are so important!

Hadjadj J, Yatim N, Barnabei L, et al. **Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients.** Science. 2020 Aug 7;369(6504):718-724. PubMed: https://pubmed.gov/32661059. Full-text: https://doi.org/10.1126/science.abc6027

Interferons (IFNs) play an important role in the inhibition of viral replication. After performing an integrated immune analysis on a cohort of 50 COVID-19 patients with various disease severity, Benjamin Terrier and colleagues observed a distinct phenotype in severe and critical patients. These patients had a highly impaired interferon (IFN) type I response (characterized by no IFN-β and low IFN-α production and activity), which was associated with a persistent blood viral load and an exacerbated inflammatory response. The authors propose that type I IFN deficiency is a hallmark of severe COVID-19 and infer

that severe COVID-19 patients might be relieved from the IFN deficiency through IFN administration and from exacerbated inflammation through anti-inflammatory therapies that target IL-6 or TNF-α.

See also the comment by Gary Grajales-Reyes and Marco Colonna. **Interferon responses in viral pneumonias.** Science 2020; 369: 626-627. Full-text: https://science.sciencemag.org/content/369/6504/626

Clinical

Perez-Guzman PN, Daunt A, Mukherjee S, et al. **Clinical characteristics and predictors of outcomes of hospitalized patients with COVID-19 in a multi-ethnic London NHS Trust: a retrospective cohort study.** Clin Infect Dis 2020, published 7 August. Full-text: https://doi.org/10.1093/cid/ciaa1091

In the UK, ethnic minorities are disproportionately affected by COVID-19. Shevanthi Nayagam and colleagues evaluated the factors associated with mortality in patients admitted for COVID-19 in three large London hospitals. As of 1 May, 381 of 614 patients (62%) were discharged alive, 178 (29%) died and 55 (9%) remained hospitalized. The authors provide evidence that, beyond the widely reported factors associated with increased COVID-19 mortality (age, sex and severe hypoxemia on admission), thrombocytopenia, leukocytosis, hypoalbuminemia and reduced eGFR are also significantly associated with increased in-hospital death. They also find an association of increased odds of death among black (compared to white) patients, when adjusted for age, sex, burden of comorbidities and severity of disease on admission.

Wang K, Luo J, Tan F, et al. **Acute pancreatitis as the initial manifestation in two cases of COVID-19 in Wuhan, China.** Open Forum Infect Dis 2020, published 7 August. Full-text: https://doi.org/10.1093/ofid/ofaa324

Weimin Li and colleagues describe two cases of COVID-19 (two males, 42 and 35 years old) with acute pancreatitis as the initial manifestation.

Brener MI, Kaslow SR. **Where Do the Children Play?** N Engl J Med. 2020 Aug 6;383(6):e35. PubMed: https://pubmed.gov/32459914. Full-text: https://doi.org/10.1056/NEJMp2011100

A dual-physician couple — a cardiology fellow and a general surgery resident —narrate their experience of memorizing the ARDSNet ladder for ratios of positive end-expiratory pressure and fraction of inspired oxygen instead of learning the ins and outs of coronary angiography and laparoscopy. In the

middle of their unexpected experience: their 3½ year-old son and the Zoom session decision to keep him safe.

Privacy

Gerke S, Shachar C, Chai PR, Cohen IG. **Regulatory, safety, and privacy concerns of home monitoring technologies during COVID-19.** Nat Med 2020, published 7 August. Full-text: https://doi.org/10.1038/s41591-020-0994-1

Sara Gerke and colleagues describe how healthcare is shifting from the clinic to the home where people are treated via telehealth services and are monitored for signs and symptoms with the help of smartwatches, apps, and other technologies, including artificial intelligence. Learn how these sometimes revolutionary technologies raise major concerns pertaining to safety and privacy. A peek at the healthcare world of tomorrow.

9 August

Epidemiology

Baker MG, Anglemyer A. **Successful Elimination of Covid-19 Transmission in New Zealand.** N Engl J Med 2020, published 7 August. Full-text: https://www.nejm.org/doi/full/10.1056/NEJMc2025203

In mid-March, informed by science-based advocacy, national New Zealand leaders switched from a mitigation strategy to an elimination strategy. The government implemented a stringent countrywide lockdown which lasted 7 weeks (26 March – mid-May). Now, New Zealand views itself in the post-elimination stage, and public life has returned to near normal. The only cases identified are among international travelers who are kept in government-managed quarantine or isolation for 14 days after arrival. Michael Baker and Andrew Anglemyer conclude that rapid, science-based risk assessment linked to early, decisive government action was critical. The geographical isolation of New Zealand was another trump card the country had up its sleeve.

Heywood AE, Macintyre CR. **Elimination of COVID-19: what would it look like and is it possible?** Lancet 2020, published 6 August. Full-text: https://doi.org/10.1016/S1473-3099(20)30633-2

Anita Haywood and Raina Macintyre remember that the elimination of any infectious disease is ambitious, requiring substantial resources. They suggest a zero-case scenario of not less than three months before declaring an area

SARS-CoV-2-free. For obvious reasons, islands or island states have the best chances to achieve this goal.

Moscola J, Sembajwe G, Jarrett M, et al. **Prevalence of SARS-CoV-2 Antibodies in Health Care Personnel in the New York City Area.** JAMA 2020, published 6 August. https://doi.org/10.1001/jama.2020.14765

Health care personnel (HCP) working in New York City had a high exposure risk for SARS-CoV-2 infection. To address this concern, the Northwell Health System, the largest in New York State, offered voluntary antibody testing to all HCPs. Now Karina Davidson and colleagues report the prevalence of SARS-CoV-2 among HCPs and associations with demographics, primary work location and type, and suspicion of viral exposure. They found a 13.7% prevalence of SARS-CoV-2 antibodies (5523 of 40,329 HCWs tested) which was similar to that among adults randomly tested in New York State (14.0%).

Petersen MS, Strøm M, Christiansen DH, Fjallsbak JP, Eliasen EH, Johansen M, et al. **Seroprevalence of SARS-CoV-2–specific antibodies, Faroe Islands.** Emerg Infect Dis 2020 Nov. Published August 2020. Full-text: https://doi.org/10.3201/eid2611.202736

Maria Petersen and colleagues conducted a nationwide study of the prevalence of SARS-CoV-2 infection in the Faroe Islands, an autonomous territory within the Kingdom of Denmark with a population of around 50,000. Of 1,075 randomly selected participants, 6 (0.6%) tested seropositive for antibodies to the virus. At present, small islands tend to have low seropositivity rates.

Transmission

Totura A, Livingston V, Frick O, Dyer D, Nichols D, Nalca A. **Small particle aerosol exposure of African green monkeys to MERS-CoV as a model for highly pathogenic coronavirus infection.** Emerg Infect Dis 2020. Published August 2020. Full-text: https://doi.org/10.3201/eid2612.201664

For the initial development of a MERS-CoV primate model, Allison Totura and colleagues exposed 12 African green monkeys to 10^3, 10^4, or 10^5 PFU target doses of aerosolized MERS-CoV. Clinical disease signs that replicated human cases of MERS were observed in all groups but were most pronounced in the group that received the highest dose of MERS-CoV. It would be interesting to investigate if a dose-dependent increase of respiratory disease signs can be replicated in a SARS-CoV-2 animal model.

Immunology

Guo C, Li B, Ma H, et al. **Single-cell analysis of two severe COVID-19 patients reveals a monocyte-associated and tocilizumab-responding cytokine storm.** Nat Commun. 2020 Aug 6;11(1):3924. PubMed: https://pubmed.gov/32764665. Full-text: https://doi.org/10.1038/s41467-020-17834-w

In this study, Kun Qu and colleagues profiled the single-cell transcriptomes of 13,239 peripheral blood mononuclear cells (PBMCs) isolated prior to and following tocilizumab-induced remission. They identified a severe stage-specific monocyte subpopulation that contributed to the inflammatory cytokine storm in patients. Although tocilizumab treatment attenuated the inflammation, immune cells, including plasma B cells and $CD8^+$ T cells, still exhibited robust humoral and cellular antiviral immune responses.

Genetics

Ortiz-Fernández L, Sawalha AH. **Genetic variability in the expression of the SARS-CoV-2 host cell entry factors across populations.** *Genes Immun* 2020, published 6 August. Full-text: https://doi.org/10.1038/s41435-020-0107-7

Clinical

Kaige Wang, Jianfei Luo, Fen Tan, Jiasheng Liu, Zhong Ni, Dan Liu, Panwen Tian, Weimin Li, Acute pancreatitis as the initial manifestation in two cases of COVID-19 in Wuhan, China, *Open Forum Infectious Diseases*, , ofaa324, https://doi.org/10.1093/ofid/ofaa324

Tingting Liao, Zhengrong Yin, Juanjuan Xu, Zhilei Lv, Sufei Wang, Limin Duan, Jinshuo Fan, Yang Jin, **The correlation between clinical features and viral RNA shedding in outpatients with COVID-19**, *Open Forum Infectious Diseases*, https://doi.org/10.1093/ofid/ofaa331

Severe COVID

Prescott HC, Girard TD. **Recovery From Severe COVID-19: Leveraging the Lessons of Survival From Sepsis.** JAMA 2020, published 5 August. Full-text: https://doi.org/10.1001/jama.2020.14103

Up to 20% of patients hospitalized with COVID-19 will develop viral sepsis and acute respiratory distress syndrome (ARDS). Of those who survive, how many patients are likely to experience long-lasting morbidity? Hallie Prescott and Timothy Girard review what is known about long-term outcomes after severe

disease caused by other coronaviruses (SARS and MERS)***. Despite the limited data available for severe COVID-19, they suggest following the practices that are recommended for recovery from sepsis.

Ahmed H, Patel K, Greenwood DC, et al. **Long-term clinical outcomes in survivors of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks after hospitalisation or ICU admission: A systematic review and meta-analysis.** J Rehabil Med. 2020 May 31;52(5):jrm00063. PubMed: https://pubmed.gov/32449782. Full-text: https://www.medicaljournals.se/jrm/content/abstract/10.2340/16501977-2694

Comorbidities

Williams RD II, Shah A, Tikkanen R, et al. **Do Americans face greater mental health and economic consequences from covid-19? Comparing the US with other high-income countries.** Commonwealth Fund 2020, published 6 August. Full-text: https://www.commonwealthfund.org/publications/issue-briefs/2020/aug/americans-mental-health-and-economic-consequences-COVID19

One-third of U.S. adults reported experiencing stress, anxiety, and great sadness that was difficult to cope with by themselves, a significantly higher proportion than in other countries. Over 30 percent of Americans faced negative economic impacts due to the pandemic, significantly more than in the comparison high-income countries. Can the US do more regarding mental health, an existing concern before COVID-19? See also the comment by Janice Hopkins Tanne: **Mental health and economic problems are worse in US than in other rich nations.** BMJ 2020, Aug 6;370:m3110. PubMed: https://pubmed.gov/32764109. Full-text: https://doi.org/10.1136/bmj.m3110

Collateral Effects

Gluckman TJ, Wilson MA, Chiu S, et al. **Case Rates, Treatment Approaches, and Outcomes in Acute Myocardial Infarction During the Coronavirus Disease 2019 Pandemic.** JAMA Cardiol 2020, published 7 August. Full-text: https://doi.org/10.1001/jamacardio.2020.3629

Out of fear of contracting SARS-CoV-2, large numbers of patients avoided hospitalization during the COVID-19 pandemic. After analyzing 15,244 hospitalizations involving 14,724 patients with acute myocardial infarction, Tyler Gluckman and colleagues found that patients hospitalized for acute myocardial infarction during the early COVID-19 period had an increased ob-

served/expected mortality ratio which was associated disproportionately with patients with ST-segment elevation myocardial infarction (STEMI).

Pediatrics

Godfred-Cato S, Bryant B, Leung J, et al. **COVID-19–Associated Multisystem Inflammatory Syndrome in Children — United States, March–July 2020.** MMWR Morb Mortal Wkly Rep. ePub: 7 August 2020. Full-text: http://dx.doi.org/10.15585/mmwr.mm6932e2

Multisystem inflammatory syndrome in children (MIS-C) is a rare but severe condition that has been reported approximately 2–4 weeks after the onset of COVID-19 in children and adolescents. Now Shana Godfred-Cato and colleagues report 570 US MIS-C patients who met the CDC case definition as of July 29. A total of 203 (35.6%) of the patients had a clinical course consistent with previously published MIS-C reports, characterized predominantly by shock, cardiac dysfunction, abdominal pain, and markedly elevated inflammatory markers, and almost all had positive SARS-CoV-2 test results (Class 1). The remaining 367 (64.4%) of MIS-C patients (Class 2 and 3) had manifestations that appeared to overlap with acute COVID-19 or had features of Kawasaki disease. 364 patients (63.9%) required care in an intensive care unit ICU. Ten patients (1.8%) died. The median patient age was 8 years (range = 2 weeks–20 years). Approximately two thirds of the children had no preexisting underlying medical conditions.

10 August

Epidemiology

Kalk A, Schultz A. **SARS-CoV-2 epidemic in African countries—are we losing perspective?** Lancet, August 07, 2020. Full-text: https://doi.org/10.1016/S1473-3099(20)30563-6

Important comment on modelling studies predicting a huge death toll for some African countries. In the Democratic Republic of the Congo and Malawi, for instance, only 2-3% of the population is older than 65 years. According to the two authors (who work in these countries), the lockdown measures proposed by others do not appear applicable to the African continent and might cause more harm than SARS-CoV-2 itself.

Virology

Wolff G, Limpnes RW, Zevenhoven-Dobbe JC, et al. **A molecular pore spans the double membrane of the coronavirus replication organelle**. Science 06 Aug 2020: eabd3629. Full-text: https://doi.org/10.1126/science.abd3629

Coronavirus replication is associated with virus-induced cytosolic double-membrane vesicles, which may provide a tailored micro-environment for viral RNA synthesis in the infected cell. Using cellular electron cryo-microscopy, the authors visualized a molecular pore complex that spans both membranes of the double-membrane vesicle and would allow export of RNA to the cytosol. Although the exact mode of function of this molecular pore remains to be elucidated, it would clearly represent a key structure in the viral replication cycle that may offer a specific drug target.

Immunology

Grajales-Reyes GE, Colonna M. **Interferon responses in viral pneumonias**. Science 07 Aug 2020: Vol. 369, Issue 6504, pp. 626-627. Full-text: https://science.sciencemag.org/content/369/6504/626

IFNs are important cytokines of the innate and adaptive immune system and are classified into three main types: I (α-or β), II (γ), and tive summarizes the complexity of IFN responses in SARS-CoV-2 infection. Research is needed to establish whether IFN-λ and type I IFNs have similar effects or whether one is more beneficial or detrimental than the other. It should be conclusively established whether type I IFN responses are augmented in the lungs of COVID-19 patients in contrast to the suppressed type I IFN responses observed in the blood. Further research will be necessary to determine whether suppression of blood type I IFN in critically ill COVID-19 patients is due to the ability of SARS-CoV-2 proteins to interfere with IFN signaling.

Diagnosis

Sapkota D, Søland TM, Galtung HK, et al. **COVID-19 salivary signature: diagnostic and research opportunities**. J Clin Pathol 2020 Aug 7. Full-text: https://doi.org/10.1136/jclinpath-2020-206834

As a non-invasive approach with possibility for self-collection, saliva collection circumvents to a great extent the limitations associated with the use of nasopharyngeal/oropharyngeal swabs. This review summarizes the clinical and scientific basis for the potential use of saliva for COVID-19 diagnosis and disease monitoring. Additionally, Dipak Sapkota and colleagues discuss saliva-

based biomarkers and their potential clinical and research applications related to COVID-19.

Clinical

Lee S, Kim T, Lee E, et al. **Clinical Course and Molecular Viral Shedding Among Asymptomatic and Symptomatic Patients With SARS-CoV-2 Infection in a Community Treatment Center in the Republic of Korea**. JAMA Intern Med, August 6, 2020. Full-text: https://doi.org/10.1001/jamainternmed.2020.3862

This cohort study included 303 patients in a community treatment center in the Republic of Korea, among them 110 (36.3%) asymptomatic at the time of isolation (21 developed symptoms during isolation). The cycle threshold values of RT-PCR for SARS-CoV-2 ("viral load") in asymptomatic patients were similar to those in symptomatic patients. Of note, the Ct values from lower respiratory tract specimens tended to decrease more slowly in asymptomatic patients than in symptomatic (including pre-symptomatic) patients.

Collateral

Nicolay N, Mirinaviciute G, Mollet T, et al. **Epidemiology of measles during the COVID-19 pandemic, a description of the surveillance data, 29 EU/EEA countries and the United Kingdom, January to May 2020**. Eurosurveillance August 6, 2020. Volume 25, Issue 31. Full-text: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.31.2001390

Interesting: The number of measles cases declined in the EU and UK in 2020. Reported cases to The European CDC decreased from 710 to 54 between January and May. However, according to the authors, under-diagnoses and under-reporting during the COVID-19 pandemic should be ruled out before concluding that reduced measles circulation is due to social distancing and any community control measures taken to control COVID-19.

Treatment

Ivashchenko AA, Dmitriev KA, Vostokova NV, et al. **AVIFAVIR for Treatment of Patients with Moderate COVID-19: Interim Results of a Phase II/III Multicenter Randomized Clinical Trial.** Clin Infect Dis. 2020 Aug 9:ciaa1176. PubMed: https://pubmed.gov/32770240. Full-text: https://doi.org/10.1093/cid/ciaa1176

In May 2020 the Russian Ministry of Health granted fast-track marketing authorization to the RNA polymerase inhibitor favipiravir for the treatment of COVID-19 patients. In the pilot stage of a Phase II/III clinical trial, 60 patients hospitalized with COVID-19 pneumonia were randomized to two different dosing groups or standard of care. Favipiravir enabled SARS-CoV-2 viral clearance in 62.5% of patients within 4 days and was safe and well-tolerated. The proportion of patients who achieved negative PCR on day 5 on both dosing regimens was twice as high as in the control group ($p < 0.05$).

Hayem G, Huet T, Jouveshomme S, et al. **Anakinra for severe forms of COVID-19 – Authors' reply**. Lancet August 07, 2020. Full-text: https://doi.org/10.1016/S2665-9913(20)30274-5

Discussion about a cohort study on anakinra, an interleukin (IL)-1 receptor antagonist. The authors compared 52 consecutive patients with 44 historical patients. Now, three replies address mainly methodological issues. According to the authors, their study was "not perfect from a statistical point of view... only high-quality randomized trials can avoid confounding factors, but the urgent context of the COVID-19 pandemic means randomized trials are not always appropriate". However, several randomized trials are underway: on August 10, https://clinicaltrials.gov listed 16 Phase II/III studies.

Xia X, Li K, Wu L, et al. **Improved clinical symptoms and mortality among patients with severe or critical COVID-19 after convalescent plasma transfusion**. Blood 2020, 136 (6): 755–759. Full-text: https://doi.org/10.1182/blood.2020007079

Same issue: uncontrolled, retrospective data (but huge numbers). This group presents the results of 1430 patients with severe or critical COVID-19 who received standard treatment only and 138 patients who also received ABO-compatible COVID-19 convalescent plasma (CCP). Despite the higher severity level, only 3 patients (2.2%) died in the CCP group through April 20, reducing the mortality rate compared with that in the standard treatment group (4.1%). However, confounding factors (i.e., biased patient assignments) in this retrospective study could not be ruled out. In addition, complete data on neutralizing antibody titers in CCP units were not available, limiting the power of evaluating the correlation between the quality of donor plasma and efficacy.

Pediatrics

Kim L, Whitaker M, O'Halloran A, et al. **Hospitalization Rates and Characteristics of Children Aged <18 Years Hospitalized with Laboratory-Confirmed COVID-19 — COVID-NET, 14 States, March 1–July 25, 2020**. MMWR Morb Mortal Wkly Rep. ePub: 7 August 2020. Full-text: http://dx.doi.org/10.15585/mmwr.mm6932e3

COVID-NET conducts population-based surveillance for laboratory-confirmed COVID-19–associated hospitalizations in 14 US states. From March 1 to July 25, 576 children hospitalized with COVID-19 were reported to COVID-NET. Although the cumulative COVID-19–associated hospitalization rate among children was low compared with that among adults, weekly hospitalization rates in children increased during the surveillance period. Children can develop severe COVID-19 illness; during the surveillance period, one in three children was admitted to the ICU. Hispanic and black children had the highest rates of COVID-19–associated hospitalization.

11 August

Prevention

Lazzari S. **Prevention**. In: COVID Reference 2020.04, 4th updated edition, published 11 August. Full-text: https://covidreference.com/prevention

Stefano Lazzari, specialist in Public Health and Preventive Medicine, gives a 5000-word overview of this most important topic in a world without a COVID-19 vaccine. See also the PDF (320 pages) of the updated Fourth CR Edition.

Ramírez-Cervantes KL, Romero-Pardo V, Pérez-TovarC, et al. **A medicalized hotel as a public health resource for the containment of Covid-19: more than a place for quarantining.** J Public Health 2020, published 10 August. Full-text: https://doi.org/10.1093/pubmed/fdaa129

Karen Lizzette Ramírez-Cervantes and colleagues describe the implementation of a medicalized hotel in Madrid for the containment of COVID-19. Between March and 9 May 2020, 399 patients were admitted; 59% (235) were migrants; the main reason for referral (58%) was a lack of housing conditions for quarantining, including overcrowding. The hotel provided medical care and housing to a subgroup of a vulnerable population who could not afford a safe quarantine.

Vaccine

Dagotto G, Yu J, Barouch DH. **Approaches and Challenges in SARS-CoV-2 Vaccine Development.** Cell Host Microbe 2020, published 10 August. Full-text: https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(20)30455-8

Progress in SARS-CoV-2 vaccine development to date has been faster than for any other pathogen in history. In this perspective, Dan Barouch, Gabriel Dagotto and Jingyou Yu discuss three topics that are critical for SARS-CoV-2 vaccine development:

1. Antigen selection and engineering
2. Pre-clinical challenge studies in non-human primate models
3. Immune correlates of protection

Diagnostics

Kilic T, Weissleder R, Lee H. **Molecular and Immunological Diagnostic Tests of COVID-19: Current Status and Challenges.** iScience. 2020 Jul 25;23(8):101406. PubMed: https://pubmed.gov/32771976. Full-text: https://doi.org/10.1016/j.isci.2020.101406

We are presenting this article more than two weeks after publication – an almost inexcusable delay. Allocate at least half an hour to read the review by Tugba Kilic, Ralph Weissleder and Hakho Lee – it's 16 pages. The authors describe currently available tests to detect either the virus (SARS-CoV-2) or virus-induced immune responses, explaining how the tests work and comparing their performance (see the graphical abstract). Discover also the shortcomings of certain tests and future needs.

Clinical

Crosby SS. **My COVID-19.** Ann Intern Med 2020, published 11 August. Full-text: https://www.acpjournals.org/doi/10.7326/M20-5126

In this *On Being a Doctor* report, Sondra Crosby, working at the center of the Boston coronavirus storm in March 2020, remembers a myriad of symptoms after coming down with COVID-19 herself. Read about her shortness of breath, confusion, not eating for 5 days, keeping in the prone position and a nauseating and horrid odor. With the exception of a handful of mediocre and uninspired politicians, this is not something you would wish on your worst enemy.

Treatment

Cain DW, Cidlowski JA. **After 62 years of regulating immunity, dexamethasone meets COVID-19.** Nat Rev Immunol 2020, published 10 August. Full-text: https://doi.org/10.1038/s41577-020-00421-x

The RECOVERY trial showed that treatment with dexamethasone, a synthetic glucocorticoid, enhanced the survival of critically ill patients with COVID-19. Not only was dexamethasone more effective than remdesivir (dexamethasone reduced COVID-19-related mortality while remdesivir didn't), but it is also cheap, widely available and comes with 60 years of safety profiling. In this two-page comment, Derek Cain and John Cidlowski discuss the immunological impacts of glucocorticoid therapy for COVID-19.

Comorbidities

Restivo DA, Centonze D, Alesina A, Marchese-Ragona R. **Myasthenia Gravis Associated With SARS-CoV-2 Infection.** Ann Intern Med 2020, published 10 August. Full-text: https://www.acpjournals.org/doi/10.7326/L20-0845

Myasthenia gravis is an autoimmune disease in which antibodies bind to acetylcholine receptors (AChRs) or to functionally related molecules in the postsynaptic membrane at the neuromuscular junction. Now Domenico Restivo and colleagues describe 3 patients without previous neurologic or autoimmune disorders who were diagnosed with myasthenia gravis within 5 to 7 days after fever onset related to COVID-19. The authors speculate that antibodies directed against SARS-CoV-2 proteins might cross-react with AChR subunits.

Newborns

Patil UP, Maru S, Krishnan P et al. **Newborns of COVID-19 mothers: short-term outcomes of colocating and breastfeeding from the pandemic's epicenter.** J Perinatol 2020, published 10 August. Full-text: https://doi.org/10.1038/s41372-020-0765-3

The authors report on 45 newborns born to SARS-CoV-2 positive mothers. The majority of positive mothers, 27 (60%), were asymptomatic. Mothers were encouraged to provide skin-to-skin care and breastfeeding. All the newborns were tested for SARS-CoV-2; only 3 (6.6%) tested positive (see Figure 1). Those three newborns were monitored until two consecutive tests obtained at

least 24 gh apart were nega
gesting transient colonization.

Digital

Murray CJL, Alamro NMS, Hwang H, Lee U. **Digital public health and COVID-19.** Lancet Public Health 2020, published 10 August. Full-text: https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(20)30187-0/fulltext

Data have been central to public health ever since John Snow used maps and case reports to identify the Broad Street pump as the source of cholera in London in 1854. Today, in a way that was unimaginable just 15 years ago, digital technology collects data through administrative interfaces, sensors and social media. Now Christopher Murray and colleagues summarize how the new data webs can transform the public health response. A preview:

1. Timely tracking of the COVID-19 pandemic
2. Forecasting the next hotspot
3. Speeding up the data collection for a large fraction of the population
4. Contact tracing via tracing apps
5. Interactive data visualization for communication to the media, the public, decision influencers, and decision makers
6. Targeted control strategies at the city or neighborhood level

Beyond your tectonic plate borders

Abbott A. **Inside the mind of an animal.** Nature 2020, published 11 August. Full-text: https://www.nature.com/articles/d41586-020-02337-x

In this *Nature* feature, Alison Abbott explores how brains create emotions and other internal states such as aggression and desire.

German

Drosten C. **Ein Plan für den Herbst.** Die Zeit 2020, published 5 August. Full-text: https://www.zeit.de/2020/33/corona-zweite-welle-eindaemmung-massnahmen-christian-drosten

If you read German, read this article by Germany's top virologist Christian Drosten. The subtitle: "Die Treiber der Epidemie aufspüren, die Quarantäne verkürzen, die Tests genauer auswerten – mit dieser Strategie können wir in

einer zweiten Welle verhindern, dass es zu einem erneuten Lockdown kommt."

12 August

Transmission

Lednicky JA, Lauzardo M, Fan ZH, et al. **Viable SARS-CoV-2 in the air of a hospital room 1 with COVID-19 patients.** medRxiv 2020, posted 4 August. Pre-print: https://www.medrxiv.org/content/10.1101/2020.08.03.20167395v1

John A. Lednicky and colleagues isolated viable virus from air samples collected 2 to 4.8 meters away from two COVID-19 patients. The genome sequence of the SARS-CoV-2 strain isolated was identical to that isolated from the NP swab from the patient with an active infection. Estimates of viable viral concentrations ranged from 6 to 74 TCID50 units/L of air. This paper has not yet been peer-reviewed.

Chagla Z, Hota S, Khan S, Mertz D, and the International Hospital and Community Epidemiology Group. **Airborne Transmission of COVID-19**. Clin Infect Dis 2020, published 11 August. Full-text: https://doi.org/10.1093/cid/ciaa1118

Zain Chagla and colleagues discuss the paper by Morawska L, Milton DK, *It is Time to Address Airborne Transmission of COVID-19* (Clin Infect Dis 2020, 6 July). They agree that there is potential for the transmission by aerosols, especially in poorly ventilated indoor crowded environments. However, they argue that the main mode of transmission of SARS-CoV-2 is short range through droplets and close contact. Explore this one-page comment to see how the debate continues.

Bigelow BF, Tang O, Toci GR, et al. **Transmission of SARS-CoV-2 Involving Residents Receiving Dialysis in a Nursing Home — Maryland, April 2020**. MMWR Morb Mortal Wkly Rep. ePub: 11 August 2020. Full-text: http://dx.doi.org/10.15585/mmwr.mm6932e4

Nursing home residents who receive hemodialysis are at higher risk for SARS-CoV-2 infections. Benjamin Bigelow and colleagues investigated a COVID-19 outbreak in a Maryland nursing home. The prevalence of infection among residents undergoing dialysis was 47% (15 of 32) as compared to those not receiving dialysis (16%; 22 of 138) ($p < 0.001$). The authors recommend strict

control practices throughout the dialysis process, e.g., transportation, time spent in waiting areas, spacing of machines, and cohorting.

Prevention

Schünemann HJ, Akl EA, Chou R, et al. **Use of facemasks during the COVID-19 pandemic.** Lancet Respir Med. 2020 Aug 3:S2213-2600(20)30352-0. PubMed: https://pubmed.gov/32758441. Full-text: https://doi.org/10.1016/S2213-2600(20)30352-0

SARS-CoV-2 infected people are infectious for at least 48 h before symptom onset (pre-symptomatic); in addition, some people have only minor symptoms (paucisymptomatic) while others remain entirely asymptomatic. Will face masks protect us? Partly, yes, but will it be worth the public's money or outweigh any potential harms? It depends, say Holger Schünemann and colleagues. In a setting with high baseline risks, such as health-care workers caring for a superspreading patient with COVID-19, wearing a mask may prevent the infection in up to one out of two health-care workers; consequently, there is a strong recommendation that all such individuals should wear a face mask, despite uncertainty in the evidence. In highly populated areas that have high infection rates—eg, USA, India, Brazil, or South Africa—the use of masks will probably outweigh any potential downsides. Read more about the sometimes difficult choices about the type of face mask, including cost, equity, acceptability, and feasibility.

Ebrahim SH, Rahmen NMM, Imtiaz R, et al. **Forward planning for disaster-related mass gatherings amid COVID-19.** Lancet Planet Health 2020, published 11 August. Full-text: https://doi.org/10.1016/S2542-5196(20)30175-3

Occurrences of extreme humid heat, higher than the optimal human survivability limit of 35° C, have more than doubled in frequency since 1979, leading to an increased frequency of tropical cyclones. Ziad Memish and colleagues now explain that all disasters cause large-scale population movements – making physical distancing in the new COVID-world almost impossible. If you are involved in disaster planning, discover all the details you need to keep in mind.

Immunology

Zhang J, Wang X, Xing X, et al. **Single-cell landscape of immunological responses in patients with COVID-19.** Nat Immunol 2020, published 12 August. Full-text: https://doi.org/10.1038/s41590-020-0762-x

Fu-Sheng Wang and colleagues profiled the immunological response landscape in 13 patients with COVID-19 at single-cell resolution, illustrating the dynamic nature of cellular responses during disease progression. First, patients with COVID-19 showed a concerted and strong IFN-α response, an overall acute inflammatory response and an enhanced migration ability. Second, broad immune activation was observed in patients with COVID-19, evidenced by increased proportions of activated T, pro T and plasma B cells. Third, the proportions of active state T cell clusters were significantly higher in patients with COVID-19 and with a preferential enrichment of effector T cell subsets, such as $CD4^+$ effector-GNLY, $CD8^+$ effector-GNLY and NKT CD160 cells in moderate patients and an NKT CD56 subset in severe patients. Finally, at the early phase of convalescence, the state of the immune system was not fully restored. How long will it take to achieve full immune recovery after COVID-19?

Pathogenesis

Arunachalam PS, Wimmers F, Mok CKP, Perera RAPM, et al. **Systems biological assessment of immunity to mild versus severe COVID-19 infection in humans.** Science 2020, published 11 August. Full-text: http://doi.org/10.1126/science.abc6261

There is something wrong with our innate immune system responding to SARS-CoV-2. Bali Pulendran and colleagues analyzed immune responses in 76 COVID-19 patients and 69 healthy individuals and found a spatial dichotomy in the innate immune response, characterized by suppression of peripheral innate immunity, in the face of proinflammatory responses reported in the lung. In PBMCs of COVID-19 patients, there was reduced expression of HLA-DR and pro-inflammatory cytokines by myeloid cells, and impaired mTOR signaling and IFN-α production by plasmacytoid DCs. In contrast, there were enhanced plasma levels of inflammatory mediators, including EN-RAGE (S100A12, a biomarker of pulmonary injury), TNFSF14, and oncostatin-M. The authors suggest that these three molecules and their receptors could represent attractive therapeutic targets.

See also the Stanford Press News, 11 August: Study reveals immune-system deviations in severe COVID-19 cases.

Vaccine

Mulligan MJ, Lyke KE, Kitchin N, et al. **Phase 1/2 study of COVID-19 RNA vaccine BNT162b1 in adults.** Nature 2020, published 12 August. Full-text: https://doi.org/10.1038/s41586-020-2639-4

Mark Mulligan, Kirsten Lyke, Nicholas Kitchin, Judith Absalon and colleagues report the safety, tolerability, and immunogenicity data from an ongoing study among 45 healthy adults, randomized to receive 2 doses, separated by 21 days, of 10 µg, 30 µg, or 100 µg of **BNT162b1**. BNT162b1, developed by BioNTech and Pfizer, is a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine that encodes trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD). A clear dose-level response in elicited neutralizing titers was observed after doses 1 and 2 with a particularly steep dose response between the 10 µg and 30 µg dose levels. Geometric mean neutralizing titers reached 1.9- to 4.6-fold that of a panel of COVID-19 convalescent human sera at least 14 days after a positive SARS-CoV-2 PCR. The clinical testing of BNT162b1 is taking place in the context of a broader, ongoing COVID-19 vaccine development program by both companies. That program includes the clinical testing of three additional vaccine candidates, including candidates encoding the full-length spike.

Clinical

Uppuluri EM, Shapiro NL. **Development of pulmonary embolism in a non-hospitalized patient with COVID-19 who did not receive venous thromboembolism prophylaxis.** Am J Health Syst Pharm 2020, published 11 August. Full-text: https://doi.org/10.1093/ajhp/zxaa286

Ellen Uppuluri and Nancy Shapiro report a the case of a 32-year-old, overweight (weight, 90 kg; body mass index, 28) male who was treated for COVID-19 in an emergency department (ED) and discharged home. Twelve days later he was found to have a PE. The authors suggest that non-hospitalized patients with COVID-19 may be at higher risk for VTE than patients with other medical illnesses.

Poletti P, Tirani M, Cereda D, et al. **Age-specific SARS-CoV-2 infection fatality ratio and associated risk factors, Italy, February to April 2020.** Euro Surveill. 2020 Aug;25(31). PubMed: https://pubmed.gov/32762797. Full-text: https://doi.org/10.2807/1560-7917.ES.2020.25.31.2001383

Piero Poletti, Marcello Tirani and colleagues analyzed 5,484 close contacts of COVID-19 cases in Italy. Infection fatality ratio was 0.43% for individuals

younger than 70 years and 10.5% for older individuals. The risk of death after infection was 62% lower in clusters identified after 16 March 2020 and 1.8-fold higher for males.

	Contacts	SARS-CoV-2 positive	Deaths	%
0–19	692	304	0	
20–49	1,951	885	0	
50–59	1,241	648	3	**0.46**
60–69	867	494	7	**1.42**
70–79	485	335	23	**6.87**
≥ 80	248	158	29	**18.35**
Male	2,398	1,220	33	**2.70**
Female	3,086	1,604	29	**1.81**
Comorbidities				
None	122	113	1	**0.88**
Cardiovascular	350	316	51	**16.14**
Respiratory	50	49	8	**16.33**
Oncological	106	92	11	**11.96**
Diabetes/metabolic	93	79	13	**16.46**
Unknown	4,947	2,335	9	**0.39**

13 August

Epidemiology

Steinberg J, Kennedy ED, Basler C, et al. **COVID-19 Outbreak Among Employees at a Meat Processing Facility — South Dakota, March–April 2020**. MMWR Morb Mortal Wkly Rep 2020;69:1015–1019. Full-text: http://dx.doi.org/10.15585/mmwr.mm6931a2

Detailed report of an outbreak in a meat processing facility in South Dakota. From March 16 to April 25, 25.6% (929) of employees and 8.7% (210) of their contacts were diagnosed with COVID-19; two employees died. The highest attack rates occurred among employees who worked < 6 feet (2 meters) from one another on the production line.

Virology

Starr TN, Greaney AJ, Hilton SK, et al. **Deep mutational scanning of SARS-CoV-2 receptor binding domain reveals constraints on folding and ACE2 binding**. Cell August 11, 2020. Full-text: https://doi.org/10.1016/j.cell.2020.08.012

The receptor-binding domain (RBD) of the SARS-CoV-2 spike glycoprotein mediates viral attachment to ACE2 receptor, and is a major determinant of host range and a dominant target of neutralizing antibodies. These researchers from Seattle have systematically changed every amino acid in the RBD and determine the effects of the substitutions on Spike expression, folding, and ACE2 binding. The work identifies structurally constrained regions that would be ideal targets for COVID-19 countermeasures and demonstrates that mutations in the virus which enhance ACE2 affinity can be engineered but have not, to date, been naturally selected during the pandemic.

Pathogenesis

Brest P, Refae S, Mograbi B, et al. **Host polymorphisms may impact SARS-CoV-2 infectivity**. Trends Genetics August 10, 2020. Full-text: https://doi.org/10.1016/j.tig.2020.08.003

In their comment, the authors support the hypothesis of genetic influence on individual susceptibility to COVID-19 infection. Germinal polymorphisms may regulate the expression of the SARS-CoV-2 cellular target itself and proteases controlling the process of its shedding or, conversely, its internalization.

Transmission, Prevention

Sickbert-Bennett EE, Samet J, Clapp PW, et al. **Filtration Efficiency of Hospital Face Mask Alternatives Available for Use During the COVID-19 Pandemic**. JAMA Intern Med. Published online August 11, 2020. Full-text: https://doi.org/10.1001/jamainternmed.2020.4221

Face masks can be old, but they must fit. This quality improvement study evaluating 29 face mask alternatives found that expired N95 respirators and sterilized, used N95 respirators can be used when new N95 respirators are not available. Other alternatives may provide less effective filtration. The performance of N95 respirators in the wrong size had a slightly decreased performance.

Huong NQ, Nga NTT, Long NV, et al. **Coronavirus testing indicates transmission risk increases along wildlife supply chains for human consumption in Viet Nam, 2013-2014**. PLoS One. 2020 Aug 10;15(8):e0237129. PubMed: https://pubmed.gov/32776964. Full-text: https://doi.org/10.1371/journal.pone.0237129

These researchers from Vietnam identified six known coronaviruses in bats and rodents, clustered in three Coronaviridae genera. Most notably among field rats, the odds of coronavirus RNA detection were highest in field rats sold and served in restaurants (55.6%, 84/151). The mixing of multiple coronaviruses, and their apparent amplification along the wildlife supply chain into restaurants, suggests maximal risk for end consumers and likely underpins the mechanisms of zoonotic spillover to people.

Greenhalgh T, Knight M, A'Court, et al. **Management of post-acute covid-19 in primary care**. BMJ 2020; 370. Full-text: https://doi.org/10.1136/bmj.m3026

Nice and pragmatic summary of the management of COVID-19 after the first three weeks (which is currently based on limited evidence). Key messages: Approximately 10% of people experience prolonged illness. Many such patients recover spontaneously (if slowly) with holistic support, rest, symptomatic treatment, and gradual increase in activity. Home pulse oximetry can be helpful in monitoring breathlessness.

Comorbidities

Rivinius R, Kaya Z, Schramm R, et al. **COVID-19 among heart transplant recipients in Germany: a multicenter survey**. Clin Res Cardiol. 2020 Aug 11. PubMed: https://pubmed.gov/32783099. Full-text: https://doi.org/10.1007/s00392-020-01722-w

A multicenter survey of all heart transplant centers in Germany evaluating the current status of COVID-19 among adult heart transplant recipients. Eight of 21 patients (38.1%) displayed a severe course needing invasive mechanical ventilation, seven of whom died.

Inciarte A, Gonzalez-Cordon A, Rojas J, et al. **Clinical characteristics, risk factors, and incidence of symptomatic COVID-19 in adults living with HIV: a single-center, prospective observational study**. AIDS. 2020 Aug 7. PubMed: https://pubmed.gov/32773471. Full-text: https://doi.org/10.1097/QAD.0000000000002643

53 out of 5683 (0.9% confidence interval 0.7-1.2%) PLWH in Barcelona were diagnosed with COVID-19. Clinical presentation, severity rate, and mortality were not dependent on any HIV-related or antiretroviral-related factor. COVID-19 standardized incidence rate was lower in PLWH than in the general population.

Severe COVID-19

Mustafa AK, Alexander PJ, Joshi DJ, et al. **Extracorporeal Membrane Oxygenation for Patients With COVID-19 in Severe Respiratory Failure**. JAMA Surg. 2020 Aug 11. PubMed: https://pubmed.gov/32780089. Full-text: https://doi.org/10.1001/jamasurg.2020.3950

According to this retrospective report on 40 patients, single-access, dual-stage venovenous ECMO with early extubation appears to be safe and effective in patients with COVID-19 respiratory failure. Ongoing studies are required, however, to further define the long-term outcomes of this approach.

Treatment

Bradfute SB, Hurwitz I, Yingling AV, et al. **SARS-CoV-2 Neutralizing Antibody Titers in Convalescent Plasma and Recipients in New Mexico: An Open Treatment Study in COVID-19 Patients**. J Infect Dis. 2020 Aug 11:jiaa505. PubMed: https://pubmed.gov/32779705. Full-text: https://doi.org/10.1093/infdis/jiaa505

This single-arm interventional trial measured neutralizing antibodies (Nab) and total antibody titers before and after CP transfusion over a 14-day period in 12 hospitalized COVID-19 patients. NAb titers in the donor CP units were low (<1:40 to 1:160) and had no effect on recipient neutralizing activity one day after transfusion. Pre-screening of CP may be necessary for selecting donors with high levels of neutralizing activity for infusion into patients with COVID-19.

14 August

Epidemiology

Ward H, Atchison C, Whitaker M, et al. **Antibody prevalence for SARS-CoV-2 following the peak of the pandemic in England: REACT2 study in 100,000 adults.** Imperial College London 2020. Pre-print:

https://www.imperial.ac.uk/media/imperial-college/institute-of-global-health-innovation/Ward-et-al-120820.pdf

By the end of June, an estimated 3.4 million people, or slightly under 6% of the UK population, had antibodies to the virus and had likely had COVID-19. London had the highest numbers (13%), while the South West had the lowest (3%). This is the result of the REACT (REal Time Assessment of Community Transmission) study, by Helen Ward, Paul Elliott and colleagues from the Imperial College London, using antibody finger-prick self-testing at home to track past infections. Black, Asian and minority ethnic (BAME) individuals were between two and three times as likely to have had SARS-CoV-2 infection compared to white people. An interesting trend: young people aged 18-24 had the highest rates (8%), while older adults aged 65 to 74 were least likely to have been infected (3%).

Transmission

Luo L, Liu D, Liao X, et al. **Contact Settings and Risk for Transmission in 3410 Close Contacts of Patients With COVID-19 in Guangzhou, China: A Prospective Cohort Study.** Ann Intern Med. 2020 Aug 13. PubMed: https://pubmed.gov/32790510. Full-text: https://doi.org/10.7326/M20-2671

Chen Mao and colleagues traced 3410 close contacts of 391 SARS-CoV-2 infected index cases between 13 January and 6 March 2020. 127 contacts (3.7%) were secondarily infected. Compared with the household setting (10.3%), the secondary attack rate was lower for exposures in healthcare settings (1.0%) and on public transportation (0.1%). Interestingly, although not unexpectedly, the secondary attack rate increased with the severity of index cases, from 0.3% for asymptomatic to 3.3% for mild, 5.6% for moderate, and 6.2% for severe or critical cases. Index cases with expectoration were associated with higher risk for secondary infection (13.6% vs. 3.0% for index cases without expectoration).

Immunology

Sekine T, Perez-Potti A, Rivera-Ballesteros O, et al. **Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19.** Cell 2020, published 14 August. Full-text: https://www.cell.com/cell/fulltext/S0092-8674(20)31008-4

SARS-CoV-2-specific memory T cells will probably be critical for long-term immune protection. In this Cell paper, Marcus Buggert and colleagues mapped the functional and phenotypic landscape of SARS-CoV-2-specific T cell responses in unexposed individuals, exposed family members, and indi-

viduals with acute or convalescent COVID-19. They found that 1) acute phase SARS-CoV-2-specific T cells display an activated cytotoxic phenotype; 2) vs broad and polyfunctional SARS-CoV-2-specific T cell responses in convalescent phase; and 3) SARS-CoV-2-specific T cell responses are detectable even in seronegative individuals. The fact that many individuals with asymptomatic or mild COVID-19, after SARS-CoV-2 exposure or infection, generated highly durable and functionally replete memory T cell responses, not uncommonly even in the absence of detectable humoral responses, suggests that natural exposure or infection could prevent recurrent episodes of severe COVID-19.

Treatment

Ledford H. **Antibody therapies could be a bridge to a coronavirus vaccine — but will the world benefit?** Nature 2020, published 11 August. Full-text: https://www.nature.com/articles/d41586-020-02360-y

Are monoclonal antibodies a bridging solution before the general availability of a vaccine? Heidi Lenford reminds us that monoclonals are complex and expensive to produce, leaving people from poor countries locked out.

Comorbidities

Passamonti F, Cattaneo C, Arcaini L, et al. **Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study.** Lancet Haematol 2020, published 13 August. Full-text: DOI:https://doi.org/10.1016/S2352-3026(20)30251-9

In this 74-author study from Italy, Francesco Passamonti and colleagues report a retrospective study which included patients with a diagnosis of a hematological malignancy between 25 February and 18 May, 2020, with laboratory-confirmed and symptomatic COVID-19. 198 (37%) of 536 patients died. Progressive disease status, diagnosis of acute myeloid leukemia, indolent non-Hodgkin lymphoma, aggressive non-Hodgkin lymphoma or plasma cell neoplasms were associated with worse overall survival. See also the comment by Samuel Rubinstein and Jeremy Warner: **COVID-19 and haematological malignancy: navigating a narrow strait.** Lancet Haematol 2020, published 13 August. Full-text: https://doi.org/10.1016/S2352-3026(20)30252-0

Holman N, Knighton P, Kar P, et al. **Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-**

based cohort study. Lancet Diabetes Endocrinol 2020, published 13 August. Full-text: https://doi.org/10.1016/S2213-8587(20)30271-0

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Barron E, Bakhai C, Kar P, et al. **Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study.** Lancet Diabetes Endocrinol 2020, published 13 August. Full-text: https://doi.org/10.1016/S2213-8587(20)30272-2

A double hit by Jonathan Valabhji and colleagues! In the first paper (Holman et al.), the authors did a population-based cohort study of people with diabetes in the UK. Between 16 February and 11 May 2020, 1,604 people with type 1 diabetes and 36,291 people with type 2 diabetes died from all causes. Of these deaths, 464 in people with type 1 diabetes and 10,525 in people with type 2 diabetes were defined as COVID-19 related, of which 289 (62.3%) and 5,833 (55.4%), respectively, occurred in people with a history of cardiovascular disease or with renal impairment (eGFR < 60 mL/min per 1.73 m^2). Increased COVID-19-related mortality also corresponded with glycemic control and body mass index.

In the second paper (Barron et al.), the authors did a whole-population study assessing risks of in-hospital death with COVID-19 between 1 March and 11 May 2020. Among the 23,698 in-hospital COVID-19-related deaths, a third occurred in people with diabetes: 7,434 (31.4%) in people with type 2 diabetes, 364 (1.5%) in those with type 1 diabetes, and 69 (0.3%) in people with other types of diabetes.

Tartof SY, Qian L, Hong V, et al. **Obesity and Mortality Among Patients Diagnosed With COVID-19: Results From an Integrated Health Care Organization.** Ann Intern Med. 2020 Aug 12. PubMed: https://pubmed.gov/32783686. Full-text: https://doi.org/10.7326/M20-3742

In this retrospective cohort study, Sara Tartof and colleagues determined the adjusted effect of body mass index (BMI), associated comorbidities, sociodemographic factors, and other factors on risk for death due to COVID-19. Compared with patients with a BMI of 18.5 to 24 kg/m^2, those with BMIs of 40 to 44 kg/m^2 and greater than 45 kg/m^2 had relative risks of 2.68 and 4.18, respectively. This risk was most striking among those aged 60 years or younger and men. The authors found no increased risk for death associated with Black or Latino race/ethnicity or other sociodemographic characteristics. See also the comment by David Kass: **COVID-19 and Severe Obesity: A Big Problem?** Ann Intern Med. 2020 Aug 12. PubMed: https://pubmed.gov/32783685. Full-text: https://doi.org/10.7326/M20-5677

Collateral Effects

McGuckin B. **Dental Triaging: past, present and future.** BDJ In Pract 2020;33: 22–23. Full-text: https://doi.org/10.1038/s41404-020-0472-y

Does a 'lost' upper anterior crown constitute a dental emergency and require an urgent non-scheduled appointment? It used to be, but in COVID times, it isn't anymore, despite the emotional distress for the patient. Read these and other considerations in a short overview of dental triage yesterday, today and tomorrow. The next time you go to the dentist, you'll remember Bronagh McGuckin.

Poisoning

Yip L, Bixler D, Brooks DE, et al. **Serious Adverse Health Events, Including Death, Associated with Ingesting Alcohol-Based Hand Sanitizers Containing Methanol - Arizona and New Mexico, May-June 2020.** MMWR Morb Mortal Wkly Rep. 2020 Aug 14;69(32):1070-1073. PubMed: https://pubmed.gov/32790662. Full-text: https://doi.org/10.15585/mmwr.mm6932e1

Don't ingest alcohol-based hand sanitizer products, remind Luke Yip and colleagues after 15 cases of poisoning and four deaths. We would add: And don't inject disinfectants – they don't "knock it out in a minute".

Education

Rubin EJ, Baden LR, Morrissey S. **Building a Successful Public Health Response to Covid-19.** Audio interview (25:18). N Engl J Med 2020; 383:e67. Access: https://www.nejm.org/doi/full/10.1056/NEJMe2027574

The editors discuss the varied use of public health measures to control SARS-CoV-2 transmission in countries around the world, as well as recent vaccine developments.

Beyond your plate borders

Hall S. **Pluto's dark side spills its secrets - including hints of a hidden ocean.** Nature. 2020 Jul;583(7818):674-678. PubMed: https://pubmed.gov/32728264. Full-text: https://doi.org/10.1038/d41586-020-02082-1

Award-winning science journalist Shannon Hall introduces you to the dark side of Pluto. Listen also to the audio long-read (18:10): https://media.nature.com/original/magazine-assets/d41586-020-02327-z/d41586-020-02327-z_18253418.mpga

Spanish

If you read Spanish, read **Cómo mejorar la ventilación en interiores y otros cinco retos prioritarios frente a la segunda ola.** El País 2020, published 14 August. Full-text: https://elpais.com/ciencia/2020-08-14/como-mejorar-la-ventilacion-en-interiores-y-otros-cinco-retos-prioritarios-frente-a-la-segunda-ola.html

Javier Salas explica que la ciencia todavía tiene que dar respuestas a cuestiones como el papel de los niños y cómo se producen la mayoría de los contagios.

15 August

Virology

Sun Z, Cai X, Gu C et al. **Survival of SARS-COV-2 under liquid medium, dry filter paper and acidic conditions.** Cell Discov **6,** 57 (2020). Full-text: https://doi.org/10.1038/s41421-020-00191-9

Zhenghong Yuan, Youhua Xie, Di Qu and colleagues show that SARS-COV-2 can survive for 3 days in liquid medium or on dry filter paper. At high titers, the virus might also be able to survive under acidic conditions that mimic the gastric environment.

Immunology

Zhang F, Gan R, Zhen Z, et al. **Adaptive immune responses to SARS-CoV-2 infection in severe versus mild individuals.** Sig Transduct Target Ther **5,** 156 (2020). Full-text: https://doi.org/10.1038/s41392-020-00263-y

Zhiwei Huang and colleagues profiled adaptive immune cells of PBMCs from recovered COVID-19 patients with varying disease severity using single-cell RNA and TCR/BCR V(D)J sequencing. They observed multiple differences between severe patients (SPs) and mild/moderate patients (MPs) including TCR and BCR clonal expansion and diversity, isotype distribution of antibody sequences, V(D)J gene segments usage preference, and dysregulation of peripheral blood lymphocyte subsets. Higher levels of BCR clonal expansion and B-

cell activation are present in the SP group, indicating that a more robust humoral immune response happens in severe infection. The authors conclude that SPs and MPs may experience different cellular and humoral immune responses, likely related to different degrees of disease severity.

Vaccine

Xia S, Duan K, Zhang Y, et al. **Effect of an Inactivated Vaccine Against SARS-CoV-2 on Safety and Immunogenicity Outcomes: Interim Analysis of 2 Randomized Clinical Trials.** JAMA. 2020 Aug 13:e2015543. PubMed: https://pubmed.gov/32789505. Full-text: https://doi.org/10.1001/jama.2020.15543

An Pan, Xiaoming Yang and colleagues provide the first interim safety, tolerability, and immune response results for a β-propiolactone–inactivated whole-virus vaccine adjuvanted in 0.5 mg of aluminum hydroxide. The incidence rate of adverse reactions in the current study (15.0% among all participants) was not significantly different between the vaccine groups and the active control (alum) groups; it was also lower compared with results of other SARS-CoV-2 candidate vaccines. The neutralizing antibody response suggested that the inactivated vaccine may effectively induce antibody production, but the optimal interval between injections and times of booster injections of the inactivated vaccine remains unclear. In the discussion, find more about ADE and VAERD. See also the comment by Mark Mulligan: **An Inactivated Virus Candidate Vaccine to Prevent COVID-19.** JAMA. 2020 Aug 13. PubMed: https://pubmed.gov/32789500. Full-text: https://doi.org/10.1001/jama.2020.15539

Clinical

Alwan NA. **A negative COVID-19 test does not mean recovery.** Nature 2020, published 11 August. Full-text: https://www.nature.com/articles/d41586-020-02335-z

Data from a UK smartphone app for tracking symptoms suggests that at least one in ten of those reporting are ill for more than three weeks. Clinicians have an idea of who is at increased risk of dying from COVID, but they don't know who is more likely to experience prolonged ill health following symptomatic, or even asymptomatic, SARS-CoV-2 infection. Nisreen Alwan insists that we need a new 'recovery' definition. That definition must include duration, severity and fluctuation of symptoms, as well as functionality and quality of life. The narrow narrative of death as the only bad outcome from COVID

needs broadening to include people becoming less healthy, less capable, less productive and living with more pain.

Treatment

Biran N, Ip A, Ahn J, et al. **Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study.** Lancet Rheumatol 2020, published 14 August. Full-text: https://doi.org/10.1016/S2665-9913(20)30277-0

Noa Biran, Andrew Ip and colleagues did a retrospective observational cohort study with 764 COVID-19 patients who required support in the ICU. In the final analysis, they included 210 patients who received tocilizumab (400 mg in a one-time scheme, with a second dose permitted at the point of worsening oxygenation) and 420 who did not receive tocilizumab. 358 (57%) of 630 patients died, 102 (49%) who received tocilizumab and 256 (61%) who did not receive tocilizumab. In the primary multivariable Cox regression analysis with propensity matching, an association was noted between receiving tocilizumab and decreased hospital-related mortality (hazard ratio 0.64, 95% CI 0.47–0.87; p = 0.0040). Results of ongoing randomized controlled trials are awaited. See also the comment: Campochiaro C, Dagna L. **The conundrum of interleukin-6 blockade in COVID-19.** Lancet Rheumatol 2020, published 14 August. Full-text: https://doi.org/10.1016/S2665-9913(20)30287-3, where Corrado Campochiaro and Lorenzo Dagna superbly summarize the questions for the future: "Have we correctly identified the right COVID-19 population for treatment with anti-inflammatory drugs? Are systemic inflammatory markers reliable enough for selecting patients with hyperinflammation? Do increased concentrations of a specific cytokine imply that its neutralization will be effective in COVID-19? What is the degree of immunosuppression we are aiming for in SARS-CoV-2 infection?"

Co-morbidities

Solomon DA, Sherman AC, Kanjilal S. **Influenza in the COVID-19 Era.** Jama 2020, published 14 August. Full-text: https://doi.org/10.1001/jama.2020.14661

In some years and in some countries, the annual influenza epidemic can result in tens of thousands in deaths. Now clinicians face a second respiratory virus associated with morbidity and mortality several-fold higher than that of influenza. In this short *Insight* article, Daniel Solomon and colleagues stress the importance of widespread implementation of seasonal influenza vaccination and preservation of non-pharmacologic interventions (such as mandato-

ry face coverings in public, closure of schools and retail spaces, and restrictions on movement) until community immunity is achieved through an effective SARS-CoV-2 vaccine and/or natural infection.

Society

Kroshus E, Hawrilenko M, Tandon PS, Christakis DA. **Plans of US Parents Regarding School Attendance for Their Children in the Fall of 2020: A National Survey.** JAMA Pediatr 2020, published 14 August. Full-text: https://doi.org/10.1001/jamapediatrics.2020.3864

What do parents plan to do about school attendance in the coming fall, and what factors are influencing these plans? These are the questions Emily Kroshus and colleagues addressed in their cross-sectional survey study in June 2020. 31% of a sample of 730 parents indicated they would probably or definitely keep their child home this fall, and 49% indicated that they would probably or definitely send their child to school this fall. The authors conclude that schools should act soon to address parental concerns and provide options for parents who decide to keep their child home. See also the Editorial by Nathaniel Beers and colleagues: Dooley DG, Simpson JN, Beers NS. **Returning to School in the Era of COVID-19.** JAMA Pediatr 2020, published 14 August. Full-text: https://doi.org/10.1001/jamapediatrics.2020.3874

French

Carpentier A, Pommier F. **Covid-19 : comment certains malades deviennent des supercontaminateurs.** Le Monde 2020, published 15 August. Audio link: https://www.lemonde.fr/videos/video/2020/08/15/covid-19-comment-certains-malades-deviennent-des-supercontaminateurs_6049016_1669088.html

If you understand French, listen to this short audio (7:28) about superspreaders, R_0 (R naught) and the dispersion coefficient K. By Arthur Carpentier and Félix Pommier.

16 August

Epidemiology

Sebhatu A, Wennberg K, Arora-Jonsson S, et al. **Explaining the homogeneous diffusion of COVID-19 nonpharmaceutical interventions across heterogeneous countries**. PNAS August 11, 2020. Full-text: https://doi.org/10.1073/pnas.2010625117

What drives OECD countries to adopt COVID-19 restrictive policies such as lockdowns and school closures? These Swedish researchers found that government policies are strongly driven by the policies initiated in other countries. The level of democracy also matters: While strong democracies are slower to initiate restrictive policies, they are more likely to follow the policies of nearby countries. Following the lead of others rather than making decisions based on the specific situation of the country may have led to countries locking down too early or too late.

Virology

Alm E, Broberg EK, Connor T. **Geographical and temporal distribution of SARS-CoV-2 clades in the WHO European Region, January to June 2020**. Eurosurveillance Volume 25, Issue 32, 13/Aug/2020. Full-text: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.32.2001410

How do genetic clades distribute between European countries? Erik Alm and colleagues have applied the available nomenclatures to describe broad geographical and temporal trends in the distribution of SARS-CoV-2 genetic clades and discuss potential genomic surveillance objectives at the European level.

Immunology

Gniffke EP, Harrington WE, Dambauskas N, et al. **Plasma from recovered COVID-19 subjects inhibits spike protein binding to ACE2 in a microsphere-based inhibition assay**. J Infect Dis August 15, 2020. Full-text: https://doi.org/10.1093/infdis/jiaa508

Edward Gniffke and colleagues from Seattle present a microsphere-based flow cytometry assay that quantifies the ability of plasma to inhibit the binding of spike protein to ACE2. This inhibition assay may be broadly useful in routine clinical evaluation of functional immunity in recovered patients (selecting the most potent post-convalescent plasma) and evaluating the functionality of anti-SARS2 antibodies produced in response to vaccines.

Diagnostics

Singanayagam A, Patel M, Charlett A, et al. **Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020**. Eurosurveillance August 13, 2020, 25, Issue 32. Full-text: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.32.2001483

Using the Ct values from semi-quantitative RT-PCR can be a valuable proxy for infectious virus detection and may help to inform decision-making on infection control. Culturing virus from 324 samples (253 cases) that tested positive by RT-PCR, this large study found a strong relationship between Ct value and ability to recover infectious virus. The study also adds to the evidence on duration of infectiousness following mild-to-moderate COVID-19. At 10 days after symptom onset, probability of culturing virus declined to 6%. Of note, Ct values and the presence of infectious virus were similar in samples from asymptomatic and pre-symptomatic persons.

Prevention

Patterson EI, Prince T, Anderson ER, et al. **Methods of inactivation of SARS-CoV-2 for downstream biological assays**. J Infect Dis, August 15, 2020. Full-text: https://doi.org/10.1093/infdis/jiaa507

To facilitate the transfer of infectious samples from high containment laboratories, Edward Patterson and colleagues from Liverpool School of Tropical Medicine have tested methods commonly used to inactivate virus and prepare the sample for additional experiments. Incubation at 80° C, a range of detergents, Trizol reagents and UV energies were successful at inactivating a high titer of SARS-CoV-2. Methanol and paraformaldehyde incubation of infected cells also inactivated the virus. The protocols presented here can provide a framework for in-house inactivation of SARS-CoV-2.

Hatfield KM, Reddy SC, Forsberg K, et al. **Facility-Wide Testing for SARS-CoV-2 in Nursing Homes — Seven U.S. Jurisdictions, March–June 2020**. MMWR Morb Mortal Wkly Rep 2020;69:1095–1099. Full-text: http://dx.doi.org/10.15585/mmwr.mm6932e5

Again and again: If you have a case a nursing home, test everyone, residents and HCP, immediately. In regression analyses among 88 nursing homes with a documented case before facility-wide testing occurred, each additional day between identification of the first case and completion of facility-wide testing was associated with identification of 1.3 additional cases. Among 62 facilities that could differentiate results by resident and HCP status, an estimated 1.3 HCP cases were identified for every three resident cases.

Treatment

Jorgensen SC, Burry L, Tse CL, et al. **Baricitinib: Impact on COVID-19 coagulopathy?** Clin Infect Dis, August 2020. Full-text: https://doi.org/10.1093/cid/ciaa1208

The JAK-inhibitor baricitinib interrupts the signaling of multiple cytokines implicated in COVID-19 immunopathology and may also exert antiviral effects. Several trials are underway. Sarah Jorgensen and colleagues highlight a potential adverse effect that could be problematic for COVID-19 patients: baricitinib's dose-dependent association with arterial and venous thromboembolic events. It is possible that the pro-thrombotic tendencies could exacerbate a hypercoagulable state, underscoring the importance of restricting the use of baricitinib to clinical trials.

Cerda-Contreras C, Nuzzolo-Shihadeh L, Camacho-Ortiz A. **Baricitinib as treatment for COVID-19: friend or foe of the pancreas?** Clin Infect Dis, August 14m 2020. Full-text: https://doi.org/10.1093/cid/ciaa1209

These authors present a case of pancreatitis occurring during baricitinib administration.

Collateral damage

Editorial. **The EVALI outbreak and vaping in the COVID-19 era**. The Lancet Respiratory Medicine 2020, published 14 August. Full-text: https://doi.org/10.1016/S2213-2600(20)30360-X

From August 2019 to February 2020, 2,807 cases of EVALI (e-cigarette, or vaping, product use-associated lung injury) were reported to the CDC, including 68 deaths. Symptoms of EVALI may overlap with those of some infectious respiratory diseases, including COVID-19. This editorial highlights current knowledge and how the effects of vaping might now be colliding with the risk of COVID-19. Several experts have asked for e-cigarettes to be withdrawn from the market during the pandemic.

Bayram H, Köktürk N, Elbek O, et al. **Interference in scientific research on COVID-19 in Turkey**. Lancet 2020, 396: 463-464, August 15, 2020. Full-text: https://doi.org/10.1016/S0140-6736(20)31691-3

Ethics as a second step? The Turkish Ministry of Health has announced a mandatory application for permission for research on COVID-19, before any application is made to ethics committees. Hasan Bayram and colleagues are worried about these restrictions on independent research in Turkey and hope that the decision will be taken back in compliance with the Turkish Constitution.

17 August

Virology

Sarkar M, Saha S. **Structural insight into the role of novel SARS-CoV-2 E protein: A potential target for vaccine development and other therapeutic strategies**. PLoS ONE August 13, 15(8). Full-text: https://doi.org/10.1371/journal.pone.0237300 Full-text:

Coronaviruses have four main structural proteins: Nucleocapsid protein (N), Spike protein (S), Membrane protein (M), and Envelope protein (E). The E protein is the smallest and is involved in a wide spectrum of functional repertoire. Using the bioinformatics and structural modelling approach, the authors modelled the structure of E and give insights into the functional role of this protein that has a low disparity and low mutability.

