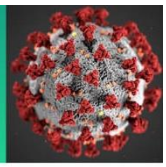
COVID-19 Science Update



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Intended for use by public health professionals responding to the COVID-19 pandemic.

***** Available on-line at https://www.cdc.gov/library/covid19 *****

*****This week and next week the CDC COVID-19 Science Update will only be produced on Tuesday, 11/17 and Tuesday, 11/24. The CDC COVID-19 Science Update will not be produced on Friday, 11/20, or Friday, 11/27.*****

COVID-19 and Return to College

The increase in COVID-19 cases among younger persons points to a need to implement effective mitigation strategies to protect college students returning to campus, as well as the neighboring communities. Six out of 10 colleges and universities re-opened in the fall with in-person classes, either full-time or combined with online classes. Safely bringing students and faculty back to campus will require testing and mitigation measures to prevent SARS-CoV-2 transmission. Optimal testing strategies for in-person classes and variables associated with likelihood of holding in-person classes at colleges and universities are discussed in the following papers.

PEER-REVIEWED

A. Evaluation of COVID-19 testing strategies for repopulating college and university campuses: A decision tree analysis. Van Pelt *et al.* Journal of Adolescent Health (November 3, 2020).

Key findings:

- Strategies that included RT-PCR testing of in-coming students identified more cases than symptom-based screening alone; however, all strategies failed to detect a portion of the cases.
    - Using only symptom-based screening, less than 50% of true positive cases will be detected.
    - Testing all students on arrival, and again 7 days later, will detect the greatest number of cases.
- At higher prevalence of infection, repeat testing will detect more true positives per test, but will cost more.

Methods: A decision tree analysis was used to evaluate testing strategies for safely repopulating a university with 20,000 students. The analysis evaluated five strategies: (1) classifying students with symptoms as having COVID-19 (no testing); 2) testing done on symptomatic students, (3) testing all students, (4) testing all students and retesting *symptomatic* students with a negative first test, and (5) testing all students and retesting *all* students with a negative first test. Costs estimates for given strategies were estimated. *Limitations:* Disease prevalence was based on national estimates; no analyses of testing strategies later in the semester.

PREPRINTS (NOT PEER-REVIEWED)

B. Causal impacts of teaching modality on U.S. COVID-19 spread in fall 2020 semester. Badruddoza & Amin medRxiv (November 3, 2020).

Key findings:

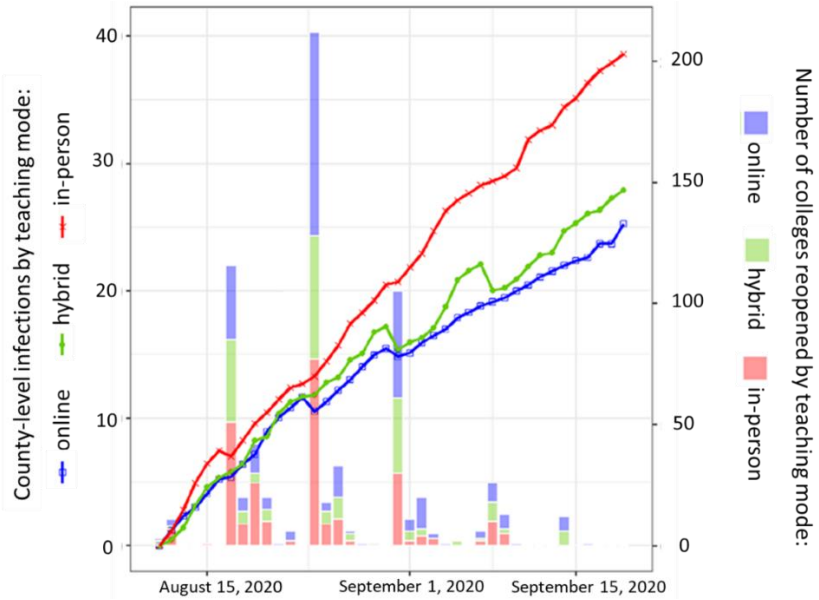
- Reopening colleges was associated with increased COVID-19 cases and deaths.
- Colleges with in-person classes are in counties with rapidly increasing COVID-19 cases (Figure).

- Daily new COVID-19 cases increased in the fall 2020 semester by 1.87 cases per 100,000 population.

- The variables most strongly associated ($p < 0.05$) with adopting online teaching modes vs in-person enrollment were higher student enrollments, larger endowments per student, being a public (vs private) institution, individual mask policies, and prevalence of specific political party affiliation in the community.
- There was a negative association between the percentage of county residents staying home and disease spread.

