CLINICAL CARE OPTIONS®
INFECTIOUS DISEASE

Comprehensive COVID-19 Slideset: Diagnosis and Transmission

Version 1 – December 29, 2021

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Faculty Disclosures

Arthur Kim, MD, has disclosed that he is on the drug and safety monitoring board of Kintor Pharmaceuticals.

Sharon Lewin, AO, FRACP, PhD, FAAHMS, has disclosed that she has received consulting fees from AbbVie, Gilead Sciences, and ViiV Healthcare; funds for research support from Leidos; and other financial or material support from Gilead Sciences, Merck, and ViiV Healthcare.

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Global Epidemiology and Transmission

The CSSE at Johns Hopkins: Global COVID-19 Dashboard

Confirmed Cases Global: 266,145,318	Deaths Global: 5,259,255
▪ US: 49,097,146 ▪ India: 34,641,561 ▪ Brazil: 22,143,091 ▪ UK: 10,523,325 ▪ Russia: 9,661,865	▪ US: 788,418 ▪ Brazil: 615,636 ▪ India: 473,537 ▪ Mexico: 295,203 ▪ UK: 146,056

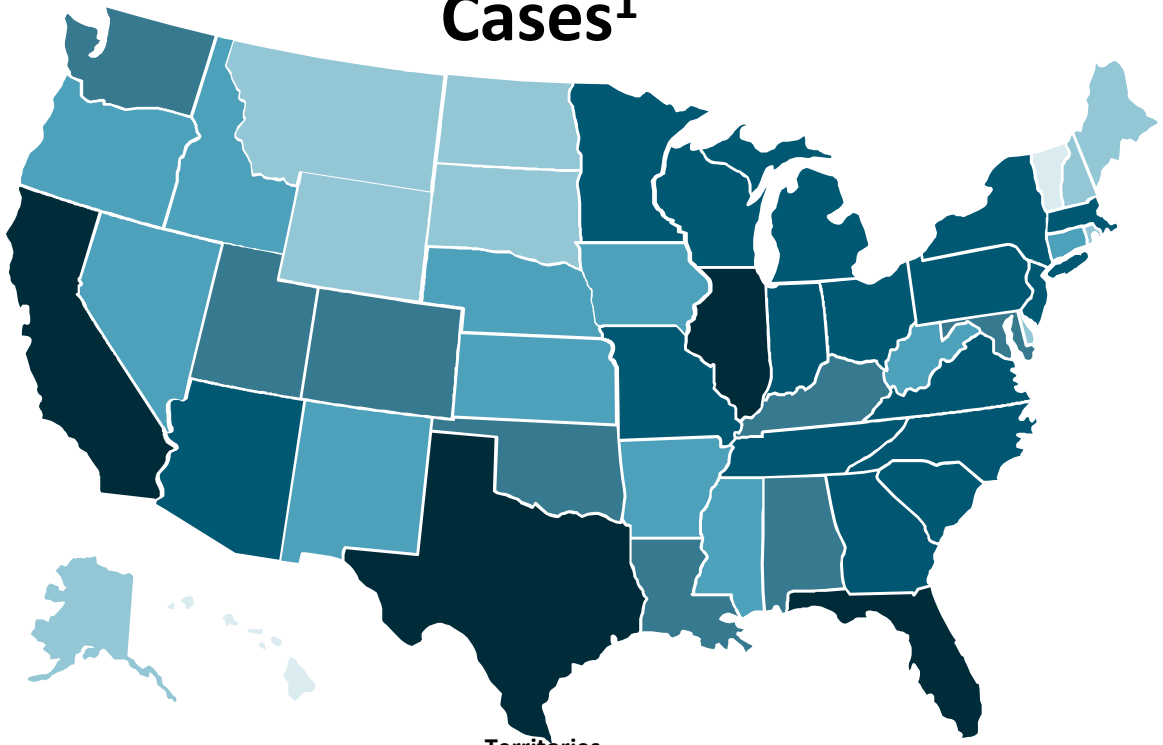
Last updated: December 6, 2021

Dong. Lancet Infect Dis. 2020;20:533. coronavirus.jhu.edu/map.html.

Slide credit: clinicaloptions.com

CDC: COVID Data Tracker

Cases[1]



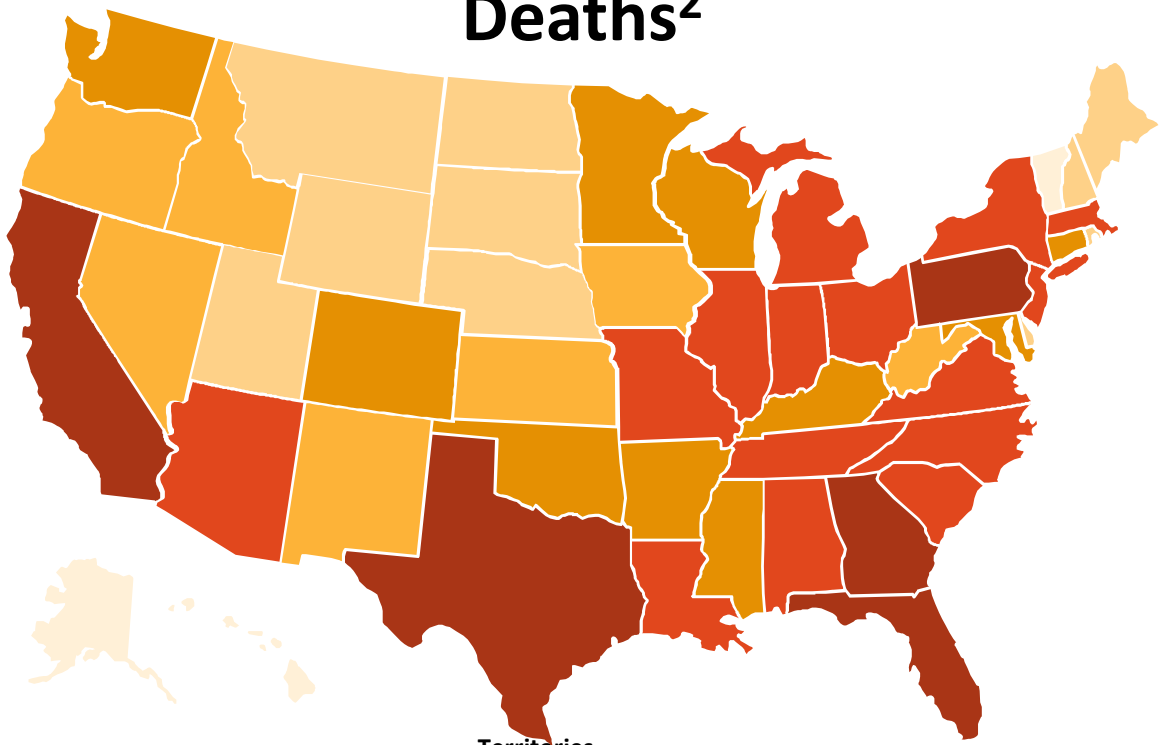
Territories

Total Cases | AS | FSM | GU | MP | PW | RMI | VI

Data not available

4.0-85.1k | 111.8-194.9k | 298.7-534.6k | 592.7-848.1k | 919.3k - 1.8M | 1.8-5.1M

Deaths[2]



Territories

AS | FSM | GU | MP | PW | RMI | VI

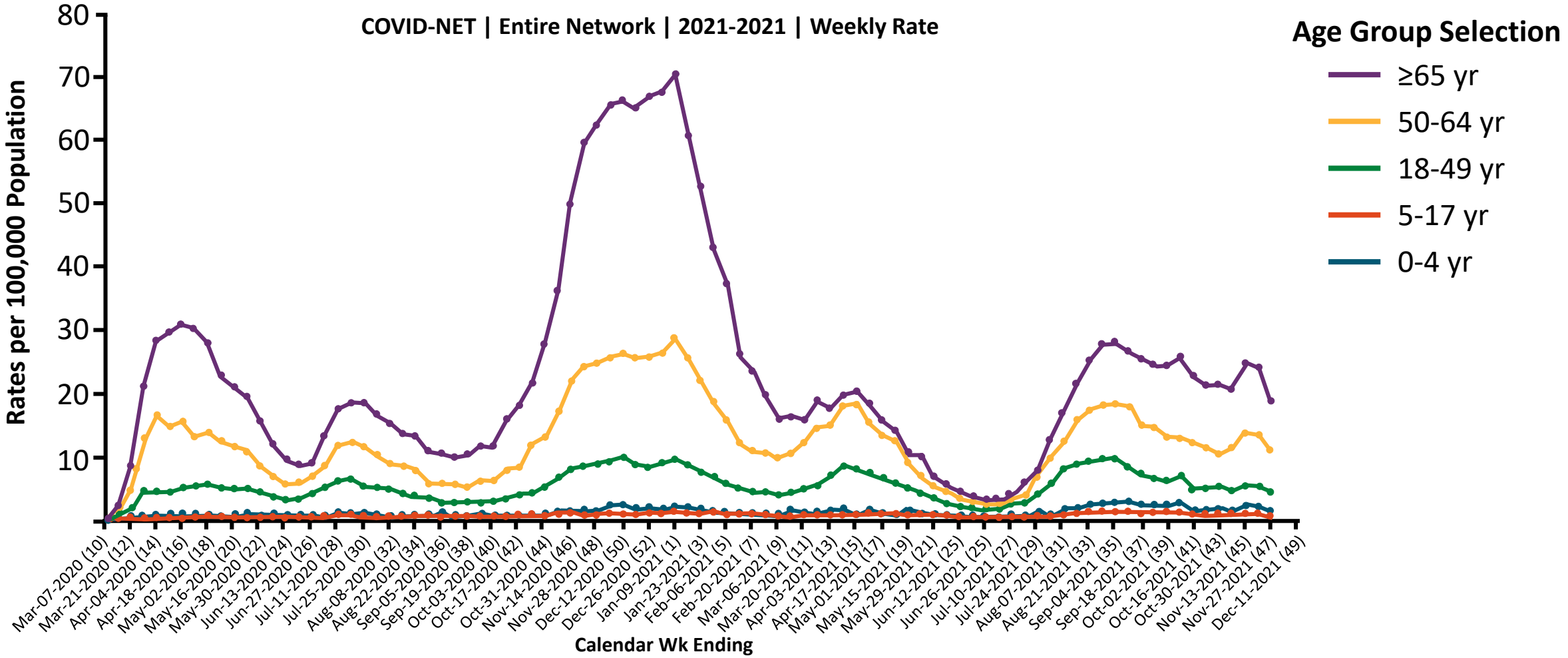
Data not available

0-1.0k | 1.2-3.6k | 4.0-8.1k | 8.7-11.3k | 14.3-29.5k | 30.7-74.0k

1. covid.cdc.gov/covid-data-tracker/#cases_totalcases. 2. covid.cdc.gov/covid-data-tracker/#cases_totaldeaths. Last updated: December 6, 2021

Slide credit: clinicaloptions.com

COVID-NET: Lab-Confirmed COVID-19–Associated Hospitalization Rates Stratified by Age

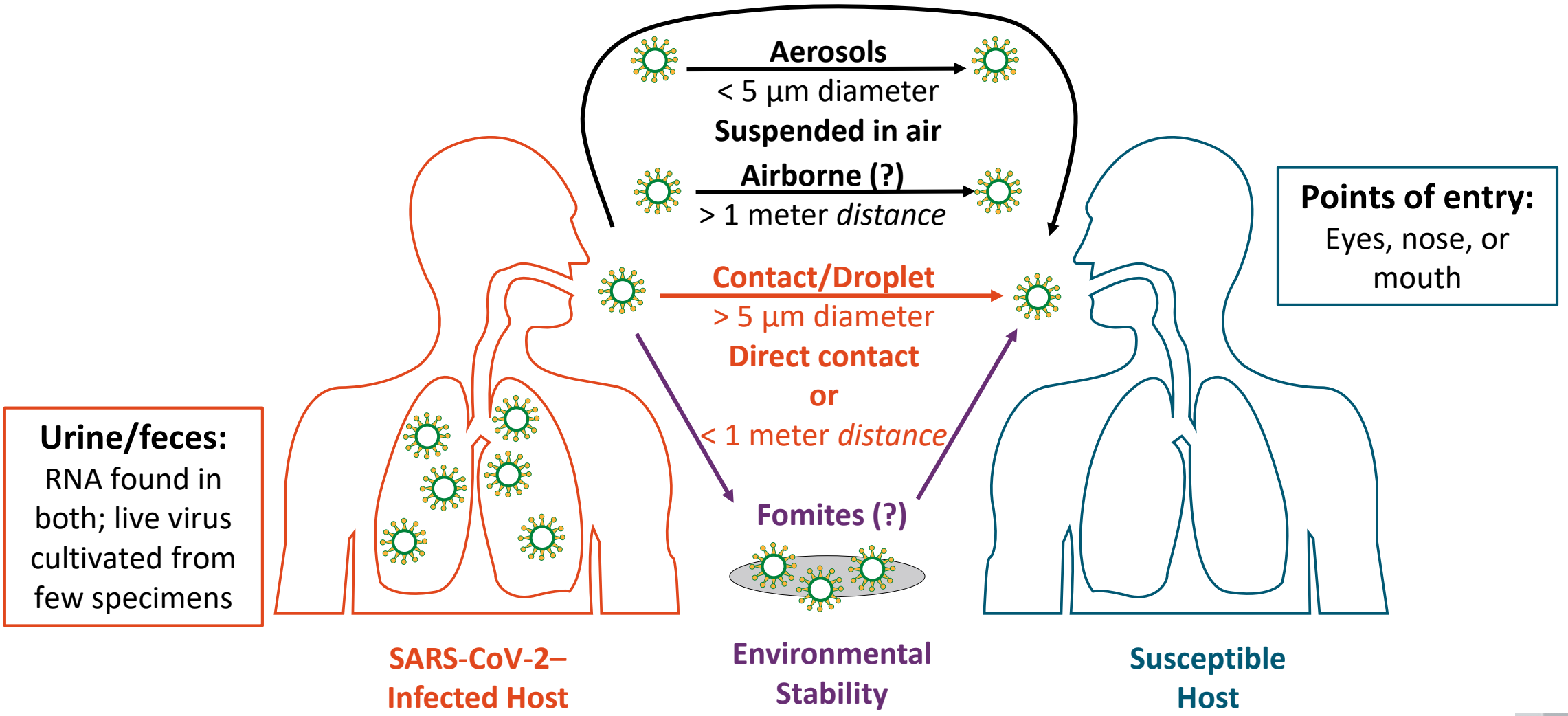


Covers ~10% of US population: 99 counties in 14 states (CA, CO, CT, GA, IA, MD, MI, MN, NM, NY, OH, OR, TN, UT)

gis.cdc.gov/grasp/COVIDNet/COVID19_3.html

Slide credit: clinicaloptions.com

Proposed Routes of SARS-CoV-2 Transmission



Galbadage. Front Public Health. 2020;8:163. WHO. Scientific Brief. July 9, 2020.

Slide credit: clinicaloptions.com

Rapid Inactivation of SARS-CoV-2 Aerosols in Sunlight

- In vitro simulations suggest a **90% loss of infectivity in 8-19 min** for SARS-CoV-2 aerosols exposed to mid to high intensity sunlight

Suspension Matrix at 20°C	Simulated Sunlight	Tests, n	Mean $k_{infectivity}$, min^{-1} (SD)	Mean Decay Rate, %/min (SD)
Simulated saliva	None	18	0.008 (0.011)	0.8 (1.1)
	Mid intensity	3	**0.121 (0.017)**	**11.4 (1.5)**
	High intensity	8	**0.306 (0.097)**	**26.1 (7.1)**
Culture medium	None	16	0.013 (0.012)	1.2 (1.2)
	Mid intensity	4	0.169 (0.062)	15.4 (5.3)
	High intensity	7	0.182 (0.041)	16.6 (3.3)

Results pooled across tests of varying relative humidity as this factor not found to significantly affect viral decay.

Schuit. J Infect Dis. 2020;222:564.

Slide credit: clinicaloptions.com

Key Considerations on Modes of SARS-CoV-2 Transmission

- Person-to-person considered predominant mode of transmission, mainly via respiratory droplets from **coughing, sneezing, singing, talking, or breathing**[1,2]
  - High-level viral shedding evident in upper respiratory tract[3,4]
  - Airborne transmission suggested by multiple studies, but frequency unclear in absence of aerosol-generating procedures in healthcare settings[2]
- Virus **rarely cultured in respiratory samples > 9 days after symptom onset**, especially in patients with mild disease[5]
- Multiple studies describe a correlation between **reduced infectivity with decreases in viral loads** and rises in neutralizing antibodies[5]
- ACOG: "Data indicate that vertical transmission appears to be uncommon"[6]

1. www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/how-covid-spreads.html. Last updated July 14, 2021.
2. WHO. Scientific Brief. July 9, 2020. 3. Wölfel. Nature. 2020;581:465. 4. Zou. NEJM. 2020;382:1177.
5. WHO. Scientific Brief. June 17, 2020. 6. ACOG. COVID-19 FAQs for Obstetrician-Gynecologists, Obstetrics.

Slide credit: clinicaloptions.com

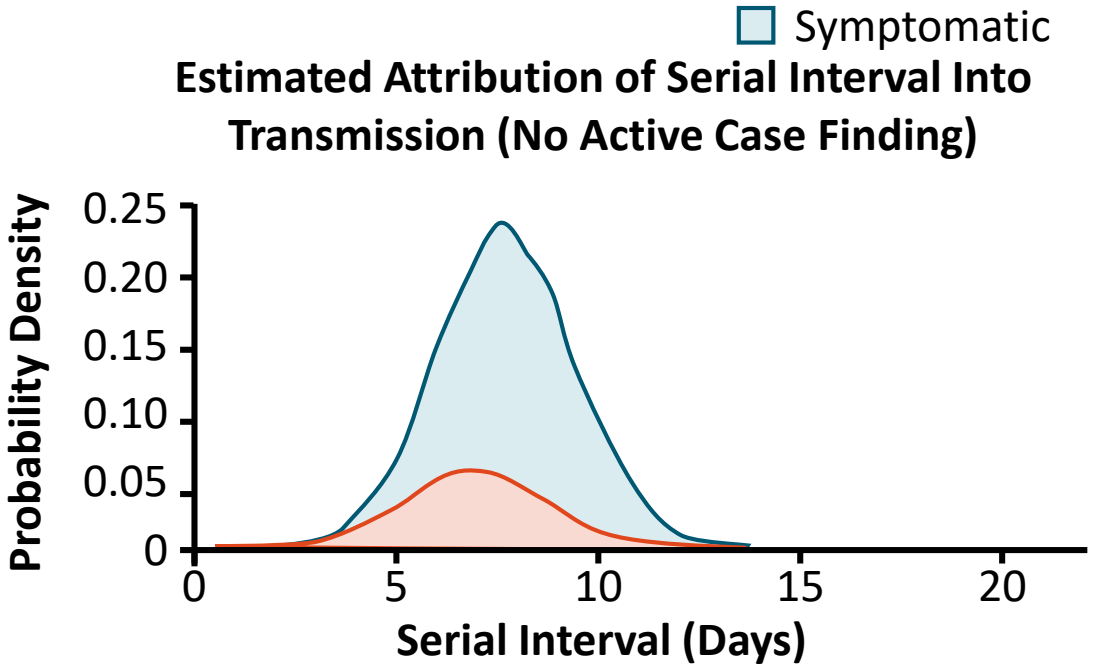
Timing of SARS-CoV-2 Transmission Based on Symptoms

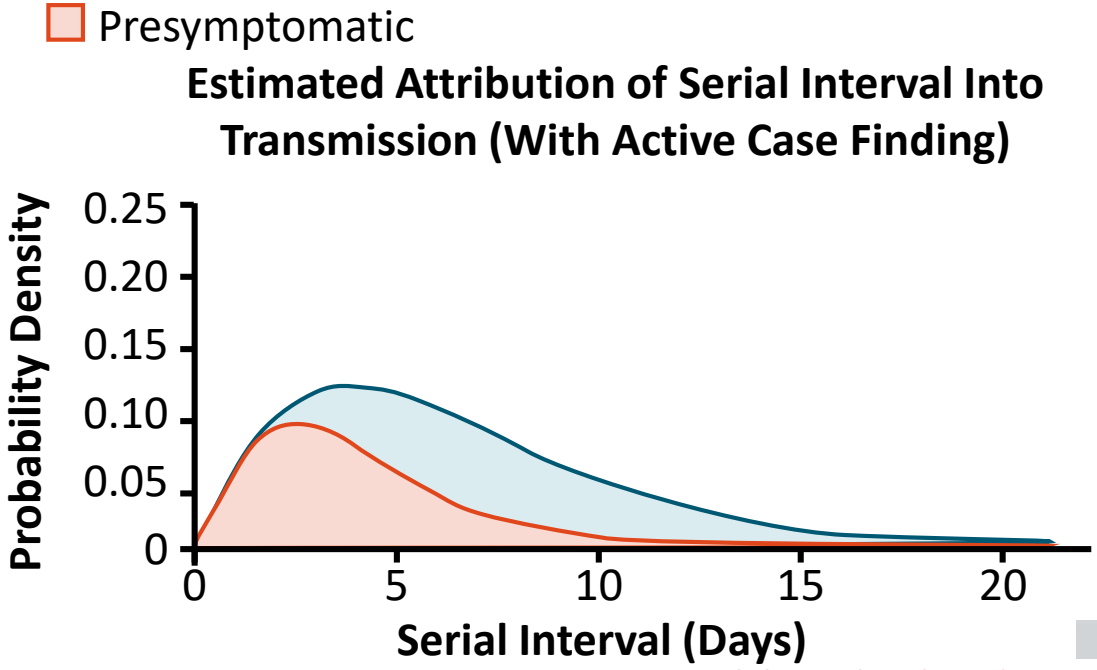
- Prospective study of lab-confirmed COVID-19 cases (n = 100) and their close contacts (n = 2761) in Taiwan[1]
  - Paired index-secondary cases (n = 22) occurred more frequently with exposure **just before or within 5 days of symptom onset** vs later
- **Pre-symptomatic infections**
  - Accounted for 6.4% of locally acquired infections in a study in Singapore (N = 157)[2]
  - Modelling study of transmission in China (n = 154) estimated that 44% of transmissions may have occurred just before symptoms appeared[3]
- One systematic review and meta-analysis estimated that the proportion of total infections that are **truly asymptomatic ranges from 4% to 40% (pooled estimate of 17%)**[4]
  - Asymptomatic transmission rates ranged from 0% to 2.2% vs symptomatic transmission rates of 0.8% to 15.4%
  - 3 studies reported that the cycle threshold from RT-PCR assays did not differ between symptomatic and asymptomatic individuals

1. Cheng. JAMA Intern Med. 2020;180:1156. 2. Wei. MMWR. 2020;69:411.
3. He. Nature Medicine. 2020;26:672. 4. Byambasuren. JAMMI. 2020;5:223.