Lau SKP, Wong ACP, Luk HKH, Li KSM, Fung J, He Z, et al. **Differential tropism of SARS-CoV and SARS-CoV-2 in bat cells**. Emerg Infect Dis. 2020 Dec [date cited]. Full-text: https://doi.org/10.3201/eid2612.202308

SARS-CoV-2 did not replicate efficiently in 13 bat cell lines, whereas SARS-CoV replicated efficiently in kidney cells of its ancestral host, the Rhinolophus sinicus bat, suggesting different evolutionary origins. Structural modeling showed that RBD/RsACE2 binding may contribute to the differential cellular tropism. Although SARS-CoV-2 is closely related to SARS-CoVs in bats and pangolins, none of the existing animal viruses represents the immediate ancestor of SARS-CoV-2.

Transmission

Lewis NM, Chu VT, Ye D, et al. **Household Transmission of SARS-CoV-2 in the United States**. Clinical Infectious Diseases, 16 August 2020. Full-text: https://doi.org/10.1093/cid/ciaa1166

Nathaniel M Lewis and colleagues sought to estimate the household secondary infection rate (SIR) of SARS-CoV-2 and evaluate potential risk factors for secondary infection among 58 households in Utah and Wisconsin. Fifty-two of 188 household contacts acquired secondary infections (SIR: 28%, 95% CI: 22–34%). Of note, household contacts to COVID-19 patients with immunocompromised conditions had increased odds of infection (OR: 15.9, 95% CI: 2.4–106.9) as well as household contacts who themselves had diabetes mellitus (OR: 7.1, 95% CI: 1.2–42.5).

Garigliany M, Van Laere A-S, Clercx C, Giet D, Escriou N, Huon C, et al. **SARS-CoV-2 natural transmission from human to cat, Belgium, March 2020**. Emerg Infect Dis. 2020 Dec [date cited]. Full-text: https://doi.org/10.3201/eid2612.202223

Mutien Garigliany from Liège, Belgium, and colleagues report a human-to-cat transmission. A household cat was productively infected with the SARS-CoV-2 virus excreted by its owner, and the infection caused a non-fatal but nevertheless severe disease.

Diagnostics

González-González E, Trujillo-de Santiago G, Lara-Mayorga IM. **Portable and accurate diagnostics for COVID-19: Combined use of the miniPCR thermocycler and a well-plate reader for SARS-CoV-2 virus detection**. PLOS August 13, 2020. Full-text: https://doi.org/10.1371/journal.pone.0237418

These Mexican researchers demonstrate the use of the mini-PCR, a commercial compact and portable PCR device recently available on the market, in combination with a commercial well-plate reader as a diagnostic system. The accuracy and simplicity of this diagnostics strategy may provide a cost-efficient and reliable alternative for COVID-19 pandemic testing, particularly in underdeveloped regions but also for deployment in point-of-care SARS-CoV-2 detection.

Clinical

Tatu AL, Nadasdy T, Bujoreanu FC. **Familial Clustering of COVID-19 Skin Manifestations**. Dermatol Ther. 2020 Aug 14:e14181. PubMed: https://pubmed.gov/32794366. Full-text: https://doi.org/10.1111/dth.14181

Does genetics play a role in the manifestation of viral exanthems? Probably, according to this report of a familial clustering of a maculopapular COVID-19 rash. Among 8 people in a family who contracted SARS-CoV-2 infection, only the 4 who were related by blood presented dermatological manifestations.

Comorbidities

Lee J, Foote MB, Lumish M, et al. **Chemotherapy and COVID-19 Outcomes in Patients With Cancer**. J Clin Oncol 2020, August 14, 2020. Full-text: https://ascopubs.org/doi/full/10.1200/JCO.20.01307

Among a total of 309 patients with cancer and concurrent COVID-19 at the Memorial Sloan Kettering Cancer Center, cytotoxic chemotherapy administered within 35 days of a COVID-19 diagnosis was not significantly associated with a severe or critical COVID-19 event (HR, 1.10; 95% CI, 0.73 to 1.60). How-

ever, patients with active hematologic or lung malignancies, peri–COVID-19 lymphopenia, or baseline neutropenia had worse COVID-19 outcomes. Findings remained consistent in a multivariate model and in multiple sensitivity analyses.

Boettler T, Marjot T, Newsome N, et al. **Impact of COVID-19 on the care of patients with liver disease: EASL-ESCMID position paper after 6 months of the pandemic**. J Hepatol 2020, Aug 4. Full-text: https://doi.org/10.1016/j.jhepr.2020.100169

High COVID-19 mortality rates have been reported in patients with pre-existing chronic liver disease and cirrhosis: this excellent review serves as an update on the previous position paper summarizing the evidence for liver disease involvement during COVID-19 and also provide some recommendations on how to return to routine care.

Solomon MD, McNulty EJ, Rana JS, et al. **The Covid-19 Pandemic and the Incidence of Acute Myocardial Infarction**. N Engl J Med 2020; 383:691-693, August 13, 2020. Full-text: https://doi.org/10.1056/NEJMc2015630

Using data from Kaiser Permanente Northern California, a large health care delivery system with 255 clinics providing care for more than 4.4 million persons throughout Northern California, Mathew Solomon and colleagues show that the weekly rates of hospitalization for acute myocardial infarction decreased by up to 48% during the COVID-19 period. Decreases were similar among patients with NSTEMI (incidence rate ratio, 0.51) and those with STEMI (0.60). Of note, demographic characteristics, hemodynamic measures on admission, initial and peak troponin I values, and the burden of other examined co-existing conditions were similar in patients who presented during the COVID-19 period and in those who presented before the first case of COVID-19 occurred.

Treatment

Singh VP, El-Kurdi B, Rood C. **What underlies the benefit of famotidine formulations used during COVID-19?** Gastroenterology. 2020 Aug 7. PubMed: https://pubmed.gov/32777281. Full-text: https://doi.org/10.1053/j.gastro.2020.07.051

While results of the randomized clinical trial on the benefits of intravenous famotidine in treating COVID-19 (NCT04370262) are excitedly awaited, Vijay P. Singh and colleagues speculate on the potential mechanisms of action of this drug.

18 August

Transmission

Bui DP, McCaffrey K, Friedrichs M, et al. **Racial and Ethnic Disparities Among COVID-19 Cases in Workplace Outbreaks by Industry Sector — Utah, March 6–June 5, 2020.** MMWR Morb Mortal Wkly Rep. ePub: 17 August 2020. Full-text: http://dx.doi.org/10.15585/mmwr.mm6933e3

We need to understand which types of work have the highest exposure risk for SARS-CoV-2. In Utah, US, from March to June 2020, approximately 12% of confirmed COVID-19 cases were associated with workplace outbreaks. The 210 workplace outbreaks occurred in 15 of 20 industry sectors; nearly half of all workplace outbreaks occurred in three sectors: Manufacturing (43; 20%), Construction (32; 15%) and the Wholesale Trade (29; 14%); 58% (806 of 1,389) of workplace outbreak-associated cases occurred in these three sectors. David Bui and colleagues recommend that mitigation strategies should be culturally and linguistically responsive to racial/ethnic minority workers disproportionately affected by COVID-19.

Immunology

Addetia A, Crawford K, Dingens A, et al. **Neutralizing antibodies correlate with protection from SARS-CoV-2 in humans during a fishery vessel outbreak with high attack rate.** medRxiv 2020, posted 14 August. Full-text: https://doi.org/10.1101/2020.08.13.20173161

What are the immunological correlates of protection against SARS-CoV-2? The ongoing Phase III vaccine trials might provide an answer within months. In the meantime, Alexander Greninger and colleagues provide insights into the protective nature of neutralizing antibodies. Their data source? Shipping vessels, "particularly useful candidates for assessing protection from SARS-CoV-2 infection". Here they report an outbreak of SARS-CoV-2 among 122 crewmembers with an attack rate greater than 85% - a fairly high percentage due to high population density and multiple contacts between people on ships. Preeminently, none of three individuals with pre-existing neutralizing antibodies were infected. (Their neutralizing titers [1:174, 1:161, 1:3082] were in the typical range of titers observed in humans who have been infected with SARS-CoV-2 within the previous few months.) These findings are consistent with data from animal models, in which the elicitation of high titers of neutralizing antibodies was protective against re-challenge with SARS-CoV-2. The paper has not yet been peer reviewed.

Laing AG, Lorenc A, del Molino del Barrio I, et al. **A dynamic COVID-19 immune signature includes associations with poor prognosis.** Nat Med 2020, published 17 August. Full-text: https://doi.org/10.1038/s41591-020-1038-6

Over the coming months, we will get a clearer view of 1) correlates of immunoprotection, such as virus-specific antibodies that limit disease and 2) correlates of immune dysregulation, such as cytokine over-production that may promote disease. Adrian Hayday, Manu Shankar-Hari and colleagues now explain that collectively, those correlates can compose a core disease-associated immune signature. They identified a core peripheral blood immune signature across 63 hospital-treated patients with COVID-19 who were otherwise highly heterogeneous. The signature includes discrete changes in B and myelomonocytic cell composition, profoundly altered T cell phenotypes, selective cytokine/chemokine upregulation and SARS-CoV-2-specific antibodies. One set of traits, including a triad of IP-10, interleukin-10 and interleukin-6, anticipate subsequent clinical progression. The immune signature is provided as a large dataset supported by an online portal, www.immunophenotype.org,

Carter MJ, Fish M, Jennings A, et al. **Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection.** Nat Med 2020, published 18 August. Full-text: https://doi.org/10.1038/s41591-020-1054-6

Second article by Manu Shankar-Hari today. He, Shane Tibby and colleagues performed peripheral leukocyte phenotyping in 25 patients with pediatric multisystem inflammatory syndrome in children (MIS-C) temporally associated with SARS-CoV-2. Their data suggest that MIS-C is an immunopathogenic illness distinct from Kawasaki disease.

Diagnostic

Hachim A, Kavian N, Cohen CA et al. **ORF8 and ORF3b antibodies are accurate serological markers of early and late SARS-CoV-2 infection.** Nat Immunol 2020, published 17 August. Full-text: https://doi.org/10.1038/s41590-020-0773-7

A broader landscape of antibody responses to a range of viral proteins may help in detecting the immunogenicity of SARS-CoV-2 infection and understanding pathogenesis and immunity. Sophie Valkenburg, Niloufar Kavian, Asmaa Hachim and colleagues used the luciferase immunoprecipitation system (LIPS) assay to assess the antibody responses to a panel of 15 SARS-CoV-2

antigens; four structural proteins (S, N, M and E), three S subunits (S1, S2 and S2′), the se
ORF10) and one relevant NSP within ORF1ab (NSP1). Their data suggest that the combinational use of ORF3b, ORF8 and N may be a high-performing marker of infection at early and late time points.

Clinical

Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. **Management of post-acute covid-19 in primary care.** BMJ. 2020 Aug 11;370:m3026. PubMed: https://pubmed.gov/32784198. Full-text: https://doi.org/10.1136/bmj.m3026

Up to 10% of people may experience prolonged illness after COVID-19. Trish Greenhalgh and colleagues give a thorough overview of the management of post-acute COVID-19 ("long COVID"). A must-read for all practitioners.

See also Crosby SS: *My COVID-19* (Top 10, July 11) and Draulans D: *Scientist who fought Ebola and HIV reflects on facing death from COVID-19* (Top 10, May 11).

Treatment

Trezza A, Iovinelli D, Santucci A, et al. **An integrated drug repurposing strategy for the rapid identification of potential SARS-CoV-2 viral inhibitors.** Sci Rep 10, 13866 (2020). Full-text: https://doi.org/10.1038/s41598-020-70863-9

Until an effective vaccine is available, repurposing FDA-approved drugs could significantly shorten the time and reduce the cost compared to *de novo* drug discovery. Here Ottavia Spiga and colleagues combine molecular dynamics simulations (MD), Supervised MD (SuMD), Steered MD (SMD) and interaction energy calculations, and showed that simeprevir (an HCV drug withdrawn from the European market in 2018) and lumacaftor (used in cystic fibrosis) bind the receptor-binding domain of the Spike protein with high affinity and prevent ACE2 interaction.

Pediatrics

Jiang L, Tang K, Levin M et al. **COVID-19 and multisystem inflammatory syndrome in children and adolescents.** Lancet Infect Dis 2020, published 17 August. Full-text: https://doi.org/10.1016/S1473-3099(20)30651-4

Children and adolescents make up only a small percent of all COVID-19 cases. However, in the past months, reports from Europe, North America, Asia, and Latin America described children and adolescents with COVID-19-associated

multisystem inflammatory conditions which are both similar and distinct from other well described inflammatory syndromes in children, including Kawasaki disease, Kawasaki disease shock syndrome, and toxic shock syndrome. In this review, Zulfiqar Bhutta and colleagues provide an overview of the epidemiology, causes, clinical features, and current treatment protocols.

Society

Greve JE, Gambino L. **'It is what it is': Michelle Obama picks Trump apart in gripping DNC speech.** The Guardian 2020, published 18 August. Full-text: https://www.theguardian.com/us-news/2020/aug/17/michelle-obama-democratic-convention-joe-biden

No need for comment.

Journal News

Ledford H. **What the immune response to COVID-19 says about the prospects for a vaccine.** Nature 2020, published 17 August. Full-text: https://www.nature.com/articles/d41586-020-02400-7

Again: can the human immune system mount a lasting defense against the pandemic virus SARS-CoV-2? Read about the Common Cold Study (snorting a nostrilful of solution containing a coronavirus), cataloguing antibody and immune-cell responses, sterilizing immunity and Plans B and T.

19 August

Virology

Ke Z, Oton J, Qu K, et al. **Structures and distributions of SARS-CoV-2 spike proteins on intact virions.** Nature 2020, published 17 August. Full-text: https://doi.org/10.1038/s41586-020-2665-2

Fully understanding how SARS-CoV-2 Spike (S) proteins function and how they interact with the immune system, requires knowledge of the structures, conformations and distributions of S trimers within virions. Now John Briggs and colleagues collect viral particles from infected cells and determine the high-resolution structure, conformational flexibility and distribution of S trimers *in situ* on the virion surface. They express optimism that cryo-electron microscopy can be used to study antibody binding to S in the context of the viral surface. Such studies would provide insights into how neutralizing antibodies block virus infection, particularly for antibodies against mem-

brane-proximal regions of S, and could thus inform design of immunogens for vaccination.

Turoňová B, Sikora M, Schürmann C, et al. **In situ structural analysis of SARS-CoV-2 spike reveals flexibility mediated by three hinges.** Science 2020, published 18 August. Full-text: https://science.sciencemag.org/content/early/2020/08/17/science.abd5223

If you are not a virologist, *cryo electron tomography, sub-tomogram averaging* and *molecular dynamics simulations* may all be Greek to you. To structurally analyze the SARS-CoV-2 Spike (S) protein *in situ*, Martin Beck, Jacomina Locker, Gerhard Hummer and colleagues did exactly that. They show that the stalk domain of S contains three hinges, giving the head unexpected orientational freedom, and propose that the hinges allow S to scan the host cell surface, shielded from antibodies by an extensive glycan coat.

Transmission

Asadi S, Gaaloul ben Hnia N, Barre RS, et al. **Influenza A virus is transmissible via aerosolized fomites.** Nat Commun 11, 4062 (2020). Full-text: https://doi.org/10.1038/s41467-020-17888-w

SARS-CoV-2 can be transmitted via droplets, fomites and possibly aerosol. Will we need to get accustomed to a fourth transmission route, *aerosolized fomites*? That's what Nicole Bouvier and colleagues suggest, although for now only for influenza A virus. They show that dried influenza virus remains viable in the environment, on materials like paper tissues and on the bodies of living animals, long enough to be aerosolized on non-respiratory dust particles that can transmit infection through the air to new mammalian hosts. Will we soon see a paper about SARS-CoV-2 transmission via aerosolized fomites?

Prevention

Grassly NC, Pons-Salort M, Parker EPK, et al. **Comparison of molecular testing strategies for COVID-19 control: a mathematical modelling study.** Lancet Infect Dis 2020, published 18 August. Full-text: https://doi.org/10.1016/S1473-3099(20)30630-7

Tedros Adhanom Ghebreyesus didn't get everything right in the SARS-CoV-2 pandemic, but he was right when he recommended: "Test, test, test!" (WHO, 16 March 2020; see also our Prevention chapter), but countries have taken different approaches and the effectiveness of alternative strategies is unknown. Now Nicolas Grassly and colleagues from the Imperial College COVID-

19 Response Team investigate the potential impact of different testing and isolation strategies on SARS-CoV-2 transmission. Their conclusion: "Molecular testing can play an important role in prevention of SARS-CoV-2 transmission, especially among health-care workers and other high-risk groups, but no single strategy will reduce *R* below 1 at current levels of population immunity. Immunity passports based on antibody tests or tests for infection face substantial technical, legal, and ethical challenges.

Immunology

Young BE, Fong SW Chan YH, et al. **Effects of a major deletion in the SARS-CoV-2 genome on the severity of infection and the inflammatory response: an observational cohort study.** Lancet 2020, published 18 August. Full-text: https://doi.org/10.1016/S0140-6736(20)31757-8

In January and February 2020, a SARS-CoV-2 variant with a 382-nucleotide deletion (Δ382) in the ope
in Singapore. Now Lisa Ng, Gavin Smith and colleagues compared the clinical outcomes and immune responses of patients infected with wild type and Δ382
SARS-CoV-2. Of 131 patients enrolled onto the study, 92 (70%) were infected with the wild type virus, ten (8%) had a mix of wild type and Δ382-variant viruses, and 29 (22%) had only the Δ382 variant. Their finding: development of hypoxia requiring supplemental oxygen was less frequent in the Δ382 variant group (0 of 29 patients) than in the wild type only group (26 [28%] of 92). They conclude that "further study of these variants could improve our understanding of SARS-CoV-2 virology and pathogenesis and could have implications for the development of treatments and vaccines."

Clinical

Iadecola C, Anrather J, Kamel H. **Effects of COVID-19 on the nervous system.** Cell 2020, published 19 August. Full-text: https://www.cell.com/cell/fulltext/S0092-8674(20)31070-9

Many hospitalized COVID-19 patients exhibit neurological manifestations, ranging from headache and loss of smell, to confusion and disabling strokes. The disease might also take a toll on the nervous system in the long term. Follow Costantino Iadecola, Josef Anrather and Hooman Kamel in this appraisal of the potential for neurotropism and mechanisms of neuropathogenesis of SARS-CoV-2.

Comorbidities

Ellul MA, Benjamin L, Singh B, et al. **Neurological associations of COVID-19.** Lancet Neurol 2020;19:767-83. PubMed: https://pubmed.gov/32622375. Full-text: https://doi.org/10.1016/S1474-4422(20)30221-0

Recognition of neurological disease associated with SARS-CoV-2 in patients whose respiratory infection is mild or asymptomatic may prove challenging, especially if primary COVID-19 illness occurred weeks earlier. Tom Solomon and colleagues navigate you through the neurological complications of COVID-19 in this 'Rapid (15 pages) Review".

Fifi JT, Mocco J. **COVID-19 related stroke in young individuals.** Lancet Neurol 2020;19:713-715. Full-text: https://doi.org/10.1016/S1474-4422(20)30272-6

SARS-CoV-2 infection may cause thrombotic vascular events. In patients presenting with large vessel stroke during the COVID-19 pandemic, COVID-19 patients were significantly younger, with a mean age of 59 years, than patients who tested negative for SARS-CoV-2, who had a mean age of 74 years. Johanna Fifi and J Mocco recommend that, in otherwise healthy, young patients who present with stroke during the pandemic, the diagnosis of COVID-19 should be thoroughly investigated.

Journal Feature

Editorial. **Progress report on the coronavirus pandemic.** Nature 2020, published 19 August. Full-text: https://www.nature.com/articles/d41586-020-02414-1

In the first of a series of editorials, *Nature* looks back at some of the key findings from the scientists race to demystify SARS-CoV-2: cracking the virus code, comorbidities, modes of infection, aerosols and asymptomatic infection.

McKenna M. **The antibiotic paradox: why companies can't afford to create life-saving drugs.** Nature 2020, published 19 August. Full-text: https://www.nature.com/articles/d41586-020-02418-x

The antibiotic market seems to be broken. For almost two decades, the large corporations that once dominated antibiotic discovery have been fleeing the business. It takes around 20 years to see any profit from a newly developed antibiotic and prices the companies can charge for antibiotics are too low to support the cost of developing them. Join Maryn McKenna while she discov-

ers omadacycline (trade name: Nuzyra) which went on sale in the US in 2019 for use against bacterial infections.

20 August

Epidemiology

Rivera F, Safdar N, Ledeboer N, et al. **Prevalence of SARS-CoV-2 asymptomatic infections in two large academic health systems in Wisconsin**. Clinical Infectious Diseases 19 August 2020. Full-text: https://doi.org/10.1093/cid/ciaa1225

From April 6 2020 to June 4 2020, a total of 11,654 asymptomatic patients were tested for SARS-CoV-2 in two large academic health systems in two counties of Wisconsin. Since early April 2020, both health systems implemented SARS-CoV-2 testing on all hospitalizations, on all patients scheduled for elective surgeries, including deliveries, or among all patients with known SARS-CoV-2 exposure in the absence of symptoms. In total, only 61 (0.52%) were positive. In both of these counties, rates were low, despite the higher incidence of COVID-19 in Milwaukee county.

Transmission

Chambers C, Krogstad P, Betrand K, et al. **Evaluation for SARS-CoV-2 in Breast Milk From 18 Infected Women**. JAMA August 19, 2020. Full-text: https://doi.org/10.1001/jama.2020.15580

There are some case reports on the detection of SARS-CoV-2 in breast milk. Christina Chambers and colleagues examined 64 breast milk samples from 18 infected women. Although SARS-CoV-2 RNA was detected in one milk sample, the viral culture for that sample was negative. These data suggest that SARS-CoV-2 RNA does not represent replication-competent virus and that breast milk may not be a source of infection for the infant.

Immunology

Bunders M, Altfeld M. **Implications of sex differences in immunity for SARS-CoV-2 pathogenesis and design of therapeutic interventions**. Immunity August 14, 2020. Full-text: https://doi.org/10.1016/j.immuni.2020.08.003

Women show stronger immune responses against pathogens and vaccines, but also in higher susceptibility to autoimmune diseases. But do sex differences in immunity contribute to better control of SARS-CoV-2 in women? In

their elegant review, Madeleine Bunders and Marcus Altfeld summarize current knowledge on the basic biological pathways that underlie differences in immune responses between women and men.

Neidleman J, Luo X, Frouard J, et al. **SARS-CoV-2-specific T cells exhibit phenotypic features of robust helper function, lack of terminal differentiation, and high proliferative potential**. Cell Rep Med 2020, August 19. Full-text: https://doi.org/10.1016/j.xcrm.2020.100081

The phenotypes of SARS-CoV-2-specific T cells remain poorly defined. Jason Neidleman and colleagues conducted an in-depth phenotypic analysis of SARS-CoV-2-specific CD4+ and CD8+ T cells circulating in the bloodstream of nine individuals who had recently recovered from COVID-19. This was achieved by combining detection of specific T cells together with CyTOF, a mass spectrometry-based single-cell phenotyping method that uses antibodies conjugated to metal lanthanides to quantify expression levels of both surface and intracellular proteins. The main results: T cells were diverse, exhibited features different from antigen-specific T cells against CMV, included cells with both lymphoid and tissue homing potential, harbored phenotypic features of functional effector cells, and were long-lived and capable of homeostatic proliferation. The results suggest that long-lived and robust T cell immunity is generated following natural SARS-CoV-2 infection and support an important role for SARS-CoV-2-specific T cells in host control of COVID-19.

Kaneko N, Kuo HH Boucau J, et al. **Loss of Bcl-6-expressing T follicular helper cells and germinal centers in COVID-19**. Cell August 19, 2020. Full-text: https://doi.org/10.1016/j.cell.2020.08.025

Examining postmortem thoracic lymph nodes and spleens in acute SARS-CoV-2 infection, Naoki Kaneko and colleagues from Ragon Institute (Massachusetts, USA) found a striking absence of lymph node and splenic germinal centers and Bcl-6 expressing B cells, defective Bcl-6+ T follicular helper cell generation and differentiation and dysregulated SARS-CoV-2 specific humoral immunity early in COVID-19 disease. According to the authors, the underlying basis for the loss of germinal centers is best explained by the striking failure of differentiation of Bcl-6+ T follicular helper cells likely because of dramatic changes in the extra-follicular cytokine milieu driven by TH1 cells and the aberrant local production of TNF-α in lymphoid organs. Their results provide a mechanistic explanation for the limited durability of humoral immunity and the less robust somatic hypermutation seen in this disease following natural infection.

Guervilly C, Burtey S, Sabatier F, et al. **Circulating Endothelial Cells as a Marker of Endothelial Injury in Severe COVID -19**. J Infect Dis 19 August 2020, jiaa528, https://doi.org/10.1093/infdis/jiaa528.

In this retrospective study, Christophe Guervilly and colleagues from Marseille measured circulating endothelial cells (CEC) in the blood of 99 patients with COVID-19. Patients in the intensive care units (ICU) had significantly higher CEC counts than non-ICU patients and the extent of endothelial injury was correlated with putative markers of disease severity and inflammatory cytokines. These data provide *in vivo* evidence that endothelial injury is a key feature of COVID-19.

Vaccine

Hassan AP, Kafai NM, Dmitriev IP. **A single-dose intranasal ChAd vaccine protects upper and lower respiratory tracts against SARS-CoV-2**. Cell August 19, 2020. Full-text: https://doi.org/10.1016/j.cell.2020.08.026

In their animal experiments on mice expressing the ACE receptor, Ahmed Hassan and colleagues from St. Louis, US show the protective activity of a chimpanzee adenovirus-vectored vaccine encoding a pre-fusion stabilized Spike protein. Of note, intramuscular dosing induced robust systemic humoral and cell-mediated immune responses but did not confer sterilizing immunity. In contrast, a single intranasal dose induced high levels of neutralizing antibodies, promoted systemic and mucosal IgA and T cell responses, and virtually completely prevented SARS-CoV-2 infection in both the upper and lower respiratory tracts.

Clinical

Yehia BR, Winegar A, Fogel R, et al. **Association of Race With Mortality Among Patients Hospitalized With Coronavirus Disease 2019 (COVID-19) at 92 US Hospitals**. JAMA Netw Open. 2020;3(8):e2018039. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.18039

In this cohort study of 11,210 individuals with COVID-19 presenting for care at 92 hospitals across 12 states, there was no difference in all-cause, in-hospital mortality between white and black patients after adjusting for age, sex, insurance status, comorbidity, neighborhood economics, and site of care.

Wu F, Liu M, Wang A, et al. **Evaluating the Association of Clinical Characteristics With Neutralizing Antibody Levels in Patients Who Have Recovered From Mild COVID-19 in Shanghai, China**. JAMA Intern Med August 18, 2020. Full-text: https//doi.org/10.1001/jamainternmed.2020.4616

In this cohort study of 175 patients who recovered from mild COVID-19, neutralizing antibody titers (NAbs) varied substantially at the time of discharge. NAbs were detected in patients from day 4 to 6 and reached peak levels from day 10 to 15 after disease onset. Of note, there were 10 patients whose NAb titers were less than the detectable level of the assay.

Treatment

Kasgari HA, Moradi S, Shabani AM, et al. **Evaluation of the efficacy of sofosbuvir plus daclatasvir in combination with ribavirin for hospitalized COVID-19 patients with moderate disease compared with standard care: a single-centre, randomized controlled trial**. J Antimicrob Chemoth, 19 August 2020. Full-text: https://doi.org/10.1093/jac/dkaa332

The first randomized controlled trial in adult patients hospitalized with COVID-19 in Ghaem Shahr Razi Hospital (Iran) to evaluate the efficacy and safety of the two HCV drugs sofosbuvir and daclatasvir in combination with ribavirin (SDR) compared with standard of care. Though were trends in favor of the SDR arm for recovery and lower death rates, the trial was too small to make definite conclusions. In addition, there was an imbalance in the baseline characteristics between the arms.

21 August

Transmission

Hoehl S, Karaca O, Kohmer M, et al. **Assessment of SARS-CoV-2 Transmission on an International Flight and Among a Tourist Group**. JAMA Netw Open August 18, 2020, 3(8). Full-text: https://doi.org/10.1001/jamanetworkopen.2020.18044

Two likely SARS-CoV-2 transmissions on a 4.5-hour flight from Tel Aviv to Frankfurt, with 7 index cases. Both passengers were seated within two rows of an index case. According to the authors, it could be speculated that the rate may have been reduced further had the passengers worn masks.

Bhaskar ME, Arun S. **SARS-CoV-2 Infection Among Community Health Workers in India Before and After Use of Face Shields**. JAMA August 17, 2020. Full-text: https://doi.org/10.1001/jama.2020.15586

This observational study describes transmission before and after the use of face shields (made of polyethylene terephthalate) in health workers in Chennai, India. Before the introduction of face shields, 12/62 workers were infected, while visiting 5,880 homes with 31,164 persons (222 positive for SARS-CoV-2). After the introduction, among 50 workers (previously uninfected) who continued to provide counseling, visiting 18,228 homes with 118,428 persons (2682 positive), no infection occurred.

Diagnosis

Kiran U, Gokulan CG, Kuncha SK, et al. **Easing diagnosis and pushing the detection limits of SARS-CoV-2**. Biology Methods and Protocols, August 20, 2020. Full-text: https://doi.org/10.1093/biomethods/bpaa017

A more effective and reliable method of SARS-CoV-2 detection. Udan Kiray and colleagues show that the currently used and most reliable RT-PCR based SARS-CoV-2 procedure can be further simplified to make it faster, safer, and economical by eliminating the RNA isolation step.

Clinical

Tucker NR, Chaffin M, Bedi KC Jr, et al. **Myocyte-Specific Upregulation of ACE2 in Cardiovascular Disease: Implications for SARS-CoV-2-Mediated Myocarditis**. Circulation. 2020 Aug 18;142(7):708-710. PubMed: https://pubmed.gov/32795091 . Full-text: https://doi.org/10.1161/CIRCULATIONAHA.120.047911

Nathan Tucker and colleagues assessed ACE2 expression by performing bulk and single nucleus RNA-Seq on the left ventricles of 11 individuals with dilated cardiomyopathy, 15 individuals with hypertrophic cardiomyopathy, and 16 controls with non-failing hearts. Data suggest that previous cardiovascular disease is a predominant driver of cardiomyocyte-specific increased transcription of ACE2, providing a pathologic link for SARS-CoV–associated viral myocarditis.

Severe COVID-19

Hanley B, Naresh KN, Roufosse C, et al. **Histopathological findings and viral tropism in UK patients with severe fatal COVID-19: a post-mortem study**. Lancet Microbe August 20, 2020. Full-text: https://doi.org/10.1016/S2666-5247(20)30115-4

Ten cases of fatal COVID-19 showed diffuse alveolar damage, thrombosis, hemophagocytosis, and immune cell depletion. The authors report several novel autopsy findings including pancreatitis, pericarditis, adrenal microinfarction, secondary disseminated mucormycosis, and brain microglial activation.

Comorbidities

Cheng X, Liu YM, Li H, et al. **Metformin Use Is Associated with Increased Incidence of Acidosis but not Mortality in Individuals with COVID-19 and Pre-existing Type 2 Diabetes**. Cell Metabol August 20, 2020. Full-text: https://doi.org/10.1016/j.cmet.2020.08.013

Retrospective cohort study of 1,213 hospitalized individuals with COVID-19 and pre-existing type 2 diabetes (T2D). Metformin use was significantly associated with a higher incidence of acidosis, particularly in cases with severe COVID-19, but not with 28-day COVID-19-related mortality. Furthermore, metformin use was significantly associated with reduced heart failure and inflammation. These findings provide some evidence in support of continuing metformin treatment in individuals with COVID-19 and pre-existing T2D, but acidosis and kidney function should be carefully monitored.

Treatment

Karlsen APH, Wiberg S, Laigaard J, Pedersen C, Rokamp KZ, Mathiesen O. **A systematic review of trial registry entries for randomized clinical trials investigating COVID-19 medical prevention and treatment**. PLoS One. 2020 Aug 20;15(8):e0237903. PubMed: https://pubmed.gov/32817689 . Full-text: https://doi.org/10.1371/journal.pone.0237903

A global snapshot overview of COVID-19 interventions: Anders Peder Højer Karlsenand and colleagues systematically screened trial registry entries via the WHO ICTR Platform and 33 trial registries up to June 23, 2020. In total, 1,303 RCTs from 71 countries were identified (47% blinded), planning to include a total of 611,364 participants. Recruitment was ongoing in 54% of trials and completed in 8%. The five most frequent investigational categories were immune modulating drugs (20%), unconventional medicine (13%), antimalari-

al drugs (9%), antiviral drugs (8%) and respiratory adjuncts (6%). The five most frequently tested unimodal interventions were: chloroquine/hydroxychloroquine (113 trials with 199,841 participants); convalescent plasma (64 trials with 11,840 participants); stem cells (51 trials with 3,370 participants); tocilizumab (19 trials with 4,139 participants) and favipiravir (19 trials with 3,210 participants).

Park JJ, Decloedt EH, Rayner CR. **Clinical trials of disease stages in COVID 19: complicated and often misinterpreted**. Lancet August 20, 2020. Full-text: https://doi.org/10.1016/S2214-109X(20)30365-X

Important comment, emphasizing the nuances and differences of COVID-19 disease states in clinical trials. Although it is clear that some therapies have no clinical benefits in patients admitted to hospital, Jay JH Park and colleague argue that there is much uncertainty, and thus clinical equipoise, to justify continuing clinical trials in other COVID-19 disease states.

Lin DY, Zeng D, Eron JJ. **Evaluating the Efficacy of Therapies in COVID-19 Patients**. Clinical Infectious Diseases, August 21, 2020. Full-text: https://doi.org/10.1093/cid/ciaa1231

Some thoughts on clinical endpoints. To provide a full picture of the clinical course of a patient and make complete use of available data, the authors consider the trajectory of clinical status over the entire follow-up period. They also show how to combine the evidence of treatment effects on the occurrences of various clinical events and compare the proposed and existing endpoints through extensive simulation studies.

Pediatrics

Yonker LM, Neilan AM, Bartsch Y, et al. **Pediatric SARS-CoV-2: Clinical Presentation, Infectivity, and Immune Responses**. J Pediatrics August 19, 2020. Full-text: https://doi.org/10.1016/j.jpeds.2020.08.037

Lael Yonker and colleagues from Massachusetts General Hospital in Boston postulate that children may be a potential source of contagion in the SARS-CoV-2 pandemic in spite of milder disease or lack of symptoms. A total of 192 children (mean age 10.2 years) were enrolled, among them 49 children with acute SARS-CoV-2 infection. Nasopharyngeal viral load was highest in children in the first 2 days of symptoms, significantly higher than hospitalized adults with severe disease. Age did not impact viral load, but younger children had lower ACE2 expression.

22 August

Epidemiology

Hatcher SM, Agnew-Brune C, Anderson M, et al. **COVID-19 Among American Indian and Alaska Native Persons — 23 States, January 31–July 3, 2020**. MMWR Morb Mortal Wkly Rep 2020, published 19 August 2020. Full-text: http://dx.doi.org/10.15585/mmwr.mm6934e1

American Indian and Alaska Native (AI/AN) persons appear to be disproportionately affected by the COVID-19 pandemic. Now Sarah Hatcher et al. report that the overall COVID-19 incidence among AI/AN persons was 3.5 times that among white persons (594 per 100,000 AI/AN population compared with 169 per 100,000 white population). The authors discuss the factors which most likely contributed to the observed elevated incidence.

Jiménez MC, Cowger TL, Simon LE, Behn M, Cassarino N, Bassett MT. **Epidemiology of COVID-19 Among Incarcerated Individuals and Staff in Massachusetts Jails and Prisons.** JAMA Netw Open 2020;3(8). Full-text: https://doi.org/10.1001/jamanetworkopen.2020.18851

Of 14,987 individuals incarcerated across Massachusetts prison facilities, 1032 confirmed cases of COVID-19 were reported among incarcerated individuals (n 1960) and staff (n 664) among incarcerated individuals was nearly 3 times that of the Massachusetts general population and 5 times the US rate. Monik Jiménez et al. stress that access to testing without coercion, de-carceration, and contact tracing are necessary to decrease harm from COVID-19 to incarcerated people and their communities.

Transmission

Link-Gelles R, DellaGrotta AL, Molina C, et al. **Limited Secondary Transmission of SARS-CoV-2 in Child Care Programs — Rhode Island, June 1–July 31, 2020.** MMWR Morb Mortal Wkly Rep. ePub: 21 August 2020. Full-text: http://dx.doi.org/10.15585/mmwr.mm6934e2

Ruth Link-Gelles et al. report a possible secondary transmission in four of the 666 child-care programs in Rhode Island that were allowed to reopen. The apparent absence of secondary transmission within the other 662 child-care programs was likely the result of efforts to contain SARS-CoV-2 transmission,

in particular maximum class sizes and use of face masks for adults. The authors conclude that adherence to current CDC recommendations remains critical to reducing transmission in child-care settings, including wearing of masks by adults, limiting mixing between established student-teacher groups, staying home when ill, and cleaning and disinfecting frequently touched surfaces.

Diagnostics

Stites EC, Wilen CB. **The Interpretation of SARS-CoV-2 Diagnostic Tests.** Med 2020, published 21 August. Full-text: https://doi.org/10.1016/j.medj.2020.08.001

There is evidence that physicians struggle with proper probabilistic test interpretation. Here, Edward Stites and Craig Wilen provide answers to questions such as, Should asymptomatic individuals be tested? What does it mean to test positive (or negative)? How shall we interpret tests for "immunity passports"? They review the general principles of SARS-CoV-2 test interpretation and warn that improper utilization can potentially have unintended negative consequences.

Clinical

Nachtigall I, Lenga P, Jóźwiak K, et al. **Clinical course and factors associated with outcomes among 1904 patients hospitalized with COVID-19 in Germany: an observational study.** Clin Microbiol Infect 2020, published 18 August. Full-text: https://doi.org/10.1016/j.cmi.2020.08.011

In Germany, the COVID-19 pandemic has been associated with a lower case fatality rate (CFR) compared with other Western and Central European countries. The reason? Age! During the first COVID-19 wave in spring 2020, the median age of SARS-CoV-2 infected people in Germany was much lower than in Italy, for example. As younger people have a more benign clinical course, the German CFR remained low. However, once German patients with COVID-19 were admitted to an intensive care unit (ICU), the mortality rate was 29% and thus comparable to other European countries. This is the result of a retrospective cohort study of 1904 patients (median age: 73 years) admitted to a national network of German hospitals, by Irit Nachtigall, Julius Dengler and colleagues. As expected, the authors also find that the most prominent risk factors for death are male sex, pre-existing lung disease, and increased patient age. The mortality rates in detail:

Overall	17%
• Patients admitted to the ICU	29%
o Ventilated	33%
o Non-ventilated	23%

Yueh B. **The Worst Patient—A Physician With COVID-19.** JAMA Otolaryngol Head Neck Surg 2020, published 20 August. Full-text: https://doi.org/10.1001/jamaoto.2020.2435

As an accomplished surgeon who has missed fewer than 2 weeks of work in 30 years, proud that you operated 2 weeks later with a broken leg and ankle ski lift accident, how could you possibly accept to miss week after week with COVID-19? Bevan Yueh had a hard time. Read about denial, whistleblowers, 500 cc spirometry and nightmares!

Treatment

Spinner CD, Gottlieb RL, Criner GJ, et al. **Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial.** JAMA 2020, published 21 August. Full-text: https://doi.org/10.1001/jama.2020.16349

In this open-label trial, Christoph D. Spinner et al. found that hospitalized patients with moderate COVID-19 (pulmonary infiltrates and room-air oxygen saturation > 94%) who received a 5-day course of remdesivir had a better clinical status compared with those randomized to standard care at 11 days after initiation of treatment. There were **no significant differences** between the remdesivir and standard care groups in

- duration of oxygen therapy
- duration of hospitalization
- all-cause mortality

The authors acknowledge that the differences in clinical status between the remdesivir and control groups is of uncertain clinical importance.

Our forecast: remdesivir will be remembered as the AZT of the COVID-19 pandemic – cumbersome to administrate, low efficacy, expensive. As soon as truly efficient drugs are available, remdesivir will sink quietly into oblivion. The first nail in the remdesivir coffin is dexamethasone. As Erin McCreary and Derek Angus conclude in their editorial: “Whether remdesivir offers incre-

mental benefit over corticosteroids, which are widely available and inexpensive, is unknown." (McCreary EK, Angus DC. **Efficacy of Remdesivir in COVID-19.** JAMA 2020, published 21 August. Full-text: https://doi.org/10.1001/jama.2020.16337)

Severe COVID

Manson JJ, Crooks C, Naja M, et al. **COVID-19-associated hyperinflammation and escalation of patient care: a retrospective longitudinal cohort study.** Lancet Rheumatol 2020, published 21 August. Full-text: https://doi.org/10.1016/S2665-9913(20)30275-7

Jessica Manson et al. define a phenotype of COVID-19-associated hyperinflammation (COV-HI) by measurement of readily available routine clinical parameters:

1. C-reactive protein (greater than 150 mg/L or doubling within 24 h from greater than 50 mg/L) **and** 2)

   or

2. Ferritin (greater than 1500 µg/L)

Of patients with COV-HI on admission, 36/90 patients (40%) died during follow-up compared with 46/179 (26%) of the patients without COV-HI on admission, indicating the existence of a high-risk inflammatory phenotype. The authors conclude that COV-HI might be useful to stratify patients in trial design. See also the critical comment by Kiran Reddy and colleagues (Reddy K, Rogers AJ, McAuley DF: **Delving beneath the surface of hyperinflammation in COVID-19.** Lancet Rheumatol 2020, published 21 August. Full-text: https://doi.org/10.1016/S2665-9913(20)30304-0).

Pediatrics

Dolhnikoff M, Ferreira Ferranti J, de Almeida Monteiro RA, et al. **SARS-CoV-2 in cardiac tissue of a child with COVID-19-related multisystem inflammatory syndrome.** Lancet Child Adolesc Health 2020, published 20 August. Full-text: https://doi.org/10.1016/S2352-4642(20)30257-1

In a post-mortem analysis of cardiac tissue by electron microscopy, Marisa Dolhnikoff et al. report identified spherical viral particles of 70 – 100 nm in diameter, consistent in size and shape with the Coronaviridae family, in the extracellular compartment and within several cell types—cardiomyocytes, capillary endothelial cells, endocardium endothelial cells, macrophages, neutrophils, and fibroblasts. The autopsy showed myocarditis, pericarditis, and

endocarditis, with intense and diffuse tissue inflammation, and necrosis of cardiomyocytes. The authors conclude that clinical, echocardiographic, and laboratory findings strongly indicate that heart failure was the main determinant of the fatal outcome.

Education

Rubin EJ, Baden LR, Morrissey S. **Covid-19 and Contact Tracing**. N Engl J Med 2020; 383:e73. Access: https://www.nejm.org/doi/full/10.1056/NEJMe2028055

In this audio interview (27:42), the editors discuss the use of contact tracing to limit the spread of SARS-CoV-2 and the challenges posed by certain characteristics of the virus.

Society & Prevention

Smith D. **Obama's stark message: America must save itself from Trump.** The Guardian 2020, published 20 August. Full-text: https://www.theguardian.com/us-news/2020/aug/19/obama-dnc-speech-trump-democracy-america

No comment needed.

Spanish

If you read Spanish, read Jan C, Enano VL. **Del autorrastreo en La Rioja al fin de las 'party boats' en Baleares, así aplica cada comunidad las medidas de Sanidad.** El País 2020, published 22 August. Full-text: https://elpais.com/sociedad/2020-08-22/del-autorrastreo-en-la-rioja-al-fin-de-las-party-boats-en-baleares-asi-aplica-cada-comunidad-las-medidas-de-sanidad.html

Cecilia Jan and Virginia López Enano present detailed to-do lists elaborated by the Spanish government and regional authorities in view of the second pandemic COVID-19 wave. A must-read (if you can) of > 5,000 words!

23 August

Virology

Zhao P, Praissman JL, Grant OC, et al. **Virus-Receptor Interactions of Glycosylated SARS-CoV-2 Spike and Human ACE2 Receptor.** bioRxiv. 2020 Jul 24:2020.06.25.172403. PubMed: https://pubmed.gov/32743578. Full-text: https://doi.org/10.1101/2020.06.25.172403

A detailed understanding of SARS-CoV-2 Spike binding to ACE2 is critical for elucidating the mechanisms of viral binding and entry, as well as for the rational design of effective therapeutics. Here Lance Wells, Peng Zhao and colleagues utilize glycomics-informed glycoproteomics to characterize site-specific microheterogeneity of glycosylation for a recombinant trimer Spike mimetic immunogen and for a soluble version of human ACE2. The authors generate molecular dynamics simulations of each glycoprotein alone and interacting with one another. Their data and related similar findings might provide a framework to facilitate the production of immunogens, vaccines, antibodies, and inhibitors as well as providing additional information regarding mechanisms by which glycan microheterogeneity is achieved.

Immunology

Ejemel M, Li Q, Hou S, et al. **A cross-reactive human IgA monoclonal antibody blocks SARS-CoV-2 spike-ACE2 interaction.** Nat Commun. 2020 Aug 21;11(1):4198. Full-text: https://doi.org/10.1038/s41467-020-18058-8

Pre- or post-exposure immunotherapies with neutralizing antibodies? Yang Wang, Monir Ejemel and colleagues describe a cross-reactive human IgA monoclonal antibody, termed MAb362, which binds to both SARS-CoV-1 and SARS-CoV-2 Spike proteins and competitively blocks ACE2 receptor binding. When converted to secretory IgA, MAb326 also neutralizes authentic SARS-CoV-2 virus. The authors suggest that such SARS-CoV-2 specific IgA antibodies might provide immunity against SARS-CoV-2 by inducing mucosal immunity within the respiratory system, a potentially critical feature of an effective vaccine.

Lu S, Zhao Y, Yu W, et al. **Comparison of nonhuman primates identified the suitable model for COVID-19.** Sig Transduct Target Ther 5, 157 (2020). Full-text: https://doi.org/10.1038/s41392-020-00269-6

Within 6 months after SARS-CoV-2 was first reported, five kinds of animals were developed into models to study COVID-19: the mouse, ferret, tree shrew,

golden hamster, and a nonhuman primate (NHP) species. Now Xiaozhong Peng, Shuaiyao Lu and colleagues characterized SARS-CoV-2 infection in three NHP models of COVID-19: Old World monkeys *Macaca mulatta* (*M. mulatta*) and *Macaca fascicularis* (*M. fascicularis*) and New World monkeys *Callithrix jacchus* (*C. jacchus*). *M. mulatta* most closely recapitulated human-like conditions, including increased inflammatory cytokine expression and pathological changes in the pulmonary tissues.

Pathogenesis

Johansen MD, Irving A, Montagutelli X, et al. **Animal and translational models of SARS-CoV-2 infection and COVID-19.** Mucosal Immunol. 2020 Aug 20:1-15. PubMed: https://pubmed.gov/32820248. Full-text: https://doi.org/10.1038/s41385-020-00340-z

Elucidating the mechanisms of pathogenesis will enable the identification of the most effective therapies. Head-to-head comparison of existing drugs, testing of safety, and the development of new and targeted preventions and treatments is most efficiently achieved using representative animal models of primary infection with validation of findings in primary human cells and tissues. Philip Hansbro, Matt Johansen and colleagues explore and discuss the diverse animal, cell and tissue models that are being used and developed. A 10-page read with 246 references for your weekend pleasure.

Vaccine

Feng L, Wang Q, Shan C, et al. **An adenovirus-vectored COVID-19 vaccine confers protection from SARS-COV-2 challenge in rhesus macaques.** Nat Commun 11**,** 4207 (2020). Full-text: https://doi.org/10.1038/s41467-020-18077-5

Ling Chen, Liqiang Feng and colleagues report the generation of a replication-incompetent recombinant serotype 5 adenovirus, Ad5-S-nb2, which elicited systemic S-specific antibody and cell-mediated immune (CMI) responses in mice and rhesus macaques both after intramuscular injection and intranasal inoculation. At 30 days after a single vaccination with Ad5-S-nb2, macaques were protected against SARS-CoV-2 challenge.

Clinical

McCarty TR, Hathorn KE, Redd WD, et al. **How Do Presenting Symptoms and Outcomes Differ by Race/Ethnicity Among Hospitalized Patients with COVID-19 Infection? Experience in Massachusetts**. Clin Infect Dis 2020, published 22 August. Full-text: https://doi.org/10.1093/cid/ciaa1245

Pre-existing societal inequities, many of which are a result of long-standing structural racism, place Black and Latinx communities and individuals at greater risk of being adversely affected by such disasters. But is there an association between race/ethnicity and clinically relevant hospitalization outcomes, including in-hospital mortality? Walter Chan, Thomas McCarthy and colleagues give us a differentiated appraisal in this retrospective analysis of nine Massachusetts hospitals including all consecutive adult patients hospitalized with laboratory-confirmed COVID-19 (n = 379). Latinx patients were younger, had fewer cardiopulmonary disorders, were more likely to be obese, more frequently reported fever and myalgia, and had lower D-dimer levels compared to white patients ($p < 0.05$). However, after controlling for confounders (age, gender, obesity, cardiopulmonary comorbidities, hypertension, and diabetes), no significant differences in in-hospital mortality, ICU admission, or mechanical ventilation by race/ethnicity were found. In other words, despite a disproportionate infection rate among Black and Latinx individuals, when their disease is severe enough to require hospitalization, these patients do just as well in terms of important outcomes, including mortality.

Stefanini GG, Chiarito M, Ferrante G, et al. **Early detection of elevated cardiac biomarkers to optimise risk stratification in patients with COVID-19.** Heart. 2020 Aug 14:heartjnl-2020-317322. PubMed: https://pubmed.gov/32817312. Full-text: https://doi.org/10.1136/heartjnl-2020-317322

An early risk stratification is crucial in order to identify the patients that might benefit from intense monitoring and aggressive treatment strategies. Here Giulio Stefanini et al. stratify 397 patients according to elevated levels of high-sensitivity cardiac troponin I (hs-TnI, a biomarker of myocardial injury), B-type natriuretic peptide (BNP, a biomarker of cardiac stress) or both measured within 24 hours after hospital admission. The rate of mortality was higher in patients with elevated hs-TnI (22.5%), BNP (33.9%) or both (55.6%) as compared with those without elevated cardiac biomarkers (6.25%). The authors recommend cardiac biomarkers to be systematically assessed in patients with COVID-19 at the time of hospital admission.

Treatment

Matsuzawa Y, Ogawa H, Kimura K, et al. **Renin-angiotensin system inhibitors and the severity of coronavirus disease 2019 in Kanagawa, Japan: a retrospective cohort study.** Hypertens Res. 2020 Aug 21. PubMed: https://pubmed.gov/32820236. Full-text: https://doi.org/10.1038/s41440-020-00535-8

Again, does a previous use of angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II type-1 receptor blockers (ARBs) affect the clinical manifestations and prognosis of COVID-19 patients? Yasushi Matsuzawa et al. analyzed 151 consecutive patients (mean age 60 [illegible] years) wit
2 infection in a retrospective observational study. Age [illegible] ≥ 65 years
icantly associated (odds ratio 6.63) with the primary composite outcome (1. in-hospital death, 2. extracorporeal membrane oxygenation, 3. mechanical ventilation, including invasive and non-invasive methods, and 4. admission to the intensive care unit). In COVID-19 patients with hypertension, previous ACEI/ARB use was significantly associated with a lower occurrence of new-onset or worsening mental confusion (OR 0.06). The authors conclude that ACEIs/ARBs could be beneficial for the prevention of confusion in COVID-19 patients with hypertension.

Lane JCE, Weaver J, Kostka K. **Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study.** Lancet Rheumatol 2020, published 21 August. Full-text: https://doi.org/10.1016/S2665-9913(20)30276-9

Hydroxychloroquine (HCl) is like some presidents: it is useless and people should stop talking about it. As a matter of fact, we stopped reporting on the HCl soap opera weeks ago. If, nonetheless, you cannot resist watching newer episodes, here you go: when combined with azithromycin, as sung by a French bard, hydroxychloroquine increases the risk of heart failure and cardiovascular mortality.

We stop reporting after these 62 words. The paper was published by Patrick Ryan, Daniel Prieto-Alhambra, Jennifer Lane and colleagues on behalf of a 62-author team.

French

If you read French, read Santi P, Hecketsweiler C. **Coronavirus : pourquoi le port obligatoire du masque se généralise en France ;** Le Monde 2020, published 22 August. Full-text : https://www.lemonde.fr/planete/article/2020/08/22/de-nice-a-lille-la-france-se-convertit-au-port-du-masque_6049607_3244.html

Wearing face masks outdoors is now fully or partially imposed in around 12,300 (one third of all) municipalities, and will be in businesses, colleges and high schools from September 1. Pascale Santi and Chloé Hecketsweiler analyze the history of face mask acceptance.

24 August

Top 20 on Face Masks

Almost all organizations recommend masks for the general public. Unfortunately, earlier in the pandemic, many did exactly the opposite – due to limited data but also due to concerns about diminished mask supply for healthcare workers and out of fear that masked individuals might be tempted to ignore rules of social distancing. In addition, conflicting national guidelines have led to variable public compliance. A few physicians, in line with some COVidiots, still argue against face masks. Even in late April, for example, Ulrich Montgomery, a radiologist (!) and chairperson of the "World Medical Association", declared with superb ignorance that masks were nonsense. Sadly, he attracted less attention when he later declared that his statement was a mistake (and it was a gruesome mistake); doubts are always difficult to dispel once they are raised.

Do you need some arguments to convince your patients to wear a face mask? Here we present the Top 20 studies on their effectiveness and/or efficacy.

Human experiments

Leung NH, Chu Dk, Shiu EY. **Respiratory virus shedding in exhaled breath and efficacy of face masks**. Nature Med 2020, April 3. Full-text: https://doi.org/10.1038/s41591-020-0843-2

This study from Hong Kong quantified virus in respiratory droplets and aerosols in exhaled breath. In total, 111 participants (infected with seasonal coronavirus, influenza or rhinovirus) were randomized to wear or not to wear a simple surgical face mask. Results suggested that masks could be used by ill

people to reduce onward transmission. In respiratory droplets, seasonal coronavirus was detected in 3/10 (aerosols: 4/10) samples collected without face masks, but in 0/11 (aerosols: 0/11) from participants wearing face masks. Influenza viruses were detected in 6/23 (aerosols: 8/23) without masks, compared to 1/27 (aerosols: 6/27!) with masks. For rhinovirus, there were no significant differences. Of note, the authors also identified virus in some participants who did not cough at all during the 30 min exhaled breath collection, suggesting droplet and aerosol routes of transmission from individuals with no obvious signs or symptoms.

Ho KF, Lin LY, Weng SP, Chuang KJ. **Medical mask versus cotton mask for preventing respiratory droplet transmission in micro environments**. Sci Total Environ. 2020 Sep 15;735:139510. PubMed: https://pubmed.gov/32480154 . Full-text: https://doi.org/10.1016/j.scitotenv.2020.139510

This heroic study from Taiwan recruited 211 (!) adult volunteers with 208 confirmed cases of influenza and 6 suspected cases of COVID-19. Volunteers had to wear medical masks and self-designed triple-layer cotton masks in a regular bedroom and a car (a Toyota) with air conditioning. Four 1-hour repeated measurements of particles with a size range of 20-1000 nm, temperature and relatively humidity, and cough/sneeze counts per hour were conducted for each volunteer. There was no significant difference in NC0.02-1 or cough/sneeze counts between volunteers with medical masks and cotton masks in a bedroom or a car.

Animal experiments

Chan JF, Yuan S, Zhang AJ, et al. **Surgical mask partition reduces the risk of non-contact transmission in a golden Syrian hamster model for Coronavirus Disease 2019 (COVID-19)**. Clin Infect Dis. 2020 May 30:ciaa644. PubMed: https://pubmed.gov/32472679 . Full-text: https://doi.org/10.1093/cid/ciaa644

Surgical mask use for COVID-19-challenged hamsters vs naïve hamsters significantly reduced transmission in those with the virus.

Lab experiments

Anfinrud P, Stadnytskyi V, Bax CE, Bax A. **Visualizing Speech-Generated Oral Fluid Droplets with Laser Light Scattering.** N Engl J Med. 2020 May 21;382(21):2061-2063. PubMed: https://pubmed.gov/32294341. Full-text: https://doi.org/10.1056/NEJMc2007800

Illustration of how liquid droplets exhaled during speech can linger in the air.

Rodriguez-Palacios A, Cominelli F, Basson AR, Pizarro TT, Ilic S. **Textile Masks and Surface Covers-A Spray Simulation Method and a "Universal Droplet Reduction Model" Against Respiratory Pandemics**. Front Med (Lausanne). 2020 May 27;7:260. PubMed: https://pubmed.gov/32574342 . Full-text: https://doi.org/10.3389/fmed.2020.00260

First, a rapid spray-simulation model of droplets (mimicking a sneeze) was validated, using a bacterial suspension to quantify the extent by which widely available household textiles reduced the ejection of long-distance flights of droplets. To facilitate the enumeration of macro-droplets and invisible micro-droplets, spray simulations were conducted over nutritious-media agar surfaces and incubated for 24 h to enable colony-forming-droplet-unit formation. The study demonstrated that two-layer household textiles produced a profound reduction of environmental droplet contamination as effectively as medical-grade materials.

Observational studies

Wang Y, Tian H, Zhang L, et al. **Reduction of secondary transmission of SARS-CoV-2 in households by face mask use, disinfection and social distancing: a cohort study in Beijing, China**. BMJ Glob Health. 2020;5. Full-text: https://doi.org/10.1136/bmjgh-2020-002794

A retrospective cohort study of 124 households with an index SARS-CoV-2 case and 355 uninfected household contacts. Households in which masks were used by at least 1 family member (including the index case) before the development of symptoms by the index case were associated with decreased risk for incident infections, after adjustment for other hygiene and infection control practices, physical distance to index case, environmental factors, and presence of diarrhea in the index case (adjusted odds ratio, 0.21, 95% CI, 0.06 to 0.79).

Hendrix MJ, Walde C, Findley K, Trotman R. **Absence of Apparent Transmission of SARS-CoV-2 from Two Stylists After Exposure at a Hair Salon with a Universal Face Covering Policy - Springfield, Missouri, May 2020**. MMWR Morb Mortal Wkly Rep. 2020 Jul 17;69(28):930-932. PubMed: https://pubmed.gov/32673300 . Full-text: https://doi.org/10.15585/mmwr.mm6928e2

Among 139 clients exposed to two symptomatic hair stylists with confirmed COVID-19 while both the stylists and the clients wore face masks, not a single symptomatic secondary case was observed; among 67 clients tested for SARS-CoV-2, all tests were negative. At least one hair stylist was infectious: all four close household contacts became ill.

Wang X, Ferro EG, Zhou G, Hashimoto D, Bhatt DL. **Association Between Universal Masking in a Health Care System and SARS-CoV-2 Positivity Among Health Care Workers**. JAMA. 2020 Jul 14. PubMed: https://pubmed.gov/32663246 . Full-text: https://doi.org/10.1001/jama.2020.12897

In March 2020, a large health care system in Massachusetts (12 hospitals, > 75,000 employees), implemented universal masking of all HCWs and patients with surgical masks. During the pre-intervention period, the SARS-CoV-2 positivity rate increased exponentially, with a case doubling time of 3.6 days. During the intervention period, the positivity rate decreased linearly from 14.65% to 11.46%, with a weighted mean decline of 0.49% per day and a net slope change of 1.65% more decline per day compared with the pre-intervention period.

Bielecki M, Züst R, Siegrist D, et al. **Social distancing alters the clinical course of COVID-19 in young adults: A comparative cohort study**. Clinical Infectious Diseases, 29 June 2020. Full-text: https://doi.org/10.1093/cid/ciaa889

Viral inoculum during infection or mode of transmission may be key factors determining the clinical course of COVID-19. Masks may reduce this inoculum. After an outbreak at a Swiss Army base, soldiers had to keep a distance of at least 2 m from each other at all times, and in situations where this could not be avoided (e.g., military training), they had to wear a surgical face mask. Of the 354 soldiers infected prior to the implementation of social distancing, 30% fell ill from COVID-19. None of the soldiers in a group of 154, where infections ocurred after implementation of social distancing, developed COVID-19.

Chen Y, Qin G, Chen J, et al**. Comparison of Face-Touching Behaviors Before and During the Coronavirus Disease 2019 Pandemic**. JAMA Netw Open 2020;3(7):e2016924. https://doi.org/10.1001/jamanetworkopen.2020.16924

Is wearing face masks really associated with reduced face-touching behaviors? Using videos recorded in public transportation stations, streets, and parks among the general population in several countries, this study found that mask wearing was associated with reduced face-touching behavior, especially touching of the eyes, nose, and mouth. Authors conclude that the reduction of face-touching behaviors by mask wearing could contribute to curbing the COVID-19 pandemic.

Nir-Paz R, Grotto I, Strolov I, et al. **Absence of in-flight transmission of SARS-CoV-2 likely due to use of face masks on board**. J Travel Med. 2020 Jul 14:taaa117. PubMed: https://pubmed.gov/32662832 . Full-text: https://doi.org/10.1093/jtm/taaa117

During a 14-hour flight of 11 passengers and 4 crew members in which 2 positive SARS-COV-2 were on board, no new viral acquisitions were found, probably due to the use of masks.

Epidemiological studies

Lyu W, Wehby GL. **Community Use Of Face Masks And COVID-19: Evidence From A Natural Experiment Of State Mandates In The US**. Health Aff (Millwood). 2020 Jun 16. PubMed: https://pubmed.gov/32543923 . Full-text: https://doi.org/10.1377/hlthaff.2020.00818

This study provides evidence from a natural experiment on the effects of state government mandates in the US for face mask use in public issued by 15 states plus Washington DC between April 8 and May 15. Mandating face mask use in public was associated with a decline in the daily COVID-19 growth rate by 0.9, 1.1, 1.4, 1.7, and 2.0 percentage points in 1–5, 6–10, 11–15, 16–20, and 21+ days after implementation, respectively. Estimates suggest as many as 230,000–450,000 COVID-19 cases were possibly averted by May 22, 2020 due to these mandates.

Zhang R, Li Y, Zhang AL, Wang Y, Molina MJ. **Identifying airborne transmission as the dominant route for the spread of COVID-19**. Proc Natl Acad Sci U S A. 2020 Jun 30;117(26):14857-14863. PubMed: https://pubmed.gov/32527856 . Full-text: https://doi.org/10.1073/pnas.2009637117

By analyzing the trend and mitigation measures in Wuhan, Italy, and New York City, this work illustrates that the difference with and without mandated face covering represents the determinant in shaping the pandemic trends in the three epicenters. This protective measure alone significantly reduced the number of infections, that is, by over 78,000 in Italy from April 6 to May 9 and over 66,000 in New York City from April 17 to May 9.

Mathematical modelling studies

Worby CJ, Chang HH. **Face mask use in the general population and optimal resource allocation during the COVID-19 pandemic**. Nat Commun. 2020 Aug 13;11(1):4049. PubMed: https://pubmed.gov/32792562 . Full-text: https://doi.org/10.1038/s41467-020-17922-x

The use of face masks among the general public is an effective strategy in mitigating transmission of SARS-CoV-2 under a range of scenarios. Even with a limited protective effect, face masks can reduce total infections and deaths, and can delay the peak time of the epidemic.

Fisman DN, Greer AL, Tuite AR. **Bidirectional impact of imperfect mask use on reproduction number of COVID-19: A next generation matrix approach**. Infect Dis Model. 2020 Jul 4;5:405-408. PubMed: https://pubmed.gov/32691014. Full-text: https://doi.org/10.1016/j.idm.2020.06.004

Same direction: Even modest mask effectiveness for reduction of transmission of COVID-19 could have important effects on epidemic dynamics, especially with regard to pre-symptomatic transmission (40%).

Systematic reviews and meta-analyses

Chu DK, Akl EA, Duda S, Solo K, Yaacoub S, Schünemann HJ. **COVID-19 Systematic Urgent Review Group Effort (SURGE) study authors. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis**. Lancet. 2020 Jun 1. PubMed: https://pubmed.gov/32497510 . Full-text: https://doi.org/10.1016/S0140-6736(20)31142-9

This systematic review identified 172 observational studies across 16 countries and 44 relevant comparative studies in healthcare and non-healthcare settings. Face mask use could result in a large reduction in risk of infection (n = 2,647; adjusted OR 0.15, 95% CI 0.07 to 0.34) SARS-CoV-2, SARS-CoV, and MERS-CoV. The association with protection from infection was more pronounced with N95 or similar respirators (aOR 0·04, 95% CI 0·004 to 0·30) compared to other masks (aOR 0·33, 95% CI 0·17 to 0·61). However, the latter were better than wearing no mask (see below, mathematical modelling).

Liang M, Gao L, Cheng C, et al. **Efficacy of face mask in preventing respiratory virus transmission: A systematic review and meta-analysis**. Travel Med Infect Dis. 2020 May 28:101751. PubMed: https://pubmed.gov/32473312 . Full-text: https://doi.org/10.1016/j.tmaid.2020.101751

This meta-analysis of 21 studies suggests that mask use provided a significant protective effect. Use of masks by healthcare workers and non-healthcare workers can reduce the risk of respiratory virus infection by 80% (OR = 0.20, 95% CI = 0.11-0.37) and 47% (OR = 0.53, 95% CI = 0.36-0.79).