Methods: Use of metrics of new daily COVID-19 cases and COVID-19-related deaths in the county to describe the effects of college teaching modality on spread of disease for 745 US institutions and surrounding communities. The probability of choosing each teaching mode was calculated with multinomial logistic regression. *Limitations:* Student-specific infections are not addressed; method for classifying counties with multiple colleges with different teaching modes not explained.

Figure:



Note: From Badruddoza *et al*. County-level growth of COVID-19 cases in counties by teaching modality for in-person, online, or hybrid classes. Opening date for colleges by teaching modality shown in bars from August 10 to September 19, 2020. Licensed under CC-BY-ND 4.0.

Implications for 2 studies (Van Pelt *et al*. and Badurddoza & Amin) These two articles highlight measures that colleges and universities can use to mitigate COVID-19. As discussed in Walke *et al*., institutional resources, cost of testing, and the possibility of distance learning need to be considered when re-opening schools. These articles show that decisions regarding type of teaching are also influenced by the surrounding communities, such as locally enacted preventative measures and the local political environment. Being aware of these influences may guide administrators in decision-making regarding re-opening campuses.

Immunity

Antibodies to SARS-CoV-2, particularly neutralizing antibodies, appear to wane over time. Long-term protection against SARS-CoV-2 may rely on the maintenance of memory immune cells that quickly re-activate upon secondary infection, primarily B cells that produce antibodies and T cells that help B cells and kill virus-infected cells. The duration of SARS-CoV-2-specific cell-mediated immunity – i.e. immunity not mediated by antibody – is not well understood. Following are two recent pre-print studies examining the longevity of memory B and T cell responses against SARS-CoV-2.

PREPRINTS (NOT PEER-REVIEWED)

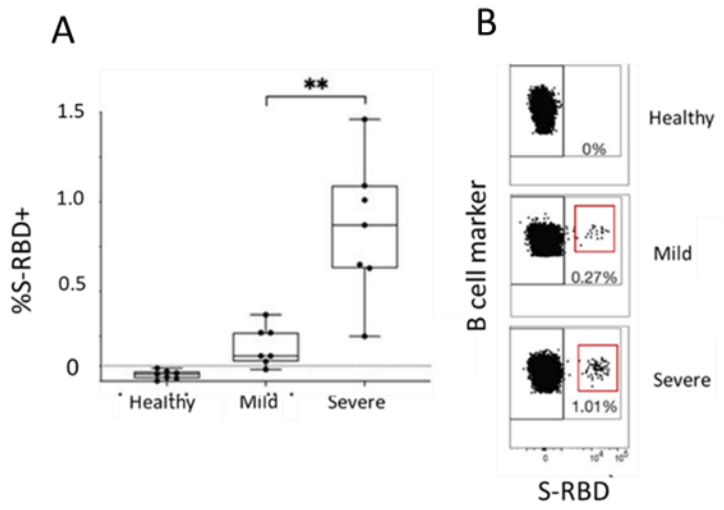
A. Durable SARS-CoV-2 B cell immunity after mild or severe disease**.** Ogega *et al.* MedRxiv (October 30, 2020).

Key findings:

- B cells recognizing SARS-CoV-2 spike protein receptor binding domain (S-RBD) were detected in 13 of 14 participants with COVID-19 (Figure, A).
    - Four (57%) of seven patients with mild COVID-19 had S-RBD-specific immature B cells and antibody-secreting cells (ASC) and six (86%) had detectable memory B cells (MBC).
    - 100% of moderate-to-severe COVID-19 patients had S-RBD-specific B cells of all types (immature, ASC, and MBC).
- The frequency of S-RBD specific MBC was significantly higher in patients with moderate-to-severe COVID-19 compared with mild COVID-19 (mean S-RBD+ frequency 0.85% vs. 0.20%, p = 0.004) (Figure, B).
    - The single individual with SARS-CoV-2 infection but without detectable S-RBD-specific MBC was asymptomatic.

Methods: S-RBD-specific B cells from seven ambulatory patients with mild COVID-19 and seven hospitalized patients with moderate-to-severe COVID-19, and cryopreserved cells from healthy blood donors collected prior to the COVID-19 pandemic were evaluated. *Limitations*: Maximum time from symptom onset to B cell sampling was 104 days (median 54 days); small sample size.