Presymptomatic vs Symptomatic Transmission

- Transmission events in Shenzen, China were inferred to be symptomatic or presymptomatic using the probability for symptom onset on a given day following exposure
- Estimated that 23% of transmissions occurred prior to symptom onset before active case finding was implemented, increased to 46% with accelerated case isolation





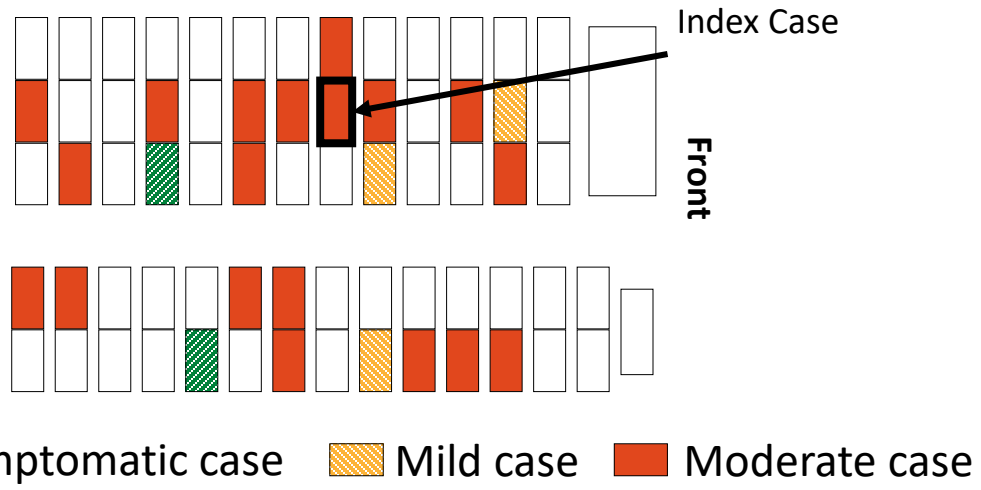
Liu. Wellcome Open Res. 2020;5:58.

Slide credit: clinicaloptions.com

SARS-CoV-2 Transmission in Indoor Settings With Recirculated Air

- An outbreak investigation of COVID-19 among lay Buddhists worshipping at a temple in Zhejiang, China (N = 299)
  - Travel: ~ 50 min each way
  - Worship event: ~ 150 min (mostly outdoors)

Layout of Secondary Cases in Relation to Index Case in Bus



Area of Exposure	Cases	Total	Attack Rate (95% CI)	Relative Risk (95% CI)	*P* Value
Bus 1	0	60	0 (0-6.0)	Ref	--
Temple (excluding those arriving on bus 2)	7	232	3.0 (1.3-6.2)	Ref	--
Bus 2 (index case)	23	67	34.3 (24.1-46.3)	--	
▪ Relative risk vs bus 1	--	--	--	42.2 (2.6-679.3)	<.01
▪ Relative risk vs temple (excluding bus 2)	--	--	--	11.4 (5.1-25.4)	<.01

Shen. JAMA Intern Med. 2020;180:1665.

Slide credit: clinicaloptions.com

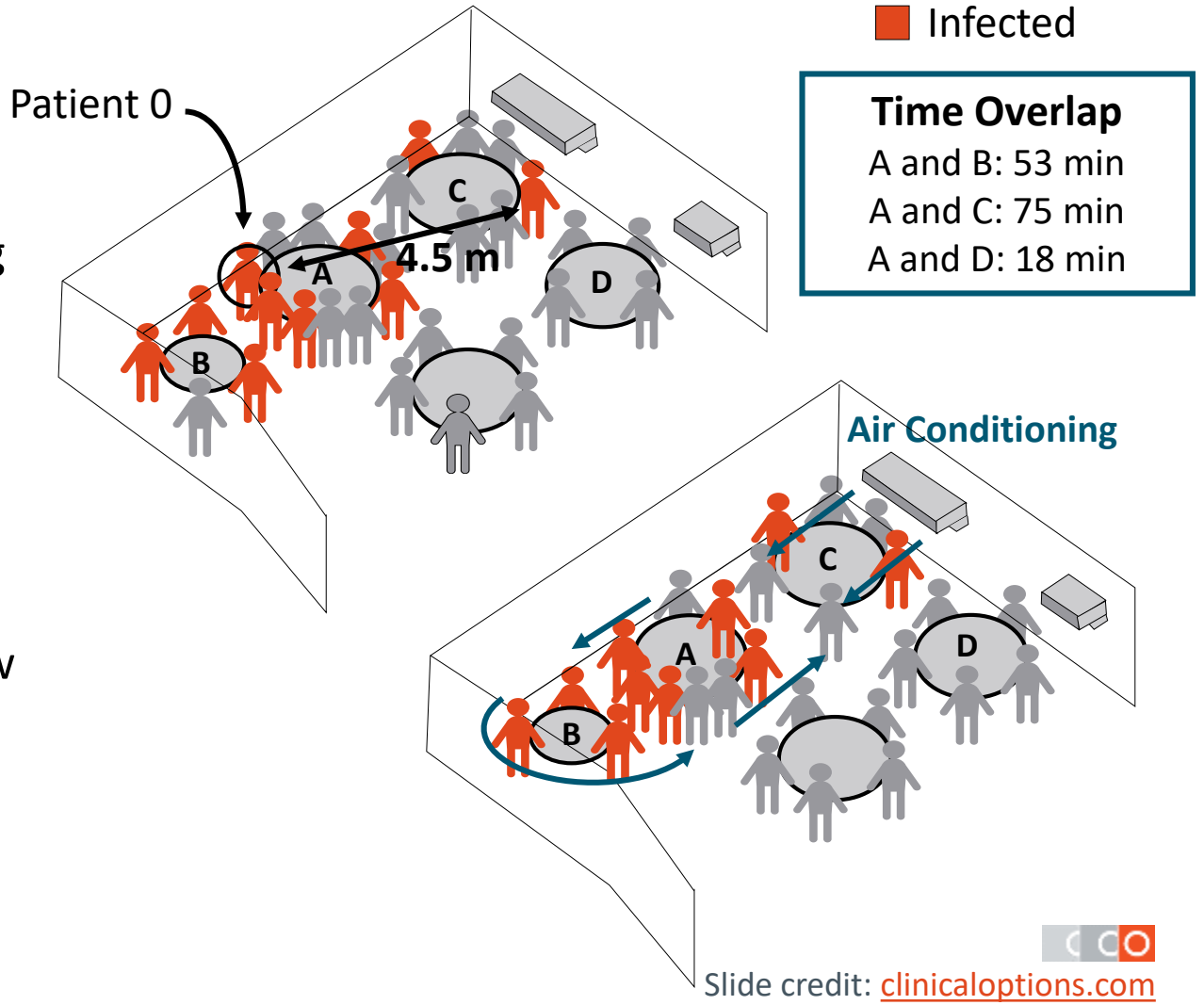
SARS-CoV-2 Transmission in Enclosed vs Outdoor Settings

- Study in Japan traced contacts of 110 people with COVID-19 in ten indoor clusters and assessed the environment in which transmission between contacts occurred[1]
  - 27 primary cases generated secondary cases (24.6%)
- Odds that a primary case transmitted SARS-CoV-2 in an enclosed environment **18.7 x higher** compared with odds of estimated transmission rates in an open-air environment (95% CI: 6.0-57.9)[1]
- **6 of 7 superspreading events** (to 3 or more people) occurred in enclosed environments (OR vs open-air environments: 32.6; 95% CI: 3.7-289.5)[1]
- Consistent with cluster in Germany from indoor work meeting, cluster from a ski chalet France, cluster from choir practice in the US, and church- and hospital-associated clusters in South Korea[2-5]

1. Nishiura. medRxiv;[Preprint]. Note: this study has not been peer reviewed. 2. Hijnen. Emerg Infect Dis. 2020;26:1935.
3. Danis. Clin Infect Dis. 2020;71:825. 4. Hamner. MMWR. 2020;69:606. 5. Shim. Int J Infect Dis. 2020;93:339.

SARS-CoV-2 Transmission: Recirculated Air and Poor Ventilation

- 3 families (A, B, and C) ate lunch at a restaurant on January 24, 2020, at 3 neighboring tables
  - 10 of those sitting at these tables (including the index case) were later found to have been infected with SARS-CoV-2 at the restaurant
  - None of the waiters or 68 patrons at the remaining 15 tables became infected
  - Authors note that these results do not show that long-range aerosol transmission can occur in *any* indoor space, but that transmission may occur in crowded/poorly ventilated spaces



Li. Build Environ. 2021;107788.

Slide credit: clinicaloptions.com

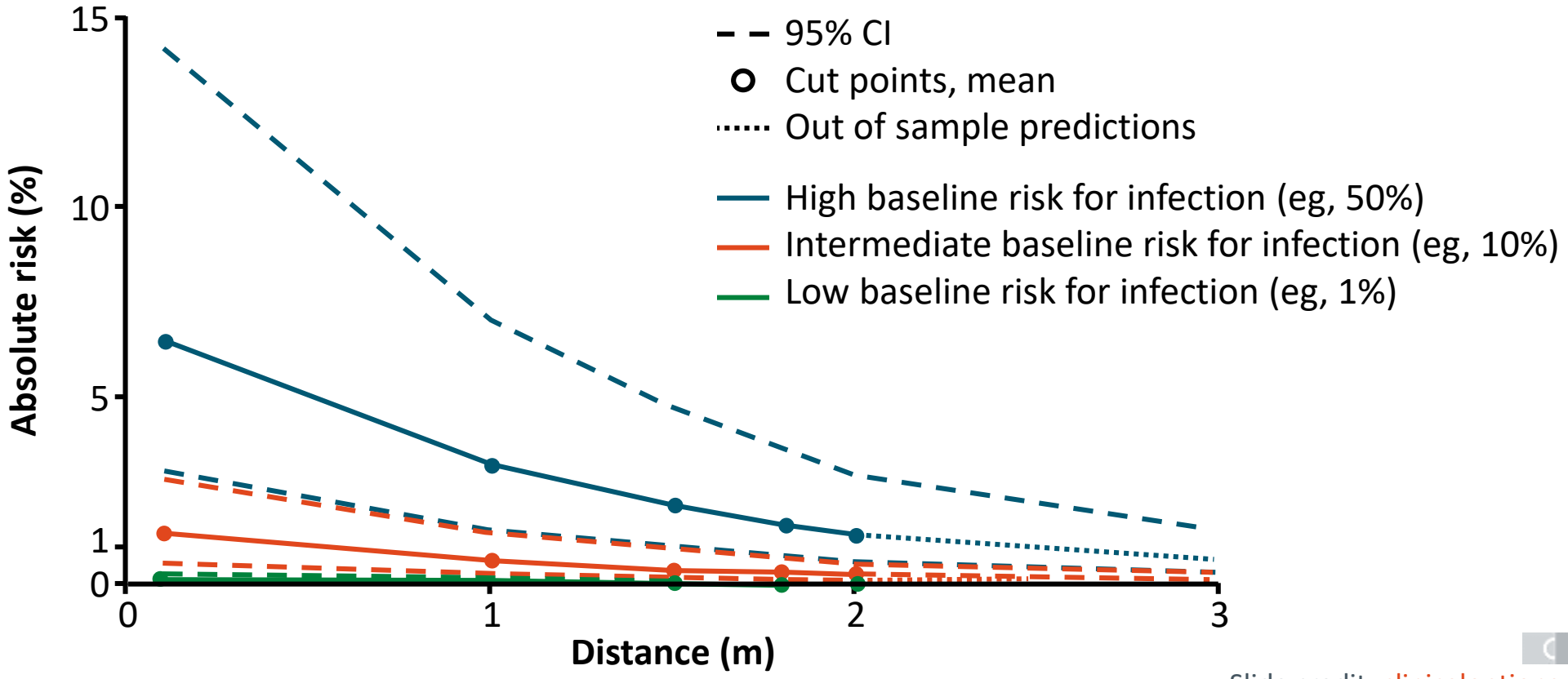
Summary of SARS-CoV-2 Transmission Across Settings

- Crowded enclosed spaces facilitate SARS-CoV-2 transmission
- Transmission rates in enclosed spaces appear to be correlated with duration of exposure
  - Longer duration → greater risk of transmission
- Airborne transmission hypothesized
  - Biologically plausible → aerosol generated with greater than normal force or if air current moves aerosol > 1 meter and droplets remain intact
- Continued observational study and sentinel animal study required to better understand airborne transmission potential

Slide credit: clinicaloptions.com

Physical Distance and Transmission

- Systematic review and meta-analysis of data from 172 studies investigating the spread of SARS-CoV-2, SARS, and MERS (n = 10,736)



Chu. Lancet. 2020;395:1973.

Slide credit: clinicaloptions.com

Efficacy of Face Coverings in Prevention of SARS-CoV-2 Transmission

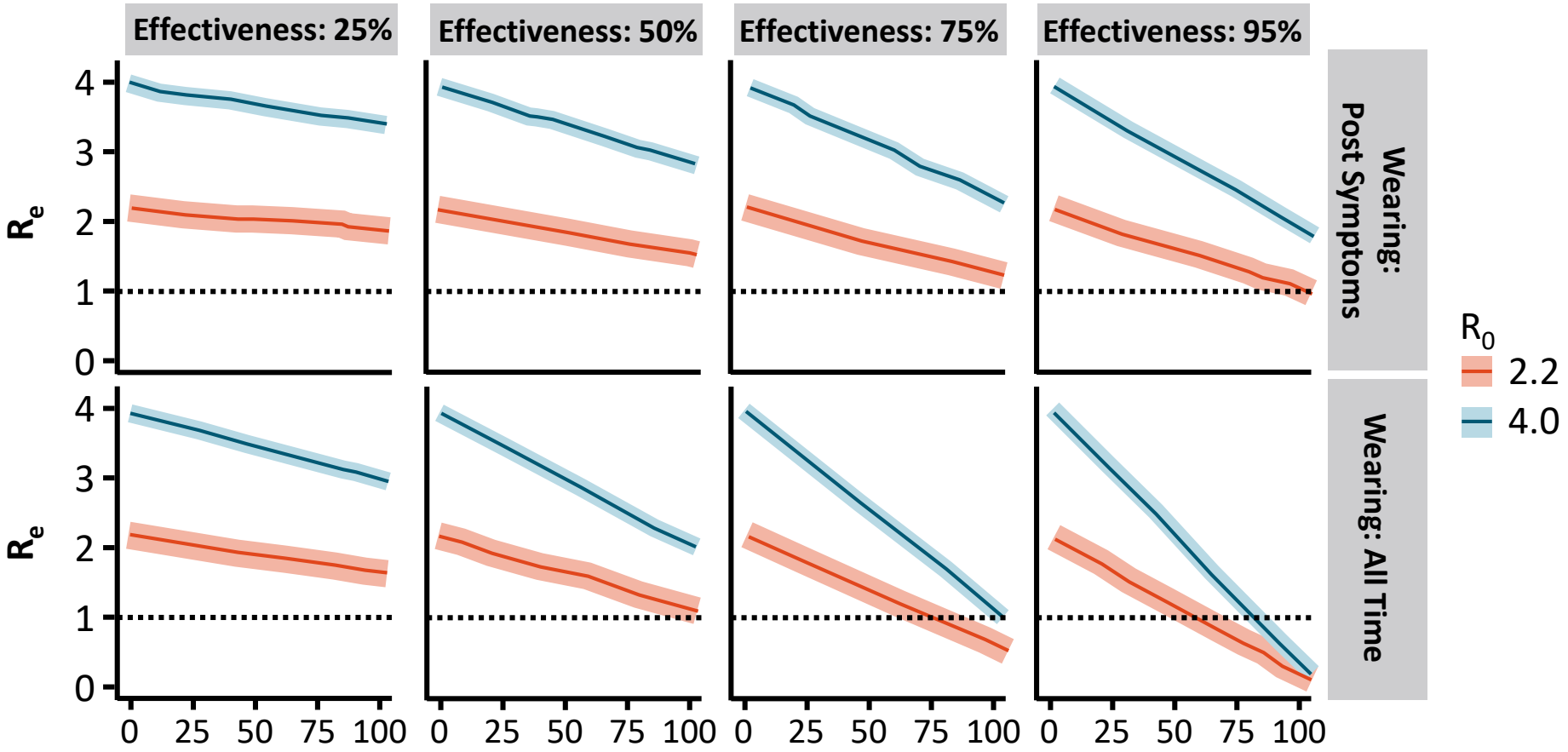
- Systematic review and meta-analysis of data from 172 studies investigating the spread of SARS-CoV-2, SARS, and MERS (n = 2647)[1]
  - Face mask use (surgical, N95, or cotton mask) resulted **in large reduction in infection (OR: 0.15; 95% CI: 0.07-0.34)**
  - Association was stronger for N95 or respirators vs disposable or 12-16 layer cotton masks ($P_{interaction}$ = .090)
- Study of human coronaviruses in exhaled breath of children and adults with acute respiratory illnesses wearing surgical face masks vs no mask (N = 246)[2]
  - Virus detected in **respiratory droplets** in 3 of 10 samples collected without face masks vs **0 of 11 samples with a mask (*P* = .07)**
  - Virus detected in **aerosols** in 4 of 10 samples collected without face masks vs **0 of 11 samples with a mask (*P* = .02)**

1. Chu. Lancet. 2020;395:1973. 2. Leung. Nat Med. 2020;26:676.

Slide credit: clinicaloptions.com

Predicted Efficacy of Face Masks on SARS-CoV-2 Transmission Dynamics

- Simulations with branching process model to investigate the reduction in transmission by wearing face masks on the R_e (expected number of new cases caused by a single infectious person at any given point)



Stutt. Proc Math Phys Eng Sci. 2020;476:20200376.

Slide credit: clinicaloptions.com

Nonpharmacologic Preventive Interventions

Recommended Prevention Strategies[1,2]
Identify and quickly test suspect cases with subsequent isolation of infected individuals
Quarantine close contacts of infected individuals
Wash hands often with soap and water
Maintain social distance (~6 ft)
Wear cloth face cover indoors, in pubic, in crowds[3,4]
Practice respiratory etiquette
Disinfect frequent-touch surfaces regularly
Avoid crowds, close-contact settings, and poorly ventilated spaces
Get a COVID-19 vaccine and booster

- Inactivation of SARS-CoV, MERS-CoV, and other endemic human coronaviruses readily accomplished with 62% to 71% ethanol, 0.5% hydrogen peroxide, or 0.1% sodium hypochlorite (in 1 min)[5]
  - 0.05% to 0.2% benzalkonium chloride, 0.02% chlorhexidine digluconate less effective

1. www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html. 2. WHO. Scientific Brief. July 9, 2020.
3. Leung. Nat Med. 2020;26:676. 4. Chu. Lancet. 2020;395:1973. 5. Kampf. J Hosp Infect. 2020;104:246.

Preventing SARS-CoV-2 Transmission Based on the Evidence

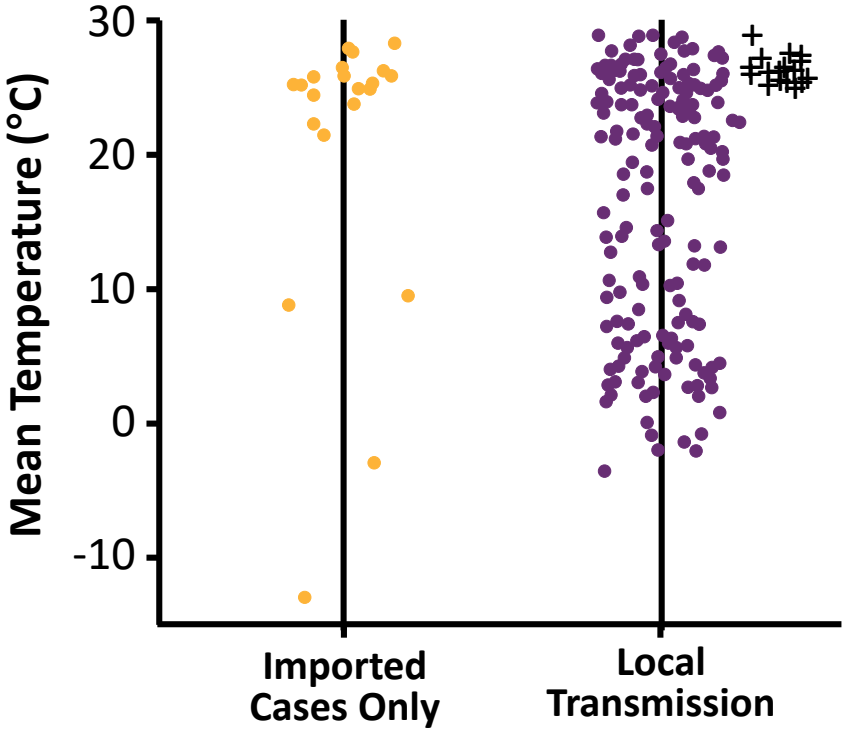
- Protecting yourself
  - Physical distancing > 1 meter
  - Handwashing and disinfection of frequent-touch surfaces to prevent fomite transmission
  - PPE for healthcare workers
- Protecting others with a mask when physical distancing not possible
  - Caregivers for elderly persons, those with comorbidities
  - Confined spaces (eg, railway cars, locations with poor ventilation)

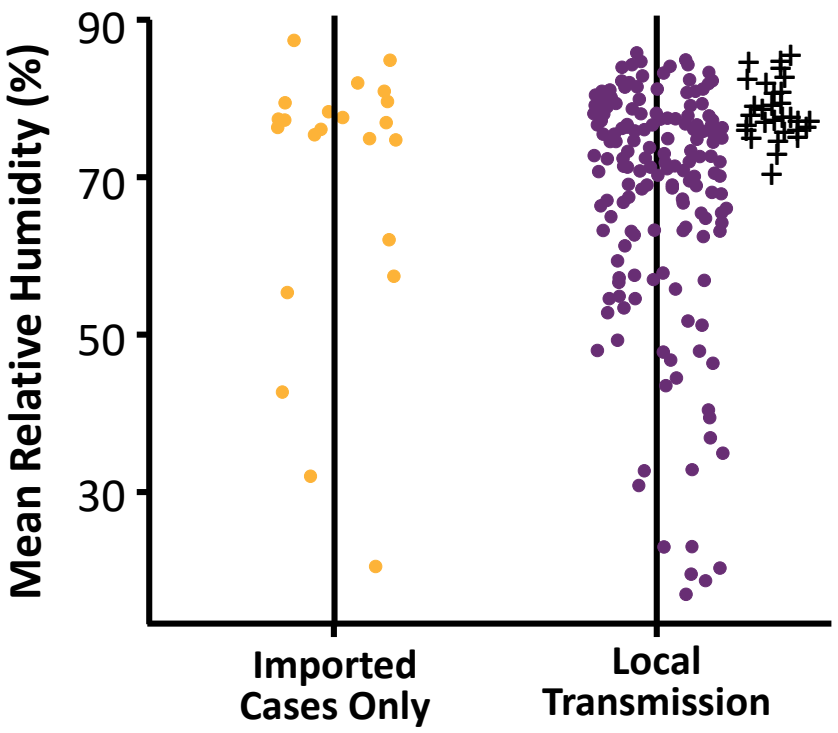
WHO. COVID-19 advice for the public. Last updated October 1, 2021.