Cloth masks

Zangmeister CD, Radney JG, Vicenzi EP, Weaver JL. **Filtration Efficiencies of Nanoscale Aerosol by Cloth Mask Materials Used to Slow the Spread of SARS-CoV-2.** ACS Nano. 2020 Jul 28;14(7):9188-9200. PubMed: https://pubmed.gov/32584542 . Full-text: https://doi.org/10.1021/acsnano.0c05025

A setailed study, evaluating cloth materials. Results indicate that there is a complex interplay between fabric type, weave, and yarn count and the filtration of nanometer-sized aerosol particles. No measured cloth masks performed as well as an N95. However, the best performing cloth materials had moderate yarn counts with visible raised fibers.

Konda A, Prakash A, Moss GA, Schmoldt M, Grant GD, Guha S. **Aerosol Filtration Efficiency of Common Fabrics Used in Respiratory Cloth Masks.** ACS Nano. 2020 May 26;14(5):6339-6347. PubMed: https://pubmed.gov/32329337. Full-text: https://doi.org/10.1021/acsnano.0c03252

The aerosol filtering efficiency of different materials, thicknesses, and layers used in properly fitted homemade masks was found to be similar to that of the medical masks that were tested.

Mueller AV, Eden MJ, Oakes JM, et al. **Quantitative Method for Comparative Assessment of Particle Removal Efficiency of Fabric Masks as Alternatives to Standard Surgical Masks for PPE**. Matter July 09, 2020. Full-text: https://doi.org/10.1016/j.matt.2020.07.006

Cloth masks tested had widely varying mean particle removal efficiencies (< 30% to near 90%), with some cloth masks achieving similar particle removal efficiencies as commercial surgical masks.

Conclusions

Yes, each of the above studies can be criticized. And yes, seasonal coronaviruses may differ from SARS-CoV-2, hamsters are not (yet) humans, there may be other things leading to the incidental decline of new infections paralleling the introduction of face masks, and cloth masks are less effective than surgical masks. Agreed. You will find many issues in each study that you can do better (if so, then do so!). However, decisions in the current pandemic have to be made on the basis of best available information, even if that information is imperfect. This crisis is an emergency. We need risk reduction rather than absolute prevention. Imagine you make an emergency call to the fire brigade, whereupon they refuse to come, because they need "more information"...

The self-proclaimed experts, who never tire of doubting the sense of masks, should ask themselves why they are actually doing this. Have they ever called for perfect data on the seatbelt obligation, helmets, smoking bans, speed limits in road traffic? Why does a piece of cloth covering their noses rile them up so much, what is the problem?

The prayer wheel-like demand for better studies or more data is redundant. We know enough.

25 August

Virology

Wang Z, Zhang L, Wu M. **Human-viral chimera: a novel protein affecting viral virulence and driving host T-cell immunity.** Sig Transduct Target Ther 5, 167 (2020). Full-text: https://doi.org/10.1038/s41392-020-00272-x

Zhenling Wang, Li Zhang and Min Wu discuss the paper by Ho et al. (see below) which shows that RNA viruses like influenza A can produce previously unrecognized chimeric proteins containing both viral and human genetic

information, which can then affect virulence and modulate T cell responses in hosts. They conclude that this finding could lend critical insight into designing novel approaches to control emerging viral infections, such as SARS-CoV-2. (Ho JSY, Angel M, Ma Y, et al. **Hybrid Gene Origination Creates Human-Virus Chimeric Proteins during Infection.** Cell. 2020 Jun 25;181(7):1502-1517.e23. PubMed: https://pubmed.gov/32559462. Full-text: https://doi.org/10.1016/j.cell.2020.05.035)

Latinne A, Hu B, Olival KJ et al. **Origin and cross-species transmission of bat coronaviruses in China.** Nat Commun 11, 4235 (2020). Full-text: https://www.nature.com/articles/s41467-020-17687-3

All coronaviruses (CoV) known to infect humans are zoonotic, or of animal origin, with many thought to originate in bat hosts. Now Peter Daszak, Alice Latinne and colleagues analyze their macroevolution, cross-species transmission and dispersal and present a phylogenetic analysis suggesting a likely origin for SARS-CoV-2 in bats of the genus *Rhinolophus*. They also show that host-switching occurs more frequently and across more distantly related host taxa in alpha- than beta-CoVs and is more highly constrained by phylogenetic distance for beta-CoVs. The authors identify the host taxa and geographic regions that define hotspots of CoV evolutionary diversity in China that could help target bat-CoV discovery for proactive zoonotic disease surveillance.

Basic Research

Zhao H, To KKW, Sze K et al. **A broad-spectrum virus- and host-targeting peptide against respiratory viruses including influenza virus and SARS-CoV-2.** Nat Commun 11, 4252 (2020). Full-text: https://doi.org/10.1038/s41467-020-17986-9

Kwok-Yung Yuen, Hanjun Zhao and colleagues report a mouse β-defensin-4-derived antiviral peptide P9R exhibiting broad-spectrum antiviral activities against the enveloped SARS-CoV-2, MERS-CoV, SARS-CoV, A(H1N1)pdm09, A(H7N9) virus, and the non-enveloped rhinovirus. The authors suggest that the antiviral activity of P9R depends on the direct binding to viruses and the inhibition of virus-host endosomal acidification, which provides a proof of concept that virus-binding alkaline peptides can broadly inhibit pH-dependent viruses.

Immunology

Crooke SN, Ovsyannikova IG, Kennedy RB et al. **Immunoinformatic identification of B cell and T cell epitopes in the SARS-CoV-2 proteome.** Sci Rep 10, 14179 (2020). Published 25 August. Full-text: https://doi.org/10.1038/s41598-020-70864-8

Immunoinformatics for T cell and B cell epitopes? Here Gregory Poland, Stephen Crooke and colleagues used a series of open-source algorithms and webtools to analyze the proteome of SARS-CoV-2 and identify putative T cell and B cell epitopes. They identified 41 T cell epitopes (5 HLA class I, 36 HLA class II) and 6 B cell epitopes that could serve as promising targets for peptide-based vaccine development against this emerging global pathogen.

Vaccine

Price WN 2nd, Rai AK, Minssen T. **Knowledge transfer for large-scale vaccine manufacturing.** Science. 2020 Aug 21;369(6506):912-914. PubMed: https://pubmed.gov/32792464. Full-text: https://doi.org/10.1126/science.abc9588

Identifying an effective SARS-CoV-2 vaccine and prove its safety in huge clinical trials is only the first step. The next step is not less challenging: manufacturing vaccines at enormous scale. In this Policy Forum, law school scholars Nicholson Price, Arti Rai and Timo Minssen explain that fast manufacturing will require not only physical capacity but also access to knowledge not contained in patents or in other public disclosures. Follow the authors on a path through the jungle of licenses, know-how transfer, hostage taking and manufacturing secrecy, and discover why large biopharmaceutical firms are now willing to share information that they might previously have viewed as providing competitive advantage.

Callaway E. **The unequal scramble for coronavirus vaccines — by the numbers.** Nature 2020, published 24 August. Full-text: https://www.nature.com/articles/d41586-020-02450-x

Will SARS-CoV-2 vaccines be only for the rich? Ellen Callaway shows how wealthy countries have struck deals to buy more than two billion doses of coronavirus vaccine. Find out that the UK is the world's highest per-capita buyer, with 340 million purchased: around 5 doses for each citizen. And read more about COVAX, spearheaded by GAVI, a Geneva-based funder of vaccines for low-income countries, along with CEPI and the World Health Organization. It aims to secure 2 billion vaccine doses. One billion are for 92 low- and

middle-income countries and economies (LMICS), which encompass half the world's population.

Clinical

Pezzini A, Padovani A. **Lifting the mask on neurological manifestations of COVID-19.** Nat Rev Neurol 2020, published 28 August. Full-text: https://doi.org/10.1038/s41582-020-0398-3

Another review. Alessandro Pezzini and Alessandro Padovani present preclinical research suggesting that SARS-CoV-2 could be responsible for many neurological manifestations, and summarize the biological pathways that could underlie each neurological symptom.

Collateral Effects

Lee LYW, Cazier JB, Starkey T, et al. **COVID-19 prevalence and mortality in patients with cancer and the effect of primary tumour subtype and patient demographics: a prospective cohort study.** Lancet Oncol 2020, published 24 August. Full-text: https://doi.org/10.1016/S1470-2045(20)30442-3

Patients with cancer have been reported to be at increased risk of infection with SARS-CoV-2 and a more severe disease course. Here Gary Middleton, Lennard Lee and colleagues compare cancer patients with and without COVID-19 and analyses the effect of tumor features (primary subtype and stage) and patient demographics (age and sex) on the risk and trajectory of COVID-19 disease. Some results:

1. The all-cause case–fatality rate in patients with cancer after SARS-CoV-2 infection was significantly associated with increasing age, rising from 0.10 in patients aged 40–49 years to 0.48 in those aged 80 years and older.
2. Patients with hematological malignancies (leukemia, lymphoma, and myeloma) had a more severe COVID-19 trajectory compared with patients with solid organ tumors.
3. Patients with hematological malignancies who had recent chemotherapy had an increased risk of death during COVID-19-associated hospital admission (odds ratio 2.09).

Malik AA, Safdar N, Chandir S, et al. **Tuberculosis control and care in the era of COVID-19.** Health Policy and Planning 2020, published 24 August. Full-text: https://doi.org/10.1093/heapol/czaa109

Reports from India, China and Pakistan suggest a daily decline in tuberculosis case notification of 75 – 80% in the last few months with testing in Pakistan decreasing up to 80%. Is this the end of the Zero TB Initiative launched in October 2015 which aimed to create 'islands of TB elimination'? See the six recommendations by Amyn Malik et al.

26 August

Epidemiology

Perkins TA, Cavany SM, Moore SM, et al. **Estimating unobserved SARS-CoV-2 infections in the United States**. PNAS August 21, 2020. Full-text: https://doi.org/10.1073/pnas.2005476117

The authors quantified unobserved infections in the United States during the early weeks of the epidemic. After a national emergency was declared, fewer than 10% of locally acquired, symptomatic infections in the US were detected over a period of a month. This gap in surveillance during a critical phase of the epidemic resulted in a large, unobserved reservoir by early March. Testing was a major limiting factor in assessing the extent of SARS-CoV-2 transmission during its initial invasion into the US.

Virology, Immunology

To KK, Hung IF, Ip JD, et al. **COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing**. Clinical Infectious Diseases, 25 August 2020, ciaa1275. Full-text: https://doi.org/10.1093/cid/ciaa1275

The first case of re-infection? During recent weeks, there has been probably no other case report gaining so much media attention as this 33-year old gentleman residing in Hong Kong. By the end of March, a mildly symptomatic SARS-CoV-2 infection was confirmed by a positive posterior oropharyngeal saliva PCR on March 26, 2020. On August 15, 142 days later, the patient returned to Hong Kong from Spain via the United Kingdom and was tested positive by SARS-CoV-2 RT-PCR on the posterior oropharyngeal saliva taken for entry screening at the Hong Kong airport. Of note, the patient remained asymptomatic during the second episode but had elevated CRP, relatively high viral load with gradual decline, and seroconversion of SARS-CoV-2 IgG during the second episode, suggesting that this was a genuine episode of acute infection. Viral genomes from first and second episodes belonged to different clades/lineages. Kwok-Yung Yuen, Kelvin Kai-Wang To and colleagues discuss several implications of this case.

Damas J, Hughes GM, Keough KC, et al. **Broad host range of SARS-CoV-2 predicted by comparative and structural analysis of ACE2 in vertebrates**. PNAS August 21, 2020 Full-text: https://doi.org/10.1073/pnas.2010146117

Joana Damas and colleagues utilized a unique dataset of ACE2 sequences from 410 vertebrate species, including 252 mammals, to study the conservation of ACE2 and its potential to be used as a receptor by SARS-CoV-2. A large number of mammals were identified that can potentially be infected by SARS-CoV-2 via their ACE2 proteins. Species with the highest risk for SARS-CoV-2 infection were wildlife and endangered species. However, the authors urge caution not to overinterpret their predictions, given the limited infectivity data for the species studied.

Transmission

Rhee C, Kanjilal S, Baker M, et al. **Duration of SARS-CoV-2 Infectivity: When is it Safe to Discontinue Isolation?** Clinical Infectious Diseases, 25 August 2020, ciaa1249. Full-text: https://doi.org/10.1093/cid/ciaa1249

Persistently positive RT-PCRs generally do not reflect replication-competent virus. SARS-CoV-2 infectivity rapidly decreases thereafter to near-zero after about 10 days in mild-to-moderately-ill patients and 15 days in severely-to-critically-ill and immunocompromised patients. This review summarizes evidence-to-date on the duration of infectivity of SARS-CoV-2.

Singanayagam A, Patel M, Charlett A. **Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020.** Euro Surveill. 2020;25(32). Full-text: https://doi.org/10.2807/1560-7917.ES.2020.25.32.2001483

More on "viral load" and infectivity. Virus culture was attempted from 324 samples (from 253 cases) that tested positive for SARS-CoV-2 by RT-PCR. RT-PCR cycle threshold (Ct) values correlated strongly with cultivable virus. Probability of culturing virus declined to 8% in samples with Ct > 35 and to 6% (95% CI: 0.9–31.2%) 10 days after onset; it was similar in asymptomatic and symptomatic persons.

Lesho E, Reno L, Newhart D, et al. **Temporal, Spatial, and Epidemiologic Relationships of SARS-CoV-2 Gene Cycle Thresholds: A Pragmatic Ambidirectional Observation.** Clinical Infectious Diseases, 25 August 2020, ciaa1248. Full-text: https://doi.org/10.1093/cid/ciaa1248

Same direction. This prospective serial sampling of 70 patients revealed clinically relevant cycle thresholds (Ct, "viral load"), namely a Ct of 24 ("high viral load"), 34, and > 40 ("negative") that occurred 9, 26, and 36 days after symptom onset. Of note, race, gender, or corticosteroids did not appear to influence RNA-positivity. A retrospective analysis of 180 patients revealed that initial Ct did not correlate with requirement for admission or intensive care.

Diagnostics

Ren L, Fan G, Wu W, et al. **Antibody Responses and Clinical Outcomes in Adults Hospitalized with Severe COVID-19: A Post hoc Analysis of LOTUS China Trial**. Clin Infect Dis. 2020 Aug 25:ciaa1247. PubMed: https://pubmed.gov/32840287. Full-text: https://doi.org/10.1093/cid/ciaa1247

A retrospective analysis of patients from the LOTUS trial which showed no effect of lopinavir/r in patients with severe COVID-19. From 191 patients included in the trial, a total of 576 blood and 576 throat swabs samples were taken at days 1, 5, 10, 14, 21 and 28 after recruitment, until death or discharge, whichever came first. IgM, IgG against N, S and RBD and NAbs developed in most patients but did not correlate clearly with clinical outcomes. The levels of IgG antibodies against N, S and RBD were related to viral clearance.

Del Valle DM, Kim-Schulze S, Huang HH, et al. **An inflammatory cytokine signature predicts COVID-19 severity and survival**. Nat Med. 2020 Aug 24. PubMed: https://pubmed.gov/32839624. Full-text: https://doi.org/10.1038/s41591-020-1051-9

Can inflammatory cytokine levels can help predict disease course? Probably yes. Upon admission to the Mount Sinai Health System in New York, cytokines were measured in 1484 patients. When adjusting for disease severity, common laboratory inflammation markers, hypoxia and other vitals, demographics, and a range of comorbidities, IL-6 and TNF-α serum levels remained independent and significant predictors of disease severity and death. These findings were validated in a second cohort of 231 patients. Diane Marie del Valle and colleagues propose that serum IL-6 and TNF-α levels should be considered in the management and treatment of patients with COVID-19 to stratify prospective clinical trials, guide resource allocation and inform therapeutic options.

Severe COVID-19

Lang C, Jaksch P, Hoda MA, et al. **Lung transplantation for COVID-19-associated acute respiratory distress syndrome in a PCR-positive patient**. Lancet Resp Med, August 25, 2020. Full-text: https://doi.org/10.1016/S2213-2600(20)30361-1

An incredible case of a brave, otherwise healthy 44-year-old woman from Klagenfurt, Austria. After a battle of 52 days with critical COVID-19, ECMO and several complications, a comprehensive interdisciplinary discussion on the direction of treatment resulted in a consensus that the lungs of the patient had no potential for recovery. On day 58, a suitable donor organ became available and a sequential bilateral lung transplant was performed. At day 144, the patient remained well. Despite the success of this case, Christian Lang and his colleagues emphasize that lung transplantation is an option for only a small proportion of patients.

Cypel M, Keshavjee S. **When to consider lung transplantation for COVID-19**. Lancet Resp Med, August 25, 2020. Full-text: https://doi.org/10.1016/S2213-2600(20)30393-3

Well written editorial reviewing this case. The authors list ten considerations that they believe should be carefully weighed when assessing a patient with COVID-19-associated ARDS regarding potential candidacy for lung transplantation (< 65 years, only single-organ dysfunction, sufficient time for lung recovery, radiological evidence of irreversible lung disease, such as severe bullous destruction or established fibrosis etc.).

27 August

Epidemiology

Maxmen A. **Why the United States is having a coronavirus data crisis.** Nature 2020, published 25 August. Full-text: https://www.nature.com/articles/d41586-020-02478-z

Is the United States emerging as a Second-World country from the SARS-CoV-2 pandemic? The country suffers from a dearth of data, writes Amy Maxmen in this *Nature* news article. Reliable information on who is infected, why and where is simply missing. How could this happen?

Models

Totura A, Livingston V, Frick O, Dyer D, Nichols D, Nalca A. **Small Particle Aerosol Exposure of African Green Monkeys to MERS-CoV as a Model for Highly Pathogenic Coronavirus Infection.** Emerg Infect Dis. 2020 Aug 3;26(12). PubMed: https://pubmed.gov/32744989. Full-text: https://doi.org/10.3201/eid2612.201664

Aysegul Nalca, Allison Totura and colleagues propose the development of an African green monkey (AGM) model of coronavirus infection by aerosol as a first step to establishing a platform for medical countermeasure testing against highly pathogenic coronaviruses. The authors observed a dose-dependent increase of respiratory disease signs after exposure to 10^3, 10^4, or 10^5 PFU target doses of aerosolized MERS-CoV. All 12 monkeys survived for the 28-day duration of the study.

Transmission

Simha PP, Rao PSM. **Universal trends in human cough airflows at large distances featured.** Physics of Fluids 32, 081905 (2020). Published 25 August. Full-text: https://doi.org/10.1063/5.0021666

Fine droplets can pass through layers of masks and are carried away by the exhaled airflow unlike larger droplets that settle down due to gravity. Now Padmanabha Prasanna Simha and Prasanna Simha Mohan Rao visualize the flow fields of coughs under various mouth covering scenarios. The results:

1. N95 masks are the most effective at reducing the horizontal spread of a cough (spread: 0.1 and 0.25 meters).
2. A simple disposable mask can reduce the spread to 0.5 meters, while an uncovered cough can travel up to 3 meters.
3. Coughing into the elbow? Not very effective! Unless covered by a sleeve, a bare arm cannot form the proper seal against the nose necessary to obstruct airflow and a cough is able to leak through any openings and propagate in many directions.
4.

Garigliany M, Van Laere AS, Clercx C, et al. **SARS-CoV-2 Natural Transmission from Human to Cat, Belgium, March 2020.** Emerg Infect Dis. 2020 Aug 12;26(12). PubMed: https://pubmed.gov/32788033. Full-text: https://doi.org/10.3201/eid2612.202223

And another human-to-cat transmission of SARS-CoV-2.

Prevention

Blaisdell LL, Cohn W, Pavell JR, Rubin DS, Vergales JE. **Preventing and Mitigating SARS-CoV-2 Transmission — Four Overnight Camps, Maine, June–August 2020.** MMWR Morb Mortal Wkly Rep. ePub: 26 August 2020. DOI: http://dx.doi.org/10.15585/mmwr.mm6935e1

You can let the virus lose, but you can also control it. Here Laura Blaisdell et al. report insights from four overnight summer camps with 1,022 attendees where a multilayered prevention and mitigation strategy was successful in identifying and isolating three asymptomatic COVID-19 cases and preventing secondary transmission. Discover the meticulous planning and preparation of the camps. Perfection can be helpful in life.

Immunology

Fagiani F, Catanzaro M, Lanni C. **Molecular features of IGHV3-53-encoded antibodies elicited by SARS-CoV-2.** Sig Transduct Target Ther 5, 170 (2020). Full-text: https://doi.org/10.1038/s41392-020-00287-4

Francesca Fagiani, Michele Catanzaro and Cristina Lanni discuss in detail the paper by Yuan et al. we presented on July 14. Remember: Yuan and collaborators analyzed 294 anti-SARS-CoV-2 antibodies from COVID-19 patients and showed that the immunoglobulin heavy variable 3-53 (IGHV3-53) represents the most frequently used IGHV gene. They conclude that the characterization of these IGHV3-53 antibodies is a promising starting point for rational vaccine design.

Vaccine

Slaoui M, Hepburn M. **Developing Safe and Effective Covid Vaccines — Operation Warp Speed's Strategy and Approach.** N Engl J Med 2020, published 26 August. Full-text: https://doi.org/10.1056/NEJMp2027405

What is OWS and what does it do? Moncef Slaoui and Matthew Hepburn from Operation Warp Speed explain the forces behind a national vaccine strategy. The players: Pfizer and BioNTech, AstraZeneca and Oxford University, Janssen, Moderna, Janssen, Novavax, Sanofi/GSK. Will they succeed in this unprecedented endeavor?

Diagnostics

Perera RAPM, Tso E, Tsang OTY, et al. **SARS-CoV-2 Virus Culture and Subgenomic RNA for Respiratory Specimens from Patients with Mild Coronavirus Disease.** Emerg Infect Dis. 2020 Aug 4;26(11). PubMed: https://pubmed.gov/32749957. Full-text: https://doi.org/10.3201/eid2611.203219

Viral RNA detection by RT-PCR does not prove the presence of infectious virus; culture isolation of virus is a better indication of contagiousness. Now Malik Peiris, Ranawaka Perera and colleagues attempt viral isolation in 68 specimens from 35 patients at different times after symptom onset to define the kinetics of viral isolation in upper respiratory specimens. Their findings suggest that patients with mild or moderate illness might be less contagious 8 days after symptom onset. Mildly ill patients who have clinically recovered and are not immunocompromised might therefore be discharged from containment > 9 days after symptom onset, as long as they are not being discharged into settings that contain other highly vulnerable persons.

Collateral Effects

Hamadani JD, Hasan MI, Baldi AJ, et al. **Immediate impact of stay-at-home orders to control COVID-19 transmission on socioeconomic conditions, food insecurity, mental health, and intimate partner violence in Bangladeshi women and their families: an interrupted time series.** Lancet Global Health 2020, published 25 August. Full-text:: https://doi.org/10.1016/S2214-109X(20)30366-1

In many countries, lockdowns exacerbate the risk of food insecurity and intimate partner violence. Here Sant-Rayn Pasricha, Jena Derakhshani Hamadani and colleagues analyze the impact lockdown orders on women and their families in rural Bangladesh. They randomly selected and invited the mothers of 3016 children to participate in the study, 2424 of whom provided consent. Almost all women reported a reduction in paid work for the family. Median monthly family income fell from US$212 at baseline to $59 during lockdown, and the proportion of families earning less than $1·90 per day rose from almost 0% to 47%. Before the pandemic, 5.6% and 2.7% experienced moderate and severe food insecurity, respectively. This increased to 36.5% and 15.3% during the lockdown. Find more information about intimate violence (emotional, physical, sexual).

Beyond your plate borders

McGuire AL, Gabriel S, Tishkoff SA, et al. **The road ahead in genetics and genomics.** Nat Rev Genet. 2020 Aug 24:1-16. PubMed: https://pubmed.gov/32839576. Full-text: https://doi.org/10.1038/s41576-020-0272-6

Twelve leading researchers reflect on the key challenges and opportunities faced by the field of genetics and genomics. Read about ethical and policy issues, privacy and discrimination, humility and solidarity, and why the genomics of the future must be a genomics for all, regardless of ethnicity, geography or ability to pay. Thirteen fascinating pages for the upcoming weekend.

28 August

Virology

Dinnon KH, Leist SR, Schäfer A et al. **A mouse-adapted model of SARS-CoV-2 to test COVID-19 countermeasures**. Nature, August 27, 2020. Full-text: https://doi.org/10.1038/s41586-020-2708-8

Unfortunately, standard laboratory mice do not support infection with SARS-CoV-2 due to incompatibility of the S protein to the murine ortholog (mACE2) of the human receptor, complicating model development. Sometimes it is better to modify the virus (vs the mouse): Kenneth H. Dinnon et al. altered the SARS-CoV-2 receptor binding domain allowing viral entry via mACE, using reverse genetics to remodel the interaction between S and mACE2. This resulted in a recombinant virus (SARS-CoV-2 MA) that could utilize mACE2 for entry. SARS-CoV-2 MA replicated in both the upper and lower airways of both young adult and aged standard lab mice. Importantly, disease was more severe in aged mice, and showed more clinically relevant phenotypes than those seen in HFH4-hACE2 transgenic mice. This model may be helpful in studying COVID-19 pathogenesis.

Immunology

Takahashi T, Ellingson MK, Wong P, et al. **Sex differences in immune responses that underlie COVID-19 disease outcomes**. Nature August 26, 2020. Full-text: https://doi.org/10.1038/s41586-020-2700-3

This in-depth analysis performed on 137 COVID-19 patients may provide an explanation for the world-wide observed sex biases (more severe courses and deaths among males). Takehiro Takahashi and colleagues revealed that male

patients had higher plasma levels of innate immune cytokines such as IL-8 and IL-18 along with more robust induction of non-classical monocytes. A poor T cell response negatively correlated with patients' age and was associated with worse disease outcome in male patients, but not in female patients. Conversely, higher innate immune cytokines were associated with worse disease progression in female patients, but not in male patients.

Bruchez A, Sha K, Johnson J, et al. **MHC class II transactivator CIITA induces cell resistance to Ebola virus and SARS-like coronaviruses**. Science 27 Aug 2020. Full-text: https://doi.org/10.1126/science.abb3753

CIITA (the major histocompatibility class II transactivator) is a master regulator of the MHC class II genes which are critical for normal immune function. Anna Bruchez, Ky Sha and colleagues show how proteins such as CIITA are involved in host defense against a range of viruses. They also identified an additional function of these proteins beyond their roles in antigen presentation. CIITA induces resistance by activating expression of the p41 isoform of invariant chain CD74, which inhibits viral entry by blocking cathepsin-mediated processing of the Ebola glycoprotein. CD74 p41 can also block the endosomal entry pathway of coronaviruses, including SARS-CoV-2.

Diagnostics

Lepak AJ, Chen DJ, Buys A, et al. **Utility of Repeat Nasopharyngeal SARS-CoV-2 RT-PCR Testing and Refinement of Diagnostic Stewardship Strategies at a Tertiary Care Academic Center in a low Prevalence Area of the United States**. Open Forum Infectious Diseases, August 27, 2020. Full-text: https://doi.org/10.1093/ofid/ofaa388

The clinical sensitivity of PCR testing may be higher than previously believed. Among a total of 660 patients who had more than one SARS-CoV-2 PCR test performed, the initial test was negative in 638. There were only 6 negative-to-positive conversions (0.9%). All 6 were outpatients undergoing a "person under investigation" work-up 5-17 days after an initial negative result. In > 260 inpatients with repeat testing, the authors found no instances of negative-to-positive conversion including those undergoing PUI or asymptomatic evaluation.

Clinical

Hagman K, Hedenstierna M, Gille-Johnson P, et al. **SARS-CoV-2 RNA in serum as predictor of severe outcome in COVID-19: a retrospective cohort study**. Clinical Infectious Diseases, August 28, 2020. Full-text: https://doi.org/10.1093/cid/ciaa1285

SARS-CoV-2 in serum is unfavorable. In this retrospective study of 167 COVID-19 patients who underwent serum PCR analysis at hospital admission, 3 of 106 serum PCR negative patients and 15 of 61 positive patients died. The hazard ratios for critical disease and all-cause mortality were 7.2 (95% CI 3.0-17) and 8.6 (95% CI 2.4-30) for patients with a positive serum PCR.

Comorbidities

Almario CV, Chey WD, Spiegel BMR. **Increased Risk of COVID-19 Among Users of Proton Pump Inhibitors**. Am J Gastroenterol. 2020 Aug 25. PubMed: https://pubmed.gov/32852340 . Full-text: https://doi.org/10.14309/ajg.0000000000000798

Do PPIs increase the odds for acquiring SARS-CoV-2 infection? Maybe. Using an online survey of 53,130 participants (3,386 with a positive test), Christopher V Almario and colleagues found that individuals using PPIs either once daily (aOR 2.15; 95% CI, 1.90-2.44) or twice daily (aOR 3.67; 95% CI, 2.93-4.60) had significantly increased odds for reporting a positive COVID-19 test when compared with those not taking PPIs. Individuals taking histamine-2 receptor antagonists were not at elevated risk. However, before you stop your PPI: please consider that like all observational studies, this study is very susceptible to confounding (for example, people suffering from other comorbidities may be more likely to take PPIs). Moreover, people participating in this survey were not representative of the general population. Let's keep an eye out for more data.

Treatment

Mather JF, Seip RL, McKay RG. **Impact of Famotidine Use on Clinical Outcomes of Hospitalized Patients With COVID-19**. Am J Gastroenterol. 2020 Aug 26. PubMed: https://pubmed.gov/32852338 . Full-text: https://journals.lww.com/ajg/Documents/AJG-20-2074_R1.pdf

Another retrospective study reporting on a potential clinical benefit of famotidine. This propensity-matched observational study included 878 consecutive COVID-19-positive patients admitted to Hartford hospital (a tertiary care hospital in Connecticut, USA) between February 24 and May 13 2020. In

total, 83 (9.5%) patients received famotidine. These patients were somewhat younger (63.5 vs 67.5 years) but did not differ with respect to baseline demographics or pre-existing comorbidities. Use of famotidine was associated with a decreased risk of in-hospital mortality (odds ratio 0.37, 95% CI 0.16-0.86) and combined death or intubation (odds ratio 0.47, 95% CI 0.23-0.96). Patients receiving famotidine displayed lower levels of serum markers for severe disease including CRP, procalcitonin and ferritin levels. Logistic regression analysis demonstrated that famotidine was an independent predictor of both lower mortality and combined death/intubation.

Pediatrics

Dhir SK, Kumar J, Meena J, et al. **Clinical Features and Outcome of SARS-CoV-2 Infection in Neonates: A Systematic Review**. Journal of Tropical Pediatrics, August 28. Full-text: https://doi.org/10.1093/tropej/fmaa059

Congenital infection is rare. This comprehensive literature search (up until June 9, 2020) identified 1,992 pregnant women, of which 1,125 (56.5%) gave birth to 1141 neonates. Of these, 58 neonates were reported with SARS-CoV-2 infection. Postpartum acquisition was the commonest mode of infection, and only 4 had a congenital infection.

Ma N, Li P, Wang X, et al. **Ocular Manifestations and Clinical Characteristics of Children With Laboratory-Confirmed COVID-19 in Wuhan, China**. JAMA Ophthalmol, August 26, 2020. Full-text: https://doi.org/10.1001/jamaophthalmol.2020.3690

In this cross-sectional study of 216 children hospitalized with COVID-19 in Wuhan, China, 49 (22.7%) had (mild, self-healing) ocular manifestations, including conjunctival discharge, eye rubbing, and conjunctival congestion. Children with systemic symptoms or cough were more likely to develop ocular symptoms.

Sola AM, David AP, Rosbe KW, et al. **Prevalence of SARS-CoV-2 Infection in Children Without Symptoms of Coronavirus Disease 2019**. JAMA Pediatr. August 25, 2020. Full-text: https://doi.org/10.1001/jamapediatrics.2020.4095

Estimating the epidemic in children. Overall, the prevalence of positive SARS-CoV-2 test results in children without symptoms at 28 children's hospitals across the US was low (0.65%, 95% CI, 0.47%-0.83%): Only 250 of 33,041 children were PCR positive through 29 May 2020. Of note, there was a strong as-

sociation between prevalence and contemporaneous weekly incidence of COVID-19 in the general population.

29 August

Immunology

Cox RJ, Brokstad KA. **Not just antibodies: B cells and T cells mediate immunity to COVID-19.** Nat Rev Immunol. 2020 Aug 24:1-2. PubMed: https://pubmed.gov/32839569. Full-text: https://doi.org/10.1038/s41577-020-00436-4

Antibodies to SARS-CoV-2 may be maintained for only a few months, especially in patients with mild COVID-19. No antibodies, no protection? Relax and remember that memory B cells and T cells may be maintained even if there are no measurable levels of serum antibodies. Rebecca Cox and Karl Brokstad outline our current understanding of B cell and T cell immunity to SARS-CoV-2. Will this immunity last forever? Probably not, as has been shown this week by Kwok-Yung Yuen, Kelvin Kai-Wang To and colleagues: *COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing*). In this case, the first and the second SARS-CoV-2 episodes were just 142 days apart.

Models

Winkler ES, Bailey AL, Kafai NM, et al. **SARS-CoV-2 infection of human ACE2-transgenic mice causes severe lung inflammation and impaired function.** Nat Immunol. 2020 Aug 24. PubMed: https://pubmed.gov/32839612. Full-text: https://doi.org/10.1038/s41590-020-0778-2

Michael Diamond, Emma Winkler and colleagues evaluated transgenic mice expressing the human angiotensin I-converting enzyme 2 (ACE2) receptor driven by the epithelial cell cytokeratin-18 (K18) promoter (K18-hACE2). Intranasal inoculation with SARS-CoV-2 resulted in high levels of viral infection in lungs, with spread to other organs. A decline in pulmonary function occurred 4 days after peak viral titer and correlated with infiltration of monocytes, neutrophils and activated T cells. The mice rapidly lost weight after 4 days post-infection (dpi) and began to succumb to disease at 7 dpi. Read more about a massively upregulated innate immune response.

Diagnostics

Wyllie AL, Fournier J, Casanovas-Massana A, et al. **Saliva or Nasopharyngeal Swab Specimens for Detection of SARS-CoV-2.** N Engl J Med 2020, published 28 August. Full-text: https://doi.org/10.1056/NEJMc2016359

Detecting more SARS-CoV-2 RNA copies in *saliva* specimens than in *nasopharyngeal swab* specimens? Finding that a higher percentage of saliva samples than nasopharyngeal swab samples are positive up to 10 days after the COVID-19 diagnosis? Screening 495 asymptomatic health care workers who provided both saliva and nasopharyngeal samples and discovering, to your surprise, more positive results in the saliva samples? That's what Nathan Grubaugh, Anne Wyllie and colleagues reported in a letter to the NEJM. Read more about fewer direct interactions between health care workers and patients, a possibly lower risk of nosocomial infection and lower demands for personal protective equipment.

Vogels CBF, Brackney D, Wang J, et al. **SalivaDirect: Simple and sensitive molecular diagnostic test for SARS-CoV-2 surveillance.** medRxiv 2020, posted 4 August. Full-text: https://doi.org/10.1101/2020.08.03.20167791

More information about the previous article (same research group). Here Nathan Grubaugh, Anne Wyllie, Chantal Vogels and colleagues explain how SalivaDirect might improve accessibility, scalability and cost ($1.29-$4.37/sample) of SARS-CoV-2 testing. The test has been granted an emergency use authorization by the U.S. Food and Drug Administration (FDA) on August 15. This paper has not yet been peer-reviewd.

See also the August 15 Yale Newsletter and the info page of the Grubaugh Lab.

Pediatrics

Hurst JH, Heston SM, Chambers HN, et al. **SARS-CoV-2 Infections Among Children in the Biospecimens from Respiratory Virus-Exposed Kids (BRAVE Kids) Study.** medRxiv 2020, posted 21 August. Full-text: https://doi.org/10.1101/2020.08.18.20166835

Data from the BRAVE Kids study, Matthew Kelly, Jillian Hurst and colleagues describe the clinical and epidemiological characteristics of 382 children and adolescents who had close contact with a SARS-CoV-2-infected individual. Children aged 6 - 13 years were frequently asymptomatic (39%) and had respiratory symptoms less often than younger children (29% *vs* 48%) or adolescents (29% *vs* 60%). Compared to children aged 6 - 13 years, adolescents more frequently reported influenza-like (61% *vs* 39%), gastrointestinal (27% *vs* 9%; p

= 0.002), and sensory symptoms (42% *vs* 9%), and had more prolonged illnesses [median (IQR) duration: 7 (4, 12) *vs* 4 (3, 8) days]. The authors also found that SARS-CoV-2-infected children were more likely to be Hispanic ($p < 0.0001$), less likely to have asthma ($p = 0.005$), and more likely to have an infected sibling contact ($p = 0.001$) than uninfected children.

Journal Feature

Mallapaty S. **The coronavirus is most deadly if you are older and male — new data reveal the risks.** Nature 2020, published 28 August. Full-text: https://www.nature.com/articles/d41586-020-02483-2

The year 2020 is not a good time to be old... and a man. Smriti Mallapathy gives an overview of the stark statistics from the first detailed studies into the mortality risks for COVID-19.

30 August

Prevention

Jones NR, Qureshi ZU, Temple RJ, Larwood JPJ, Greenhalgh T, Bourouiba L. **Two metres or one: what is the evidence for physical distancing in covid-19?** BMJ. 2020 Aug 25;370:m3223. PubMed: https://pubmed.gov/32843355. Full-text: https://doi.org/10.1136/bmj.m3223

Physical distancing is only one part of a wider public health approach to containing the COVID-19 pandemic. But is one meter sufficient? Or should it be two, or even more? Follow Lydia Bourouiba, Nicolas Jones and colleagues on a tour about distance, ventilation, occupancy, exposure time, people-air-surface-space management and indoor space and air managements.

Bae SH, Shin H, Koo H-Y, Lee SW, Yang JM, Yon DK. **Asymptomatic transmission of SARS-CoV-2 on evacuation flight.** Emerg Infect Dis 2020, published 21 August. Full-text: https://doi.org/10.3201/eid2611.203353

Infected on the aircraft toilet? Dong Keon Yon and Sung Hwan Bae report data on an 11-hour flight from Milan to South Korea with 299 asymptomatic passengers. Before boarding, strict infection control procedures were implemented (physical examinations, medical interviews, body temperature checks, removal of symptomatic passengers from the flight, etc.). The authors suggest that one patient may have been infected during the flight. On the flight, she wore an N95 mask, except when she used a toilet. The toilet was

shared by passengers sitting nearby, including an asymptomatic patient. She was seated 3 rows away from the asymptomatic patient. The authors discuss as most plausible explanation "that she became infected by an asymptomatic but infected passenger while using an onboard toilet".

Immunology

Xu C, Li, H, Flavell RA. **A special collection of reviews on frontiers in immunology.** Cell Res 2020, published 28 August. Full-text: https://doi.org/10.1038/s41422-020-00403-7

And now the jewels of the day! Are you ready for an immunology *tour de force*? Be guided by Chenqi Xu, Hua-Bing Li and Richard Flavell through 11 reviews on the frontier of the field:

1. Direct (tumor) and indirect (micro-environment) modifiers (Jedd Wolchok and colleagues)
2. Future directions to reduce the risk of immune-related adverse events (irAEs; Vijay Kurchoo and colleagues)
3. Alternative paths to target immune checkpoints in cancer (Chenqi Xu and colleagues)
4. Antitumor roles of the cGAS-STING pathway (Zhejian Chen and colleagues)
5. Immunometabolism (Hongbo Chi and colleagues)
6. Interplay between immune signaling and metabolism (Richard Flavell and colleagues)
7. Targeting metabolic intermediates and enzymes in inflammation (Eva Pålsson-McDermott and Luke O'Neill)
8. Inflammasome activation (Thirumala-Devi Kanneganti and colleagues)
9. ILC development/heterogeneity (Christoph Klose and David Artis)
10. Microbiome-immunity crosstalk in the intestine and extra-intestinal organs (Eran Elinav and colleagues)
11. Transcriptional and epigenetic basis of Treg cell development and function (Shimon Sakaguchi and Naganari Ohkura)

The papers in detail:

1. Murciano-Goroff YR, Warner AB, Wolchok JD. **The future of cancer immunotherapy: microenvironment-targeting combinations.** Cell Res. 2020 Jun;30(6):507-519. PubMed: https://pubmed.gov/32467593. Full-text: https://doi.org/10.1038/s41422-020-0337-2

2. Schnell A, Bod L, Madi A, Kuchroo VK. **The yin and yang of co-inhibitory receptors: toward anti-tumor immunity without autoimmunity.** Cell Res. 2020 Apr;30(4):285-299. PubMed: https://pubmed.gov/31974523. Full-text: https://doi.org/10.1038/s41422-020-0277-x
1. He X, Xu C. **Immune checkpoint signaling and cancer immunotherapy.** Cell Res. 2020 Aug;30(8):660-669. PubMed: https://pubmed.gov/32467592. Full-text: https://doi.org/10.1038/s41422-020-0343-4
2. Yum S, Li M, Chen ZJ. **Old dogs, new trick: classic cancer therapies activate cGAS.** Cell Res. 2020 Aug;30(8):639-648. PubMed: https://pubmed.gov/32541866. Full-text: https://doi.org/10.1038/s41422-020-0346-1
3. Saravia J, Raynor JL, Chapman NM, Lim SA, Chi H. **Signaling networks in immunometabolism.** Cell Res. 2020 Apr;30(4):328-342. PubMed: https://pubmed.gov/32203134. Full-text: https://doi.org/10.1038/s41422-020-0301-1
4. Shyer JA, Flavell RA, Bailis W. **Metabolic signaling in T cells.** Cell Res. 2020 Aug;30(8):649-659. PubMed: https://pubmed.gov/32709897. Full-text: https://doi.org/10.1038/s41422-020-0379-5
5. Pålsson-McDermott EM, O'Neill LAJ. **Targeting immunometabolism as an anti-inflammatory strategy.** Cell Res. 2020 Apr;30(4):300-314. PubMed: https://pubmed.gov/32132672. Full-text: https://doi.org/10.1038/s41422-020-0291-z
6. Christgen S, Place DE, Kanneganti TD. **Toward targeting inflammasomes: insights into their regulation and activation.** Cell Res. 2020 Apr;30(4):315-327. PubMed: https://pubmed.gov/32152420. Full-text: https://doi.org/10.1038/s41422-020-0295-8
7. Klose CSN, Artis D. **Innate lymphoid cells control signaling circuits to regulate tissue-specific immunity.** Cell Res. 2020 Jun;30(6):475-491. PubMed: https://pubmed.gov/32376911. Full-text: https://doi.org/10.1038/s41422-020-0323-8
8. Zheng D, Liwinski T, Elinav E. **Interaction between microbiota and immunity in health and disease.** Cell Res. 2020 Jun;30(6):492-506. PubMed: https://pubmed.gov/32433595. Full-text: https://doi.org/10.1038/s41422-020-0332-7
9. Ohkura N, Sakaguchi S. **Transcriptional and epigenetic basis of Treg cell development and function: its genetic anomalies or variations in autoimmune diseases.** Cell Res. 2020 Jun;30(6):465-474. PubMed: https://pubmed.gov/32367041. Full-text: https://doi.org/10.1038/s41422-020-0324-7

Clinical

Jones E. **The psychology of protecting the UK public against external threat: COVID-19 and the Blitz compared.** Lancet Psychiatry 2020, published 27 August. Full-text: https://doi.org/10.1016/S2215-0366(20)30342-4

Do the SARS-CoV-2 pandemic and the German World War 2 aerial bombing campaign against the UK (*The Blitz*) have something in common? Exposure of the civilian population to a sustained threat, leading to a range of protective measures and behavioral regulations? Follow Edgar Jones on this trip through a phoney war, shelter occupation, deep shelter, adaptation to threat, second wave and risk communication. Your Sunday read.

Treatment

Nadkarni GN, Lala A, Bagiella E, et al. **Anticoagulation, Mortality, Bleeding and Pathology Among Patients Hospitalized with COVID-19: A Single Health System Study.** J Am Coll Cardiol 2020, published 26 August. Full-text: https://doi.org/10.1016/j.jacc.2020.08.041

In this retrospective analysis of 4,389 patients, Valentin Fuster, Girish Nadkarni, Anuradha Lala and colleagues examine the association of in-hospital anticoagulation (AC) with in-hospital outcomes and describe thromboembolic findings on autopsies. Compared to no anticoagulation, therapeutic and prophylactic anticoagulation were associated with lower in-hospital mortality and intubation.

Comorbidities

Webb GJ, Marjot T, Cook JA, et al. **Outcomes following SARS-CoV-2 infection in liver transplant recipients: an international registry study.** Lancet Gastroenterol Hepatol 2020, published 28 August. Full-text: https://doi.org/10.1016/S2468-1253(20)30271-5

No increased risk of death for patients with liver transplants. In this multicenter cohort study, Gwilym Webb et al. collected data on 151 adult liver transplant recipients from 18 countries and 627 patients who had not undergone liver transplantation. After adjusting for age, sex, creatinine concentration, obesity, hypertension, diabetes, and ethnicity, liver transplantation did not significantly increase the risk of death in patients with SARS-CoV-2 infection. However, ICU admission (43 [28%] *vs* 52 [8%], p<0·0001) and invasive ventilation (30 [20%] *vs* 32 [5%], p < 0·0001) were more frequent in the liver transplant cohort.

Pediatrics

Swann OV, Holden KA, Turtle L, et al. **Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study.** BMJ 2020, published 27 August. Full-text: http://dx.doi.org/10.1136/bmj.m3249

In this prospective observational cohort study, Malcolm Semple, Olivia Swann and colleagues report on 651 children and young people aged less than 19 years. Median age was 4.6 years, 35% (225/651) were under 12 months old. 18% (116/632) of children were admitted to critical care. Six patients died in hospital, all of whom had profound comorbidity. The 11% (52/456) who met the WHO MIS-C criteria were five times more likely to be admitted to critical

care. Ethnicity seems to be a factor in both critical care admission and MIS-C. The authors also identified a systemic mucocutaneous-enteric symptom cluster in acute cases that shares features with MIS-C. They suggest that the WHO MIS-C preliminary case definition be refined.

Society

Susskind D, Vines D. **The economics of the COVID-19 pandemic: an assessment.** Oxford Review of Economic Policy 2020, published 29 August. Full-text: https://doi.org/10.1093/oxrep/graa036

The COVID-19 pandemic is creating challenges that have been compared to the Spanish Flu Pandemic (minus World War I, fortunately) and the Great Depression. Here Daniel Susskind and David Vines discuss the economic effects and interventions as well as the need for reforming business and finance and international cooperation. They conclude that although the post-Second World War institutions have served the world remarkably well, now, following the COVID-19 pandemic, they need strengthening and reinvigorating. Listen to the final sentences: "Because the pandemic is such a very large event, we need to realize that the world faces a very large choice. We can do what the world did in the late 1940s, when the institutional choices which were made helped to support the golden age of global growth during the 1950s and 1960s. Or we can instead allow what happened in the 1930s to happen all over again."

31 August

Epidemiology

Westhaus S, Weber FA, Schiwy S, et al. **Detection of SARS-CoV-2 in raw and treated wastewater in Germany - Suitability for COVID-19 surveillance and potential transmission risks**. Sci Total Environ 2020 August 18;751:141750. PubMed: https://pubmed.gov/32861187. Full-text: https://doi.org/10.1016/j.scitotenv.2020.141750

Detailed Analysis of a set of samples from nine wastewater treatment plants in North Rhine-Westphalia, Germany. Main conclusions: Yes, SARS-CoV-2 can be detected in wastewater in Germany using RT-qPCR. The total load of gene equivalents in wastewater correlated with the cumulative and the acute number of COVID-19 cases reported in the respective catchment areas. Thus, wastewater-based epidemiology can be regarded as a complementary meas-

ure to survey the outbreak. Note - negative tests for replication potential indicate that wastewater might be no major route for transmission to humans.

Graham NSN, Junghans C, McLaren R, et al. **High rates of SARS-CoV-2 seropositivity in nursing home residents**. J Infection August 26, 2020. Full-text: https://doi.org/10.1016/j.jinf.2020.08.040

What incredibly high infection rates in nursing homes! During March - April 2020 the authors investigated outbreaks in four UK nursing homes where 40% of 394 residents tested positive on RT-PCR. Now they demonstrate that COVID-19 infection was considerably more widespread. Seventy-two percent of nursing home residents (95% CI 66 – 77) were anti-SARS-CoV-2 IgG antibody positive, representing 173 of 241 residents available and consenting to testing. This included 93% of those tested who were previously RT-PCR positive and 59% of those who were previously RT-PCR negative. Seropositivity was not associated with the presence of comorbidities.

Fouillet A, Pontais I, Caserio-Schönemann C. **Excess all-cause mortality during the first wave of the COVID-19 epidemic in France, March to May 2020**. Eurosurveillance 2020;25(34. Full-text: https://doi.org/10.2807/1560-7917.ES.2020.25.34.2001485

Through a weekly all-cause mortality surveillance system in France, the authors observed a major all-cause excess mortality from March to May 2020 (25,030 deaths, mainly among elderly people). Five metropolitan regions were the most affected, particularly the Île-de-France and the Grand-Est regions. However, assessing the excess mortality related to COVID-19 is complex because of the potential protective effect of the lockdown period on other causes of mortality.

Virology

O'Leary VB, Ovsepian SV. **Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Trends in Genetics**. Published August 26, 2020. Full-text: https://doi.org/10.1016/j.tig.2020.08.014

Brief review of the genome of SARS-CoV-2. Valerie Bríd O'Leary and Saak Victor Ovsepian also provide a fun fact you should know before you die: The SARS-CoV-2 non-structural protein 3 has a 46% similarity to a protein also found in a ray-finned fish *Labrus bergylta* (Ballan wrasse), a protogynous hermaphrodite, that begins life as a female yet with territorial dominance be-

comes male. If you are tempted to try CoV-2-protein: wrasses have firm meat and taste excellent.

Sardar R, Satish D, Birla S. **Integrative analyses of SARS-CoV-2 genomes from different geographical locations reveal unique features potentially consequential to host-virus interaction, pathogenesis and clues for novel therapies**. Heliyon August 20, 2020. Full-text: https://doi.org/10.1016/j.heliyon.2020.e04658

Integrative analysis of SARS-CoV-2 genome sequences from different countries, confirming unique features absent in other evolutionarily related coronavirus family genomes, which presumably confer unique infection, transmission and virulence capabilities to the virus. This work explores the functional impact of the virus mutations on its proteins and interaction of its genes with host antiviral mechanisms.

Prevention

Sauceda JA, Neilands TB, Lightfoot M, Saberi P. **Findings from a probability-based survey of U.S. households about prevention measures based on race, ethnicity, and age in response to SARS-CoV-2**. J Infect Dis. 2020 Aug 29:jiaa554. PubMed: https://pubmed.gov/32860499. Full-text: https://doi.org/10.1093/infdis/jiaa554

This survey in a "nationally-representative" sample of 2,029 US adults revealed that all groups engaged in the same prevention behaviors, but Whites reported being more likely to use digital tools to report/act on symptoms and seek testing, versus African Americans and Latinos. Individual behaviors may not explain COVID-19 case disparities, and digital tools for tracking should be focus on uptake among racial/ethnic minorities.

Diagnostics

Weiss S, Klingler J, Hioe C, et al. **A High Through-Put Assay For Circulating Antibodies Directed Against The S Protein Of Severe Acute Respiratory Syndrome Coronavirus 2 (Sars-Cov-2)**. J Infect Dis. 2020 Aug 29:jiaa531. PubMed: https://pubmed.gov/32860510. Full-text: https://doi.org/10.1093/infdis/jiaa531

Svenja Weiss and colleagues developed a Luminex binding assay to assess simultaneously the presence of COVID-19-specific antibodies in human serum and plasma. Clear differentiation was achieved between specimens from infected and uninfected subjects, and a wide range of serum/plasma antibody

levels were delineated in infected subjects. Since the Luminex Ab assay can simultaneously test qualitatively and quantitatively for RBD and S protein Abs and can be performed in < 2.5 hours with 5 - 10 ng of antigen per test, it provides a platform that will result in cost savings and the processing of large numbers of samples per day.

Clinical

Boulle A, Davies MA, Hussey H, et al. **Risk factors for COVID-19 death in a population cohort study from the Western Cape Province, South Africa**. Clin Infect Dis. 2020 Aug 29:ciaa1198. PubMed: https://pubmed.gov/32860699. Full-text: https://doi.org/10.1093/cid/ciaa1198

The by far longest co-author list of the day. Around 300 researchers were needed to evaluate risk factors among 3,460,932 patients (16% HIV+) in South Africa. In total, 22,308 were diagnosed with COVID-19, of whom 625 died. COVID-19 death was associated with male sex, increasing age, diabetes, hypertension and chronic kidney disease. HIV and current tuberculosis were independently associated with increased COVID-19 mortality. Adjusted hazard ratio for mortality was 2.14 for HIV (95% CI 1.70-2.70), with similar risks across strata of viral load and immunosuppression. Current and previous tuberculosis were also associated with COVID-19 death (aHRs 2.70 and 1.51).

White PL, Dhillon R, Cordey A, et al. **A national strategy to diagnose COVID-19 associated invasive fungal disease in the ICU**. Clin Infect Dis. 2020 Aug 29:ciaa1298. PubMed: https://pubmed.gov/32860682. Full-text: https://doi.org/10.1093/cid/ciaa1298

P Lewis White and colleagues from Wales have screened 135 patients admitted to Welsh ICUs with COVID-19 infection for invasive fungal co-infection. The incidence was 26.7% (14.1% aspergillosis, 12.6% yeast infections). The overall mortality rate was 53% and 31% in patients with and without fungal disease, respectively. The use of corticosteroids and history of chronic respiratory disease increased the likelihood of aspergillosis. The authors conclude that screening using a strategic diagnostic approach and antifungal prophylaxis of patients with risk factors will likely enhance the management of COVID-19 patients.

Comorbidities

Piñana JL, Xhaard A, Tridello G, et al. **Seasonal human coronaviruses respiratory tract infection in recipients of allogeneic hematopoietic stem**

cell transplantation. J Infect Dis. 2020 Aug 29:jiaa553. PubMed: https://pubmed.gov/32860509. Full-text: https://doi.org/10.1093/infdis/jiaa553

In this retrospective multicenter study, which included 402 allo-HCT recipients (adults and children) with upper and/or lower respiratory tract disease (RTD) caused by seasonal HCoV diagnosed through multiplex PCR assays 2012-2019, a significant morbidity was found. HCoV infection frequently required hospitalization (18%), oxygen administration (13%) and ICU admission (3%). Three-month overall mortality after HCoV detection was 7% in the full cohort and 16% in those with lower RTD. Three conditions were identified with higher mortality in recipients with lower RTD: low absolute lymphocyte counts, corticosteroids and, not suprisingly, ICU admission.

September 2020

1 September

Epidemiology

Seemann T, Lance CR, Sherry NL, et al. **Tracking the COVID-19 pandemic in Australia using genomics.** Nat Commun 11, 4376 (2020). Full-text: https://doi.org/10.1038/s41467-020-18314-x

Genomic sequencing for rapid identification of SARS-CoV-2 transmission chains? That's what Benjamin P. Howden and Torsten Seemann did in Victoria, Australia (1,333 COVID-19 cases). They combined extensive whole-genome sequencing and epidemiologic data to investigate the source of individual cases and identify distinct genomic clusters, including large clusters associated with social venues, healthcare visits and cruise ships. The authors demonstrate the critical role of multiple SARS-CoV-2 importations by returned international travelers in driving transmission in Australia, with travel-related cases responsible for establishing ongoing transmission lineages (each with 3–9 cases) accounting for over half of locally acquired cases.

Immunology

Thieme CJ, Anft M, Paniskaki K, et al. **Robust T cell response towards spike, membrane, and nucleocapsid SARS-CoV-2 proteins is not associated with recovery in critical COVID-19 patients.** Cell Reports Medicine 2020, published 29 August. Full-text: https://doi.org/10.1016/j.xcrm.2020.100092

Nina Babel, Constantin Thieme and colleagues performed a comprehensive characterization of the T cell response against S-, M- and N- SARS-CoV-2 proteins in patients with different COVID-19 severity and unexposed donors. Surprise: the T cell response of critical COVID-19 patients is robust and comparable or even superior to non-critical patients. The authors would thus disprove the hypothesis of insufficient SARS-CoV-2-reactive immunity in critical COVID-19. Expect some intense discussions.

Hunting for antibodies to combat COVID-19. Biopharma dealmakers 2020, published 1 September. Full-text: https://www.nature.com/articles/d43747-020-01115-y

The development of highly successful monoclonal antibody-based therapies for cancer and immune disorders has created a wealth of expertise and manufacturing capabilities. Is there room for monoclonals for prevention or treatment of severe COVID-19 before the general availability of vaccines and efficient antiviral drugs? Find out how the 'COVID-19 antibodysphere' (Amgen, AstraZeneca, Vir, Regeneron, Lilly, Adagio) is building partnerships.

Pediatrics

Han MS, Choi EH, Chang SH, et al. **Clinical Characteristics and Viral RNA Detection in Children With Coronavirus Disease 2019 in the Republic of Korea.** JAMA Pediatr. Published online August 28, 2020. Full-text: https://doi.org/10.1001/jamapediatrics.2020.3988

How many pediatric SARS-CoV-2 cases would doctors miss if they focused on only testing symptomatic patients? Maybe up to 90%, say Jong-Hyun Kim, Eun Hwa Choi, Mi Seon Han and colleagues from Korea. In this case series of children with COVID-19, 20 children (22%) were asymptomatic during the entire observation period. Among 71 symptomatic cases, only 6 (9%) were diagnosed at the time of symptom onset while 47 children (66%) had unrecognized symptoms before diagnosis and 18 (25%) developed symptoms after diagnosis. The authors conclude that there is no other good alternative to extensive testing for early detection of SARS-CoV-2 infection.

Summary of the clinical symptoms (91 patients):

Asymptomatic	22%
Cough	41%
Fever > 38º C	30%
Sore throat	29%
Runny nose	27%
Diarrhea	12%
Loss of sense of taste	12%

Fifty-one percent had "mild" disease, 22% "moderate" disease and 2% "severe" disease. No patient required intensive care.

DeBiasi RL, Delaney M. **Symptomatic and Asymptomatic Viral Shedding in Pediatric Patients Infected With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): Under the Surface.** JAMA Pediatr. Published online August 28, 2020. Full-text: https://doi.org/10.1001/jamapediatrics.2020.3996

Roberta DeBiasi and Meghan Delaney comment on the previous study and underline the three "take-home points":

1. Not all infected children have symptoms, and even those with symptoms are not necessarily recognized in a timely fashion.
2. Duration of symptoms in symptomatic infected pediatric patients varies widely.
3. Virus was detectable for a mean of 17.6 days overall and was detectable for a prolonged period of time in all cohorts of children, whether symptoms were present or not. (Detectability does not mean infectivity in all cases, though.)

Important summary in view of the current school re-openings.

Journal Feature

Viglione G. **How many people has the coronavirus killed?** Nature 2020, published 1 September. Full-text: https://www.nature.com/articles/d41586-020-02497-w

Excess mortality, the comparison of expected deaths with ones that actually happened, may be the most robust way to gauge the impact of the pandemic. According to data from more than 30 countries for which estimates of excess deaths are available, Giuliana Viglione shows there could be more deaths than those officially attributed to COVID-19.

Education

Centor RM, D'Alessio FR. **Annals On Call - Regulatory T Cells: Treatment for COVID-19?** Ann Intern Med 2020, published 1 September. Audio podcast (23:29): https://www.acpjournals.org/doi/10.7326/A19-0037

Discussion of the potential use of regulatory T cells to treat patients with acute respiratory distress syndrome associated with COVID-19. *Annals* articles discussed include [Gladstone DE, Kim BS, Mooney K, et al. **Regulatory T Cells for Treating Patients With COVID-19 and Acute Respiratory Distress Syndrome: Two Case Reports**. Ann Int Med 2020, Jul 6. Full-text:

https://www.acpjournals.org/doi/10.7326/L20-0681] which we presented in the July 8 Top 10.

French

If you read French, read Bellier U. **De l'« inutilité » pour le grand public à l'obligation généralisée, sept mois de consignes sur le masque en France.** Le Monde 2020, publié le 29 août. Texte intégral : https://www.lemonde.fr/societe/article/2020/08/29/six-mois-de-consignes-sur-le-masque-en-france_6050316_3224.html

Ulysse Bellier rappelle l'usage du masque depuis le début de l'épidémie et sept mois de recommendations parfois contradictoires.

2 September

Transmission

Kang M, Wi J, Yuan J, et al. **Probable Evidence of Fecal Aerosol Transmission of SARS-CoV-2 in a High-Rise Building.** Ann Intern Med 2020, published 1 September. Full-text: https://doi.org/10.7326/M20-0928

Nanshan Zhong, Min Kang and colleagues report 9 infected patients in 3 families. While the first family had a history of travel to the coronavirus disease 2019 (COVID-19) epicenter Wuhan, the other 2 families had no travel history and a later onset of symptoms. The families lived in 3 vertically aligned flats connected by drainage pipes in the master bathrooms. The authors suggest that virus-containing fecal aerosols may have been produced in the associated vertical stack during toilet flushing after use by the index patients. This report reminds us of a SARS-1 outbreak in March 2003 among residents of Amoy Gardens, Hong Kong, with a total of 320 SARS cases in less than three weeks (see www.SARSReference.com, page 65).

See also the comment by Michael Gormley [Gormley M. **SARS-CoV-2: The Growing Case for Potential Transmission in a Building via Wastewater Plumbing Systems.** Ann Intern Med 2020, published 1 September. Full-text: https://doi.org/10.7326/M20-6134] concludes that that wastewater plumbing systems, particularly those in high-rise buildings, deserve closer investigation, both immediately in the context of SARS-CoV-2 and in the long term, because they may be a reservoir for other harmful pathogens.

Deng W, Bao L, Gao H, et al. **Ocular conjunctival inoculation of SARS-CoV-2 can cause mild COVID-19 in rhesus macaques.** Nat Commun 11, 4400 (2020). Full-text: https://doi.org/10.1038/s41467-020-18149-6
If you are exploring extra-respiratory routes of SARS-CoV-2 transmission, read the article by Chuan Qin, Wei Deng and colleagues. The authors inoculated five rhesus macaques with SARS-CoV-2 conjunctivally, intratracheally, and intragastrically. The *conjunctivally* infected animal had a higher viral load in the nasolacrimal system than the *intratracheally* infected animal but also showed mild interstitial pneumonia, suggesting distinct viral distributions.

Prevention

Vermaa S, Dhanak M, Frankenfield J. **Visualizing droplet dispersal for face shields and masks with exhalation valves featured.** Physics of Fluids 32, 091701 (2020). Full-text; https://doi.org/10.1063/5.0022968

Are you tempted to substitute your standard surgical masks for clear plastic face shields? Don't, recommend Siddhartha Verma, Manhar Dhanak and John Frankenfield! Find out why widespread public use of plastic face shields could have an adverse effect on mitigation efforts.

Immunology

Gudbjartsson DF, Norddahl GL, Melsted P, et al. **Humoral Immune Response to SARS-CoV-2 in Iceland.** N Engl J Med 2020, published 1 September. Full-text: https://doi.org/10.1056/NEJMoa2026116

How long will people be protected from reinfection by SARS-CoV-2? Generally, many months, as may be expected from a coronavirus infection. In this study by Kari Stefansson, Daniel Gudbjartsson and colleagues, over 90% of 1,215 qPCR-positive persons tested positive with two pan-Ig SARS-CoV-2 antibody assays and remained seropositive 120 days after diagnosis, with no decrease of antibody levels. Another piece of good news: the infection fatality risk in Iceland was 0.3%. Less good news: only 0.9% of Icelanders were infected with SARS-CoV-2 indicating that the Icelandic population is vulnerable to a second wave of infection.

See also the editorial by Galit Alter and Robert Seder: Alter G, Seder R: **The Power of Antibody-Based Surveillance.** N Engl J Med 2020, published 1 September. Full-text: https://doi.org/10.1056/NEJMe2028079. In particular, they stress the utility of antibody assays as highly cost-effective alternatives to PCR testing for population-level surveillance, which is critical to the safe reopening of cities and schools.

Varadé J, Magadán S, González-Fernández Á. **Human immunology and immunotherapy: main achievements and challenges.** Cell Mol Immunol 2020, published 2 September. Full-text: https://doi.org/10.1038/s41423-020-00530-6

The review for your next sleepless night – 18 pages and 332 references. The trio Jezabel Varadé, Susana Magadán and África González-Fernández will take you on a trip to the past and the future of immunotherapy.

Vaccine

Giamarellos-Bourboulis EJ, Tsilika M, Moorlag S. **ACTIVATE: randomized clinical trial of BCG vaccination against infection in the elderly.** Cell 2020, published 31 August. Full-text: https://doi.org/10.1016/j.cell.2020.08.051

In this double-blind, randomized trial, 198 elderly patients received BCG or placebo vaccine at hospital discharge and were followed for 12 months. At interim analysis (78 patients allocated to placebo vaccination and 72 patients allocated to BCG vaccination), Evangelos Giamarellos-Bourboulis et al. found that BCG vaccination significantly increased the time to first infection (median 16 weeks compared to 11 weeks after placebo). The incidence of new infections was 42.3% after placebo vaccination and 25.0% after BCG vaccination; most of the protection was against respiratory tract infections of probable viral origin. Any effect on SARS-CoV-2 infection? The number of individuals participating in the trial was too low to allow for any conclusions. Larger trials will provide the answer.