Figure:



Note: Adapted from Ogega *et al*. The percent of S-RBD-specific memory B cells from healthy participants, participants with mild-COVID-19, or participants with severe COVID-19. A. Box and whiskers plots show summary of participants (whiskers are minimum to maximum). B. dot plot shows representative data from each group, with **the population of B cells binding to S-RBD highlighted in the box**. ** Indicates p ≤0.01. Licensed under CC-BY-ND 4.0.

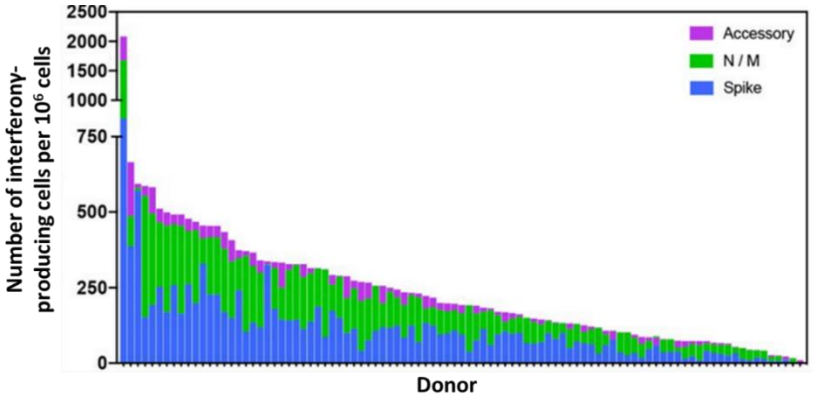
B. Robust SARS-CoV-2-specific T cell immunity is maintained at 6 months following primary infection. Zuo *et al.* BioRxiv (November 2, 2020).

Key findings:

- Evidence of SARS-CoV-2-specific T cell responses was found in all donors at 6 months (Figure).
- Median T cell responses were 50% higher in donors who had symptomatic infection compared with asymptomatic infection.
- T cell responses at six months correlated with peak antibody levels against the SARS-CoV-2 nucleoprotein, receptor binding domain (RBD), and spike proteins.

Methods: Blood samples from 100 convalescent plasma donors were analyzed to characterize the cellular immune response measured by production of interferon-γ six months after SARS-CoV-2 infection, and to measure peak antibody levels against SARS-CoV-2 nucleoprotein, RBD, and spike proteins. *Limitations*: No assessment of immune responses beyond six months.

Figure:



Note: Adapted from Zuo *et al*. Cellular response against SARS-CoV-2 proteins (**spike**, **nucleoprotein/membrane proteins [N/M],** and a **pool of other SARS-CoV-2 peptides [accessory]**) at six months following primary infection. Licensed under CC-BY-ND 4.0.

Implications for 2 studies (Ogega *et al.* & Zuo *et al.*): Memory B and T cells could provide durable immunity to SARS-CoV-2 even after serum antibodies decline, particularly in symptomatic individuals. A commentary from Wise, J. highlights that durable T cell responses against a range of SARS-CoV-2 proteins might point to potential new vaccine targets.

Epidemiology

PEER-REVIEWED

Transmission of SARS-CoV-2 on mink farms between humans and mink and back to humans. Munnink *et al.* Science (November 10, 2020).

Key findings:

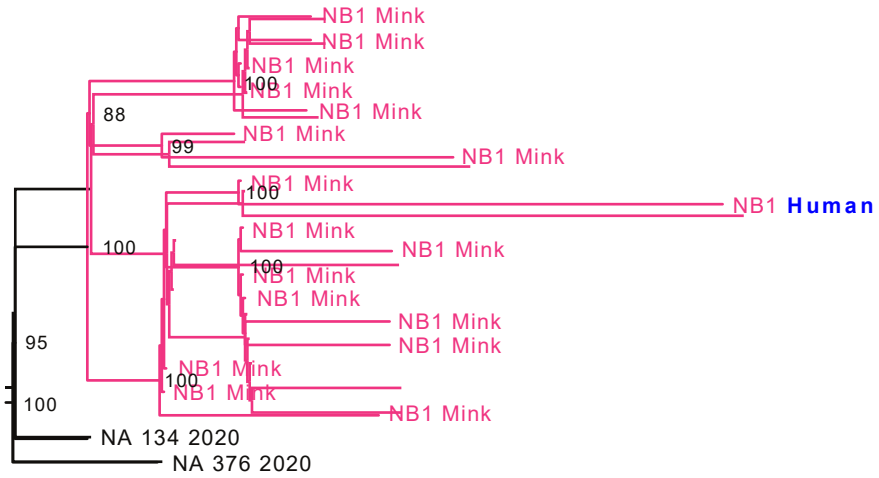
- Of 97 mink farm employees tested, 43/88 (49%) were positive by RT-PCR, 38/75 (51%) had detectable antibodies, and 66/97 (67%) had evidence of SARS-CoV-2 infection by RT-PCR or serology.
- The mink and human strains clustered closely together (Figure).
    - There was greater phylogenetic relatedness between farm-related human and mink cases than between farm-related human and community cases within the same postal code.