Considering Climate in COVID-19 Mitigation Strategies

- *"No evidence has suggested that warmer conditions will reduce the effectiveness of SARS-CoV-2 transmission to an extent that few additional interventions are needed to curb its spread… At present, policy makers must focus on reducing physical contact within communities"*

WHO Transmission Status (as of Apr 8, 2020) vs Temperature and Humidity (Jan 1 - Mar 31, 2020)





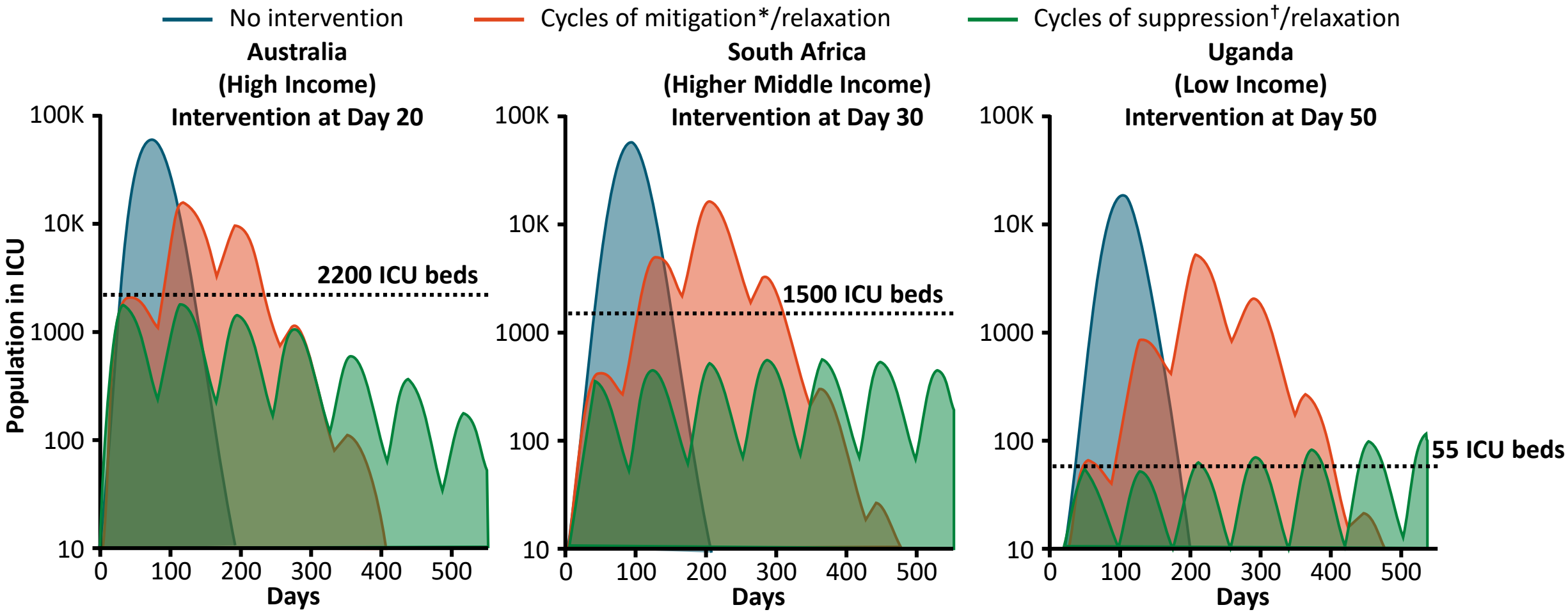
Seasonal averages population adjusted for each country

+ denotes country with average temperature > 25°C and relative humidity > 70%

O'Reilly. Lancet Planet Health. 2020;4:e172.

Slide credit: clinicaloptions.com

Multivariate Prediction Model of Dynamic Interventions

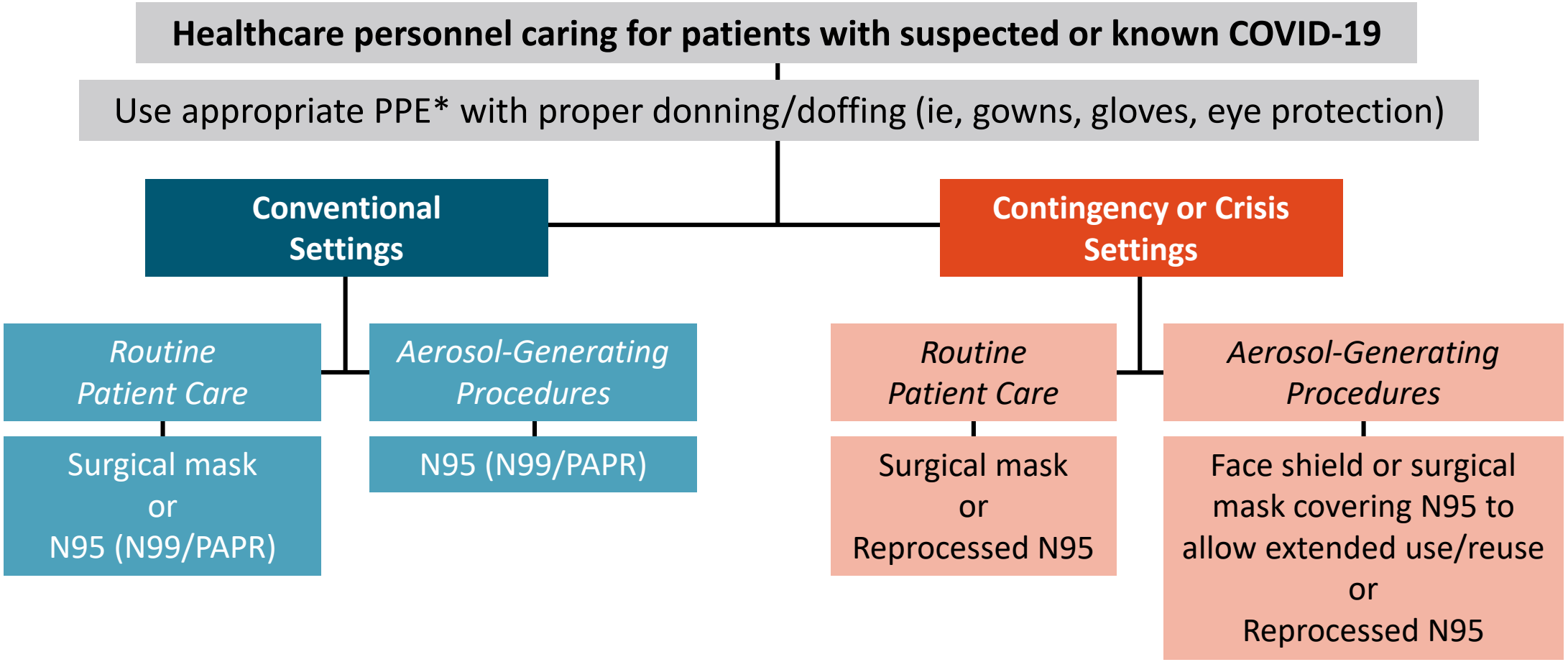


*Combination measures including general social distancing, hygiene rules, case-based isolation, shielding of vulnerable groups, school closures, or restricting large public events; target $R = 0.8$. †Additional measures of strict physical distancing including lockdown; target $R = 0.5$.

Chowdhury. Eur J Epidemiol. 2020;35:389.

Slide credit: clinicaloptions.com

IDSA: SARS-CoV-2 Infection Prevention



*IDSA makes no recommendation regarding double vs single glove or shoe cover vs no shoe cover use.

IDSA. COVID-19 Guideline, Part 2: Infection Prevention. Version 2.0.0.

Slide credit: clinicaloptions.com

Influence of Population Heterogeneity on Naturally Acquired Herd Immunity to SARS-CoV-2

- Mathematical model to illustrate how population heterogeneity affects herd immunity
  - Age-structured: categorized into 6 different age groups with varying levels of contact
  - Activity-structured: categorized into 3 different social activity groups with varying levels of contact

Herd Immunity Thresholds, %	R_0 = 2.0		R_0 = 2.5		R_0 = 3.0	
	Disease-induced*	Classical†	Disease-induced*	Classical	Disease-induced*	Classical
Homogeneous population	50.0	50.0	60.0	60.0	66.7	66.7
Age-structured population	46.0	50.0	55.8	60.0	62.5	66.7
Activity-structured population	37.7	50.0	46.3	60.0	52.5	66.7
Age- and activity-structured population	34.6	50.0	43.0	60.0	49.1	66.7

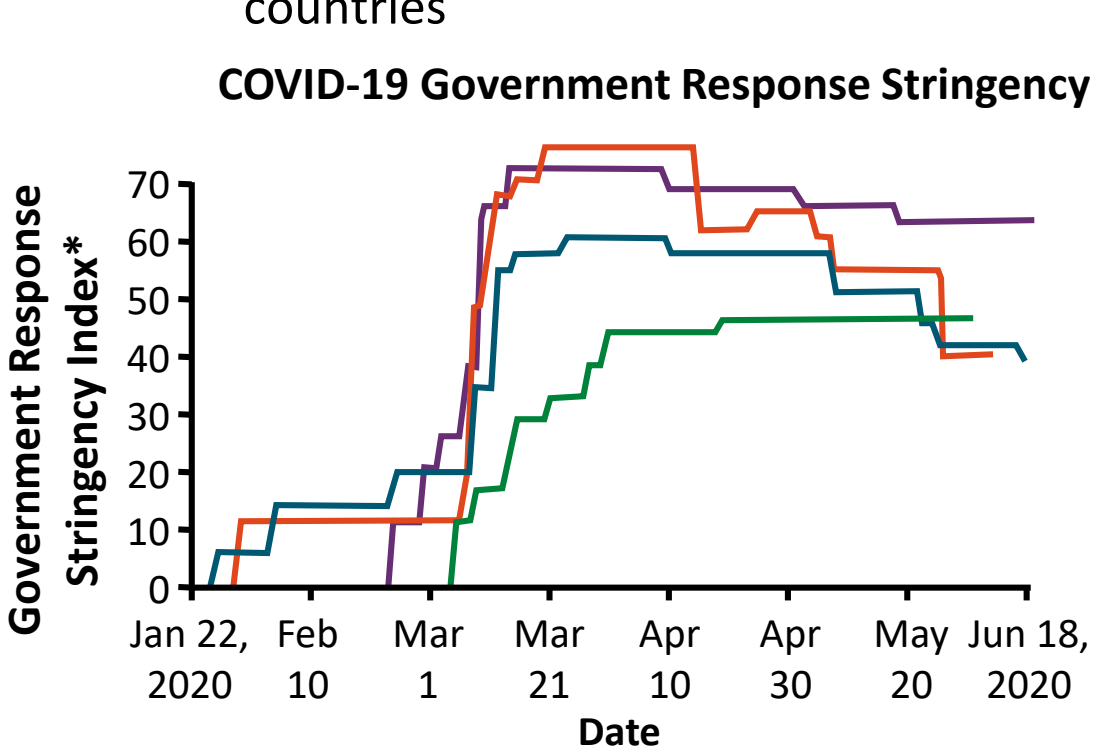
*Approximates the implementation of preventative measures early that are then lifted late in the outbreak. †Assumes that immunity is uniformly distributed among different types of individuals.

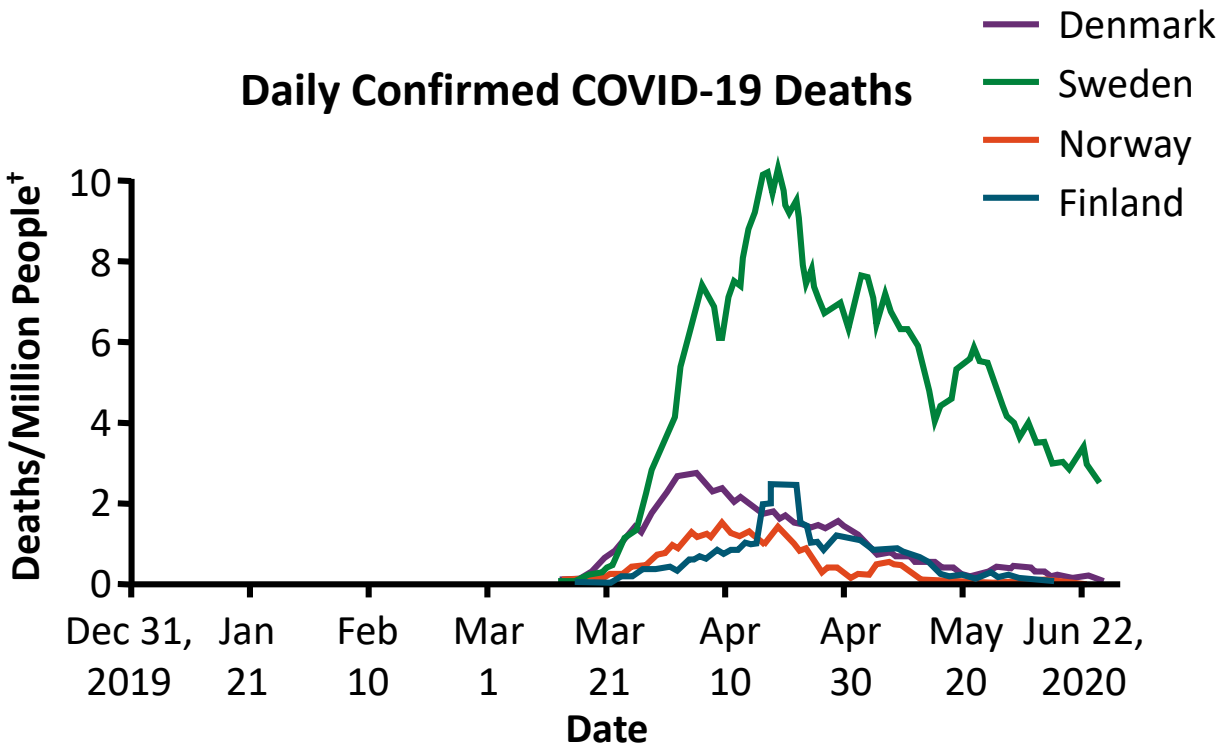
Britton. Science. 2020;369:846.

Slide credit: clinicaloptions.com

Less Stringent Mitigation Measures: Sweden

- Sweden permitted limited infection to continue by controlled viral spread to potentially reach herd immunity
  - To July 2020, higher mortality rate and prolonged outbreak compared with other Scandinavian countries





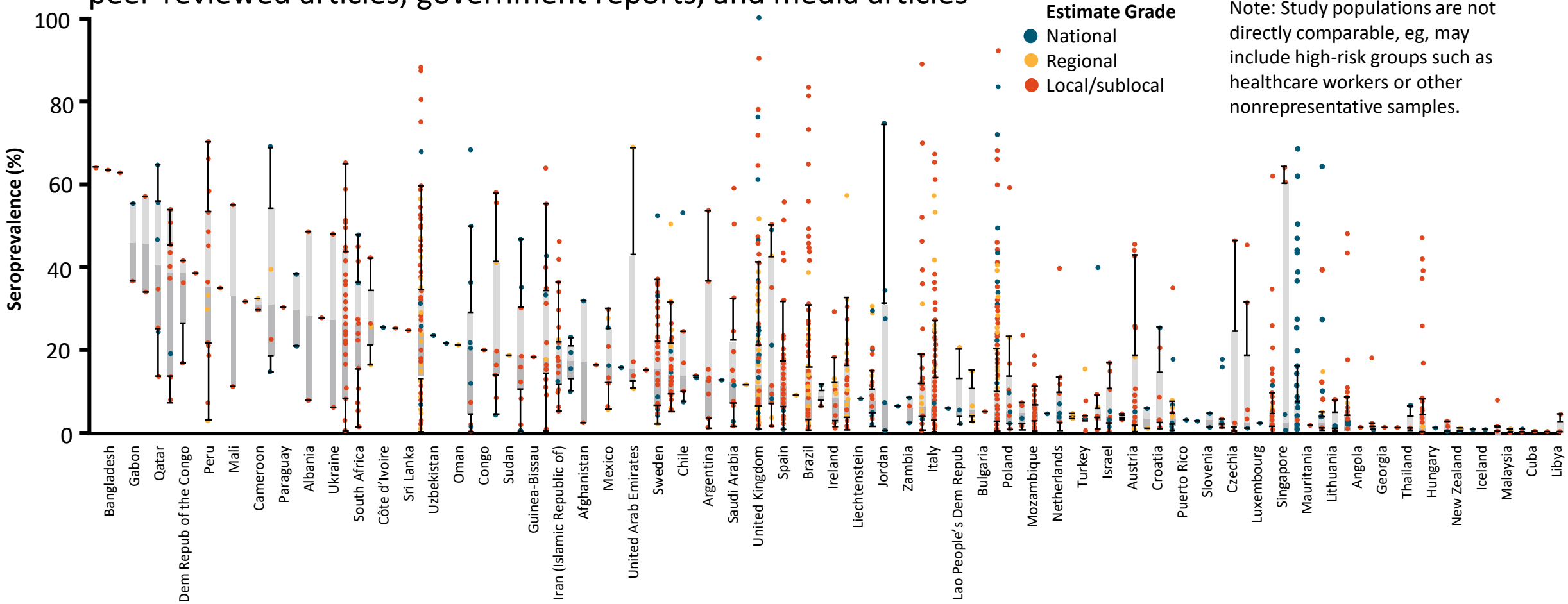
*Composite measure of school closures, workplace closures, and travel bans. †7-day rolling average.

Orlowski. J R Soc Med. 2020;113:292.

Slide credit: clinicaloptions.com

SeroTracker: SARS-CoV-2 Seroprevalence Estimates by Country

- Systematic integration of global serosurveillance projects, sourcing prevalence data from preprints, peer-reviewed articles, government reports, and media articles



serotracker.com/en/Analyze.

Epidemiology in Healthcare Workers

US and UK Frontline HCWs: Risk of COVID-19

- Prospective, observational cohort study in the United States and United Kingdom using *COVID Symptom Study* smartphone app, registered with Clinicaltrials.gov
- 99,795 frontline HCWs and 2,035,395 community individuals participated from March 24 to April 23, 2020
  - > 90% of participants from UK
  - 4.7% reported being a frontline HCW
  - Primary outcome was self-reported positive SARS-CoV-2 test
- 5543 reported incidences of positive tests among 23,435,272 person-days
  - Median age: 44 yr (IQR: 32-57)
- After country-specific inverse-probability weighting for predictors of testing, HCWs > 3 times more likely to report a positive SARS-CoV-2 test vs general population

Increased HCW Risk	UK	US	Overall
HR (95% CI)	3.43 (3.18-3.69)	1.97 (1.36-2.85)	3.4 (3.37-3.43)

P <.0001

Nguyen. Lancet. 2020;5:E475. NCT04331509.

Slide credit: clinicaloptions.com

US and UK Frontline HCWs: Impact of PPE

Risk of Positive SARS-CoV-2 Test	Adequate PPE	Reused PPE	Inadequate PPE
Overall			
▪ Event/person-days	592/332,901	146/80,728	157/60,916
▪ Unadjusted HR (95% CI)	1 (reference)	1.46 (1.21-1.76)	1.32 (1.10-1.57)
▪ Multivariate-adjusted HR (95% CI)	1 (reference)	1.46 (1.21-1.76)	1.31 (1.10-1.56)
Exposure to patient with documented COVID-19			
▪ Event/person-days	280/50,571	91/23,751	83/11,675
▪ Unadjusted HR (95% CI)	4.93 (4.07-5.97)	5.12 (3.94-6.64)	5.95 (4.57-7.76)
▪ Multivariate-adjusted HR (95% CI)	4.83 (3.99-5.85)	5.06 (3.90-6.57)	5.91 (4.53-7.71)

- In post hoc analysis, even after adjusted for exposure to patients with COVID-19, **non-White healthcare workers more frequently reported reused PPE or inadequate PPE** (adjusted OR: 1.49; 95% CI: 1.36-1.63)

Nguyen. Lancet. 2020;5:E475.

Slide credit: clinicaloptions.com

US and UK Frontline HCWs: Impact of Setting

Participant Setting	Age-Adjusted Risk of SARS-CoV-2+ HR (95% CI)	Multivariate-Adjusted Risk of SARS-CoV-2+ HR (95% CI)	HCWs Reporting Reused PPE, %	HCWs Reporting Inadequate PPE, %
General community	1 (reference)	1 (reference)	—	—
Front-line HCW				
▪ Inpatient	23.6 (21.2-26.3)	24.3 (21.8-27.1)	23.7	11.9
▪ Nursing homes	16.5 (13.6-20.0)	16.24 (13.4-19.7)	15.4	16.9
▪ Outpatient hospital clinics	10.6 (8.1-14.3)	11.2 (8.4-14.9)	16.3	12.2
▪ Home health sites	7.79 (5.6-10.9)	7.9 (5.6-11.0)	14.7	15.9
▪ Ambulatory clinics	6.9 (4.9-9.0)	6.9 (5.1-9.4)	19.3	11.8
▪ Other	9.42 (7.4-12.0)	9.5 (7.5-12.1)	12.0	13.8

- **In post hoc analysis, Black, Asian, and minority ethnic HCWs more likely to work in inpatient settings or nursing homes (adjusted OR: 1.13; 95% CI: 1.03-1.23)**

Nguyen. Lancet. 2020;5:E475.

