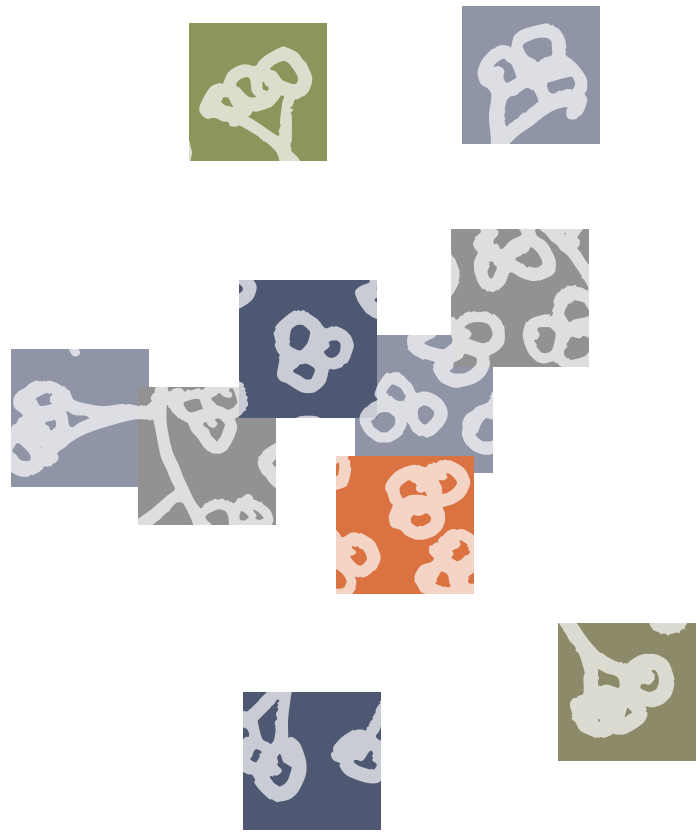
Christian Hoffmann
Bernd Sebastian Kamps

COVID REFERENCE *top10*

Daily Science vol. 2/2



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Volume 2

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COVID Reference Top 10

Daily Science
Volume 2

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Preface

The pandemic continues, Europe enters lockdown again. We will need this second volume.

Christian Hoffmann & Bernd Sebastian Kamps

31 October 2020

Preface to Volume 1

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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Content

October 2020 (2)

16 October

Special Paper

WHO Solidarity Trial Consortium, Pan, H, Peto R, et al. **Repurposed antiviral drugs for COVID-19; interim WHO SOLIDARITY trial results.** medRxiv 2020, posted 15 October. Full-text: https://doi.org/10.1101/2020.10.15.20209817

Will remdesivir soon join the hydroxychloroquine and lopinavir graveyard? Interim results from the Solidarity Therapeutics Trial, coordinated by the World Health Organization, indicate that remdesivir, hydroxychloroquine, lopinavir and interferon regimens appear to have little or no effect on hospitalized COVID-19, as indicated by overall mortality, initiation of ventilation and duration of hospital stay. This paper is currently being peer-reviewed.

See also the press articles in

English: Boseley S. **Remdesivir has very little effect on Covid-19 mortality, WHO finds.** The Guardian 2020, published 16 October. Full-text: https://www.theguardian.com/world/2020/oct/16/remdesivir-has-very-little-effect-on-covid-19-mortality-who-finds-trial-drug-coronavirus

Results from gold-standard trial described as sobering, as drug found not to improve survival rates

Spanish: Domínguez N. **La OMS confirma que ninguno de los fármacos contra la covid que estaba probando salva vidas.** El País 2020, published 16 October. Full-text: https://elpais.com/ciencia/2020-10-16/la-oms-confirma-que-ninguno-de-los-farmacos-contra-la-covid-que-estaba-probando-salva-vidas.html

Los datos del ensayo Solidarity confirman que ni la cloroquina ni el remdesivir ni otros dos tratamientos reducen la mortalidad.

Top 10 Special: Transmission

The 5th COVID Reference Edition will be published this month. These are 13 among the important papers we will include in the *Transmission* chapter. The topics:

1. Review
2. Super-spreading
3. Transmission terminology
4. Spit happens
5. Aerosolized fomites
6. Fecal aerosol transmission
7. Fomites
8. Bus
9. Leisure
10. Workplace: Meat-processing plant
11. Workplace: Musician
12. Choir

Review

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

1. Eric Meyerowitz et al. present a comprehensive review of the evidence of human SARS-CoV-2 transmission (Meyerowitz 2020). Their key points:
2. Respiratory transmission is the dominant mode of transmission.
3. Vertical transmission occurs rarely; transplacental transmission has been documented.
4. 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.
5. Direct contact and fomite transmission are presumed but are likely only an unusual mode of transmission.
6. 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.

Super-spreading

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 (Adam 2020). 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.

Transmission terminology

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 should clarify the terminology to distinguish between aerosols and droplets using a size threshold of 100 μm, not the historical 5 μm (Prather 2020). 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 seconds within 2 m of the source and can be sprayed like tiny cannonballs onto nearby individuals.

Spit happens

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 (Bax 2020). 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

Aerosolized fomites

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 (Asadi 2020). Will we soon see a paper about SARS-CoV-2 transmission via aerosolized fomites?

Fecal aerosol 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 (Kang M 2020). 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.

Fomites

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 (Mondelli 2020).

Bus

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 (Shen Y 2020). 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.

Leisure

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 (Szablewski 2020). Attack rates increased with increasing length of time spent at the camp, with staff members having the highest attack rate (56%).

Workplace: Meat-processing plant

Günther T, Czech-Sioli M, Indenbirken D, et al. **SARS-CoV-2 outbreak investigation in a German meat processing plant.** EMBO Mol Med. 2020 Oct 4:e202013296. PubMed: https://pubmed.gov/33012091. Full-text: https://doi.org/10.15252/emmm.202013296

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 (Günther 2020). 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.

Workplace: Musician

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 (Plautz 2020).

Choir

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!

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. 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.

17 October

Transmission

Atrubin D, Wiese M, Bohinc B. **An Outbreak of COVID-19 Associated with a Recreational Hockey Game** — Florida, June 2020. Full-text: http://dx.doi.org/10.15585/mmwr.mm6941a4

On June 16, 2020, a recreational ice hockey game was played between two teams, each consisting of 11 players (typically six on the ice and five on the bench at any given time). The players were men aged 19–53 years. During the 5 days after the game, 15 persons (14 of the 22 players and a rink staff member) experienced signs and symptoms compatible with coronavirus disease 2019 (COVID-19).

Do you remember our September 12 Top 10? In an unintentional experiment, the German national team of amateur boxers 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

prior. All 25 persons tested positive for SARS-CoV-2. 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

Immunology

Leisman DE, Ronner L, Pinotti R, et al. **Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes.** Lancet Respir Dis 2020, pubished 16 October. Full-text: https://doi.org/10.1016/S2213-2600(20)30404-5

Daniel Leisman and colleagues question the role of a cytokine storm in COVID-19-induced organ dysfunction after a systematic review and meta-analysis of 25 COVID-19 studies (n = 1245 patients) and four trials each in sepsis (n = 5320), cytokine release syndrome (n = 72), and acute respiratory distress syndrome unrelated to COVID-19 (n = 2767). Mean interleukin-6 concentrations were nearly 100 times higher in patients with cytokine release syndrome (3110.5 pg/mL), 27 times higher in patients with sepsis (983.6 pg/mL), and 12 times higher in patients with acute respiratory distress syndrome unrelated to COVID-19 (460 pg/mL). The authors conclude that alternative mechanisms of COVID-19-induced organ dysfunction are worth considering and that immune-activating treatments (i.e., interferons, IL-7, or checkpoint inhibition) might merit investigation.