Obstetrics

Allotey J, Stallings E, Bonet M, et al. **Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis.** BMJ 2020, published 1 September. Full-text: https://doi.org/10.1136/bmj.m3320

In this 'living review' and meta-analysis of 77 studies, Shakila Thangaratinam, John Allotey and colleagues warn that pregnant women are less likely to manifest COVID-19 related symptoms of fever and myalgia than non-pregnant women of reproductive age and are potentially more likely to need intensive care treatment for COVID-19. Unsurprisingly, risk factors for severe COVID-19 in pregnancy would include increasing maternal age, high body mass index, and pre-existing comorbidities.

Society

Kishore N, Kiang MV, Engø-Monsen K, et al. **Measuring mobility to monitor travel and physical distancing interventions: a common framework for mobile phone data analysis.** Lancet Digital Health 2020, published 1 September. Full-text: https://doi.org/10.1016/S2589-7500(20)30193-X

Google and Apple will soon be loading our mobile phones with coronavirus-tracking technology and use our mobility data to monitor physical distancing (see The Guardian). Will they respect the principles of privacy and data protection? Now Caroline Buckee, Nishant Kishore and colleagues describe a common syntax for how aggregated data are used in research and policy. The authors argue that data protection are vital in assessing more technical aspects of aggregation and should be an important central feature to guide partnerships with governments who make use of research products.

Spanish

If you read Spanish, read Ansede M. **Expertos de la OMS alertan de que una vacuna aprobada con prisas podría "empeorar" la pandemia.** El País 2020, published 1 September. Full-text: https://elpais.com/ciencia/2020-09-01/expertos-de-la-oms-alertan-de-que-una-vacuna-aprobada-con-prisas-podria-empeorar-la-pandemia.html

Los científicos critican "las presiones políticas y económicas" para autorizar inyecciones experimentales cuanto antes. Among other artices, Manuel Ansede discusses Krause P, Fleming TR, Longini I, Henao-Restrepo AM, Peto R; World Health Organization Solidarity Vaccines Trial Expert Group. **COVID-19 vaccine trials should seek worthwhile efficacy.** Lancet. 2020 Aug 27:S0140-6736(20)31821-3. PubMed: https://pubmed.gov/32861315. Full-text: https://doi.org/10.1016/S0140-6736(20)31821-3

French

If you read French, read the following articles:

Vaudano M, Dagoern G, Sénécat A : **Coronavirus : pourquoi tant de contaminations et si peu de morts ?** Le Monde 2020, publié le 29 août. Lien : https://www.lemonde.fr/les-decodeurs/article/2020/08/26/covid-19-pourquoi-la-hausse-des-cas-ne-permet-pas-encore-de-conclure-a-une-deuxieme-vague_6050010_4355770.html

Le nombre de cas confirmés de Covid-19 augmente régulièrement depuis le milieu de l'été, mais le bilan humain reste relativement stable. Rien ne permet, pour autant, de prévoir la fin de l'épidémie.

Dagorn G. **Coronavirus : masque, densité, aération… évaluez le risque de transmission en un coup d'œil.** Le Monde 2020, publié le 1 septembre. Lien : https://www.lemonde.fr/les-decodeurs/article/2020/09/01/coronavirus-masque-densite-aeration-evaluez-le-risque-de-transmission-en-un-coup-d-il_6050612_4355770.html

Les risques de contamination varient grandement en fonction du type d'activité, du milieu et de la circulation de l'air. Voici comment vous y retrouver.

3 September

Epidemiology

Self WH, Tenforde MW, Stubblefield WB, et al. **Seroprevalence of SARS-CoV-2 Among Frontline Health Care Personnel in a Multistate Hospital Network — 13 Academic Medical Centers, April–June 2020**. MMWR. Full-text: http://dx.doi.org/10.15585/mmwr.mm6935e2

Many appear to go undetected: among 3,248 HCWs who routinely cared for COVID-19 patients in 13 US academic medical centers from February 1, 2020, 194 (6%) had evidence of previous SARS-CoV-2 infection, with considerable variation by location that generally correlated with community cumulative incidence. Among 194 participants who had SARS-CoV-2 antibodies, 56 (29%) did not recall any symptoms consistent with an acute viral illness in the preceding months and 133 (69%) did not have a previous positive test result demonstrating an acute SARS-CoV-2 infection. Prevalence of SARS-CoV-2 antibodies was lower among personnel who reported always wearing a face covering while caring for patients (6%), compared with those who did not (9%).

Vaccine

Keech C, Albert G, Cho I, et al. **Phase 1–2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine**. NEJM September 2, 2020, Full-text: https://doi.org/10.1056/NEJMoa2026920

NVX-CoV2373 is a recombinant SARS-CoV-2 nanoparticle vaccine composed of trimeric full-length SARS-CoV-2 spike glycoproteins and Matrix-M1 adju-

vant. In 83 participants younger than 60 years of age, two injections of NVX-CoV2373 delivered in the deltoid muscle on day 0 and 21 appeared to be safe. Immune responses exceeded levels in COVID-19 convalescent serum, showing high neutralizing antibody responses and T cells with a predominant Th1 phenotype. Phase 2 has started.

Clinical

Yelin D, Wirtheim E, Vetter P, et al. **Long-term consequences of COVID-19: research needs**. Lancet Inf Dis September 01, 2020. Full-text: https://doi.org/10.1016/S1473-3099(20)30701-5

Weeks and months after the onset of acute COVID-19, people continue to suffer. But how many? In their important comment on the trajectory of people recovering from COVID-19, Dana Yelin addresses the key issues. A clear definition of patient inclusion criteria, a common protocol, and uniform definitions of outcomes and ways to measure them are required.

Buetti N, Patrier J, Le Hingrat Q, et al. **Risk factors for SARS-CoV-2 detection in blood of critically ill patients**. Clinical Infectious Diseases, 02 September 2020. Full-text: https://doi.org/10.1093/cid/ciaa1315

Of 81 blood samples for SARS-CoV-2 detection (from 42 critically ill patients), 30 (37%) were positive. Immunosuppression (OR 12.16, 95% CI 1.74-84.93, p = 0.013) and chronic renal failure (OR 5.98) increased the risk for SARS-CoV-2 detection in the blood. In contrast to previous reports, SARS-CoV-2 detection in the blood was not associated with 6-week mortality.

Comorbidities

Keller N, Chantrel F, Krummel T. **Impact of first-wave COronaVIrus disease 2019 infection in patients on haemoDIALysis in Alsace: the observational COVIDIAL study**. Nephrology Dialysis Transplantation, September 2, 2020. Volume 35, Issue 8, August 2020, Pages 1338–1411. Full-text: https://doi.org/10.1093/ndt/gfaa170

Prospective observational study conducted in eight HD facilities in Alsace, France. Among 1,346 HD patients, 123 tested positive for COVID-19. Case fatality rate was 24%. While patients presented severe forms of the disease, they often displayed atypical symptoms, with the CRP level being highly associated with risk of death.

Treatment

The RECOVERY Collaborative Group. **Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report**. NEJM July 17, 2020. Full-text: https://doi.org/10.1056/NEJMoa2021436

With a press release on June 16, 2020 reporting the results of the UK-based RECOVERY trial, treatment of COVID-19 underwent a major change. In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% *vs* 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% *vs* 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94) but not among those who were receiving no respiratory support at randomization (17.8% *vs* 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55). Why is this mentioned here again? Because the RECOVERY results had a huge impact on other randomized clinical trials (RCTs) around the world. Many trials were stopped prematurely following the press release and are now, unfortunately, underpowered. Three of them were now published in the JAMA:

Dequin PF, Heming N, Meziani F, et al. **Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19A Randomized Clinical Trial**. JAMA September 2, 2020. Full-text: https://doi.org/10.1001/jama.2020.16761

1. CAPE COD trial (France). Multicenter double-blinded RCT, in 149 (290 planned) critically-ill patients admitted to the intensive care unit (ICU) for COVID-19–related acute respiratory failure. The primary outcome, treatment failure on day 21, occurred in 32 of 76 patients (42.1%) in the hydrocortisone group compared with 37 of 73 (50.7%) in the placebo group (p = 0.29).

Tomazini BM, Maia IS, Cavalcanti AB. **Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19. The CoDEX Randomized Clinical Trial**. JAMA September 2, 2020. https://doi.org/10.1001/jama.2020.17021

2. CoDEX (Brazil). Multicenter, open-label RCT in 299 COVID-19 patients (350 planned) with moderate-to-severe ARDS. Twenty mg of dexamethasone intravenously daily for 5 days, 10 mg of dexamethasone daily for 5 days or until ICU discharge, plus standard care (n = 151) or

standard care alone (n = 148). Patients randomized to the dexamethasone group had a mean 6.6 ventilator-free days during the first 28 days vs 4.0 ventilator-free days in the standard care group (difference, 2.26; 95% CI, 0.2-4.38; p = 0.04). There was no significant difference in the prespecified secondary outcomes of all-cause mortality at 28 days, ICU-free days during the first 28 days, mechanical ventilation duration at 28 days, or the 6-point ordinal scale at 15 days.

The Writing Committee for the REMAP-CAP Investigators. **Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19.** JAMA September 2, 2020. https://doi.org/10.1001/jama.2020.17022

3. REMAP-CAP (different countries). In this Bayesian RCT, 384 patients were randomized to fixed-dose (n = 137), shock-dependent (n = 146), and no (n = 101) hydrocortisone. Treatment with a 7-day fixed-dose course or shock-dependent dosing of hydrocortisone, compared with no hydrocortisone, resulted in 93% and 80% probabilities of superiority, respectively, with regard to the odds of improvement in organ support–free days within 21 days. However, due to the premature halt of the trial, no treatment strategy met pre-specified criteria for statistical superiority, precluding definitive conclusions.

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. **Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19. A Meta-analysis**. JAMA September 2, 2020. doi:10.1001/jama.2020.17023

A prospective meta-analysis that pooled data from 7 randomized clinical trials that evaluated the efficacy of corticosteroids in 1703 critically ill patients with COVID-19. The fixed-effect summary odds ratios for the association with mortality were 0.64 (95% CI, 0.50-0.82; p < 0.001) for dexamethasone compared with usual care or placebo, 0.69 (95% CI, 0.43-1.12; p = 0.13) for hydrocortisone and 0.91 (95% CI, 0.29-2.87; p = 0.87) for methylprednisolone, respectively. There was no suggestion of an increased risk of serious adverse events. See also the editorial: Prescott HC, Rice TW. **Corticosteroids in COVID-19 ARDS: Evidence and Hope During the Pandemic.** JAMA 2020, published 2 September. Full-text: https://jamanetwork.com/journals/jama/fullarticle/2770275

Sterne J, Rice T, Diaz J. **Corticosteroids for COVID-19 – New Evidence of Benefit.** Jama Network 2020, published 2 September. Link: https://www.youtube.com/watch?v=XfDWjPxhKcE

A conversation with Jonathan Sterne, Todd Rice and Janet Diaz on the latest research supporting the use of hydrocortisone and dexamethasone for treatment of COVID-19 ARDS.

4 September

Epidemiology

Lordan R, FitzGerald GA, Grosser T. **Reopening schools during COVID-19**. Science 04 Sep 2020: Vol. 369, Issue 6508, pp. 1146. Full-text: https://doi.org/10.1126/science.abe5765

A note from daily practice. On Thursday, September 3, at our infectious disease clinic in Hamburg, Germany, we found a young male teacher (under 40 years old) to be PCR positive. For the previous three days, he had given lectures to at least 12 classes, despite having (mild) symptoms. How to avoid, how to deal with this situation? This editorial gives some answers, recommending different mitigation strategies for the re-opening of schools.

The national COVID-19 outbreak monitoring group. **COVID-19 outbreaks in a transmission control scenario: challenges posed by social and leisure activities, and for workers in vulnerable conditions, Spain, early summer 2020**. Eurosurveillance Volume 25, Issue 35, 03/Sep/2020. Full-text: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.35.2001545

From mid-June to 2 August, excluding single household outbreaks, 673 outbreaks were notified in Spain. There were two main settings where over 55% of active outbreaks (303/551) and over 60% (3,815/6,208) of active outbreak cases originated: First, social settings such as family gatherings or private parties (112 outbreaks, 854 cases), followed by those linked to leisure venues such as bars, restaurants, or clubs (34 outbreaks, over 1,230 cases). Second, occupational settings (representing 20% of all active outbreaks), mainly among workers in the fruit and vegetable sector (31 outbreaks and around 500 cases) and workers at slaughterhouses or meat processing plants (12 outbreaks and around 360 cases).

Immunology

Chen X, Pan Z, Yue S, et al. **Disease severity dictates SARS-CoV-2-specific neutralizing antibody responses in COVID-19**. Sig Transduct Target Ther 5, 180 (2020). Full-text: https://doi.org/10.1038/s41392-020-00301-9

High neutralizing antibody (NAb) capacity in severe cases, no NAbs in asymptomatic patients: In a cohort of 59 recovered patients with various disease severity, Xiangyu Chen and colleagues observed a positive correlation between serum neutralizing capacity and disease severity, revealing the tremendous heterogeneity of SARS-CoV-2-specific NAb responses. Their findings also suggest that the collection of plasma from COVID-19 recovered patients should be restricted to those with moderate to severe symptoms for passive antibody therapy.

Singh M, Bansal V, Feschotte C, et al. **A single-cell RNA expression map of human coronavirus entry factors**. Cell Reports. September 03, 2020. Full-text: https://doi.org/10.1016/j.celrep.2020.108175

Using single-cell transcriptomics across various healthy human tissues, Manvendra Singh and colleagues have profiled 28 SARS-CoV-2 and coronavirus-associated receptors and factors (SCARFs) that facilitate and/or restrict viral entry. Both pro- and anti-viral factors are highly expressed within the nasal epithelium, with potential age-dependent variation. The data provide a valuable resource for future studies of the basic biology and pathology of SARS-CoV-2 and other coronaviruses. However, the authors urge caution not to overinterpret their findings. The main problem is that SCARF expression within and between individuals is bound to be heavily modulated by genetic and environmental factors, including infection by SARS-CoV-2 and other pathogens.

DeKosky BJ. **A molecular trap against COVID-19**. Science 04 Sep 2020: Vol. 369, Issue 6508, pp. 1167-1168. Full-text: https://doi.org/10.1126/science.abe0010

The cell surface peptidase angiotensin-converting enzyme 2 (ACE2) is the primary receptor for the spike (S) fusion protein that facilitates cell entry of SARS-CoV-2. This vasopeptidase is expressed on the surface of epithelial cells in many tissues, including the lung, heart, blood vessels, kidneys, and gastrointestinal tract. Brandon J. DeKosky from the University of Kansas gives a great overview on ACE2-mediated viral entry, the growing understanding of ACE2 interaction and potential methods of blocking it.

Lee W, Ahn JH, Park HH et al. **COVID-19-activated SREBP2 disturbs cholesterol biosynthesis and leads to cytokine storm**. Sig Transduct Target Ther September 3, 2020, 5, 186. Full-text: https://doi.org/10.1038/s41392-020-00292-7

Sterol regulatory element binding proteins (SREBPs) regulate the gene expressions involved in lipid cholesterol biosynthesis. During recent years, it has become increasing clear that SREBPs are involved in immunity/inflammation and several studies have demonstrated the critical importance of SREBP pathway in preventing overproduction of proinflammatory cytokines from macrophages. Wonhwa Lee and colleagues describe here how SREBP-2 is activated by SARS-CoV-2 and show that SREBP-2 can serve as an indicator for severity diagnosis and therapeutic target for preventing a cytokine storm and lung damage in severe COVID-19 patients.

Transmission

Shen Y, Li C, Dong H. **Community Outbreak Investigation of SARS-CoV-2 Transmission Among Bus Riders in Eastern China**. JAMA Intern Med, September 1, 2020. Full-text: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2770172

If you take the bus, choose seats near a window (and open it). On January 19, 2020, 68 individuals (including the source patient) took a bus on a 100-minute round trip to attend a worship event. In total, 24 (35%) received a diagnosis of COVID-19 after the event. The authors were able to identify seats for each passenger and divided bus seats into high-risk and low-risk zones. Passengers in the high-risk zones had moderately but non-significantly higher risk of getting COVID-19 than those in the low-risk zones. On the 3-seat side of the bus, except for the passenger sitting next to the index patient, none of the passengers sitting in seats close to the bus window developed infection. In addition, the driver and passengers sitting close to the bus door also did not develop infection, and only 1 passenger sitting by an operable window developed infection. The absence of a significantly increased risk in the part of the bus closer to the index case suggested that airborne spread of the virus may at least partially explain the markedly high attack rate observed.

Pathology

Borczuk AC, Salvatore SP, Seshan SV et al. **COVID-19 pulmonary pathology: a multi-institutional autopsy cohort from Italy and New York City**. Mod Pathol, September 2, 2020. https://doi.org/10.1038/s41379-020-00661-1

In order to systematically evaluate a large number of lung autopsy specimens from multiple institutions, a detailed examination was performed in a series of 68 cases of COVID-19 positive patients, autopsied in New York City and Italy. A consistent pattern of tracheobronchitis, alveolar injury, and vascular/thrombotic disease was found in patients with frequent co-morbidities such as hypertension and diabetes. Correlation of immunohistochemistry and RNA *in situ* findings and duration of disease was performed in 23 cases. Interestingly, the majority of lung autopsies had evidence of viral infection in the lung during the first two weeks of disease but not beyond this period.

Clinical

Sax P. **An ID Doctor's Confrontation with His Own Case of COVID-19 – An Interview with Dr. Michael Saag**. Open Forum Infectious Diseases 04 September 2020, Volume 7, Issue 9, 1 September 2020. Full-text: https://doi.org/10.1093/ofid/ofaa395

Read how Michael Saag, a well-known HIV researcher from the University of Alabama, Birmingham, was confronted with his own infection, after picking up the virus from his son. Read about his thoughts on the evening of the sixth day, when the cytokine storm started. And how he spent the following 8 days and nights, watching his pulse race like a hawk and knowing that in the next 15 minutes, it might drop below 90 and he would end up in the hospital. Also available as a podcast.

Comorbidities

Mato AR, Roeker LE, Lamanna N, et al. **Outcomes of COVID-19 in patients with CLL: a multicenter international experience**. Blood September 3, 2020, 136 (10): 1134–1143. Full-text: https://ashpublications.org/blood/article/136/10/1134/461426/Outcomes-of-COVID-19-in-patients-with-CLL-a

Among 198 CLL patients diagnosed with symptomatic COVID-19 across 43 international centers, the overall case fatality rate was 33%, although 25% remain admitted. Watch-and-wait and treated subgroups had similar rates of admission, ICU admission, intubation and mortality. Of note, CLL-directed treatment with Bruton tyrosine kinase inhibitors (BTKis, have been proposed

as a potential treatment for COVID-19) at COVID-19 diagnosis did not impact survival, though BTKis were held during the COVID-19 course for most patients.

5 September

Immunology

Sattler A, Angermair S, Stockmann H, et al. **SARS-CoV-2 specific T-cell responses and correlations with COVID-19 patient predisposition.** J Clin Invest. 2020 Aug 24:140965. PubMed: https://pubmed.gov/32833687. Full-text: https://doi.org/10.1172/JCI140965

Are there individual factors that determine the successful (or unsuccessful) mounting of an immune response, deciding between life and death? Could altered T cell function put some patients at risk? Here Arne Sattler et al. analyze cellular responses to three viral proteins and suggest a link between individual patient predisposition with respect to age and comorbidity and impairment of CoV-2 specific Th1-type cellular immunity.

Vaccine

Logunov DY, Dolzhikova IV, Zubkova OV, et al. **Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia.** Lancet 2020, published 4 September. Full-text: https://doi.org/10.1016/S0140-6736(20)31866-3

It was high time to see some data on an "approved" vaccine. See also the comment by Naor Bar-Zeev and Tom Inglesby [Bar-Zeev N, Inglesby T. **COVID-19 vaccines: early success and remaining challenges.** Lancet 2020, published 4 September. Full-text: https://doi.org/10.1016/S0140-6736(20)31867-5].

Fisher KA, Bloomstone SJ, Walter J, et al. **Attitudes Toward a Potential SARS-CoV-2 Vaccine: A Survey of U.S. Adults.** Ann Intern Med 2020, published 4 September. Full-text: https://doi.org/10.7326/M20-3569

In a few months, when we have a vaccine, will people get vaccinated? In a study of 991 participants, Kimberly Fisher and colleagues found that 57.6% of (n = 571) intended to be vaccinated, 31.6% (n = 313) were not sure, and 10.8% (n = 107) did not intend to be vaccinated. Factors independently associated

with vaccine hesitancy (a response of "no" or "not sure") included younger age, Black race, lower educational attainment, and not having received the influenza vaccine in the prior year. The authors conclude that targeted and multipronged efforts will be needed to increase acceptance of a COVID-19 vaccine.

Treatment

Robinson PC, Richards D, Tanner HL, Feldmann M. **Accumulating evidence suggests anti-TNF therapy needs to be given trial priority in COVID-19 treatment.** Lancet 2020, published 4 September. Full-text: https://doi.org/10.1016/S2665-9913(20)30309-X

A major component of deteriorating lung function in patients with COVID-19 is capillary leak, a result of inflammation driven by key inflammatory cytokines: TNF, IL-1, IL-6, and vascular endothelial growth factor. Administration of anti-TNF to patients for treatment of autoimmune disease leads to reductions in all of these key inflammatory cytokines. Now Marc Feldmann and colleagues describe the rationale for trialing anti-TNF therapies for the COVID-19-related hyperinflammation (or cytokine release) syndrome. The authors advocate that few current treatments under investigation have this level of supportive evidence.

Furtado RHM, Berwanger O, Fonseca HA, et al. **Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial.** Lancet 2020, published 4 September. Full-text: https://doi.org/10.1016/S0140-6736(20)31862-6

Hydroxychloroquine (HCl) was useless, the combination HCl + azithromycin was useless and azithromycin alone in the treatment of COVID-19 is useless too. In this randomized clinical trial at 57 centers in Brazil, Otavio Berwanger, Remo Furtado and colleagues enrolled patients who needed oxygen supplementation of more than 4 L/min flow, high-flow nasal cannula, or mechanical ventilation (non-invasive or invasive). 214 were assigned to the azithromycin group and 183 to the control group. Azithromycin had no effect.

See also the comment by Catherine Oldenburg and Thuy Doan [Oldenburg CE, Doan T. **Azithromycin for severe COVID-19.** Lancet 2020, published 4 September. Full-text: https://doi.org/10.1016/S0140-6736(20)31863-8].

Education

Rubin EJ, Baden LR, Morrissey S. **Understanding Antibody Testing in Covid-19.** Audio interview (23:52). N Engl J Med 2020; 383:e85. Access: https://doi.org/10.1056/NEJMe2028992

The editors discuss antibody-based testing for prior infection with SARS-CoV-2, the interpretation of test results, and the implications for vaccine development.

Spanish

If you read Spanish, read Andrino B, Grasso D, Llaneras K. **¿Qué dicen los datos del coronavirus esta semana? El curso arranca con los casos al alza en más de 30 provincias** | La información de la expansión de la COVID-19 en España, actualizada con información de casos, hospitalizados y fallecidos. El primer mapa muestra el ritmo de contagios y la incidencia de casos en cada provincia. Los colores resumen la situación – El País 2020, published every Friday. Full-text: https://elpais.com/sociedad/2020-07-29/el-mapa-del-coronavirus-por-provincias-asi-avanzan-los-casos-en-espana.html?rel=friso-portada

German

If you read German, read **Was Sie über Corona-Schnelltests wissen müssen** | Ein Ergebnis in wenigen Minuten, egal, wo man gerade ist: Werden Schnelltests schon bald den Verlauf der Pandemie verändern? Das sagt die Forschung | Die Zeit 2020, veröffentlicht am 5. September – Von Florian Schumann und Alisa Schröter

6 September

Epidemiology

Barbarossa MV, Fuhrmann J, Meinke JH, et al. **Modeling the spread of COVID-19 in Germany: Early assessment and possible scenarios**. PLoS One. 2020 Sep 4;15(9):e0238559. PubMed: https://pubmed.gov/32886696. Full-text: https://doi.org/10.1371/journal.pone.0238559

Maria Vittoria Barbarossa and colleagues have used complex mathematical models to reproduce data of the early evolution of the COVID-19 outbreak in Germany, taking into account the effect of actual and hypothetical non-pharmaceutical interventions. Interesting finding: a partial (and gradual)

lifting of introduced control measures could soon be possible if accompanied by further increased testing activity, strict isolation of detected cases, and reduced contact to risk groups. However, in scenarios without appropriate measures, simulations predict incredibly high peaks in active cases and alarmingly high numbers of deaths far into the future. If no restrictive measures and interventions were to be (re)introduced, the simulation of the model results in about 32 million total infections and 730,000 deaths over the course of the epidemic, which seems to occur only by the end of the summer 2021 under the assumption that no reliable treatment becomes available before then. Just saying.

Marossy A, Rakowicz S, Bhan A, et al. **A study of universal SARS-CoV-2 RNA testing of residents and staff in a large group of care homes in South London**. J Infect Dis. 2020 Sep 5:jiaa565. PubMed: https://pubmed.gov/32889532. Full-text: https://doi.org/10.1093/infdis/jiaa565

One of the largest studies of care homes in Europe, involving 2,455 individuals tested irrespective of symptoms. Combined nose and throat swab testing for SARS-CoV-2 RNA was carried out in residents and staff across 37 care homes in the London Borough of Bromley across a three-week period. Overall, the point prevalence of SARS-CoV-2 infection was 6.5% with a higher rate in residents (9.0%) than in staff (4.7%). A key finding was the high proportion of asymptomatic infection detected in staff (69%) and residents (51%) with evidence of under-detection of symptoms by care home staff.

Prevention

Lazzari S. **Prevention**. In: COVID Reference 2020.04, 4th updated edition, published 6 September. Full-text: https://covidreference.com/prevention

Lazzari S. **Prevenzione**. In: COVID Reference Italy 2020.04, Quarta edizione attualizzata, pubblicato il 6 settembre 2020. Testo integrale: https://covidreference.com/prevention_it

Stefano Lazzari, specialist in Public Health and Preventive Medicine, gives a 5000-word overview of the most important topic in a world without a COVID-19 vaccine: **Prevention**. See also the PDF of the updated 4th CR Edition (330 pages).

Immunology

Nielsen SC, Yang F, Jackson KJ, et al. **Human B cell clonal expansion and convergent antibody responses to SARS-CoV-2.** Cell Host Microbe September 03, 2020. Full-text: https://doi.org/10.1016/j.chom.2020.09.002

Sandra C.A. Nielsen and colleagues from Stanford analyzed the evolution of the human antibody response to SARS-CoV-2 in detail and over time in 13 COVID-19 patients. They sequenced the immune globulin heavy chain (IGHVs) genes of the B cell antigen receptors (BCRs) and captured the hallmarks of clonal evolution, such as somatic hypermutation (SHM, a programmed process of mutation in the variable regions of immunoglobulin by which the immune system adapts to new foreign elements). After early recruitment of B cells expressing a limited subset of IGHV genes, immune response progresses to a robust polyclonal response of B cells with broader IGHV gene usage and extensive class switching to IgG and IgA sub-classes with limited SHM in the initial weeks of infection. Antibody sequences across SARS-CoV-2 infected patients were convergent, highlighting stereotyped naïve responses to this virus. Notably, some patients had B cell clones expressing convergent IGH to other CoV RBD antibodies. These patients had the highest SARS-CoV RBD antibody IgG levels, suggesting that IGH sequencing data are able to predict the fine specificity of human serological response.

Chan KK, Dorosky D, Sharma P, et al. **Engineering human ACE2 to optimize binding to the spike protein of SARS coronavirus 2.** Science 04 Sep 2020: Vol. 369, Issue 6508, pp. 1261-1265. Full-text: https://doi.org/10.1126/science.abc0870

By using deep mutagenesis, Kui K. Chan and colleagues have identified mutations in angiotensin-converting enzyme 2 (ACE2, critical for binding of SARS-CoV-2) that increase spike binding across the interaction surface. Their mutational landscape provides a blueprint for understanding the specificity of the interaction between ACE2 and spike. Combining mutations gave ACE2 variants with high affinities that rival those of monoclonal antibodies and a stable dimeric variant showed potent SARS-CoV-2 and -1 neutralization *in vitro*. In addition, the similarity to the natural receptor may limit the possibility of viral escape.

Kox M, Waalders NJB, Kooistra EJ, Gerretsen J, Pickkers P. **Cytokine Levels in Critically Ill Patients With COVID-19 and Other Conditions.** JAMA. 2020 Sep 3. PubMed: https://pubmed.gov/32880615. Full-text: https://doi.org/10.1001/jama.2020.17052

Time to rethink the "cytokine storm"? Matthijs Kox and colleagues from Nijmegen have compared 46 COVID-19 patients with ARDS admitted to their ICU, 66 with septic shock with or without ARDS, 30 out-of-hospital cardiac arrest and 62 patients with multiple trauma. Of note, most cytokine levels were significantly lower in COVID-19 than in septic shock and not higher than in OHCA and trauma patients, suggesting that COVID-19 may not be characterized by the cytokine storm.

Van Elslande J, Vermeersch P, Vandervoort K, et al. **Symptomatic SARS-CoV-2 reinfection by a phylogenetically distinct strain**. Clinical Infectious Diseases, September 5. Full-text: https://doi.org/10.1093/cid/ciaa1330

A handful of accounts of reinfection — people who recovered from COVID-19, only to test positive for the disease again later — has fed concerns that immunity might be short-lived. Jan Van Elslande and colleagues from Leuven, Belgium present another case. In this 51-year-old woman, re-infection occurred three months later and the illness was milder than the first episode.

Vaccine

Tostanoski LH, Wegmann F, Martinot AJ, et al. **Ad26 vaccine protects against SARS-CoV-2 severe clinical disease in hamsters**. Nat Med. 2020 Sep 3. PubMed: https://pubmed.gov/32884153. Full-text: https://doi.org/10.1038/s41591-020-1070-6

It's not only protection from infection but also from severe disease. In hamsters, a single immunization with an adenovirus serotype 26 vector-based vaccine expressing a stabilized SARS-CoV-2 spike protein elicited binding and neutralizing antibody responses and protected against weight loss, pneumonia and mortality.

Comorbidities

Meltzer DO, Best TJ, Zhang H, et al. **Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results**. JAMA Netw Open September 3, 2020;3(9):e2019722. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.19722

Is treatment for vitamin D deficiency associated with reductions in the risk of COVID-19? Maybe. In this retrospective cohort study of 489 patients who had a vitamin D level measured in the year before COVID-19 testing, the relative risk of testing positive for COVID-19 was 1.77 times greater for patients with likely deficient vitamin D status compared with patients with likely sufficient

vitamin D status. However, as with all retrospective studies, be aware of confounding: vitamin D deficiency may be a consequence associated with a range of chronic health conditions or behavioral or environmental factors that increase COVID-19 risk.

Severe COVID-19

Schultz MJ, Teng MS, Brenner MJ. **Timing of Tracheostomy for Patients With COVID-19 in the ICU—Setting Precedent in Unprecedented Times**. JAMA Otolaryngol Head Neck Surg September 3, 2020. Full-text: https://doi.org/10.1001/jamaoto.2020.2630

When to perform tracheostomy (and how)? Marcus J. Schultz and colleagues review the current evidence and give a nice overview of misconceptions that predispose to uncontrolled variation in tracheostomy among COVID-19 patients. However, the bottom line is: Decisions on tracheostomy must be personalized; some patients may be awake but cannot yet be extubated (favoring tracheostomy), whereas other patients may have immediate, severe hypoxemia when lying supine or with any period of apnea (favoring deferral).

Charre C, Icard V, Pradat P, et al**. Coronavirus disease 2019 attack rate in HIV-infected patients and in preexposure prophylaxis users**. AIDS. 2020 Oct 1;34(12):1765-1770. PubMed: https://pubmed.gov/32889852. Full-text: https://doi.org/10.1097/QAD.0000000000002639

Caroline Charre analyzed the COVID-19 attack rate in a small group of HIV-infected patients and in PrEP users in the Rhône county, France, and compared it with the general population. No differences were observed.

7 September

Epidemiology

Khan A, Bieh KL, El-Ganainy A, et al. **Estimating the COVID-19 Risk during the Hajj Pilgrimage**. Journal of Travel Medicine, 05 September 2020. Full-text: https://doi.org/10.1093/jtm/taaa157

The Hajj, which is held in Makkah, Kingdom of Saudi Arabia (KSA), attracts around 2.5 million Muslim pilgrims from over 150 countries annually. Based on risk estimates, the Ministry of Hajj and Umra announced a reduction in the number of pilgrims and the exclusion of foreign pilgrims from the 2020 Hajj. This was probably a wise decision: The authors calculate that the exist-

ing number of designated ward and ICU beds in the Hajj areas would be saturated once the total Hajj population exceeds around 10-15% of the previous five years' average.

Nayar KR, Koya SF, Ramakrishnan V, et al. **Call to avert acceleration of COVID-19 from India's Sabarimala pilgrimage of 25 million devotees**. Journal of Travel Medicine, 05 September 2020, taaa153. Full-text: https://doi.org/10.1093/jtm/taaa153

The next problem. The forthcoming Sabarimala annual Hindu pilgrimage of 41 days duration normally held during the months of November to December at the Sabarimala peak in India is attended by (yes, you're reading correctly) an average of 25 million pilgrims. Currently, for routine non-mass gathering visits to Sabarimala, the State Government requires all pilgrims to submit a negative SARS-CoV-2 antigen test result through the online queue system. But this may be impractical and insufficient when 25 million devotees or more congregate during the annual pilgrimage. Unlike the Hajj pilgrimage (see above) which is international, the quota is based on and restricted through a visa process, participation in Sabarimala pilgrimage, a domestic event, is uncoordinated and required no registration for participation until last year. The authors discuss the options.

Moreland A, Herlihy C, Tynan MA, et al. **Timing of State and Territorial COVID-19 Stay-at-Home Orders and Changes in Population Movement - United States, March 1-May 31, 2020**. MMWR Morb Mortal Wkly Rep. 2020 Sep 4;69(35):1198-1203. PubMed: https://pubmed.gov/32881851 . Full-text: https://doi.org/10.15585/mmwr.mm6935a2

People are compliant to mandatory stay-at-home orders. Based on location data from mobile devices, in 97.6% of counties these orders were associated with decreased median population movement after the order start date, relative to the period before the order was implemented.

Immunology

Li W, Schäfer A, Kulkarni SS, et al. **High potency of a bivalent human VH domain in SARS-CoV-2 animal models**. Cell September 04, 2020. Full-text: https://doi.org/10.1016/j.cell.2020.09.007

Antibody domains and fragments such as VH (heavy chain variable domain, 15 kDa) are attractive antibody formats for candidate therapeutics. They may have better tissue penetration compared to full-sized antibodies. Wei Li and

colleagues from Pittsburgh have isolated and screened several VH binders for their affinities, ACE2 competition and stabilities. One of those VHs, ab8, in an Fc (human IgG1, crystallizable fragment) fusion format, showed potent neutralization activity and specificity against SARS-CoV-2 both *in vitro* and in mice and hamsters, possibly enhanced by its relatively small size.

Cañete PF, Vinuesa CG. **COVID-19 makes B cells forget, but T cells remember. Cell, September 04, 2020**. Full-text: https://doi.org/10.1016/j.cell.2020.09.013

Based on two papers recently published in Cell (see below, Sekine et al, Kaneko et al.), Pablo F. Cañete and Carola G. Vinuesa speculate in their editorial that although SARS-CoV-2 may blunt long-lived antibody responses, immune memory might still be achieved through virus-specific memory T cells.

Sekine T, Perez-Potti A, Rivera-Ballesteros O, et al. **Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19.** Cell 2020, published 14 August. Full-text: https://www.cell.com/cell/fulltext/S0092-8674(20)31008-4 (see our presentation on 14 August).

Kaneko N, Kuo HH Boucau J, et al. **Loss of Bcl-6-expressing T follicular helper cells and germinal centers in COVID-19**. Cell August 19, 2020. Full-text: https://doi.org/10.1016/j.cell.2020.08.025 (see our presentation on 20 August).

Clinical

Blackburn J, Yiannoutsos CT, Carroll AE, Halverson PK, Menachemi N. **Infection Fatality Ratios for COVID-19 Among Noninstitutionalized Persons 12 and Older: Results of a Random-Sample Prevalence Study.** Ann Intern Med. 2020 Sep 2. PubMed: https://pubmed.gov/32877214. Full-text: https://doi.org/10.7326/M20-5352

This study combines prevalence estimates from a state-wide random sample with Indiana (US) vital statistics data of confirmed COVID-19 deaths. The overall non-institutionalized IFR in the state was remarkably low: 0.26%. The demographic-stratified IFR varied most by age, race, ethnicity, and sex. Persons younger than 40 years had an IFR of 0.01%; those aged 60 or older had an IFR of 1.71%. Whites had an IFR of 0.18%; non-Whites had an IFR of 0.59%.

Quast T, Andel R, Gregory S, Storch EA. **Years of life lost associated with COVID-19 deaths in the United States**. Journal of Public Health, 07 September 2020, fdaa159. Full-text: https://doi.org/10.1093/pubmed/fdaa159

Years of life lost (YLL) estimates the number of years that those who died would have lived if they had not contracted the specified condition. This study of roughly the first 5 months of the COVID-19 epidemic in the USA, calculating the YLLs by jurisdiction and gender, estimates 1.2 million YLLs due to COVID-19.

Treatment

Squillace N, Pozzi MR, Gustinetti G, et al. **Therapy of SARS-Coronavirus-2 pneumonia: is there an optimal IL-6 cut-off for successful tocilizumab treatment**? Clin Infect Dis. 2020 Sep 4:ciaa1282. PubMed: https://pubmed.gov/32886768 . Full-text: https://doi.org/10.1093/cid/ciaa1282

Nicola Squillace from Milano compared 16 patients who were discharged within 30 days from first tocilizumab (TCZ) dose (group A) vs 16 patients who had prolonged hospitalization or died within 30 days from first TCZ administration (group B). Before and after TCZ, IL-6 levels were markedly higher in group B, suggesting a high burden of inflammation, not sufficiently inhibited by receptor blockade. Larger, controlled trials on TCZ are urgently needed.

De Oliveira B, Mallat J. **Efficacy of Tocilizumab for treatment of severe COVID-19 Pneumonia: more evidence is needed**. Clin Infect Dis. 2020 Sep 4:ciaa1284. PubMed: https://pubmed.gov/32886762 . Full-text: https://doi.org/10.1093/cid/ciaa1284

This is exactly what this comment on another retrospective study is saying. Bruno De Oliveira and Jihad Mallat argue that the current level of evidence supporting the use of TCZ is weak and based on lower-quality studies.

Pregnancy, pediatrics

Pirjani R, Hosseini R, Soori T, et al. **Maternal and neonatal outcomes in COVID-19 infected pregnancies: a prospective cohort study**. Journal of Travel Medicine, 05 September 2020, taaa158. Full-text: https://doi.org/10.1093/jtm/taaa158

In this prospective study, a total of 66 COVID-19 infected pregnant women who were admitted to Arash Hospital in Tehran, Iran from March 1 to Sep 1,

2020, were compared with 133 non-infected pregnant women. No differences were found with regard to preterm birth, low birth weight, gestational diabetes, preeclampsia, intrauterine growth restriction, preterm rupture of membrane, stillbirth, postpartum hemorrhage, neonatal intensive care unit admission and sepsis.

Vietnamese

If you read Vietnamese, read *Khanh Phan Nguyen Quoc, Hà Xuan Nam, Kim Le Thi Anh, et al:* ***CR4 Việt Nam*** *(290 pages).* Published 6 September. Link: https://www.CovidReference.com/vn

Press

Farrar J. **Let's get real. No vaccine will work as if by magic, returning us to 'normal'.** The Guardian 2020, published 6 September. Full-text: https://www.theguardian.com/commentisfree/2020/sep/06/lets-get-real-no-vaccine-will-work-as-if-by-magic-returning-us-to-normal

Jeremy Farrar about accelerating vaccine development without compromising safety, vaccinating priority groups worldwide, and European political leadership.

8 September

Virology

Callaway E. **The coronavirus is mutating — does it matter?** Nature 2020, published 8 September. Full-text: https://www.nature.com/articles/d41586-020-02544-6

Is there evolutionary pressure on the virus to spread better? Maybe later, but not now. At a time when nearly everyone on the planet is susceptible, "every single person that it comes to is a good piece of meat (William Hanage)". Follow Ewen Callaway on a 'Current Knowledge Tour' about SARS-CoV-2 mutations

Immunology

Peng Y, Mentzer AJ, Liu G, et al. **Broad and strong memory CD4⁺ and CD8⁺ T cells induced by SARS-CoV-2 in UK convalescent individuals following COVID-19.** Nat Immunol 2020, published 7 September. Full-text: https://doi.org/10.1038/s41590-020-0782-6

Are SARS-CoV-2-specific $CD8^+$ T cells protective? That's one conclusion of the paper by Tao Dong, Yanchun Peng. After studying T cell memory in 42 patients following recovery from COVID-19 (28 with mild disease and 14 with severe disease) and 16 unexposed donors, the authors found that the proportion of the T cell response attributable to $CD8^+$ (rather than $CD4^+$) T cells was increased in mild cases. They also report a robust and diverse T cell response targeting multiple structural and non-structural regions of SARS-CoV-2 in most resolved cases, irrespective of whether the individual had mild or severe infection (see below, Swadling + Maini 2020). The authors conclude that the identification of non-spike dominant $CD8^+$ T cell epitopes suggests the potential importance of including non-spike proteins such as NP, M and ORFs in future vaccine designs.

See also the comment by Leo Swadling and Mala Maini: [**T cells in COVID-19 — united in diversity.** *Nat Immunol* 2020, published 7 September. Full-text: https://doi.org/10.1038/s41590-020-0798-y] they insist that careful delineation of the frequency, specificity, functionality and durability of T cells during COVID-19 is vital to understanding how to use them as biomarkers and targets for immunotherapies or vaccines.

Vaccine

Jeyanathan M, Afkhami S, Smaill F, et al. **Immunological considerations for COVID-19 vaccine strategies.** Nat Rev Immunol 2020, published 4 September. Full-text: https://doi.org/10.1038/s41577-020-00434-6

In this review, Zhou Xing, Mangalakumari Jeyanathan and colleagues describe the immunological principles of SARS-CoV-2 vaccine development and analyze the current vaccine candidates, their strengths and potential shortfalls. They also make inferences about their chances of success. A hazardous undertaking.

Diagnostics

Ogata AF, Maley AM, Wu C, et al. **Ultra-sensitive Serial Profiling of SARS-CoV-2 Antigens and Antibodies in Plasma to Understand Disease Progression in COVID-19 Patients with Severe Disease.** Clin Chem 2020, published 8 September. Full-text: https://doi.org/10.1093/clinchem/hvaa213

We all know about SARS-CoV-2 PCR and serology tests. What about SARS-CoV-2 *antigen assays*? David Walt, Alana Ogata and colleagues saw the potential to identify active infection and monitor disease progression. Now they describe Single Molecule Array (Simoa) assays to quantitatively detect SARS-CoV-2 spike, S1 subunit, and nucleocapsid antigens in the plasma of 64 COVID-19 positive patients, 17 COVID-19 negative patients, and 34 pre-pandemic patients. They detected SARS-CoV-2 S1 and N antigens in 41 out of 64 COVID-19 positive patients. In these patients, full antigen clearance in plasma was observed a mean of 5 ± 1 days after seroconversion. Importantly, the correlation between patients with high concentrations of S1 antigen and ICU admission (77%) and time to intubation (within one day) was statistically significant. SARS-CoV-2 viral antigens associated with disease progression, such as respiratory failure, in patients with COVID-19? Congratulations!

Crone MA, Priestman M, Ciechonska M, et al. **A role for Biofoundries in rapid development and validation of automated SARS-CoV-2 clinical diagnostics.** Nat Commun 11, 4464 (2020). Full-text: https://doi.org/10.1038/s41467-020-18130-3

Diagnostic testing is essential not only for the identification of infection in patients but also for tracking and containment of viral spread within communities, and daily screening of medical frontline workers. Here, Paul Freemont, Michael Crone and colleagues present a reagent-agnostic automated SARS-CoV-2 testing platform that can be quickly scaled and that is operational in two London hospitals with a testing capacity of 2000 samples per day. The authors report the performance of the overall workflow and detection of SARS-CoV-2 in patient samples using RT-qPCR, CRISPR-Cas13a, and RT-LAMP.

Tang MS, Case JB, Franks CE, et al. **Association between SARS-CoV-2 neutralizing antibodies and commercial serological assays.** Clin Chem 2020, published 7 September. Full-text: https://doi.org/10.1093/clinchem/hvaa211

Are the results of commercially available SARS-CoV-2 serological assays correlated to the presence of neutralizing antibodies? (Remember: methods for the detection and quantification of neutralizing antibodies are relatively low-

throughput and limited to Biosafety Level 3-equipped research laboratories!) Christopher Farnsworth, Mei San Tang and colleagues looked for neutralizing antibodies to SARS-CoV-2 in specimens from 48 patients with PCR-confirmed COVID-19 and a positive result by the Roche Elecsys anti-SARS-CoV-2 (nucleocapsid), Abbott SARS-CoV-2 IgG (nucleocapsid), or EUROIMMUN (EI) SARS-CoV-2 IgG (S1) assays. They found modest correlation, but poor concordance and NPA between the Roche, Abbott and EI SARS-CoV-2 assays for the detection of SARS-CoV-2 neutralizing antibodies.

[Sentence of the day: "The emergence of commercially available serological assays for the detection of antibodies to SARS-CoV-2 has outpaced scientific understanding of their immunological meaning and their value in clinical decision making."]

Clinical

Fernandes Valente Takeda C, Moura de Almeida M, Gonçalves de Aguiar Gomes R, et al. **Case Report: Recurrent Clinical Symptoms of COVID-19 in Healthcare Professionals: A Series of Cases from Brazil.** Am J Trop Med Hyg. 2020 Sep 4. PubMed: https://pubmed.gov/32888288. Full-text: https://doi.org/10.4269/ajtmh.20-0893

Luciano Pamplona de Góes Cavalcanti, Christianne Fernandes Valente Takeda and colleagues describe six cases of recurrent SARS-CoV-2 infection in Brazilian healthcare professionals. The time elapsed between the onset of symptoms in the two episodes ranged from 53 to 70 days. Most recurrences progressed without complications. Unfortunately, sequencing of the virus was not possible.

Society

Horton R. **Covid-19 has exposed the reality of Britain: poverty, insecurity and inequality.** The Guardian 2020, published 8 September. Full-text: https://www.theguardian.com/commentisfree/2020/sep/08/covid-19-britain-poverty-insecurity-inequality-fairer-society

Can only a fairer society can lay the foundations for economic recovery, and build resilience to future crises? Richard Horton, the Lancet Editor-in-Chief, explains why.

Spanish

If you read Spanish, read Zafra I. **Así es la nueva escuela que debe resistir al coronavirus.** El País, publicado el 6 de septiembre. Full-text: https://elpais.com/educacion/2020-09-06/asi-es-la-nueva-escuela-que-debe-resistir-al-coronavirus.html

8,2 millones de alumnos vuelven a las aulas, seis meses después del inicio del cierre escolar. Ignacio Zafra describe 7 situaciones:

1. El camino al colegio
2. Entrada al centro
3. Aulas burbujas y aulas con distancia
4. La semipresencialidad
5. El patio, lugar seguro
6. Un caso de COVID-19 en la escuela
7. El comedor

French

If you read French, read Éditorial. **Tests Covid-19 : une situation préoccupante.** Le Monde 2020, publié le 7 septembre. Texte intégral : https://www.lemonde.fr/idees/article/2020/09/07/tests-covid-19-une-situation-preoccupante_6051284_3232.html

Alors que la hausse des contaminations s'accélère, l'intensification de la stratégie de dépistage des autorités a entraîné de sévères dysfonctionnements, qui montrent que l'ensemble du dispositif a atteint ses limites.

9 September

Epidemiology

Gandhi M, Rutherford GW. F**acial Masking for Covid-19 — Potential for "Variolation" as We Await a Vaccine**. NEJM September 8, 2020. Full-text: https://doi.org/10.1056/NEJMp2026913

In this perspective, Monica Gandhi and George W. Rutherford review the growing evidence that universal facial masking might help reduce the severity of disease and ensure that a greater proportion of new infections are asymptomatic. If this hypothesis is borne out, universal masking could become a form of "variolation" (inoculation) that would generate immunity and thereby slow the spread of the virus.

Vaccine

Phillips N, Cyranoski D, Mallapathy S. **A leading coronavirus vaccine trial is on hold: scientists react**. Nature News September 9, 2020. Full-text: https://www.nature.com/articles/d41586-020-02594-w

This article summarizes what is known about the news of the day: AstraZeneca has reported a case of a transverse myelitis in a person who received AZD1222, an adenoviral-vector vaccine that harnesses a cold-causing 'adenovirus' isolated from chimpanzees. The Phase III trial was "voluntarily paused". However, details of the adverse event, including how serious it was and when it happened, have not been reported. It is still unclear whether the person received the vaccine or placebo. Let's wait for the details.

Shah S, Patel J, Alchaki AR. **Development of Transverse Myelitis after Vaccination. A CDC/FDA Vaccine Adverse Event Reporting System (VAERS) Study, 1985–2017**. Neurology April 10, 2018; 90. Abstract: https://n.neurology.org/content/90/15_Supplement/P5.099

In the meantime, you may read this review of 119 cases of transverse myelitis (TM) occurring after vaccination, reported during a period of over 30 years to the FDA. Although the reporting rate of post-vaccination TM was in the range expected in the general population, the unbalanced distribution of these cases in the first 6 weeks after vaccination suggested that the association between vaccination and some cases may not be coincidental. (For antivaxxers: this is rare!)

Diagnostics

Watson J, Richter A, Deeks J. **Testing for SARS-CoV-2 antibodies**. BMJ September 8, 2020. Full-text: https://doi.org/10.1136/bmj.m3325

This brilliant article offers an approach to antibody testing in individuals with and without symptoms suggestive of current or past SARS-CoV-2 infection. The sensitivity and specificity of antibody tests vary over time and results should be interpreted in the context of clinical history. The authors give a practical overview of the pitfalls of antibody testing and how to communicate risk and uncertainty.

Behrens GM, Cossmann a, Stakov MV, et al. **Strategic Anti-SARS-CoV-2 Serology Testing in a Low Prevalence Setting: The COVID-19 Contact (CoCo) Study in Healthcare Professionals**. Infect Dis Ther 2020 Sep 4. Full-text: https://doi.org/10.1007/s40121-020-00334-1

At Hannover Medical School, Georg Behrens and colleagues have screened 1080 samples from 217 HCP for anti-SARS CoV-2 (S1) IgG. Only one out of eight initial positive results were confirmed by alternative serology tests or showed in vitro neutralisation against live SARS-CoV-2. When assessing anti-SARS-CoV-2 immune status in individuals with low pre-test probability, it may be better to confirm positive results from single measurements by alternative serology tests or functional assays.

Jacobs JL, Mellors JW. **Detection of SARS-CoV-2 RNA in Blood of Patients with COVID-19: What Does It Mean**? Clinical Infectious Diseases, 08 September 2020- Full-text: https://doi.org/10.1093/cid/ciaa1316

Jana Jacobs and John Mellors (among the first researchers in the early 90's who established HIV viral load as a strong predictor of progression) say: we still don't know enough. According to this brief review, the clinical significance of SARS-CoV-2 "RNAaemia" needs to be defined.

Clinical

Sauer F, Dagrenat C, Couppie P, et al. **Pericardial effusion in patients with COVID-19: case series**. European Heart Journal 09 September 2020. Full-text: https://doi.org/10.1093/ehjcr/ytaa287

Three patients aged 51–84 developed a pericarditis related to COVID-19, associated for two of them with a myocarditis. All three were treated with colchicine and their condition improved rapidly.

Pregnancy

Henninghausen L, Lee HK. **Activation of the SARS-CoV-2 receptor Ace2 through JAK/STAT-dependent enhancers during pregnancy**. Cell Rep September 06, 2020. Full-text: https://doi.org/10.1016/j.celrep.2020.108199

The ACE2 gene is expressed in mammary tissue and activated during pregnancy and lactation through intronic enhancers built on the transcription factor STAT5.

Pediatrics

Consiglio CR, Cotugno N, Sardh F, et al. **The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19**. Cell September 06, 2020. Full-text: https://www.cell.com/cell/fulltext/S0092-8674(20)31157-0

Paper of the day, giving important insights into MIS-C. Petter Brodin, Paolo Palma, Nils Landegren, Camila Rosat Consiglio and colleagues compared 41 children with mild SARS-CoV-2 infection with 13 children presenting with MIS-C and 28 children presenting with Kawasaki disease prior to the COVID-19 pandemic. They show that inflammatory response in MIS-C differs from the cytokine storm of severe acute COVID-19, shares several features with Kawasaki disease, but also differs from this condition with respect to T cell subsets, IL-17A and biomarkers associated with arterial damage. Finally, auto-antibody profiling suggests multiple auto-antibodies that could be involved in the pathogenesis of MIS-C.

Ahmed M, Advani S, Moreira A, et al. **Multisystem inflammatory syndrome in children: A systematic review**. EClinical Medicine September 04, 2020. Full-text: https://doi.org/10.1016/j.eclinm.2020.100527

This review included 39 observational studies with 662 MIS-C patients. While 71% of children were admitted to the intensive care unit (22% required mechanical ventilation), only 11 deaths (1.7%) were reported. Fever (100%), abdominal pain or diarrhea (74%), and vomiting (68%) were the most common clinical presentation.

10 September

Prevention

Salas RN, Schultz JM, Solomon CG. **The Climate Crisis and Covid-19 — A Major Threat to the Pandemic Response.** N Engl J Med 2020, 383:e70. Published 10 September. Full-text: https://doi.org/10.1056/NEJMp2022011

Will the climate crisis challenge our response to the COVID-19 pandemic? Yes, it might, reply Renee Salas, James Shultz and Caren G. Solomon. They propose short-term strategies for managing climate-related extreme events during the COVID-19 Pandemic:

1. Extreme events (e.g., hurricanes, wildfires): evacuation and sheltering
2. Extreme heat: remaining at home and in cool locations

Find the details in this *Perspective* article.

Vaccine

Abbasi J. **COVID-19 and mRNA Vaccines-First Large Test for a New Approach.** JAMA. 2020 Sep 3. PubMed: https://pubmed.gov/32880613. Full-text: https://doi.org/10.1001/jama.2020.16866

mRNA vaccines like BNT162b2 from BioNTech and Pfizer and mRNA-1273 by Moderna have 'the potential to be truly transformative' (Drew Weissman) but have never been tested in large-scale human trials. Now both vaccines have entered Phase 3 trials, which together will enroll an estimated 60,000 volunteers. Follow Jennifer Abbasi on a tour of 'proof in the pudding' and mRNA vaccines beyond COVID-19.

Diagnostics

Tromberg BJ, Schwetz, TA, Pérez-Stable EJ, et al. **Rapid Scaling Up of Covid-19 Diagnostic Testing in the United States — The NIH RADx Initiative.** N Engl J Med 2020, published 10 September. Full-text: https://doi.org/10.1056/NEJMsr2022263

Expanding the capacity, throughput, and speed of returning results will contribute to curb the COVID-19 pandemic. Francis Collins, Bruce Tromberg and colleagues describe the US Rapid Acceleration of Diagnostics (RADx) program, its goals, and its focus on underserved populations.

Clinical

Cunningham JW, Vaduganathan M, Claggett BL, et al. **Clinical Outcomes in Young US Adults Hospitalized With COVID-19.** JAMA Intern Med 2020, published 9 September. Full-text: https://doi.org/10.1001/jamainternmed.2020.5313

Does COVID-19 spare young people? Of course not. Here is the proof by Scott Solomon, Jonathan Cunningham and colleagues. They investigated the outcomes of 3222 young adults (age 18 to 34 years) hospitalized for COVID-19. 684 patients (21%) required intensive care, 331 (10%) mechanical ventilation, and 88 patients (2.7%) died. Morbid obesity and hypertension were associated with a greater risk of death or mechanical ventilation. Importantly, young

adults age 18 to 34 years with multiple risk factors (morbid obesity, hypertension, and diabetes) faced risks similar to 8862 middle-aged (age 35-64 years) adults without these conditions.

See also the short comment by Katz MH. **Regardless of Age, Obesity and Hypertension Increase Risks With COVID-19.** JAMA Intern Med 2020, published 9 September. Full-text: https://doi.org/10.1001/jamainternmed.2020.5415 and

Rhee C, Baker M, Vaidya V, et al. **Incidence of Nosocomial COVID-19 in Patients Hospitalized at a Large US Academic Medical Center.** JAMA Netw Open. 2020;3(9):e2020498. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.20498

How adequate are COVID-19 infection control practices in acute care hospitals? Look at nosocomial transmission of SARS-CoV-2! Here, Chanu Rhee et al. analyzed 9149 patients admitted to a large academic medical center, 697 of whom tested positive for SARS-CoV-2 infection. Of these, only 1 case was deemed to be hospital-acquired, most likely from a pre-symptomatic spouse who was visiting daily and diagnosed with COVID-19 before visitor restrictions and masking were implemented. The authors conclude that nosocomial COVID-19 was rare even during the height of the pandemic. At least at Brigham and Women's Hospital, Boston, USA.

Treatment

Cao L, Goreshnik I, Coventry B, et al. **De novo design of picomolar SARS-CoV-2 miniprotein inhibitors.** Science 2020, published 9 September. Full-text: https://doi.org/10.1126/science.abd9909

Targeting the interaction between the SARS-CoV-2 Spike protein and the human ACE2 receptor has become a global sport. The ultimate goal: delivery of a viral inhibitor into the nose and into the respiratory system for treatment of early infection, maybe even for prophylaxis. Now David Baker, Longxing Cao and colleagues report computer-designed mini-proteins (20-fold smaller than a full antibody molecule) that might rival SARS-CoV-2 neutralizing antibodies in its protective actions. The authors believe that in the future it will become possible to generate ultra-high-affinity, pathogen-neutralizing designs within weeks of obtaining a genome sequence.

Comorbidities

Rodgers GP, Gibbons GH. **Obesity and Hypertension in the Time of COVID-19.** JAMA 2020, published 9 September. Full-text: https://doi.org/10.1001/jama.2020.16753

If you are interested in US prevalence and trends for obesity and controlled hypertension from 1999 through 2018, read this editorial about the following two papers:

Ogden CL, Fryar CD, Martin CB, et al. **Trends in obesity prevalence by race and Hispanic origin—1999-2000 to 2017-2018.** JAMA 2020, published 9 September. Full-text: https://doi.org/10.1001/jama.2020.14590
Muntner P, Hardy ST, Fine LJ, et al. **Trends in blood pressure control among US adults with hypertension, 1999-2000 to 2017-2018.** JAMA 2020, published 9 September. Full-text: https://doi.org/10.1001/jama.2020.14545

Education

Rubin EJ, Baden LR, Morrissey S. **Guidelines for Covid-19 Vaccine Deployment.** Audio interview (30:04). N Engl J Med 2020; 383:e88. Access: https://doi.org/10.1056/NEJMe2025927

The editors discuss guidelines for the deployment of potential SARS-CoV-2 vaccines from the CDC and the National Academies, as well as new information on two candidate vaccines.

Society

Tambyraja AL. **New Order, New Hope.** N Engl J Med 2020, published 9 September. Full-text: https://doi.org/10.1056/NEJMp2016142

Try this with your medical students who join you in an operating room. "There's a giant flood coming that will devastate the earth and its inhabitants. You've got a big boat in which to preserve human civilization. There's room for 100 citizens of the world and 5 doctors. Which doctors do you want to take on the boat?" Join Andrew Tambyraja in this game.

Press

Farrar J. **Let's get real. No vaccine will work as if by magic, returning us to 'normal'.** The Guardian 2020, published 6 September. Full-text: https://www.theguardian.com/commentisfree/2020/sep/06/lets-get-real-no-vaccine-will-work-as-if-by-magic-returning-us-to-normal

Jeremy Farrar about accelerating vaccine development without compromising safety, vaccinating priority groups worldwide, and European political leadership.

11 September

Epidemiology

Worobey M, Pekar J, Larsen BB, et al. **The emergence of SARS-CoV-2 in Europe and North America.** Science 2020, published 10 September. Full-text: https://doi.org/10.1126/science.abc8169

The first early interventions successfully prevented early introduction of the virus into Germany and the US. But subsequent introductions found sustained European and North America transmission networks during the first two months of 2020: first in Italy around the end of January, then in Washington State around the beginning of February, followed by New York City later that month. Here, Philippe Lemey, Michael Worobey delineate when widespread community transmission was first established on both continents (see Figure 6) and clarify the period before SARS-CoV-2 establishment when contact tracing and isolation might have been most effective. Delaying COVID-19 outbreaks by even a few weeks in the US and Europe (the public health response to the WA1 case in Washington State, and a particularly impressive response in Germany to an early outbreak), bought crucial time for their own cities, as well as other countries and cities, to prepare for the virus when it finally did arrive. Don't miss this paper.

Virology

Finkel Y, Mizrahi O, Nachshon A, et al. **The coding capacity of SARS-CoV-2.** Nature 2020, published 9 September. Full-text: https://doi.org/10.1038/s41586-020-2739-1

Eight months into the COVID-19 pandemic, do we know everything about SARS-CoV-2? Maybe not, say Noam Stern-Ginossar, Yaara Finkel and colleagues and delineate a new highly complex landscape of translation products, including translation of 23 novel viral open reading frames (ORFs) and revealed the relative production of canonical viral proteins. The functional significance and antigenic potential of these ORFs will soon be explored.

Unchwaniwala N, Ahlquist P. **Coronavirus dons a new crown.** Science 2020, published 11 September. Full-text: https://doi.org/10.1126/science.abe0322

Nuruddin Unchwaniwala and Paul Ahlquist discuss the paper by Montserrat Bárcena, Georg Wolff et al. [Wolff G, Limpens RWAL, Zevenhoven-Dobbe JC, et al. **A molecular pore spans the double membrane of the coronavirus replication organelle.** Science. 2020 Aug 6:eabd3629. PubMed: https://pubmed.gov/32763915. Full-text: https://doi.org/10.1126/science.abd3629] tried to understand how progeny (+)RNA genomes are released from double-membrane vesicles.

Transmission

Bedford T, Greninger AL, Roychoudhury P, et al. **Cryptic transmission of SARS-CoV-2 in Washington state.** Science 2020, published 10 September. Full-text: https://doi.org/10.1126/science.abc0523

Trevor Bedford et al. analyzed 453 SARS-CoV-2 genomes collected between 20 February and 15 March 2020 from infected patients in Washington State, US. The result: most SARS-CoV-2 infections derived from a single introduction in late January or early February 2020 which subsequently spread locally before active community surveillance was implemented. These results, again, highlight the critical need for widespread surveillance for community transmission of SARS-CoV-2.

Prevention

Clipman SJ, Wesolowski AP, Gibson DG, et al. **Rapid real-time tracking of non-pharmaceutical interventions and their association with SARS-CoV-2 positivity: The COVID-19 Pandemic Pulse Study.** Clin Infect Dis. 2020 Sep 2. PubMed: https://pubmed.gov/32877921. Full-text: https://doi.org/10.1093/cid/ciaa1313

Is the impact of non-pharmaceutical interventions (NPIs) on SARS-CoV-2 positivity quantifiable? That's what Sunil Solomon, Steven Clipman and colleagues tried to understand. They surveyed a random sample of more than 1,000 people to examine associations between NPI adoption and self-reported SARS-CoV-2 positivity. SARS-CoV-2 infection was *negatively* associated with strict social distancing (adjusted Odd Ratio for outdoor social distancing [aOR]: 0.10) and *positively* associated with transport use (aOR for ≥ 7 times vs. never: 4.29) and visiting a place of worship (aOR for ≥ 3 times vs. never: 16.0).

Clinical

Meizlish ML, Pine AB, Bishai JD. **A neutrophil activation signature predicts critical illness and mortality in COVID-19.** medRxiv 2020, posted 2 September. Full-text: https://doi.org/10.1101/2020.09.01.20183897

In this pre-published article, Hyung Chun, Alfred Lee, Matthew Meizlish and colleagues carried out proteomic profiling of plasma and analyzed clinical data from over 3,300 patients. Their findings suggest that increased circulating levels of neutrophil activators (G-CSF, IL-8) and neutrophil effectors (RETN, LCN2, HGF, and MMP8) might identify non-critically ill patients who are at risk of becoming critically ill. Attention: this article has not yet been peer reviewed!

Treatment

Editorial. **Curing COVID-19.** Lancet Infect Dis 2020, published 10 September. Full-text: https://doi.org/10.1016/S1473-3099(20)30706-4

In the future, we will have effective therapies but for now we basically have just dexamethasone and hydrocortisone.