Slide credit: clinicaloptions.com

COVID-NET: COVID-19–Associated Hospitalization Surveillance Network

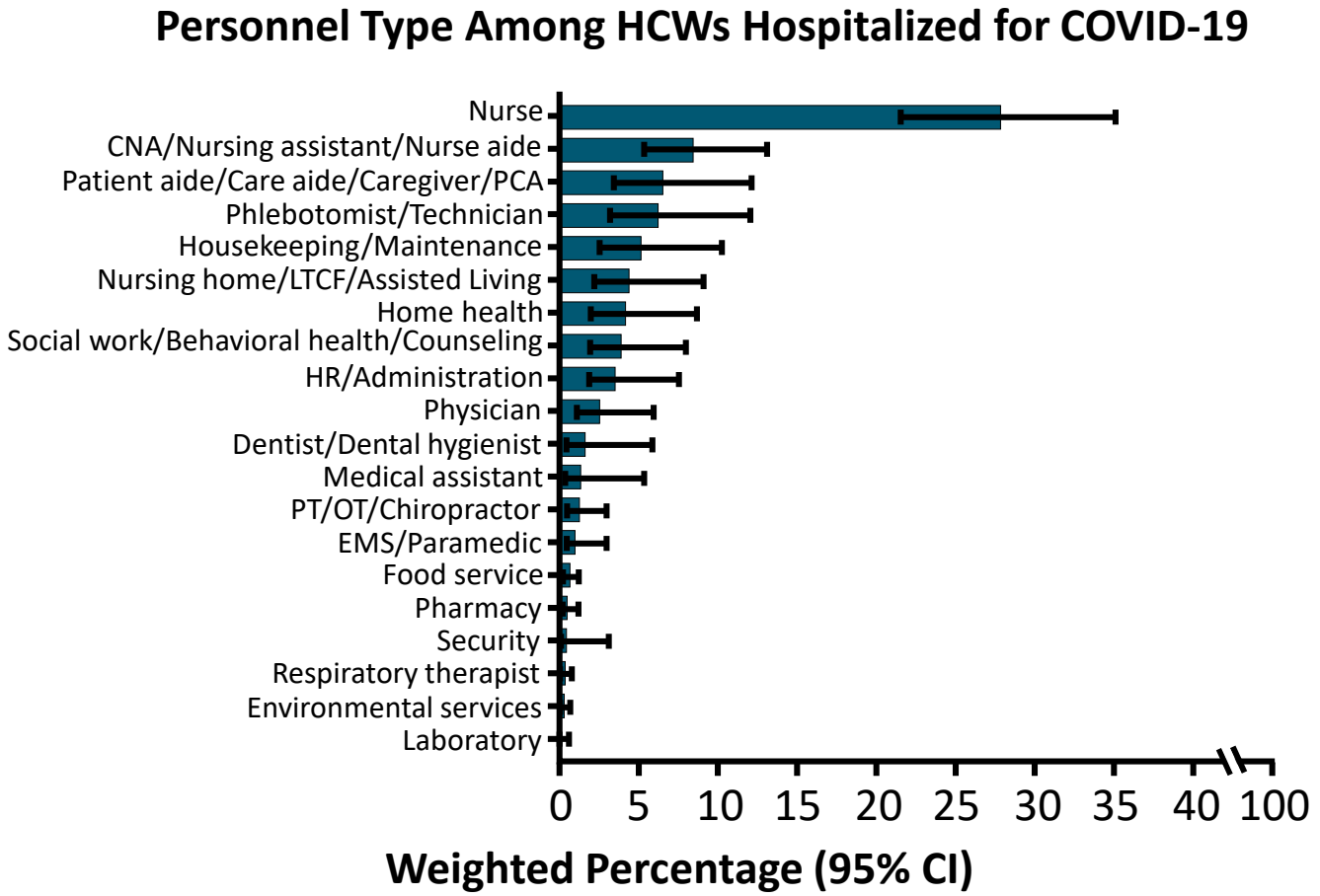
- Analysis of COVID-19–related hospitalization data from 13 US states, March 1 to May 21, 2020
- HCW status known for 6760 hospitalized persons
  - 6.5% (438/6760) were HCWs
    - Median age 49 yr (IQR: 38-57)
    - 71.9% (315/438) female
    - 73% (320/438) with obesity
- HCW outcomes similar in severity to those reported for persons hospitalized with COVID-19 in general population
  - 27.5% admitted to ICU
  - 15.8% received invasive mechanical ventilation
  - 4.2% mortality rate

Kambhampati. MMWR. 2020;69:1576.

Slide credit: clinicaloptions.com

COVID-NET: Hospitalizations of HCW by Personnel Type

- 438 HCWs hospitalized with COVID-19
  - 67.4% in direct patient contact roles
  - 36.3% nurses or nursing aides
- Although HCWs with direct patient contact had higher rates of hospitalization, it remains unknown if exposed in the workplace or community



Kambhampati. MMWR. 2020;69:1576.

Slide credit: clinicaloptions.com

HCWs and Their Households: Risk of Hospitalization

- Study population (March 1 to June 6, 2020)
  - 157,445 Scottish HCWs aged 18-65 yr, 57.3% in patient-facing roles
  - 229,905 household members of HCWs
  - General population aged 18-65 yr hospitalized with COVID-19 during study period
- Primary outcome: ***admission to hospital with COVID-19***
  - 360/2097 (17.2%) of all persons hospitalized with COVID-19 were HCWs or their household members

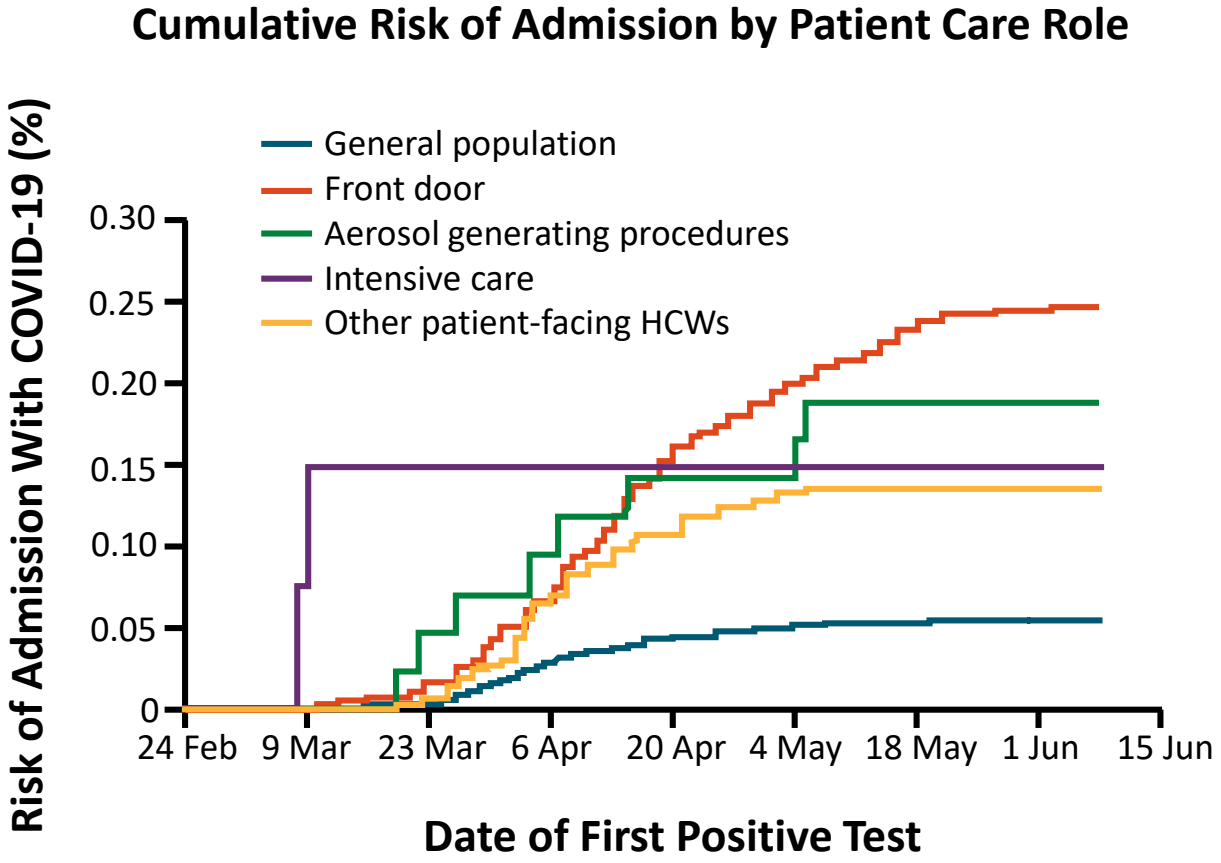
Risk of COVID-19 Hospitalization	Patient-Facing HCWs	Households of Patient-Facing HCWs	Nonpatient-Facing HCWs	General Population
HR (95% CI)	3.30 (2.13-5.13)	1.79 (1.10-2.91)	0.81 (0.52-1.26)	0.86 (0.49-1.51)

Shah. BMJ. 2020;371:m3582.

Slide credit: clinicaloptions.com

HCWs and Their Households: Impact of Patient Care Role

- *"Front door"* workers (eg, paramedics), *ICU* workers, and workers in *non-ICU but aerosol-generating* settings (eg, respiratory medicine wards) experienced higher risk than other patient-facing HCWs: **HR: 2.09 (95% CI: 1.49-2.94)**



Shah. BMJ. 2020;371:m3582.

Slide credit: clinicaloptions.com

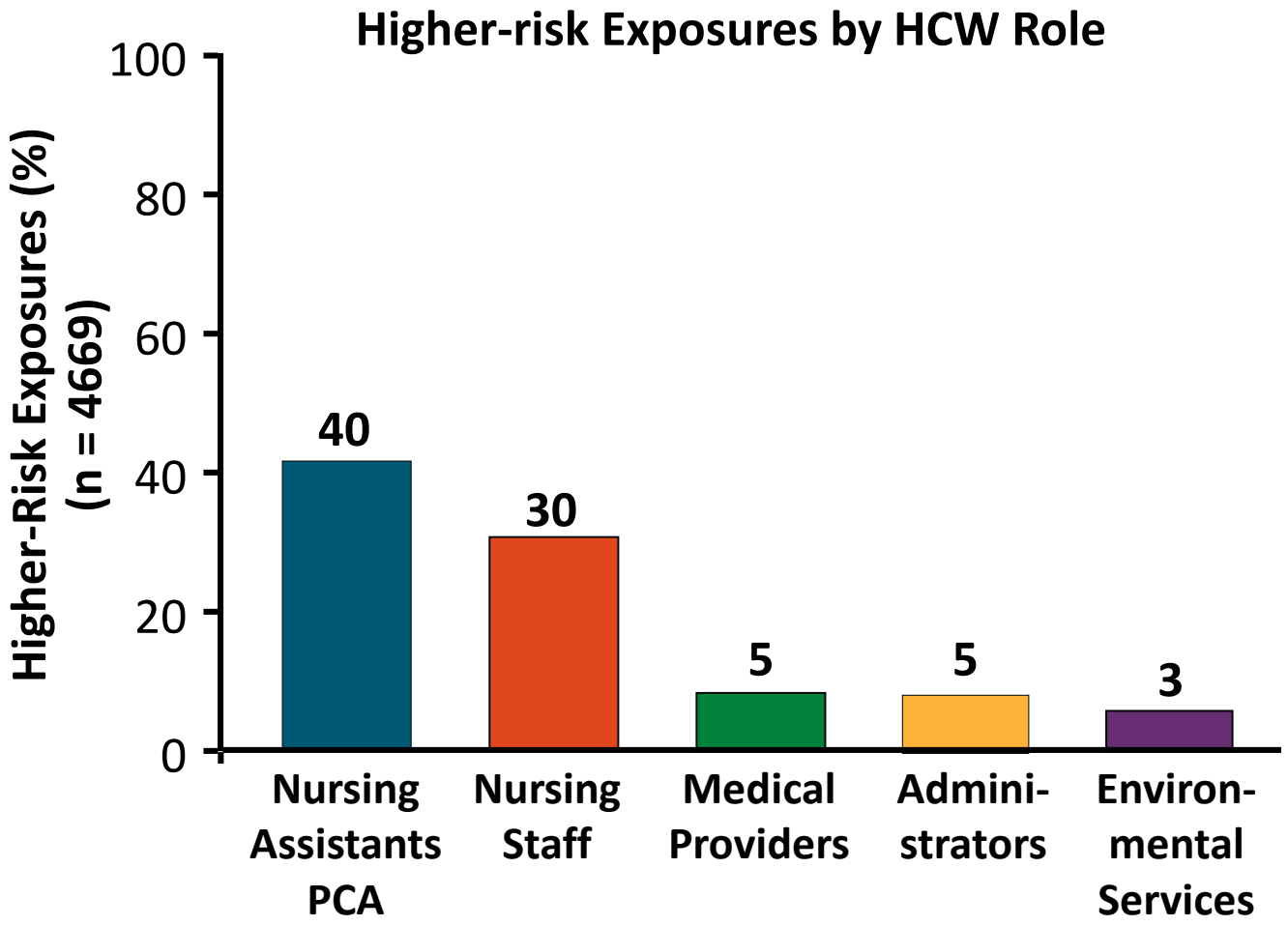
Minnesota Department of Health: SARS-CoV-2 Exposure and Infection Among HCW

- On March 6, 2020, MN Department of Health required healthcare facilities to start reporting HCW exposures to persons with confirmed COVID-19
- 21,406 HCW exposures assessed from March 6 to July 11, of which 5374 were considered "higher-risk exposures" defined as:
  - Close, prolonged contact with a patient with confirmed COVID-19 or their secretions or excretions while not wearing recommended PPE
  - Close, prolonged contact with persons with COVID-19 in the household or community
- 66% of higher-risk exposures involved direct patient care
- 34% of higher-risk exposures involved coworkers, social, or household contacts

Fell. MMWR. 2020;69:1605.

Slide credit: clinicaloptions.com

Minnesota Department of Health: SARS-CoV-2 Exposure and HCW Role



- Among 4020/5374 higher-risk exposures for whom age data available, mean age: 39 yr (range: 16-80)
- Among 4669/5374 higher-risk exposures for whom HCW role data available, > 70% in nursing-related roles
- 7% of all higher-risk exposures associated with positive SARS-CoV-2 result within 14 days

Fell. MMWR. 2020;69:1605.

Slide credit: clinicaloptions.com

Minnesota Department of Health: Higher Risk Exposures and Facility Type

Characteristic, n (%)	Skilled Nursing	Assisted Living	Group Home	Acute Care	Ambula-tory Care	Other Settings	Overall
All HCW with higher-risk exposures	1396 (26)	799 (15)	381 (7)	1953 (36)	306 (6)	539 (10)	5374 (100)
HCW with higher-risk exposure who tested SARS-CoV-2+ within 14 days	120 (8.6)	65 (8.1)	62 (16.3)	58 (3.0)	20 (6.5)	48 (8.9)	373/5374 (6.9)
HCW with higher-risk exposure returned to work during 14-day monitoring period*	500 (55.4)	283 (60.1)	100 (52.4)	382 (37.2)	65 (44.5)	134 (43.9)	1464/3043 (48.1)
HCW with higher-risk exposure reported working with symptoms during 14-day monitoring period*	41 (4.5)	25 (5.3)	9 (4.7)	13 (1.3)	3 (2.1)	7 (2.3)	98/3043 (3.2)

*3043 of 5372 HCW with higher-risk exposures enrolled in MN Department of Health daily monitoring for a 14-day period.

Fell. MMWR. 2020;69:1605.

Slide credit: clinicaloptions.com

Screening and Diagnosis

WHO: Suspect Case Definition

1

Acute onset of fever and cough **OR** ≥ 3 of the following: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia, nausea/vomiting, diarrhea, altered mental status

AND 1 of the following **epidemiologic criteria** within 14 days of symptom onset:

- Residing or working in an area with high risk of transmission*
- Residing or travel to an area with community transmission
- Working in any healthcare setting

*Closed residential settings, humanitarian settings such as camp and camp-like settings for displaced persons.

OR:

2

Patient with severe acute respiratory illness (acute respiratory infection with history of fever or measured fever ≥ 38°C and a cough; onset within last 10 days; requires hospitalization)

OR:

3

Asymptomatic person not meeting **epidemiologic criteria** with a positive SARS-CoV-2 antigen-RDT (NAAT required for confirmation)

WHO COVID-19 Case Definition. Updated December 16, 2020.
www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.2

WHO: Probable Case Definition

1 Acute onset of fever and cough **OR** ≥ 3 of the following: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia, nausea/vomiting, diarrhea, altered mental status

AND: Contact of probable or confirmed case **OR** linked to a COVID-19 cluster*

*Symptomatic individuals linked by time, location, and common exposures with ≥ 1 NAAT-confirmed case or ≥ 2 epidemiologically linked persons with positive Ag- RDTs.
†Typically includes hazy opacities with peripheral and lower lung distribution on chest radiography; multiple bilateral ground glass opacities with peripheral and lower lung distribution on chest CT; or thickened pleural lines, B lines, or consolidative patterns on lung ultrasound.

OR:

2 Suspect case with chest imaging suggestive of COVID-19 disease†

OR:

3 Recent onset of loss of smell/taste without another identified cause

OR:

4 Unexplained death in an adult with respiratory distress who was a contact of a probable or confirmed case **OR** linked to a COVID-19 cluster*

WHO COVID-19 Case Definition. Updated December 16, 2020.
www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.2

CDC: Testing Recommendations for Current SARS-CoV-2 Infection

- "Positive test results using a viral test (NAAT or antigen) in persons with signs or symptoms consistent with COVID-19 indicate that the person has COVID-19, independent of vaccination status of the person."

Who Should Get Tested
Persons with COVID-19 signs or symptoms, *regardless of vaccination status*
Unvaccinated close contacts (within 6 feet for ≥15 min over 24 hr with a known case) without symptoms
Anyone advised by healthcare provider or public health official

www.cdc.gov/coronavirus/2019-ncov/hcp/testing-overview.html.

Slide credit: clinicaloptions.com

Types of Tests for SARS-CoV-2

- **NAAT:** detects the presence of viral RNA, indicating infection; gold standard for diagnosis
- **Antigen assays:** immunoassays that detect the presence of viral antigens, indicating infection
- **Antibody assays:** detect IgM and IgG antibodies against the virus, indicating past infection; useful for COVID-19 surveillance and epidemiology

Overview of Testing for SARS-CoV-2 (COVID-19). Updated October 22, 2021. www.cdc.gov/coronavirus/2019-ncov/hcp/testing-overview.html

Slide credit: clinicaloptions.com

Common COVID-19 Diagnostic Methods: NAAT vs Antigen Testing

Characteristic	Nucleic Acid Amplification Test (NAAT)	Antigen Test
Intended use	▪ Detect current infection	▪ Detect current infection
Analyte detected	▪ Viral RNA	▪ Viral antigens
Specimen types	▪ Nasal, nasopharyngeal, sputum, saliva	▪ Nasal, nasopharyngeal
Sensitivity	▪ Varies by test, but generally high (68% to 100%)	▪ Moderate (63.7% to 79%)
Specificity	▪ High (92% to 100%)	▪ High (98.5% to 99.8%)
Test complexity	▪ Varies by test	▪ Relatively easy to use
Authorized for POC	▪ Most are not, some are	▪ Most are, some are not
Turnaround time	▪ 15 min to > 2 days	▪ 15 min to > 2 days
Cost	▪ Moderate (~ $100/test)	▪ Low (~ $5 to $50/test)
Considerations	▪ Primary method for COVID-19 diagnosis with multiple RT-PCR kits available ▪ SARS-CoV-2 RNA undetectable by ~ Day 14 after onset of illness in some cases/samples	▪ Reduced sensitivity vs PCR may result in false negatives ▪ May be necessary to confirm with NAAT ▪ At-home tests authorized by FDA

Udugama. ACS Nano. 2020;14:3822. Lee. Front Immunol. 2020;11:879.
CDC. Interim guidance for antigen testing for SARS-CoV-2. Last updated September 9, 2021.

Slide credit: clinicaloptions.com

Common COVID-19 Diagnostic Methods: Antibodies

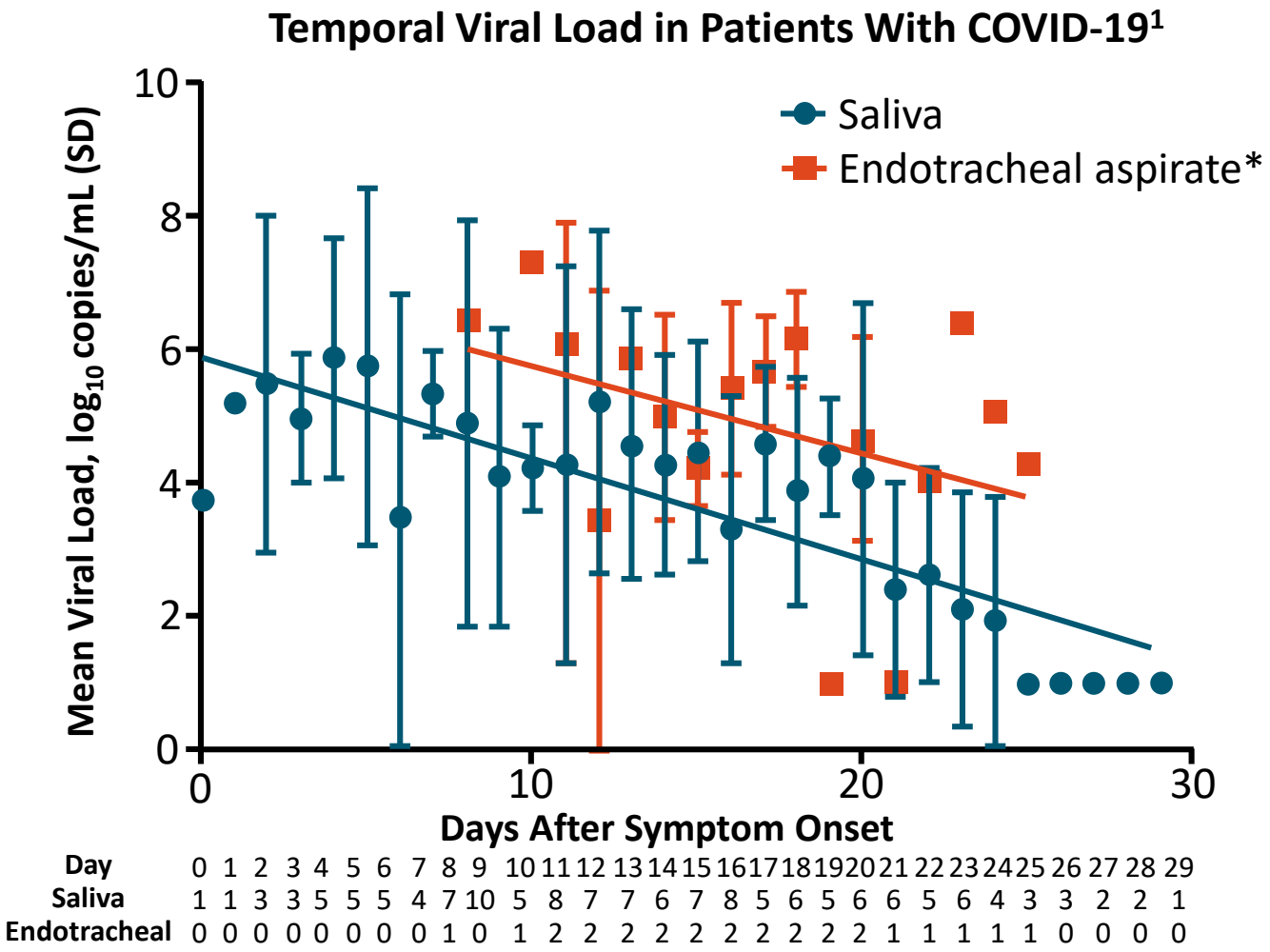
Serologic Assays	
Typically indicate	▪ Past infection, but may have some utility in diagnosis of current infection among those presenting late or when RT-PCR negative/unavailable
Specimen sources	▪ Most often blood serum or plasma, but may include saliva, sputum, or other biological fluids
Considerations	▪ Provides a delayed but wider window of time for detection ▪ May be useful for COVID-19 surveillance and identification of convalescent plasma donors ▪ **False negatives**: Low sensitivity in first wk after symptoms with subsequent rises during second/third wk and scant data thereafter; unclear if low-level antibody detectable in cases of mild/asymptomatic disease ▪ **False positives**: Due to cross-reactivity ▪ Uncertain if positive read = immune protection if re-exposed

Deeks. Cochrane Database Syst Rev. 2020;6:CD013652. Lee. Front Immunol. 2020;11:879. Carter. ACS Cent Sci. 2020;6:591.