Lee S, Channappanavar R, Kanneganti TD. **Coronaviruses: Innate Immunity, Inflammasome Activation, Inflammatory Cell Death, and Cytokines.** Trends Immunol 2020, published 15 October. Full-text: https://doi.org/10.1016/j.it.2020.10.005

The authors develop the current understanding of innate immune responses, inflammasome activation, inflammatory cell death pathways, and cytokine secretion during SARS-CoV, MERS-CoV, and SARS-CoV-2 infection. Your Sunday morning review.

Vaccine

Xia S, Zhang Y, Wang Y, e al. **Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial.** Lancet Infect Dis 2020, published 15 October. Full-text: https://doi.org/10.1016/S1473-3099(20)30831-8

A Chinese candidate vaccine, BBIBP-CorV (Beijing Institute of Biological Products), based on inactivated coronavirus, seems to be safe and elicits an antibody response. This is the first study of an inactivated SARS-CoV-2 vaccine to include participants older than 60 years. In these participants, antibodies took up to 42 days to be detected, compared with 28 days for participants aged 18 to 59. As expected, antibody levels were lower in those aged 60 to 80 years. Two-dose immunization with 4 μg vaccine on days 0 and 21 or days 0 and 28 achieved higher neutralizing antibody titers than the single 8 μg dose or 4 μg dose on days 0 and 14. A Phase III trial of BBIBP-CorV is currently underway in Abu Dhabi and the United Arab Emirates.

See also the comment by Isakova-Sivak I, Rudenko L. **A promising inactivated whole-virion SARS-CoV-2 vaccine.** Lancet Infect Dis 2020, published 15 October. Full-text: https://doi.org/10.1016/S1473-3099(20)30832-X

Krause PR, Grubner MF. **Emergency Use Authorization of Covid Vaccines — Safety and Efficacy Follow-up Considerations.** N Engl J Med 2020, published 16 October. Full-text: https://doi.org/10.1056/NEJMp2031373

There should be no emergency use authorization (EUA) of any COVID-19 vaccine without a median follow-up duration of at least 2 months after completion of the full phase 3 vaccination regimen. Normally, the FDA requires at least 6 months of safety follow-up for serious and other medically attended adverse events in a sufficient number of vaccinees. Philip Krause and Marion Gruber warn that any curtailment of this minimum follow-up could destroy the scientific credibility for future vaccines in the United States. Also see FDA's Vaccines and Related Biological Products Committee Open Hearing, 22 Oct 2020, https://www.youtube.com/watch?v=1XTiL9rUpkg&feature=youtu.be.

Kurup D, Wirblich C, Ramage H, et al. **Rabies virus-based COVID-19 vaccine CORAVAX™ induces high levels of neutralizing antibodies against SARS-CoV-2.** npj Vaccines 5, 98 (2020). Full-text: https://doi.org/10.1038/s41541-020-00248-6

The authors show the rapid development of a novel, efficient, and safe COVID-19 vaccine using a rabies virus-based vector. Both a live and an inactivated rabies virus containing the SARS-CoV-2 spike S1 protein induces potent virus-neutralizing antibodies at much higher levels than seen in the sera of convalescent patients.

Society

Brown RC, Kelly D, Wilkinson D, Savulescu J. **The scientific and ethical feasibility of immunity passports.** Lancet Infect Dis 2020, published 16 October. Full-text: https://doi.org/10.1016/S1473-3099(20)30766-0

Immunity passports are much less *en vogue* than during the first months of the pandemic: unethical and impractical, based on insufficient knowledge about what COVID-19 immunity, possibly a 'perverse' incentive and with doubtful economic benefits, and possibly discriminatory effects. If you want to read a pro-passport pleading about 'people's freedom', check this paper. Not necessarily convincing. Maybe not a must-read.

Society, Prevention

The Editorial Board. **End Our National Crisis.** The New York Times 2020, published 16 October. Full-text: https://www.nytimes.com/interactive/2020/10/16/opinion/donald-trump-worst-president.html

The greatest threat to American democracy since World War II.

Spanish

If you read Spanish, read Valdés I. **"No ser intubado cuando es imprescindible mata en minutos"** – El País 2020, published 17 October. Full-text: https://elpais.com/espana/madrid/2020-10-16/no-ser-intubado-cuando-es-imprescindible-mata-en-minutos.html

Borja Quintana y Antonio Planas, presidente de la Sociedad Madrileña de Anestesiología, Reanimación y Terapéutica del Dolor y secretario de la Sociedad Española de este área, repasan la situación de su especialidad durante la pandemia.

French

If you read French, read **Covid-19 : « L'hôpital n'a pas les moyens d'affronter la deuxième vague épidémique »** – Le Monde 2020, published 17 October. Full-text : https://www.lemonde.fr/idees/article/2020/10/17/covid-19-l-hopital-n-a-pas-les-moyens-d-affronter-la-deuxieme-vague-epidemique_6056367_3232.html

Faute de moyens, la seule solution pour freiner la progression du virus repose sur le respect par tous des mesures barrières, selon la Fédération des infirmiers de réanimation. Un extrait : « Si les prévisions épidémiologiques se

confirment, cette nouvelle vague sera plus haute et plus durable. Nous ne pourrons pas lui faire face, d'abord par manque de places en réanimation : le pays disposait de 5 000 lits de réanimation avant la première vague épidémique et c'est toujours le cas aujourd'hui. L'Etat annonce 12 000 lits de réanimation mobilisables, en ouvrant 7 000 lits supplémentaires... Mais ils ne sont pas équipés du matériel adapté pour ces soins complexes et aucune réserve de professionnels n'existe pour les ouvrir. »

18 October

Transmission

Sugano N, Ando W, Fukushima W. **Cluster of Severe Acute Respiratory Syndrome Coronavirus 2 Infections Linked to Music Clubs in Osaka, Japan**. J Infect Dis. 2020 Oct 13;222(10):1635-1640. PubMed: https://pubmed.gov/32840606. Full-text: https://doi.org/10.1093/infdis/jiaa542

Detailed contact tracing in Osaka, Japan: The data of 108 cases comprising a cluster were linked to 4 music clubs. In total, 51 cases attended a live music club only once and all index cases for secondary transmission were asymptomatic at the time of contact with other people. Substantial exposure occurred within a few hours. Asymptomatically infected persons can transmit the virus as soon as 2 days after infection. Bad news for music clubs.

Okarska-Napierała M, Mańdziuk J, Kuchar E. **SARS-CoV-2 cluster in nursery, Poland**. Emerg Infect Dis. 2021 Jan. Full-text: https://doi.org/10.3201/eid2701.203849

Several reports have implied little to no SARS-CoV-2 transmission among children and from children to adults. In this cluster that emerged in a single nursery in Poland within 2 weeks of its reopening, a high infection attack rate among children was found. The cluster involved a total of 29 persons; 8 were children attending the nursery, and 12 were the children's family members who did not enter the facility. The high attack rates could be explained by prolonged close contact between very young children, who are less able to adjust to control measures. However, these observations question the role of young children in driving the COVID-19 pandemic.