- Potential mink-to-human transmitted SARS-CoV-2 infections did not have differences in signs, duration, or severity compared with human-to-human transmitted infections.

Methods: Outbreak investigations were performed when respiratory signs and increased mortality for minks were reported to the Dutch Agriculture authorities. Investigations at 16 mink farms sought to identify the source of the outbreak, trace contacts and track movement of animals, vehicles, and people. SARS-CoV-2 diagnostic testing for mink and human samples was performed using RT-PCR and by antibody testing. Viral genomes were sequenced for PCR-positive samples with Ct values ≤32. *Limitations*: The investigation could not exclude the role that exposures from untested animals or humans might have played in transmission; temporary farm workers not tested.

Implications: SARS-CoV-2 outbreaks in mink farms are well-documented and resulted in recently-abandoned plans to cull Denmark's 17 million minks. This paper provides phylogenetic data suggestive of mink-to-human SARS-CoV-2 transmission; however, directionality of transmission is challenging to definitively demonstrate using phylogenetics. Concerns about potential mutations in SARS-CoV-2 from animal-to-human transmission that may lead to more rapid spread or jeopardize vaccine efficacy may be premature.

Figure:



Note: Adapted from Munnink *et al*. Phylogenetic tree of **mink** and **human** sequences found in a single farm (NB1) and the closest matching human sequences from the **national SARS-CoV-2 database** (NA 134 2020, and NA 376 2020). Numbers in black represent the bootstrapping values using all Dutch SARS-CoV-2 sequences. From Munnink et al., Transmission of SARS-CoV-2 on mink farms between humans and mink and back to humans, Science. Reprinted with permission from AAAS.

Repeated cross-sectional sero-monitoring of SARS-CoV-2 in New York City. Stadlbauer *et al.* Nature (November 3, 2020).

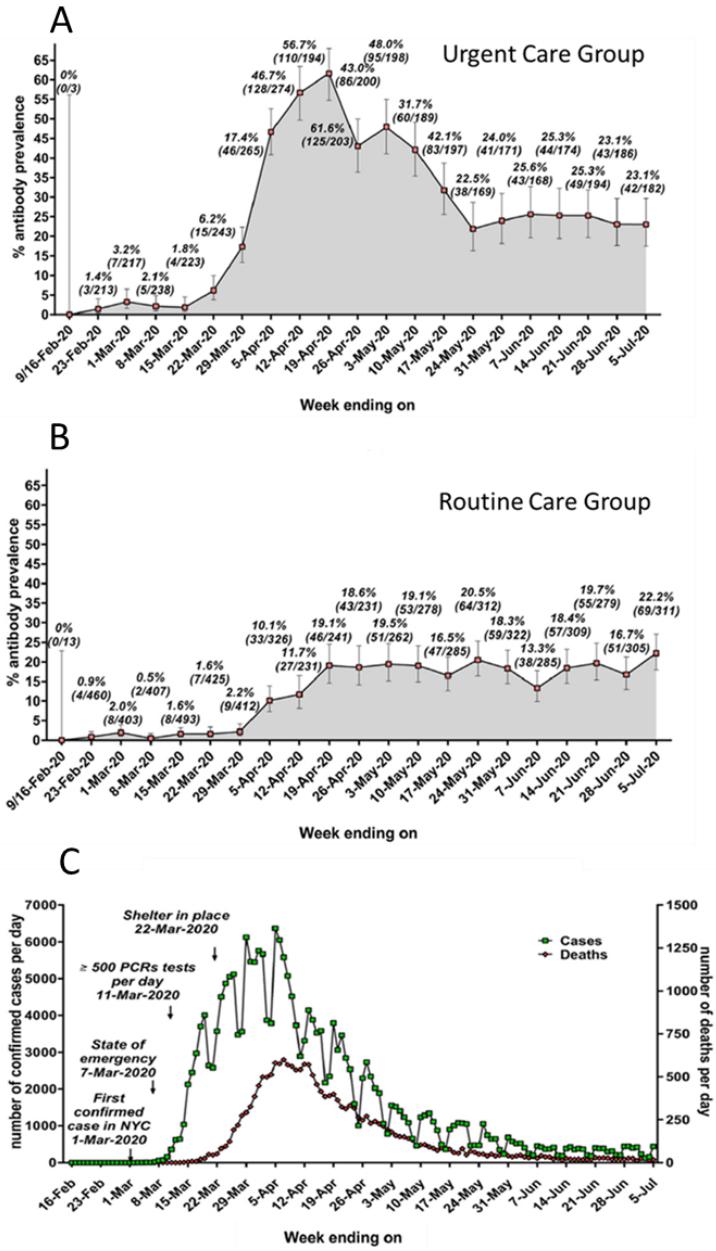
Key findings:

- A rapid rise in SARS-CoV-2 seroprevalence (6.2%) was detected in the urgent care (UC) group (Figure, A) compared with the routine care (RC) group, coinciding with the surge of new confirmed SARS-CoV-2 infections and related hospitalizations in New York City.
    - The uptick in seropositivity lagged approximately 1–2 weeks behind the increase in new cases (Figure A, C).
- There was a longer delay between the increase in confirmed cases and the increase in seroprevalence in the RC group (Figure B, C).
- Seroprevalence in the UC group declined to levels seen in the RC group coinciding with a drop in incidence of SARS-CoV-2 cases between May and July 2020 (Figures A, C).

Methods: Weekly cross-sectional analysis of anti-SARS-CoV-2 spike antibodies on 10,691 plasma samples randomly collected from patients at Mount Sinai Hospital in New York City from February 9 to July 5, 2020. Seroprevalence was compared between an UC group (meant to capture seropositive individuals) and a RC group (meant to capture visits unrelated to COVID-19 and resemble the general population). *Limitations*: Non-random, non-representative sampling.

Implications: This will be the first of a series of repeated cross-sectional seroprevalence studies to understand the dynamics of SARS-CoV-2 transmission, seroconversion, and the stability of antibody responses over the course of a COVID-19 outbreak.

Figure:



Note: Adapted from Stadlbauer *et al*. Serum antibody prevalence in the UC group **(A)** and in the RC group **(B)**, and **number of confirmed cases/day** and **number of deaths per day,** February–July 2020 **(C)**. Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer [Nature] Repeated cross-sectional sero-monitoring of SARS-CoV-2 in New York City, Stadlbauer *et al*. COPYRIGHT 2020 (https://www.nature.com/articles/s41586-020-2912-6).

Outcomes of contact tracing in San Francisco, California—test and trace during shelter-in-place. Sachdev *et al.* JAMA Internal Medicine (November 2, 2020).

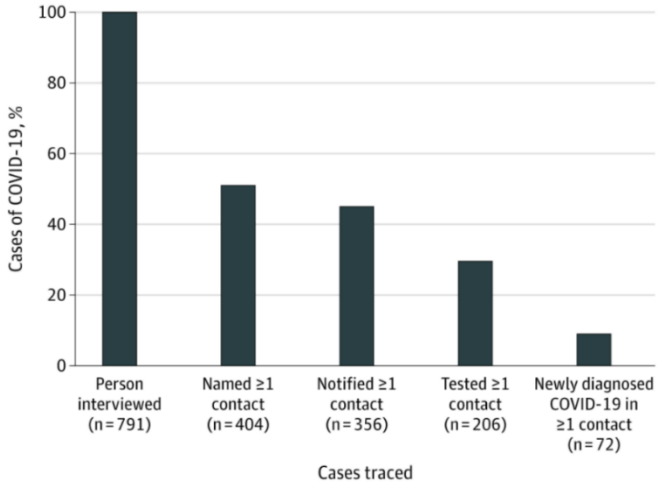
Key findings:

- COVID-19 contact tracing program reached more than 85.4% of cases (Figure) and 83.8% of contacts.
- The secondary attack rate was higher among household compared with non-household contacts (111 of 983 [11.3%] and 9 of 231 [3.9%], respectively; p <0.001).
- Median time from symptom onset for a case to notifying and testing the contact was 6 days.
    - The median time from symptom onset to receipt of test results was 5 days.
    - Case interviews occurred on average 1 day after the test result and the first contact was notified on average 1 day after that.