Temporal Profile of SARS-CoV-2 Viral Load

- Serial viral loads assessed via RT-PCR of posterior oropharyngeal saliva or endotracheal aspirate* collected from hospitalized patients in Hong Kong with laboratory confirmed COVID-19 (N = 23)[1]
- Viral loads highest during first wk following symptom onset[1]
- Ideally, diagnostic tests are done when viral load is high

*Intubated patients.

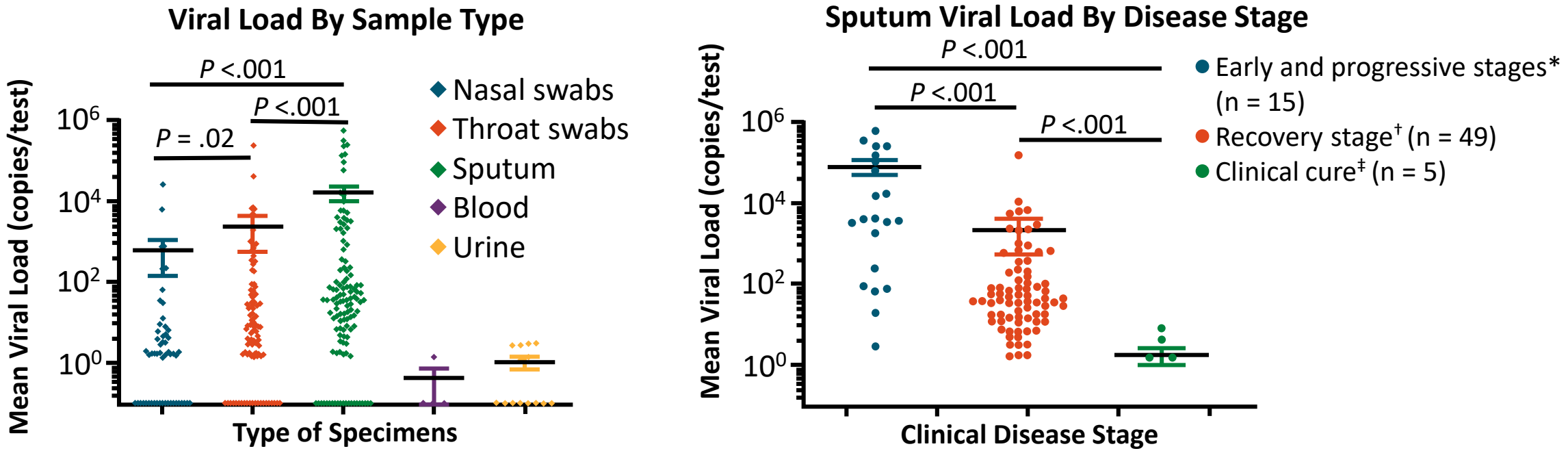


1. To. Lancet Infect Dis. 2020;20:565.

Slide credit: clinicaloptions.com

Viral Load Varies by Sample Type and Disease Stage

- Viral load assessed via digital droplet PCR of samples collected from patients in Beijing with laboratory confirmed COVID-19 (N = 76)

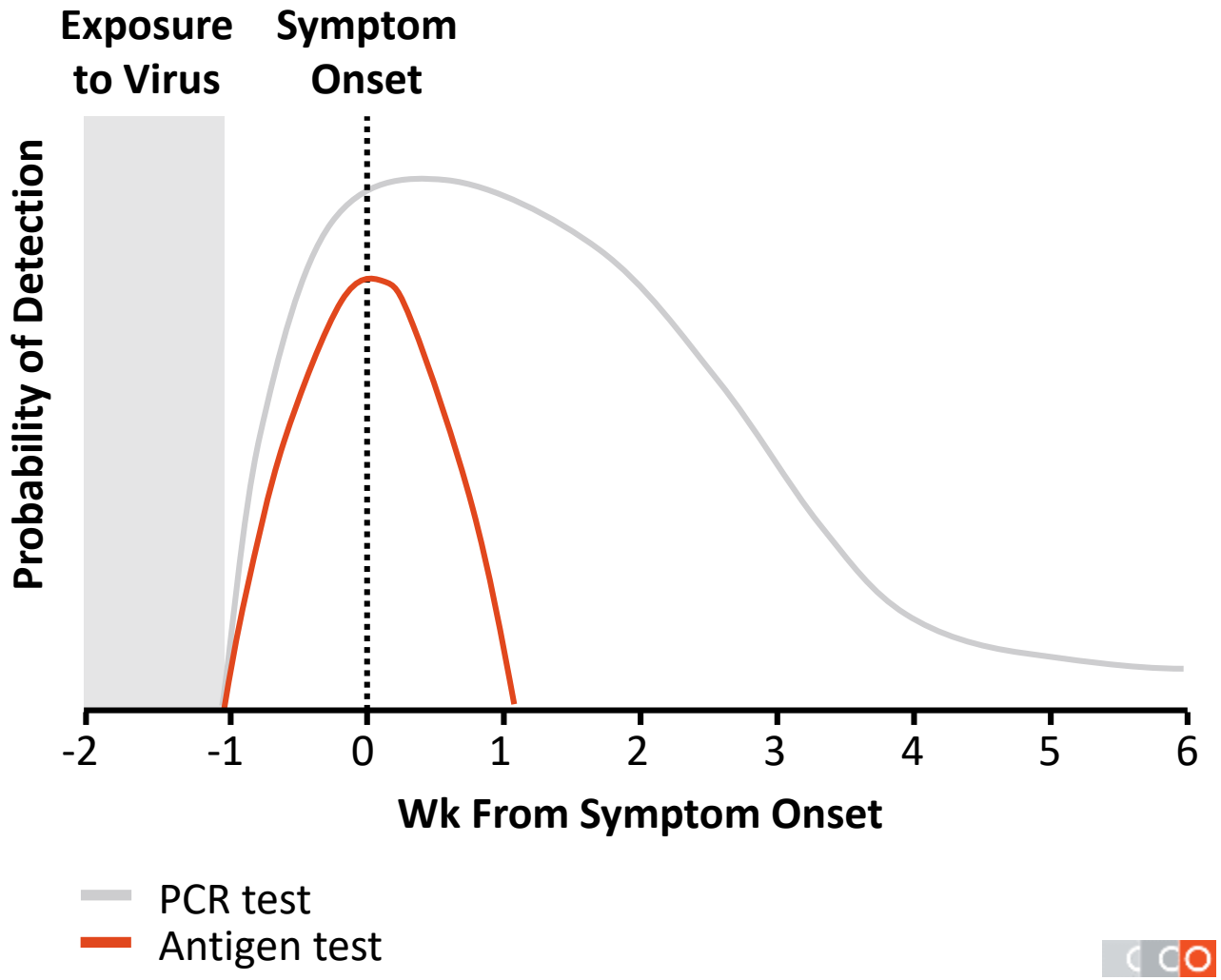


*Early stage: multifocal bilateral or isolated round ground-glass opacity with or without patchy consolidations and prominent peripherally subpleural distribution on chest CT. Progressive stage: Increasing number, range, or density of lung lesions on chest CT. †Recovery phase: lesions gradually absorbed. ‡Clinical cure: temperature recovery for > 3 days, improvement in respiratory symptoms, absorption of lung lesions, and 2 consecutive negative RT-PCR results from respiratory samples tested at least 1 day apart.

Yu. Clin Infect Dis. 2020;71:793.

Timing of PCR and Antigen Tests

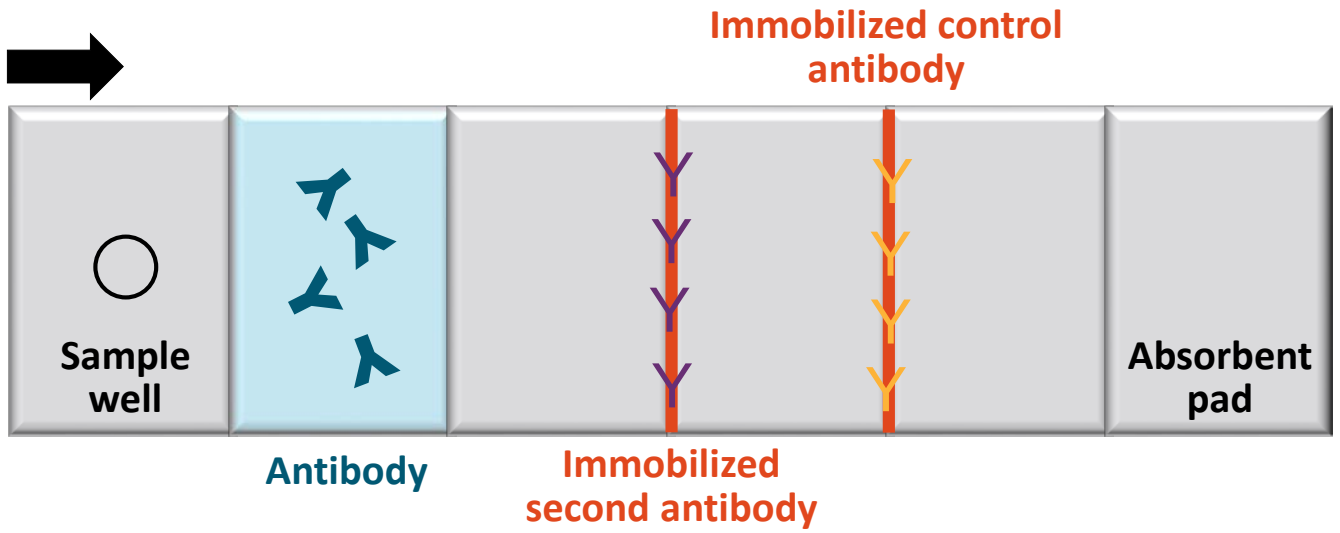
- Both RNA and antigen are detectable before symptom onset
- Antigen declines quickly after symptom onset, but RNA is detectable for weeks



www.nature.com/articles/d41586-020-02661-2

Slide credit: clinicaloptions.com

How Antigen Tests Work



- Sample is mixed with a solution to release specific viral proteins and is applied to a paper strip
- Capillary action draws the solution over an antibody to a viral protein. The antigen–antibody complex flows to the test line, which contains immobilized antibodies that bind the antigen–antibody complex
- The solution flows past a control line, which has immobilized antibodies to an antigen commonly found in the nose or pharynx
- Some tests can be read by eye, like a home pregnancy test. Others use immunofluorescence, immunoluminescence, or other methods that must be read by machine

Koczula. Essays Biochem. 2016;60:111. www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas#individual-antigen.

Slide credit: clinicaloptions.com

Available Antigen Diagnostic Tests for SARS-CoV-2

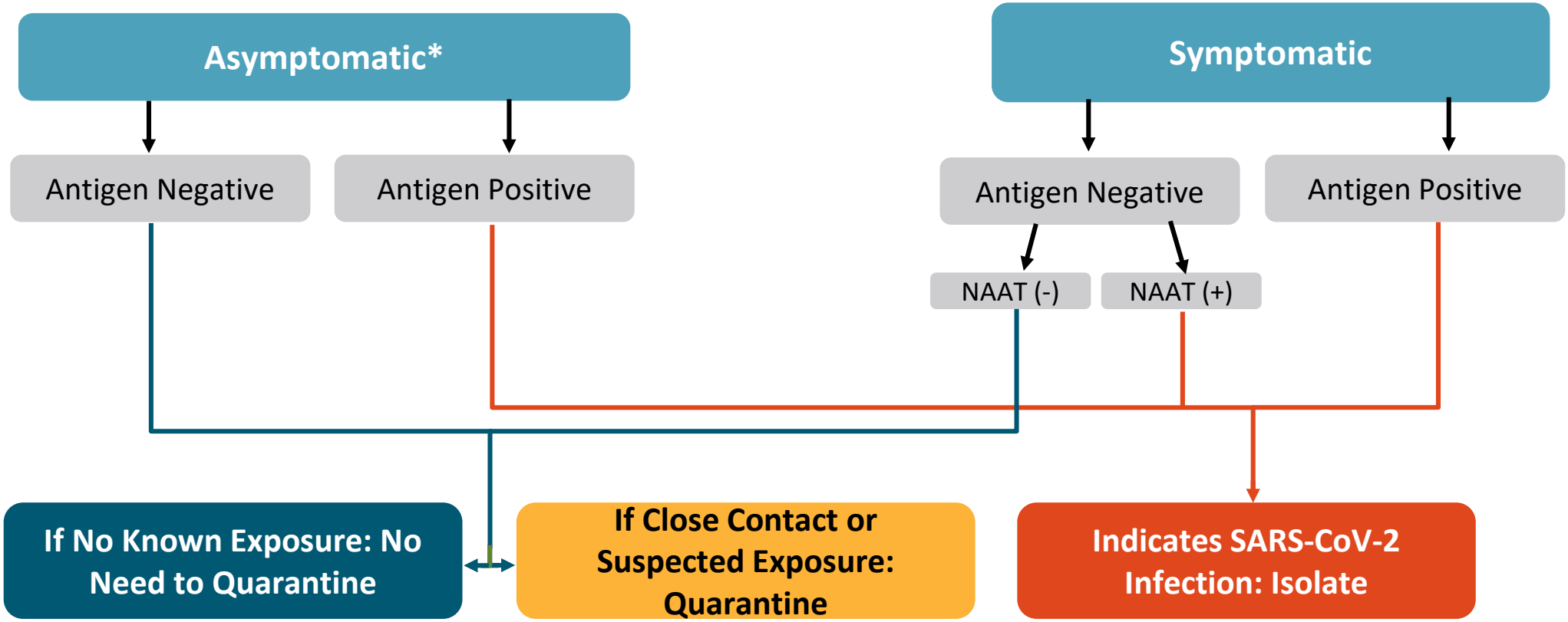
- In the US, the FDA has granted 38 individual EUAs for antigen tests
  - 6 tests are restricted to laboratories certified to perform high or moderate complexity tests
  - 32 tests may be performed in patient care settings operating under a CLIA Certificate of Waiver, such as a medical office
  - 12 tests may be performed by patients *at home*

Examples of Home-Based Tests	Patient Access	Authorized Ages
QuickVue At-Home COVID-19 Test	Rx required	≥14 yr
Ellume COVID-19 Home Test	OTC	≥2 yr
BinaxNOW COVID-19 Ag Card Home Test	Rx required	≥4 yr
QuickVue At-Home OTC COVID-19 Test	OTC	≥14 yr
BinaxNOW COVID-19 Antigen Self Test	OTC	≥15 y
BinaxNOW COVID-19 Ag Card Home Test	OTC	≥15 yr
InteliSwab COVID-19 Rapid Test	Rx required	≥15 yr
InteliSwab COVID-19 Rapid Test	OTC	≥15 yr
CareStart COVID-19 Antigen Home Test	OTC	≥2 yr
BD Veritor At-Home COVID-19 Test	OTC	≥2 yr

www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas#individual-antigen. Updated November 1, 2021.

Slide credit: clinicaloptions.com

CDC Antigen Testing Algorithm



*Asymptomatic people who are fully vaccinated should follow CDC's guidance on testing for people who are fully vaccinated. Asymptomatic people who have had a SARS-CoV-2 infection in the last 3 mo should follow CDC's guidance on testing for those within 90 days of their initial infection. For those who are traveling or have recently traveled, please refer to CDC's guidance for domestic and international travel during the COVID-19 pandemic.

CDC. Interim guidance for antigen testing for SARS-CoV-2. Last updated September 9, 2021.

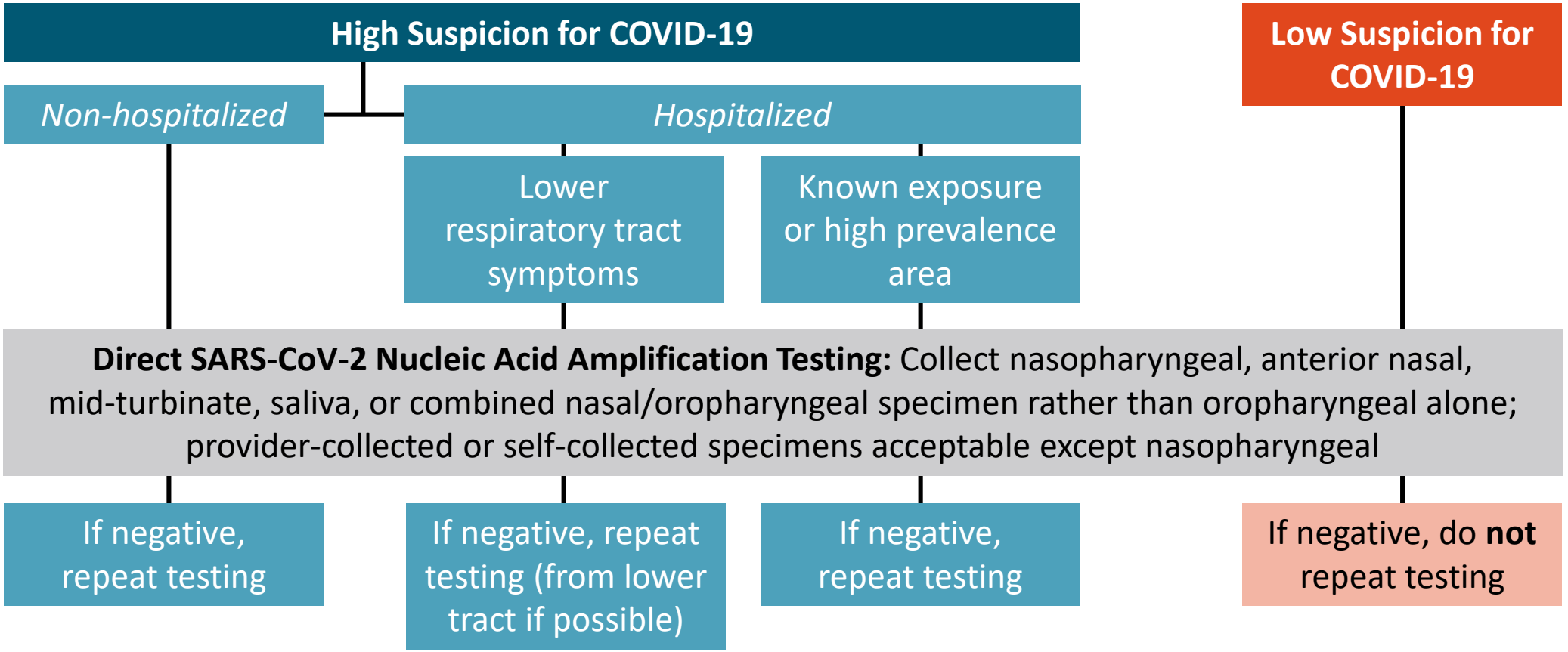
Slide credit: clinicaloptions.com

Diagnostic Accuracy (Infection: Yes/No?) of PCR and Antigen

- Best if performed on patients with symptoms consistent with COVID-19
  - In persons with COVID-19 pneumonia, upper respiratory tract PCR may be negative
- For both symptomatic and asymptomatic:
  - If antigen is positive, then infected, but a negative antigen test does not exclude infection
- For asymptomatic:
  - Window from time of infection until first positive test is longer for antigen test than for PCR and may remain negative

Slide credit: clinicaloptions.com

IDSA: SARS-CoV-2 Nucleic Acid Testing of Symptomatic Individuals



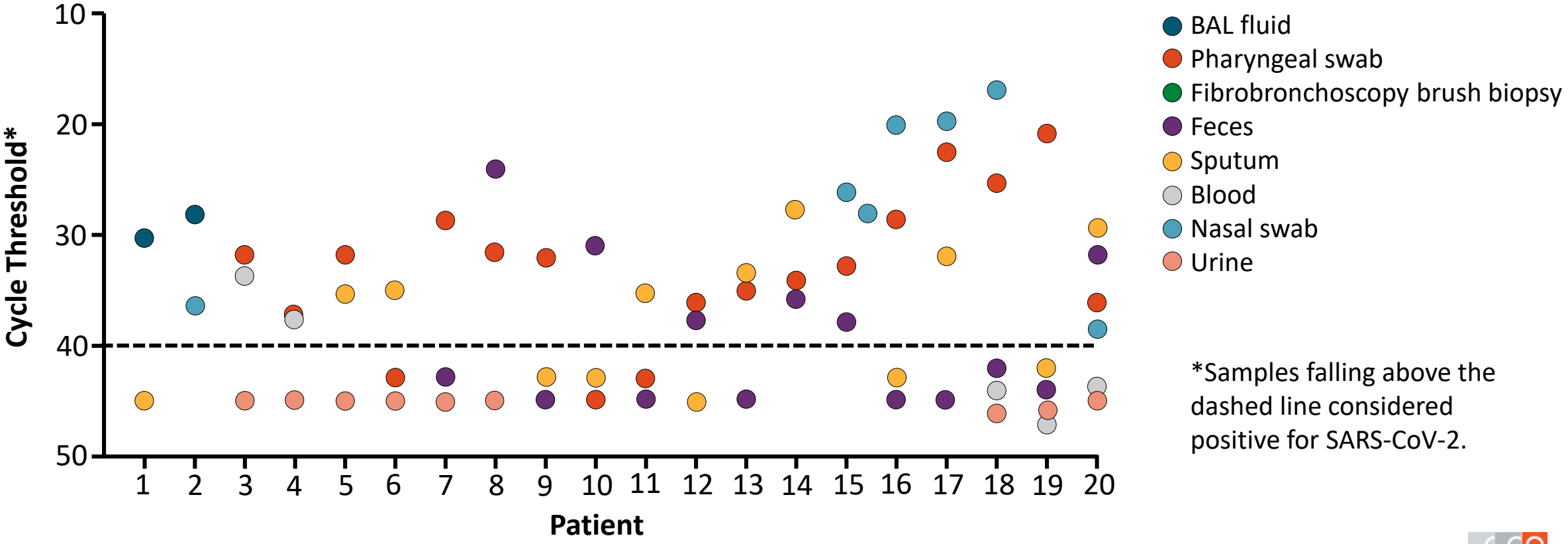
Prioritize testing for symptomatic patients. If resources adequate, consider testing select asymptomatic persons (eg, exposed, before organ or stem cell transplantation, hospital admission in area of high prevalence, major time-sensitive surgery, AGP with limited PPE).