Diagnostic

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 2019**. J Infect Dis. 2020 Oct 13;222(10):1612-1619. PubMed: https://pubmed.gov/32738137. Full-text: https://doi.org/10.1093/infdis/jiaa487

Use sputum, not deep throat saliva. This study prospectively examined 563 serial samples collected during the virus shedding periods of 50 patients: 150 deep throat saliva (DTS, patients first cleared their throat by gargling with their own saliva, and then they spit out the DTS into a sterile bottle), 309 pooled-nasopharyngeal (NP) and throat swabs, and 104 sputum (self-collected, patients were asked to cough out sputum and spit into a sterile plastic bottle). Deep throat saliva had the lowest overall RT-PCR-positive rate (69% vs 89% for sputum and 81% for pooled NP and throat swabs) and the lowest viral RNA concentration (mean log copy/mL 3.54 vs 5.03 and 4.63, respectively).

Clinical

Kontis V, Bennett JE, Rashid T, et al. **Magnitude, demographics and dynamics of the effect of the first wave of the COVID-19 pandemic on all-cause mortality in 21 industrialized countries**. Nat Med (2020). Full-text: https://doi.org/10.1038/s41591-020-1112-0

The total death toll for the first wave of the COVID-19 pandemic for 21 industrialized countries (not including US or Germany). England, Wales and Spain experienced the largest effect: ~100 excess deaths per 100,000 people, equivalent to a 37% (30–44%) relative increase in England and Wales and 38% (31–45%) in Spain.

Bilinski A, Emanuel EJ. **COVID-19 and Excess All-Cause Mortality in the US and 18 Comparison Countries**. JAMA October 12, 2020. Full-text: https://doi.org/10.1001/jama.2020.20717

Alyssa Bilinski and Ezekiel Emanuel have compared 14 countries with all-cause mortality data, finding similar patterns. In countries with moderate COVID-19 mortality, excess all-cause mortality remained negligible throughout the pandemic. In countries with high COVID-19 mortality, excess all-cause mortality reached as high as 102/100,000 in Spain, while in the US it was 72/100,000. However, since May, excess all-cause mortality was higher in the US than in all high-mortality countries, due possibly to several factors, in-

cluding weak public health infrastructure and a decentralized, inconsistent US response to the pandemic.

Gold JA, Rossen LM, Ahmad FB, et al. **Race, Ethnicity, and Age Trends in Persons Who Died from COVID-19 — United States, May–August 2020**. MMWR Morb Mortal Wkly Rep. ePub: 16 October 2020. Full-text: http://dx.doi.org/10.15585/mmwr.mm6942e1

This report provides information on how demographic and geographic factors have changed among COVID-19–associated deaths during May–August 2020. Of 114,411 COVID-19–associated deaths, 51% of decedents were non-Hispanic White, 24% were Hispanic or Latino (Hispanic), and 19% were non-Hispanic Black. The percentage of Hispanic decedents increased from 16.3% in May to 26.4% in August. Data suggest that the geographic shift from the Northeast to the South and West alone does not entirely account for this increase.

Mascitti H, Bonsang B, Dinh A, et al. **Clinical cutaneous features of patients infected with SARS-CoV-2 hospitalized for pneumonia: a cross-sectional study**. Open Forum Infectious Diseases, 18 October 2020. Full-text: https://doi.org/10.1093/ofid/ofaa394

Various dermatological signs were seen in 59 COVID-19 patients, a macular rash being the most frequent. All cutaneous features could be related to a vascular leak process.

Severe COVID-19

Thomas R, Lotfi T, Morgano GP, et al. **Update Alert 2: Ventilation Techniques and Risk for Transmission of Coronavirus Disease, Including COVID-19**. Annals Int Med 13 October 2020. Full-text: https://doi.org/10.7326/L20-1211

Update of a living systematic review on ventilation techniques, analyzing all new studies published until the end of July. Bottom line: Nothing new. Non-invasive ventilation may have similar effects to IMV on mortality, but the evidence is uncertain.

Collateral damage

Marchetti D, Fontanesi L, Mazza C, et al. **Parenting-Related Exhaustion During the Italian COVID-19 Lockdown**. Journal of Pediatric Psychology,17 October 2020. Full-text: https://doi.org/10.1093/jpepsy/jsaa093

Who suffers the most? While many countries prepare for a second lockdown, this study took a look on the psychological consequences during the first wave, performing interviews with a total of 1226 parents via a demographic questionnaire. Seventeen percent reported significant parenting-related exhaustion and most parents reported a clinically alarming level of distress. Multiple regression analyses showed that greater parenting-related exhaustion was predicted by psychological distress, lower parental resilience, motherhood, fewer perceived social connections, and being single, as well as having a child with special needs, having a large number of children, and having younger children.

Treatment

Rajasingham R, Bangdiwala AS, Nicol MR, et al. **Hydroxychloroquine as pre-exposure prophylaxis for COVID-19 in healthcare workers: a randomized trial.** Clinical Infectious Diseases 17 October 2020. Full-text: https://doi.org/10.1093/cid/ciaa1571

No, **HC**Q does not work as prophylaxis, even in **HC**W. This huge double-blinded RCT included 1483 healthcare workers with ongoing exposure to persons with SARS-CoV-2. Participants across the US and Canada were randomized to HCQ 400 mg once weekly or twice weekly for 12 weeks. The incidence of COVID-19 (laboratory-confirmed or symptomatic compatible illness) was 0.27 events per person-year with once-weekly and 0.28 events per person-year with twice-weekly hydroxychloroquine, compared with 0.38 events per person-year with placebo. This was not statistically significant.

Pediatrics

Dumitriu D, Emeruwa UN, Hanft E, et al. **Outcomes of Neonates Born to Mothers With Severe Acute Respiratory Syndrome Coronavirus 2 Infection at a Large Medical Center in New York City**. JAMA Pediatr. Published online October 12, 2020. Full-text: https://doi.org/10.1001/jamapediatrics.2020.4298

Of 101 neonates born to mothers with perinatal SARS-CoV-2 infections at a single institution, 2 (2.0%) had positive test results for SARS-CoV-2, but none had clinical evidence of COVID-19, despite most infants sleeping in the same

room with mothers and direct breastfeeding. This study endorses the benefits of sleeping in the same room, breastfeeding, and delayed bathing on newborn outcomes and suggests that separating mothers positive for SARS-CoV-2 and their newborns and avoiding direct breastfeeding may not be warranted to prevent SARS-CoV-2 transmission.

19 October

Epidemiology

Moozhipurath RK, Kraft L, Skiera B. **Evidence of protective role of Ultraviolet-B (UVB) radiation in reducing COVID-19 deaths**. Sci Rep 10, 17705 (2020). Full-text: https://doi.org/10.1038/s41598-020-74825-z

Serious? The authors applied a fixed-effect log-linear regression model to a panel dataset of 152 countries over 108 days (n = 6524). They used the cumulative number of COVID-19 deaths and case-fatality rate (CFR) as the main dependent variables and isolated the ultraviolet index (UVI) effect from potential confounding factors. After controlling for time-constant and time-varying factors, the authors found a significant negative association between UVI and COVID-19 deaths, indicating evidence of the protective role of ultraviolet B (UVB) in mitigating COVID-19 deaths. If confirmed via clinical studies, then the possibility of mitigating COVID-19 deaths via sensible sunlight exposure or vitamin D intervention would be highly attractive.

Virology

Lu S, Zhao Y, Yu W, et al. **Comparison of nonhuman primates identified the suitable model for COVID-19**. Signal Transduct Target Ther. 2020 Oct 19;5(1):157. PubMed: https://pubmed.gov/32814760. Full-text: https://doi.org/10.1038/s41392-020-00269-6

The authors characterized SARS-CoV-2 infection in three non-human primate species: Old World monkeys Macaca mulatta (M. mulatta) and Macaca fascicularis (M. fascicularis) and New World monkey Callithrix jacchus (C. jacchus). Susceptibilities of Old World and New World monkeys to SARS-CoV-2 differed markedly. Macaca mulatta seemed to be the most suitable for modeling COVID-19.