Severe COVID

Shah GL, DeWolf S, Lee YJ, et al. **Favorable outcomes of COVID-19 in recipients of hematopoietic cell transplantation.** J Clin Invest. 2020 Sep 8:141777. PubMed: https://pubmed.gov/32897885. Full-text: https://doi.org/10.1172/JCI141777

Can you safely perform hematopoietic cell transplantation in patients with COVID-19? In this retrospective study, Miguel-Angel Perales, Gunjan Shah and colleagues identified 77 SARS-CoV-2 + cellular therapy recipients (Allo = 35, Auto = 37, CAR-T = 5; median time from cellular therapy 782 days. Without active malignancy, overall clinical outcome was favorable. Survival at 30 days was 78%. In the *Discussion*, you'll find information about the lymphocyte populations that are key for the anti-viral response and immune reconstitution.

Economy

Tan-Torres Edejer T, Hanssen O, Mirelman A, et al. **Projected health-care resource needs for an effective response to COVID-19 in 73 low-income and middle-income countries: a modelling study.** Lancet Global Health 2020, published 9 September. Full-text: https://doi.org/10.1016/S2214-109X(20)30383-1

What are the costs of pandemic preparedness if current COVID-19 transmission levels are maintained or scenarios where transmission is increased or decreased by 50%? Here Tessa Tan-Torres Edejer et al. project the number of COVID-19 cases for 73 low-income and middle-income countries (LMICs) with each scenario in both 4- and 12-week timeframes. The cost estimates vary between US$33 and $US52. The authors also show which pillars of strategic preparedness and response drive the costs: clinical case management (54%), maintaining essential services (21%), rapid response and case investigation (14%), and infection prevention and control (9%).

Spanish

If you read Spanish, read Hierro L. **Cómo las multinacionales usan la covid-19 para vender comida basura.** El País 2020, published 10 September. Full-text:
https://elpais.com/elpais/2020/09/08/planeta_futuro/1599575186_749126.html

Mientras que pacientes con obesidad y enfermedades como diabetes, hipertensión y cáncer sufren más el virus SARS-CoV-2, los principales fabricantes mundiales de ultraprocesados, alcohol y bebidas azucaradas usan distintas tácticas y se aprovechan de la pandemia para intentar obtener ganancias. Una discusión completa de Lola Hierro.

French

Vincent F. **Covid-19 : le défi des soignants face au mystère des symptômes persistants.** Le Monde 2020, published 11 September. Full-text : https://www.lemonde.fr/planete/article/2020/09/11/covid-19-le-defi-des-soignants-face-au-mystere-des-symptomes-persistants_6051746_3244.html

Les professionnels de santé sont confrontés à un afflux de patients ayant contracté le nouveau coronavirus lors de la première vague, et qui ont des symptômes persistants malgré des examens cliniques normaux.

Favier S. **Covid-19 : aux Etats-Unis, des scientifiques s'injectent leur propre vaccin sans essai clinique préalable.** Le Monde 2020, published 11 September. Full-text : https://www.lemonde.fr/planete/article/2020/09/11/covid-19-aux-etats-unis-des-scientifiques-s-injectent-leur-propre-vaccin-sans-essai-clinique-prealable_6051812_3244.html

Au cas où vous auriez eu encore des doutes...
☺

German

If you read German, read **Wie gut sind wir vorbereitet?** Die Zeit 2020, published 11 September. Full-text: https://www.zeit.de/2020/38/coronavirus-herbst-winter-gesundheitssystem-schulen

Die kalte Jahreszeit kommt. Das Virus bleibt. Und während Deutschland auf die Entwicklung der Infektionszahlen starrt, stellt sich die Frage danach, wie gut Krankenhäuser, Gesundheitsämter und Schulen gerüstet sind. | Von Andreas Sentker, Ingo Malcher, Marcus Rohwetter, Edda Grabar, Linda Fischer, Viola Kiel, Jeannette Otto, Christian Heinrich, Katharina Menne, Jens Tönnesmann and Mariam Lau.

12 September

Prevention

Silver SR, Li J, Boal WL, Shockey TL, Groenewold MR. **Prevalence of Underlying Medical Conditions Among Selected Essential Critical Infrastructure Workers — Behavioral Risk Factor Surveillance System, 31 States, 2017–2018.** MMWR Morb Mortal Wkly Rep 2020;69:1244–1249. Full-text: http://dx.doi.org/10.15585/mmwr.mm6936a3

Many essential workers are at risk of SARS-CoV-2 infection because their jobs require close contact with patients, the public, or coworkers. Now Sharon Silver et al. analyzed **6 occupation groups:**

1. health practitioners (licensed health care professionals except technicians/technologists)
2. health technicians and technologists
3. other health care support (except home health)
4. patient and personal care aides in the home health industry (home health aides)

5. protective services (correctional officers, police, sheriffs, patrol officers, firefighters, and their supervisors)
6. teachers (preschool through grade 12)

and 7 **industry groups:**

1. ambulatory health care
2. hospitals
3. nursing homes (nursing and residential care facilities)
4. essential retail (grocery/other food stores, alcohol stores, pharmacies, and gas stations)
5. food manufacturing
6. transit (bus service/urban transit, taxi/limousine, postal services, and couriers/messengers)
7. trucking

The results: A high prevalence of underlying medical conditions increases the risks for severe COVID-19 illness among **home health aides, other health care support workers, and nursing home, trucking, and transit industry workers**. The authors recommend that for all essential workers, and particularly those at high risk because of underlying medical conditions, exposure controls should be intensified. In addition, health care access should be optimized to prevent and treat underlying conditions.

Virology

Yang J, Petitjean SJL, Koehler M. **Molecular interaction and inhibition of SARS-CoV-2 binding to the ACE2 receptor.** Nat Commun 11, 4541 (2020). Full-text: https://doi.org/10.1038/s41467-020-18319-6

What do we know about the dynamics of the binding of the spike (S) glycoprotein to the ACE2 receptor at the single-molecule level? Try atomic force microscopy. David Alsteens, Jinsung Yang and colleagues demonstrate, both on model surfaces and on living cells, that the receptor binding domain serves as the binding interface within the S-glycoprotein with the ACE2 receptor and extract the kinetic and thermodynamic properties of this binding pocket. Then they examined how several ACE2-derived peptide fragments could interfere with the S1–ACE2 complex formation. Peptides mimicking the N-terminal helix of the ACE2 receptor showed the best results. New therapeutic candidates?

Transmission

If you read German, read *Anonymous.* **Deutsche Box-Olympiamannschaft mit Coronavirus infiziert.** Die Zeit 2020, published 12 September. Full-text: https://www.zeit.de/sport/2020-09/trainingslager-oesterreich-deutsche-box-olympiamannschaft-coronavirus-infektion-quarantaene

In an unintentional experiment, the German national team of amateur boxers has proved that you can achieve a 100% transmission rate in a small group within days. In a training camp, some of the 18 athletes and 7 coaches and supervisors had cold symptoms four days ago. Now all 25 persons have tested positive for SARS-CoV-2. So far, no serious cases.

Ehrhardt J , Ekinci A , Krehl H , et al. **Transmission of SARS-CoV-2 in children aged 0 to 19 years in childcare facilities and schools after their reopening in May 2020, Baden-Württemberg, Germany.** Euro Surveill. 2020;25(36). Full-text: https://doi.org/10.2807/1560-7917.ES.2020.25.36.2001587

After post-lockdown reopening of schools and childcare facilities in May 2020 in Baden-Württemberg, Germany, child-to-child transmission appeared uncommon. Stefan Brockmann, Jonas Ehrhardt and colleagues anticipate that, with face mask use and frequent ventilation of rooms, transmission rates in schools/childcare facilities could remain low, even if class group sizes were increased.

Lopez AS, Hill M, Antezano J, et al. **Transmission Dynamics of COVID-19 Outbreaks Associated with Child Care Facilities — Salt Lake City, Utah, April–July 2020.** MMWR Morb Mortal Wkly Rep. ePub: 11 September 2020. Full-text: http://dx.doi.org/10.15585/mmwr.mm6937e3

Cuc Tran, Adriana Lopez and colleagues describe 12 children who acquired SARS-CoV-2 infection in child-care facilities. All had mild or no symptoms. They transmitted the virus to at least 12 (26%) of 46 non-facility contacts. The authors conclude that testing children who might not have symptoms could improve control of transmission from child-care attendees to family members.

Fisher KA, Tenforde MW, Feldstein LR, et al. **Community and Close Contact Exposures Associated with COVID-19 Among Symptomatic Adults ≥18 Years in 11 Outpatient Health Care Facilities — United States, July 2020.** MMWR Morb Mortal Wkly Rep 2020;69:1258–1264. Full-text: http://dx.doi.org/10.15585/mmwr.mm6936a5

Eating and drinking and socializing? Everything may well return to normal in about two years. In the meantime, note that adults with a positive SARS-CoV-2 test result were found to be twice as likely to have had dinner at a restaurant than those with negative test results. Kiva Fisher and colleagues conclude that eating and drinking on-site at locations that offer such options might be important risk factors associated with SARS-CoV-2 infection. Bars and restaurants are in for a rough autumn and winter season.

Diagnostics

Fauter M, Viel S, Zaepfel S, et al. **Low glycosylated ferritin is a sensitive biomarker of severe COVID-19.** Cell Mol Immunol (2020). Full-text: https://doi.org/10.1038/s41423-020-00544-0

Clinical

Crameri GAG, Bielecki M, Züst R, et al. **Reduced maximal aerobic capacity after COVID-19 in young adult recruits, Switzerland, May 2020.** Euro Surveill. 2020;25(36):pii=2001542. Full-text: https://doi.org/10.2807/1560-7917.ES.2020.25.36.2001542

Take a cohort of young, predominantly male military recruits (173 men, 26 women) with a median age of 21 years and compare a fitness test after a diagnosis of SARS-CoV-2 infection (median: 45 days; range: 31–58 days) with a baseline test performed 3 months before the infection. What did Jeremy Werner Deuel, Giovanni Crameri and colleagues find? A decrease in maximal aerobic capacity (VO2 max) among COVID-19 convalescent but not among asymptomatic and not-infected recruits. Ca 19% of COVID-19 convalescent recruits showed a decrease of VO2 max of more than 10% as compared with baseline before infection. Never stop following your patients.

Rajpal S, Tong MS, Borchers J, et al. **Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection.** JAMA Cardiol. Published online September 11, 2020. Full-text: https://doi.org/10.1001/jamacardio.2020.4916

Recent studies have raised concerns of myocardial inflammation after recovery from COVID-19, even in asymptomatic or mildly symptomatic patients. Here, Saurabh Rajpal et al. performed a comprehensive cardiac magnetic resonance (CMR) examination including cine, T1 and T2 mapping, extracellular volume fraction, and late gadolinium enhancement (LGE), on a 1.5-T scanner in 26 SARS-CoV-2 infected competitive athletes. Four of them (15%) had CMR findings suggestive of myocarditis and 8 additional athletes (30.8%) exhibited LGE without T2 elevation suggestive of prior myocardial injury. Long-term follow-up is required to understand CMR changes in competitive athletes.

Press

Boseley S. **The Covid-19 vaccine gamble: where bets have been placed and why.** The Guardian 2020, published 11 September. Full-text: https://www.theguardian.com/world/2020/sep/11/the-covid-19-vaccine-gamble-where-bets-have-been-placed-and-why

Wealthy nations have ordered millions of doses of unproven candidate vaccines, but equal access will be the key to beating the virus.

Bland A, Murphy S, Busby M. **'It's world-leadingly bad, is what it is': the week Covid surged again in UK.** The Guardian 2020, published 11 September. Full-text: https://www.theguardian.com/politics/2020/sep/11/its-world-leadingly-bad-is-what-it-is-the-week-covid-surged-again-in-uk

Queues for tests are growing, Tory MPs are agitated and doctors are sceptical about the 'moonshot'.

Spanish

If you read Spanish, read Ansede M. **Ocho meses sin tratamiento curativo contra la covid y sin solución a la vista.** El País 2020, published 12 September. Full-text: https://elpais.com/ciencia/2020-09-11/ocho-meses-sin-tratamiento-curativo-contra-la-covid-y-sin-solucion-a-la-vista.html

La investigación de terapias contra el coronavirus acumula fracasos, pero los especialistas han optimizado sus escasas armas y han logrado reducir la mortalidad.

13 September

Epidemiology

Thomas LJ, Hunag O, Yin F, et al. **Spatial heterogeneity can lead to substantial local variations in COVID-19 timing and severity**. PNAS September 10, 2020. Full-text: https://doi.org/10.1073/pnas.2011656117

Loring J. Thomas and colleagues examined the potential impact of local spatial heterogeneity on COVID-19, modelling the diffusion of SARS-CoV-2 in populations whose contacts are based on spatially plausible network structures. They focus here on the urban context, examining 19 different cities in the US. The main results: The spread of COVID-19 is much "burstier" than in standard epidemiological models, with substantial local disparities in timing and severity and long lags between local outbreaks. Spatial heterogeneity may produce dramatic differences in social exposures to those with the illness, and may stress health care delivery systems in ways that are not well captured by standard models.

Transmission

Bax A, Bax CE, Stadnytskyi V, Anfinrud P. **SARS-CoV-2 transmission via speech-generated respiratory droplets**. Lancet Inf Dis September 11, 2020. Full-text: https://doi.org/10.1016/S1473-3099(20)30726-X

Spit happens. This group published the impressive NEJM video, visualizing speech-generated oral fluid droplets and suggesting that normal speaking might be an important mode of transmission. Here, the four authors vigorously resist the criticism of other authors who argued that the video experiments were unrealistic. They also provide nice new videos showing speech droplets emitted by four people, when speaking the phrase "spit happens" with the face positioned about 10–15 cm behind a thin sheet of intense green laser light.

Anfinrud P, Stadnytskyi V, Bax CE, Bax A. **Visualizing Speech-Generated Oral Fluid Droplets with Laser Light Scattering**. N Engl J Med. 2020 May 21;382(21):2061-2063. PubMed: https://pubmed.gov/32294341. Full-text: https://doi.org/10.1056/NEJMc2007800

New video: https://www.youtube.com/watch?v=ooVjNth4ut8

Immunology

Habel JR, Nguyen TH, van de Sandt CE, et al. **Suboptimal SARS-CoV-2–specific CD8+ T cell response associated with the prominent HLA-A*02:01 phenotype**. PNAS September 10, 2020. Full-text: https://doi.org/10.1073/pnas.2015486117

Jennifer R. Habel and colleagues from Melbourne investigated circulating SARS-CoV-2–specific CD8 T cells from 18 COVID-19 patients. For two HLA-A*02:01 SARS-CoV-2–specific CD8 T cell epitopes, they found that, while *ex vivo* frequencies of responding T cells were approximately five-fold higher than for pre–COVID-19 samples, they were ~10-fold lower than for influenza or EBV-specific memory CD8 T cells. Additionally, SARS-CoV-2–specific CD8 T cells recovered from convalescent COVID-19 patients had an atypically high prevalence of stem cell memory, central memory, and naïve phenotypes. This raises questions concerning the integrity of the epitope-specific CD8 T cell response in COVID-19.

Pathogenesis

Manne BK, Denorme F, Middleton EA, et al. **Platelet gene expression and function in patients with COVID-19**. Blood September 10, 2020, 136 (11): 1317–1329. Full-text: https://doi.org/10.1182/blood.2020007214

Platelet hyperreactivity may contribute to COVID-19 pathophysiology. Bhanu Kanth Manne and colleagues found distinct changes in the gene expression profile of circulating platelets of 25 COVID-19 patients, mainly in pathways associated with protein ubiquitination, antigen presentation, and mitochondrial dysfunction. Though ACE2 was not detected in platelets, mRNA from the SARS-CoV-2 N1 gene was detected in platelets from 2 of 25 COVID-19 patients, suggesting that platelets may take-up SARS-COV-2 mRNA independent of ACE2. Platelet activation and aggregation were increased and could partially be attributed to increased MAPK pathway activation and thromboxane generation.

Bunyavanich S, Grant C, Vicencio A, et al. **Racial/Ethnic Variation in Nasal Gene Expression of Transmembrane Serine Protease 2 (TMPRSS2)**. JAMA September 10, 2020. Full-text: https://doi.org/10.1001/jama.2020.17386

SARS-CoV-2 uses transmembrane serine protease 2 (TMPRSS2) to facilitate viral entry. Nasal TMPRSS2 expression was significantly higher in 47 black individuals compared with 25 Asian, 81 Latino, mixed race/ethnicity, and 123 White individuals based on linear regression. There were no significant asso-

ciations between TMPRSS2 expression and sex, age, or asthma. Higher nasal expression of TMPRSS2 may contribute to the higher burden of COVID-19 among Black individuals.

Diagnostics

Procop GW, Shrestha NK, Vogel S, et al. **A Direct Comparison of Enhanced Saliva to Nasopharyngeal Swab for the Detection of SARS-CoV-2 in Symptomatic Patients**. J Clin Microbiol Sep 2020, JCM.01946-20. Full-text: https://doi.org/10.1128/JCM.01946-20

The next study showing that saliva works as well as NPS (although the overall viral load in saliva is somewhat lower). An "enhanced" saliva specimen (strong sniff, elicited cough, and collection of saliva/secretions) was collected without transport media prior to nasopharyngeal swab from 216 patients with symptoms deemed consistent with COVID-19. There was a 100% positive agreement (38/38 positive specimens) and 99.4% negative agreement (177/178 negative specimens). The one discrepant specimen had the presence of SARS-CoV-2 confirmed in the saliva specimen using an alternate FDA EUA assay. The overall mean difference in crossing threshold (Ct) values for the positive NPS and saliva specimens was -3.61 (remember: low Ct = higher viral load, 95% CI -5.78 to -1.44).

Van Praet JT, Coene A, Van De Moortele K et al. **Comparison of four commercial SARS-CoV-2 IgG immuno-assays in RT-PCR negative patients with suspect CT findings**. Infection (2020). Full-text: https://doi.org/10.1007/s15010-020-01523-3

If PCR is negative, serology testing may be helpful. Jens T. Van Praet and colleagues analyzed 17 patients with suspicious CT findings but (repeatedly) negative nasopharyngeal PCR screening. After disease duration of at least 14 days, 12/17 were found to be positive by different anti-SARS-CoV-2 IgG immunoassays. Clinical specificity was suboptimal in some N-based ELISA kits.

Treatment

Furlow B. **COVACTA trial raises questions about tocilizumab's benefit in COVID-19**. Lancet Rheumatology. September 09, 2020. Full-text: https://doi.org/10.1016/S2665-9913(20)30313-1

At the end of the day, nothing but steroids? On July 29, Hoffmann-La Roche announced disappointing results from its much-anticipated phase 3 COVACTA trial of tocilizumab (TCZ), raising questions about the efficacy of IL-6 block-

ade in patients with severe COVID-19 pneumonia. TCZ did not improve patient mortality, although patients spent roughly a week less in hospital compared with those given placebo (the full results of the trial have not yet been published). Bryant Furlow argues that it may be too early to quit this strategy. Cautious interpretation of COVACTA is needed, in view of the study's broad patient selection criteria and other study design factors. Tocilizumab continues to be evaluated in the RECOVERY trial. Let's hope that it works.

Cheng LL, Guan WJ, Duan CY, et al. **Effect of Recombinant Human Granulocyte Colony–Stimulating Factor for Patients With Coronavirus Disease 2019 (COVID-19) and Lymphopenia**. A Randomized Clinical Trial. JAMA Intern Med September 10, 2020. Full-text: https://doi.org/10.1001/jamainternmed.2020.5503

G-CSF may be helpful in some patients. Lin-ling Cheng and colleagues performed an open-label trial at 3 participating centers in China, randomizing 200 patients with lymphopenia and no comorbidities to usual care alone or usual care plus 3 doses of recombinant human G-CSF (5 μg/ kg, subcu ly at days 0-2). Time to clinical improvement was similar between groups. However, the proportion of patients progressing to acute respiratory distress syndrome, sepsis, or septic shock was lower in the rhG-CSF group (2% vs 15%). Mortality was also lower (2% vs 10%). According to the authors, larger studies that include a broader range of patients with COVID-19 should be conducted.

Patell R, Bogue T, Koshy A, et al. **Postdischarge thrombosis and hemorrhage in patients with COVID-19**. Blood 2020, 136 (11): 1342–1346. Full-text: https://doi.org/10.1182/blood.2020007938

Rushad Patell and colleagues conducted a retrospective observational cohort study of 163 discharged COVID-19 patients not receiving anticoagulation (26% had required ICU care). The cumulative incidence of thrombosis (including arterial and venous events) at day 30 following discharge was 2.5% (95% CI, 0.8-7.6). The cumulative incidence of major hemorrhage was 0.7% and of clinically relevant non-major bleeds was 2.9%, emphasizing the need for randomized data to inform recommendations for universal post-discharge thromboprophylaxis.

Spanish

If you read Spanish, read Aunión JA. **La escuela en la era covid: cómo sacar adelante a la generación que deberá pagar las deudas de la pandemia.** El País 2020, published 12 September. Full-text: https://elpais.com/educacion/2020-09-12/la-escuela-en-la-era-covid-como-sacar-adelante-a-la-generacion-que-debera-pagar-las-deudas-de-la-pandemia.html

Expertos, alumnos y profesores de todo el mundo cuentan su experiencia y esbozan los retos a los que se enfrenta el sistema educativo.

14 September

Lost and Found, or "The Zebra Fish Collection"

Crazy times – we are approaching 50,000 COVID-19 citations on PubMed. These days publishing must go fast, sometimes even faster, sometimes too fast. Here we present 10 examples:

Song W, Li J, Zou N, Guan W, Pan J, Xu W. **Clinical features of pediatric patients with coronavirus disease (COVID-19)**. J Clin Virol. 2020 Jun;127:104377. PubMed: https://pubmed.gov/32361323. Full-text: https://doi.org/10.1016/j.jcv.2020.104377

In asymptomatic children, the "median time to SARS-CoV-2 nucleic acid test (NAT)" positivity once exposed to a family member with confirmed infection was 15.5 days." Which primers did they use?

Sri Santosh T, Parmar R, Anand H, Srikanth K, Saritha M. **A Review of Salivary Diagnostics and Its Potential Implication in Detection of Covid-19**. Cureus. 2020 Apr 17;12(4):e7708. PubMed: https://pubmed.gov/32313785. Full-text: https://doi.org/10.7759/cureus.7708

"The coronavirus disease (Covid-19) pandemic is the biggest challenge and global health crisis for the world since World War Two." A strong statement for a review on salivary swabs.

Bompard F, Monnier H, Saab I, et al. **Pulmonary embolism in patients with Covid-19 pneumonia. Eur Respir J**. 2020 May 12:2001365. PubMed: https://pubmed.gov/32398297. Full-text: https://doi.org/10.1183/13993003.01365-2020

Abstract: "We report an overall 24% (95% CI; 17–32%) cumulative incidence of pulmonary embolism in patients with COVID-19 pneumonia, 50% (30–70%) in ICU and 18% (12–27%) in other patients."

Well, that's it. At this point, the abstract was truncated for the conflict of interest statement. This reads as follows: "Conflict of interest: Dr. BOMPARD has nothing to disclose. Conflict of interest: Dr. MONNIER has nothing to disclose. Conflict of interest: Dr. SAAB has nothing to disclose. Conflict of interest: Dr. TORDJMAN has nothing to disclose. Conflict of interest: Dr. ABDOUL has nothing to disclose. Conflict of interest: Dr. FOURNIER reports personal fees from GENERAL ELECTRIC, non-financial support from GUERBET, personal fees from JANSSEN, from NOVARTIS, outside the submitted work;. Conflict of interest: Dr. SANCHEZ reports personal fees and non-financial support from BTG, grants and personal fees from BOSTON SCIENTIFIC, grants, personal fees and non-financial support from BAYER, grants, personal fees and non-financial support from BMS, personal fees from SANOFI AVENTIS, grants from DAIICHI SANKYO, during the conduct of the study; grants, personal fees and non-financial support from MSD, grants from BOEHRINGER INGELHEIM, outside the submitted work;. Conflict of interest: Dr. LORUT reports non-financial support from Covidien AG, non-financial support from NOVATECH SA, non-financial support from PROXILIO, outside the submitted work;. Conflict of interest: Dr. CHASSAGNON has nothing to disclose. Conflict of interest: Dr. REVEL reports personal fees from MSD FRANCE, non-financial support from GUERBET, outside the submitted work."

Yes, transparency is important. But didn't we want the data?

Coleman JJ, Manavi K, Marson EJ, Botkai AH, Sapey E. **COVID-19: to be or not to be; that is the diagnostic question.** Postgrad Med J. 2020 Jul;96(1137):392-398. PubMed: https://pubmed.gov/32522844. Full-text: https://doi.org/10.1136/postgradmedj-2020-137979

Yawn. To employ or not to employ a Top 10 quotation (gnawed to the bone), that is the question. Sometimes, it may be better "not to".

Lu QB, Jiang WL, Zhang X, et al. **Comorbidities for fatal outcome among the COVID-19 patients: A hospital-based case-control study.** J Infect. 2020 Jul 27:S0163-4453(20)30507-7. PubMed: https://pubmed.gov/32731000. Full-text: https://doi.org/10.1016/j.jinf.2020.07.026

Six comorbidities showed significant associations with the disease outcome, with malignancy exhibiting the highest risk of death, followed by CKD, CVD,

hypertension, CHD, and DM. So many abbreviations that "the comorbidities significantly affected the outcome **of OCVID-19** (*sic*)". [OVID?]

Chandra A, Rao N, Srivastava D. **Dialysis in Northern India during COVD-19 pandemic: trying to maintain a balance**. Int Urol Nephrol. 2020 Jun 1:1-2. PubMed: https://pubmed.gov/32488757. Full-text: https://doi.org/10.1007/s11255-020-02524-9

The journal International Urology and Nephrology (impact 2018: 1.598) publishes original papers on a broad range of topics in urology, nephrology and andrology. "100% of authors who answered a survey reported that they would definitely publish or probably publish in the journal again". 100%! Including these authors and editors (who obviously skipped the proof editing phase) and report striking new findings on a hitherto unknown phenomenon: The **COVD-19** (*sic*) pandemic?

Liao M, Liu Y, Yuan J, et al. **Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19**. Nat Med. 2020 May 12. PubMed: https://pubmed.gov/32398875. Full-text: https://doi.org/10.1038/s41591-020-0901-9

Dear folks from Nature Medicine: We love you. We love your brilliant articles, papers, stories. But why did it take more than ten years to publish an abstract that "proinflammatory monocyte-derived macrophages were abundant in the bronchoalveolar lavage fluid from patients with severe **COVID-9** (*sic*)"? Just asking.

Khalil MI, Salih MA, Mustafa AA. **Broad beans (Vicia faba) and the potential to protect from COVID-19 coronavirus infection**. Sudan J Paediatr. 2020;20(1):10-12. PubMed: https://pubmed.gov/32528195. Full-text: https://doi.org/10.24911/SJP.106-1585398078

Broad beans (Vicia faba), grown in Northern Sudan, proved to incorporate a high content of unsaturated fatty acids and in particular linoleic acid (46.41%). It forms a traditional meal in Sudan and in several Middle East countries. Hence, it is here recommended to be taken as the main meal in combination with sesame oil, as it is commonly practiced in Sudan. Theoretically, it has the potential to protect from COVID-19 coronavirus infections. According to the authors, their "proposal needs to be confirmed by further experimental and clinical research". We agree.

Zhao A, Li Z, Ke Y, et al. **Dietary Diversity among Chinese Residents during the COVID-19 Outbreak and Its Associated Factors**. Nutrients. 2020 Jun 6;12(6):E1699. PubMed: https://pubmed.gov/32517210. Full-text: https://doi.org/10.3390/nu12061699

This study explored the dietary diversity during lockdown in China. Important finding: "Online ordering and delivery services were popular and could serve as a feasible method to obtain and purchase food". We agree (however, no doubt that controlled studies are needed).

Neff EP. **COVID-19 Q&A: Collaborating and coordinating keeps a zebrafish facility going**. Lab Anim (NY). 2020 May;49(5):136-137. PubMed: https://pubmed.gov/32296170. Full-text: https://doi.org/10.1038/s41684-020-0534-0

No, please, last but not least, do not forget the zebrafish in this crisis.

15 September

Immunology

Schäfer R, Spohn G, Bechtel M, et al. **Human Mesenchymal Stromal Cells are resistant to SARS-CoV-2 Infection under Steady State, Inflammatory Conditions and in the Presence of SARS-CoV-2 infected Cells.** Stem Cell Rep September 11, 2020. Full-text: https://doi.org/10.1016/j.stemcr.2020.09.003

Mesenchymal Stem/Stromal Cells (MSC) may ameliorate pulmonary inflammation in ARDS and clinical trials assessing the potential of MSC for COVID-19 treatment are underway. Richard Schäfer and colleagues from Frankfurt show that MSC are resistant to SARS-CoV-2 infection. MSC carry ACE2 and TMPRSS2 only at very low levels on the cell surface and retain their immunomodulation potential supporting their potential applicability for COVID-19 treatment.

Transmission

Luo K, Lei Z, Hai Z, et al. **Transmission of SARS-CoV-2 in Public Transportation Vehicles: A Case Study in Hunan Province, China**. Open Forum Infectious Diseases 13 September 2020, ofaa430. Full-text: https://doi.org/10.1093/ofid/ofaa430

Transmission in a bus. The tour coach was 11.3 meters long and 2.5 meters wide with 49 seats, fully occupied with all windows closed and the ventilation system on during the 2.5-hour trip. Among the 49 passengers (including the driver) who shared the ride with the index person, eight tested positive and eight developed symptoms. The index person sat in the second-to-last row, and the infected passengers were distributed over the middle and rear rows.

Diagnostics

Poon KS, Tee NW. **Caveats of Reporting Cycles Threshold from SARS-CoV-2 Qualitative PCR Assays: A Molecular Diagnostic Laboratory Perspective**. Clinical Infectious Diseases, 15 September 2020, ciaa1399. Full-text: https://doi.org/10.1093/cid/ciaa1399

A note of caution regarding Ct values as a surrogate indicator of 'quantity' in a qualitative PCR assay ("viral load"). Lok-Siong Poon and Nancy Wen-Sim Tee argue that results are not portable across different assays, different gene targets and different specimen types.

Clinical

Kiang MV, Irizarry RA, Buckee CO, et al. **Every Body Counts: Measuring Mortality From the COVID-19 Pandemic**. Ann Int Med, September 11, 2020. Full-text: https://doi.org/10.7326/M20-3100

This brilliant article discusses the current difficulties of disaster death attribution and describes the strengths and limitations of relying on death counts from death certificates, estimations of indirect deaths, and estimations of excess mortality.

Muscatello DJ, McIntyre PB. **Comparing mortalities of the first wave of coronavirus disease 2019 (COVID-19) and of the 1918–19 winter pandemic influenza wave in the USA**. International Journal of Epidemiology, 15 September 2020, dyaa186. Full-text: https://doi.org/10.1093/ije/dyaa186

David J Muscatello and Peter B McIntyre used indirect age standardization to calculate standardized mortality ratios (SMRs) for the 1918–19 winter influenza pandemic wave, with the reference mortality rate being COVID-19 death rates for New York City. They also used mortality data for the 2009 pandemic and the severe 2017–18 season as comparators. All-age COVID-19 mortality rates remain substantially lower than those documented in the 1918–19 influ-

enza pandemic, recognizing that 1918–19 mortality was inflated by lack of now routine treatments. The age-adjusted, all-age mortality rate for the 1918–19 winter wave of the influenza pandemic was 6.7 times higher than COVID-19 cumulative mortality rates to 2 June 2020. In < 45-year-olds, the SMR was 42 times higher for influenza in 1918–19 than for COVID in 2020. However, in ≥ 45-year-olds, the SMR was 44% lower in 1918–19 than for COVID in 2020. COVID-19 mortality was more than 10-fold higher than a severe influenza season, and more than 300-fold higher than the 2009–10 influenza pandemic.

Marshall M. **The lasting misery of coronavirus long-haulers**. Nature September 14, 2020, 585, 339-341. Full-text: https://www.nature.com/articles/d41586-020-02598-6

Doctors are now concerned that the pandemic will lead to a significant surge of people battling lasting illnesses and disabilities. Because the disease is so new, no one knows yet what the long-term impacts will be. This article gives some insights on how some people are still battling crushing fatigue, lung damage and other symptoms of 'long COVID', several months after acute illness.

Zong Y, Gu Y, Yu H, et al. **Thrombocytopenia Is Associated with COVID-19 Severity and Outcome: An Updated Meta-Analysis of 5637 Patients with Multiple Outcomes.** Laboratory Medicine, 15 September 2020, lmaa067. Full-text: https://doi.org/10.1093/labmed/lmaa067

A meta-analysis of 24 studies, showing a weighted incidence of thrombocytopenia in COVID-19 patients of 12.4% (95% CI 7.9%–17.7%). The meta-analysis of binary outcomes (with and without thrombocytopenia) indicated the association between thrombocytopenia and a 3-fold enhanced risk of a composite outcome of intensive care unit admission, progression to acute respiratory distress syndrome, and mortality (odds ratio 3.49; 95% CI, 1.57–7.78).

De Souza L, Nwanji V, Kaur G. **An auspicious triumph of recovery from dialysis-requiring acute kidney injury in COVID-19 in a patient with chronic kidney disease, α1 antitrypsin deficiency, and liver transplant: A case report.** Clin Nephrol. 2020 Sep 10. PubMed: https://pubmed.gov/32909541. Full-text: https://doi.org/10.5414/CN110294

Never give up. Luisa De Souza and colleagues report a unique case of an immunosuppressed 67-year-old female with A1AT deficiency and liver trans-

plant with baseline chronic kidney disease (CKD) stage IIIa, recovering from COVID-19 mediated hypoxic respiratory failure complicated by AKI requiring provisional renal replacement therapy.

Comorbidities

Dandachi D, Geiger G, Montgomery MW, et al. **Characteristics, Comorbidities, and Outcomes in a Multicenter Registry of Patients with HIV and Coronavirus Disease-19**. Clin Inf Dis 2020 Sep 9. Full-text: https://doi.org/10.1093/cid/ciaa1339.

Among 286 HIV-infected patients who were included by US healthcare providers, mortality rates were 9.4% (27/286) overall, 16.5% (27/164) among those hospitalized, and 51.5% (24/47) among those admitted to an ICU. Older age, chronic lung disease, and hypertension were associated with severe outcomes. A lower CD4 count (< 200 cells/mm³) was associated with the primary and secondary endpoints. There was no association between the antiretroviral regimen or lack of viral suppression and predefined outcomes.

Fraser J, Mousley J, Testro A, Smibert OC, Koshy AN. **Clinical Presentation, Treatment, and Mortality Rate in Liver Transplant Recipients With Coronavirus Disease 2019: A Systematic Review and Quantitative Analysis**. Transplant Proc. 2020 Jul 30:S0041-1345(20)32634-8. PubMed: https://pubmed.gov/32891405. Full-text: https://doi.org/10.1016/j.transproceed.2020.07.012

A systematic search was performed for articles published up to June 15, 2020, revealing 223 liver transplant recipients with COVID-19 in 15 studies. Immunosuppression was modified in 32.8% of recipients. The case fatality rate was 19.3%. Dyspnea on presentation, diabetes mellitus, and age 60 years or older were significantly associated with increased mortality ($P \leq 0.01$) with a trend to a higher mortality rate observed in those with hypertension and those receiving corticosteroids at the time of COVID-19 diagnosis.

16 September

Epidemiology

Kissle SM, Kishore N, Prabhu M, et al. **Reductions in commuting mobility correlate with geographic differences in SARS-CoV-2 prevalence in New York City.** Nat Commun 11, 4674 (2020). Full-text: https://doi.org/10.1038/s41467-020-18271-5

SARS-CoV-2 prevalence varied substantially between New York City boroughs between 22 March and 3 May 2020 (for example, Manhattan: 11.3%; South Queens: 26.0%). These differences in prevalence correlate with antecedent reductions in commuting-style mobility between the boroughs. Prevalence was lowest in boroughs with the greatest reductions in morning movements out of and evening movements into the borough.

Rogers JH, Link AC, McCulloch D, et al. **Characteristics of COVID-19 in Homeless Shelters.** Ann Intern Med 2020, published 15 September. Full-text: https://doi.org/10.7326/M20-3799

In this cross-sectional, community-based surveillance study of 14 homeless shelters in King County, Washington, Helen Chu, Julia Rogers and colleagues divided the number of positive cases by the total number of participant encounters, regardless of symptoms. Among 1434 encounters, 29 (2%) cases of SARS-CoV-2 infection were detected across 5 shelters. Eighty-six percent of persons with positive test results slept in a communal space rather than in a private or shared room.

Transmission

Milani GP, Bottino I, Rocchi A, et al. **Frequency of Children vs Adults Carrying Severe Acute Respiratory Syndrome Coronavirus 2 Asymptomatically**. JAMA Pediatr. Published online September 14, 2020. Full-text: https://doi.org/10.1001/jamapediatrics.2020.3595

Early reports suggested that children, often asymptomatic, might be facilitators of SARS-CoV-2 transmission and amplify local outbreaks. Here, Carlo Agostini, Gregorio Milani and colleagues conducted a study among individuals hospitalized in Milan. About 1% of children and 9% of adults without any symptoms or signs of SARS-CoV-2 infection tested positive for SARS-CoV-2. The authors conclude that their data do not support the hypothesis that children are at higher risk of carrying SARS-CoV-2 asymptomatically than adults. Attention: a retrospective analysis.

Prevention

Dubbink JH, Branco TM, Ballah Kamara KB, et al. **COVID-19 treatment in sub-Saharan Africa: if the best is not available, the available becomes the best.** Travel Med Infect Dis. 2020 Sep 11:101878. PubMed: https://pubmed.gov/32927051. Full-text: https://doi.org/10.1016/j.tmaid.2020.101878

Martin Grobusch, Jan Dubbink and colleagues discuss the management of COVID-19 in sub-Saharan Africa, in a context of lack of health care workers and health care infrastructure. The authors conclude that locally accessible resources should be adapted to deliver realistic solutions. The highest possible, yet realistic level of care is better than no care at all.

Biochemistry

Sorokina M, Teixeira MC, Barrera J, et al. **Structural models of human ACE2 variants with SARS-CoV-2 Spike protein for structure-based drug design.** Sci Data 7, 309 (2020). Full-text: https://doi.org/10.1038/s41597-020-00652-6

Understanding the variation of ACE2 in the human population is of critical importance for the development of therapeutic strategies against coronaviruses. Here, the authors built 242 structural models of variants of human ACE2 bound to the receptor binding domain (RBD) of the SARS-CoV-2 surface spike glycoprotein (S protein). They hope that their dataset will help accelerate the design of therapeutics against SARS-CoV-2.

Immunology

Greaney AJ, Starr TN, Gilchuk P, et al. **Complete mapping of mutations to the SARS-CoV-2 spike receptor-binding domain that escape antibody recognition.** bioRxiv 2020, posted 10 September. Full-text: https://doi.org/10.1101/2020.09.10.292078

The authors describe a mutational scanning method to map how all amino-acid mutations in the SARS-CoV-2 spike receptor-binding domain (RBD) could prevent binding by ten human antibodies. The complete escape maps might allow for the design of escape-resistant antibody cocktails–including cocktails of antibodies that compete for binding to the same surface of the RBD but have different escape mutations. A surprise finding: antibody cocktails do not have to target distinct regions of the RBD in order to resist viral escape. The paper has not yet been peer reviewed.

Clinical

Bixler D, Miller AD, Mattison CP, et al. **SARS-CoV-2–Associated Deaths Among Persons Aged <21 Years — United States, February 12–July 31, 2020.** MMWR Morb Mortal Wkly Rep. ePub: 15 September 2020. Full-text: http://dx.doi.org/10.15585/mmwr.mm6937e4

SARS-CoV-2 infection is usually mild in children. Who are those who die nonetheless? Danae Bixler et al. analyzed 121 SARS-CoV-2–associated deaths among persons aged < 21 years. 12 (10%) were infants and 85 (70%) were aged 10–20 years. Hispanic, non-Hispanic Black and non-Hispanic American Indian/Alaskan Native persons accounted for 94 (78%) of these deaths. They conclude that (1) all persons aged < 21 years exposed to SARS-CoV-2 should be monitored for complications and that (2) infants, children, adolescents, and young adults, particularly those from racial and ethnic minority groups at higher risk, those with underlying medical conditions, and their caregivers, need clear, consistent, and developmentally, linguistically, and culturally appropriate COVID-19 prevention messages (e.g., related to mask wearing, physical distancing, hand hygiene).

Society

Editorial. **Scientific American Endorses Joe Biden.** Scientific American 2020, published 15 September. Full-text: https://www.scientificamerican.com/article/scientific-american-endorses-joe-biden/

A species unable to adapt to climate change will either perish or, at best, see their numbers or ecological impact decline. This principle partly applies to human super-organizations such as nations. Here, the editors of the 175-year-old magazine *Scientific American* set an example of promising flexibility. Climate change is currently humanity's greatest challenge, infinitely greater than the comparatively innocuous SARS-CoV-2, but human inventiveness – and flexibility! – should ultimately find a global treatment.

The Lancet COVID-19 Commissioners, Task Force Chairs, and Commission Secretariat. ***Lancet* COVID-19 Commission Statement on the occasion of the 75th session of the UN General Assembly.** Lancet 2020, published 14 September. Full-text: https://doi.org/10.1016/S0140-6736(20)31927-9

The *Lancet* Commission statement defines the four main global challenges posed by the pandemic:

1. Suppressing the pandemic by means of pharmaceutical and non-pharmaceutical interventions;
2. Overcoming humanitarian emergencies, including poverty, hunger, and mental distress, caused by the pandemic;
3. Restructuring public and private finances in the wake of the pandemic;
4. Rebuilding the world economy in an inclusive, resilient, and sustainable way.

Find the proposals for governments, civil society, and UN institutions in this 19-page read for your next weekend.

Journal Feature

Marshall M. **How COVID-19 can damage the brain.** Nature 2020, published 15 September. Full-text: https://www.nature.com/articles/d41586-020-02599-5

Some people who become ill with the coronavirus develop neurological symptoms. Scientists are struggling to understand why.

Spanish

If you read Spanish, read Blanco PR, Clemente Y. **Qué debe hacer un colegio cuando detecta algún caso de covid.** El País, 16 September. Full-text: https://elpais.com/educacion/2020-09-16/que-debe-hacer-un-colegio-si-hay-uno-o-varios-casos-de-covid.html

Sanidad ha elaborado una guía de actuación con pautas para contener la expansión del coronavirus en los centros educativos aunque serán las comunidades autónomas las que elaboren los protocolos concretos.

17 September

Epidemiology / Immunology

Ng DL, Goldgof GM, Shy BR, et al. **SARS-CoV-2 seroprevalence and neutralizing activity in donor and patient blood.** Nat Commun 11, 4698 (2020). https://doi.org/10.1038/s41467-020-18468-8

In April 2020, SARS-CoV-2 seroprevalence was low in the San Francisco Bay Area (0.26% in 387 hospitalized patients; 0.1% in 1,000 blood donors). Charles Y. Chiu, Dianna Ng and colleagues also describe the longitudinal dynamics of immunoglobulin-G (IgG), immunoglobulin-M (IgM), and *in vitro* neutralizing antibody titers in COVID-19 patients. The median time to seroconversion

ranged from 10.3–11.0 days for these 3 assays. The authors provide evidence that seropositive results using SARS-CoV-2 anti-nucleocapsid protein IgG and anti-spike IgM assays are generally predictive of *in vitro* neutralizing capacity.

Virology

Shannon A, Selisko B, Le N. **Rapid incorporation of Favipiravir by the fast and permissive viral RNA polymerase complex results in SARS-CoV-2 lethal mutagenesis.** Nat Commun 11, 4682 (2020). https://doi.org/10.1038/s41467-020-18463-z

The SARS-CoV-2 RNA-dependent-RNA-polymerase (RdRp) is a promising therapeutic target for polymerase inhibitors. Here, Bruno Canard, Ashleigh Shannon and colleagues propose that favipiravir could exert an antiviral effect through lethal mutagenesis. They also suggest that the RdRp complex might be an Achilles heel for SARS-CoV-2. Hopefully SARS-CoV-2 has more than just one Achilles heel.

Transmission

Adam DC, Wu P, Wong JY, et al. **Clustering and superspreading potential of SARS-CoV-2 infections in Hong Kong.** Nat Med (2020). Full-text: https://doi.org/10.1038/s41591-020-1092-0

Dillon Adam, Peng Wu and colleagues identified 4–7 superspreading events (SSEs) across 51 clusters (n = 309 cases) and estimate that 19% (95% confidence interval, 15–24%) of cases seeded 80% of all local transmissions. After controlling for age, transmission in social settings was associated with more secondary cases than households when controlling for age. Social settings are likely to become major battle grounds of coming SARS-CoV-2 waves.

Immunology

Edridge AWD, Kaczorowska J, Hoste ACR, et al. **Seasonal coronavirus protective immunity is short-lasting.** Nat Med (2020). https://doi.org/10.1038/s41591-020-1083-1

If you nurture the secret hope that SARS-CoV-2 immunity will be long-lasting, read this paper by Lia van der Hoek, Arthur Edridge and colleagues. They monitored healthy individuals for more than **35 years**, measuring increases in antibodies to the structural coronavirus capsid protein for each seasonal coronavirus (HCoV-NL63, HCoV-229E, HCoV-OC43 and HCoV-HKU1). Reinfec-

tion with the same seasonal coronavirus occurred frequently by 12 months after infection.

Huang AT, Garcia-Carreras B, Hitchings MDT, et al. **A systematic review of antibody mediated immunity to coronaviruses: kinetics, correlates of protection, and association with severity.** Nat Commun 11, 4704 (2020). https://doi.org/10.1038/s41467-020-18450-4

Derek A. T. Cummings, Angkana Huang and colleagues review the scientific literature on antibody immunity to coronaviruses and propose 5 areas of focus: 1) antibody kinetics, 2) correlates of protection, 3) immunopathogenesis, 4) antigenic diversity and cross-reactivity, and 5) population seroprevalence. Your 12-page review for the weekend.

Diagnostics

Joung J, Ladha A, Saito M, et al. **Detection of SARS-CoV-2 with SHERLOCK One-Pot Testing.** N Engl J Med 2020, published 16 September. Fulltext: https://doi.org/10.1056/NEJMc2026172

CRISPR (clustered regularly interspaced short palindromic repeats)–based diagnostic tests are *en vogue*. Now Feng Zhang, Julia Joung and colleagues describe a simple SARS-CoV-2 test that combines simplified extraction of viral RNA with isothermal amplification and CRISPR-mediated detection. You'll get the results in an hour with minimal equipment. First results (n = 202+/200-): sensitivity 93.1%, specificity 98.5%.

Guglielmi G. **Fast coronavirus tests: what they can and can't do.** Nature 2020, published 16 September. Full-text: https://www.nature.com/articles/d41586-020-02661-2

Rapid antigen tests are designed to tell in a few minutes whether someone is infectious. Will they be game changers?

Guglielmi G. **'We didn't model that people would go to a party if they tested positive'.** Nature 2020, published 11 September. Full-text: https://www.nature.com/articles/d41586-020-02611-y

Develop an RNA-based saliva test, deploy scalable testing as part of a campus's effort to reopen as safely as possible, and build a model to figure out how the epidemic might evolve on the campus. If you forget to model that

some people might choose to go to a party although they know that they are positive, your model won't work. Listen to chemist Martin Burke.

Collateral Effects

Evans ML, Lindauer M, Farrell ME. **A Pandemic within a Pandemic — Intimate Partner Violence during Covid-19.** N Engl J Med 2020, published 16 September. Full-text: https://doi.org/10.1056/NEJMp2024046

Stay-at-home orders led to many workers being furloughed, laid off, or told to work from home. They also left many intimate partner violence victims trapped with their abusers. Megan Evans, Margo Lindauer and Maureen Farrell put the 2020 lockdown experiences into perspective.

Education

Rubin EJ, Baden LR, Morrissey S. **Operation Warp Speed and Covid-19 Therapeutics.** Audio interview (25:54). N Engl J Med 2020; 383:e92. Access: https://doi.org/10.1056/NEJMe2029886

The editors look beyond Operation Warp Speed's work in SARS-CoV-2 vaccine development to its investigation of new preventive and therapeutic agents.

Spanish

If you read Spanish, read Grasso D, Zafra M, Ferrero B, et al. **Covid de ricos, covid de pobres: las restricciones de la segunda ola exponen las desigualdades de Madrid.** El País 2020, published 17 September. Full-text: https://elpais.com/espana/madrid/2020-09-16/covid-de-ricos-covid-de-pobres-las-restricciones-de-la-segunda-ola-exponen-las-desigualdades-de-madrid.html

Daniele Grasso, Mariano Zafra, Berta Ferrero, Miguel Cantón, Fernando Peinado y Juan Diego Quesada explican que el número de contagios es mayor en las zonas más vulnerables, donde más pesarán las posibles limitaciones.

18 September

Virology

Benton DJ, Wrobel AG, Xu P, et al. **Receptor binding and priming of the spike protein of SARS-CoV-2 for membrane fusion.** Nature (2020). https://doi.org/10.1038/s41586-020-2772-0

After investigating the binding of ACE2 to the furin-cleaved form of SARS-CoV-2 S by cryoEM, Steven Gamblin, Donald Benton and colleagues propose mechanistic suggestions for the early stages of SARS-CoV-2 infection of cells. The authors classified ten different molecular species including the unbound, closed spike trimer, the fully open ACE2-bound trimer, and dissociated monomeric S1 bound to ACE2.

Transmission

Meyerowitz EA, Richterman A, Gandhi RT, Sax PE. **Transmission of SARS-CoV-2: A Review of Viral, Host, and Environmental Factors.** Ann Intern Med 2020, published 17 September. Full-text: https://doi.org/10.7326/M20-5008

Eric Meyerowitz et al. present a comprehensive review of the evidence of human SARS-CoV-2 transmission. Their key points:

1. Respiratory transmission is the dominant mode of transmission.
2. Vertical transmission occurs rarely; transplacental transmission has been documented.
3. Cats and ferrets can be infected and transmit to each other, but there are no reported cases to date of transmission to humans; minks transmit to each other and to humans.
4. Direct contact and fomite transmission are presumed but are likely only an unusual mode of transmission.
5. Although live virus has been isolated from saliva and stool and viral RNA has been isolated from semen and blood donations, there are no reported cases of SARS-CoV-2 transmission via fecal–oral, sexual, or bloodborne routes. To date, there is 1 cluster of possible fecal–respiratory transmission.

Prevention

Zeng W, Wang X, Li J, et al. **Association of Daily Wear of Eyeglasses With Susceptibility to Coronavirus Disease 2019 Infection.** JAMA Ophthalmol. Published online September 16, 2020. Full-text: https://doi.org/10.1001/jamaophthalmol.2020.3906

Yiping Wei, Weibiao Zeng and colleagues describe 276 patients from Hubei Province, China, at the beginning of the pandemic. They found that the proportion of the patients who reported routinely wearing eyeglasses more than 8 hours per day (5.8%; 16 of 276 patients) was lower than in the general population (31.5%). The authors suggest that daily wearers of eyeglasses may be less susceptible to COVID-19. See also the comment by Maragakis LL. **Eye Pro-**

tection and the Risk of Coronavirus Disease 2019: Does Wearing Eye Protection Mitigate Risk in Public, Non–Health Care Settings? JAMA Ophthalmol 2020, published 16 September. Full-text: https://doi.org/10.1001/jamaophthalmol.2020.3909

Immunology

Jones D, Helmreich S. **A history of herd immunity.** Lancet 2020, published 19 September. Full-text: https://doi.org/10.1016/S0140-6736(20)31924-3

Do you remember the discussion about herd immunity in March 2020? And one of those who imprudently endorsed the notion who ended up needing intensive care? David Jones and Stefan Helmreich point out that "The language of herd immunity is part of the problem. A herd usually describes domesticated animals, especially livestock. Herd animals like cows, goats, or sheep are sacrificed for human consumption. Few humans want to be part of that kind of herd." Follow them on voyage through history.

Huang M, Lu Q, Zhao H, et al. **Temporal antibody responses to SARS-CoV-2 in patients of coronavirus disease 2019.** Cell Discov 6, 64 (2020). https://doi.org/10.1038/s41421-020-00209-2

Wuxiang Guan, Min Huang and colleagues assessed the longitudinal clinical, laboratory, viral, and immunological data from 366 COVID patients. SARS-CoV-2-specific IgM and IgG antibody titer reached the peak levels at 3–4 weeks. The authors predict IgM to last for about two months while IgG titer might diminish 7 months after symptom onset. Patients with older age or severe disease achieved a higher IgG level than patients of younger age and mild disease.

Xi Y. **Convalescent plasma therapy for COVID-19: a tried-and-true old strategy?** Sig Transduct Target Ther 5, 203 (2020). https://doi.org/10.1038/s41392-020-00310-8

Yongzhi Xi discusses the benefits and challenges of convalescent plasma therapy. One major challenge is the antibody-dependent enhancement (ADE) of viral infection mediated by pre-existing enhancing, non-neutralizing, or sub-neutralizing levels of antibodies from the convalescent plasma administered.

Grant OC, Montgomery D, Ito K, Woods RJ. **Analysis of the SARS-CoV-2 spike protein glycan shield reveals implications for immune recognition.** Sci Rep 10, 14991 (2020). https://doi.org/10.1038/s41598-020-71748-7

Robert Woods, Oliver Grant and colleagues elucidate the role of glycans which might shield from antibody recognition up to 40% of the underlying protein surface of the S glycoprotein trimer. Could glycans alter the innate or adaptive immune response? And, given that glycan microheterogeneity varies between individuals, and depends on many factors, including age, underlying disease and ethnicity, is this a molecular basis for the observed differential susceptibilities among individuals to SARS-CoV-2 infection?

Diagnostics

Gibani MM, Toumazou C, Sohbati M, et al. **Assessing a novel, lab-free, point-of-care test for SARS-CoV-2 (CovidNudge): a diagnostic accuracy study.** Lancet Microbe 2020, published 17 September. Full-text: https://doi.org/10.1016/S2666-5247(20)30121-X

Access to rapid diagnosis is key to the control of the SARS-CoV-2 pandemic. In the future, point-of-care testing could relieve pressure on centralized laboratories and increase overall testing capacity. Here, Graham Cooke, Malick Gibani and colleagues describe a sensitive, specific, and rapid point of care test for the presence of SARS-CoV-2 without laboratory handling or sample pre-processing. Their CovidNudge test 2 had 94% sensitivity and 100% specificity when compared with standard laboratory-based RT-PCR.

Treatment

Liu STH, Lin H, Baine I, et al. **Convalescent plasma treatment of severe COVID-19: a propensity score–matched control study.** Nat Med (2020). https://doi.org/10.1038/s41591-020-1088-9

Retrospective, propensity score–matched case–control study assessment in 39 patients. Patients who received convalescent plasma required somewhat less oxygen; preliminary data might suggest a mortality benefit. The authors conclude that greater numbers and a randomized trial are needed to draw definitive conclusions about the efficacy of convalescent plasma for the treatment of COVID-19.

Spanish

If you read Spanish, read Valdés I. **El 64% de las UCI de Madrid ya están ocupadas por enfermos de covid.** El País 2020, published 18 September. Full-text: https://elpais.com/sociedad/2020-09-17/el-64-de-las-uci-de-madrid-ya-estan-ocupadas-por-enfermos-de-covid.html

La capacidad original de intensivos de la región es de 641 camas... Este jueves, ya había 409 pacientes graves ocupando esas camas: el 63,8%.

19 September

Recovering

After more than six months of studying the scientific COVID-19 literature you might wish to take a break. What if you did something completely different? For example, learning a few Italian words. The Covid Reference team has prepared for you a **fine free package** of audio files and PDFs (even a cellphone app!). Enjoy! The link: http://4Elisa.com/Audio

Epidemiology

Ruktanonchai NW, Floyd JR, Lai S, et al. **Assessing the impact of coordinated COVID-19 exit strategies across Europe.** Science 2020, published 18 September. Full-text: https://doi.org/10.1126/science.abc5096

Ruktanonchai et al. used mobility data from smartphones to estimate movements between administrative units across Europe before and after the implementation of NPIs (non-pharmaceutical interventions) for COVID-19. The result: if countries do not coordinate their NPIs when they relax lockdown, resurgence of disease occurs faster. Remember: collaboration is better than unilateralism. Some people should have thought about that before voting Brexit.

Prevention

CDC 20200918. **Overview of Testing for SARS-CoV-2 (COVID-19).** Centers for Disease Control 2020, updated 18 September. Accessed 19 September. Full-text: https://www.cdc.gov/coronavirus/2019-ncov/hcp/testing-overview.html

As has happened often this year, the US is arriving late. Yesterday, the CDC rectified their recommendations on testing. The update: any person who comes into contact with a known carrier of the virus should be tested for the

virus, even if the person is asymptomatic. See also the comment by McCarthy T. **CDC makes U-turn on Covid testing guidelines that prompted backlash.** The Guardian 2020, published 18 September. Full-text: https://www.theguardian.com/world/2020/sep/18/cdc-guidelines-coronavirus-testing-published-despite-objection-scientists

Chia ML, Chau DHH, Lim KS. **Managing COVID-19 in a Novel, Rapidly Deployable Community Isolation Quarantine Facility.** Ann Intern Med 2020, published 17 September. Full-text: https://doi.org/10.7326/M20-4746

Where would you ideally accommodate low-risk COVID-19 patients? Singapore chose to implement large-scale institutional isolation units, so-called Community Care Facilities (CCFs). These massive-scale isolation facilities are a delicate balance between prioritizing safety for all and ensuring holistic patient care. Read about converting existing public spaces, augmented by telemedicine, 3758 patient admissions and close to 5000 medical consults in one month.

Diagnostics

Norman M, Gilboa T, Ogata AF, et al. **Ultrasensitive high-resolution profiling of early seroconversion in patients with COVID-19.** Nat Biomed Eng (2020). https://doi.org/10.1038/s41551-020-00611-x

The authors describe an assay which uses dye-encoded antigen-coated beads to quantify the levels of immunoglobulin G (IgG), IgM and IgA antibodies against four SARS-CoV-2 antigens - as early as the day of the first positive nasopharyngeal PCR test after symptom onset. The ultra-sensitivity enables plasma to be diluted 4,000×, greatly reducing the degree of non-specific circulating immunoglobulin binding.

Ding X, Yin K, Li Z, et al. **Ultrasensitive and visual detection of SARS-CoV-2 using all-in-one dual CRISPR-Cas12a assay.** Nat Commun 11, 4711 (2020). https://doi.org/10.1038/s41467-020-18575-6

The authors describe an all-in-one dual CRISPR-Cas12a (AIOD-CRISPR) assay which allows all components to be incubated in one pot for CRISPR-based nucleic acid detection, enabling simple, all-in-one molecular diagnostics without the need for separate and complex manual operations. Furthermore, a low-cost hand warmer (~$0.3) was used as an incubator of the AIOD-CRISPR assay to detect clinical samples within 20 min, enabling an instrument-free, visual SARS-CoV-2 detection at the point of care.

Clinical

Lee SW, Yang JM, Moon SY, et al. **Association between mental illness and COVID-19 susceptibility and clinical outcomes in South Korea: a nationwide cohort study.** Lancet Psychiatry 2020, published 17 September. Full-text: https://doi.org/10.1016/S2215-0366(20)30421-1

People with a pre-existing diagnosis of a mental illness are not at increased risk of infection with SARS-CoV-2. This is the result of a large-scale cohort study with propensity score matching using a South Korean national health insurance claims database. Among the patients who tested positive for SARS-CoV-2, after propensity score matching, 109 (8·3%) of 1320 patients without a mental illness had severe clinical outcomes of COVID-19 compared with 128 (9·7%) of 1320 with a mental illness (adjusted OR 1·27, 95% CI 1·01–1·66).

Treatment

Zhou Y, Wang F, Tang J, Nussinov R, Cheng F. **Artificial intelligence in COVID-19 drug repurposing.** Lancet Digital Health 2020, published 18 September. Full-text: https://doi.org/10.1016/S2589-7500(20)30192-8

Drug repurposing (a technique whereby existing drugs are used to treat emerging and challenging diseases such as COVID-19) might reduce development timelines and overall costs. This review introduces guidelines on how to use artificial intelligence (AI) for accelerating drug repurposing.

Co-morbidities

Agren D. **Understanding Mexican health worker COVID-19 deaths.** Lancet 2020, published 19 September. Full-text: https://doi.org/10.1016/S0140-6736(20)31955-3

More health workers seem to have died in Mexico than anywhere else. Why? Limited specialized equipment of poor quality. Working conditions, workplace safety, job continuity (contracts) have all also been cited. Mexico also keeps “a very disaggregated register of the numbers on health worker deaths.”

Pediatrics

Harwood R, Allin B, Jones CE, et al. **A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process.** Lancet Child Adolesc Health 2020, published 18 September. Full-text: https://doi.org/10.1016/S2352-4642(20)30304-7

The document describes the initial investigation of children with suspected pediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS), including blood markers to help determine the severity of disease, an echocardiogram, and a viral and septic screen to exclude other infectious causes of illness. Find more about the recommended treatment options which include intravenous immunoglobulin, methylprednisolone, and biological therapies. These include IL-1 antagonists (eg, anakinra), IL-6 receptor blockers (eg, tocilizumab), and anti-TNF agents (eg, infliximab) for children with Kawasaki disease-like phenotype and non-specific presentations.

French

If you read French, read Gozlan M. **Covid-19 : quand de jeunes enfants ramènent le coronavirus à la maison.** Le Monde 2020, published 17 September. Full-text : https://www.lemonde.fr/blog/realitesbiomedicales/2020/09/17/covid-19-quand-de-jeunes-enfants-ramenent-le-coronavirus-a-la-maison

Les jeunes enfants infectés par le coronavirus au sein de crèches et garderies peuvent transmettre le virus à la maison aux membres de la famille.

Morel S. **Madrid, de nouveau épicentre du Covid-19, limite la liberté de mouvement de 850 000 personnes.** Le Monde 2020, published 19 September. Full-text: https://www.lemonde.fr/international/article/2020/09/19/madrid-de-nouveau-epicentre-du-covid-19-limite-la-liberte-de-mouvement-de-850-000-personnes_6052849_3210.html

A compter de lundi, les rassemblements de plus de six personnes sont interdits dans toute la région, forte de 6,6 millions d'habitants, et la liberté de mouvement est sérieusement restreinte dans 37 quartiers de Madrid et de sa proche banlieue, représentant plus de 850,000 personnes.

20 September

Virology

Yao H, Song Y, Chen Y, et al. **Molecular architecture of the SARS-CoV-2 virus.** Cell 2020, published 14 September. Full-text: https://doi.org/10.1016/j.cell.2020.09.018

How does a virus pack its ~30 kb long single-segmented RNA in a ~80 nm diameter lumen? Here, Sai Li, Lanjuan Li and Hangping Yao report the molecular assembly of the authentic SARS-CoV-2 virus using cryo-electron tomography and subtomogram averaging. From ~2300 intact virions, the authors provide molecular insights into the structures of spikes in the pre- and post-fusion conformations, the ribonucleoproteins and how they assemble on the authentic virus. They also analyzed the detailed glycan compositions of the native spikes.

Yurkovetskiy L, Wang X, Pascal KE, et al. **Structural and Functional Analysis of the D614G SARS-CoV-2 Spike Protein Variant.** Cell 2020, published 15 September. Full-text: https://doi.org/10.1016/j.cell.2020.09.032

The SARS-CoV-2 spike (S) protein variant D614G supplanted the ancestral virus worldwide in a matter of months, suggesting that the mutation confers a replication advantage. Here, the authors show that D614G is more infectious than the ancestral form on human lung cells, colon cells, and on cells rendered permissive by ectopic expression of human ACE2 or of ACE2 orthologs, while not altering S protein synthesis, processing, or incorporation into SARS-CoV-2 particles. Remember that the D614G variant is not associated with more severe COVID-19.

Transmission

Khanh NC, Thai PQ, Quach H-L, Thi NA-H, Dinh PC, Duong TN, et al. **Transmission of severe acute respiratory syndrome coronavirus 2 during long flight.** Emerg Infect Dis 2020, published 18 September. Full-text: https://doi.org/10.3201/eid2611.203299

The authors report a cluster of cases among passengers on VN54 (Vietnam Airlines), a 10-hour commercial flight from London to Hanoi on March 2, 2020. Among the 16 persons in whom SARS-CoV-2 infection was detected, 12 (75%) were passengers seated in business class along with the only symptomatic person (attack rate 62%). The authors find that blocking middle seats, currently recommended by the airline industry, may in theory prevent some

in-flight transmission events but seems to be insufficient to prevent superspreading events. They conclude that the risk for on-board transmission of SARS-CoV-2 during long flights is real and has the potential to cause COVID-19 clusters of substantial size, even in business class–like settings with spacious seating arrangements well beyond the established distance used to define close contact on airplanes.

(Note that at the time, March 2, the use of face masks was not mandatory on airplanes or at airports, and there was no social distancing on the aircraft.)

Immunology

Piccoli L, Park YJ, Tortorici MA, et al. **Mapping neutralizing and immunodominant sites on the SARS-CoV-2 spike receptor-binding domain by structure-guided high-resolution serology.** Cell 2020, published 16 September. Full-text: https://doi.org/10.1016/j.cell.2020.09.037

David Veesler, Luca Piccoli and colleagues provide an extensive analysis of Ab responses to SARS-CoV-2 S, 526 RBD (receptor-binding domain) and N in more than 600 SARS-CoV-2 infected individuals with different clinical outcomes. They found that the SARS-CoV-2 RBD is immunodominant, accounting for 90% of serum neutralizing activity and that RBD antibodies decline with a half-life of ~50 days. They also identified two major receptor-binding motif antigenic sites. The authors are confident that their results "will guide the design of COVID-19 vaccines and therapeutics".