IDSA. COVID-19 Guideline, Part 3: Diagnostics. Version 2.0.0. Last updated: December 23, 2020.

Slide credit: clinicaloptions.com

SARS-CoV-2 Detection by RT-PCR Across Different Clinical Specimens

- Among 1070 specimens from 205 COVID-19 patients in China, highest SARS-CoV-2 positivity rates observed with BAL fluid (93%), sputum (72%), nasal swab (63%)



*Samples falling above the dashed line considered positive for SARS-CoV-2.

Wang. JAMA. 2020;323:1843.

Slide credit: clinicaloptions.com

Estimated Sensitivity and Specificity Based on Clinical Sample Collection

Test, % (95% CI)		Studies, n	Sensitivity	Specificity
Sample location	▪ Upper respiratory tract	3	76 (51-100)	100 (99-100)
	▪ Lower respiratory tract		89 (84-94)	100 (99-100)
Specimen type*	▪ Saliva without coughing	9	90 (85-93)	98 (93-100)
	▪ Saliva with coughing	3	99 (94-100)	96 (83-99)
	▪ Oropharyngeal	4	76 (58-88)	98 (96-99)
	▪ Anterior nasal	2	89 (83-94)	100 (99-100)
	▪ Mid-turbinate	5	95 (83-99)	100 (89-100)
	▪ Anterior nasal/oropharyngeal	2	95 (69-99)	99 (92-100)
Number of nasopharyngeal swabs	▪ Single test	3	71 (65-77)	100 (99-100)
	▪ Repeat test		88 (80-96)	100 (99-100)

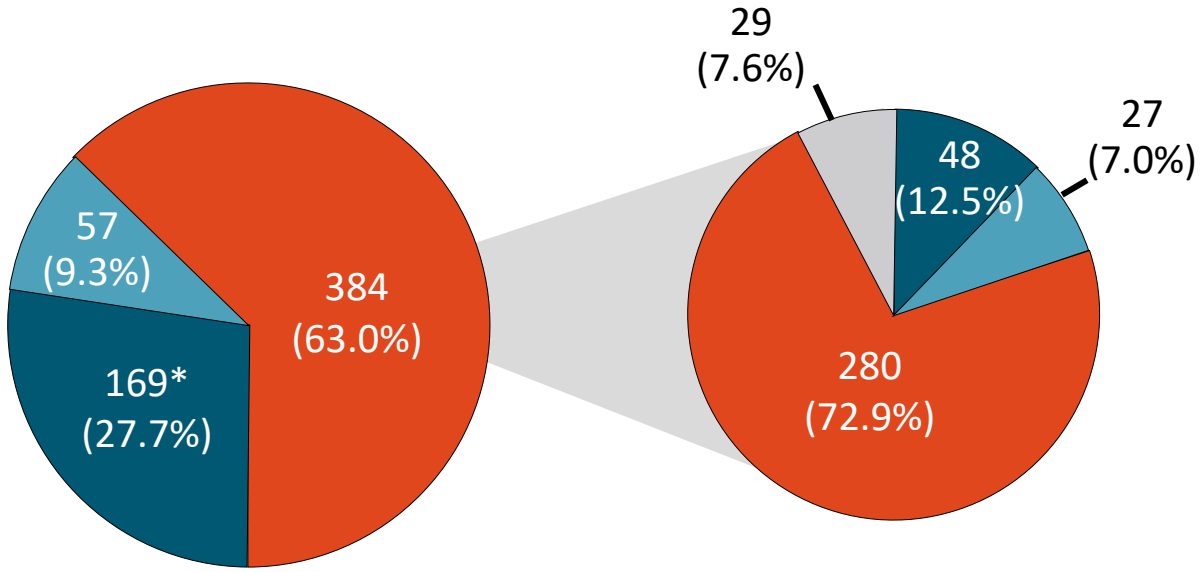
*Not head-to-head comparisons. Variability across studies in performance among swab types, process of swab collection, nucleic acid amplification assays, gene targets, and interpretive criteria defining assay positivity.

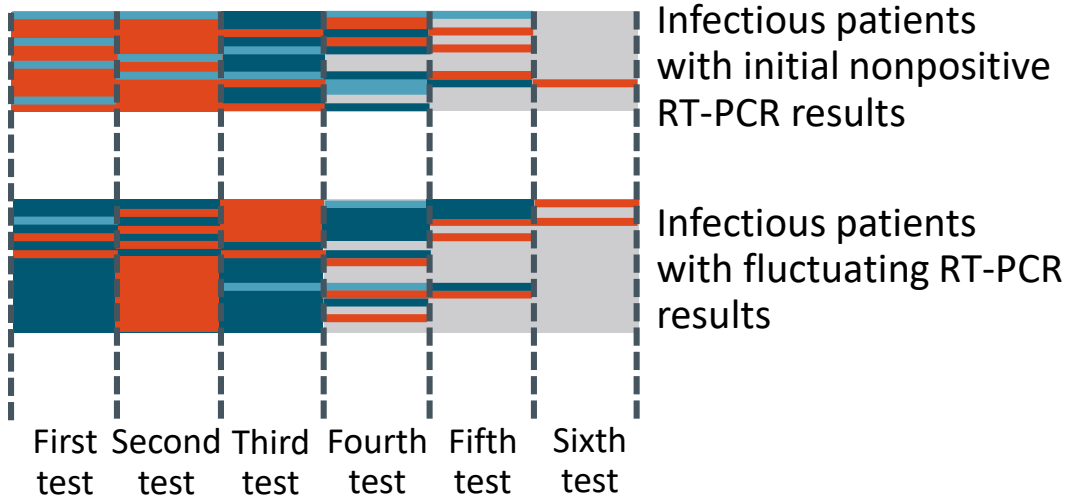
IDSA. COVID-19 Guideline, Part 3: Diagnostics. Version 2.0.0. Last updated: December 23, 2020.

Slide credit: clinicaloptions.com

Potential for False-Negative Results

- Retrospective study of hospitalized patients in Wuhan, China, clinically diagnosed with COVID-19 pneumonia (ie, chest CT imaging suggestive of viral pneumonia; N = 610)
  - Among patients with an initial negative results, 48 (12.5%) were confirmed positive on a second test, 7 (1.8%) on a third test, 4 (1%) on a fourth test, and 1 (0.3%) on a fifth test





*Includes 1 weakly positive.

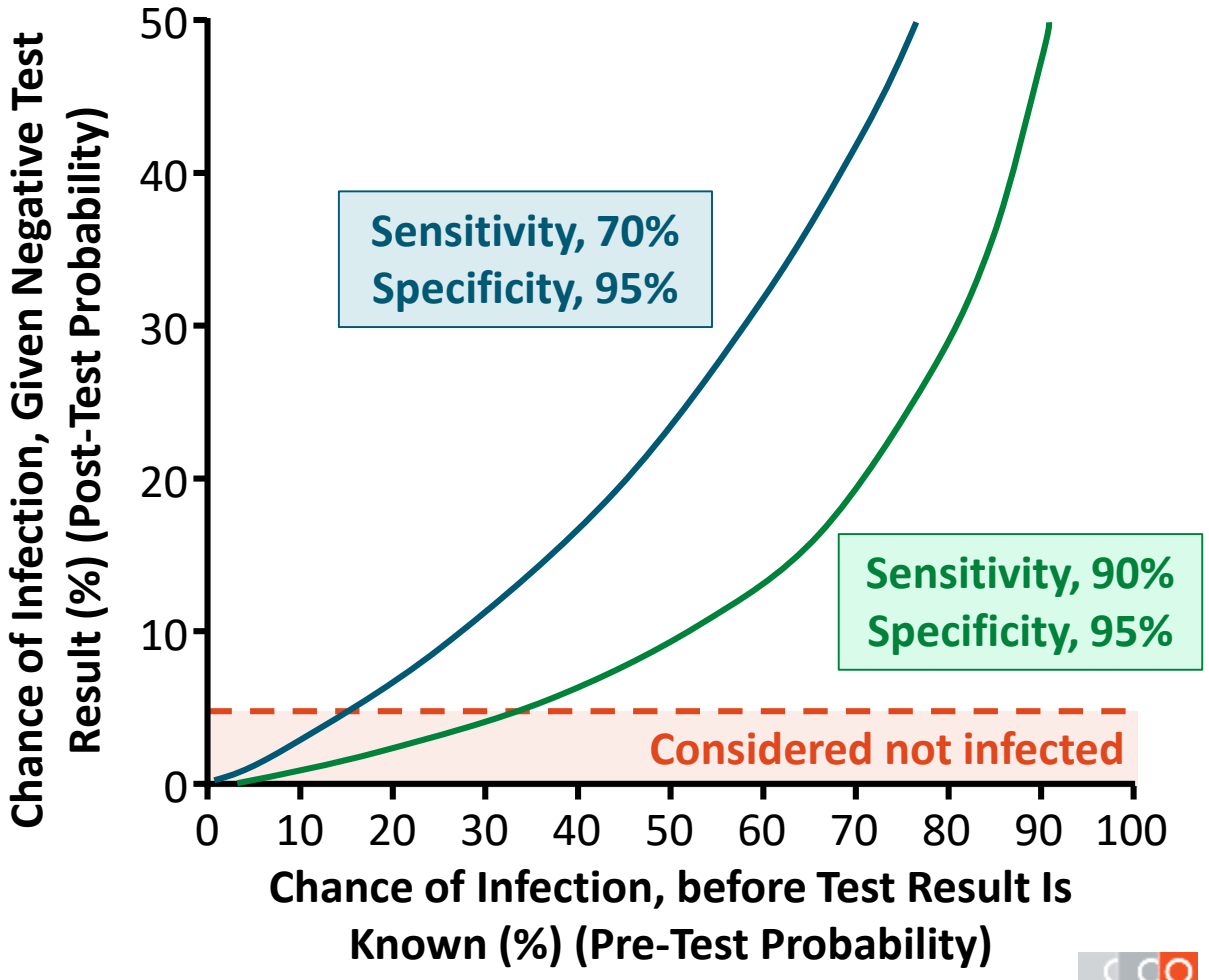
Positive Dubious positive Negative Not available

Li. J Med Virol. 2020;92:903.

Slide credit: clinicaloptions.com

False-Negative Results: Clinician Perspective on Challenges and Implications

- *"Diagnostic testing will help in safely opening the country, but only if the tests are highly sensitive, validated under realistic conditions"*
- *"The FDA should ensure that manufacturers provide details of tests' clinical sensitivity and specificity at time of market authorization"*
- *"Measuring test sensitivity in asymptomatic people is an urgent priority"*
- *"Negative results even on a highly sensitive test cannot rule out infection if the pretest probability is high"*
- *"Thresholds for ruling out infection need to be developed for a variety of clinical situations"*



Woloshin. NEJM. 2020;383:e38.

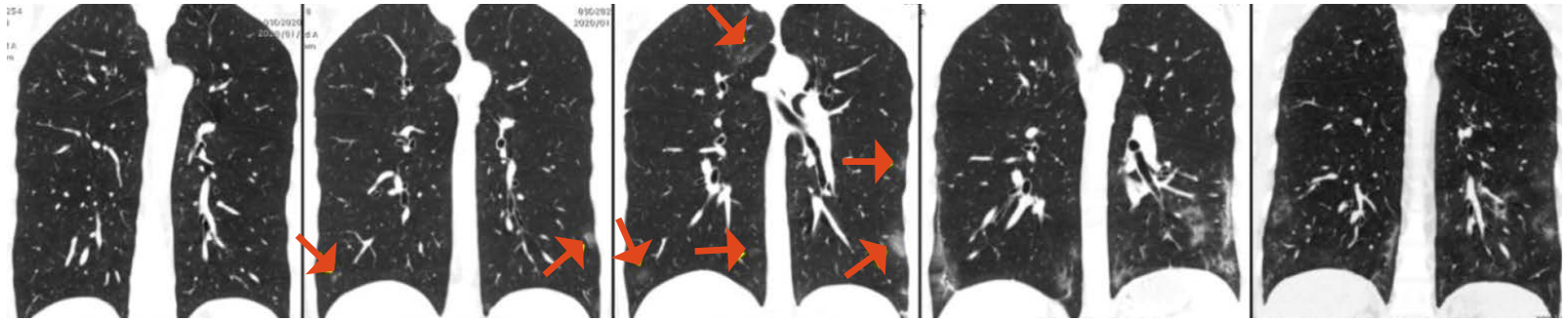
Slide credit: clinicaloptions.com

Chest CT Abnormalities

- Most common hallmark features on chest CT images include bilateral peripheral ground-glass opacities and consolidations of the lungs with peak lung involvement between 6 days and 11 days post-symptom onset[1-3]
- In a study in Wuhan, China, chest CT imaging demonstrated a sensitivity of 97% and specificity of 25% with RT-PCR as the reference (N = 1014)[4]
  - 60% to 93% of patients had initial positive lung CT consistent with COVID-19 *before* the initial positive RT-PCR result

29-Yr-Old Man Presenting With Fever for 6 Days[4]

→ Ground-glass opacities



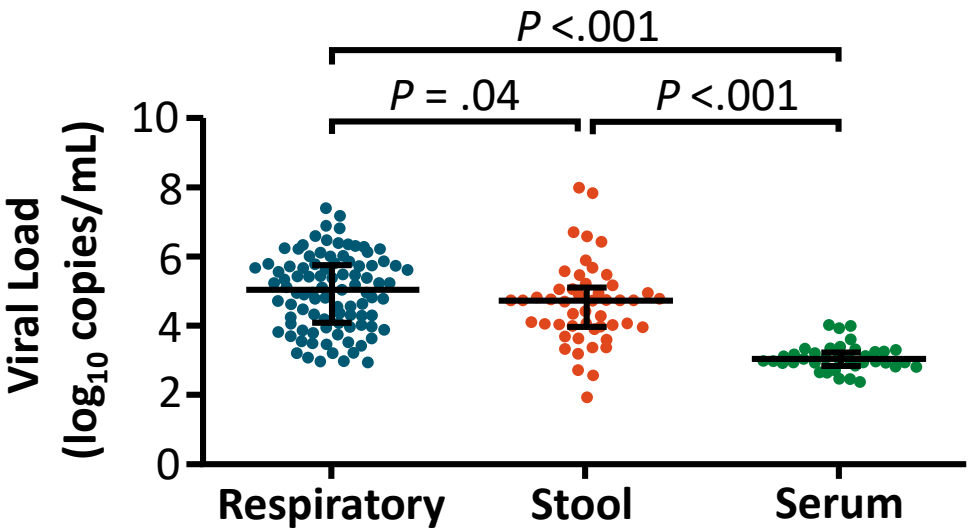
Day 6 Day 9 Day 11 Day 17 Day 23

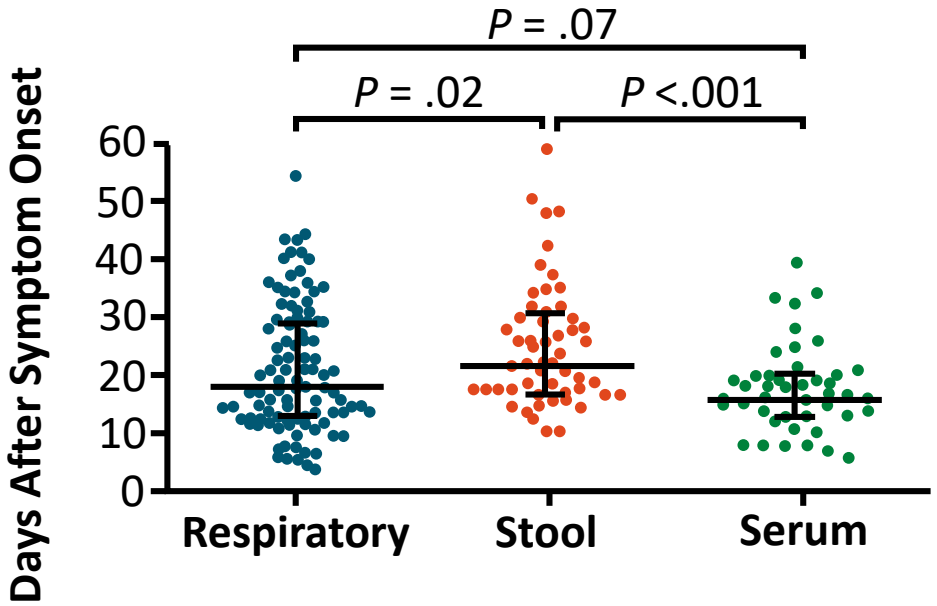
1. Bernheim. Radiology. 2020;295:685. 2. Pan. Radiology. 2020;295:715. 3. Wang. Radiology. 2020;296:E55. 4. Ai. Radiology. 2020;296:E32.

Slide credit: clinicaloptions.com

SARS-CoV-2 in Stool

- Reports of negative pharyngeal and sputum viral tests but fecal samples testing positive for SARS-CoV-2[1]
- Similar viral load but significantly longer duration of viral detection in stool vs respiratory samples[2]

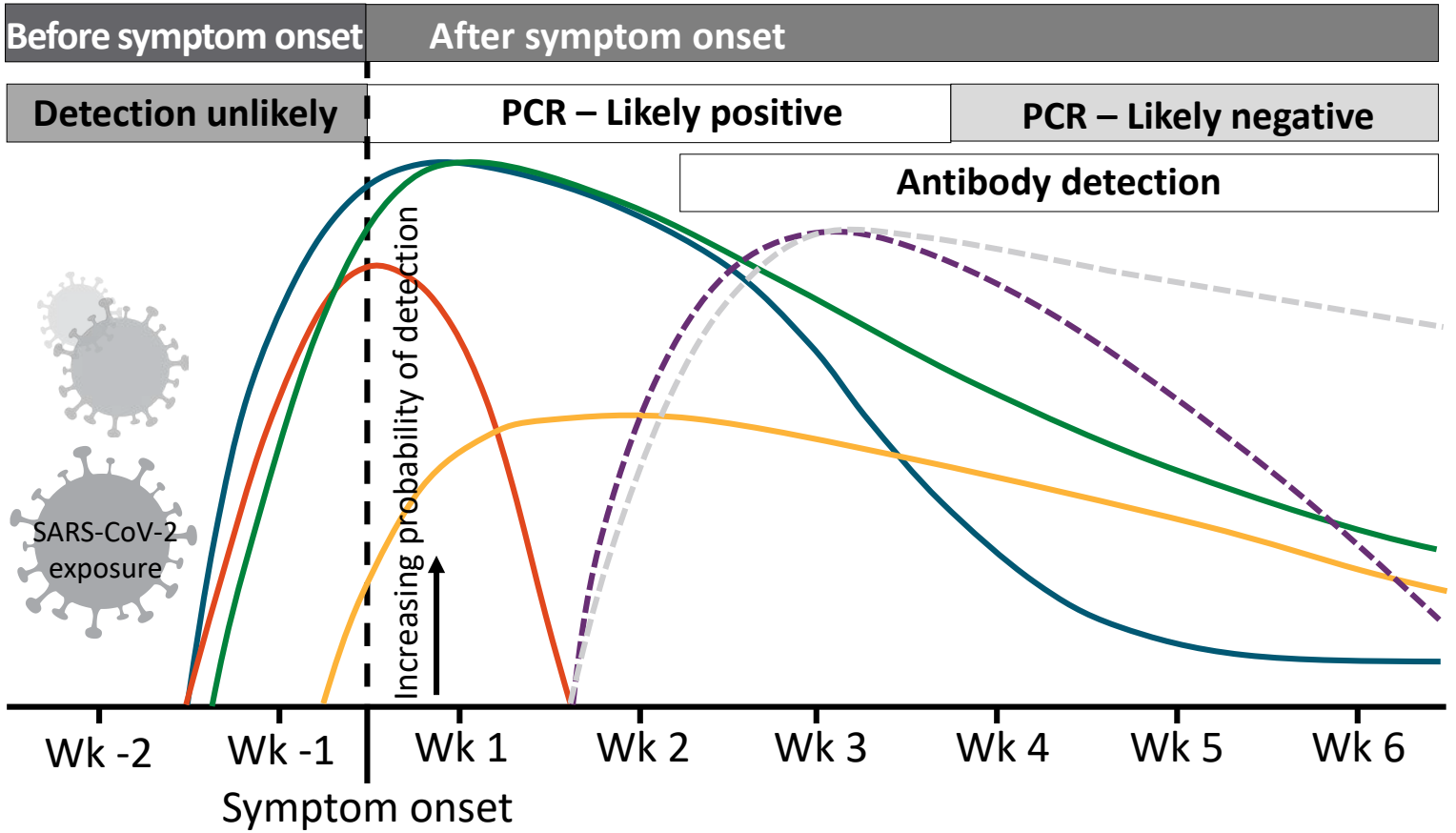




1. Chen. Am J Gastroenterol. 2020;115:790. 2. Zheng. BMJ. 2020;369:m1443.

Slide credit: clinicaloptions.com

Temporal Considerations for Diagnosis



- Nasopharyngeal swab PCR
- Virus isolation from respiratory tract
- Bronchoalveolar lavage/sputum PCR
- Stool PCR
- IgM antibody
- IgG antibody

Slide credit: clinicaloptions.com

Viral Antibody Response

- Viral infection results in the production of antibodies of different isotypes with varying targets and specificities
- **High-affinity antibodies** generated via maturation with somatic rearrangements and hypermutation of Ig genes
- **Nonneutralizing antibodies**: recognize viral epitopes that do not extinguish infective virus
- **Neutralizing antibodies**: recognize viral epitopes that eliminate or greatly diminish infective virus; critical for preventing reinfection
  - Development of nonneutralizing antibodies typically precedes that of neutralizing antibodies

Functional Activity of Ig Isotypes	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Neutralization	+	-	++	++	++	++	++	-
Opsonization	+	-	+++	-	++	+	+	-
Sensitization for NK cell killing	-	-	++	-	++	-	-	-
Sensitization of mast cells	-	-	+	-	+	-	-	+++
Complement activation	+++	-	++	+	+++	-	+	-

Neurath. Encyclopedia of Virology. 2008;56.