Immunology

Perico L, Benigni A, Casiraghi F, et al. **Immunity, endothelial injury and complement-induced coagulopathy in COVID-19**. Nat Rev Nephrol (2020). Full-text: https://doi.org/10.1038/s41581-020-00357-4

Nice review on pathogenic mechanisms underlying SARS-CoV-2 infection and COVID-19, as well as on the critical role of the immunological hyper-response — characterized by widespread endothelial damage, complement-induced blood clotting and systemic microangiopathy — in disease exacerbation.

Liu B, Han J, Cheng X et al. **Reduced numbers of T cells and B cells correlates with persistent SARS-CoV-2 presence in non-severe COVID-19 patients**. Sci Rep 10, 17718 (2020). Full-text: https://doi.org/10.1038/s41598-020-73955-8

In total, 37 non-severe patients with persistent SARS-CoV-2 presence that were transferred to Zhongnan hospital of Wuhan were retrospectively recruited to the PP (persistently positive) group, which was further allocated to the PPP group (n = 19) and the PPN group (n = 18), according to their testing results after 7 days (N = negative). The PPP subgroup had markedly reduced B cells and T cells compared to the PPN group and healthy subjects. Finally, paired results of these lymphocyte subpopulations from 10 PPN patients demonstrated that the number of T cells and B cells significantly increased when the SARS-CoV-2 tests turned negative.

Transmission

Chau NVV, Hong NTT, Ngoc NM, et al. **Superspreading event of SARS-CoV-2 infection at a bar, Ho Chi Minh City, Vietnam**. Emerg Infect Dis. 2021 Jan. Full-text: https://doi.org/10.3201/eid2701.203480

From 10:00 PM on March 14 until 2:30 AM of the next day, a 43-year old man participated in a St. Patrick's Day celebration at a bar in Ho Chi Minh City. The bar had 2 indoor areas for clients, a 300 m^2 area downstairs and an 50 m^2 area upstairs, with no mechanical ventilation. During opening hours, the left and right entrances were typically kept closed to facilitate cooling with air conditioners that recycle indoor air; the middle entrance was kept open. The bar also has naturally ventilated outdoor spaces. Results: 12 additional cases at the bar (and more, via contacts of people infected there).

Clinical

Pimenoff VN, Elfström M, Baussano I, et al. **Estimating total excess mortality during a COVID-19 outbreak in Stockholm, Sweden**. Clinical Infectious Diseases. Full-text: https://doi.org/10.1093/cid/ciaa1593

Ville Pimenoff estimates that since January 2020, the accumulated excess mortality in the Stockholm region at week 18 was +23% compared with the average over the previous ten years. Of note, comparison with the number of reported COVID-19-related deaths in the 5 week peak period of the outbreak found that 26% of the excess mortality during the COVID-19 epidemic was not recognized as COVID-19-related, either via public health data or by the regional morgue.

Lu QB, Zhang Y, Liu MJ , et al. **Epidemiological parameters of COVID-19 and its implication for infectivity among patients in China, 1 January to 11 February 2020**. Euro Surveill. 2020;25(40). Full-text: https://doi.org/10.2807/1560-7917.ES.2020.25.40.2000250

Using a large database of > 2000 COVID-19 cases and potential transmission pairs of cases, the authors estimate the median incubation period to be 7.2 (95% confidence interval: 6.9–7.5) days. The median serial and generation intervals were similar, 4.7 (95% CI: 4.2–5.3) and 4.6 (95% CI: 4.2–5.1) days, respectively. Pediatric cases < 18 years had a longer incubation period than adult age groups (p = 0.007).

Severe COVID-19

Rodrigues JY, Le Pape P, Lopez O, et al. **Candida auris: a latent threat to critically ill patients with COVID-19**, Clinical Infectious Diseases. Full-text: https://doi.org/10.1093/cid/ciaa1595

Jose Y Rodrigues and colleagues report on 20 cases of fungemia in hospitalized patients with SARS-CoV-2 infection in 4 institutions in the northern region of Colombia from June to September 2020. Nineteen of the 20 patients had received steroids and 15/19 were had non-albicans Candida fungemia.

Co-morbidities

Martínez-López J, Mateos M, Encinas C. et al. **Multiple myeloma and SARS-CoV-2 infection: clinical characteristics and prognostic factors of inpatient mortality**. Blood Cancer J. 10, 103 (2020). Full-text: https://doi.org/10.1038/s41408-020-00372-5

A retrospective cohort, looking at 167 MM patients from 73 Spanish hospitals. Compared to non-cancer patients, mortality was 50% higher. The main predictors of inpatient mortality for MM were male sex, age > 65 years, renal disease, and active/progressive disease.

Treatment

Keretsu S, Bhujbal SP, Cho SJ. **Rational approach toward COVID-19 main protease inhibitors via molecular docking, molecular dynamics simulation and free energy calculation**. Sci Rep 10, 17716 (2020). Full-text: https://doi.org/10.1038/s41598-020-74468-0

Saquinavir instead of lopinavir? The authors found 15 potential 3CLpro inhibitors with higher binding affinity than that of an α-ketoamide inhibitor determined via X-ray structure. Among them, saquinavir and three investigational drugs aclarubicin, TMC-310911, and faldaprevir can be suggested as potential 3CLpro inhibitors. The authors recommend further experimental investigation of these compounds.

20 October

Genetics

Severe Covid-19 GWAS Group, Ellinghaus D, Degenhardt F, et al. **Genomewide Association Study of Severe Covid-19 with Respiratory Failure.** N Engl J Med. 2020 Oct 15;383(16):1522-1534. PubMed: https://pubmed.gov/32558485. Full-text: https://doi.org/10.1056/NEJMoa2020283

Only a small proportion of patients with SARS-CoV-2 infection have respiratory compromise, a respiratory distress syndrome, and multiorgan failure. Who is to blame, the virus or the host? To help answer this question, Andre Franke, Tom Karlsen and 404 colleagues, on behalf of *The Severe Covid-19 GWAS Group*, conducted a genome-wide association study involving patients with COVID-19 and severe disease (defined as respiratory failure) at seven hospitals in the Italian and Spanish epicenters of the SARS-CoV-2 pandemic in Europe: 835 patients and 1255 control participants from Italy and 775 patients and 950 control participants from Spain. The group identified associations between the risk of severe COVID-19 and a multigene locus at 3p21.31 and the *ABO* blood group locus at 9q34.2. The HLA region did not show any association signal.

See also the comment by Kaser A. **Genetic Risk of Severe Covid-19.** N Engl J Med. 2020 Oct 15;383(16):1590-1591. PubMed: https://pubmed.gov/33053291.

Full-text: https://doi.org/10.1056/NEJMe2025501. The preliminary response to our initial question: The determinants of disease severity appear to reside almost exclusively in host factors, not in viral genetic variation.