Methods: Case investigation and contact tracing for 1,394 COVID-19 cases identified in San Francisco, California between April 13 and June 8, 2020. The study period included dates after which universal testing for COVID-19 contacts, regardless of symptoms, was recommended. The proportion of people who were interviewed and for whom close contacts were identified, with at least 1 contact being notified, was calculated. Median number of days (with IQR) taken to process each step was reported. *Limitations*: Underreporting of close contacts.

Implications: In order to maximize the impact of contact tracing on mitigating the spread of COVID-19, metrics such as these are needed, and efforts must be made to address testing delays and to improve contact identification.

Figure:



Note: Adapted from Sachdev *et al*. Percentages for people with COVID-19 at selected stages of contact tracing implementation. Reproduced with permission from JAMA Internal Medicine. Sachdev *et al.*, Outcomes of contact tracing in San Francisco, California—test and trace during shelter-in-place. DOI:10.1001/jamainternmed.2020.5670.

Proportion of asymptomatic infection among COVID-19 positive persons and their transmission potential: A systematic review and meta-analysis. Yanes-Lane *et al.* PLOS One (November 7, 2020).

Key findings:

- 24 studies report that the proportion of asymptomatic individuals among individuals testing positive for SARS-CoV-2 ranged from:
    - 20%–75% for the general population.
    - 8.2%–50% for contacts of known cases.
    - 45%–100% of obstetric patients presenting to hospitals.

  - 42%–66.7% of nursing home residents; 0%–50% of nursing home staff.
  - 50%–87.8% in congregate settings such as temporary homeless shelter.
  - 76.2% of retail workers (single study).
- 18.8% (18/96) of contacts of asymptomatic index patients were SARS-CoV-2 positive in pooled analysis of 5 transmission studies.

Methods: Review of 28 moderate or high-quality studies systematically testing for COVID-19 through June 22, 2020, assessing the proportion of infections occurring in asymptomatic individuals and transmission. *Limitations*: Included mainly small studies of people with COVID-19 (n <100), limiting estimate precision; contact tracing in studies was limited which may bias the results; study heterogeneity limited ability to analyze by age group or sex.

Implications: The proportion of asymptomatic infections appears high in many groups. As asymptomatic individuals may have considerable transmission potential, symptom-based testing is insufficient to eliminate transmission. High quality studies in representative general population samples are needed to better understand the role of asymptomatic individuals in the transmission of SARS-CoV-2.

Diagnostics

Antigen (Ag) tests may provide an easier point-of-care alternative to RT-PCR testing to detect infected individuals by detecting SARS-CoV-2 proteins rather than RNA. The Abbott BinaxNOW™ COVID-19 Ag Card (Binax-CoV2) is a 15-minute test that recently received an emergency use authorization by the US Food and Drug Administration for testing symptomatic individuals for SARS-CoV-2 infection. The US Department of Health and Human Services has ordered 150 million Binax-CoV2 rapid antigen tests, many of which are targeted for high-risk settings.

PREPRINTS (NOT PEER-REVIEWED)

Performance characteristics of a rapid SARS-CoV-2 antigen detection assay at a public plaza testing site in San Francisco. Pilarowski *et al.* MedRxiv (posted November 12, 2020).

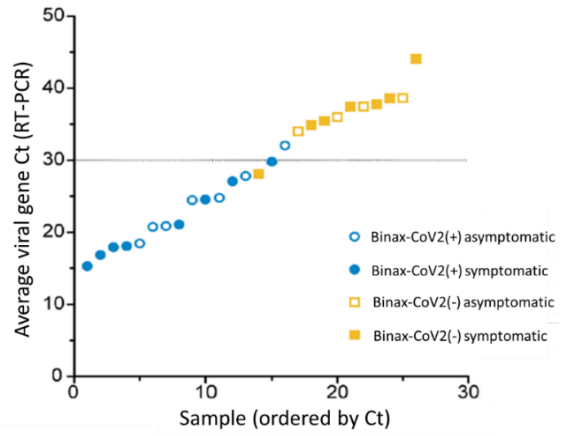
Key findings:

- Criteria for a positive test for the Binax-CoV2 rapid Ag test had to be adjusted when used to screen asymptomatic individuals.
  - When using the manufacturer's recommendation to read any line as "positive," 9 (64%) of 14 Binax-CoV2-positive tests were likely false positives.
- Performance in asymptomatic subjects improved when a positive result was defined as a band extending the full width of the testing strip, regardless of intensity.
  - Sensitivity was 93.8% (95% CI 68.1%-99.8%, n = 16) and specificity was 100%, (95% CI 99.6%-100%, n = 855).
- Samples with false negative Binax-CoV2 tests had low viral loads (high Ct values) (Figure).