Slide credit: clinicaloptions.com

SARS-CoV-2 Antibody Tests

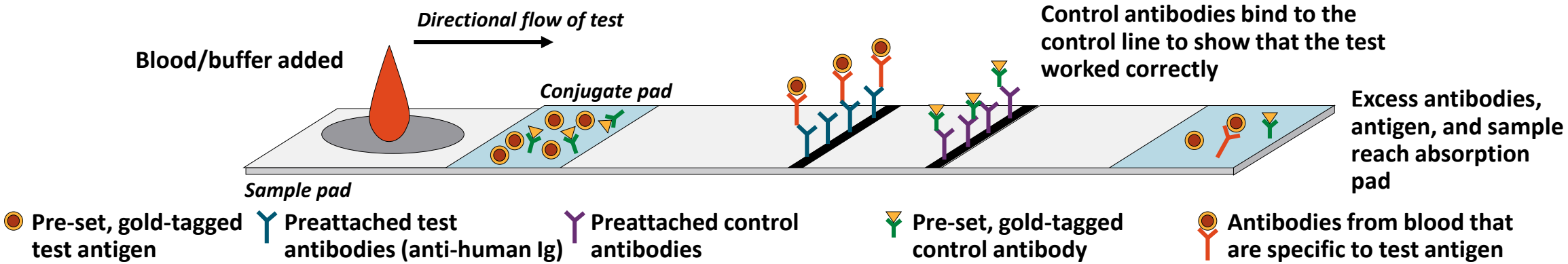
Type of Test[1]	Time to Results[1]	Sensitivity[2]	Specificity[2]	What It Tells Us[1]	What It Cannot Tell Us[1]
Rapid serology test	10-30 min	0% (0-6 days, IgG) to 100%	94.8% to 100%	Presence of antiviral antibodies (qualitative)	Antibody titer, neutralizing activity
ELISA	2-5 hr	13.9% (0-10 days) to 100%	94.4% to 100%	Presence and level of antiviral antibodies (quantitative)	Neutralizing activity
Neutralization assay	3-5 days	NR	NR	Presence of antibodies that can inhibit virus growth (ex vivo)	May miss antibodies to viral proteins not involved in replication
Chemiluminescent immunoassay	1-2 hr	26.1% (0-7 days) to 100%	97.2% to 100%	Presence and level of antiviral antibodies (quantitative)	Neutralizing activity

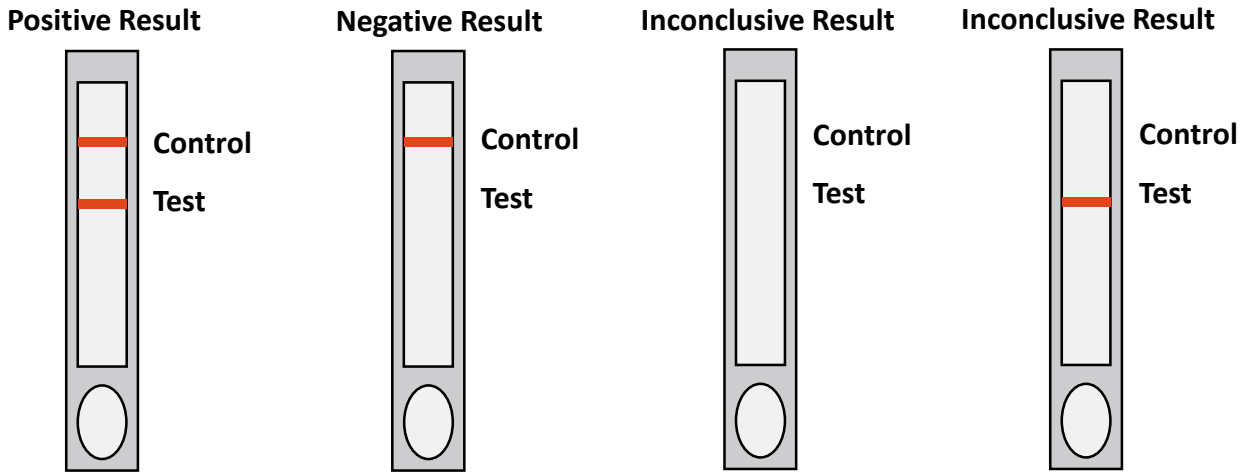
1. www.centerforhealthsecurity.org/covid-19TestingToolkit/testing-basics/types-of-COVID-19-tests/serology-tests.html#types-of-serology-tests.
2. www.centerforhealthsecurity.org/covid-19TestingToolkit/serology/Serology-based-tests-for-COVID-19.html. Last updated December 6, 2021.

Slide credit: clinicaloptions.com

Point-of-Care Antibody Testing for SARS-CoV-2

- RDTs approved in US (via EUA), EU, and China





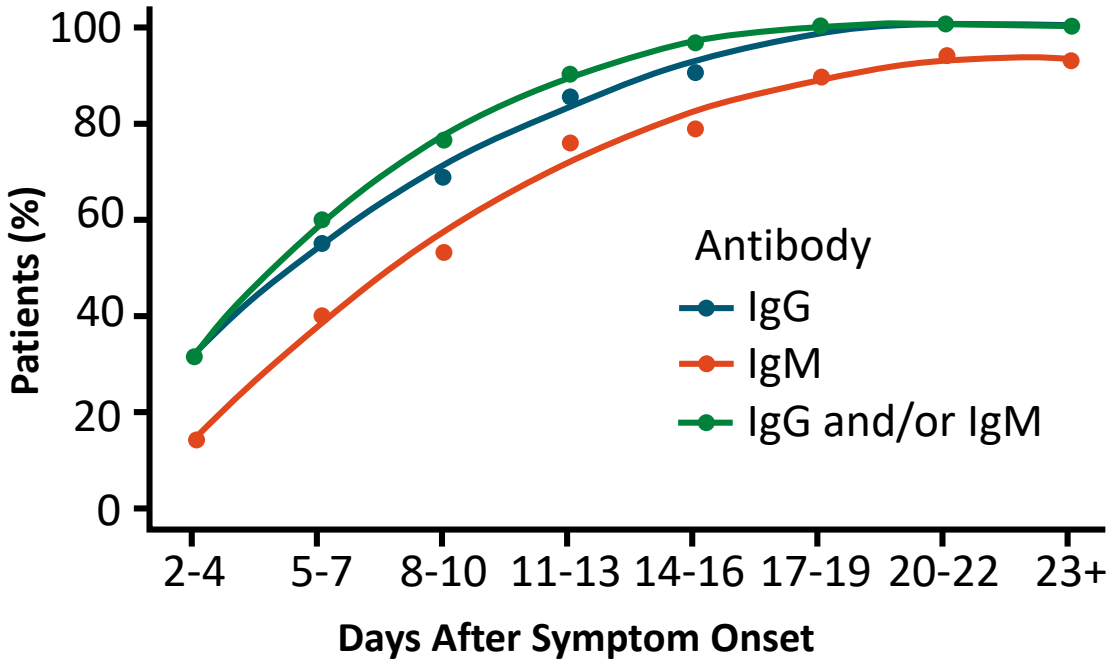
Li. J Med Virol. 2020;92:1518.

Slide credit: clinicaloptions.com

Antibody Response to SARS-CoV-2 in China

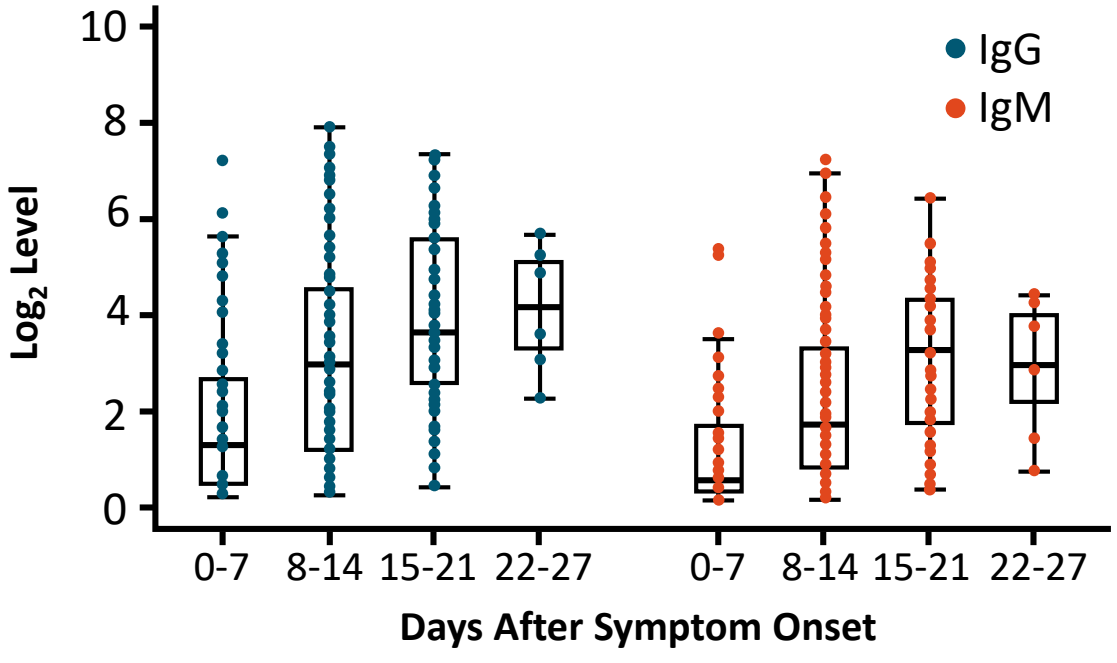
- Antibodies detected by chemiluminescence enzyme immunoassay in patients with COVID-19* (N = 262) enrolled at 3 hospitals in Hubei, China

Rates of Detection of Anti–SARS-CoV-2 IgM and IgG



Total Patients:	22	45	70	79	70	47	17	13

Antibody Levels



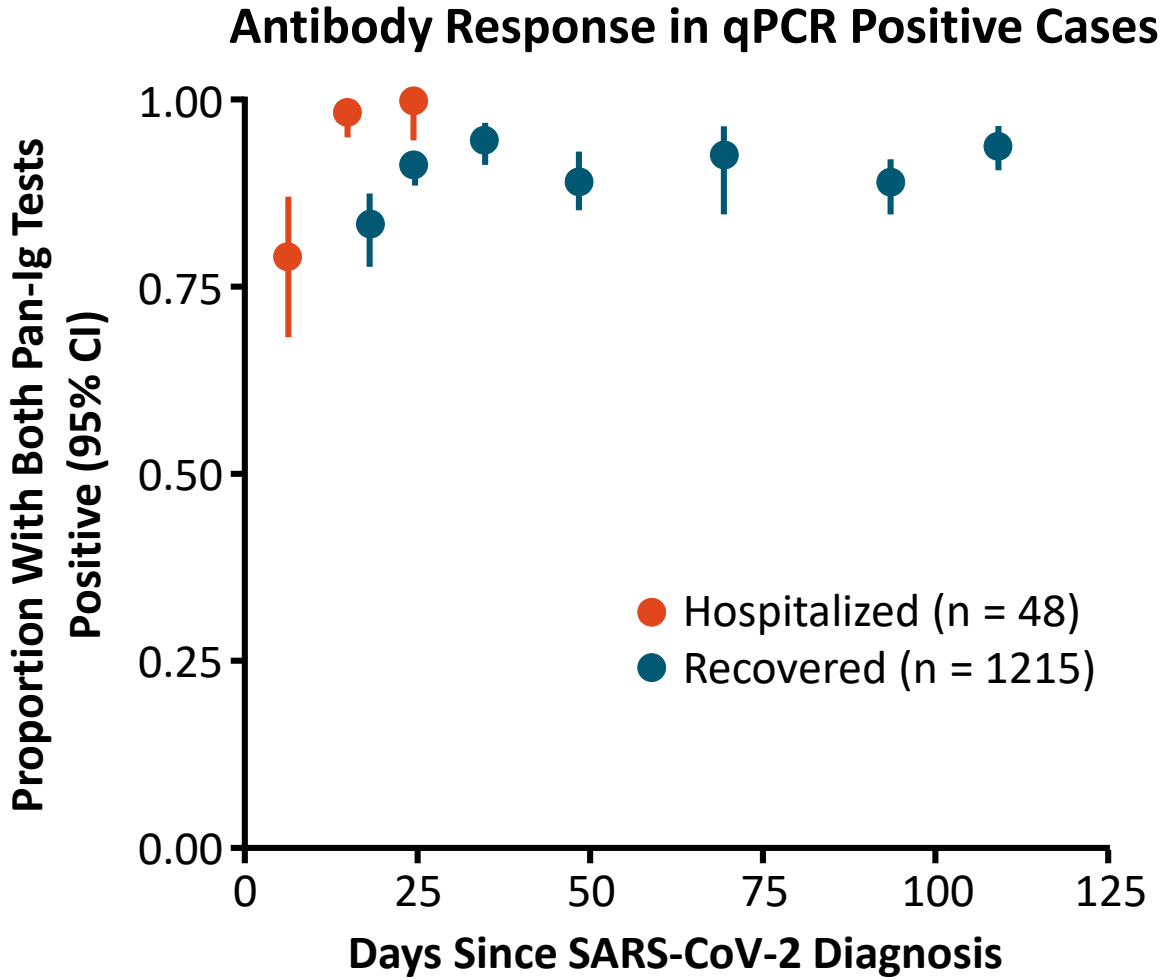
Total Patients:	54	130	71	7	54	130	71	7

*Confirmed by RT-PCR assays on nasal or pharyngeal swabs.

Long. Nat Med. 2020;26:845.

Slide credit: clinicaloptions.com

Antibody Response to SARS-CoV-2 in Iceland



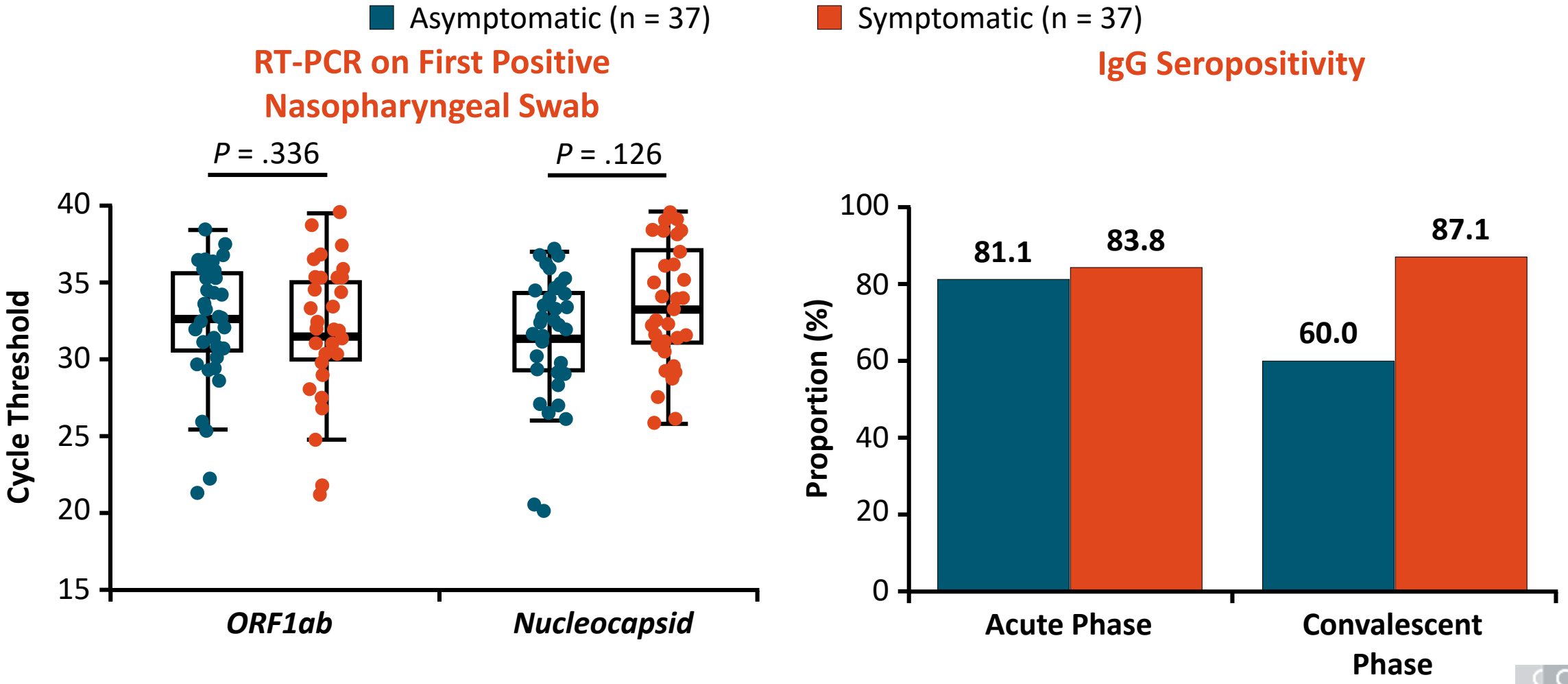
SARS-CoV-2 Seroprevalence, %	Persons Tested, n	Positive Pan-Ig Antibody Test*	
		Both	Single
2017	472	0	0.2
Early 2020	470	0	0.9
Health care†	18,609	0.2	0.6
Reykjavik†	4843	0.4	0.8
Vestmannaeyjar†	663	0.5	1.1
Quarantine	4222	2.3	3.1
Hospitalized	48	93.8	97.9
Recovered	1215	91.1	95.1

*Anti-N and anti-S1-RBD tests; latest available sample used.
†Excludes persons with positive qPCR results, those quarantined.

Gudbjartsson. NEJM. 2020;382:2302.

Slide credit: clinicaloptions.com

Viral and Immunologic Dynamics Among COVID-19 Patients by Symptomology



Long. Nat Med. 2020;26:1200.

Slide credit: clinicaloptions.com

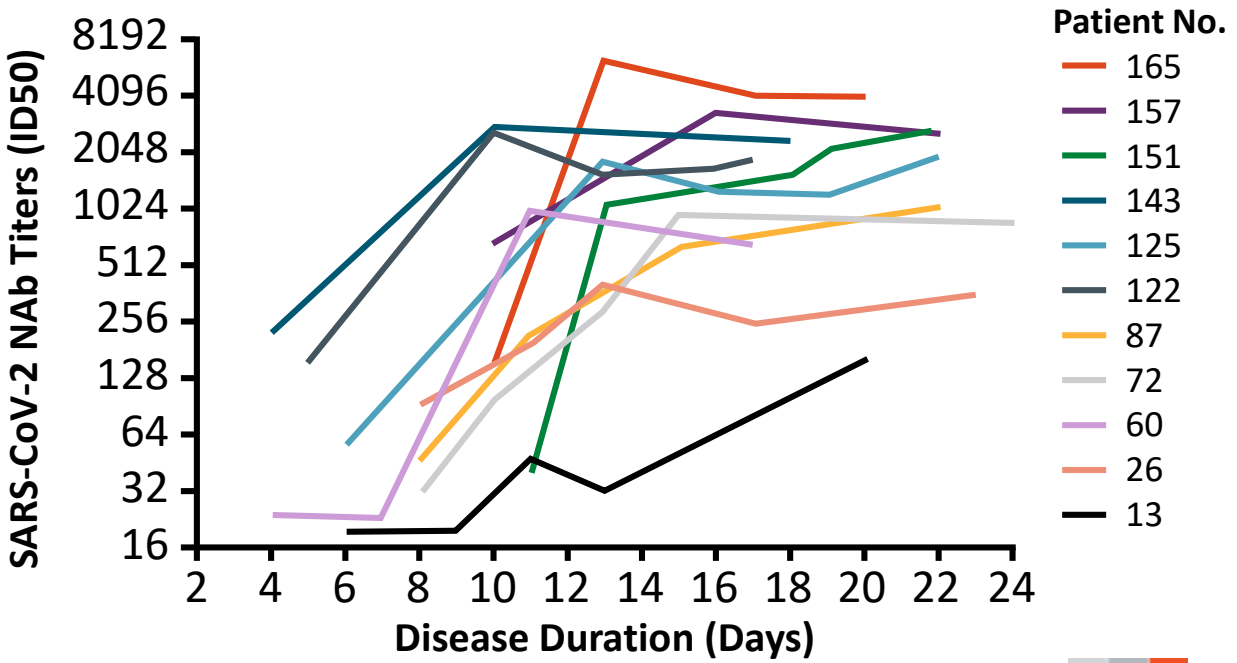
Neutralizing Antibodies to SARS-CoV-2

- Plasma collected from recovered patients with COVID-19 who had mild symptoms (N = 175)
- Neutralizing antibody titers* varied

NAb Titers	Value (N = 175)
Titer range, ID50	< 40 to 21,567
Patients with undetectable level, %	6
Patients with detectable level, %	
▪ ID50: < 500 (very low)	30
▪ ID50: 500-999 (medium low)	17
▪ ID50: 1000-2500 (medium high)	39
▪ ID50: > 2500 (high)	14

*Assessed via pseudotyped, lentiviral vector-based assay.

- Neutralizing and spike-binding antibodies emerged concurrently between 10-15 days following disease onset

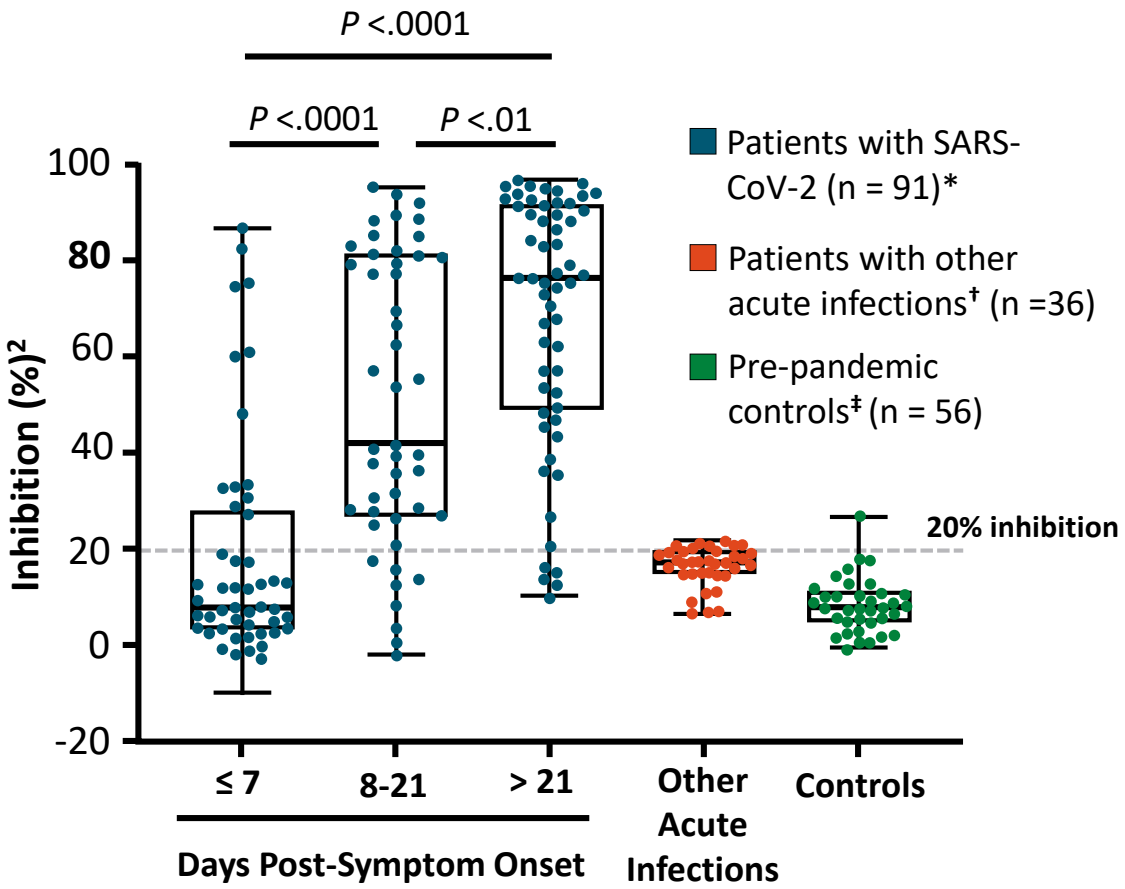


Wu. JAMA Intern Med. 2020;189:10.