Virology

Rattanapisit K, Shanmugaraj B, Manopwisedjaroen S. et al. **Rapid production of SARS-CoV-2 receptor binding domain (RBD) and spike specific monoclonal antibody CR3022 in Nicotiana benthamiana**. Sci Rep 10, 17698 (2020). Full-text: https://doi.org/10.1038/s41598-020-74904-1

This study demonstrates the rapid production of the RBD of SARS-CoV-2 and mAb CR3022 in Nicotiana benthamiana using a transient expression system. The plant-produced RBD showed specific binding to the receptor of SARS-CoV-2 (ACE2), confirming its structural integrity. Further, the plant-produced mAb CR3022 exhibited binding to SARS-CoV-2, but it failed to neutralize the virus *in vitro*. Overall, this study provides a proof-of-principle for the rapid production of SARS-CoV-2 antigens or monoclonal antibodies in a plant expression system in order to produce diagnostic reagents, vaccines and therapeutics.

Transmission

Richmond CS, Sabin AP, Jobe DA, et al. **SARS-CoV-2 sequencing reveals rapid transmission from college student clusters resulting in morbidity and deaths in vulnerable populations.** medRxiv 2020, posted 14 October. Full-text: https://doi.org/10.1101/2020.10.12.20210294

The title says it all: a substantial SARS-CoV-2 outbreak coincided with the return to in-person instruction at three local academic institutions. From 111 sequenced genomes the authors identified rapid transmission of the virus into more vulnerable populations. One of the variants made its way into two care homes, infecting 8 residents. Two died. MedRxiv article – not yet peer reviewed.

Prevention

Lauterbach K. **Will Germany's effective Covid strategy work again as it enters a second wave?** The Guardian 2020, published 19 October. Full-text: https://www.theguardian.com/commentisfree/2020/oct/19/germany-covid-second-wave-virus

The first wave taught us that if politicians and scientists work together, they have more chance of beating this virus.

Immunology

Dong J, Huang B, Wang B, et al. **Development of humanized tri-specific nanobodies with potent neutralization for SARS-CoV-2.** Sci Rep 10, 17806 (2020). Full-text: https://doi.org/10.1038/s41598-020-74761-y

Llamas against SARS-CoV2? In May, Djambo Dong et al. identified humanized VHHs that bind to S protein and block the S/ACE2 interaction (see article below; a VHH antibody [or nanobody] is the antigen binding fragment of heavy-chain-only antibodies). Now the authors use computer-aided design to construct multi-specific VHH antibodies fused to human IgG1 Fc. The resulting tri-specific VHH-Fc antibodies show potent S1 binding, S1/ACE2 blocking, and SARS-CoV-2 pseudovirus neutralization.

Dong J, Huang B, Jia Z, et al. **Development of multi-specific humanized llama antibodies blocking SARS-CoV-2/ACE2 interaction with high affinity and avidity.** Emerg Microbes Infect. 2020 Dec;9(1):1034-1036. PubMed: https://pubmed.gov/32403995. Full-text: https://doi.org/10.1080/22221751.2020.1768806

Schwarzkopf S, Krawczyk A, Knop D, Klump H, Heinold A, Heinemann FM, et al. **Cellular immunity in COVID-19 convalescents with PCR-confirmed infection but with undetectable SARS-CoV-2–specific IgG.** Emerg Infect Dis. 2021 Jan. Full-text: https://wwwnc.cdc.gov/eid/article/27/1/20-3772_article

Sina Schwarzkopf and colleagues from Essen University, Germany have investigated immune responses among a group of convalescent, potential blood donors in Germany who had PCR-confirmed SARS-CoV-2 infection. Sixty days after onset of symptoms, 13/78 (17%) study participants had borderline or negative results to an ELISA detecting IgG against the S1 protein. Cellular immunity toward any of the SARS-CoV-2 antigens was detectable in 7/9 (78%) participants who had a low antibody ratio < 1.

Clinical

Yang W, Kandula S, Huynh M, et al. **Estimating the infection-fatality risk of SARS-CoV-2 in New York City during the spring 2020 pandemic wave: a model-based analysis.** Lancet Infect Dis 2020, published 19 October. Full-text: https://doi.org/10.1016/S1473-3099(20)30769-6

The infection-fatality risk (IFR) is the risk of death among all infected individuals including those with asymptomatic and mild infections. Here, Wan Yang and colleagues report on the outcome of SARS-CoV-2 infection during the first wave in New York City. They found an overall IFR of 1.39%. Age was the all-important factor: 25–44 years: 0.11%; 45–64 years: 0.94%; 65-74 years: 4.9%; 75 years and older: 14.2%. The sample size reported is impressive: 205,639 people with laboratory-confirmed SARS-CoV-2, and 21,447 confirmed and probable COVID-19-related deaths.

Severe COVID

Leiter RE. **Reentry.** N Engl J Med. 2020 Oct 14. PubMed: https://pubmed.gov/33053276. Full-text: https://doi.org/10.1056/NEJMp2027447

"While we try to heal from the collective trauma we experienced in our hospital over the worst 4 months of the local epidemic, I struggle to know where to look. Peering into the future, given what we see on the news, saturates me with dread. And yet it's too early to look back. Perspective can't develop in the presence of open wounds."

Potential Drugs

El-Hachem N, Eid E, Nemer G, et al. **Integrative transcriptome analyses empower the anti-COVID-19 drug arsenal.** ISCIENCE (2020). Full-text: https://doi.org/10.1016/j.isci.2020.101697

Searching for potential therapeutic targets, the authors used integrative data-driven computational analyses on large transcriptomic datasets encompassing both *in vitro* and *in vivo* SARS-CoV-2-infected samples as well as normal human lung biopsy samples. They provide a repertoire of drug repurposing candidates, identify TNF-NFkB signaling as a targetable hallmark for COVID-19 and suggest BTK inhibitors as repurposable candidates for COVID-19.

Society, Prevention

The Editors. **Why *Nature* supports Joe Biden for US president.** Nature 2020, published on 14 October. Full-text: https://www.nature.com/articles/d41586-020-02852-x

"We cannot stand by and let science be undermined. Joe Biden's trust in truth, evidence, science and democracy make him the only choice in the US election."

Spanish

If you read Spanish, read de Miguel R. **El Reino Unido da luz verde a un ensayo que infectará con el coronavirus a personas sanas.** El País 2020, published 20 October. Full-text: https://elpais.com/ciencia/2020-10-20/el-reino-unido-da-luz-verde-a-un-ensayo-que-infectara-con-el-coronavirus-a-personas-sanas.html

El llamado Desafío Humano permite acelerar la comprobación de la eficacia de las vacunas. Algunos científicos cuestionan la utilidad y la ética del método.

French

If you read French, read Mesmer P, Pons P. **Lutte contre le Covid-19 : les leçons sud-coréenne et japonaise.** Le Monde 2020, published 19 October. Full-text: https://www.lemonde.fr/idees/article/2020/10/19/lutte-contre-le-covid-19-les-lecons-sud-coreenne-et-japonaise_6056519_3232.html

La Corée du Sud et le Japon ont été relativement épargnés par le Covid-19 et ignorent la déconnexion entre pouvoir et population. Respect de l'hygiène et responsabilité collective s'y enseignent dès l'école.

Deutsch

If you read German, read Köppe J. **Wie tödlich ist Covid-19?** Der Spiegel 2020, published 20 October. Full-text: https://www.spiegel.de/wissenschaft/medizin/corona-diskussion-ueber-studie-der-weltgesundheitsorganisation-wie-toedlich-ist-covid-19-wirklich-a-9d05b174-87fd-44e4-a1a3-da9760fad1d5

Eine Studie der WHO hat Verwirrung gestiftet: Ist die Sterblichkeit bei Corona-Infizierten viel niedriger als angenommen? Ein genauerer Blick auf die Zahlen offenbart ein Missverständnis.