Methods: In September 2020, 878 people participated in testing in San Francisco, CA. Binax-CoV2 cards were read by 2 independent observers with a third on hand to be a "tie-breaker." Lab confirmation was done via RT-PCR testing. *Limitations*: The Binax-CoV2 Ag test currently is validated on symptomatic COVID-19 patients, full validation on asymptomatic individuals has not been done.

Implications: Since the Binax-CoV2 rapid test may be used to screen asymptomatic individuals, the data shown here will be critical in establishing guidance for validating this use case. Manabe *et al.* outline the need for screening tests that can rapidly identify infectious individuals to prevent outbreaks.

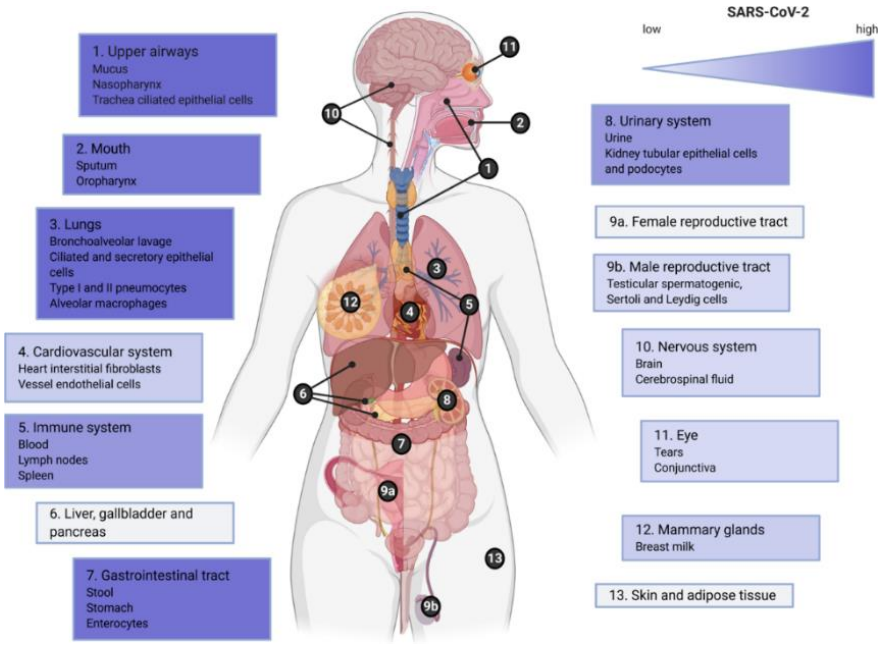
Figure:



Note: Adapted from Pilarowski *et al*. Average Ct from all 26 RT-PCR-positive participants for **Binax-CoV2(+)** and **Binax-CoV2(-)** participants with and without symptoms. Licensed under CC-BY-NC-ND 4.0.

In Brief

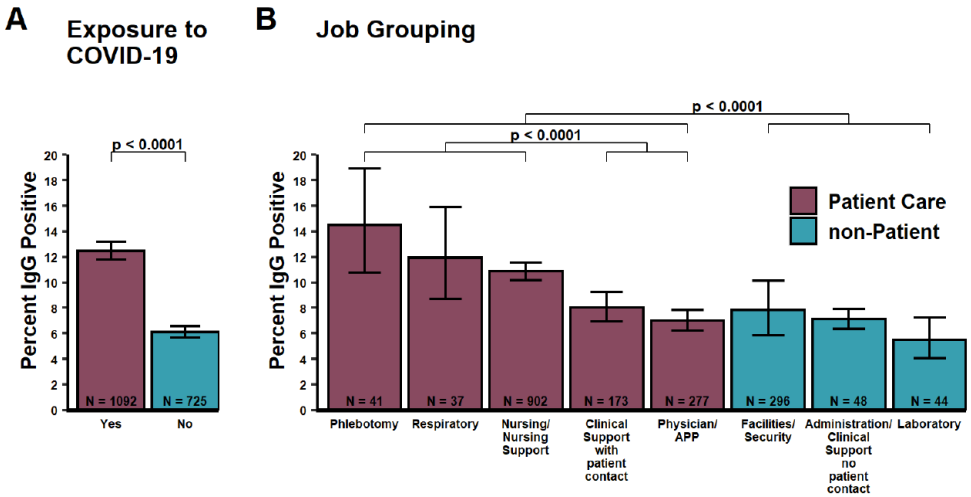
- Trypsteen *et al.* **On the whereabouts of SARS-CoV-2 in the human body: A systematic review.** Plos Pathogens. A review of 186 studies demonstrating the presence of SARS-CoV-2 in organs and tissues throughout the body.