Slide credit: clinicaloptions.com

Measuring Virus Neutralization Without High Containment Facilities

- Neutralization can be measured multiple ways
- Classical methods use live or pseudotyped virus and determine the serum dilution that inhibits virus growth[1,2]
- The surrogate viral neutralization test (sVNT) is a simpler method that assesses binding to ACE2[1,2]



*Included 71 mild cases, 17 moderate cases, and 3 severe cases. †Included patients with seasonal coronavirus infections or other acute infections (e.g. dengue, CMV, or EBV). ‡Serum from a random cohort of patients in Australia obtained in 2018.

1. Tan. Nat Biotechnol. 2020;38:1073. 2. Bond. J Infect Dis. 2020;222:1280.

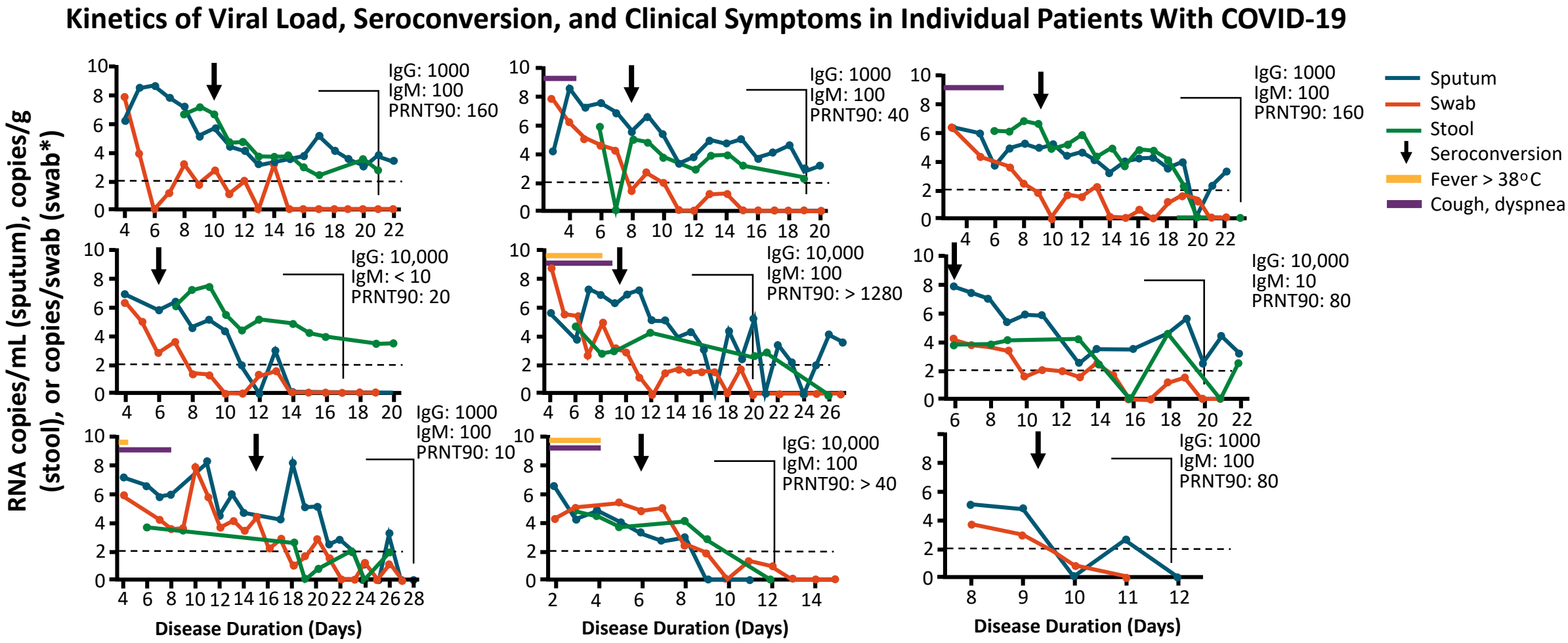
Slide credit: clinicaloptions.com

SARS-CoV-2 Antibodies by Age and Disease Severity

- Limited understanding of magnitude and duration of antibody responses in persons with different disease severity, genetic backgrounds, comorbidities, age, and/or infection history[1]
- One study of patients with mild symptoms who recovered reports significantly higher plasma NAb titers (P <.001) and spike-binding titers (P <.001 to P = .03, depending on protein examined) in older and middle-aged patients compared with younger patients[2]
  - Unknown whether the higher level of NAbs observed in older patients might be protective
- Higher IgG titers in patients with severe disease (n = 20) vs nonsevere disease (n = 110) 2 wk following symptom onset (P = .001)[3]
  - However, authors note that small sample size for patients in severe and critical condition limit conclusion that can be drawn from this observation
- Another study reports no difference in IgG antibody levels between patients with mild/moderate vs severe disease (N = 76)[4]

1. Bryant. Sci Immunol. 2020;5:eabc6347. 2. Wu. JAMA Intern Med. 2020;180:1356.
3. Long. Nat Med. 2020;26:845. 4. Phipps. Am J Clin Pathol. 2020;154;459.

SARS-CoV-2 Detection via Swab vs Serology



*Oro- and nasopharyngeal throat swabs persevered in 3 mL of viral transport medium.

Wölfel. Nature. 2020;581:465.

Slide credit: clinicaloptions.com

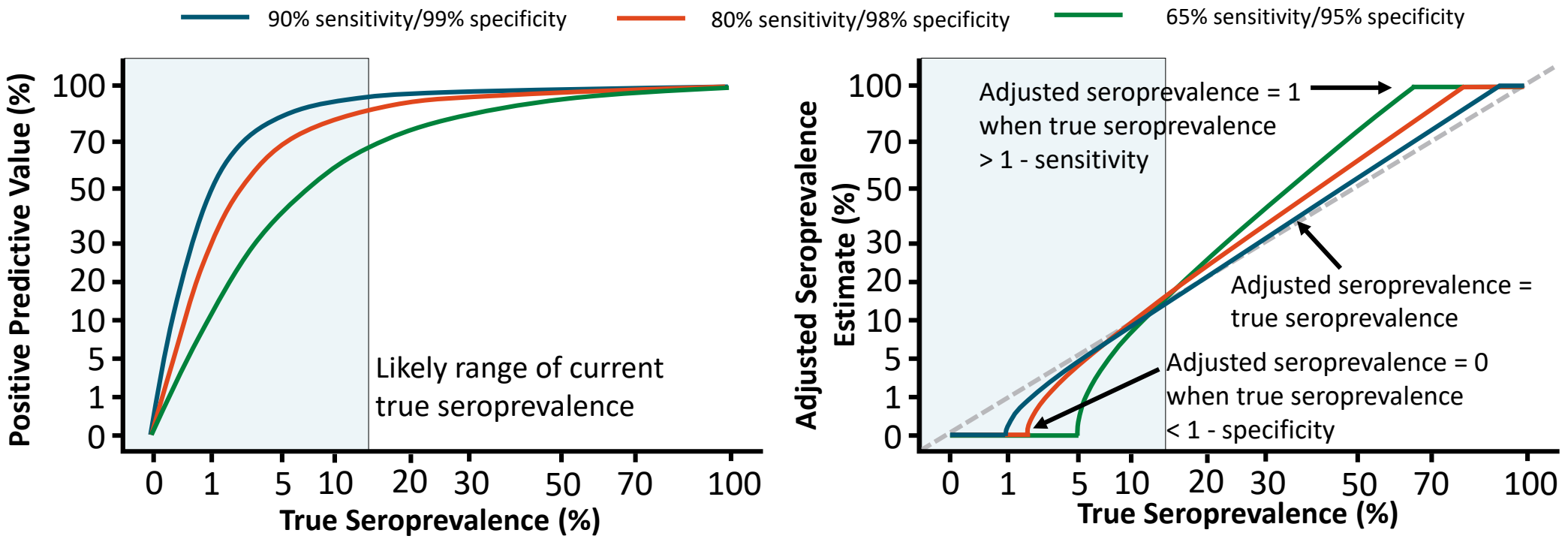
SARS-CoV-2 Serology for Diagnosis: Current Recommendations

- CDC: *"Antibody testing does not replace virologic testing and should not be used to establish the presence or absence of acute SARS-CoV-2 infection."*[1]
- Royal College of Pathologists of Australasia[2]:
  - *"Molecular testing on a single throat with deep nasal swab is the current test of choice for the diagnosis of acute COVID-19 infection"*
  - *"COVID-19 IgG/IgM rapid tests will miss patients in early stages of disease when they are infectious to other people"*
- WHO: *"…recommends the use of Ag-RDTs that meet minimum performance requirements of ≥ 80% sensitivity and ≥ 97% specificity. Ag-RDTs are less sensitive than NAAT, particularly in asymptomatic populations, but careful selection of cohorts for testing can mitigate this limitation"*[3]

1. www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html
2. www.rcpa.edu.au/getattachment/bf9c7996-6467-44e6-81f2-e2e0cd71a4c7/COVID19-IgG-IgM-RAPID-POCT-TESTS.aspx
3. www.who.int/publications/i/item/antigen-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays

SARS-CoV-2 Serology in Epidemiology

- Serology tests with high but < 100% specificity may lead to false-positive results when used in areas with low incidence
  - Example: A test with 96% specificity and 90% sensitivity used in an area where 5% of population has been infected → 54% of positive results would indicate true infection



Bryant. Sci Immunol. 2020;5:eabc6347.

Slide credit: clinicaloptions.com

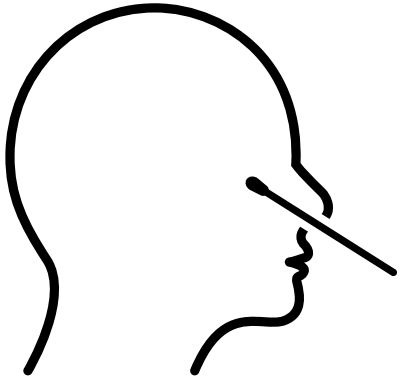
At-Home Tests

Comparison of At-Home COVID-19 Tests

Test Characteristic	Lucira COVID-19 All-In-One Test Kit[1]	Ellume COVID-19 Home Test[2]	BinaxNOW COVID-19 Ag Card Home Test[3]
Prescription required	Yes	No	Yes
Additional equipment or support required	None	Smartphone	None
Age	≥ 14 yr if self-collected, ≥ 2 yr if adult-collected	≥ 16 yr if self-collected, ≥ 2 yr if adult-collected	≥ 15 yr if self-collected, ≥ 2 yr if adult-collected
Time to results	30 min	15 min	15 min
Clinical scenario	Suspected of COVID-19 by HCP	With or without symptoms/epidemiological reasons to suspect COVID-19 infection	Suspected of COVID-19 by HCP within 7 days of symptom onset
SARS-CoV-2 detection	RNA from N gene	Nucleocapsid antigens	Nucleocapsid antigens
PPA, % (95% CI)	94.1 (85.5-98.4)	95 (82-99)	84.6 (76.8-90.6)
NPA, % (95% CI)	98.0 (89.4-99.9)	97 (93-99)	98.5 (96.6-99.5)

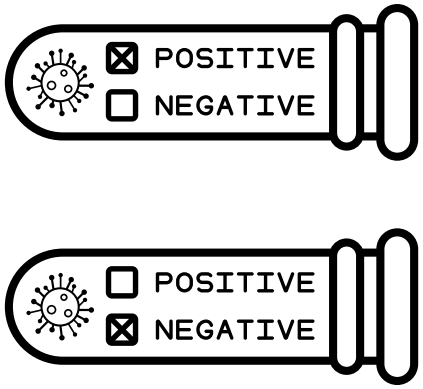
1. Lucira COVID-19 All-In-One Test Kit. Fact Sheet for HCPs. HCP Instructions for Use.
2. Ellume COVID-19 Home Test. Fact Sheet for HCPs. Product Information Leaflet. Product Overview for HCPs.
3. BinaxNOW COVID-19 Ag Card Home Test. Fact Sheet for HCPs. HCP Instructions for Use.

Instructions for Use of *Lucira COVID-19 All-In-One Test Kit*

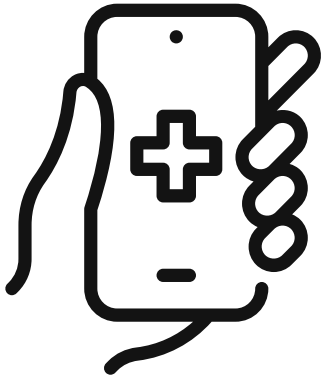


Step 1
Swab nose, 5x per nostril

Step 2
Stir swab 15x in sample vial



Step 3
Receive results in 30 min



Step 4
Seek treatment, if warranted

- Deploys RT-LAMP technology to detect RNA from N gene of SARS-CoV-2; successful amplification creates pH/color change
- Store test kits at ambient temperature (ie, 15-30°C or 59-86°F)

Lucira COVID-19 All-In-One Test Kit. Fact Sheet for HCPs. HCP Instructions for Use.

Slide credit: clinicaloptions.com

Clinical Evaluation of *Lucira COVID-19 All-In-One Test Kit*

- Community testing study of symptomatic individuals suspected of COVID-19; self-collected nasal swabs tested by Lucira COVID-19 All-In-One Test Kit compared with high sensitivity molecular SARS-CoV-2 assay (N = 101)

Lucira COVID-19 All-In-One Kit Results, n	FDA-Approved Molecular SARS-CoV-2 Assay Results, n	
	Positive	Negative
Positive	**48**	1
Negative	3*	**49**

PPA: 94.1%
(95% CI: 85.5-98.4)

NPA: 98.0%
(95% CI: 89.4-99.9)

*Occurred in subjects with reference test Ct values >37.5.
n = 1 invalid result (0.99% invalid rate); n = 2 retests (1.98% retest rate).

This test "has been designed to minimize the likelihood of false positive test results. However, it is still possible that this test can give a false positive result, even when used…where prevalence is below 5%."

Lucira COVID-19 All-In-One Test Kit. Fact Sheet for HCPs. HCP Instructions for Use.

Slide credit: clinicaloptions.com

FDA EUA of *Ellume COVID-19 Home Test*

". . . authorized for non-prescription home use. . . from mid-turbinate nasal swabs that are self-collected by an individual ≥16 yr of age, or are collected by an adult from an individual ≥2 yr of age. This test is intended for use in individuals with or without symptoms or other epidemiological reasons to suspect a COVID-19 infection."

Do not use if prone to nosebleeds or within 6 mo of facial/head injury or surgery.

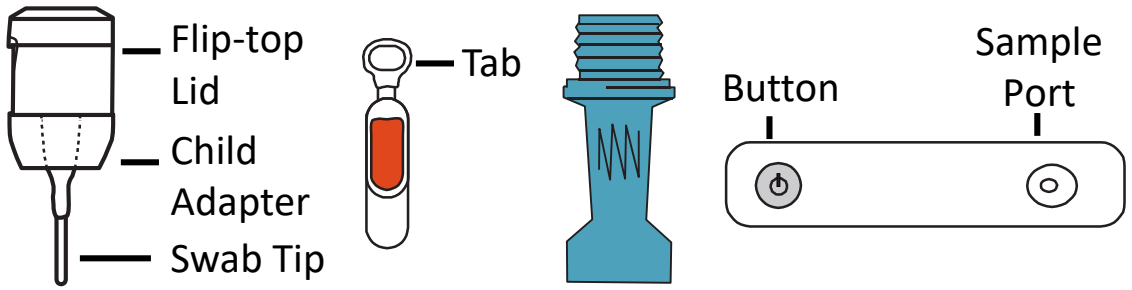
- Rapid, single-use lateral flow immunoassay for qualitative detection of SARS-CoV-2 nucleocapsid antigens
  - Interpret results in context of clinical observations, current epidemiological data
  - If positive, patient presumed contagious; CDC recommends isolation for low-risk persons until RT-PCR confirmation
  - Consult HCP if symptoms persist or worsen, regardless of test result

Ellume COVID-19 Home Test. Fact Sheet for HCPs. Product Overview for HCPs.

Slide credit: clinicaloptions.com

Instructions for Use of *Ellume COVID-19 Home Test*

Test Components



Nasal Swab With Child Adapter | **Processing Fluid** | **Dropper** | **Analyzer**

Store test in dry location at 2-30°C or 36-86°F; use test at room temperature (15-25°C or 59-77°F) away from direct sunlight.

Principle of Operation

1. Download associated app; connect Analyzer to smartphone for self-paced, step-by-step guidance
2. Add Processing Fluid to Dropper
3. Collect mid-turbinate nasal specimen, and lock swab in Dropper
4. Dispense liquid aliquot from Dropper into Sample Port of Analyzer
5. Receive results in 15 min with automatic reporting to public health authorities per local, state, and federal regulations

- Detects fluorophore-labeled viral proteins present during acute phase of infection but does not distinguish SARS-CoV from SARS-CoV-2

Slide credit: clinicaloptions.com

Clinical Evaluation of *Ellume COVID-19 Home Test*

- All-comers performance evaluation in simulated home environment across 5 geographically diverse US study sites (N = 198)
  - Symptomatic and asymptomatic individuals self-sampled, self-tested with Ellume COVID-19 Home Test; results compared with staff-collected nasal swab and high sensitivity molecular SARS-CoV-2 assay in reference lab

Ellume COVID-19 Home Test Results, n	FDA EUA Molecular SARS-CoV-2 Assay Results, n	
	Positive	Negative
Positive	**35**	5
Negative	2	**156**

PPA: 95%
(95% CI: 82-99)

NPA: 97%
(95% CI: 93-99)

In symptomatic subset (n = 64): PPA, 96%; NPA, 100%.
In asymptomatic subset (n = 134): PPA, 91%; NPA, 96%.

FDA EUA of *BinaxNOW COVID-19 Ag Card Home Test*

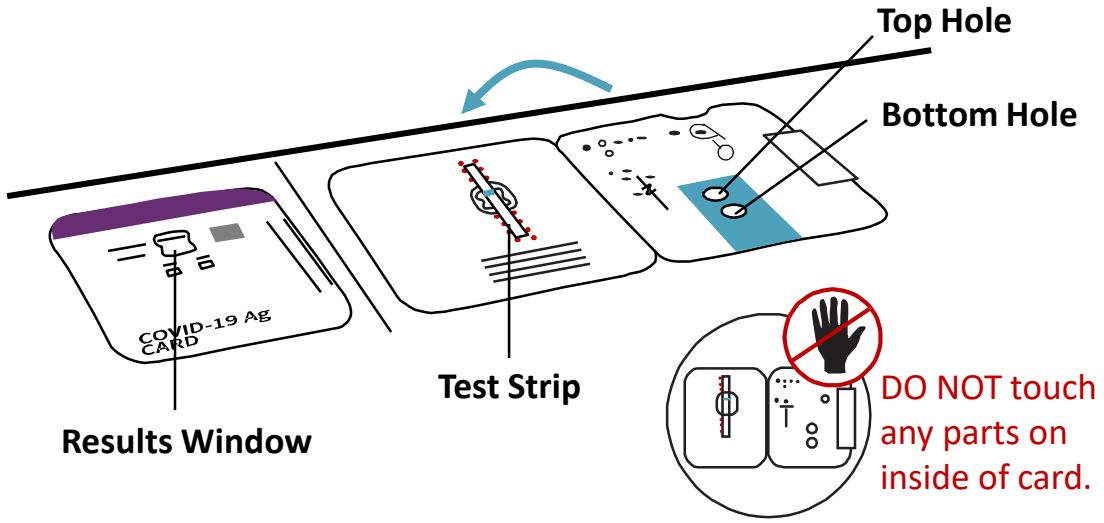
". . . authorized for prescription home use with self-collected observed direct anterior nasal (nares) swab samples from individuals ≥15 yr of age who are suspected of COVID-19 by their HCP within the first 7 days of symptom onset or adult collected nasal swab samples from individuals ≥2 yr of age who are suspected of COVID-19 by their HCP within the first 7 days of symptom onset. . . to be performed only with the supervision of a telehealth proctor."

- Rapid, single-use lateral flow immunoassay for qualitative detection of SARS-CoV-2 nucleocapsid antigens
  - Interpret results in context of clinical observations, current epidemiological data
  - If positive, patient presumed contagious; manage per current CDC guidance
  - If negative, confirm with molecular assay if necessary for patient management

BinaxNOW COVID-19 Ag Card Home Test. Fact Sheet for HCPs. HCP Instructions for Use.

Slide credit: clinicaloptions.com

Instructions for Use of *BinaxNOW COVID-19 Ag Card Home Test*



- Immunochromatographic assay interpreted via presence or absence of pink/purple lines; does not distinguish SARS-CoV from SARS-CoV-2
- Store at 2-30°C or 35.6-86°F, use at RT

Initiating Telehealth Visit & Running Test

1. Log into associated app to connect with telehealth proctor
2. Scan QR code on card; apply 6 drops of extraction liquid to top hole
3. Swab each nostril 5 times (ie, ½ to ¾ inch into nostril)
4. Insert swab into bottom hole, push toward top hole, and turn clockwise 3 times
5. Close and seal card
6. Receive results in 15 min; telehealth provider to report results to appropriate public health authorities

BinaxNOW COVID-19 Ag Card Home Test. HCP Instructions for Use.

Slide credit: clinicaloptions.com

Clinical Evaluation of *BinaxNOW COVID-19 Ag Card Home Test*

- Ongoing multi-site prospective study of US patients presenting within 7 days of COVID-19 symptom onset (N = 460)
  - Individuals self-collected a nasal swab with observation/coaching from trained proctor then performed and interpreted test; results compared with RT-PCR

BinaxNOW COVID-19 Ag Card Results, n	FDA EUA Molecular SARS-CoV-2 Assay Results, n	
	Positive	Negative
Positive	**99**	5
Negative	18	**338**

PPA: 84.6%
(95% CI: 76.8-90.6%)

NPA: 98.5%
(95% CI: 96.6-99.5%)

BinaxNOW COVID-19 Ag Card Home Test. HCP Instructions for Use.

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