Rydyznski Moderbacher C, Ramirez SI, Dan JM, et al. **Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity.** Cell 2020, published 16 September. Full-text: https://doi.org/10.1016/j.cell.2020.09.038

Age is a disturbing risk factor in SARS-CoV-2 infection. Here, Shane Crotty, Alessandro Sette, Carolyn Rydyznski Moderbacher and colleagues present a combined examination of all three branches of adaptive immunity at the level of SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T cell and neutralizing antibody responses. They confirm that the coordination of SARS-CoV-2 antigen-specific responses is disrupted in individuals > 65 years old. Scarcity of naive T cells was also associated with ageing and poor disease outcomes.

Sun Y, Kobe B, Qi J. **Targeting multiple epitopes on the spike protein: a new hope for COVID-19 antibody therapy.** Sig Transduct Target Ther 5, 208 (2020). https://doi.org/10.1038/s41392-020-00320-6

Do you remember our July 23 entry for Liu L, Wang P, Nair MS, et al. [**Potent neutralizing antibodies directed to multiple epitopes on SARS-CoV-2 spike.** Nature 2020, published 22 July. Full-text: https://doi.org/10.1038/s41586-020-2571-7]? Find now a detailed description of the paper. The authors conclude that the variety of potent neutralizing monoclonal antibodies against SARS-CoV-2 "inspires optimism that we will be able to find highly effective and safe candidates for clinical treatment of the COVID-19". Effective mAb cocktail treatments on the horizon?

Clinical

Westblade LF, Brar G, Pinheiro LC, et al. SARS-CoV-2. **Viral Load Predicts Mortality in Patients with and Without Cancer Who Are Hospitalized with COVID-19.** Cancer Cell 2020, published 15 September. Full-text: https://doi.org/10.1016/j.ccell.2020.09.007.

The predictive value of viral load? The authors measured SARS-CoV-2 viral load in nasopharyngeal swab specimens of 100 patients with cancer and 2914 without cancer who were admitted to three New York City hospitals. Overall, the in-hospital mortality rate was 38.8% among patients with a high viral load, 24.1% among patients with a medium viral load, and 15.3% among patients with a low viral load ($p < 0.001$). Similar findings were observed in patients with cancer. The authors also found that patients with hematologic malignancies had higher median viral loads than patients without cancer. They conclude that viral load measurements might be a valuable tool for clinicians in the care of hospitalized patients with COVID-19.

White-Dzuro G, Gibson LE, Zazzeron L, et al. **Multisystem effects of COVID-19: A concise review for practitioners.** Postgrad Med. 2020 Sep 14. PubMed: https://pubmed.gov/32921198. Full-text: https://doi.org/10.1080/00325481.2020.1823094

The authors review the multi-system complications of COVID-19 and treatment strategies to improve the care of critically ill COVID-19 patients. They stress that clinicians should be aware of the multi-system impact of the disease so that care can be focused on the prevention of end-organ injuries to potentially improve clinical outcomes.

Pregnancy

Zhou Y, Shi H, Liu Z, et al. **The prevalence of psychiatric symptoms of pregnant and non-pregnant women during the COVID-19 epidemic.** Transl Psychiatry 10, 319 (2020). https://doi.org/10.1038/s41398-020-01006-x

Can pregnancy shield women from depression and anxiety in these COVID times? The authors enrolled 544 pregnant women and 315 non-pregnant women. In this study, 5.3%, 6.8%, 2.4%, 2.6%, and 0.9% of pregnant women were identified to have symptoms of depression, anxiety, physical discomfort, insomnia, and post-traumatic stress disorder (PTSD), respectively. However, the corresponding prevalence rates among non-pregnant women were 17.5%, 17.5%, 2.5%, 5.4%, 5.7%, respectively. In China, pregnant women seem to have an advantage in facing mental problems caused by COVID-19.

Society

Adebisi YA, Alaran AJ, Akinokun RT, Micheal AI, Ilesanmi EB, Lucero-Prisno DE. **Sex Workers Should not Be Forgotten in Africa's COVID-19 Response.** Am J Trop Med Hyg. 2020 Sep 15. PubMed: https://pubmed.gov/32940202. Full-text: https://doi.org/10.4269/ajtmh.20-1045

Sex workers in Africa are among one of the vulnerable populations, face high levels of stigma and discrimination (and their clients?), are excluded from the government safety net and cannot observe physical distancing and other precautionary measures. A two-page perspective.

French

If you read French, read **Entre mort et vie, la zone grise du Covid-19.** Le Monde 2020, published 19 September. Full-text: https://www.lemonde.fr/idees/article/2020/09/19/entre-mort-et-vie-la-zone-grise-du-covid-19_6052842_3232.html

Alors que les bilans et les projections s'attachent à dénombrer cas, hospitalisations et décès, ils laissent dans l'ombre une dimension majeure de la maladie : ses formes longues et les séquelles associées.

21 September

Vaccinate for seasonal influenza | By Stefano Lazzari

Several authors (Richmond 2020, Jaklevic 2020, Singer 2020, Rubin 2020, Maltezoua 2020) and public health agencies are recommending expanding seasonal flu vaccination in the context of the COVID-19 pandemic. This follows concerns about the potential "double epidemic" of COVID-19 and seasonal flu during the winter months (Balakrishnan 2020, Gostin 2020).

Read more (including 26 references) at https://covidreference.com/top-10-september-21.

22 September

Epidemiology

Mecenas P, Bastos RTDRM, Vallinoto ACR, Normando D. **Effects of temperature and humidity on the spread of COVID-19: A systematic review**. PLoS One. 2020 Sep 18;15(9):e0238339. PubMed: https://pubmed.gov/32946453. Full-text: https://doi.org/10.1371/journal.pone.0238339

Don't count on the weather. This systematic review of seventeen studies found that cold and dry conditions were potentiating factors on the spread of the virus. Warm and wet climates seem to reduce the spread of COVID-19. However, these variables alone could not explain most of the variability in disease transmission. Therefore, the countries most affected by the disease should focus on health policies, even those with climates less favorable to the virus.

Immunology

Busch MH, Timmermans SAMEG, Nagy M, et al. **Neutrophils and Contact Activation of Coagulation as Potential Drivers of Covid-19**. Circulation. 2020 Sep 18. PubMed: https://pubmed.gov/32946302. Full-text: https://doi.org/10.1161/CIRCULATIONAHA.120.050656

Pieter van Paassen and colleagues from Maastricht, Netherlands have performed a comprehensive analysis on the intrinsic pathway of coagulation to characterize its role in COVID-19. By simultaneously studying potential triggers of the intrinsic pathway in 228 patients, the authors were able to identify neutrophils, neutrophil extracellular traps (NETs), and complement activation as potential drivers of this complex immuno-thrombotic disease. This

indicates that hypercoagulability and thrombotic events are driven by NETosis, contact activation, and complement. The triangular relationship with its multiple amplifying feedback loops emphasizes therapeutic multiple-target strategies to effectively dampen the immuno-thrombotic response.

Peiris M, Leung GM. **What can we expect from first-generation COVID-19 vaccines?** Lancet September 21, 2020. Full-text: https://doi.org/10.1016/S0140-6736(20)31976-0

Not much. In their important comment, Malik Peiris and Gabriel M Leung suggest that we cannot assume COVID-19 vaccines, even if shown to be effective in reducing severity of disease, will reduce viral transmission comparably. The notion that COVID-19-vaccine-induced population immunity will allow a return to pre-COVID-19 "normalcy" might be based on illusory assumptions.

Saad-Roy M, Wagner CE, Baker RE, et al. **Immune life history, vaccination, and the dynamics of SARS-CoV-2 over the next 5 years**. Science 21 Sep 2020: eabd7343. Full-text: https://doi.org/10.1126/science.abd7343

Modelling different protective efficacies and durations of the adaptive immune response to SARS-CoV-2, as well as its interactions with vaccines and non-pharmaceutical interventions, this group from Princeton found that variations in the immune response to primary SARS-CoV-2 infections and a potential vaccine could lead to dramatically different immune landscapes and burdens of critically severe cases, ranging from sustained epidemics to, *attention!*, near elimination. According to these models, even with imperfect vaccine immunity and moderate vaccination rates, a vaccination may accelerate pandemic control.

Diagnostics

Patel MM, Thornburg NH, Stubblefield WB, et al. **Change in Antibodies to SARS-CoV-2 Over 60 Days Among Health Care Personnel in Nashville, Tennessee**. JAMA September 17, 2020. Full-text: https://doi.org/10.1001/jama.2020.18796

Your COVID pass expires after a few weeks: among 19 health care workers who had anti–SARS-CoV-2 antibodies detected at baseline, 8 (42%) had antibodies that persisted above the seropositivity threshold at 60 days, whereas 11 (58%) became seronegative. The consistency in decline in the signal-to-threshold ratio regardless of the baseline ratio and a higher proportion of

asymptomatic participants becoming seronegative support the interpretation of a true decline over a 2-month period rather than an artifact of assay performance.

Clinical

Miller J, Fadel RA, Tang A, et al. **The Impact of Sociodemographic Factors, Comorbidities and Physiologic Response on 30-day Mortality in COVID-19 Patients in Metropolitan Detroit**. Clin Infect Dis. 2020 Sep 18:ciaa1420. PubMed: https://pubmed.gov/32945856. Full-text: https://doi.org/10.1093/cid/ciaa1420

In this large cohort of 3633 COVID-19 patients, those with comorbidities, advanced age, and physiological abnormalities on presentation had higher odds of death. Of note, disparities in income or source of health insurance were not associated with outcomes.

Neilan AM, Losina E, Bangs AC, et al. **Clinical Impact, Costs, and Cost-Effectiveness of Expanded SARS-CoV-2 Testing in Massachusetts**. Clin Infect Dis. 2020 Sep 18:ciaa1418. PubMed: https://pubmed.gov/32945845. Full-text: https://doi.org/10.1093/cid/ciaa1418

Anne M. Neilan and colleagues projected the clinical and economic impact of alternative testing strategies on COVID-19 incidence and mortality in Massachusetts using a microsimulation model. Four testing strategies were compared: 1) PCR testing only for patients with severe or critical symptoms warranting hospitalization; 2) PCR for any COVID-19-consistent symptoms (symptomatic), with self-isolation if positive; 3) Symptomatic and one-time PCR for the entire population; and, 4) Symptomatic with monthly re-testing for the entire population. Testing people with any COVID-19-consistent symptoms would be cost-saving compared to testing only those whose symptoms warrant hospital care. *Expanding PCR testing to asymptomatic people would decrease infections, deaths, and hospitalizations. Despite modest sensitivity, low-cost, repeat screening of the entire population could be cost-effective in all epidemic settings.*

Marinho PM, Nascimento H, Marcos AAA, Romano AC, Belfort R Jr. **Seeking clarity on retinal findings in patients with COVID-19 - Authors' reply**. Lancet. 2020 Sep 19;396(10254):e40. Full-text: https://doi.org/10.1016/S0140-6736(20)31912-7

Paula M. Marinho and colleagues reply to major concerns (5 letters) that their initial reports on retinal findings in COVID-19 patients (hyper-reflective le-

sions at the level of the ganglion cell and inner plexiform layers) were, in fact, cuts through normal retinal blood vessels. To ensure that this was not the case, the authors have excluded vertical optical coherence tomography (OCT) scans and used only horizontal scans to avoid vessel crossings. Since their initial report, they have also examined more than 150 patients, demonstrating an absence of blood flow within the retinal lesions of "many" patients, differentiating these lesions from blood vessels with active blood flow.

Treatment

Gentrey CA, Humphrey MB, Thind SK, et al. **Long-term hydroxychloroquine use in patients with rheumatic conditions and development of SARS-CoV-2 infection: a retrospective cohort study**. Lancet Rheumatology September 21, 2020. Full-text: https://doi.org/10.1016/S2665-9913(20)30305-2

Did you expect that patients with rheumatological conditions receiving chronic hydroxychloroquine therapy would be at less risk of developing SARS-CoV-2 infection than those not receiving hydroxychloroquine? No? Then you are right. The incidence did not differ between patients with or without hydroxychloroquine in this large cohort (31 of 10,703 vs 78 of 21,406; odds ratio 0.79, 95% CI 0.52–1.20, p = 0.27).

Pediatrics

Flaherman VJ, Afshar Y, Boscardin J, et al. **Infant Outcomes Following Maternal Infection with SARS-CoV-2: First Report from the PRIORITY Study**. Clin Infect Dis. 2020 Sep 18:ciaa1411. PubMed: https://pubmed.gov/32947612. Full-text: https://doi.org/10.1093/cid/ciaa1411

Among 263 initial infants enrolled in the PRIORITY study, adverse outcomes, including preterm birth, NICU admission, and respiratory disease did not differ between those born to mothers testing positive for SARS-CoV-2 (n=184) and those born to mothers testing negative (n=79). No pneumonia or lower respiratory tract infection was reported through 6-8 weeks of age. Among infants born to mothers who tested positive for SARS-CoV-2, the estimated incidence of a positive infant was low at 1.1% (0.1%, 4.0%), and infants had minimal symptoms. Overall, these results are reassuring and suggest that infants born to mothers infected with SARS-CoV-2 generally do well in the first 6-8 weeks after birth.

23 September

Epidemiology

Lash RR, Donovan CV, Fleischauer AT, et al. **COVID-19 Contact Tracing in Two Counties — North Carolina, June–July 2020**. MMWR Morb Mortal Wkly Rep. ePub: 22 September 2020. Full-text: http://dx.doi.org/10.15585/mmwr.mm6938e3

Despite aggressive efforts by health departments, many COVID-19 patients do not report contacts, and many contacts cannot be reached. Staff members in North Carolina, US have investigated 5514 (77%) persons with COVID-19 in Mecklenburg County and 584 (99%) in Randolph County: during periods of high COVID-19 incidence, 48% and 35% of patients reported no contacts, and 25% and 48% of contacts were not reached. Median interval from index patient specimen collection to contact notification was 6 days. Improved timeliness of contact tracing, community engagement, and community-wide mitigation are needed to reduce SARS-CoV-2 transmission.

Virology

Toelzer C, Gupta K, Yadav SK, et al. **Free fatty acid binding pocket in the locked structure of SARS-CoV-2 spike protein**. Science 21 Sep 2020. Full-text: https://doi.org/10.1126/science.abd3255

This group from Bristol, UK determined the structure of the SARS-CoV-2 S glycoprotein by cryo-EM. The receptor binding domains (RBDs) tightly bind the essential free fatty acid (FFA) linoleic acid (LA) in three composite binding pockets. At least four molecular features mediating LA binding to SARS-CoV-2 were identified. The LA-binding pocket presents a promising target for future development of small molecule inhibitors that, for example, could irreversibly lock S in the closed conformation and interfere with receptor interactions.

Pathogenesis

Jacob F, Pather SR, Huang WK, et al. **Human Pluripotent Stem Cell-Derived Neural Cells and Brain Organoids Reveal SARS-CoV-2 Neurotropism Predominates in Choroid Plexus Epithelium**. Cell Stem Cells September 21, 2020. Full-text: https://doi.org/10.1016/j.stem.2020.09.016

Fadi Jacob and colleagues have investigated the susceptibility of human-induced pluripotent stem cell (hiPSC)-derived monolayer brain cells and region-specific brain organoids to SARS-CoV-2 infection. Neurons and astro-

cytes were sparsely infected, but choroid plexus epithelial cells underwent robust infection, indicating a selective SARS-CoV-2 neurotropism.

Immunology

Larson D, Brodniak SL, Voegtly LJ, et al. **A Case of Early Re-infection with SARS-CoV-2.** Clin Infect Dis. 2020 Sep 19:ciaa1436. PubMed: https://pubmed.gov/32949240. Full-text: https://doi.org/10.1093/cid/ciaa1436

The next re-infection. A 42-year-old healthy male military healthcare provider became re-infected only 51 days after resolution of initial infection. Of note, his second infection was more severe, potentially due to immune enhancement, acquisition of a more pathogenic strain, or perhaps a greater inoculum of infection as the second exposure was from within household contacts.

Golinelli D, Boetto E, Maietti E, Fantini MP. **The association between ABO blood group and SARS-CoV-2 infection: A meta-analysis**. PLoS One 2020 Sep 18;15(9):e0239508. PubMed: https://pubmed.gov/32946531. Full-text: https://doi.org/10.1371/journal.pone.0239508

In this meta-analysis of 7 studies, the authors analyzed the odds of having each blood group among 7503 SARS-CoV-2 positive patients compared with 2,962,160 (!) controls. SARS-CoV-2 positive individuals were more likely to have blood group A (pooled OR 1.23, 95%CI: 1.09–1.40) and less likely to have blood group O (pooled OR = 0.77, 95%CI: 0.67–0.88).

Clinical

Garibaldi BT, Fiksel J, Muschelli J, et al. **Patient Trajectories Among Persons Hospitalized for COVID-19. A Cohort Study**. Ann Intern Med, 22 September 2020. Full-text: https://doi.org/10.7326/M20-3905

Of 787 patients admitted with mild-to-moderate disease between March 4 and April 24 in five US hospitals in Maryland and Washington, 302 (38%) progressed to severe disease or death: 181 (60%) by day 2 and 238 (79%) by day 4. Patients had markedly different probabilities of disease progression on the basis of age, nursing home residence, comorbid conditions, obesity, respiratory symptoms, respiratory rate, fever, absolute lymphocyte count, hypoalbuminemia, troponin level, and C-reactive protein level and the interactions among these factors. Using only factors present on admission, a model to predict in-hospital disease progression had an area under the curve of 0.85,

0.79, and 0.79, at day 2, 4, and 7, respectively. An interactive version of a so called "COVID-19 Inpatient Risk Calculator" (CIRC) is available at https://rsconnect.biostat.jhsph.edu/covid_predict/.

Foy BH, Carlson JC, Reinertsen E, et al. **Association of Red Blood Cell Distribution Width With Mortality Risk in Hospitalized Adults With SARS-CoV-2 Infection**. JAMA Netw Open September 23, 2020;3(9):e2022058. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.22058

Red blood cell distribution width (RDW) as a non-specific marker of illness? RDW is a component of complete blood counts that quantifies the variation of individual red blood cell (RBC) volumes and has been shown to be associated with elevated risk for morbidity and mortality in a wide range of diseases. In this large cohort study including 1641 adults diagnosed with SARS-CoV-2 infection and admitted to 4 hospitals in Boston, RDW was associated with mortality risk in Cox models (hazard ratio of 1.09 per 0.5% RDW increase and 2.01 for an RDW > 14.5% vs ≤ 14.5%).

Roncon L, Zuin M, Barco S, et al. **Incidence of acute pulmonary embolism in COVID-19 patients: Systematic review and meta-analysis**. Eur J Intern Med. 2020 Sep 17:S0953-6205(20)30349-6. PubMed: https://pubmed.gov/32958372. Full-text: https://doi.org/10.1016/j.ejim.2020.09.006

Loris Roncon and colleagues from Rovigo, Italy have analyzed data from 23 studies, including 7178 COVID-19 patients. Among patients hospitalized in general wards and intensive care units (ICU), the pooled in-hospital incidence of pulmonary embolism (PE) or lung thrombosis was 14.7% and 23.4%, respectively. Segmental/sub-segmental pulmonary arteries were more frequently involved compared to main/lobar arteries. (6.8% vs18.8%, p < 0.001). Computer tomography pulmonary angiogram (CTPA) was used in only 35%, suggesting a potential underestimation of PE cases.

Treatment

De Alencar JC, Moreira CL, Müller AD, et al. **Double-blind, randomized, placebo-controlled trial with N-acetylcysteine for treatment of severe acute respiratory syndrome caused by COVID-19**. Clinical Infectious Diseases, 23 September 2020, ciaa1443. Full-text: https://doi.org/10.1093/cid/ciaa1443

No effect of high-dose N-acetylcysteine. In this randomized clinical trial (RCT) from Brazil including 135 patients with severe COVID-19, 16 patients (24%) in

the placebo group were submitted to endotracheal intubation and mechanical ventilation, compared to 14 patients (21%) in the NAC group (p = 0.675). No difference was observed in secondary endpoints.

Wang M, Zhao Y, Hu W, et al. **Treatment of COVID-19 Patients with Prolonged Post-Symptomatic Viral Shedding with Leflunomide -- a Single-Center, Randomized, Controlled Clinical Trial**. Clin Infect Dis. 2020 Sep 21:ciaa1417. PubMed: https://pubmed.gov/32955081 . Full-text: https://doi.org/10.1093/cid/ciaa1417

No effect of leflunomide. Leflunomide is an approved antagonist of dihydroorotate dehydrogenase, has some antiviral and anti-inflammatory effects and has been widely used to treat patients with autoimmune diseases. In this small RCT from Wuhan on 50 COVID-19 patients with prolonged PCR positivity, no benefit in terms of the duration of viral shedding was observed with the combined treatment of leflunomide and IFN α-2a vs IFN α-2a alone.

24 September

Epidemiology

Brett TS, Rohani P. **Transmission dynamics reveal the impracticality of COVID-19 herd immunity strategies**. Proc Natl Acad Sci U S A. 2020 Sep 22:202008087. PubMed: https://pubmed.gov/32963094. Full-text: https://doi.org/10.1073/pnas.2008087117

Various governments have entertained the idea of achieving herd immunity through natural infection as a means of ending the long-term threat of COVID-19. This has provoked alarm in sections of the public health community. This work confirms that this alarm is well-founded: if social distancing is maintained at a fixed level, hospital capacity needs to be much larger than presently available to achieve herd immunity without exceeding capacity; otherwise, the final outbreak size will be insufficient to achieve herd immunity.

Virology

Muñoz-Fontela C, Dowling WE, Funnell SGP, et al. **Animal models for COVID-19**. Nature. 2020 Sep 23. PubMed: https://pubmed.gov/32967005. Full-text: https://doi.org/10.1038/s41586-020-2787-6

Mice, hamsters, ferrets, minks, cats, pigs, fruit bats, monkeys: a variety of murine models for mild and severe COVID-19 have been described or are under development. All will be useful for vaccine and antiviral evaluation and some share features with the human disease. According to this review (performed by a huge international collaboration), however, no murine model at present recapitulates all aspects of human COVID-19, especially unusual features such as the pulmonary vascular disease observed in adults and hyperinflammatory syndromes in children.

Immunology

Huang J, Hume AJ, Abo KM, et al. **SARS-CoV-2 Infection of Pluripotent Stem Cell-derived Human Lung Alveolar Type 2 Cells Elicits a Rapid Epithelial-Intrinsic Inflammatory Response**. Cell Stem Cell September 18, 2020. Full-text: https://doi.org/10.1016/j.stem.2020.09.013

Jessie Huang and colleagues present an *in vitro* human model that simulates the initial apical infection of alveolar epithelium with SARS-CoV-2, using induced pluripotent stem cell-derived AT2s that have been adapted to air-liquid interface culture. Their model system reveals cell-intrinsic responses of a key lung target cell to SARS-CoV-2 infection and should facilitate drug development.

Diagnostics

The National SARS-CoV-2 Serology Assay Evaluation Group. **Performance characteristics of five immunoassays for SARS-CoV-2: a head-to-head benchmark comparison**. Lancet September 23, 2020. Full-text: https://doi.org/10.1016/S1473-3099(20)30634-4

A benchmark study in immunoassay assessment. This UK group did a head-to-head assessment of five SARS-CoV-2 IgG assays, including four commercial assays (Abbott, LIAISON/DiaSorin, Elecsys/Roche, and Siemens), plus a novel in-house 384-well/Oxford ELISA in 976 (!) pre-pandemic blood samples and 536 (!) blood samples with confirmed SARS-CoV-2 infection. All assays had a high sensitivity (92.7-99.1%) and specificity (98.7-99.9%). The most sensitive test assessed was the in-house ELISA. The Siemens assay and Oxford immunoassay achieved 98% sensitivity/specificity without further optimization. However, a limitation of this work was the small number of paucisymptomatic and asymptomatic cases analyzed.

Yang OO, Ibarrondo FJ. **Loss of Anti-SARS-CoV-2 Antibodies in Mild Covid-19. Reply.** N Engl J Med. 2020 Sep 23;383(16):10.1056/NEJMc2027051#sa4. PubMed: https://pubmed.gov/32966713. Full-text: https://doi.org/10.1056/NEJMc2027051

The controversy about antibody kinetics in patients with mild COVID-19 is ongoing. Some groups have reported a rapid decline, some have observed stability. According to the authors, several factors probably explain these apparent contradictions, including varying methods used and the heterogeneity among the study participants.

Clinical

Pereyra D, Heber S, Jilma B, Zoufaly A, Assinger A. **Routine haematological parameters in COVID-19 prognosis**. The Lancet Hematology, 7, ISSUE 10, e709, October 01, 2020.

A “negative” study is sometimes valuable: After hundreds of studies emphasizing the prognostic values of clinical and laboratory chemical parameters in hospitalized COVID-19 patients, it's important to hear that it's not that easy (at least in Austria). David Pereyra and colleagues analyzed data from 210 consecutive hospitalized patients with COVID-19. In this cohort, hematological parameters such as thrombocytes, neutrophil-to-lymphocyte ratio or D-dimers did not allow prediction of patient outcome. These routine parameters, despite giving guidance on the overall health of the patient, might not always accurately indicate COVID-19-related complications.

Rubin R. **As Their Numbers Grow, COVID-19 “Long Haulers” Stump Experts**. JAMA September 23, 2020. Full-text: https://doi.org/10.1001/jama.2020.17709

In this nice perspective Rita Rubin summarizes current knowledge on people who still haven’t fully recovered from COVID-19 weeks or even months after symptoms first arose. Fatigue appears to be the most common symptom, followed by muscle or body aches, shortness of breath or difficulty breathing, and difficulty concentrating.

Treatment

Doi Y, Hibino M, Hase R, et al. **A prospective, randomized, open-label trial of early versus late favipiravir in hospitalized patients with COVID-19**. Antimicrob Agents Chemother. 2020 Sep 21:AAC.01897-20. PubMed: https://pubmed.gov/32958718. Full-text: https://doi.org/10.1128/AAC.01897-20

No effect of viral clearance with favipiravir. In this RCT, 69 patients with asymptomatic to mild COVID-19 were randomly assigned to early or late favipiravir therapy (same regimen starting day 1 or day 6). Viral clearance occurred within 6 days in 67% and 56% (adjusted hazard ratio 1.42; 95% CI 0.76–2.62). Of 30 patients who had a fever (≥ 37.5°C) on day 1, time to no fever was 2.1 days and 3.2 days (aHR, 1.88; 95% CI 0.81–4.35). During therapy, 84% developed transient hyperuricemia. Favipiravir did not significantly improve viral clearance as measured by RT-PCR by day 6 but was associated with numerical reduction in time to no fever. Neither disease progression nor death occurred in any of the patients in either treatment group during the 28-day participation.

Baicus C, Pinte L, Stoichitoiu LE, Badea C. **Hydroxychloroquine for prophylaxis of COVID-19 physicians survey: Despite lack of evidence, many would take or give to dear ones, and despite the perceived necessity of an RCT, few would participate**. J Eval Clin Pract. 2020 Sep 21. PubMed: https://pubmed.gov/32955801. Full-text: https://doi.org/10.1111/jep.13484

It does not seem entirely impossible that the authors made themselves rather unpopular with their colleagues, publishing the results of this survey performed in early April. A total of 784 Romanian doctors were interviewed about their thoughts on HCQ. Despite the lack of evidence at that time, 36% considered the evidence as existing, and 22% were ready to take or to give hydroxychloroquine prophylactically to family. Almost all (92%) considered an RCT necessary, but only 42% were willing to participate. There was only a very weak correlation (Kendall's tau _b = 0.255, p < 0.001) between the belief that an RCT is necessary and the willingness to enroll in such an RCT. In any case, the clearest paper title of the day (the discussion is remarkably short).

25 September

Immunology

Bastard P, Rosen LB, Zhang Q, et al. **Auto-antibodies against type I IFNs in patients with life-threatening COVID-19.** Science 2020, published 24 September. Full-text: https://science.sciencemag.org/content/early/2020/09/23/science.abd4585

In an outstanding paper, Jean-Laurent Casanova, Paul Bastard and colleagues highlight the crucial role of type I IFNs in protective immunity against SARS-CoV-2. The authors report an analysis of 987 patients with life-threatening COVID-19 pneumonia, 663 subjects with asymptomatic or benign SARS-CoV-2 infection and a third group of 1227 healthy volunteers. At least 10% of patients with life-threatening COVID-19 pneumonia had neutralizing auto-Abs against type I IFNs (IFN-ω: 13 patients; the 13 types of IFN-α: 36; both: 52) at the onset of critical disease.

Zhang Q, Bastard P, Liu Z, et al: **Inborn errors of type I IFN immunity in patients with life-threatening COVID-19.** Science 2020, published 24 September. Full-text: https://science.sciencemag.org/content/early/2020/09/23/science.abd4570

The title almost says it all: **there are** inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Jean-Laurent Casanova, Qian Zhang and colleagues report enrichment in rare variants predicted to be loss-of-function (LOF) at the 13 human loci known to govern TLR3- and IRF7-dependent type I interferon (IFN) immunity to influenza virus, in 659 patients with life-threatening COVID-19 pneumonia, relative to 534 subjects with asymptomatic or benign infection. The authors suggest that there may be mutations in other type I IFN-related genes in other patients with life-threatening COVID-19 pneumonia. They conclude that the administration of type I IFN might be of therapeutic benefit in selected patients, at least early in the course of SARS-CoV-2 infection.

Read also the comment by Meredith Wadman: Wadman M. **Hidden immune weakness found in 14% of gravely ill COVID-19 patients.** Science 2020, published 24 September. Full-text: https://www.sciencemag.org/news/2020/09/hidden-immune-weakness-found-14-gravely-ill-covid-19-patients

Epidemiology

Briefing. **The covid-19 pandemic is worse than official figures show.** The Economist 2020, published 26 September. Full-text: https://www.economist.com/briefing/2020/09/26/the-covid-19-pandemic-is-worse-than-official-figures-show

"As the autumnal equinox passed, Europe was battening down the hatches for a gruelling winter. Intensive-care wards and hospital beds were filling up in Madrid and Marseille—a city which, a few months ago, thought it had more or less eliminated covid-19. Governments were implementing new restrictions, sometimes, as in England, going back on changes made just a few months ago. The al-fresco life of summer was returning indoors. Talk of a second wave was everywhere."

Pathogenesis

Schultze A, Walker AJ, MacKenna B, et al. **Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: an observational cohort study using the OpenSAFELY platform**. Lancet Resp Med September 24, 2020. Full-text: https://doi.org/10.1016/S2213-2600(20)30415-X

Do treatments for respiratory disease, specifically inhaled corticosteroids (ICSs), have a protective effect? Probably not. Anna Schultze and colleagues from London have identified 148,557 people with COPD and 818,490 people with asthma who were given relevant respiratory medications in the 4 months before the index date (March 1). People with COPD who were prescribed ICSs were at increased risk of COVID-19-related death compared with those prescribed LABA–LAMA combinations (adjusted HR 1.39, 95% CI 1.10–1.76]). Compared with those prescribed short acting beta agonists only, people with asthma who were prescribed high-dose ICS were at an increased risk of death (1.55, 1.10–2.18]), whereas those given a low or medium dose were not. Sensitivity analyses showed that the apparent harmful association could be explained by relatively small health differences between people prescribed ICS and those not prescribed ICS.

Vaccine

Logunov DY, Dolzhikova IV, Zubkova OV, et al. **Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia**. Lancet. 2020 Sep 3:S0140-6736(20)31866-3. PubMed: https://pubmed.gov/32896291. Full-text: https://doi.org/10.1016/S0140-6736(20)31866-3

On September 5, we commented that it was high time to see some data on an "approved" vaccine, consisting of two recombinant adenovirus vectors carrying the spike glycoprotein (Sputnik V, presented as the world's "*premiere*"**,** like planting a tiny flag in the sea bed two and a half miles beneath the North Pole in 2007).

Bucci E, Andreev, Björkman A, et al. **Safety and efficacy of the Russian COVID-19 vaccine: more information needed**. Lancet September 21, 2020. Full-text: https://doi.org/10.1016/S0140-6736(20)31960-7

A few days later, the study received these notes of serious concerns. Dozens of authors raised doubts about the reliability of the data. The main issue (among many others): there were several data patterns which appeared repeatedly for the reported experiments. A Photoshop fake? Enrico Bucci and colleagues conclude that "in lack of the original numerical data, no conclusions can be definitively drawn on the reliability of the data presented, especially regarding the apparent duplications detected". For more details see also https://cattiviscienziati.com/2020/09/07/note-of-concern/

Logunov DY, Dolzhikova IV, Tukhvatullin AI. **Safety and efficacy of the Russian COVID-19 vaccine: more information needed – Authors' reply**. Lancet September 21, 2020. Full-text: https://doi.org/10.1016/S0140-6736(20)31970-X

The author's reply. They "confirm that individual participant data will be made available on request to DYL and that after approval of a proposal, data can be shared through a secure online platform". Shall we hold our breath?

Clinical

Buitrago-Garcia D, Egli-Gany D, Counotte MJ, et al. **Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: A living systematic review and meta-analysis**. PLOS September 22, 2020. Full-text: https://doi.org/10.1371/journal.pmed.1003346

Diana Buitrago-Garcia and colleagues did a living systematic review through June 10, 2020. Overall, in 79 studies in a range of different settings, 20% (95%

CI 17%–25%) of people with SARS-CoV-2 infection remained asymptomatic during follow-up, but biases in study designs limit the certainty of this estimate. In seven studies of defined populations screened for SARS-CoV-2 and then followed, 31% (95% CI 26%–37%) remained asymptomatic. There was some evidence that SARS-CoV-2 infection is less likely in contacts of people with asymptomatic infection.

Hughes MM, Groenewold MR, Lessem SE, et al. Update: **Characteristics of Health Care Personnel with COVID-19 - United States, February 12-July 16, 2020**. MMWR Morb Mortal Wkly Rep. 2020 Sep 25;69(38):1364-1368. PubMed: https://pubmed.gov/32970661 . Full-text: https://doi.org/10.15585/mmwr.mm6938a3

This update describes demographic characteristics, underlying medical conditions, hospitalizations, and intensive care unit (ICU) admissions, stratified by vital status, among 100,570 health care providers (HCP) (median age 41 years, 79% females) with COVID-19 reported to CDC during February 12–July 16, 2020. Of persons with known hospitalization status, 8% (6,832 of 83,202) were hospitalized and 5% (1,684 of 33,694) were treated in an ICU. Vital status was known for 67% (67,746) of HCP with COVID-19; among those, 641 (1%) died. HCP with COVID-19 who died tended to be older, male, Asian, Black, and have an underlying medical condition when compared to HCP who did not die. Nursing and residential care facilities were the most commonly reported job setting and nursing the most common single occupation type of HCP with COVID-19.

Pathogenesis

Rauch A, Dupont A, Goutay J, et al. **Endotheliopathy is induced by plasma from critically-ill patients and associated with organ failure in severe COVID-19**. Circulation. 2020 Sep 24. PubMed: https://pubmed.gov/32970476 . Full-text: https://doi.org/10.1161/CIRCULATIONAHA.120.050907

Endotheliopathy is an essential part of the pathological response to severe COVID-19, leading to respiratory failure, multi-organ dysfunction and thrombosis. Antoine Rauch and colleagues from Lille, France evaluated the cytotoxicity of plasma samples collected from COVID-19 patients on cultured human pulmonary microvascular endothelial cells. They demonstrate a direct and rapid cytotoxic effect of plasma collected from critically ill patients on vascular endothelial cells.

Treatment

Zoufaly A, Poglitsch M, Aberle JH, et al. **Human recombinant soluble ACE2 in severe COVID-19**. Lancet Resp Med September 24, 2020. Full-text: https://doi.org/10.1016/S2213-2600(20)30418-5

Human recombinant soluble ACE2 (hrsACE2) may act by binding the viral spike protein (thereby neutralizing SARS-CoV-2) and by interfering with the renin–angiotensin system. Alex Zoufaly and colleagues from Vienna report on a case of a 45-year-old woman with severe COVID-19 who was treated with hrsACE2. The virus disappeared rapidly from the serum and the patient became afebrile within hours. Phase II/III studies of hrsACE2 are ongoing.

Press

European corrispondents. **As Covid cases rise again, how are countries in Europe reacting?** The Guardian 2020, published 23 September. Full-text: https://www.theguardian.com/world/2020/sep/23/as-covid-cases-rise-again-how-are-countries-in-europe-reacting

Tighter measures are being imposed, but they vary across the continent.

Spanish

If you read Spanish, read Llaneras K, Sevillano EG. **¿Cómo son las zonas restringidas en Madrid? Más densas, con más inmigrantes y sobre todo más pobres.** El País 2020, published 21 September. Full-text: https://elpais.com/sociedad/2020-09-19/como-son-las-zonas-restringidas-en-madrid-mas-densas-con-mas-inmigrantes-y-sobre-todo-mas-pobres.html

El Gobierno regional impone confinamientos perimetrales y otras medidas como el cierre de parques en las áreas más golpeadas por el virus, donde se aprecian patrones socioeconómicos.

Andrino B, Grasso D, Llaneras K. **No es solo Madrid: el coronavirus golpea las áreas metropolitanas en la segunda ola.** El País 2020, published 21 September. Full-text: https://elpais.com/sociedad/2020-09-20/no-es-solo-madrid-el-coronavirus-golpea-las-areas-metropolitanas-en-la-segunda-ola.html

Talavera, Salamanca, Girona o Vitoria, entre otras, tienen cifras de incidencia del virus cercanas a la de la capital.

Babelia. **Por qué los humanos somos presa fácil de las pandemias.** El País 2020, published 22 September. Full-text: https://elpais.com/cultura/2020/09/21/babelia/1600704574_156848.html

El biólogo Juan Botas y el físico Juan José Gómez Cadenas aportan perspectiva histórica a la crisis sanitaria en 'Virus. La guerra de los mil millones de años', donde relatan por qué la epidemia es solo un episodio más en esa contienda. 'Babelia' publica un adelanto.

Beyond your plate borders

Garbe J, Albrecht T, Levermann A, et al. **The hysteresis of the Antarctic Ice Sheet.** Nature 585, 538–544 (2020). Full-text: https://doi.org/10.1038/s41586-020-2727-5

Antarctica's long-term sea level contribution might dramatically increase and exceed that of all other sources. Ricarda Winkelmann, Julius Garbe and colleagues show that at global warming levels around 2 degrees Celsius above pre-industrial levels, West Antarctica is committed to long-term partial collapse owing to the marine ice sheet instability. Find out what will happen between 6 and 9 degrees of warming and beyond 10 degrees. The video: https://www.youtube.com/watch?v=NrMyP5fqWMI

See also the comment by Harvey F. **Melting Antarctic ice will raise sea level by 2.5 metres – even if Paris climate goals are met, study finds.** The Guardian 2020, published 23 September. Full-text: https://www.theguardian.com/environment/2020/sep/23/melting-antarctic-ice-will-raise-sea-level-by-25-metres-even-if-paris-climate-goals-are-met-study-finds

26 September

Epidemiology

Buss LF, Prete Jr CA, Abrahim CMM, et al. **COVID-19 herd immunity in the Brazilian Amazon.** medRxiv 2020, posted 21 September. Full-text: https://doi.org/10.1101/2020.09.16.20194787

As much as 66% of the population of Manaus (two million people), Brazil, could have been infected with SARS-CoV-2. Ester Sabino, Lewis Buss and colleagues show that the transmission of SARS-CoV-2 in Manaus increased quickly during March and April and declined slowly from May to September.

In June, one month following the epidemic peak, 44% of the population was seropositive for SARS-CoV-2. After correcting for confounding factors, the authors estimate the epidemic size to be 66% by early August 2020. Note: these findings have not yet been peer reviewed.

Remember: herd immunity is defined as the proportion of a population that must be immune to an infectious disease, either by natural infection or vaccination, such that new cases decline and R_0 falls below 1 (see also https://www.nature.com/articles/d41586-020-02009-w).

Boehmer TK, DeVies J, Caruso E, et al. **Changing Age Distribution of the COVID-19 Pandemic — United States, May–August 2020.** MMWR Morb Mortal Wkly Rep. ePub: 23 September 2020. DOI: http://dx.doi.org/10.15585/mmwr.mm6939e1

First the kids, then the parents and, finally, the grandparents. Tegan Boehmer et al. show that during June–August 2020, COVID-19 incidence was highest in persons aged 20–29 years. Across the southern United States in June 2020, increases in percentage of positive SARS-CoV-2 test results among adults aged 20–39 years preceded increases among those aged ≥ 60 years by 4–15 days. The authors conclude that preventive behavior by younger adults is needed to help reduce infection and subsequent transmission to persons at higher risk for severe illness.

Transmission

An outbreak in Sallent (72 km from Barcelona) with 30 SARS-CoV-2-infected people demonstrates the risk posed by choirs and karaoke in poorly ventilated places. See the video: https://www.youtube.com/watch?v=tuQC-NTLE54. Do not sing and jump around in enclosed spaces!

Immunology

Pierce CA, Preston-Hurlburt P, Dai Y, et al. **Immune responses to SARS-CoV-2 infection in hospitalized pediatric and adult patients.** Sci Transl Med. 2020 Sep 21:eabd5487. PubMed: https://pubmed.gov/32958614. Full-text: https://doi.org/10.1126/scitranslmed.abd5487

Compared to adults, pediatric patients have a shorter length of stay in hospital, a decreased requirement for mechanical ventilation and a lower mortality. Now Betsy Herold and Carl Pierce compared cytokine, humoral, and cellular immune responses in pediatric (children and youth, age < 24 years) (n = 65) and adult (n = 60) patients with COVID-19 at a metropolitan hospital sys-

tem in New York City. Children had higher serum concentrations of IL-17A and IFN-γ which in adult patients decreased progressively with age. Read more about ***adult*** T cell responses, serum neutralizing antibody titers and antibody-dependent cellular phagocytosis.

Vaccine

Cookson C. **UK to test vaccines on volunteers deliberately infected with Covid-19.** Financial Times 2020, published 23 September. Full-text: https://www.ft.com/content/b782f666-6847-4487-986c-56d3f5e46c0b

In the world's first COVID-19 'human challenge trials' healthy volunteers will be deliberately infected with SARS-CoV-2 to assess the effectiveness of experimental vaccines. See also the CR Top 10, June 4: Jamrozik E, Selgelid MJ. **COVID-19 human challenge studies: ethical issues**. Lancet Infect Dis. 2020 May 29:S1473-3099(20)30438-2. PubMed: https://pubmed.gov/32479747. Full-text: https://doi.org/10.1016/S1473-3099(20)30438-2

Human challenge studies could accelerate vaccine development, helping to test multiple candidate vaccines. This personal view on ethical issues explains why this will be difficult. The authors argue that human challenge studies can "reasonably be considered ethically acceptable insofar as such studies are accepted internationally and by the communities in which they are done, can realistically be expected to accelerate or improve vaccine development, have considerable potential to directly benefit participants, are designed to limit and minimise risks to participants, and are done with strict infection control measures to limit and reduce third-party risks."

Diagnostics

Zamecnik CR, Rajan JV, Yamauchi KA, et al. **ReScan, a Multiplex Diagnostic Pipeline, Pans Human Sera for SARS-CoV-2 Antigens.** Cell Reports 2020, published 24 September. Full-text: https://doi.org/10.1016/j.xcrm.2020.100123

Identifying highly specific sets of antigens that are less cross-reactive with antibodies elicited by other common human CoV infections could improve future diagnostic SARS-CoV-2 tests. Here Michael Wilson, Colin Zamecnik and colleagues perform proteome-wide profiling of coronavirus antigens enriched by 98 COVID-19 patient sera and identify 9 antigens derived from 3 SARS-CoV-2 proteins as candidates for more specific, multiplexed SARS-CoV-2 serologic assays. The authors conclude that their proof-of-concept study might

have broad applicability for other emerging infectious diseases or autoimmune diseases that lack valid biomarkers. Music from the future?

Clinical

Muñoz-Price LS, Nattinger AB, Rivera F, et al. **Racial Disparities in Incidence and Outcomes Among Patients With COVID-19.** JAMA Netw Open 2020, published 25 September. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.21892

A total of 2595 patients: 785 (30.2%) African-American individuals, 1617 (62.3%) White individuals, and 193 (7.4%) of other racial groups. Silvia Muñoz-Price et al. show that in the first weeks of the COVID-19 pandemic in Milwaukee, Wisconsin, Black race was associated with a positive COVID-19 test and a subsequent need for hospitalization, but only poverty was associated with intensive care unit admission.

Kabarriti R, Brodin P, Maron MI, et al. **Association of Race and Ethnicity With Comorbidities and Survival Among Patients With COVID-19 at an Urban Medical Center in New York.** JAMA Netw Open 2020, published 25 September. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.19795

Similar results as the previous study: Andrew Racine, Rafi Kabarriti and colleagues report 5902 SARS-CoV-2 positive patients treated at a single academic medical center in New York. While non-Hispanic Black and Hispanic patients had a higher proportion of more than 2 medical comorbidities, their survival outcomes were at least as good as those of their non-Hispanic White counterparts when controlling for age, sex, and comorbidities.

Treatment

Pau AK, Aberg J, Baker J, et al. **Convalescent Plasma for the Treatment of COVID-19: Perspectives of the National Institutes of Health COVID-19 Treatment Guidelines Panel.** Ann Intern Med 2020, published 25 September. Full-text: https://doi.org/10.7326/M20-6448

The COVID-19 pandemic has intensified the tension between providing rapid access to promising therapies and generating the scientific evidence needed to establish whether those therapies are safe and effective. Here, Alice Pau et al. discuss the use of convalescent plasma for the treatment of COVID-19. They conclude that currently the data are insufficient to recommend for or against convalescent plasma for treating COVID-19.

Pregnancy

Panagiotakopoulos L, Myers TR, Gee J, et al. **SARS-CoV-2 Infection Among Hospitalized Pregnant Women: Reasons for Admission and Pregnancy Characteristics — Eight U.S. Health Care Centers, March 1–May 30, 2020.** MMWR Morb Mortal Wkly Rep 2020;69:1355–1359. DOI: http://dx.doi.org/10.15585/mmwr.mm6938e2

Some pregnant women are at increased risk for severe illness from SARS-CoV-2 infection. Now Lakshmi Panagiotakopoulos et al. report that 105 hospitalized pregnant women with SARS-CoV-2 infection were identified, including 62 (59%) hospitalized for obstetric reasons (i.e., labor and delivery or other pregnancy-related indication) and 43 (41%) hospitalized for COVID-19 illness without an obstetric reason. Prevalence of pre-pregnancy obesity and gestational diabetes were higher among pregnant women hospitalized for COVID-19–related illness (e.g., worsening respiratory status) than among those admitted for pregnancy-related treatment or procedures (e.g., delivery) and found to have COVID-19. Among the 43 pregnant women hospitalized for COVID-19, 13 (30%) required intensive care unit (ICU) admission, six (14%) required mechanical ventilation, and one died from COVID-19.

Delahoy MJ, Whitaker M, O'Halloran A, et al. **Characteristics and Maternal and Birth Outcomes of Hospitalized Pregnant Women with Laboratory-Confirmed COVID-19 — COVID-NET, 13 States, March 1–August 22, 2020.** MMWR Morb Mortal Wkly Rep 2020;69:1347–1354. DOI: http://dx.doi.org/10.15585/mmwr.mm6938e1

One in four women aged 15–49 years who had a COVID-19–associated hospitalization in the US during March 1–August 22, 2020 was pregnant. Now Miranda Delahoy et al. report 598 hospitalized pregnant women with COVID-19 (55% were asymptomatic at admission). Severe illness occurred among symptomatic pregnant women, including intensive care unit admissions (16%), mechanical ventilation (8%), and death (1%). Among all pregnancies completed during a COVID-19–associated hospitalization, 2% resulted in pregnancy losses. Pregnancy losses occurred among both symptomatic and asymptomatic hospitalized women with COVID-19.

Education

Rubin EJ, Baden LR, Morrissey S. **Eight Months of Action and Inaction against Covid-19.** Audio interview (27:02). N Engl J Med 2020; 383:e95. Access: https://doi.org/10.1056/NEJMe2030336

The editors reflect on 8 months of action and inaction against COVID-19.

Spanish

If you read Spanish, read Salas J. **El peligro de cantar en interiores en tiempos de covid.** El País 2020, published 26 September. Full-text: https://elpais.com/ciencia/2020-09-25/el-peligro-de-cantar-en-interiores-en-tiempos-de-covid.html

Un brote en Sallent de Llobregat con 30 contagiados muestra el riesgo que suponen coros y karaokes por la propagación del virus en el aire al alzar la voz en locales mal ventilado. En vídeo: El grupo de góspel barcelonés: https://www.youtube.com/watch?v=tuQC-NTLE54

See also the City Hall announcement (in Catalan): Comunicat de l'Ajuntament de Sallent en relació als casos positius per COVID-19 de la coral The River Troupe Gospel.

27 September

Transmission

Asadi S, Cappa CD, Barreda S, et al. **Efficacy of masks and face coverings in controlling outward aerosol particle emission from expiratory activities.** Sci Rep 10, 15665 (2020). Full-text: https://doi.org/10.1038/s41598-020-72798-7

Masks work with super-emittors! William D. Ristenpart, Sima Asadi and colleagues measured outward emissions of micron-scale aerosol particles by healthy humans performing various expiratory activities while wearing different types of medical-grade or homemade masks. Both surgical masks and unvented KN95 respirators reduced the outward particle emission rates by 90% and 74% on average during speaking and coughing. These masks similarly decreased the outward particle emission of a coughing super-emitter, who for unclear reasons emitted up to two orders of magnitude more expiratory particles via coughing than average. An interesting collateral finding: people speak more loudly, but do not cough more loudly, when wearing a mask.

Prevention

Wei Y, Ye Z, Cui M, Wei X**. COVID-19 prevention and control in China: grid governance.** Journal Public Health 2020, published 26 September. Full-text: https://doi.org/10.1093/pubmed/fdaa175

Grid governance is a key measure that helps to promote decentralization at the grassroots level, applied in both urban and rural communities in China. It may not be to everyone's taste as it seeks to divide the basic level of society into many responsible grids, and accordingly it inserts affairs, organizations and people into particular grids, and also uses modern technology to comprehensively and quickly complete basic information collection. But it may have been helpful in bringing the Chinese epidemic under control. Find out more about 'grid governance'.

Immunology

Schurink B, Roos E, Radonic T, et al. **Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study.** Lancet Microbe 2020, published 25 September. Full-text: https://doi.org/10.1016/S2666-5247(20)30144-0

The authors report the full body autopsy results of 21 patients at Amsterdam University Medical Centers (UMC), the Netherlands. In histological analyses of organs (sampled from nine to 21 patients per organ), an extensive inflammatory response was present in the lungs, heart, liver, kidneys, and brain. In the brain, extensive inflammation was detected, which was most pronounced in the olfactory bulbs and medulla oblongata. Their findings also suggest involvement of neutrophil extracellular traps

(NETs) in coagulopathy and prolonged activation of neutrophils in lethal COVID-19, or at least a delayed resolution of these NETs.

Nie J, Li Q, Wu J, et al. **Quantification of SARS-CoV-2 neutralizing antibody by a pseudotyped virus-based assay.** Nat Protoc 2020, published 25 September. Full-text: https://doi.org/10.1038/s41596-020-0394-5

The authors developed a pseudotyped virus-based neutralization assay against SARS-CoV-2 in biosafety level 2 facilities. The authors caution that experience in handling cells is needed before implementing this protocol.

Severe COVID

Barbaro RP, MacLaren G, Boonstra PS, et al. **Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry.** Lancet 2020, published 25 September. Full-text: https://doi.org/10.1016/S0140-6736(20)32008-0

Initial reports of extracorporeal membrane oxygenation (ECMO) use in patients with COVID-19 described very high mortality. Here Ryan Barbaro et al. report data for 1035 patients who received ECMO support from 213 hospitals in 36 countries. Of these, 6% remained hospitalized, 30% were discharged home or to an acute rehabilitation center, 10% were discharged to a long-term acute care center or unspecified location, 17% were discharged to another hospital, and 37% died.

Yadaw AS, Li YC, Bose S, et al. **Clinical features of COVID-19 mortality: development and validation of a clinical prediction model.** Lancet Digital Health 2020, published 1 October. Full-text: https://doi.org/10.1016/S2589-7500(20)30217-X

Predicting mortality among patients with COVID-19 is difficult. Here, the authors developed a COVID-19 mortality prediction model that showed high accuracy when applied to test datasets of retrospective (n=961) and prospective (n=249) patients. The authors showed that input of three highly accessible clinical parameters for a patient—age, minimum oxygen saturation, and type of patient encounter—into an automatable eXtreme Gradient Boosting (XGBoost) algorithm has the potential to accurately classify patients as likely to live or die.

Ho EP, Neo HY. COVID 19: **Prioritise Autonomy, Beneficence and Conversations Before Score-based Triage.** Age Ageing 2020, published 25 September. Full-text: https://doi.org/10.1093/ageing/afaa205

In the coming weeks, demand for intensive COVID-19 care may overwhelm ICU capacities in Spain, France, the UK and other European countries. Decisions regarding ICU admission are particularly challenging in older people, who are most likely to require critical care, but for whom benefits are most uncertain. The authors suggest that physicians should first discern if older people will benefit from critical care (beneficence) and second, if they want critical care (autonomy). Decisions should be based on individualized risk-stratification and survival weighed against burden of treatment, as well as longer-term functional deficits and quality-of-life. Tough times ahead.

Collateral Effects

Weiss DJ, Bertozzi-Villa A, Rumisha SF, et al. **Indirect effects of the COVID-19 pandemic on malaria intervention coverage, morbidity, and mortality in Africa: a geospatial modelling analysis.** Lancet Infect Dis 2020, published 25 September. Full-text: https://doi.org/10.1016/S1473-3099(20)30700-3

Under pessimistic scenarios, COVID-19-related disruption to malaria control in Africa could almost double malaria mortality in 2020, and potentially lead to even greater increases in subsequent years.

Ueda Oshima M, Sandmaier BM, Petersdorf E, et al. **Blood and marrow transplantation during the emerging COVID-19 pandemic: the Seattle approach.** Bone Marrow Transplant 2020, published 26 September. Full-text: https://doi.org/10.1038/s41409-020-01068-x

Increasing numbers of COVID-19 hospitalizations and deaths, pandemic-related stresses on healthcare resources, shelter-in-place public health measures – how can you safely perform potentially life-saving stem cell transplants in this setting? Masumi Oshima et al. describe the challenges and the collateral impact of directing clinical resources toward COVID-19-related care on cancer patients in need of stem cell transplantation.

Spanish

The world officially records 1 million deaths from Covid-19. The real tally may be almost double that. If you read Spanish, read the articles of **today's El País Special**:

Bassets M. **Un millón de muertos.** El País 2020, published 27 September. Full-text: https://elpais.com/sociedad/2020-09-26/un-millon-de-muertos.html

El mundo, en plena transformación y ante una crisis económica y política, alcanza la cifra simbólica sin perspectivas de un final cercano de la pandemia, pero mejor armado ante la segunda ola y con la esperanza de las vacunas.

Hustvedt S. **Las Pandoras de la pandemia.** El País 2020, published 27 September. Full-text: https://elpais.com/sociedad/2020-09-26/las-pandoras-de-la-pandemia.html

Los déspotas buscan un enemigo mitológico a quien culpar del virus. Sin embargo, si algo hemos aprendido de la pandemia es que la acción colectiva es lo único que puede cambiar las cosas.

De Senegal a Yakarta, una diversa geografía del dolor. El País 2020, published 27 September. Full-text: https://elpais.com/sociedad/2020-09-26/de-senegal-a-yakarta-una-diversa-geografia-del-dolor.html

Familias destrozadas de todo el mundo rememoran la muerte de sus seres queridos y lamentan el duelo que les robó el virus. Son los padres, hermanos, viudos y huérfanos de la COVID.

Sampedro J. **Un regalo envenenado de la madre naturaleza.** El País 2020, published 27 September. Full-text: https://elpais.com/sociedad/2020-09-26/un-regalo-envenenado-de-la-madre-naturaleza.html

Los gobiernos occidentales, incluido el español, minimizaron los riesgos de la COVID y la experiencia adquirida en China, un error que se puede medir en vidas humanas.

Spinney L. **Solo recordaremos su nombre.** El País 2020, published 27 September. Full-text: https://elpais.com/sociedad/2020-09-26/solo-recordaremos-su-nombre.html

Pese a sumar millones de muertos, otras enfermedades del pasado han desaparecido de la memoria colectiva.

28 September

Epidemiology

Anand S, Montez-rath M, Han J, et al. **Prevalence of SARS-CoV-2 antibodies in a large nationwide sample of patients on dialysis in the USA: a cross-sectional study.** Lancet 2020, published 25 September. Full-text: https://doi.org/10.1016/S0140-6736(20)32009-2

During the first wave of the COVID-19 pandemic, fewer than 10% of the US adult population formed antibodies against SARS-CoV-2, and fewer than 10% of those with antibodies were diagnosed. That is the result of a cross-sectional US study by Shuchi Anand et al. after testing 28,503 randomly selected adult patients receiving dialysis in July 2020. When standardized to the US dialysis population, seroprevalence ranged from 3.5% in the west to 27.2% in the

northeast. Residents of non-Hispanic Black and Hispanic neighborhoods experienced higher odds of seropositivity.

See also the comment by Barnaby Flower and Christina Atchison: Flower B, Atchison C. **SARS-CoV-2 antibody seroprevalence in patients receiving dialysis in the USA.** Lancet 2020, published 25 September. Full-text: https://doi.org/10.1016/S0140-6736(20)32006-7

Hallal PC, Hartwig FP, Horta BL, et al. **SARS-CoV-2 antibody prevalence in Brazil: results from two successive nationwide serological household surveys.** Lancet Global Health 2020, published 23 September. Full-text: https://doi.org/10.1016/S2214-109X(20)30387-9

A long way to herd immunity – and very different data from the projected 66% seropositivity rate in Manaus we presented two days ago. Cesar G Victora, Pedro Hallal and colleagues report two seroprevalence surveys in 133 sentinel cities in all Brazilian states. They included 25,025 participants in the first survey (May 14–21) and 31,165 in the second (June 4–7). Prevalence was strongly associated with Indigenous ancestry and low socioeconomic status. In the second survey, the authors observed an increased prevalence in participants aged 20–59 years and those living in crowded conditions (4.4% for those living with households with six or more people). Prevalence among Indigenous people was 6.4% compared with 1.4% among White people. Prevalence in the poorest socioeconomic quintile was 3.7% compared with 1.7% in the wealthiest quintile. The authors conclude that "these population subgroups are unlikely to be protected if the policy response to the pandemic by the national government continues to downplay scientific evidence."

Gupta V, Bhoyar RC, Jain A, et al. **Asymptomatic reinfection in two healthcare workers from India with genetically distinct SARS-CoV-2.** Clin Infect Dis 2020, published 23 September. Full-text: https://doi.org/10.1093/cid/ciaa1451

The next paper on reinfection. Vinod Scaria, Vivek Gupta and colleagues describe two healthcare workers, 25 and 28 years old, who tested positive for SARS-CoV-2 in May and again, after resuming duties in the hospital, on 21 August and 5 September, respectively. Genomic analysis showed that the SARS-CoV-2 of the reinfection was different from the virus of the first episode. Both individuals were asymptomatic in May and in August/September.

Virology

Brooke GN Prischi F. **Structural and functional modelling of SARS-CoV-2 entry in animal models.** Sci Rep 10, 15917 (2020). Full-text: https://doi.org/10.1038/s41598-020-72528-z

Greg Brooke and Filippo Prischi compared the ACE2 receptor, and TMPRSS2 and Furin proteases usage of the SARS-CoV-2 Spike glycoprotein in human and in a panel of animal models (guinea pig, dog, cat, rat, rabbit, ferret, mouse, hamster, macaque) and find that ACE2, but not TMPRSS2 or Furin, has a higher level of sequence variability in the Spike protein interaction surface, which greatly influences Spike protein binding mode. The authors also show that the Spike (S) protein recognizes macaque, hamster, and ferret in a comparable way to human ACE2. However, there were substantial differences in the binding mode of the SARS-CoV and SARS-CoV-2 S protein to guinea pigs, mice and rats ACE2.

Prevention

Han E, Tan MMJ, Turk E, et al. **Lessons learnt from easing COVID-19 restrictions: an analysis of countries and regions in Asia Pacific and Europe.** Lancet 2020, published 24 September. Full-text: https://doi.org/10.1016/S0140-6736(20)32007-9

Lockdowns cannot be sustained for the long term and governments worldwide face the challenge of easing lockdowns and restrictions while balancing various health, social, and economic concerns. Now Helena Legido-Quigley, Emeline Han and colleagues examine the approaches taken by nine high-income countries and regions that have started to ease COVID-19 restrictions: five in the Asia Pacific region (i.e., Hong Kong [Special Administrative Region], Japan, New Zealand, Singapore, and South Korea) and four in Europe (i.e., Germany, Norway, Spain, and the UK). What can we learn from these experiences?

Vaccine

Bos R, Rutten L, van der Lubbe JEM, et al. **Ad26 vector-based COVID-19 vaccine encoding a prefusion-stabilized SARS-CoV-2 Spike immunogen induces potent humoral and cellular immune responses.** npj Vaccines 5, 91 (2020). Full-text: https://doi.org/10.1038/s41541-020-00243-x

Hanneke Schuitemaker, Rinke Bos and colleagues report more details about Ad26.COV2.S which is currently being evaluated in a clinical trial (ClinicalTrials.gov: NCT04436276). Vaccines based on transgenes delivered by recombi-

nant replication-incompetent adenovirus type 26 vectors (Ad26) have previously been shown to have an acceptable safety profile in humans and are able to induce neutralizing and binding antibodies, CD4 and CD8 T cell responses and a Th1-biased immune response in animals and humans.

Diagnostics

Smyrlaki I, Ekman M, Lentini A, et al. **Massive and rapid COVID-19 testing is feasible by extraction-free SARS-CoV-2 RT-PCR.** Nat Commun 11, 4812 (2020). Full-text: https://doi.org/10.1038/s41467-020-18611-5

Scalable, rapid, and affordable COVID-19 diagnostics could help to limit the spread of SARS-CoV-2, consequently saving lives. Here, Björn Reinius, Ioanna Smyrlaki and colleagues explored procedures to circumvent RNA extraction by performing RT-PCR directly on heat-inactivated subject samples and sample lysates. Significant savings in time and cost are achieved through RNA-extraction-free protocols that are directly compatible with established PCR-based testing pipelines. The authors suggest that the direct method might be attractive in settings where repeated, cheaper, and quicker testing is desirable, for example in frequent testing of healthcare personnel.

Clinical

Schultze A,Walker AJ, MacKenna B, et al. **Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: an observational cohort study using the OpenSAFELY platform.** Lancet Respir Med 2020, published 24 September. Full-text: https://doi.org/10.1016/S2213-2600(20)30415-X

There has been speculation that inhaled corticosteroids (ICSs) might protect against infection with SARS-CoV-2 or the development of severe COVID-19. Now Ben Goldacre, Anna Schultze and colleagues show that regular ICS use does not seem to protect against COVID-19-related death among people with asthma or COPD.

Spanish

If you read Spanish, read Sadin E. **El peligro acuciante de una 'telesociedad' generalizada.** El País 2020, published 28 September. Full-text: https://elpais.com/cultura/2020/09/25/babelia/1601052166_025818.html

El trabajo, la escuela y una gran parte de la vida social se han pixelizado de un día para otro. Ese cambio repentino pone en riesgo la cohesión de una socie-

dad fracturada, que sigue dependiendo en gran medida de los vínculos físicos y carnales.

French

If you read French, read **Le Covid-19 a fait au moins un million de morts dans le monde.** Le Monde 2020, published 28 September. Full-text: https://www.lemonde.fr/planete/article/2020/09/28/coronavirus-le-covid-19-a-fait-un-million-de-morts-dans-le-monde_6053836_3244.html

Le coronavirus SARS-CoV-2 a toujours une circulation très active, notamment en Europe, en Amérique et en Asie.

29 September

Vaccine

Helfland BK, Webb M, Gartaganis SL, et al. **The Exclusion of Older Persons From Vaccine and Treatment Trials for Coronavirus Disease 2019—Missing the Target**. JAMA Intern Med, September 28, 2020. Full-text: https://doi.org/10.1001/jamainternmed.2020.5084

Those most in need are excluded: in this important review, Benjamin Helfland and colleagues analyzed clinical COVID-19 trials for age exclusions. In 232 Phase 3 clinical trials, 38 included age cut-offs and 77 had exclusions preferentially affecting older adults. Of 18 vaccine trials, 11 included age cut-offs, and the remaining 7 had broad non-specified exclusions. These findings indicate that older adults are likely to be excluded from more than 50% of COVID-19 clinical trials and 100% of vaccine trials. Why? Such exclusion will limit the ability to evaluate the efficacy, dosage, and adverse effects of the intended treatments.