Roth J. **"Viele haben geweint".** Die Zeit 2020, published 20 October. Full-text: https://www.zeit.de/politik/ausland/2020-10/ngo-facing-hunger-west-virginia-armut-cynthia-kirkhart-usa-lebensmittelverteilung

Corona hat viele Amerikaner so arm gemacht, dass sie kein Geld mehr fürs Essen haben. Zu Besuch bei einer Hilfsorganisation, die in West Virginia gegen den Hunger kämpft.

21 October

Virology

Cantuti-Castelvetri L, Ojha R, Pedro LD, et al. **Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity.** Science 2020, published 20 October. Full-text: https://doi.org/10.1126/science.abd2985

For many viruses, tissue tropism is determined by the availability of virus receptors and entry co-factors on the surface of host cells. Here, Mikael Simons, Ludovico Cantuti-Castelvetri and colleagues report that neuropilin-1 (NRP1), known to bind furin-cleaved substrates, significantly potentiates SARS-CoV-2 infectivity, an effect blocked by a monoclonal blocking antibody against NRP1. Another potential target for antiviral intervention.

Daly JL, Simonetti B, Klein K, et al. **Neuropilin-1 is a host factor for SARS-CoV-2 infection.** Science 2020, published 20 October. Full-text: https://doi.org/10.1126/science.abd3072

Again, neuropilin-1. Step-by-step: 1) SARS-CoV-2 uses the viral Spike (S) protein for host cell attachment and entry. 2) The host protease furin cleaves the full-length precursor S glycoprotein into two associated polypeptides: S1 and S2. 3) Cleavage of S generates a polybasic Arg-Arg-Ala-Arg C-terminal sequence on S1, which conforms to a C-end rule (CendR) motif that 4) binds to cell surface neuropilin-1 (NRP1) and neuropilin-2 (NRP2) receptors. Now Yohei Yamauchi, James Daly and colleagues show that the S1 CendR motif directly binds NRP1. Blocking this interaction, using RNAi or selective inhibitors, reduced SARS-CoV-2 entry and infectivity in cell culture. NRP1 binding to the CendR peptide in S1 is thus likely to play a role in the increased infectivity of SARS-CoV-2 compared with SARS-CoV. The authors conclude that the ability to target this specific interaction might provide a route for COVID-19 therapies.

Vaccine

Bangaru S, Ozorowski G, Turner HL, et al. **Structural analysis of full-length SARS-CoV-2 spike protein from an advanced vaccine candidate.** Science 2020, published 20 October. Full-text: https://doi.org/10.1126/science.abe1502

Andrew Ward, Sandhya Bangaru and colleagues describe the structure of a leading SARS-CoV-2 S vaccine candidate (NVAX-CoV2373, under development by Novavax Inc. and Novavax AB, Uppsala) based on a full-length S, residues 1-1273 which includes the transmembrane (TM) and the cytoplasmic tail (CT). The authors found that NVAX-CoV2372 is stable, homogeneous, and locked in the antigenically preferred pre-fusion conformation. After structural, biophysical, and antigenic characterization, the candidate vaccine will not face the true proof-of-principle: evaluation in humans.

Diagnostics

Azzi L. **Saliva is the Key Element for SARS-CoV-2 Mass Screening.** Clin Infect Dis 2020, published 21 October. Full-text: https://doi.org/10.1093/cid/ciaa1440

Saliva is the future of mass screening. In his comment on the paper by Isao Yokota et al. we presented on September 29, Lorenzo Azzi highlights the potential merits of saliva: it can be easily and non-invasively self-collected by the subject, thus avoiding the employment of skilled staff and the risk of viral transmission during the procedure, is more comfortable for the patient if compared with the nasopharyngeal swab, and for this reason is more frequently repeatable, with good compliance.

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

We should not forget, though, that mass screening might not be easy to implement. Look at this: Pettengill MA, McAdam AJ. **Can We Test Our Way Out of the COVID-19 Pandemic?** J Clin Microbiol 2020, published 21 October. Full-text: https://doi.org/10.1128/JCM.02225-20

Clinical

Clift AK, Keogh RH, Diaz-Ordaz K, et al. **Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study.** BMJ 2020, published 20 October. Full-text: https://doi.org/10.1136/bmj.m3731

Julia Hippisley-Cox, Ash Clift and colleagues present a new risk tool to predict a person's risk of being admitted to hospital and dying from COVID-19. They used data from 6 million patients over a 97-day period (24 January to 30 April 2020), and a further 2.2 million patients to validate its performance over two separate time periods (24 January to 30 April 2020 and 1 May to 30 June 2020). People in the top 5% for predicted risk of death accounted for 76% of COVID-19 deaths within the 97-day study period while people in the top 20% accounted for 94% of COVID-19 deaths. *We are now waiting for the model to become freely available on the internet.*

See also the comment by Matthew Sperrin: **Prediction models for covid-19 outcomes.** BMJ 2020, published 20 October. Full-text: https://doi.org/10.1136/bmj.m3777

di Filippo L, Formenti AM, Doga M, et al. **Radiological Thoracic Vertebral Fractures are highly prevalent in COVID-19 and predict disease outcomes.** J Clin Endocrinol Metabol 2020, published 21 October. Full-text: https://doi.org/10.1210/clinem/dgaa738

In this retrospective cohort study from a tertiary health-care hospital in Northern Italy, 114 SARS-CoV-2 positive patients were included. Thoracic vertebral fractures (VF) were detected in 41 patients (36%). Patients with VFs required more frequently a non-invasive mechanical ventilation compared to those without VFs ($p = 0.02$). Mortality was 22% in VFs+ group and 10% in VFs- group ($p = 0.07$). In particular, mortality was higher in patients with severe VFs compared to those with moderate and mild VFs ($p = 0.04$). The authors conclude that VF might be a useful and easy-to-measure clinical marker of fragility and poor prognosis and suggest that morphometric thoracic vertebral evaluation should be performed in all suspected COVID-19 patients undergoing chest X-rays.

Hudowenz O, Klemm P, Lange U, et al. **Case report of severe PCR-confirmed COVID-19 myocarditis in a European patient manifesting in mid January 2020.** European Heart Journal - Case Reports. Full-text: https://doi.org/10.1093/ehjcr/ytaa286

A positive polymerase chain reaction (PCR) test of SARS-CoV-2 in heart specimens: the authors present a case of severe COVID-19 myocarditis manifesting in mid-January 2020. Primarily suspected of being related to small-vessel vasculitis, the case was later revised to COVID-associated disease when the patient reported a history of travel to Tyrol. Consequently, PCR testing resulted positive in a previously obtained heart specimen. The immunosuppressive treatment was discontinued. During a follow-up visit at the end of April, the patient's recovery was stable.

Collateral Effects

Mohamed MO, Banerjee A, Clarke S, et al. **Impact of COVID-19 on cardiac procedure activity in England and associated 30-day mortality.** Eur Heart J 2020, published 20 October. Full-text: https://doi.org/10.1093/ehjqcco/qcaa079

A preview of what cardiology departments might see in the coming autumn and winter months 2020/2021. The authors analyzed the impact of COVID-19 on changes in cardiac procedure activity in England. Compared to the monthly averages (March-May) in 2018/2019, there was a deficit of 45,501 procedures between 1st January and 31st May 2020. Cardiac catheterization and device implantations were the most affected in terms of numbers (n = 19,637 and n = 10,453). No difference in 30-day mortality was observed between pre-COVID and COVID time-periods for all cardiac procedures except cardiac catheterization and cardiac device implantation.