Note: From Trypsteen *et al*. Overview of body systems where SARS-CoV-2 has been found, with darker shading indicating the strength of the evidence for the virus in that system. Licensed under CC-BY 4.0.

- Hippich *et al.* **Public health antibody screening indicates a 6-fold higher SARS-CoV-2 exposure rate than reported cases in children**. Med. This serosurvey added SARS-CoV-2 antibody testing to a diabetes screening program of 15,771 persons 1–18 years old and saw six-fold higher seroprevalence than reported cases.

- Qian *et al.* **Indoor transmission of SARS-CoV-2.** Indoor Air. Investigation from China of 318 outbreaks with ≥3 cases from January 4 to February 11, 2020, showed no outbreaks attributed to outdoor settings and only 1.6% with ≥10 cases.
- Prasitlumkum *et al.* **Incidence of myocardial injury in COVID-19-infected patients: A systematic review and meta-analysis.** Diseases. A review of 27 studies found that COVID-19-related myocardial injury ranges from 16.1%–23.8%.
- Anderson *et al.* **Challenges in creating herd immunity to SARS-CoV-2 infection by mass vaccination.** Lancet. The possible outcomes of the 45 candidate COVID-19 vaccines currently in clinical trials are discussed in the context of distribution and long-term immunity.
- Anderson *et al.* **SARS-CoV-2 antibody responses in children with MIS-C and mild and severe COVID-19.** MedRxiv. Pediatric patients with multisystem inflammatory syndrome in children (MIS-C) had higher antibody titers against SARS-CoV-2 spike IgG compared to those with severe COVID-19.
- Jay *et al.* **Neighbourhood income and physical distancing during the COVID-19 pandemic in the United States.** Nature Human Behavior. Data from a large national sample of smartphone users showed that lower-income neighborhoods practiced less physical distancing compared with higher-income neighborhoods, likely because residents of lower-income neighborhoods are more likely to work outside the home.
- Hazeldine & Lord. **Immunesenescence: A predisposing risk factor for the development of COVID-19?** Frontiers in Immunology. This article discusses the possibility that the gradual deterioration of the immune system brought on by age, could be a generic contributory factor to the development of severe COVID-19.
- Shi *et al.* **Challenges of drug development during the COVID-19 pandemic: Key considerations for clinical trial designs.** British Journal of Clinical Pharmacology. Translational science principles and strategies for conducting clinical trials in a pandemic and evaluation of trials of drug candidates, particularly repurposed drugs are reviewed.
- Milne *et al.* **Airplane boarding methods that reduce risk from COVID-19.** Safety Science. A number of methods for airplane boarding to minimize both risk and boarding times are evaluated, with videos demonstrating the process.
- Sims *et al.* **COVID-19 seropositivity and asymptomatic rates in healthcare workers are associated with job function and masking**. Clinical Infectious Diseases. Direct contact with COVID-19 patients increased the likelihood of seropositivity among employees of a Michigan healthcare system, but study participants who wore a mask during exposures were less likely to be seropositive.



Note: Adapted from Sims *et al.* **A:** Seropositivity to SARS-CoV-2 in healthcare workers **with COVID-19 patient exposure** or **without COVID-19 patient exposure**. **B:** Seropositivity to SARS-CoV-2 in healthcare workers based on job type with **patient care** or **non-patient care**. Reproduced by permission of Oxford University Press on behalf of the Infectious Diseases Society of America. Please visit: https://doi.org/10.1093/cid/ciaa1684.

- Padmanabhan *et al.* **Phase II clinical trial for evaluation of BCG as potential therapy for COVID-19**. MedRxiv. Randomized controlled trial of Bacille Calmette-Guérin (BCG) plus standard of care vs standard of care in 60 COVID-19 patients showed significant improvement in the primary outcome of the ratio of oxygen saturation to fraction of inspired oxygen, an independent indicator of acute respiratory distress syndrome with BCG.
- Rink *et al.* **Competitive sports, the coronavirus disease 2019 pandemic, and Big Ten athletics**. Circulation: Cardiovascular Quality and Outcomes. Perspective from the Big Ten Cardiac Registry Steering Committee reflecting on the reasoning behind the decisions to delay and restart the Big Ten College Football season.