Transmission

Khanh NC, Thai PQ, Quach H-L, Thi NA-H, Dinh PC, Duong TN, et al. **Transmission of severe acute respiratory syndrome coronavirus 2 during long flight**. Emerg Infect Dis. 2020 Nov [date cited]. Original Publication Date: September 18, 2020. Full-text: https://doi.org/10.3201/eid2611.203299

If you don't wear a mask, business class does not protect you from infection: Nguyen Cong Khanh, Pham Quang Thai and colleagues report on a cluster among passengers on a 10-hour commercial flight from London to Hanoi on March 2 (at that time, the use of face masks was not mandatory on airplanes

or at airports). Affected persons were passengers, crew, and their close contacts. The authors traced 217 passengers and crew to their final destinations and interviewed, tested, and quarantined them. Among the 16 persons in whom SARS-CoV-2 infection was detected, 12 (75%) were passengers seated in business class along with the only symptomatic person (attack rate 62%). Seating proximity was strongly associated with increased infection risk (risk ratio 7.3, 95% CI 1.2–46.2).

Diagnostics

Yokota I, Shane PY, Okada K, et al. **Mass screening of asymptomatic persons for SARS-CoV-2 using saliva**. Clin Infect Dis. 2020 Sep 25:ciaa1388. PubMed: https://pubmed.gov/32976596. Full-text: https://doi.org/10.1093/cid/ciaa1388

Self-collected saliva is a valuable specimen to detect SARS-CoV-2 in mass screening of asymptomatic persons. In this study including 1,924 individuals from Japan, the sensitivity of nucleic acid amplification testing with nasopharyngeal and saliva specimens were 86% (90% CI:77-93%) and 92% (90% CI:83-97%), respectively, with specificities greater than 99.9%. In positive individuals, viral load was highly correlated between NPS and saliva.

Clark AE, Lee FM. **Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Screening With Specimen Pools: Time to Swim, or Too Deep for Comfort**? Clinical Infectious Diseases28 September 2020. Full-text: https://doi.org/10.1093/cid/ciaa1145

Sample pooling is an option to reduce costs and speed results. In this approach, small volumes of samples from multiple patients are combined into a single test, resulting in substantial reagent savings. If the pooled sample returns a negative result, all patients with specimens comprising that pool are considered not to be infected. Andrew Clark and Francesca Lee discuss several caveats and argue that careful and rigorous investigation is necessary to assure that the pooling of specimens does not impact the analytical sensitivity of the assay.

Salvatore PP, Dawson P, Wadhwa A, et al. **Epidemiological Correlates of PCR Cycle Threshold Values in the Detection of SARS-CoV-2**. Clinical Infectious Diseases 28 September 2020. Full-text: https://doi.org/10.1093/cid/ciaa1469

Phillip P Salvatore and colleagues from CDC examined the relationship between Ct (Cycle Threshold) values and demographic, clinical, and epidemiological characteristics collected through participant interviews and daily symptom diaries. Among 93 household members (including index cases) who tested positive for SARS-CoV-2 by NP swab, Ct values were lowest (corresponding to higher viral RNA concentration) soon after symptom onset and are significantly correlated with time elapsed since onset ($p < 0.001$); within 7 days after symptom onset, the median Ct value was 26.5 compared with a median Ct value of 35.0 occurring 21 days after onset. Ct values were significantly lower among participants under 18 years of age ($p = 0.01$) and those reporting upper respiratory symptoms at the time of sample collection ($p = 0.001$). Ct rates were higher among participants reporting no symptoms (probably due to high Ct values among post-symptomatic participants).

Clinical

El Moheb M, Naar L, Christensen MA, et al. **Gastrointestinal Complications in Critically Ill Patients With and Without COVID-19**. JAMA September 24, 2020. Full-text: https://doi.org/10.1001/jama.2020.19400

In their research letter, Mohamad El Moheb and colleagues compared the incidence of gastrointestinal complications of 92 critically ill patients with COVID-19–induced acute respiratory distress syndrome (ARDS) vs 92 comparably ill patients with non–COVID-19 ARDS using propensity score analysis. Patients with COVID-19 were more likely to develop gastrointestinal complications (74% vs 37%; P <0.001). Specifically, patients with COVID-19 developed more transaminitis (55% vs 27%), severe ileus (48% vs 22%), and bowel ischemia (4% vs 0%). High expression of ACE 2 receptors along the epithelial lining of the gut that act as host-cell receptors for SARS-CoV-2 could explain this.

Thapa SB, Kakar TS, Mayer C, et al. **Clinical Outcomes of In-Hospital Cardiac Arrest in COVID-19**. JAMA Intern Med. Published online September 28, 2020. Full-text: https://doi.org/10.1001/jamainternmed.2020.4796

Shrinjaya Thapa and colleagues from William Beaumont Hospital in Michigan deserve the award for the most sincere results of the day. Among 1,309 patients hospitalized with COVID-19, 60 (4.6%) developed in-hospital cardiac arrest (IHCA) and underwent CPR. Among 54 patients with CPR documentation, the initial rhythm was non-shockable for 52 patients (96.3%), with 44 with pulseless electrical activity and 8 with asystole. Return of spontaneous circulation (ROSC) was achieved in 29 patients (53.7%). Now guess how many

patients of these 54 patients survived? 10? 5? Wrong. The number was zero. There was a 100% mortality rate following CPR. According to the authors, these outcomes "warrant further investigation into the risks and benefits of performing prolonged CPR in this subset of patients, especially because the resuscitation process generates aerosols that may place health care personnel at a higher risk of contracting the virus". This devastating result is likely driven by several factors, including critical illness and non-shockable initial rhythms. Additionally, presumed respiratory etiology of arrest for most patients, lack of effective treatments and potential delays in response time for donning of personal protective equipment may have contributed.

Treatment

Vlaar AP, de Bruin S, Busch M, et al. **Anti-C5a antibody IFX-1 (vilobelimab) treatment versus best supportive care for patients with severe COVID-19 (PANAMO): an exploratory, open-label, phase 2 randomised controlled trial**. Lancet Rheumatology September 28, 2020. Full-text: https://doi.org/10.1016/S2665-9913(20)30341-6

In this open-label, randomized Phase 2 trial (part of the PANAMO trial), 15/30 patients with severe COVID-19 were treated with an anaphylatoxin and complement protein C5a blocking monoclonal antibody vilobelimab. Patients were randomly assigned 1:1 to receive vilobelimab (up to seven doses of 800 mg intravenously) or best supportive care only (control group). At day 5 after randomization, the primary endpoint of mean relative change in the ratio of partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air (PaO2/FiO2) was not significantly different between groups. Kaplan-Meier estimates of mortality by 28 days were 13% (95% CI 0–31) for the vilobelimab group and 27% (4–49) for the control group. The frequency of serious adverse events was similar between groups and no deaths were considered related to treatment assignment. These secondary outcome results support the investigation of vilobelimab in a Phase 3 trial using 28-day mortality as the primary endpoint.

Campbell CM. **The opening salvo of anti-complement therapy against COVID-19**. Lancet Rheumatology September 28, 2020. Full-text: https://doi.org/10.1016/S2665-9913(20)30353-2

Comment on the above study, considering the safe use and tolerability of vilobelimab as an important milestone. According to Courtney Campbell, the secondary outcomes reported are notable - in particular the fewer pulmonary embolisms (13% versus 40%). An important caveat, however, is that pharma-

cokinetic and pharmacodynamic analysis, including C5a, are to be published separately. Investigators using the C5 complement pathway inhibitors eculizumab and ravulizumab have significantly increased their dose and dosing frequency in the acute setting of COVID-19 compared with the doses approved for use in atypical hemolytic uremic syndrome. Whether vilobelimab in this trial successfully inhibited complement C5a in the setting of severe COVID-19 remains uncertain.

Tortorici A, Beltramello M, Lempp FA. **Ultrapotent human antibodies protect against SARS-CoV-2 challenge via multiple mechanisms**. Science 24 Sep 2020: eabe3354. Full-text: https://doi.org/10.1126/science.abe3354

M. Alejandra Tortorici and colleagues report the isolation and characterization of two ultra-potent SARS-CoV-2 human neutralizing antibodies (S2E12 and S2M11) that were identified among almost 800 screened Abs isolated from 12 individuals who recovered from COVID-19. Both nAbs protect hamsters against SARS-CoV-2 challenge. Cryo-electron microscopy structures show that S2E12 and S2M11 competitively block ACE2 attachment and that S2M11 also locks the spike in a closed conformation by recognition of a quaternary epitope spanning two adjacent receptor-binding domains. Cocktails including S2M11, S2E12 or the previously identified S309 antibody broadly neutralize a panel of circulating SARS-CoV-2 isolates and activate effector functions. The authors propose that combinations of mAbs leveraging multiple distinct mechanisms of action with additive or synergistic effects could provide additional benefits for clinical application.

30 September

Epidemiology

Otte im Kampe E, Lehfeld AS, Buda Set al. **Surveillance of COVID-19 school outbreaks, Germany, March to August 2020**. Euro Surveill 2020;25(38):pii=2001645. Full-text: https://doi.org/10.2807/1560-7917.ES.2020.25.38.2001645

Only a few and mostly small COVID-19 school outbreaks have been reported in Germany overall. Since the start of the COVID-19 pandemic and until 31 August 2020, only 48 (0.5%) of documented 8,841 outbreaks in occurred in schools and included 216 cases, suggesting that containment measures in place are sufficient to reduce spillover into the community.

Wilson E, Donovan CV, Campbell M, et al. **Multiple COVID-19 Clusters on a University Campus — North Carolina, August 2020**. MMWR Morb Mortal Wkly Rep. ePub: 29 September 2020. Full-text: http://dx.doi.org/10.15585/mmwr.mm6939e3

The campus may be another story. On August 3, 2020, a North Carolina university broadly opened campus for the first time since transitioning to primarily remote learning in March. Consistent with CDC guidance at that time, steps were taken to prevent the spread of SARS-CoV-2 on campus (daily symptom checks, use of masks in all indoor common spaces and classrooms, physical distancing of ≥ 6 feet in indoor and outdoor settings). These steps were not sufficient. Within 3 weeks, 670 laboratory-confirmed cases were identified; student gatherings and congregate living settings, both on and off campus, likely contributed to the rapid spread. Bad news for students.

Virology

Rosas-Lemus M, Minasov G, Shuvalova L, et al. **High-resolution structures of the SARS-CoV-2 2′-O-methyltransferase reveal strategies for structure-based inhibitor design**. Science Signaling, September 29: Vol. 13, Issue 651, eabe1202. Full-text: https://doi.org/10.1126/scisignal.abe1202

The components of the replication-transcription complex include enzymes that regulate mRNA and genomic RNA synthesis, proofreading, and mRNA maturation. Enzymes such as nsp16 are critical for capping viral mRNAs, a tactic used by multiple RNA viruses to avoid immune detection. Monica Rosas-Lemus and colleagues performed an x-ray crystallographic study of the SARS-CoV-2 nsp16-nsp10 2′-O-methyltransferase complex, which methylates Cap-0 viral mRNAs to improve viral protein translation and to avoid host immune detection. They solved crystal structures for the methyltransferase in complex with various combinations of its methyl donor and cap structure substrates, a reaction product, and an inhibitor. These structures suggest potential treatment strategies by disrupting the formation of the active enzyme complex or blocking its catalytic activity.

Immunology, Vaccine

Shrock E, Fujimura E, Kula T, et al. **Viral epitope profiling of COVID-19 patients reveals cross-reactivity and correlates of severity**. Science 29 Sep 2020. Full-text: https://doi.org/10.1126/science.abd4250

More on antibody response. This study provides deep serological profiling of 232 COVID-19 patients and 190 pre-COVID-19 era controls, revealing over 800

epitopes in the SARS-CoV-2 proteome, among them 10 epitopes likely recognized by neutralizing antibodies. Pre-existing antibodies in controls recognized SARS-CoV-2 ORF1, while only COVID-19 patients primarily recognized spike and nucleoprotein. A machine learning model predicted SARS-CoV-2 exposure history with 99% sensitivity and 98% specificity. Individuals with more severe COVID-19 exhibited stronger and broader SARS-CoV-2 responses, and weaker antibody responses to prior infections.

Anderson EJ, Rouphael NG, Widge AT, et al. **Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults**. NEJM September 29, 2020. Full-text: https://doi.org/10.1056/NEJMoa2028436

It was high time: a Phase 1, dose-escalation, open-label trial of a messenger RNA vaccine, mRNA-1273, which encodes the stabilized prefusion SARS-CoV-2 spike protein was expanded to include 40 older adults, who were stratified according to age (56 to 70 years or ≥ 71 years). After the second immunization, serum neutralizing activity was detected in all participants by multiple methods and appeared to be similar to those previously reported among vaccine recipients between the ages of 18 and 55 years and were above the median of a panel of controls who had donated convalescent serum. Adverse events included mostly mild-to-moderate local and systemic adverse events of short duration, which occurred predominantly after the second dose.

Transmission

Mondelli MU, Colaneri M, Seminari E, et al. **Low risk of SARS-CoV-2 transmission by fomites in real-life conditions**. Lancet Infect Dis September 29, 2020. Full-text: https://doi.org/10.1016/S1473-3099(20)30678-2

Some arguments that environmental contamination leading to SARS-CoV-2 transmission is unlikely to occur in real-life conditions, provided that standard cleaning procedures and precautions are enforced. The chance of transmission through inanimate surfaces is likely less frequent than hitherto recognized.

Clinical

Kabarriti R, Brodin P, Maron MI. **Association of Race and Ethnicity With Comorbidities and Survival Among Patients With COVID-19 at an Urban Medical Center in New York**. JAMA Netw Open September 25, 2020;3(9):e2019795. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.19795

Important finding: In this cohort study of 5,902 COVID-19 patients treated at a single academic medical center in New York, survival outcomes of non-Hispanic Black and Hispanic patients were *at least as good* as those of their non-Hispanic White counterparts when controlling for age, sex, and comorbidities. This is critical to further understanding the observed population differences in mortality by race/ethnicity reported elsewhere, ie it's a question of access to care?.

Severe COVID-19

Webb BJ, Pletan ID, Jensen P, et al. **Clinical criteria for COVID-19-associated hyperinflammatory syndrome: a cohort study**. Lancet Rheumatology September 29, 2020DOI: https://doi.org/10.1016/S2665-9913(20)30343-X

Brandon Webb and colleagues propose criteria for hyperinflammation in COVID-19. Based on 299 hospitalized patients, a six-criterion additive scale was developed using the following biomarkers: fever, macrophage activation (hyperferritinemia), hematological dysfunction (neutrophil to lymphocyte ratio), hepatic injury (lactate dehydrogenase or asparate aminotransferase), coagulopathy (D dimer), and cytokinaemia (C reactive protein, interleukin-6, or triglycerides). This hyperinflammatory state, cHIS, is commonly associated with progression to mechanical ventilation and death. External validation is needed. The cHIS scale might be helpful in defining target populations for trials and immunomodulatory therapies.

Treatment

Martinot M, Jary A, Fafi-Kremer S, et al. **Remdesivir failure with SARS-CoV-2 RNA-dependent RNA-polymerase mutation in a B-cell immunodeficient patient with protracted Covid-19**. Clinical Infectious Diseases, ciaa1474, https://doi.org/10.1093/cid/ciaa1474

The occurrence of a mutation in the RdRP (D484Y) gene following failure of remdesivir (given 5 days) in a 76-year-old woman with a post-rituximab B cell immunodeficiency and persistent SARS-CoV-2 viremia. The mutation was not present before treatment.

Severe COVID

Hattenstone S. **Michael Rosen on his Covid-19 coma: 'It felt like a pre-death, a nothingness'.** The Guardian 2020, published 30 September. Full-text: https://www.theguardian.com/books/2020/sep/30/michael-rosen-on-his-covid-19-coma-it-felt-like-a-pre-death-a-nothingness

Earlier this year, the beloved children's writer Michael Rosen spent six weeks on a ventilator with coronavirus. He talks about the magic of the NHS, the mismanagement of the crisis and how his near-death experience has changed him

Pediatrics

Viner RM, Mytton OT, Bonell C, et al. **Susceptibility to SARS-CoV-2 Infection Among Children and Adolescents Compared With Adults.** A Systematic Review and Meta-analysis. JAMA Pediatr. September 25, 2020. Full-text: https://doi.org/10.1001/jamapediatrics.2020.4573

In this systematic review and meta-analysis including 32 studies, children and adolescents younger than 20 years had 44% lower odds of secondary infection with SARS-CoV-2 compared with adults 20 years and older; this finding was most marked in those younger than 10-to-14 years. This estimate did not change much when only medium-quality or high-quality studies were examined, although power was reduced and significance was attenuated. However, most studies were undertaken when strict social distancing measures had been introduced such as closures of schools and data were insufficient to conclude whether transmission of SARS-CoV-2 by children is lower than by adults.

French

If you read French, read Roucaute D. **Le port du masque permet-il de s'immuniser contre le Covid-19 ?** Le Monde 2020, published 30 September. Full-text: https://www.lemonde.fr/planete/article/2020/09/30/le-port-du-masque-permet-il-de-s-immuniser-contre-le-covid-19_6054145_3244.html

Des chercheurs avancent l'hypothèse que se couvrir le visage permet le développement de formes bénignes ou asymptomatiques de la maladie.

Cabut S. **Covid-19 : avec les médecins de la dernière chance, à la Pitié-Salpêtrière.** Le Monde 2020, published 29 September. Full-text : https://www.lemonde.fr/sciences/article/2020/09/29/covid-19-avec-les-medecins-de-la-derniere-chance-a-la-pitie-salpetriere_6053980_1650684.html

Le service de réanimation de l'hôpital parisien est spécialisé dans un système de circulation extracorporelle pour oxygéner le sang, l'ECMO, destiné à certains patients en état critique.

1 October

Epidemiology

Laxminarayan R, Dudala SR, Gopal K, et al. **Epidemiology and transmission dynamics of COVID-19 in two Indian states**. Science 30 Sep 2020: eabd7672. Full-text: https://doi.org/10.1126/science.abd7672

A detailed view into SARS-CoV-2 transmission pathways and mortality in India. Among 102,569 cases in Tamil Nadu and 22,315 cases in Andhra Pradesh who tested positive at least 30 days before the end of the study follow-up period, the overall case-fatality ratio was 2.06%. Reported cases and deaths have been concentrated in younger cohorts than expected from observations in higher-income countries, even after accounting for demographic differences across settings. Among 575,071 individuals exposed to 84,965 confirmed cases, infection probabilities ranged from 4.7-10.7% for low-risk and high-risk contact types. Same-age contacts were associated with the greatest infection risk.

Immunology, Vaccine

Prévost J, Gasser R, Beaudoin-Bussières G. **Cross-sectional evaluation of humoral responses against SARS-CoV-2 Spike**. Cell Rep Med 2020, September 29, 2020. Full-text: https://doi.org/10.1016/j.xcrm.2020.100126

Another cross-sectional study on 106 different SARS-CoV-2-infected individuals to evaluate humoral responses against SARS-CoV-2 Spike. The vast majority of infected individuals showed anti-Spike antibodies within 2 weeks after the onset of symptoms. While most individuals develop neutralizing antibodies within two weeks of infection, the level of neutralizing activity significantly decreased over time. Interestingly, anti-RBD IgM presented a stronger correlation with neutralization than IgG and IgA, suggesting that at least part of the neutralizing activity is mediated by IgM. However, it remains unclear whether this reduced level of neutralizing activity would remain sufficient to protect from re-infection.

Burki T. **The online anti-vaccine movement in the age of COVID-19.** Lancet Digit Health. 2020 Oct;2(10):e504-e505. PubMed: https://pubmed.gov/32984795. Full-text: https://doi.org/10.1016/S2589-7500(20)30227-2

About 31 million people follow anti-vaccine groups on Facebook, with 17 million people subscribing to similar accounts on YouTube. Within a decade, the anti-vaccination movement could overwhelm pro-vaccination voices online. If that came to pass, the consequences would stretch far beyond COVID-19. This article discusses some strategies.

Clinical

Clark KEN, Nevin WD, Mahungu T, Lachmann H, Singh A. **Assessment of the Haemophagocytic lymphohistiocytosis HScore in patients with COVID-19**. Clin Infect Dis. 2020 Sep 28:ciaa1463. PubMed: https://pubmed.gov/32985664. Full-text: https://doi.org/10.1093/cid/ciaa1463

Secondary hemophagocytic lymphohistiocytosis (HLH) is a rare hyperinflammatory syndrome characterized by hypercytokinemia with multiorgan failure. Given the parallel in cytokine profile between HLH and COVID-19, it has been suggested that utilizing the HScore may help identify those patients with the most severe disease, and heightened inflammatory state, who may be more likely to benefit from immunosuppression. In this cohort, the HScore didn't work. The score did not identify those patients with COVID-19 most at risk of requiring higher levels of care, or at risk of deterioration and death.

Dowd JB, Rotondi V, Mills MC. **Dangerous to claim "no clear association" between intergenerational relationships and COVID-19**. PNAS September 29, 2020. Full-text: https://doi.org/10.1073/pnas.2016831117

Do intergenerational relationships (e.g., co-residence and contacts between family members of different generations) play a major role in the spread and lethality of COVID-19? A previous study from Italy (where case fatality rate was very high earlier this year) found no clear association. The authors doubt this to be the case. It remains crucial to be mindful of risks to older adults physically interacting with younger relatives.

Comorbidities, Collateral damage

Li L, Li F, Fortunati F, et al. **Association of a Prior Psychiatric Diagnosis With Mortality Among Hospitalized Patients With Coronavirus Disease 2019 (COVID-19) Infection**. JAMA Netw Open September 30, 2020; 3(9):e2023282. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.23282

Among a total of 1685 patients who were hospitalized with COVID-19, 473 (28%) received psychiatric diagnoses prior to hospitalization. After controlling for demographic characteristics, other medical comorbidities, and hospital location, the risk of death remained significantly greater among patients with a psychiatric disorder (hazard ratio, 1.5; 95% CI, 1.1-1.9; P = .003). Reasons are unclear. Psychiatric symptoms may arise as a marker of systemic pathophysiologic processes such as inflammation, that may, in turn, predispose to mortality. Similarly, psychiatric disorders may augment systemic inflammation and compromise the function of the immune system, while psychotropic medications may also be associated with mortality risk. Or is there confounding?

Toor J, Adams ER, Aliee M, et al. **Predicted Impact of COVID-19 on Neglected Tropical Disease Programs and the Opportunity for Innovation**. Clin Infect Dis. 2020 Sep 28:ciaa933. PubMed: https://pubmed.gov/32984870. Full-text: https://doi.org/10.1093/cid/ciaa933

Due to the COVID-19 pandemic, many key neglected tropical disease (NTD) activities have been postponed. However, disruption will vary amongst the diseases and there are ways to mitigate the impact and accelerate progress towards the ambitious WHO 2030 goals.

Diagnostics

Mina MJ, Parker R, Larremore DB. **Rethinking Covid-19 Test Sensitivity — A Strategy for Containment**. NEJM September 30, 2020. Full-text: https://doi.org/10.1056/NEJMp2025631

Strong statement (overdue, IMHO): the frequent use of cheap, simple, rapid tests are essential, even if their analytic sensitivities are vastly inferior to those of benchmark tests. The key question is not how well molecules can be detected in a single sample - but how effectively infections can be detected in a population by the repeated use of a given test as part of an overall testing strategy - the sensitivity of the testing regimen.

Treatment

Abella BS, Jolkovsky EL, Biney BT, et al. **Efficacy and Safety of Hydroxychloroquine vs Placebo for Pre-exposure SARS-CoV-2 Prophylaxis Among Health Care Workers: A Randomized Clinical Trial**. JAMA Intern Med September 30, 2020. Full-text: https://doi.org/10.1001/jamainternmed.2020.6319

This was one of the last open questions regarding hydroxychloroquine (HCQ): Does a regimen of 600 mg per day reduce the transmission of SARS-CoV-2 as a pre-exposure prophylaxis strategy when taken by hospital-based health care workers? The answer is clear: No. In this double-blind, placebo-controlled randomized clinical trial that included 132 HCW and was terminated early, there was not a significant difference in PCR–confirmed SARS-CoV-2 incidence between hydroxychloroquine and placebo cohorts. Mild adverse events were more common in participants taking hydroxychloroquine compared with placebo (45% vs 26%; p = .04).

French

If you understand French, listen to Duval K. **Nouvelle religion : le covidisme.** YouTube 2020, published 29 September. Video (4:44): https://www.youtube.com/watch?v=_48gKagPaB0

"Portez le masque, la foi viendra." JC (et un peu, beaucoup moi, aussi). By Karim Duval.

2 October

Epidemiology

Buonanno P, Galletta S, Puca M, et al. **Estimating the severity of COVID-19: Evidence from the Italian epicentre**. PLOS October 1, 2020. Full-text: https://doi.org/10.1371/journal.pone.0239569

A tentative estimate of the number of deaths either directly or indirectly associated with COVID-19 as well as the total number of persons infected. The findings by Paola Buonanno and colleagues suggest that the reported number of deaths attributable to COVID-19 identified by public authorities accounts only for one half of the observed excess mortality between March 2020 and previous years.

Virology

Cheng MH, Zhang S, Porritt RA, et al. **Superantigenic character of an insert unique to SARS-CoV-2 spike supported by skewed TCR repertoire in patients with hyperinflammation.** PNAS first published September 28, 2020. Full-text: https://doi.org/10.1073/pnas.2010722117

Mary Hongying Cheng and colleagues from Pittsburgh show that SARS-CoV-2 spike contains sequence and structure motifs highly similar to those of a bacterial superantigen and may directly bind T cell receptors. They also report a skewed T cell receptor repertoire in COVID-19 patients with severe hyperinflammation, in support of such a superantigenic effect. Notably, the superantigen-like motif is not present in other SARS family coronaviruses, which may explain the unique potential for SARS-CoV-2 to cause both MIS-C and the cytokine storm observed in adult COVID-19.

Pathogenesis

Zeberg H, Pääbo S. **The major genetic risk factor for severe COVID-19 is inherited from Neanderthals**. Nature September 30, 2020. Full-text: https://doi.org/10.1038/s41586-020-2818-3

Recently, a new dataset was released from the COVID-19 Host Genetics Initiative where the region on chromosome 3 is the only region significantly associated with severe COVID-19 at the genome-wide level. The risk variant in this region confers an odds ratio for requiring hospitalization of 1.6 (95% confidence interval: 1.42-1.79). The genetic variants which are most associated with severe COVID-19 on chromosome 3 are all in high linkage disequilibrium, i.e. they are all strongly associated with each other in the population (Ref). Here, the authors show that the risk is conferred by a genomic segment of ~50 kb that is inherited from Neanderthals and is carried by ~50% of people in South Asia and ~16% of people in Europe today.

COVID-19 Host Genetics Initiative. **The COVID-19 Host Genetics Initiative, a global initiative to elucidate the role of host genetic factors in susceptibility and severity of the SARS-CoV-2 virus pandemic**. Eur J Hum Genet. 2020 Jun;28(6):715-718. PubMed: https://pubmed.gov/32404885. Full-text: https://doi.org/10.1038/s41431-020-0636-6

Transmission

Freedman DO, Wilder-Smith A. **In-flight Transmission of SARS-CoV-2: a review of the attack rates and available data on the efficacy of face masks**. Journal of Travel Medicine September 25. Full-text: https://doi.org/10.1093/jtm/taaa178.

Review of outbreaks during flights. According to the authors, the absence of large numbers of confirmed and published in-flight transmissions of SARS-CoV is encouraging but not definitive evidence that fliers are safe. At present, based on circumstantial data, strict use of masks appears to be protective. Structured prospective studies to quantitate transmission risk on flight with rigid masking protocols are now most pressing.

Diagnostics

Perreault J, FournierMJ, Beaudoin-Bussières G, et al. **Waning of SARS-CoV-2 RBD antibodies in longitudinal convalescent plasma samples within four months after symptom onset**. Blood October 1, 2020. Full-text: https://doi.org/10.1182/blood.2020008367

Josée Perreault and colleagues from Québec, Canada have performed a longitudinal analysis of the anti-RBD antibody response in 15 CCP donors (11 males, 4 females, median age of 56 years, no donor was hospitalized) who donated at least four times, during a time interval after symptom onset ranging from 33-77 days for the first donation to 66-114 days for the last donation. A decrease in anti-RBD antibody level between first and last donation was observed for all donors.

Ziegler K, Steininger P, Ziegler R, et al. **SARS-CoV-2 samples may escape detection because of a single point mutation in the N gene**. Euro Surveill. 2020;25(39). Full-text: https://doi.org/10.2807/1560-7917.ES.2020.25.39.2001650

Katharina Ziegler and colleagues found that a single nucleotide polymorphism (SNP) in the nucleoprotein gene of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a patient interfered with detection in a widely used commercial assay. Some 0.2% of the isolates in the EpiCoV database contain this SNP. Although SARS-CoV-2 was still detected by the other probe in the assay, this underlines the necessity of targeting two independent essential regions of a pathogen for reliable detection.

Sullivan CB, Schwalje AT, Jensen M, et al. **Cerebrospinal Fluid Leak After Nasal Swab Testing for Coronavirus Disease 2019**. JAMA Otolaryngol Head Neck Surg. October 1, 2020. Full-text: https://doi.org/10.1001/jamaoto.2020.3579

Christopher Blake Sullivan describes a case of a cerebrospinal fluid (CSF) leak after nasal testing for COVID-19. After nasal COVID-19 testing for an elective hernia repair, a woman in her 40s presented shortly after with unilateral rhinorrhea, headache, and vomiting. Of note, the patient had an undiagnosed skull base defect at the fovea ethmoidalis that was present on imaging dating back to 2017. The authors therefore speculate that the swab itself did not result in a violation of the bony skull base, but rather the invasive test caused trauma to the patient's pre-existing encephalocele. However, adverse events may still occur owing to complex and delicate anatomy.

Clinical

Alvarado GR, Pierson BC, Teemer ES, et al. **Symptom Characterization and Outcomes of Sailors in Isolation After a COVID-19 Outbreak on a US Aircraft Carrier**. JAMA Netw Open. October 1, 2020. 2020;3(10):e2020981. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.20981

The US Army Public Health COVID-19 Task Force describes the results of an independent investigation of the shore-based USS Theodore Roosevelt outbreak response. Of 4,085 sailors who disembarked, 736 had a diagnosis of SARS-CoV-2 (median age, 25 years; interquartile range, 22-31 years; 78% male]. Of these, 590 sailors (80.2%) were characterized as symptomatic, with a median symptom duration of 7 days (interquartile range, 5-11 days) and 146 sailors (19.8%) remained asymptomatic for the duration of the study period. With regard to clinical outcomes, 729 sailors remained in outpatient isolation, 6 were hospitalized, and 1 (a "senior listed member in his 40s") died during the study period.

Lui GC, Yip TC, Wong VW, et al. **Significantly Lower Case-fatality Ratio of Coronavirus Disease 2019 (COVID-19) than Severe Acute Respiratory Syndrome (SARS) in Hong Kong - A Territory-Wide Cohort Study**. Clin Infect Dis. 2020 Oct 1:ciaa1187. PubMed: https://pubmed.gov/33005933. Full-text: https://doi.org/10.1093/cid/ciaa1187

Among a cohort of the first 1013 COVID-19 patients (mean age, 38.4 years; 53.9% male) diagnosed from 23 January to 14 April 2020 in Hong Kong, the CFR was 0.4%, and 5% had ICU admission or death within 30 days of hospital

admission. Age and diabetes were associated with worse outcomes, whereas antiviral treatments were not.

Treatment

Burki TK. **Completion of clinical trials in light of COVID-19**. Lancet Resp Med October 01, 2020. Full-text: https://doi.org/10.1016/S2213-2600(20)30460-4

Some thoughts on how running randomized trials at the same time as dealing with large numbers of critically ill patients. No small task, but "we have to give the same urgency to research on COVID-19 as we do to the clinical need."

Society

Another piece of fake news just to stay in the news? After the April speculations about "injecting" "disinfectant" to cure COVID-19, a fake president now reports a SARS-CoV-2 infection of himself and his spouse. How to believe those who produce more fake than truth? ICU pictures might help convince us.

Spanish

If you read Spanish, read Llaneras K. **Se superan las 100 muertes al día y un debate sigue ausente: ¿cuántas son demasiadas?** El País 2020, published 2 October. Full-text: https://elpais.com/politica/2020/10/01/actualidad/1601543892_815336.html

La saturación de las UCI es un problema. Pero no olvidemos que el coronavirus puede matar miles de personas sin saturarlas. (COVID-19 deaths are 20x more than traffic accidents, 100x more than homicides).

Álvarez P. **Pandemia de desigualdad.** El País 2020, published 2 October. Full-text: https://elpais.com/sociedad/2020-10-02/pandemia-de-desigualdad.html

La covid ahonda la brecha de género: las mujeres asumen más carga de trabajo y cuidados, son más frágiles ante la pobreza y la violencia y tienen menos voz en la toma de decisiones.

French

If you read French, read Roucaute D. **Les restaurants sont-ils des lieux plus à risque pour la transmission du Covid-19 ?** Le Monde 2020, published 2 October. Full-text : https://www.lemonde.fr/planete/article/2020/10/02/les-restaurants-sont-ils-des-lieux-plus-a-risque-pour-la-contamination-par-le-sars-cov-2_6054448_3244.html

Les études actuelles ne permettent pas d'affirmer le caractère superpropagateur de tous les restaurants, mais certains lieux favorisent des situations de transmission accrue du virus.

3 October

Epidemiology

Boehmer TK, DeVies J, Caruso E, et al. **Changing Age Distribution of the COVID-19 Pandemic — United States, May–August 2020.** MMWR Morb Mortal Wkly Rep 2020;69:1404–1409. DOI: http://dx.doi.org/10.15585/mmwr.mm6939e1

First the kids, then the parents and, finally the grandparents (with unknown outcome)? During June–August 2020, SARS-CoV-2 incidence was highest in persons aged 20–29 years, who accounted for > 20% of all confirmed cases. Across the southern United States in June 2020, increases in percentage of positive SARS-CoV-2 test results among adults aged 20–39 years preceded increases among those aged ≥ 60 years by 4–15 days. The authors' recommendations:

- Restrict in-person gatherings and events
- Recommend mask use and social distancing in settings where persons socialize
- Implement safe practices at on-site eating and drinking venues
- Enforce protection measures for essential and service industry workers

Transmission

Tufekci Z. **This Overlooked Variable Is the Key to the Pandemic.** The Atlantic 2020, published 30 September. Full-text: https://www.theatlantic.com/health/archive/2020/09/k-overlooked-variable-driving-pandemic/616548/

Even non-scientists have heard about R0 (pronounced as "r-naught")—the basic reproductive number of a pathogen, a measure of its contagiousness on average. But even some scientists may have not yet encountered *k*, the measure of its dispersion. If you haven't done it before, do it now: explore *k.* It's simply a way of asking whether a virus spreads in a steady manner or in big bursts, whereby one person infects many, all at once.

Gebrekidan S, Bennhold K, Apuzzo M, Kirkpatrick DD. **Ski, Party, Seed a Pandemic: The Travel Rules That Let Covid-19 Take Flight.** The New York Times 2020 published 1 October. Full-text: https://www.nytimes.com/2020/09/30/world/europe/ski-party-pandemic-travel-coronavirus.html

ISCHGL, Austria — They came from across the world to ski in the most famous resorts of the Austrian alps...

Spanish

If you read Spanish, read Sampedro J. **El evento de Ischgl.** El País 2020, published 3 October. Full-text: https://elpais.com/ciencia/2020-10-02/el-evento-de-ischgl.html

Una estación de esquí tirolesa propagó la covid a 40 países de cinco continentes.

Immunology

Goldman JD, Wang K, Roltgen K, et al. **Reinfection with SARS-CoV-2 and Failure of Humoral Immunity: a case report.** medRxiv. 2020 Sep 25:2020.09.22.20192443. PubMed: https://pubmed.gov/32995830. Full-text: https://doi.org/10.1101/2020.09.22.20192443

The authors describe a care-home resident in their sixties with two distinct episodes of symptomatic COVID-19 separated by 144 days. After the second infection, the patient produced only low levels of antibodies which decreased over time. The authors hope to get near the point where we understand the correlates of humoral immunity required to prevent reinfection. Note: This paper has not yet been peer reviewed.

Pathogenesis

Hewitt JA, Lutz C, Florence WC, et al. on behalf of the ACTIV Preclinical Working Group. **ACTIVating Resources for the COVID-19 Pandemic: In vivo Models for Vaccines and Therapeutics.** Cell Host Microbe 2020, published 1 October. Full-text: https://doi.org/10.1016/j.chom.2020.09.016

This review provides a snapshot that recommends the suitability of models for testing vaccines and therapeutics. Several species are permissive for SARS-CoV-2 replication, and more severe disease develops in a few models (some associated with advanced age, a risk factor for human disease). The key models appear to be mice (various), hamsters and for non-human primates, rhesus macaques and African green monkeys. The authors show that no single animal model recapitulates the totality of COVID-19 pathogenesis as faithfully as in the human; therefore, the coordination and assessment of animal models is imperative.

Clinical

Morris SB, Schwartz NG, Patel P, et al. **Case Series of Multisystem Inflammatory Syndrome in Adults Associated with SARS-CoV-2 Infection — United Kingdom and United States, March–August 2020.** MMWR Morb Mortal Wkly Rep. ePub: 2 October 2020. DOI: http://dx.doi.org/10.15585/mmwr.mm6940e1

MIS-C (*multisystem inflammatory syndrome in children*) in adults? The authors report a multisystem inflammatory syndrome in adults (MIS-A), describing 27 patients who had cardiovascular, gastrointestinal, dermatologic, and neurologic symptoms without severe respiratory illness. The authors call for clinicians to consider MIS-A in adults with compatible signs and symptoms. Recall that these patients may not have positive SARS-CoV-2 PCR or antigen test results; antibody testing might be needed to confirm previous SARS-CoV-2 infection.

Drug Development

Grobler JA, Anderson AS, Fernandes P, et al. **Accelerated preclinical paths to support rapid development of COVID-19 therapeutics.** Cell Host Microbe 2020, published 1 October. Full-text: https://doi.org/10.1016/j.chom.2020.09.017

Traditional drug discovery and development usually takes years from start to finish. To accelerate this process, the authors propose a minimum data package required to move a compound through clinical development safely. Fol-

low them on an accelerated path for antivirals, immunomodulators, anticoagulants and other agents.

Severe COVID

Liu YM, Xie J, Chen MM, et al. **Kidney function indicators predict adverse outcomes of COVID-19.** Med 2020, published 2 October. Full-text: https://doi.org/10.1016/j.medj.2020.09.001

Kidney injury is one more of the clinical COVID-19 complications. In this retrospective study, the authors analyzed data from 12,413 patients. At admission, the prevalence of elevated blood urea nitrogen (BUN), elevated serum creatinine (Scr), and decreased blood uric acid (BUA) at admission was 6.29%, 5.22%, 11.66%, respectively. The authors found that elevated baseline levels of BUN and Scr, and decreased level of BUA, were associated with a high risk of mortality.

Collateral Effects

Bakouny Z, Hawley JE, Choueiri TK, et al. **COVID-19 and Cancer:Current Challenges and Perspectives.** Cancer Cell 2020, published 1 October. Full-text: https://doi.org/10.1016/j.ccell.2020.09.018

The SARS-CoV-2 pandemic has affected patients with cancer in many ways (adverse outcomes in those who developed COVID-19, impact on the delivery of cancer care, etc.). In this review, the authors discuss the biological interplay between the two diseases and give practical recommendations for the management of patients with cancer during the pandemic. They also provide some insights from the cancer research community that might help develop novel therapies for all patients with COVID-19.

Education

Rubin EJ, Baden LR, Morrissey S. **Covid-19 Testing and the Individual Physician.** Audio interview (23:56). N Engl J Med 2020; 383:e99. Access: https://www.nejm.org/doi/full/10.1056/NEJMe2030753

The editors discuss how clinicians should respond to the results of various SARS-CoV-2 tests their patients might receive.

French

If you read French, read Reverchon A. **Robert Boyer: « Le capitalisme sort considérablement renforcé par cette pandémie »** - Le Monde 2020, published 2 October. Full-text : https://www.lemonde.fr/idees/article/2020/10/02/robert-boyer-le-capitalisme-sort-considerablement-renforce-par-cette-pandemie_6054441_3232.html

Le cofondateur, dans les années 1970, de « l'école de la régulation », livre, dans un entretien au « Monde », son diagnostic du choc qui ébranle aujourd'hui l'économie mondiale, et de ses devenirs possibles.

Ratti C. **« Et si le Covid-19 nous permettait de passer du tourisme effréné au tourisme raisonné ? »** - Le Monde 2020, published 2 October. Full-text : https://www.lemonde.fr/smart-cities/article/2020/10/02/et-si-le-covid-19-nous-permettait-de-passer-du-tourisme-effrene-au-tourisme-raisonne_6054584_4811534.html

Dans une tribune au « Monde », l'architecte italien Carlo Ratti, chercheur au MIT, propose aux villes d'imaginer un nouveau modèle de tourisme, plus « raisonné », davantage fondé sur la durée.

4 October

"Long COVID-19" in mild and moderate cases – what do we know?

By Christian Hoffmann

The profound physical impairments associated with critical COVID-19 illness are well known. Many patients with severe COVID-19, especially older patients and those with ARDS, will suffer long-term complications from an intensive care unit stay and from the effects of the virus on multiple body systems such has the lung, heart, blood vessels and the CNS.

However, there is growing evidence that even in some younger people with non-severe COVID-19 the illness may continue for weeks, even months. The persistent symptoms in these so-called "long haulers" fluctuate and range from severe fatigue, breathlessness, fast heart rate with minimal exertion, chest pain, pericarditis/myocarditis, hoarseness, skin manifestations and hair loss, acquired dyslexia, headaches, memory loss, relapsing fevers, joint pains,

and diarrhea. Symptoms may arise through several mechanisms including direct organ damage and involvement of immune function and the autonomic nervous system.

Here we present the Top 10 papers, focusing on post-acute findings in patients with mild-to-moderate COVID-19.

Persistent symptoms, Quality of Life

Carfì A, Bernabei R, Landi F; Gemelli Against COVID-19 **Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19**. JAMA. 2020 Aug 11;324(6):603-605. PubMed: https://pubmed.gov/32644129. Full-text: https://doi.org/10.1001/jama.2020.12603

In Rome, 143 patients discharged from hospital were assessed ***after a mean of 60 days after onset*** of the first COVID-19 symptom. During hospitalization, 73% had evidence of pneumonia but only 15% and 5% received non-invasive or invasive ventilation, respectively. Only 13% were completely free of any COVID-19-related symptom, while 32% had 1 or 2 symptoms and 55% had 3 or more. Many patients reported fatigue (53%), dyspnea (43%), joint pain (27%) and chest pain (28%). A worsened quality of life was observed among 44% of patients. Main limitations of the study are the lack of information on symptom history before acute COVID-19 illness and the lack of details on symptom severity.

Garrigues E, Janvier P, Kherabi Y, et al. **Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19**. J Infect. 2020 Aug 25:S0163-4453(20)30562-4. PubMed: https://pubmed.gov/32853602. Full-text: https://doi.org/10.1016/j.jinf.2020.08.029

Same direction: in Paris, persistent symptoms and health-related quality of life were assessed in 120/222 patients discharged from a COVID-19 ward unit, at ***a mean of 111 days after their admission***. The most frequently reported persistent symptoms were fatigue (55%), dyspnea (42%), loss of memory (34%), concentration and sleep disorders (28% and 31%, respectively) and, yes, hair loss (20%). Of note, ward and ICU patients showed no differences with regard to these symptoms. In both groups, EQ-5D (mobility, self-care, pain, anxiety or depression, usual activity) showed a slight difference in pain in the ICU group. The main limitation of the study: a high number of patients could not be reached.

Halpin SJ, McIvor C, Whyatt G, et al. **Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation**. J Med Virol. 2020 Jul 30. PubMed: https://pubmed.gov/32729939. Full-text: https://doi.org/10.1002/jmv.26368

The Journal of Medical Virology is notorious for publishing any crap. However, even in this journal, you can find something helpful. In this study, 100 survivors discharged from a large University hospital in Leeds, UK were interviewed ***29 and 71 days (mean 48 days) after discharge***. Among 68 patients who did not need ICU care, new fatigue was the most common symptom (60%, severe in 15%), followed by breathlessness (43%). There was a clinically significant drop in EQ-5D in 46%. However, this was a single point follow-up in hospitalized patients, and results may also be subject to reporting bias. Patients who had "received ward-based care were then selected randomly from the list... until a total of 100 participants had successfully followed up".

Tenforde MW, Kim SS, Lindsell CJ, et al. **Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network - United States, March-June 2020**. MMWR 2020 Jul 31;69(30):993-998. PubMed: https://pubmed.gov/32730238. Full-text: https://doi.org/10.15585/mmwr.mm6930e1

The only US data to date, including a random sample of adults testing positive at an outpatient visit. Telephone interviews were conducted at a **median of 16 (14–21) days after the test date**. Among 292 respondents, 94% reported experiencing one or more symptoms at the time of testing; 35% of these reported not having returned to their usual state of health by the date of the interview, increasing from 26% (those aged 18–34 years), 32% (35–49 years) to 47% (≥ 50 years). Among respondents reporting cough, fatigue, or shortness of breath at the time of testing, 43%, 35%, and 29%, respectively, continued to experience these symptoms at the time of the interview.

Pulmonary findings

Crameri GAG, Bielecki M, Züst R, Buehrer TW, Stanga Z, Deuel JW**. Reduced maximal aerobic capacity after COVID-19 in young adult recruits, Switzerland, May 2020**. Euro Surveill. 2020 Sep;25(36):2001542. PubMed: https://pubmed.gov/32914744. Full-text: https://doi.org/10.2807/1560-7917.ES.2020.25.36.2001542

Probably the best study to date that analyzed physical fitness before and after infection in 199 young, predominantly male military recruits (median age of

21 years). Recruits had had a "baseline" fitness test, performed 3 months prior to a large outbreak in the company. This test included trunk muscle, and upper extremity strength by a progressive endurance run (PER with calculated maximal aerobic capacity VO2 max), prone bridge test and seated shot put test. Baseline fitness values were compared with a fitness test at a median of ***45 days (31-58 days) after SARS-CoV-2 diagnosis***, Participants were grouped into convalescent recruits with symptomatic COVID-19 (n=68), asymptomatic cases (n=77) and a naive group without symptoms or laboratory evidence of SARS-CoV-2 infection (n=54). Results: neither of the strength tests differed significantly between the groups. However, there was a statistically significant decrease in VO2 max among convalescents compared with naive and asymptomatically infected recruits. Around 19% of the COVID-19 convalescents had a decrease of more than 10% in VO2 max, while none of the naive recruits showed such a decrease. While the overall effect of COVID-19 on VO2 max might be subtle, a significant subset of patients seemed to have lost more than 10% of their initial aerobic capacity.

Zhao YM, Shang YM, Song WB, et al. **Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery.** EClinicalMedicine. 2020 Aug;25:100463. PubMed: https://pubmed.gov/32838236. Full-text: https://doi.org/10.1016/j.eclinm.2020.100463

In 55 survivors from 3 tertiary hospitals of Henan Province, China with mostly moderate COVID-19 (14 requiring additional oxygen but no mechanical ventilation), pulmonary function tests and HRCT scan of the thorax were performed ***3 months after discharge***. Although all 55 patients had returned to their original work, the presenting symptoms included gastrointestinal symptoms (31%), headache (18%), fatigue (16%) and exertional dyspnea (15%). Of note, radiological abnormalities were detected in 71% and residual abnormalities of pulmonary function were observed in 25%, mostly demonstrated diffusion reductions.

Zhang P, Li J, Liu H, et al. **Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: a 15-year follow-up from a prospective cohort study**. Bone Res. 2020 Feb 14;8:8. PubMed: https://pubmed.gov/32128276. Full-text: https://doi.org/10.1038/s41413-020-0084-5

Is this what we can expect in a decade? The authors have performed a long-term follow-up study on the lungs of 80 SARS patients (all HCW). In 2018, 15

years after being infected, pulmonary interstitial damage and functional decline caused by SARS mostly recovered, with a greater extent of recovery within 2 years after rehabilitation. However, the number of patients with impaired FEF25%–75% values was 40% (16/52) 15 years after infection, and 38% had a reduced diffusion capacity.

Cardiac findings

Puntmann VO, Carerj ML, Wieters I, et al. **Outcomes of Cardiovascular Magnetic Resonance (CMR) Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19).** JAMA Cardiol. 2020 Jul 27:e203557. PubMed: https://pubmed.gov/32730619. Full-text: https://doi.org/10.1001/jamacardio.2020.3557

The best study to date on cardiac issues, including 100 COVID-19 patients at a mean age of 49 years. The median time between ***diagnosis and CMR was 71 (64-92) day***s. Most patients had recovered at home (n=67), with only minor or moderate (n=49) or without any symptoms (n=18). Compared with pre-COVID-19 status, 36% reported ongoing shortness of breath and general exhaustion, of whom 25 noted symptoms during less-than-ordinary daily activities, such as a household chore. CMR revealed cardiac involvement in 78% and ongoing myocardial inflammation in 60%, independent of preexisting conditions, severity of COVID-19 or from the time of diagnosis. The authors concluded that "participants with a relative paucity of preexisting cardiovascular condition and with mostly home-based recovery had frequent cardiac inflammatory involvement, which was similar to the hospitalized subgroup".

Rajpal S, Tong MS, Borchers J, et al. **Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection**. JAMA Cardiol. 2020 Sep 11:e204916. PubMed: https://pubmed.gov/32915194. Full-text: https://doi.org/10.1001/jamacardio.2020.4916

A comprehensive CMR examination in 26 competitive athletes, among them 14 asymptomatic and 12 with only mild symptoms. CMR was performed ***11-53 days after recommended quarantine***. In total 4/26 (15%) had CMR findings suggestive of myocarditis and 8/26 (31%) exhibited changes suggestive of prior myocardial injury. In 7/12 of patients with pathological findings, CMR had been performed at least three weeks after the positive SARS-CoV-2 test result.

Neurological findings

Lu Y, Li X, Geng D, et al. **Cerebral Micro-Structural Changes in COVID-19 Patients - An MRI-based 3-month Follow-up Study**. EClinicalMedicine. 2020 Aug;25:100484. PubMed: https://pubmed.gov/32838240. Full-text: https://doi.org/10.1016/j.eclinm.2020.100484

Magnetic Resonance Imaging (MRI) in 60 COVID-19 patients (47 classified as mild), performed at a ***mean of 97 days from symptom onset.*** Compared with 39 age- and sex-matched non-COVID-19 volunteers, recovered COVID-19 patients showed volumetric and micro-structural abnormalities that were detected mainly in the central olfactory cortices and partially in the white matter in the right hemisphere. According to the authors, these abnormalities might cause long-term burden to COVID-19 patients after recovery.

Taken together, clinical data is still scarce. However, it is dismissive to solely attribute persisting symptoms after mild or moderate COVID-19 to anxiety or to depression or to label them as anecdotal. "COVID-19 long haulers" are no hypochondriacs. There is an urgent need to quantify long-term complications properly and accurately, including non-hospitalized patients with mild disease. Several prospective studies are underway, and we will keep you updated. In the meantime, read these 10 **additional references.**

Five good reviews and perspectives

Alwan NA, Attree E, Blair JM, et al. **From doctors as patients: a manifesto for tackling persisting symptoms of covid-19**. BMJ. 2020 Sep 15;370:m3565. PubMed: https://pubmed.gov/32933949. Full-text: https://doi.org/10.1136/bmj.m3565

Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. **Management of post-acute covid-19 in primary care**. BMJ. 2020 Aug 11;370:m3026. PubMed: https://pubmed.gov/32784198. Full-text: https://doi.org/10.1136/bmj.m3026

Marshall M. **The lasting misery of coronavirus long-haulers**. Nature. 2020 Sep;585(7825):339-341. PubMed: https://pubmed.gov/32929257. Full-text: https://doi.org/10.1038/d41586-020-02598-6

Rubin R. **As Their Numbers Grow, COVID-19 "Long Haulers" Stump Experts**. JAMA. 2020 Sep 23. PubMed: https://pubmed.gov/32965460. Full-text: https://doi.org/10.1001/jama.2020.17709

Yelin D, Wirtheim E, Vetter P, et al. **Long-term consequences of COVID-19: research needs**. Lancet Infect Dis. 2020 Oct;20(10):1115-1117. PubMed: https://pubmed.gov/32888409. Full-text: https://doi.org/10.1016/S1473-3099(20)30701-5

Five impressive case reports

Alwan NA. **Track COVID-19 sickness, not just positive tests and deaths**. Nature. 2020 Aug;584(7820):170. PubMed: https://pubmed.gov/32782377. Full-text: https://doi.org/10.1038/d41586-020-02335-z

Crosby SS. **My COVID-19**. Ann Intern Med. 2020 Aug 11. PubMed: https://pubmed.gov/32777184. Full-text: https://doi.org/10.7326/M20-5126

Draulans D. **Scientist who fought Ebola and HIV reflects on facing death from COVID-19**. Sciencemag 2020, May 8. Full-text: https://www.sciencemag.org/news/2020/05/finally-virus-got-me-scientist-who-fought-ebola-and-hiv-reflects-facing-death-covid-19

Miglis MG, Prieto T, Shaik R, Muppidi S, Sinn DI, Jaradeh S. **A case report of postural tachycardia syndrome after COVID-19**. Clin Auton Res. 2020 Sep 3:1-3. PubMed: https://pubmed.gov/32880754. Full-text: https://doi.org/10.1007/s10286-020-00727-9

Paul Garner's experience: **For 7 weeks I have been through a roller coaster of ill health, extreme emotions, and utter exhaustion**. The BMJ Opinion, 5 May 2020. Full-text: https://blogs.bmj.com/bmj/2020/05/05/paul-garner-people-who-have-a-more-protracted-illness-need-help-to-understand-and-cope-with-the-constantly-shifting-bizarre-symptoms (accessed 16 May 2020)

5 October

What did they give him?

By Christian Hoffmann

Trump is still receiving remdesivir, famotidine and dexamethasone. All relevant data on these compounds can be found in our COVID Reference book (for dexa which was added on Saturday to his therapy, see also WHO statement below). However, the most interesting treatment he has received is 8 g IV of **REGN-CoV-2**, a pair of two new monoclonal antibodies, named REGN10987 and REGN10933. Here we summarize the data published to date, based on key publications.

Hansen J, Baum A, Pascal KE, et al. **Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail**. Science. 2020 Aug 21;369(6506):1010-1014. PubMed: https://pubmed.gov/32540901 . Full-text: https://doi.org/10.1126/science.abd0827

Researchers from Regeneron have generated a large panel of antibodies against the spike protein from humanized mice and from three recovered patients. From this panel, approximately 40 antibodies with distinct sequences and potent neutralization activities were chosen for additional characterization, including antibody pairs that do not compete for binding to the receptor binding domain (RBD). REGN10987 and REGN10933 represent such a pair of antibodies: REGN10933 binds at the top of the RBD, extensively overlapping the binding site for ACE2. On the other hand, the epitope for REGN10987 is located on the side of the RBD, away from the REGN10933 epitope, and has little to no overlap with the ACE2 binding site.

Baum A, Fulton BO, Wloga E, et al. **Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies**. Science. 2020 Aug 21;369(6506):1014-1018. PubMed: https://pubmed.gov/32540904 . Full-text: https://doi.org/10.1126/science.abd0831

Proof of principle in a cell model, using vesicular stomatitis virus pseudoparticles expressing the SARS-CoV-2 spike protein. Simultaneous treatment with REGN10933 and REGN10987 precluded the appearance of escape mutants. Thus, this cocktail did not rapidly select for mutants, presumably because escape would require the unlikely occurrence of simultaneous viral mutation

at two distinct genetic sites, so as to ablate binding and neutralization by both antibodies in the cocktail.

Regeneron. **REGN-COV-2 Antibody Cocktail Program Updates, September 29, 2020**. https://investor.regeneron.com/static-files/a596a85e-e72d-4529-8eb5-d52d87a99070

The first clinical data on REGN-CoV-2 (REGN10933 + REGN10987), published online a few days ago (not peer reviewed). Regeneron called it "a descriptive analysis on the first ~275 patients", derived from a broad ongoing clinical development program. Adult, non-hospitalized COVID-19 patients with symptom onset ≤7 days from randomization and not on any putative COVID-19 therapies were randomized to receive single doses of REGN-CoV-2 at 2.4 g IV (lower dose), at 8 g IV (higher dose) or placebo. Mean age was 44 years (49% male, 55% hispanic, 42% obese, 65% with >1 risk factors for severe COVID-19). Before treatment, serology was used to divide patients into positive (n=123) versus negative (n=113). As expected, "viral load" in nasopharyngeal (NP) swabs was higher in seronegative patients (7.18 versus 3.49 log10 copies/mL). Main results showed a modest viral load reduction mainly in seronegative patients and a lack of a numerical dose-response relationship:

- REGN-COV2 appeared to reduce viral load through day 7 mainly in seronegative patients: the mean NP viral load reduction was -1.98 (high) and -1.89 log10 copies/mL (low dose), compared to -1.38 with placebo (difference versus placebo -0.56 for both dosage groups, p=0.02).
- If all patients were included (including seropositives), the reduction was -1.92 and -1.64 log10 copies/mL, compared to 1.41 with placebo (difference versus placebo -0.37, significance only seen with high dose).
- Patients with higher baseline viral levels had correspondingly greater reductions in viral load .
- Median time to symptom alleviation for the overall population (median) was 8, 6 and 9 days for high, low dose and placebo, respectively (seronegative only: 8, 6 and 13).
- As for medically-attended visits, there was a numerical reduction versus placebo, but with just 12 visits in total there was no way of discerning the relevance. Most non-hospitalized patients recovered well at home.

- Both doses were well-tolerated. Infusion reactions and severe adverse events were balanced across all groups, no deaths occurred.

That's what we have: half a log in NP swabs, after a week. There is no doubt that larger data are urgently needed, in patients with more severe disease and in older patients. If approved, Regeneron will distribute REGN-COV2 in the U.S. and Roche will be responsible for distribution outside the U.S.

Additional references

Padmanabhan P, Desikan R, Dixit NM. **The quantitative landscape of the neutralizing antibody response to SARS-CoV-2**. Full-text: https://doi.org/10.1101/2020.09.25.20201996

This article is a preprint and has not been peer-reviewed. The study collates, compares, and ranks available Nabs (including REGN10987 and REGN10933), laying out the landscape of NAb responses currently observed including in patients, and informs ongoing efforts to develop NAb-based interventions for SARS-CoV-2 infection.

Sajna KV, Kamat S. **Antibodies at work in the time of severe acute respiratory syndrome coronavirus 2**. Cytotherapy. 2020 Aug 31:S1465-3249(20)30846-X. PubMed: https://pubmed.gov/32988772 . Full-text: https://doi.org/10.1016/j.jcyt.2020.08.009

In this nice review, the authors discuss up-to-date advances in immune-based therapy for COVID-19.

Wan Y, Shang J, Sun S, et al. **Molecular Mechanism for Antibody-Dependent Enhancement of Coronavirus Entry**. J Virol. 2020 Feb 14;94(5):e02015-19. PubMed: https://pubmed.gov/31826992 . Full-text: https://doi.org/10.1128/JVI.02015-19. Print 2020 Feb 14

Antibody-dependent enhancement (ADE) of viral entry has been a major concern for antibody-based drug therapy. ADE of viral entry has been studied extensively in other viruses and has been observed in coronaviruses for decades. Some advances on molecular mechanisms.

Dyer O. Covid-19: **Trump tests positive as US cases climb**. BMJ 2020; 371 October 2, 2020. Full-text: https://doi.org/10.1136/bmj.m3861

For the record: Trump is the eighth national leader believed to have contracted the virus, joining some others who were notably dismissive of its gravity. The leaders of the UK, Brazil, Bolivia, Guatemala, Honduras, and Armenia have all had the disease, with varying symptoms. The president of Burundi, Pierre Nkurunziza, who insisted that "God will spare Burundi" from the pandemic, is believed to have become the first national leader and first Burundian to die from covid-19 in June (though his government claimed he died from heart failure).

Perano U, Baker S. **Trumpworld coronavirus tracker**. https://www.axios.com/trump-republicans-coronavirus-covid-positive-0c465d3b-b1df-4096-a1b8-6df63efbf2f7.html

Current overview about the White House outbreak.

Physician to the President. **Health Update on President Donald J. Trump** October 2, 2020. https://twitter.com/PressSec/status/1312122950133272576?ref_src=twsrc%5Etfw%7Ctwcamp%5Etweetembed%7Ctwterm%5E1312122950133272576%7Ctwgr%5Eshare_3&ref_url=https%3A%2F%2Ftime.com%2F5895771%2Ftrump-regeneron-covid-cocktail%2F

Official statement on Trump's initial treatment, given by Sean P. Conley, physician to the president. Well, "polyclonal"? Are we mistaken?

WHO. **Corticosteroids for COVID-19, living guidance September 2, 2020**. https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1

WHO suggests NOT to use corticosteroids in the treatment of patients with non-severe COVID-19. WHO recommends systemic corticosteroids for the treatment of patients with severe and critical COVID-19 (strong recommendation, based on moderate certainty evidence). However, the panel noted that the oxygen saturation threshold of 90% to define severe COVID-19 was arbitrary and should be interpreted cautiously when used for determining which patients should be offered systemic corticosteroids. For example, clinicians must use their judgement to determine whether a low oxygen saturation is a sign of severity or is normal for a given patient suffering from chronic lung disease. Similarly, a saturation above 90–94% on room air may be abnormal if the clinician suspects that this number is on a downward trend.

6 October

Epidemiology

Hicks SM, Pohl K, Neeman T, et al. **A dual antigen ELISA allows the assessment of SARS-CoV-2 antibody seroprevalence in a low transmission setting**. J Infect Dis. 2020 Oct 3:jiaa623. PubMed: https://pubmed.gov/33009908 . Full-text: https://doi.org/10.1093/infdis/jiaa623

There is low prevalence in Australia. Using an ELISA-based approach that combines IgG responses to both the Nucleocapsid and Spike-receptor binding domain antigens, the authors have shown that excellent sensitivity and specificity can be achieved in low prevalence areas. Frequency of antibodies in a cohort of 2,991 elective surgery patients providing blood samples at 10 hospital sites across Australia in June-July 2020 was only 0.28% (0 to 1.15%).

Immunology

Meckiff BJ, Ramírez-Suástegui C, Fajardo V, et al. **Imbalance of regulatory and cytotoxic SARS-CoV-2-reactive CD4+ T cells in COVID-19**. Cell October 05, 2020. Full-text: https://doi.org/10.1016/j.cell.2020.10.001

CD4+ T cells are essential for adaptive anti-viral immunity. However, due to the rarity of SARS-CoV-2-specific cells in the total CD4+ T cell populations, signals from these cells are likely to be masked by the relative abundance of other non-antigen specific CD4+ T cells. Benjamin J. Meckiff from La Jolla (USA) provides important insights into the gene expression patterns of SARS-CoV-2-reactive CD4+ T cells by performing single-cell transcriptomic analysis of > 100,000 viral antigen-reactive CD4+ T cells from 40 COVID-19 patients. They found remarkable heterogeneity in the nature of CD4+ T cell subsets that are reactive to SARS-CoV-2 and other respiratory viruses, and across individual patients with differing severity of COVID-19. In 18 hospitalized patients (compared to 22 non-hospitalized patients), proportions of cytotoxic follicular helper (TFH) cells and cytotoxic T helper cells (CD4-CTLs) responding to SARS-CoV-2 were increased, while the proportion of SARS-CoV-2-reactive regulatory T cells (TREG) were reduced. Importantly, in hospitalized COVID-19 patients, a strong cytotoxic TFH response was observed early in the illness which correlated negatively with antibody levels to SARS-CoV-2 spike protein. Polyfunctional T helper (TH)1 and TH17 cell subsets were underrepresented in the repertoire of SARS-CoV-2-reactive CD4+ T cells compared to influenza-reactive CD4+ T cells.

Transmission

Schwartz NG, Moorman AC, Makaretz A, et al. **Adolescent with COVID-19 as the Source of an Outbreak at a 3-Week Family Gathering — Four States, June–July 2020**. MMWR Morb Mortal Wkly Rep. ePub: 5 October 2020. Full-text: http://dx.doi.org/10.15585/mmwr.mm6940e2

Children can serve as the source for COVID-19 outbreaks, even when their symptoms are mild. In this outbreak that occurred during a 3-week family gathering of five households, an adolescent aged 13 years was the suspected primary patient. Among the 14 persons who stayed in the same house, 12 experienced symptoms. Of note, none of the additional six family members who maintained outdoor physical distance without face masks during two longer visits (10 and 3 hours) to the family gathering developed symptoms.

Diagnostics

Procop GW, Brock JE, Reineks EZ, et al. **A Comparison of Five SARS-CoV-2 Molecular Assays With Clinical Correlations**. Am J Clin Pathol. 2020 Oct 5:aqaa181. PubMed: https://pubmed.gov/33015712 . Full-text: https://doi.org/10.1093/ajcp/aqaa181

A total of 239 specimens (168 contained SARS-CoV-2) were tested by five nucleic acid amplification test methods. The assays that lacked a nucleic acid extraction step produced more false-negative reactions than assays that included this step. The false-negative rates were 0% for the 2019-nCoV Real-Time RT-PCR Diagnostic Panel (CDC), 3.5% for TIB MOLBIOL Assay (Roche), 2.4% for Xpert Xpress SARS-CoV-2 (Cepheid), 11.9% for Simplexa COVID-19 Direct Kit (DiaSorin), and 16.7% for the ID Now COVID-19 (Abbott). Most false negatives were seen in patients with low viral loads.