Journal Feature

Ledford H. **How obesity could create problems for a COVID vaccine.** Nature 2020, published 20 October. Full-text: https://www.nature.com/articles/d41586-020-02946-6

In this Nature news feature, senior science reporter Heidi Ledford describes fears of researchers that vaccines might not be as effective in people who are obese, a population already highly vulnerable to COVID-19.

22 October

Epidemiology

Smith GD, Blastland M, Munafò M. **Covid-19's known unknowns.** BMJ 2020;371:m3979. Full-text: https://www.bmj.com/content/371/bmj.m3979

Do we know exactly what's going on with SARS-CoV-2 and exactly what to do about it? Over the past months, we have seen strongly contrasting but apparently equally authoritative statements about almost any topic. Stop the nonsense, write Georges Davey-Smith and his colleagues. Acknowledging uncertainty a little more might improve not only the atmosphere of the debate and the science, but also public trust. In any case, the more certain someone is about COVID-19, the less you should trust them.

Immunology

Overbaugh J. **Understanding protection from SARS-CoV-2 by studying reinfection.** Nat Med 2020, published 22 October. Full-text: https://doi.org/10.1038/s41591-020-1121-z

Can understanding the risk of SARS-CoV-2 reinfection provide an avenue to understanding the path to protection against SARS-CoV-2 for vaccine development? Julie Overbaugh argues that the study of reinfection is critical because if neutralizing antibody responses are robust in people who are reinfected, this would suggest that the vaccine concepts need to be diversified. This could include considering diverse antibody epitopes, both neutralizing and non-neutralizing, and optimizing the effector function of antibodies and enhancing cellular responses.

Diagnostics

Pettengill MA, McAdam AJ. **Can We Test Our Way Out of the COVID-19 Pandemic?** J Clin Microbiol 2020, published 21 October. Full-text: https://doi.org/10.1128/JCM.02225-20

Frequent, low-cost, universal testing for SARS-CoV-2 infection and quarantining those with a positive result has been suggested as a strategy to address the COVID-19 pandemic. Could such low-sensitivity daily tests (LSDT) help us 'test our way out' of the pandemic? The authors don't think so and don't mince their words: "Using testing to prevent transmission of SARS-CoV-2 on a large scale is like using the weather report to prevent global warming." Find out why.

Clinical

Clift AK, Coupland CAC, Keogh RH, Hemingway H, Hippisley-Cox J. **COVID-19 Mortality Risk in Down Syndrome: Results From a Cohort Study Of 8 Million Adults.** Ann Intern Med. 2020 Oct 21. PubMed: https://pubmed.gov/33085509. Full-text: https://doi.org/10.7326/M20-4986

Persons with Down syndrome seem to be at an increased risk for COVID-19–related hospitalization and death. This is the result of an analysis of individual-level data in a cohort study of 8,26 million adults in the UK. The authors estimate a 4-fold increased risk for COVID-19–related hospitalization and a 10-fold increased risk for COVID-19–related death.

Car J, Koh GCH, Foong PS, Wang J. **Video consultations in primary and specialist care during the covid-19 pandemic and beyond**. BMJ 2020; 371. Full-text: https://doi.org/10.1136/bmj.m3945

At the start of the pandemic, many GPs and specialists turned to video consultations to reduce patient flow through healthcare facilities and limit infectious exposures. What was your experience? Josip Car and colleagues give you a *grand tour* of video consultations in the COVID-19 era: how to start, how to prepare patients for the consultation, suggestions for a remote physical examination, and how to switch from a video to a telephone or in-person consultation, depending on technical, patient, or clinical factors. A must-read for GPs.

Treatment

Stone JH, Frigault MJ, Serling-Boyd NJ, et al. **Efficacy of Tocilizumab in Patients Hospitalized with Covid-19.** N Engl J Med 2020, published 22 October. Full-text: https://doi.org/10.1056/NEJMoa2028836

Tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients with COVID-19. This is the result of a randomized, double-blind, placebo-controlled trial involving SARS-CoV-2 patients with hyperinflammatory states and at least two of the following signs: fever (body temperature > 38°C), pulmonary infiltrates, or the need for supplemental oxygen in order to maintain an oxygen saturation greater than 92%. John H. Stone and colleagues (for the BACC Bay Tocilizumab Trial Investigators) conclude that their data do not provide support for the concept that early interleukin 6 receptor blockade is an effective treatment strategy in moderately ill patients hospitalized with COVID-19.

Severe COVID

Cates J, Lucero-Obusan C, Dahl RM, et al. **Risk for In-Hospital Complications Associated with COVID-19 and Influenza — Veterans Health Administration, United States, October 1, 2018–May 31, 2020.** MMWR Morb Mortal Wkly Rep 2020;69:1528–1534. Full-text: http://dx.doi.org/10.15585/mmwr.mm6942e3

COVID-19 is deadlier than influenza. Now, Jordan Cates and colleagues have quantified the difference: hospitalized patients with COVID-19 had a more-than-five-times-higher risk for in-hospital death and increased risk for 17 respiratory and non-respiratory complications than did hospitalized patients with influenza. The risks for sepsis and respiratory, neurologic, and renal complications of COVID-19 were higher among non-Hispanic Black or African American and Hispanic patients than among non-Hispanic White patients.

Pediatrics

Feldstein LR, Rose EB, Horwitz SM. **Multisystem Inflammatory Syndrome in U.S. Children and Adolescents.** N Engl J Med 2020; 383:334-346. Full-text: https://doi.org/10.1056/NEJMoa2021680

SARS-CoV-2-associated multi-system inflammatory syndrome in children (MIS-C) is a life-threatening illness even in previously healthy children and adolescents. This is the result of a study presented by Manish M. Patel, Leora Feldstein and colleagues reporting on 186 children in pediatric health centers across the US. The median age was 8.3 years, and organ-system involvement included the gastrointestinal system in 171 patients (92%), cardiovascular in 149 (80%), hematologic in 142 (76%), mucocutaneous in 137 (74%) and respiratory in 131 (70%). A total of 148 patients (80%) received intensive care, 37 (20%) received mechanical ventilation, 90 (48%) received vasoactive support and 4 (2%) died.

Education

Rubin EJ, Baden LR, Morrissey S. **Tocilizumab and Covid-19.** Audio interview (32:26). N Engl J Med 2020; 383: e114. Access: https://doi.org/%2010.1056/NEJMe2032051

The editors discuss the results of a new clinical trial of tocilizumab, a monoclonal antibody that blocks the activity of the proinflammatory cytokine interleukin 6.

Society, Prevention

Rosenbaum L. **Tribal Truce — How Can We Bridge the Partisan Divide and Conquer Covid?** N Engl J Med 2020; 383:1682-1685. Full-text: https://doi.org/10.1056/NEJMms2027985

Interview with Anthony Fauci on empathy, transparency, and global disease outbreaks (at 23:03 in the podcast).

23 October

Epidemiology

Aschwanden C. **The false promise of herd immunity for COVID-19**. Nature News Feature October 21. Full-text: https://doi.org/10.1038/d41586-020-02948-4

Herd immunity has recently been discussed as a desirable result of wide-scale vaccination programs. (High levels of vaccination-induced immunity in the population benefits those who can't receive or sufficiently respond to a vaccine, such as people with compromised immune systems.) However, discussing herd immunity as a tool *in the absence of vaccines* has never been heard of before the SARS-CoV-2 pandemic. If you are tired and frustrated with distancing, lockdown and curfews and tempted by the notion of herd immunity (better: 'herd protection'), read this brilliant article by Nature's leading science writer Christie Aschwanden. Find out why proposals to largely let the virus run its course — embraced by Donald Trump's administration and others — could bring untold death and suffering. Seasonal coronaviruses that cause common colds provoke a waning immunity that seems to last approximately a year. Until proof of the contrary, we should assume immunity to SARS-CoV-2 to be comparable. Without vaccines there will be no herd immunity for the foreseeable future.

Adlhoch C, Pebody R. **What to expect for the influenza season 2020/21 with the ongoing COVID-19 pandemic in the World Health Organization European Region**. Euro Surveill. 2020;25(42):pii=2001816. Full-text: https://doi.org/10.2807/1560-7917.ES.2020.25.42.2001816

Less flu cases in this season? The positivity rate of 0.2% in the 2020 inter-seasonal period was lower than the average (1.1%) observed over the previous five inter-seasonal periods. However, although COVID-19 prevention and control measures will also support influenza prevention, influenza remains a threat to human health and a potential burden on the healthcare system.

Immunology

Youk J, Kim T, Evans KV. **Three-dimensional human alveolar stem cell culture models reveal infection response to SARS-CoV-2**. Cell Rep October 21, 2020. Full-text: https://doi.org/10.1016/j.stem.2020.10.004

The cellular response of human alveolar type 2 (hAT2) cells to SARS-CoV-2 remains elusive, due to difficulty in the long-term expansion of pure hAT2 cells. Jeonghwan Youk and colleagues now developed a technique for long-term, feeder-free human 3D alveolar type 2 cell cultures (h3ACs). According to the authors, SARS-CoV-2 infected h3ACs showed remarkable cellular and transcriptional changes far more clearly than other models, including h3BCs and 2D Vero cell lines, showing cellular tropism in the viral replication and transcription as well as the resultant reaction from the host cell.

Katsura H, Sontake V, Tata A, et al. **Human lung stem cell-based alveolospheres provide insights into SARS-CoV-2 mediated interferon responses and pneumocyte dysfunction**. Cell Rep October 21, 2020. Full-text: https://doi.org/10.1016/j.stem.2020.10.005

Hiroaki Katsura from Duke University, Durham, USA and colleagues present another new feeder-free, scalable, chemically-defined, and modular alveolosphere culture system for propagation and differentiation of human alveolar type 2 cells (AT2s/pneumocytes) derived from primary lung tissue. Cultured pneumocytes expressed the SARS-CoV-2 receptor ACE2 and could be infected with virus. Cells retained the cardinal features of AT2s, including the ability to self-renew, produce surfactants, and differentiate into AT1s. This model may offer a unique system for studying SARS-CoV-2 infection and developing effective therapies for COVID-19 and other respiratory diseases.

Ferretti AP, Kula T, Wang Y, et al. **Unbiased screens show CD8+ T cells of COVID-19 patients recognize shared epitopes in SARS-CoV-2, most of which are not located in the Spike protein**. Immunity, October 20, 2020. Full-text: https://doi.org/10.1016/j.immuni.2020.10.006

Which peptide sequences in SARS-CoV-2 are recognized by the memory CD8+ T cells of COVID-19 patients? Andrew P. Ferretti and colleagues found that CD8+ T cells predominantly recognized 3-8 shared epitopes for each HLA type studied. Of note, around ~90% of shared epitopes were not located in the Spike protein, but in ORF1ab or the nucleocapsid protein. CD8+ T cells generally did not cross-react with epitopes in the four seasonal coronaviruses.

Vaccine

Bell BP, Romero JR, Lee GM. **Scientific and Ethical Principles Underlying Recommendations from the Advisory Committee on Immunization Practices for COVID-19 Vaccination Implementation**. JAMA. 2020 Oct 22. PubMed: https://pubmed.gov/33090194. Full-text: https://doi.org/10.1001/jama.2020.20847

Discover how the US wants to distribute a vaccine. This viewpoint discusses possible prioritization scenarios. "Phase Ia" includes health care personnel who have the potential for direct or indirect exposure to patients or infectious materials. This group comprises an estimated 20 million (!) people. We will later come back to Phase Ib (and the rest) maybe in 2022.

Kreps S, Prasad S, Brownstein JS. **Factors Associated With US Adults' Likelihood of Accepting COVID-19 Vaccination**. JAMA Netw Open. 2020;3(10):e2025594. Full-text: https://doi.org/10.1001/jamanetworkopen.2020.25594

But who will accept such a vaccine (see previous paper). And when? Sarah Kreps and colleagues asked 1971 US adults, analyzing factors associated with willingness and individual preferences. Some interesting findings: The marginal mean willingness to receive a vaccine was lowest when the vaccine was recommended by President Trump. Willingness was slightly (but not significantly) higher with former Vice President Biden and significantly higher given a CDC or WHO endorsement. Respondents who indicated Democratic political partisanship were significantly more likely to report willingness than those who indicated Republican political partisanship. A vaccine originating in China was associated with a 10% lower willingness.

Diagnostic

Rubin R. **The Challenges of Expanding Rapid Tests to Curb COVID-19**. JAMA October 21, 2020. Full-text: https://doi.org/10.1001/jama.2020.21106

BinaxNOW is one of 6 point-of-care rapid antigen tests that had received an Emergency Use Authorization from the FDA as of October 10. The Trump administration awarded a contract for $760 million to Abbott for delivery of 150 million tests (Abbott said it would ship 50 million tests per month beginning in October). However, rapid point-of-care tests alone can't halt the spread of SARS-CoV-2: this interesting article describes how the rapid test BinaxNOW fueled the White House COVID-19 cluster.

Treatment

Salvarani C, Dolci G, Massari M, et al. **Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia**. A Randomized Clinical Trial. JAMA Intern Med October 20, 2020. Full-text: https://doi.org/10.1001/jamainternmed.2020.6615

The second RCT showing that tocilizumab (TCZ) doesn't work in patients with less severe disease. This prospective, open-label RCT randomized patients hospitalized with COVID-19 pneumonia to receive TCZ or standard of care in 24 hospitals in Italy. Among 126 patients with a partial pressure of arterial oxygen to fraction of inspired oxygen (Pao2/Fio2) ratio between 200 and 300 mm Hg at enrolment, the rate of the primary clinical end point (clinical worsening) was not significantly different between the control group and the TCZ group. The proportion of patients discharged within 14 and 30 days was the same (rate ratio, 0.99; 95% CI, 0.73-1.35; and 0.98; 95% CI, 0.87-1.09; respectively). According to the authors, however, their results "do not allow ruling out the possible role of tocilizumab in reducing the risk of death or intubation in patients presenting with more advanced disease". Let's hope.

Gupta S, Wang W, Hayek SS, et al. **Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19**. JAMA Intern Med October 20, 2020. Full-text: https://doi.org/10.1001/jamainternmed.2020.6252

Does it work in severe COVID-19? This multicenter cohort study that included 3924 critically ill patients admitted to participating intensive care units (ICU) at 68 hospitals across the US, patients were categorized according to whether they received or did not receive tocilizumab in the first 2 days of admission to the ICU. The risk of in-hospital death was estimated to be lower with TCZ. A total of 1544 patients (39,3%) died, including 125/433 (28,9%) treated with TCZ and 1419/3491 (40,6%) not treated with the drug. However, this was an uncontrolled study and TCZ patients were younger, had fewer co-morbidities and were more likely to receive corticosteroids on ICU admission. According to the authors, the findings "may be susceptible to unmeasured confounding, and further research from randomized clinical trials is needed". Again, let's hope.

Notes

Notes

Christian Hoffmann
Bernd Sebastian Kamps

COVID REFERENCE *top10*
Daily Science

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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