Yilmaz A, Marklund E, Andersson M, et al. **Upper respiratory tract levels of SARS-CoV-2 RNA and duration of viral RNA shedding do not differ between patients with mild and severe/critical COVID-19**. J Infect Dis. 2020 Oct 6:jiaa632. PubMed: https://pubmed.gov/33020822 . Full-text: https://doi.org/10.1093/infdis/jiaa632

Aylin Yilmaz and colleagues from Gothenburg, Sweden have analyzed viral RNA loads over time from nasopharynx/throat in 56 patients with mild and severe/critical COVID-19. Neither the viral RNA loads in the upper respiratory tract, nor the time to viral RNA clearance differed between patients with mild or severe/critical disease.

Clinical

Grasselli G, Greco M, Zanella A, et al. **Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy**. JAMA Intern Med 2020; 180(10):1345-1355. Full-text: https://doi.org/10.1001/jamainternmed.2020.3539

An update from Lombardy, Italy. This large retrospective observational cohort study included 3,988 consecutive critically ill patients referred for ICU admission until April 22, 2020. Median age was 63 (IQR 56-69) and 79.9% were men. At ICU admission, 87.3% required invasive mechanical ventilation (IMV). The median length of IMV was 10 (IQR, 6-17) days. In the subgroup of the first 1,715 patients, as of May 30, 2020, 836 (48.7%) died in the ICU. Independent risk factors associated with mortality included older age (hazard ratio 1.75), male sex (1.57), high fraction of inspired oxygen (1.14), high positive end-expiratory pressure (1.04) and history of chronic obstructive pulmonary disease (1.68), hypercholesterolemia (1.25), and type 2 diabetes (1.18).

Treatment

RECOVERY Collaborative Group, and others. **Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial**. Lancet October 5, 2020. Full-text: https://doi.org/10.1016/S0140-6736(20)32013-4

After preliminary results were made public on June 29, 2020, this is now the full paper on the lopinavir/r arm in the RECOVERY trial. Between March 19, 2020, and June 29, 2020, 1,616 patients admitted to hospital were randomly allocated to receive lopinavir/r and 3,424 patients to receive usual care. Lopinavir/r had no benefit. Overall, 374 (23%) patients allocated to lopinavir/r and 767 (22%) patients allocated to usual care died within 28 days. Results were consistent across all prespecified subgroups. No significant difference in time until discharge alive from hospital (median 11 days in both groups) or the proportion of patients discharged from hospital alive within 28 days was found. Although the lopinavir/r, dexamethasone, and hydroxychloroquine groups have now been stopped, the RECOVERY trial continues to study the effects of azithromycin, tocilizumab, convalescent plasma, and REGN-CoV2 (see our Trump special yesterday).

Wilt TJ, Kaka AS, MacDonald R, Greer N, Obley A, Duan-Porter W. **Remdesivir for Adults With COVID-19: A Living Systematic Review for an American College of Physicians Practice Points**. Ann Intern Med Oct 5, 2020. PubMed: https://pubmed.gov/33017170 . Full-text: https://doi.org/10.7326/M20-5752

And what about remdesivir? This review of published studies through 31 August 2020 (4 RCTs) indicates that in hospitalized adults with COVID-19, remdesivir "probably" improves recovery and reduces serious adverse events and may reduce mortality and time to clinical improvement, although with little to no difference in hospital length of stay. Recovery due to remdesivir may not vary by age, sex, symptom duration, or disease severity.

Jose Luis Rodriguez-Garcia, Gines Sanchez-Nievas, Juan Arevalo-Serrano, Cristina Garcia-Gomez, Jose Maria Jimenez-Vizuete, Elisa Martinez-Alfaro. **Baricitinib improves respiratory function in patients treated with corticosteroids for SARS-CoV-2 pneumonia: an observational cohort study.** Rheumatology, October 6, 2020. Full-text: https://doi.org/10.1093/rheumatology/keaa587

Janus kinase (JAK) inhibitors such as baricitinib may be beneficial in treating SARS-CoV-2 infection by inhibiting ACE2-mediated endocytosis. This observational study enrolled patients with moderate to severe SARS-CoV-2 pneumonia who received lopinavir/ritonavir and HCQ plus either corticosteroids (controls, n=50) or corticosteroids and baricitinib (n=62). A higher proportion of patients required supplemental oxygen both at discharge (62% vs 26%) and 1 month lat

for a possible synergistic effect of baricitinib and corticosteroids in SARS-CoV-2 pneumonia.

Pediatrics

Anil R. Maharaj, PhD; Huali Wu, PhD; Christoph P. Hornik, et al. **Simulated Assessment of Pharmacokinetically Guided Dosing for Investigational Treatments of Pediatric Patients With Coronavirus Disease 2019**. JAMA Pediatr October 5, 2020; 174(10):e202422. Full-text: https://doi.org/10.1001/jamapediatrics.2020.2422

This pharmacokinetic simulation study estimates appropriate pediatric-specific dosing regimens for remdesivir. The pediatric dosing for Ebola virus disease (EVD), consisting of 5 mg/kg intravenous load (day 1) followed by 2.5 mg/kg daily (≥ day 2), may be too high in children younger than 12 years (ge-

ometric mean plasma AUC 0 to infinity values were 147% to 256% of the adult value for simulations based on dosing recommendations for EVD).

French

If you read French, read **Covid-19 : en Ile-de-France, plus de 40 % des lits en réanimation sont occupés par des patients contaminés.** Le Monde 2020, published 6 October. Full-text : https://www.lemonde.fr/planete/article/2020/10/06/en-ile-de-france-plus-de-40-des-lits-en-reanimation-sont-occupes-par-des-malades-du-covid-19_6055013_3244.html

Sur 2 393 patients Covid-19 hospitalisés dans les huit départements d'Ile-de-France, 449 ont été admis en service de réanimation, a annoncé mardi l'ARS.

7 October

Epidemiology

Gallaway MS, Rigler J, Robinson S, et al. **Trends in COVID-19 Incidence After Implementation of Mitigation Measures — Arizona, January 22–August 7, 2020**. MMWR Morb Mortal Wkly Rep. ePub: 6 October 2020. Full-text: http://dx.doi.org/10.15585/mmwr.mm6940e3

How community mitigation measures can help slow the spread of COVID-19. Case numbers in Arizona stabilized and then decreased after sustained implementation and enforcement of statewide and locally enhanced mitigation measures, beginning approximately 2 weeks after implementation and enforcement of mask mandates and enhanced sanitation practices began on June 17; further decreases were observed during July 13–August 7, after statewide limitations and closures of certain services and businesses.

Calcagno A, Ghisetti V, Emanuele T, et al. **Risk of SARS-CoV-2 infection in healthcare workers, Turin, Italy**. Emerg Infect Dis. 2021 Jan. Full-text: https://doi.org/10.3201/eid2701.203027

Among 5,444 healthcare workers in Italy, seroprevalence was 6.9%. Seroprevalence was highest in laboratory personnel (18/175, 10.3%), although numbers were small, followed by nurse assistants (44/520, 8.5%), nurses (150/1983, 7.6%), and doctors (55/755, 7.3%).

Vogel G. **It's been so, so surreal.' Critics of Sweden's lax pandemic policies face fierce backlash**. Science October 6, 2020. Full-text: https://doi.org/10.1126/science.abf1247

Sweden's approach to the coronavirus pandemic is out of step with much of the world. Until last month, Sweden's official policy stated that people without obvious symptoms are very unlikely to spread the virus. Read how the Vetenskapsforum COVID-19 (Science Forum COVID-19) is fighting for tougher measures and how members have been pilloried or reprimanded.

Transmission

Prather KA, Marr LC, Schooley RT, et al. **Airborne transmission of SARS-CoV-2.** Science 05 Oct 2020: eabf0521. Full-text: https://doi.org/10.1126/science.abf0521

According to Kimberly Prather and colleagues, we must clarify the terminology to distinguish between aerosols and droplets using a size threshold of 100 µm, not the historical 5 µm. This size more effectively separates their aerodynamic behavior, ability to be inhaled, and efficacy of interventions. Viruses in droplets (larger than 100 µm) typically fall to the ground in less than 2 m of the source and can be sprayed like tiny cannonballs onto nearby individuals.

Clinical

Matschke J, Lütgehetmann M, Hagel C, et al. **Neuropathology of patients with COVID-19 in Germany: a post-mortem case series**. Lancet Neurology, October 5, 2020. Full-text: https://doi.org/10.1016/S1474-4422(20)30308-2

Jakob Matschke and colleagues from Hamburg, Germany have investigated the neuropathological features in the brains of 43 patients who died from COVID-19. Neuropathological changes seemed to be mild, with pronounced neuroinflammatory changes in the brainstem being the most common finding. There was no evidence for CNS damage directly caused by SARS-CoV-2. SARS-CoV-2 could be detected in the brains of 21 (53%) of 40 examined patients but was not associated with the severity of neuropathological changes.

Frontera JA, Sabadia S, Lalchan R, et al. **A Prospective Study of Neurologic Disorders in Hospitalized COVID-19 Patients in New York City**. Neurology. 2020 Oct 5:10.1212/WNL.0000000000010979. PubMed: https://pubmed.gov/33020166. Full-text: https://doi.org/10.1212/WNL.0000000000010979

Of 4,491 hospitalized COVID-19 patients, 606 (13.5%) developed a new neurologic disorder. The most common diagnoses were: toxic/metabolic encephalopathy (6.8%, temporary/reversible changes in mental status in the absence of focal neurologic deficits or primary structural brain disease, excluding patients in whom sedative or other drug effects or hypotension explained this), seizure (1.6%), stroke (1.9%), and hypoxic/ischemic injury (1.4%). No patient had meningitis/encephalitis, or myelopathy/myelitis referable to SARS-CoV-2 infection and 18/18 CSF specimens were RT-PCR negative for SARS-CoV-2. In-hospital mortality was increased for patients with neurological disorders (Hazard Ratio 1.38, 95% CI 1.17-1.62).

Schwartz A, Yogev Y, Zilberman A, et al. **Detection of SARS-CoV-2 in vaginal swabs of women with acute SARS-CoV-2 infection: a prospective study**. BJOG. 2020 Oct 5. PubMed: https://pubmed.gov/33021026. Full-text: https://doi.org/10.1111/1471-0528.16556

In this prospective study of 35 women who were diagnosed with acute SARS -CoV- 2 infectio
swabs were positive in 2 (5.7%). One was pre -menopausal an
post disease menopausal woman. Both women had mild

Severe COVID-19

Moiseev S, Avdeev S, Brovko M, et al. **Outcomes of intensive care unit patients with COVID-19: a nationwide analysis in Russia.** Anaesthesia. 2020 Oct 5. PubMed: https://pubmed.gov/33015828. Full-text: https://doi.org/10.1111/anae.15265

Same bad outcomes of ICU patients in Russia. In a nationwide study, the authors have evaluated the mortality rate in 1522 consecutive ICU patients with SARS -CoV- 2 pneumo
recovery) up to 7 July 2020. The 14- and 28-day mortality rates were 44.0% and 63.6%, respectively.

Brown J, Gregson FKA, Shrimpton A, et al. **A quantitative evaluation of aerosol generation during tracheal intubation and extubation.** Anaesthesia. 2020 Oct 6. PubMed: https://pubmed.gov/33022093. Full-text: https://doi.org/10.1111/anae.15292

This group conducted real -time, high- reso
in ultraclean ventilation operating theatres during tracheal intubation and extubation sequences. Interestingly, both intubation and extubation sequenc-

es produced less aerosol than voluntary coughing. For the sequence of tracheal intubation, in particular, the concentration of aerosol generated was several orders of magnitude less than a single cough and was only very modestly above background levels of circulating particles.

Treatment

Abi Jaoude J, Kouzy R, El Alam MB, et al. **Exclusion of Older Adults in COVID-19 Clinical Trials**. Mayo Clin Proc. 2020 Oct;95(10):2293-2294. PubMed: https://pubmed.gov/33012364. Full-text: https://doi.org/10.1016/j.mayocp.2020.08.018

A data query of the ClinicalTrials.gov registry for trials regarding COVID-19 on June 8 revealed that 206/674 COVID-19 interventional trials (30.6%) had an upper age exclusion criterion. The median upper age exclusion was 75 years. Exclusion of older patients from clinical trials dramatically increases the risk of non-representative trial populations compared with real-world counterparts.

German

If you read German, read Schumann F, Simmank J. **"Wir haben es selbst in der Hand".** Die Zeit 2020, published 6 October. Full-text: https://www.zeit.de/wissen/2020-10/christian-drosten-corona-massnahmen-neuinfektionen-herbst-winter-covid-19

Quarantäne vor Familientreffen, Halskratzen ernst nehmen und mögliche Impfungen nicht überschätzen: Was der Virologe Christian Drosten jetzt für den Corona-Winter rät.

Merlot J. **Wenn das Gehirn Schaden nimmt.** Der Spiegel 2020, published 7 October. Full-text: https://www.spiegel.de/wissenschaft/medizin/covid-19-patienten-kollateralschaden-im-gehirn-a-2b0fdc5b-7a24-4328-8593-a8ad6007796e

Gedächtnisschwund, Aufmerksamkeitsstörungen, Koma: Einige Covid-19-Patienten entwickeln neurologische Beschwerden. US-Forscher haben untersucht, wie häufig diese Leiden vorkommen.

French

If you read French, read **Covid-19 : en Ile-de-France, plus de 40 % des lits en réanimation sont occupés par des patients contaminés.** Le Monde 2020, published 6 October. Full-text : https://www.lemonde.fr/planete/article/2020/10/06/en-ile-de-france-plus-de-40-des-lits-en-reanimation-sont-occupes-par-des-malades-du-covid-19_6055013_3244.html

L'agence régionale de santé d'Ile-de-France prévoit un taux d'occupation de 50 % « dans les quinze prochains jours ». Selon des modélisations de l'Institut Pasteur, ce chiffre pourrait atteindre 100 % avant la fin du mois.

8 October

Epidemiology

Editors. **Dying in a Leadership Vacuum.** N Engl J Med 2020; 383:1479-1480. Full-text: https://www.nejm.org/doi/full/10.1056/NEJMe2029812

SARS-CoV-2 and the COVID-19 pandemic became a test of leadership. With no good options to combat a novel pathogen, countries were forced to make hard choices about how to respond. In the United States, the leaders have failed that test.

Transmission

Wang L, Didelot X, Yang J, et al. **Inference of person-to-person transmission of COVID-19 reveals hidden super-spreading events during the early outbreak phase.** Nat Commun 11, 5006 (2020). Full-text: https://doi.org/10.1038/s41467-020-18836-4

Super-spreading events are an important phenomenon in the transmission of many diseases (such as SARS-CoV-1, MERS-CoV, Ebola virus, etc.), in which certain individuals infect a disproportionately large number of people. Here Yuhai Bi, Liang Wang and colleagues show that super-spreading events played an important role in the early stage of the COVID-19 outbreak. They estimated the *dispersion parameter* to be 0.23 (95% CI: 0.13–0.39). (What is the dispersion parameter? Check this FT article: To beat Covid-19, find today's superspreading 'Typhoid Marys')

Prevention

Peeples L. **Face masks: what the data say.** Nature 2020, published 6 October. Full-text: https://www.nature.com/articles/d41586-020-02801-8

Face coverings save lives, either by preventing SARS-CoV-2 infection or by reducing the viral infectious load. They are not infallible (so keep your distance!), but a profoundly important pillar of pandemic control. Why is the debate still going on? Read this *Nature* news feature by Lynne Peeples.

Immunology

Lipsitch M, Grad YH, Sette A, Crotty S. **Cross-reactive memory T cells and herd immunity to SARS-CoV-2.** Nat Rev Immunol (2020). https://doi.org/10.1038/s41577-020-00460-4

It is not clear if cross-reactive T cell memory (which largely originates from previous exposure to circulating common cold coronaviruses) affects COVID-19 disease severity in SARS-CoV-2 infected individuals. In this *Perspective* article, the authors reflect on the immunological and epidemiological aspects and implications of pre-existing cross-reactive immune memory to SARS-CoV-2.

Pathogenesis

Nienhold R, Ciani Y, Koelzer VH, et al. **Two distinct immunopathological profiles in autopsy lungs of COVID-19.** Nat Commun 11, 5086 (2020). https://doi.org/10.1038/s41467-020-18854-2

Immune responses in the lungs of deceased COVID-19 patients remain poorly characterized. Here, the authors describe two immunopathological patterns in the lungs of fatal COVID-19 patients based on ISG (interferon stimulated genes) expression:

Pattern 1

- high local expression of interferon stimulated genes (ISG^{high}) and cytokines
- high viral loads
- limited pulmonary damage

Pattern 2

- severely damaged lungs
- low ISGs (ISG^{low}), low viral loads
- abundant infiltrating activated $CD8^+$ T cells and macrophages.

ISG^{high} patients died significantly earlier after hospitalization than ISG^{low} patients.

Vaccine

McAuley AJ, Kuiper MJ, Durr PA, et al. **Experimental and in silico evidence suggests vaccines are unlikely to be affected by D614G mutation in SARS-CoV-2 spike protein.** npj Vaccines 5, 96 (2020). https://doi.org/10.1038/s41541-020-00246-8

The D614G mutation of the SARS-CoV-2 spike protein has been speculated to adversely affect the efficacy of vaccines. In this article, S. Vasan, Alexander McAuley and colleagues claim that there is no experimental evidence to support this speculation. They performed virus neutralization assays using sera from ferrets that received two doses of the INO-4800 COVID-19 vaccine, and Australian virus isolates (VIC01, SA01 and VIC31) which either possess or lack this mutation.

Clinical

Liotta EM, Batra A, Clark JR, et al. **Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients.** Ann Clin Transl Neurol. 2020 Oct 5. PubMed: https://pubmed.gov/33016619. Full-text: https://doi.org/10.1002/acn3.51210

Is encephalopathy independently associated with higher mortality in hospitalized patients with COVID-19? That's the conclusion of a study of 509 consecutive patients admitted within a hospital network in Chicago between 5 March and 6 April 2020. The increased mortality, independent of respiratory severity, parallels previous reports about sepsis -associated enc
and delirium -associated mor
retrospective study. Keep an eye on the subject.

Severe COVID

Altschul DJ, Unda SR, Benton J, et al. **A novel severity score to predict inpatient mortality in COVID-19 patients.** Sci Rep 10, 16726 (2020). Full-text: https://doi.org/10.1038/s41598-020-73962-9

Determining which patients are at high risk of severe illness or mortality is essential for appropriate clinical decision making. By analyzing the date from 4711 SARS-CoV-2 infected patients, the authors developed a COVID-19 severity score ranging from 0 to 10, consisting of age, oxygen saturation, mean ar-

terial pressure, blood urea nitrogen, C-reactive protein, and the international normalized ratio. The probability of mortality was 11.8%, 39% and 78% for patients with either a low (0–3), moderate (4–6) or high (7–10) COVID-19 severity score.

Education

Rubin EJ, Baden LR, Morrissey S. **Covid-19 and the President.** Audio interview (24.58). N Engl J Med 2020; 383: e104. Access: https://doi.org/10.1056/NEJMe2031183

The editors discuss treatments Trump has reportedly received for COVID-19, the rationale for them, and what is known about the risks and benefits.

Press

Gee A. **Texas doctor, 28, dies of Covid: 'She wore the same mask for weeks, if not months'.** The Guardian 2020, published 7 October. Full-text: https://www.theguardian.com/us-news/2020/oct/07/texas-doctor-adeline-fagan-covid-coronavirus

Adeline Fagan tested positive in early July and died in September – as US health workers lost to COVID skew younger and lack protective equipment.

Spanish

If you read Spanish, read Menárguez AT. **Dilema en los colegios con los aerosoles: ¿pasar frío o riesgo de contagio?** El País 2020, published 8 October. Full-text: https://elpais.com/educacion/2020-10-07/dilema-en-los-colegios-con-los-aerosoles-pasar-frio-o-riesgo-de-contagio.html

Abrir las ventanas todo el día es la única guía para protegerse en las aulas de la transmisión por vía aérea. No hay protocolos específicos para el invierno (¡!).

9 October

Epidemiology

Rudberg A, Havervall S, Månberg A, et al. **SARS-CoV-2 exposure, symptoms and seroprevalence in healthcare workers in Sweden.** Nat Commun 11, 5064 (2020). https://doi.org/10.1038/s41467-020-18848-0

High transmission rate among Swedish healthcare workers. Among 2149 individuals recruited between April 14th and May 8th, the seroprevalence of IgG antibodies against SARS-CoV-2 was 19.1%. Seroprevalence was associated with patient contact (OR 2.9, 95% CI 1.9–4.5) and COVID-19 patient contact (OR 3.3, 95% CI 2.2–5.3). The majority of study participants were women (85%) and the mean age was 44 (SD 12) years. Fifty-three healthcare workers (13%) reported severe symptoms.

Immunology

Sagar M, Reifler K, Rossi M, et al. **Recent endemic coronavirus infection is associated with less severe COVID-19.** J Clin Invest. 2020 Sep 30:143380. PubMed: https://pubmed.gov/32997649. Full-text: https://doi.org/10.1172/JCI143380

The four endemic coronaviruses (eCoV: HCoV-OC43, -HKU1, -NL63, and -229E), the most common etiologic agents for the seasonal "common cold", share sequence homology with SARS-CoV-2. Here, Joseph Mizgerd, Manish Sagar and colleagues show that individuals with a previously detected eCoV infection had less severe COVID-19 illness. They report the analysis of 15,928 patients who had at least one CRP-PCR (comprehensive respiratory panel polymerase chain-reaction) test. A positive test was previously detected in 875 of these patients (termed eCoV+), and the remaining 15,053 individuals (classified as eCoV-) never had a documented eCoV infection. The authors suggest that pre-existing immune responses against endemic human coronaviruses can mitigate disease manifestations from SARS-CoV-2 infection.

	eCoV-	eCoV+
SARS-CoV-2 tested (% of total)	1679 (11.2)	133 (15.2)
SARS-CoV-2+, no. (% of tested)	437 (26.0)	33 (24.8)
Hospitalized, no. (% of SARS-CoV-2+)	231 (52.9)	21 (63.6)
Intensive care unit, no. (% of hospitalized)	65 (28.1)	1 (4.8)
Mechanical ventilation, no. (% of hospitalized)	38 (16.4)	0 (0)

Pre-clinical

Yuan S, Wang R, Chan JF, et al. **Metallodrug ranitidine bismuth citrate suppresses SARS-CoV-2 replication and relieves virus-associated pneumonia in Syrian hamsters.** Nat Microbiol (2020). Full-text: https://doi.org/10.1038/s41564-020-00802-x

Metal compounds have sometimes been used as antimicrobial agents. Here, Hongzhe Sun, Shuofeng Yang and colleagues explore their antiviral activities by testing a set of metallodrugs and related compounds. The authors identify the viral helicase as a druggable target and ranitidine bismuth citrate, a commonly used drug for the treatment of *Helicobacter pylori* infection, as a potent anti-SARS-CoV-2 agent, both in *vitro* and *in vivo*.

French

If you read French, read Herzberg N. **Le Covid-19, une maladie socialement inégalitaire.** Le Monde 2020, published 9 October. Full-text: https://www.lemonde.fr/societe/article/2020/10/09/le-covid-19-une-maladie-socialement-inegalitaire_6055347_3224.html

La première publication de l'enquête EpiCov, lancée par l'Institut national de la santé et de la recherche médicale (Inserm), avec le concours de la direction de la recherche, des études, de l'évaluation et des statistiques (Drees), de l'Insee et de l'agence de sécurité sanitaire Santé publique France (SpF). Résultat : *« un effet cumulatif des inégalités sociales »*. Ainsi, *« les groupes sociaux les plus concernés par le risque d'exposition, qui adoptent tout autant les gestes barrières, sont aussi ceux qui ont été les plus contaminés par le virus »*, insiste l'enquête dans sa conclusion. Eux qui enregistrent, par ailleurs, le plus de pathologies associées, *« au risque de développer des formes graves de la maladie »*. Eux enfin qui ont *« connu une dégradation particulièrement marquée de leur situation financière »* pendant le confinement.

* * * No article 4-10 today. Four hour session at the dentist's. * * *

10 October

Epidemiology

Rader B, Scarpino SV, Nande A, et al. **Crowding and the shape of COVID-19 epidemics.** Nat Med 2020, published 5 October. Full-text: https://doi.org/10.1038/s41591-020-1104-0

The dynamic of the current SARS epidemics in Greater Paris and Madrid are reason for concern. In this article, Moritz Kraemer, Benjamin Rader and colleagues predict that crowded cities worldwide could experience more prolonged epidemics. The 2020/2021 autumn and winter season will be a hard time.

Oster AM, Caruso E, DeVies J, Hartnett KP, Boehmer TK. **Transmission Dynamics by Age Group in COVID-19 Hotspot Counties — United States, April–September 2020.** MMWR Morb Mortal Wkly Rep. ePub: 9 October 2020. Fulltext: http://dx.doi.org/10.15585/mmwr.mm6941e1

Understanding whether increasing incidence is predominantly occurring in specific age groups is important for identifying opportunities to prevent or reduce transmission. Here the authors analyze hotspot counties, particularly those in the US South and West. The positivity rate increased earliest in younger persons (18-24 years), followed by several weeks of increasing positivity among older age groups.

Virology

Bruchez A, Sha K, Johnson J, et al. **MHC class II transactivator CIITA induces cell resistance to Ebola virus and SARS-like coronaviruses.** Science 2020, published 9 October. Full-text: https://doi.org/10.1126/science.abb3753

The concerted efforts of antiviral factors within cells are central to host cell defense. Without these factors, the cell remains defenseless against potentially harmful pathogens (Wells 2020). Here, the authors show that the major histocompatibility complex (MHC) class II transactivator (CIITA) has antiviral activity against Ebola virus (EBOV). They show that CIITA induces resistance by up-regulation of the p41 isoform of CD74, which blocks cathepsin-mediated cleavage of viral GPs, thereby preventing viral fusion. CD74 p41 can also block the endosomal entry pathway of coronaviruses, including SARS-CoV-2.

See also the comment by Wells, AI, Coyne CB. **Inhibiting Ebola virus and SARS-CoV-2 entry.** Science 2020, published 9 October. Full-text: https://doi.org/10.1126/science.abe2977

Transmission

Wilson RF, Sharma AJ, Schluechtermann S, et al. **Factors Influencing Risk for COVID-19 Exposure Among Young Adults Aged 18–23 Years — Winnebago County, Wisconsin, March–July 2020.** MMWR Morb Mortal Wkly Rep. ePub: 9 October 2020. DOI: http://dx.doi.org/10.15585/mmwr.mm6941e2

Still in the US: What are the drivers of behaviors that might influence risk for COVID-19 exposure among young adults? In a remote US county, these were low severity of disease outcome; peer pressure; and exposure to misinformation, conflicting messages, or opposing views regarding masks. A scientifically inspired national prevention policy would have been helpful.

Prevention

Eden E, Frencken J, Gao S, et al. **Managing dental caries against the backdrop of COVID-19: approaches to reduce aerosol generation.** Br Dent J 229, 411–416 (2020). https://doi.org/10.1038/s41415-020-2153-y

SARS-CoV-2 can be transmitted via aerosols – a particular concern for dentists who need to perform procedures that produce aerosol. Ece Eden et al. aim to remove or reduce the generation of aerosols during the management of carious lesions (use of high-viscosity glass-ionomer sealants, atraumatic restorative treatment, silver diamine fluoride, the Hall Technique and resin infiltration). May we give you some personal advice? If you have a problem with your teeth, **fix them now!** In a few weeks, it may be more difficult or less safe to get dental care.

Pathogenesis

Zizzo G, Cohen PL. **Imperfect storm: is interleukin-33 the Achilles heel of COVID-19?** Lancet Rheumatol 2020, published 9 October Full-text: https://doi.org/10.1016/S2665-9913(20)30340-4

Could interleukin (IL)-33 be the great director of the COVID Pathogenesis Orchestra, driving all stages of disease (i.e., asymptomatic, mild–moderate, severe–critical, and chronic–fibrotic)? That's the hypothesis developed by Gaetano Zizzo and Philip Cohen. You will need time to plough through the paper (9 pages, 101 references).

Treatment

Baum A, Ajithdoss D, Copin R, et al. **REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters.** Science 2020, published 9 October. Full-txt: https://doi.org/10.1126/science.abe2402

The authors evaluate REGN-COV2, a cocktail of two neutralizing antibodies (REGN10987+REGN10933) targeting non-overlapping epitopes on the SARS-CoV-2 spike protein, in rhesus macaques and golden hamsters. REGN-COV2 can reduce virus load and decrease virus-induced pathological sequalae in rhesus macaques. In hamsters, the cocktail limited weight loss and evidence of pneumonia in the lungs. It is too early to predict the clinical usefulness of this cocktail in COVID-19 patients. It is currently being tested in clinical trials.

Beigel JH, Tomashek KM, Dodd LE, et al. **Remdesivir for the Treatment of Covid-19 - Final Report.** N Engl J Med. 2020 Oct 8:NEJMoa2007764. PubMed: https://pubmed.gov/32445440. Full-text: https://doi.org/10.1056/NEJMoa2007764

The final part of a preliminary report (see our May 23 Top 10) of a promotional presentation at the White House almost 6 months ago. The paper confirms that of a total of 1062 patients, those who received remdesivir had a median recovery time of 10 days (95% confidence interval [CI], 9 to 11), as compared with 15 days (95% CI, 13 to 18) among those who received placebo. John Beigel et al. also confirm that remdesivir had no statistically significant impact on mortality. Dexamethasone holds more promise than remdesivir: The RECOVERY Collaborative Group. **Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report**. NEJM July 17, 2020. Full-text: https://doi.org/10.1056/NEJMoa2021436 (see also our July 18 comment).

No Treatment

RECOVERY Collaborative Group, Horby P, Mafham M, et al. **Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19.** N Engl J Med. 2020 Oct 8. PubMed: https://pubmed.gov/33031652. Full-text: https://doi.org/10.1056/NEJMoa2022926

If you are still interested in hydroxychloroquine (most clinicians are not), see here the results of a randomized trial by the RECOVERY Collaborative Group. The conclusion: among hospitalized patients, those who received hydroxychloroquine did not have a lower incidence of death at 28 days than those who received usual care.

Severe COVID

Avilés-Jurado FX, Prieto-Alhambra D, González-Sánchez N, et al. **Timing, Complications, and Safety of Tracheotomy in Critically Ill Patients With COVID-19.** JAMA Otolaryngol Head Neck Surg. Published online October 08, 2020. Full-text: http://doi.org/10.1001/jamaoto.2020.3641

How safe is an early bedside surgical tracheotomy in patients with coronavirus disease 2019 (COVID-19)? The authors analyze data from 50 patients (mean [SD] age, 63.8 [9.2] years; 33 [66%] male). The median time from intubation to tracheotomy was 9 days (interquartile range, 2-24 days). The successful weaning rate was higher in the early tracheotomy group than in the late tracheotomy group (adjusted hazard ratio, 2.55), but the difference was not statistically significant. There was no infection among surgeons within 4 weeks after the last tracheotomy.

Spanish

If you read Spanish, read Saldaña C, Mouzo J. **"Están primando más la política que la salud. Están jugando con nosotros"** – El País 2020, published 10 October. Full-text: https://elpais.com/sociedad/2020-10-09/estan-primando-mas-la-politica-que-la-salud-estan-jugando-con-nosotros.html

El embrollo político y jurídico de las últimas semanas en Madrid pone en cuestión la credibilidad de las medidas entre la población. Los expertos advierten de que el retraso en las restricciones ha provocado más enfermos.

11 October

Virology

Vann KR, Tencer AH, Kutateladze TG. **Inhibition of translation and immune responses by the virulence factor Nsp1 of SARS-CoV-2.** Sig Transduct Target Ther 5, 234 (2020). Full-text: https://doi.org/10.1038/s41392-020-00350-0

A major virulence factor of SARS-CoV is the non-structural protein 1 (Nsp1) which suppresses host gene expression by ribosome association (see our July 18 CR Top 10: Thoms M, Buschauer R, Ameismeier M, et al. **Structural basis for translational shutdown and immune evasion by the Nsp1 protein of SARS-CoV-2.** Science 17 Jul 2020: eabc8665. Full-text: https://doi.org/10.1126/science.abc8665). The authors briefly review Nsp1's ability to downregulate the innate immune responses. A new drug target?

Immunology

Hu F. Chen F, Ou Z, et al. **A compromised specific humoral immune response against the SARS-CoV-2 receptor-binding domain is related to viral persistence and periodic shedding in the gastrointestinal tract.** Cell Mol Immunol (2020). Full-text: https://doi.org/10.1038/s41423-020-00550-2

Do some people have lower levels of and slower generation of viral receptor-binding domain (RBD)-specific IgA and IgG antibodies and fail to create a robust protective humoral immune response? Which might result in SARS-CoV-2 persistence in the gastrointestinal tract and possibly in active viral shedding? That's the hypothesis of Feng Li, Fengyu Hu and colleagues who report 21 patients who were readmitted for hospitalization after detection of SARS-CoV-2 after discharge. The authors detected SARS-CoV-2 in anal samples (15 of 21, 71.4%). Three patients had active viral replication in their gastrointestinal tracts but not in their respiratory tracts.

Pathogenesis

Aid M, Busman-Sahay K, Vidal SJ, et al. **Vascular Disease and Thrombosis in SARS-CoV-2 Infected Rhesus Macaques.** Cell 2020, published 9 October. Full-text: https://doi.org/10.1016/j.cell.2020.10.005

Clinical features that drive SARS-CoV-2 pathogenesis in humans include inflammation and thrombosis. Here, Dan Barouch, Malika Aid and colleagues demonstrate endothelial disruption and vascular thrombosis in histopathologic sections of lungs from both humans and rhesus macaques infected with SARS-CoV-2. They observed macrophage infiltrates in lung and upregulation of macrophage, complement, platelet activation, thrombosis, and proinflammatory markers, including C-reactive protein, MX1, IL-6, IL-1, IL-8, TNFα, and NF-κB. These results suggest a model in which upregulation of inflammatory and complement pathways leads to recruitment of macrophages and neutrophils, activation of platelets, and triggering of the coagulation cascade, resulting in endothelial damage and thrombosis. The authors conclude that these data might point to therapeutic targets in the interferon, inflammatory, coagulation, and complement pathways.

Ivanisenko NV, Seyrek K, Kolchanov NA, et al. **The role of death domain proteins in host response upon SARS-CoV-2 infection: modulation of programmed cell death and translational applications.** Cell Death Discov. 6, 101 (2020). Full-text: https://doi.org/10.1038/s41420-020-00331-w

Cell death pathways might play a key role in SARS-CoV-2 infection. Go on an explorative tour on apoptosis, pyroptosis, and necroptosis which play an important role in viral pathogenesis and host antiviral response. The authors present four open questions.

Li S, Zhang Y Guan Z, et al. **SARS-CoV-2 triggers inflammatory responses and cell death through caspase-8 activation.** Sig Transduct Target Ther 5, 235 (2020). Full-text: https://doi.org/10.1038/s41392-020-00334-0

The underlying mechanisms of virus-triggered inflammatory responses are still being investigated. Ke Peng, Shufen Li and colleagues report that SARS-CoV-2 infection of lung epithelial cells triggered cell death and inflammatory responses through the activation of caspase-8. (Caspase-8 is a master regulator of several cell death pathways, including apoptosis, necroptosis, and pyroptosis). The authors present the analysis of postmortem lung sections of fatal COVID-19 patients.

Diagnostics

Brandsma E, Verhagen HJMP, van de Laar TJW, et al. **Rapid, sensitive and specific SARS coronavirus-2 detection: a multi-center comparison between standard qRT-PCR and CRISPR based DETECTR.** J Infect Dis 2020. Full-text: https://doi.org/10.1093/infdis/jiaa641

We will need faster and cheaper alternatives to qRT-PCR. Here Emile van den Akker, Eelke Brandsma and colleagues compare DETECTR (a combination of isothermal reverse transcriptase loop mediated amplification [RT-LAMP] and subsequent Cas12 bystander nuclease activation by amplicon targeting ribonucleoprotein complexes) with qRT-PCR to diagnose COVID-19 on 378 patient samples. The authors report a 95% reproducibility between the two tests. DETECTR was 100% specific for SARS-CoV-2 relative to other human coronaviruses.

Treatment

Rogers R, Shehadeh F, Mylona EK, et al. **Convalescent plasma for patients with severe COVID-19: a matched cohort study.** Clin Infect Dis 2020, published 10 October. Full-text: https://doi.org/10.1093/cid/ciaa1548

The efficacy of convalescent plasma (CP) for the treatment of COVID-19 remains unclear. In this matched cohort analysis of hospitalized patients with severe COVID-19, 64 patients who received CP a median of 7 days after symptom onset were compared to a matched control group of 177 patients. There

was a signal for an increased rate of hospital discharge among patients 65 years old or greater, but no significant difference in the risk of in-hospital mortality between the two groups.

Severe COVID

Overmyer KA, Shishkova E, Miller IJ, et al. **Large-scale Multi-omic Analysis of COVID-19 Severity.** Cell Systems 2020, published 7 October. Full-text: https://doi.org/10.1016/j.cels.2020.10.003

In this cohort study involving 128 patients with and without COVID-19 diagnosis, Ariel Jaitovich, Katherine Overmyer and colleagues monitored thousands of biomolecules in relation to the COVID-19 disease severity and outcomes. They mapped more than 200 molecular features with high significance to COVID-19 status and severity, many involved in complement activation, dysregulated lipid transport, and neutrophil activation. The authors make their data available through a free web resource – https://covid-omics.app, calling for experts worldwide to mine these data.

Spanish

If you read Spanish, read Galocha A. **¿En qué fase está cada vacuna?** El País 2020, published 10 October. Full-text: https://elpais.com/ciencia/2020-10-10/en-que-fase-esta-cada-vacuna.html

La vuelta a la vida anterior pasa por el desarrollo en tiempo récord de una vacuna contra la COVID de entre los 213 proyectos en marcha.

12 October

Top 10 Epidemiology

The 5th COVID Reference Edition will be published this month. These are 10 among the important papers we will include in the Epidemiology chapter.

Changing the course of the pandemic

Bielecki M, Züst R, Siegrist D, et al. **Social distancing alters the clinical course of COVID-19 in young adults: A comparative cohort study**. Clin Inf Dis, June 29, 2020. Full-text: https://doi.org/10.1093/cid/ciaa889

Grasso D, Zafra M, Ferrero B, et al. **Covid de ricos, covid de pobres: las restricciones de la segunda ola exponen las desigualdades de Madrid.** El País 2020, published 17 September. Full-text: https://elpais.com/espana/madrid/2020-09-16/covid-de-ricos-covid-de-pobres-las-restricciones-de-la-segunda-ola-exponen-las-desigualdades-de-madrid.html

Might reducing the viral SARS-CoV-2 inoculum not only reduce the probability of infection but also favor an asymptomatic infection while still generating immunity? That was the suggestion by Michel Bielecki et al. in June 2020 (Bielecki 2020), later developed later by Monica Gandhi and George W. Rutherford (Ghandi 2020). If universal facial masking might help reduce the severity of disease and ensure that a greater proportion of new infections are asymptomatic, it would be a giant leap to pandemic control. If universal masking could be proved to be a form of "variolation" (inoculation), it would be the finding of the year.

SARS-CoV-2 Introduction

Emergence in Europe and North America

Worobey M, Pekar J, Larsen BB, et al. **The emergence of SARS-CoV-2 in Europe and North America.** Science 2020, published 10 September. Full-text: https://doi.org/10.1126/science.abc8169

Despite the early successes in containment, SARS-CoV-2 eventually took hold in both Europe and North America during the first two months of 2020: first in Italy around the end of January, then in Washington State around the beginning of February, and followed by New York City later that month (Worobey 2020; see also Figure 6).

Brazil

Candido DS, Claro M, de Jesus JG, et al. **Evolution and epidemic spread of SARS-CoV-2 in Brazil.** Science 23 Jul 2020:eabd2161. Full-text: https://doi.org/10.1126/science.abd2161

Sequencing of hundreds of genomes showed that more than 100 international virus introductions in Brazil with 76% of Brazilian strains falling into three clades that were introduced from Europe between 22 February and 11 March 2020 (Candido 2020).

Seroprevalance

Mumbai, India

Kolthur-Seetharam U, Shah D, Shastri J, Juneja S, Kang G, Malani A, Mohanan M, Lobo GN, Velhal G, Gomare M. **SARS-CoV2 Serological Survey in Mumbai by NITI-BMC-TIFR.** Tata Institute of Fundamental Research (TIFR) 2020, published 29 June. Full-text: https://www.tifr.res.in/TSN/article/Mumbai-Serosurvey%20Technical%20report-NITI.pdf

In a cross-sectional survey in Mumbai, India, the prevalence of SARS-CoV-2 infection in three areas in Mumbai (called 'wards') was around 57% in the slum areas of Chembur, Matunga and Dahisar, and 16% in neighboring non-slums (Kolthur-Seetharam 2020). If these data are confirmed, some Mumbai areas would soon reach herd immunity and could return to a pre-COVID way of life. For many countries in the world, this would be the best piece of news since the beginning of the pandemic.

Manaus, Brazil

Buss LF, Prete Jr CA, Abrahim CMM, et al. **COVID-19 herd immunity in the Brazilian Amazon.** medRxiv 2020, posted 21 September. Full-text: https://doi.org/10.1101/2020.09.16.20194787

Will this paper be accepted by the peers? As much as 66% of the population of Manaus (two million people), Brazil, could have been infected with SARS-CoV-2. Ester Sabino, Lewis Buss and colleagues show that the transmission of SARS-CoV-2 in Manaus increased quickly during March and April and declined more slowly from May to September. In June, one month following the epidemic peak, 44% of the population was seropositive for SARS-CoV-2. After correcting for confounding factors, the authors estimate the epidemic size to be 66% by early August 2020.

Remember: herd immunity is defined as the proportion of a population that must be immune to an infectious disease, either by natural infection or vaccination, such that new cases decline and R_0 falls below 1 (see also https://www.nature.com/articles/d41586-020-02009-w).

Frontline healthcare workers: US

Self WH, Tenforde MW, Stubblefield WB, et al. **Seroprevalence of SARS-CoV-2 Among Frontline Health Care Personnel in a Multistate Hospital Network — 13 Academic Medical Centers, April–June 2020**. MMWR. Full-text: http://dx.doi.org/10.15585/mmwr.mm6935e2

Many cases appear to go undetected: among 3,248 HCWs who routinely cared for COVID-19 patients in 13 US academic medical centers from February 1, 2020, 194 (6%) had evidence of previous SARS-CoV-2 infection, with considerable variation by location that generally correlated with community cumulative incidence. Among 194 participants who had SARS-CoV-2 antibodies, 56 (29%) did not recall any symptoms consistent with an acute viral illness in the preceding months and 133 (69%) did not have a previous positive test result demonstrating an acute SARS-CoV-2 infection. Prevalence of SARS-CoV-2 antibodies was lower among personnel who reported always wearing a face covering while caring for patients (6%), compared with those who did not (9%).

Frontline healthcare workers: London

Houlihan CF, Vora N, Byrne T, et al. **Pandemic peak SARS-CoV-2 infection and seroconversion rates in London frontline health-care workers**. Lancet July 09, 2020. Full-text: https://doi.org/10.1016/S0140-6736(20)31484-7

High-risk frontline healthcare workers (HCV) are really at high risk. In a prospective cohort study in an acute National Health Service hospital trust in London, 25% of HCWs were already seropositive at enrolment (26 March to 8 April) and a further 20% became seropositive within the first month of follow-up (Houlihan 2020). Most infections occurred between March 30 and April 5, the week with the highest number of new cases in London.

School Openings

Cheng SY, Wang J, Shen AC, et al. **How to Safely Reopen Colleges and Universities During COVID-19: Experiences From Taiwan**. Ann Int Med 2020, Jul 2. Full-text: https://doi.org/10.7326/M20-2927

Taiwan is one of the few countries where schools are functioning normally. To secure the safety of students and staff, the Ministry of Education in Taiwan established general guidelines, including a combination of strategies such as – our future? - active campus-based screening and access control; school-based screening and quarantine protocols; student and faculty quarantine when warranted; mobilization of administrative and health center staff; regulation

of dormitories and cafeterias; and reinforcement of personal hygiene, environmental sanitation, and indoor air ventilation practices (Cheng SY 2020). Depressing (un monde de con), but probably necessary.

Second Wave

NCOMG. The national COVID-19 outbreak monitoring group. **COVID-19 outbreaks in a transmission control scenario: challenges posed by social and leisure activities, and for workers in vulnerable conditions, Spain, early summer 2020**. Eurosurveillance Volume 25, Issue 35, 03/Sep/2020. Full-text: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.35.2001545

From mid-June to 2 August, excluding single household outbreaks, 673 outbreaks were notified in Spain (NCOMG 2020). There were two main settings where over 55% of active outbreaks (303/551) and over 60% (3,815/6,208) of active outbreak cases originated: First, social settings such as family gatherings or private parties (112 outbreaks, 854 cases), followed by those linked to leisure venues such as bars, restaurants, or clubs (34 outbreaks, over 1,230 cases). Second, occupational settings (representing 20% of all active outbreaks), mainly among workers in the fruit and vegetable sector (31 outbreaks and around 500 cases) and workers at slaughterhouses or meat processing plants (12 outbreaks and around 360 cases).

Future Pandemics

Rigorous wildlife disease surveillance

Watsa M. **Rigorous wildlife disease surveillance**. Science 10 Jul 2020, 369: 145-147. Full-text: https://doi.org/10.1126/science.abc0017

Emerging infectious diseases (EID) associated with the wildlife trade remain the largest unmet challenge of current disease surveillance efforts. International or national conventions on pathogen screening associated with animals, animal products or their movements are urgently needed (Watsa 2020). Internationally recognized standard for managing wildlife trade on the basis of known disease risks should be established.

13 October

Virology

Riddell S, Goldie S, Hill A, et al. **The effect of temperature on persistence of SARS-CoV-2 on common surfaces.** Virol J 17, 145 (2020). Full-text: https://doi.org/10.1186/s12985-020-01418-7

It might seem that SARS-CoV-2 could remain infectious for longer time periods than generally considered until recently. Shane Riddell et al. measured the survival rates of infectious SARS-CoV-2 on several common surface types. They incubated the inoculated surfaces at 20 °C, 30 °C and 40 °C and sampled at various time points. The authors report isolation of viable virus for up to 28 days at 20 °C from common surfaces such as glass, stainless steel and both paper and polymer banknotes. A temperature of 40 °C, however, didn't seem to suit the virus: it survived less than 24 h.

Note of the Editor: After more than 6 months living in the new SARS-CoV-2 world, this study might not change my behavior.

Epidemiology

Soper GA. **The lessons of the pandemic.** Science 1919, published 30 May. Full-text: https://science.sciencemag.org/content/49/1274/501

Do some time travel.

Prevention

The European Union (EU) has agreed today on a traffic light system for travel amid the second COVID-19 wave. The member states will share the latest epidemiological data with the European Centre for Disease Control which will publish a map of Europe (also including data from the Schengen Associated States), updated weekly, in a variety of colours depending on the risk in a given region. There will be no restrictions if you are travelling from a "green" region. When travelling from an "orange" or a "red" region, national governments may ask you to get tested or undergo quarantine. Governments will give clear and timely information before they introduce such measures. Find more information at https://ec.europa.eu/info/live-work-travel-eu/health/coronavirus-response/travel-during-coronavirus-pandemic_en

Andronico A, Kiem CT, Paireaux J, et al. **Evaluating the impact of curfews and other measures on SARS-CoV-2 transmission in French Guiana.** medRxiv 2020, posted 12 October. Full-text: https://doi.org/10.1101/2020.10.07.20208314

Might curfews be a less costly alternative, both economically and socially, to complete lockdowns? In French Guiana, an overseas département, a combination of curfews and targeted lockdowns in June and July 2020 was sufficient to avoid saturation of hospitals. On weekdays, residents were first ordered to stay at home 11 p.m., then at 9 p.m., later again at 7 p.m., and finally at 5 p.m. On weekends, everyone had to stay at home from 1 p.m. on Saturday (Andronico 2020). Whether curfews can be successfully adapted to other areas than French Guaiana, is not known. French Guaiana is a young territory with a median age is 25 years and the risk of hospitalisation following infection was only 30% that of France. About 20% of the population had been infected with SARS-CoV-2 by July 2020 (Andronico 2020). Be prepared, though, to see some curfew orders over the coming six months.

Immunology

Tillett RL, Sevinsky JR, Hartley PD, et al. **Genomic evidence for reinfection with SARS-CoV-2: a case study.** Lancet Infect Dis 2020, published 12 October. Full-text: https://doi.org/10.1016/S1473-3099(20)30764-7

Mark Pandori, Richard Tillett and colleagues report a 25-year patient who had two positive SARS-CoV-2 tests, the first on April 18, 2020, and the second on June 5, 2020, separated by two negative tests done during follow-up in May, 2020. Their analysis indicates that the patient was infected by SARS-CoV-2 on two separate occasions by a genetically distinct virus. Intriguingly, the second infection was symptomatically more severe than the first. The authors recommend that all individuals, whether previously diagnosed with COVID-19 or not, should take identical precautions to avoid infection with SARS-CoV-2. We cross our fingers that this case is the exception rather than the rule.

Posten D, Weisblum Y, Wise H, et al. **Absence of SARS-CoV-2 neutralizing activity in pre-pandemic sera from individuals with recent seasonal coronavirus infection.** medRxiv 2020, published 11 October. Full-text: https://doi.org/10.1101/2020.10.08.20209650

Bad news from Rockefeller University. Paul Bieniasz, Daniel Poston and colleagues measured neutralizing activity against SARS-CoV-2 in pre-pandemic

sera from patients with prior PCR-confirmed seasonal coronavirus infection. While neutralizing activity against seasonal coronaviruses was detected in nearly all sera, cross-reactive neutralizing activity against SARS-CoV-2 was undetectable. The authors conclude that while it is possible that there are rare instances of individuals possessing antibodies from prior seasonal HCoV infection may be able to also target SARS-CoV-2 S, their data would argue against a broad role for pre-existing protective humoral immunity against SARS-CoV-2. These findings have not yet been peer reviewed.

Vaccine

Dong Y, Dai T, Wei Y, et al. **A systematic review of SARS-CoV-2 vaccine candidates.** Sig Transduct Target Ther 5, 237 (2020). Full-text: https://doi.org/10.1038/s41392-020-00352-y

The 11-page review for your next weekend. The authors provide an overview of the experimental and clinical data obtained from recent SARS-CoV-2 vaccines trials, and highlight certain potential safety issues that require consideration when developing vaccines. Learn more about antigen design, important and unimportant epitopes, structure design, suitable delivery system and adjuvants.

Severe COVID

de Nooijer AH, Grondman I, Janssen NAF, et al. **Complement activation in the disease course of COVID-19 and its effects on clinical outcomes**. J Infect Dis 2020, published 10 October. Full-text: https://doi.org/10.1093/infdis/jiaa646

In this prospective, longitudinal, single center study, Leo Joosten, Aline de Nooijer and colleagues analyzed plasma concentrations of complement factors C3a, C3c, and terminal complement complex (TCC) for 197 patients with confirmed COVID-19. Complement factors C3a, C3c and TCC were significantly increased in plasma of COVID-19 patients compared to healthy controls ($p<0.05$). These complement factors were especially elevated in ICU patients during the entire disease course ($p<0.005$ for C3a and TCC).

Spanish

If you read Spanish, read Galarraga Gortázar N. **Manaos plantea incógnitas a la inmunidad de rebaño.** El País 2020, pubished 12 October. Full-text: https://elpais.com/sociedad/2020-10-11/manaos-plantea-incognitas-a-la-inmunidad-de-rebano.html

Un repunte de los contagios en la capital de la Amazonia brasileña siembra dudas sobre un estudio que apuntaba que la ciudad era la primera del mundo en contener el virus sin hacer nada

14 October

Epidemiology

Jefferies S, French N, Gilkison G, et al. **COVID-19 in New Zealand and the impact of the national response: a descriptive epidemiological study.** The Lancet 2020, published 13 October. Full-text: https://doi.org/10.1016/S2468-2667(20)30225-5

New Zealand's government response resulted in low burden of disease, low levels of population disease disparities, and the initial achievement of COVID-19 elimination (Jefferies 2020, Robert 2020). Here, Sarah Jefferies et al. describe 1503 COVID-19 cases from Feb 2 to May 13, after which time community transmission ceased in New Zeeland, including 95 (6.3%) hospital admissions and 22 (1.5%) COVID-19 deaths. 1034 (69%) cases were imported or import related, tending to be younger adults, of European ethnicity, and of higher socioeconomic status. 702 (47%) cases were linked to 34 outbreaks.

See also the comment by Robert A. **Lessons from New Zealand's COVID-19 outbreak response.** The Lancet 2020, published 13 October. Full-text: https://doi.org/10.1016/S2468-2667(20)30237-1

Prevention

Macron E. **Curfew in France.** France 2, October 14, 8 p.m. Link: https://www.france.tv/france-2/journal-20h00/1987881-edition-du-mercredi-14-octobre-2020.html

As we disclosed yesterday (see the comment on the paper by Andronico et al, https://covidreference.com/top-10-october-13; a great thanks to our contact at the Élysée Palace!), Emmanuel Macron, the French President, has announced this evening a 9 p.m. – 6 a.m. curfew of at least four weeks. The curfew which will be in place for four weeks from midnight on Saturday, October

17, affects around 20 million people (30% of the French population) in Île-de-France (literally "Island of France") and eight other cities (Lille, Rouen, Saint-Etienne, Toulouse, Lyon, Grenoble, Aix-en-Provence and Montpellier). A lesson of science some other countries can only dream of.

Immunology

Willyard C. **How anti-ageing drugs could boost COVID vaccines in older people.** Nature 2020, published 14 October. Full-text: https://www.nature.com/articles/d41586-020-02856-7

COVID-19 poses the greatest threat to older people, but vaccines often don't work well in this group. Scientists hope drugs that rejuvenate the immune system will help. A Nature News Feature by Cassandra Willyard.

Poland GA, Ovsyannikova IG, Kennedy RB. **SARS-CoV-2 immunity: review and applications to phase 3 vaccine candidates.** Lancet 2020, published 13 October. Full-text: https://doi.org/10.1016/S0140-6736(20)32137-1

A mere 11 months ago, we didn't know anything about SARS-CoV-2 and COVID-19. Now we are developing vaccines, antivirals, and monoclonal antibodies. In this review, the authors discuss what is known about human humoral and cellular immune responses to SARS-CoV-2 and relate this knowledge to the COVID-19 vaccines currently in phase 3 clinical trials. Will vaccines induce protective immunity? How long will this immunity maintained? Will we need multiple vaccine types for different populations (i.e., immune-immature infants, children, pregnant women, immunocompromised individuals, and immunosenescent individuals aged ≥65 years). Can unrelated vaccines (measles, mumps, and rubella vaccine and the Bacillus Calmette–Guérin vaccine) elicit trained innate immunity and confer protection against COVID-19? These are some of the questions you will explore with the authors.

Barnes CO, Jette CA, Abernathy ME, et al. **SARS-CoV-2 neutralizing antibody structures inform therapeutic strategies.** Nature 2020, published 12 October. Full-text: https://doi.org/10.1038/s41586-020-2852-1

To determine structural correlates of SARS-CoV-2 neutralization, the authors solved 8 new structures of distinct COVID-19 human neutralizing antibodies (hNAbs) in complex with SARS-CoV-2 spike trimer or the receptor-binding domain (RBD). Structural comparisons allowed classification into several categories according to which part of the spike protein's cell-attachment region they recognize. These categories might later provide rules for assigning cur-

rent and future human RBD-targeting antibodies into classes, evaluating avidity effects, suggesting combinations for clinical use, and providing insight into immune responses against SARS-CoV-2.

Collateral Effects

Been JV, Burgos Ochoa L, Bertens LCM. **Impact of COVID-19 mitigation measures on the incidence of preterm birth: a national quasi-experimental study.** Lancet Public Health 2020, published 13 October. Full-text: https://doi.org/10.1016/S2468-2667(20)30223-1

In this large national quasi-experimental study spanning a 10-year period, substantial reductions in preterm births were observed following implementation of the first national COVID-19 mitigation measures in the Netherlands on March 9, 2020. Babies born at the lowest gestational ages and those with the lowest birthweights were consistently underrepresented in our cohort throughout the study period.

Spanish

If you read Spanish, read

Ansede M. **Seis personas entre 40 millones de casos: el misterio de los reinfectados por el coronavirus.** El País, published 14 October. Full-text: https://elpais.com/ciencia/2020-10-13/seis-personas-entre-40-millones-de-casos-el-misterio-de-los-reinfectados-por-el-coronavirus.html

La comunidad científica duda si media docena de reinfecciones documentadas son excepciones o los primeros avisos de lo que será habitual en el futuro

Valdés I. **"Era como intentar apagar un incendio en toda una ciudad con un cubo de agua"** – El País 2020, published 14 October. Full-text: Full-text: https://elpais.com/sociedad/2020-10-13/era-como-intentar-apagar-un-incendio-en-toda-una-ciudad-con-un-cubo-de-agua.html

Miguel Sánchez, jefe de UCI en el hospital Clínico San Carlos de Madrid, coordina el equipo que gestiona desde marzo los traslados de enfermos graves entre los centros de la comunidad

15 October

Epidemiology

Alwan NA, Burgess RA, Ashworth S, et al. **Scientific consensus on the COVID-19 pandemic: we need to act now.** Lancet 2020, published 15 October. Full-text: https://doi.org/10.1016/S0140-6736(20)32153-X

Herd immunity against SARS-CoV-2? Allowing large uncontrolled outbreaks in the low-risk population while protecting the vulnerable? Developing population immunity in the low-risk population, which will eventually protect the vulnerable? The authors don't beat about the bush: "Dangerous fallacy unsupported by scientific evidence." Their conclusion: "Japan, Vietnam, and New Zealand, to name a few countries, have shown that robust public health responses can control transmission, allowing life to return to near-normal, and there are many such success stories. The evidence is very clear: controlling community spread of COVID-19 is the best way to protect our societies and economies until safe and effective vaccines and therapeutics arrive within the coming months. We cannot afford distractions that undermine an effective response; it is essential that we act urgently based on the evidence."

Poirier C, Luo W, Majumder MS, et al. **The role of environmental factors on transmission rates of the COVID-19 outbreak: an initial assessment in two spatial scales.** Sci Rep 10, 17002 (2020). Full-text: https://doi.org/10.1038/s41598-020-74089-7

Bad news for CCOs ('Coronavirus Climate Optimists'): changes in weather (i.e., increase of temperature and humidity as spring and summer months arrive in the Northern Hemisphere) may not necessarily lead to declines in case counts without the implementation of drastic public health interventions. Only absolute humidity might play a role.

Virology

Gordon DE, Hiatt J, Bouhaddou M, et al. (Total: 200 authors) **Comparative host-coronavirus protein interaction networks reveal pan-viral disease mechanisms.** Science 2020, published 15 October. Full-text: https://doi.org/10.1126/science.abe9403

Nevan Krogan, David Gordon and colleagues – a group of 200 researchers – uncovered molecular processes used by coronaviruses MERS, SARS-CoV1 and SARS-CoV2 to manipulate host cells. The researchers from six countries found 73 human proteins with which components of all three types of the virus en-

ter into bonds and thus influence the survival of infected cells in culture. Host factors that functionally impinge on coronavirus proliferation include Tom70, a mitochondrial chaperone protein that interacts with both SARS-CoV-1 and SARS-CoV-2 Orf9b. The consortium also discovered cell surface molecules that are influenced by all three coronaviruses and that bind to already approved drugs, for example an antipsychotic and an anti-inflammatory drug.

Prevention

Oltermann P. **Berlin gives middle finger to anti-maskers in tourism agency ad.** The Guardian 2020, published 14 October. Full-text: https://www.theguardian.com/world/2020/oct/14/berlin-gives-middle-finger-to-anti-maskers-in-tourism-agency-ad

An ad placed in local papers by the German capital's senate as part of a public information campaign shows an elderly woman presenting her outstretched middle finger to the camera, next to the words: "A finger-wag for all those without a mask: we stick to corona rules." John F. Kennedy would add: "Ich bin ein Berliner."

Vaccine

Walsh EE, Frenck RW, Falsey AR, et al. **Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates.** N Engl J Med 2020, published 15 October. Full-text: https://www.nejm.org/doi/full/10.1056/NEJMoa2027906?query=featured_home

Safety and immunogenicity data from a phase 1 trial of RNA-based Pfizer/BioNTech vaccines. In both younger (18 to 55 years of age) and older adults (65 to 85 years of age), the two vaccine candidates elicited similar dose-dependent SARS-CoV-2–neutralizing geometric mean titers, comparable or higher than the geometric mean titer of a panel of SARS-CoV-2 convalescent serum samples. The data presented here by Judith Absalon, Edward Walsh and colleagues include those that guided the companies' decision to advance BNT162b2 at the 30-μg dose level to the phase 2–3, international trial to evaluate its safety and efficacy in participants 18 to 85 years of age.

Education

Rubin EJ, Baden LR, Morrissey S. **Vaccinology and Covid-19.** Audio interview (32:26). N Engl J Med 2020; 383: e109. Access: https://doi.org/10.1056/NEJMe2031646

The editors discuss discuss the fundamental concepts behind candidate vaccines against SARS-CoV-2 and the status of ongoing clinical trials.

French

Yesterday evening, the French President Emmanuel Macron ordered a curfew for 20 million people for at least four weeks. At 9 p.m., everybody at home. This move was inspired by the results of a paper by Andronico A, Kiem CT, Paireaux J, et al. (**Evaluating the impact of curfews and other measures on SARS-CoV-2 transmission in French Guiana.** medRxiv 2020, posted 12 October. Full-text: https://doi.org/10.1101/2020.10.07.20208314.) However, nobody knows if curfews can be successfully adapted to other areas than French Guaiana. French Guaiana is a young territory with a median age is 25 years and the risk of hospitalisation following infection was only 30% that of France. About 20% of the population had been infected with SARS-CoV-2 by July 2020 (Andronico 2020). Expect more countries to adopt curfews over the coming weeks and be prepared for curfews lasting considerably longer than one month. If you read French, read one or more of the following articles.

Marot L. **En Guyane, un couvre-feu évolutif efficace contre la première vague de l'épidémie de Covid-19.** Le Monde 2020, published 15 October. Full-text: https://www.lemonde.fr/planete/article/2020/10/15/en-guyane-un-couvre-feu-evolutif-efficace-contre-la-premiere-vague-de-l-epidemie-de-covid-19_6056115_3244.html

Instauré après le confinement, le couvre-feu a été renforcé avec l'augmentation du nombre de cas, puis allégé, évitant une asphyxie totale de l'économie locale.

Covid-19 en France : forte hausse du nombre de cas déclarés et des admissions en réanimation. Le Monde 2020, published 15 October. Full-text : https://www.lemonde.fr/societe/article/2020/10/15/covid-19-en-france-forte-hausse-du-nombre-de-cas-declares-et-des-admissions-en-reanimation_6056186_3224.html

Les nouvelles admissions dans les services de réanimation des hôpitaux marquent une nette hausse depuis plusieurs jours : 171 patients lundi, 226 mardi, 193 mercredi et 219 jeudi, selon Santé publique France.

Couvre-feu, fêtes privées, télétravail… Ce qu'il faut retenir de l'intervention de Jean Castex et des ministres. Le Monde 2020, published 15 October. Full-text: https://www.lemonde.fr/politique/article/2020/10/15/couvre-feu-fetes-privees-teletravail-nouvelles-restrictions-ce-qu-il-faut-retenir-de-l-intervention-de-jean-castex_6056155_823448.html

« A 21 heures, chacun devra être chez soi. (…) Sauf exception, tous les commerces, services et lieux recevant du public seront fermés », a notamment annoncé le premier ministre.

Durand AA, Parienté J, Audureau W, Aubert R. **Covid-19: peut-on prendre le train ? Faut-il une attestation ? 24 questions sur le couvre-feu et l'état d'urgence sanitaire.** Le Monde 2020, published 15 October. Full-text: https://www.lemonde.fr/les-decodeurs/article/2020/10/15/covid-19-peut-on-prendre-le-train-qui-est-concerne-faut-il-une-attestation-24-questions-sur-le-couvre-feu-et-l-etat-d-urgence-sanitaire_6056164_4355770.html

Le gouvernement a précisé, jeudi, les modalités pratiques des mesures exceptionnelles annoncées mercredi soir par le président Emmanuel Macron.

Szadkowski M, Leloup D**. Couvre-feu, privations de liberté, surveillance de masse… Ce que George Orwell n'avait pas prévu.** Le Monde 2020, published 15 October. Full-text: https://www.lemonde.fr/pixels/article/2020/10/15/couvre-feu-privations-de-liberte-surveillance-de-masse-ce-que-george-orwell-n-avait-pas-prevu_6056160_4408996.html

Après les dernières annonces d'Emmanuel Macron sur le couvre-feu, plusieurs personnalités politiques ont à nouveau convoqué le roman « 1984 » de l'écrivain britannique. Parfois avec erreur.

Notes

Notes

Christian Hoffmann
Bernd Sebastian Kamps

COVID REFERENCE *top10*
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Here we publish in a single PDF the daily Top 10 scientific papers we have presented ever since COVID Reference's first edition on 29 March 2020. There is no secret to our procedure: the daily scanning of the literature helps us to stay afloat in the never-ending waves of new publications about SARS-CoV-2 and COVID-19. Most papers discussed in the Top 10 will eventually make it into subsequent editions of COVID Reference.

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