TGIF – today is a regular edition as we head into the weekend. I am awaiting the release from the CDC today of the studies that led to changing guidance on mask mandates. Information from internal documents state the Delta variant is more transmissible than the viruses that cause MERS, SARS, Ebola, the common cold, the seasonal flu, and smallpox, and it is as contagious as chickenpox. Still, the CDC's figures show that the vaccines are highly effective in preventing serious illness, hospitalization, and death in vaccinated people. The COVID-19 Briefing will track the results of studies to be released today and will share with this audience.

In today's Briefing under COVID-19 News I start with the McKinsey report on impact of school shutdowns last year. Next the CDC change in testing exposed vaccinated people. Last the Israel decision to offer booster doses to immunocompromised and older people.

Under Journal Review first study found that antibody levels remain high for at least 9 months after an infection with SARS-CoV-2, no matter if the individual was symptomatic or asymptomatic. The next study reports on breakthrough infection in vaccinated HCW. This was pre-Delta. Next a study on seroprevalence of SARS-CoV-2 infections in HCWs. Last a study on the use of canakinumab in COVID-19 patients with severe disease but not requiring MV.

Stay calm and relax this weekend

Ed

COVID-19 News

McKinsey Study School Shutdowns
The consulting firm examined spring 2021 test results for 1.6 million students in grades 1 through 6 across the U.S., then compared their performance with that of similar students pre-pandemic. They discovered that the pandemic-era children were, on average, about four months behind in reading and five months behind in math. McKinsey found that children in majority black schools ended the school year a full six months behind in math and reading on average. Students in schools where the average household income was below $25,000 were seven months behind in math and six months in reading. "Students who move on to the next grade unprepared are missing key building blocks of knowledge that are necessary for success," and "students who repeat a year are much less likely to complete high school and attend college."

Comment: This is a sobering report, but not a surprise. Well-to-do families were able to pay for tutors, high speed internet, and/or private school, but our most vulnerable children did not have that option. Many schools will be starting in the next 3 weeks. With the rise on Covid-19 cases and the controversy around universal masking will we see a repeat of last year and experience more disruption to their education? This report did not discuss the emotional toll the pandemic has had on our children. Let us hope we all come together and make sure our children get the education and support they deserve.

CDC Calls for Fully Vaccinated Individuals to be Tested for COVID-19 Following Exposure Even if Asymptomatic
July 27, 2021
CDC quietly updated its testing recommendations for people who are fully vaccinated. The agency now recommends fully vaccinated individuals be tested for SARS-CoV-2 (3-5 days) if they come into contact

with someone with COVID-19, even if they have no symptoms. Previously, the CDC had said that fully vaccinated people did not need to be tested after exposure to the virus unless they were experiencing symptoms except in healthcare. In addition, exposed fully vaccinated individuals should wear masks for 14 days, but do not need to quarantine.

Israel to Offer Covid-19 Booster Shots to Elderly
WSJ July 30, 2021
Israel authorized the use of a booster shot of Pfizer Inc.'s Covid-19 vaccine for people aged 60 and over starting Sunday, after early data in the country suggested vaccine protection against severe illness has waned. Healthcare providers said Thursday a third dose would be offered to those in that age group at least five months after their second shot. Data in Israel showed the vaccine's ability to prevent severe illness in this age group had dropped to 81% in July from 97% in April.

A recent study from the U.K. published in the N Engl J Med [reviewed in the Briefing July 23, 2021] found the Pfizer vaccine was 88% effective at protecting against symptomatic disease from April 5 to May 16 but didn't stratify by age groups.

Comment: Israel and France have authorized booster shots for immunocompromised patients. But physicians and immunologists in the U.S. say there isn't a clear answer yet on whether they are needed for the general population. ACIP did meet to review on July 22nd. [reviewed in the Briefing July 27th] Some members did express support for booster dose in immunocompromised people. My guess is the US will move to offer a booster to the immunocompromised and the older individuals first. This will require the FDA to revise the EUA.

Journal Review

SARS-CoV-2 Antibody Dynamics and Transmission from Community-Wide Serological Testing in the Italian Municipality of Vo
Nature Comm published online July 19, 2021
doi.org/10.1038/s41467-021-24622-7
In February and March 2020, two mass swab testing campaigns were conducted in Vo', Italy. In May 2020, they tested 86% of the Vo' population with three immuno-assays detecting antibodies against the spike and nucleocapsid antigens, a neutralization assay and PCR. They used three distinct immunological assays detecting antibodies against the S and N antigen. Subjects testing positive to PCR in February/March or a serological assay in May were tested again in November.

Table 1 Commercial assays employed in the study to identify IgG anti-SARS-CoV-2.

Test	Manufacturer	Recognised antigen	Method	Manufacturers' thresholds
LIAISON® SARS-CoV-2 S1/S2 IgG	DiaSorin	S1/S2	CLIA[a]	Negative: <12.0 AU/mL Equivocal: 12.0 ≤ x < 15.0 AU/mL Positive: ≥15.0 AU/mL
Elecsys® Anti-SARS-CoV-2	Roche	N	ECLIA[b]	Positive: <1.0 Negative: ≥1.0
ARCHITECT® SARS-CoV-2 IgG	Abbott	N	CMIA[c]	Negative: <1.4 Positive: ≥1.4

[a]Chemiluminescence immunoassay.
[b]Electro-chemiluminescence immunoassay.
[c]Chemiluminescent microparticle immunoassay.

They estimate a seroprevalence of 3.5% (95% Credible Interval (CrI): 2.8–4.3%) in May. In November, 98.8% (95% Confidence Interval (CI): 93.7–100.0%) of sera which tested positive in May still reacted against at least one antigen; 18.6% (95% CI: 11.0–28.5%) showed an increase of antibody or neutralization reactivity from May. They also saw some cases of antibody levels increasing, which could suggest potential re-infections which boosted the immune system. They found no evidence that antibody levels between symptomatic and asymptomatic infections differ significantly, suggesting that the strength of the immune response does not depend on the symptoms and the severity of the infection.

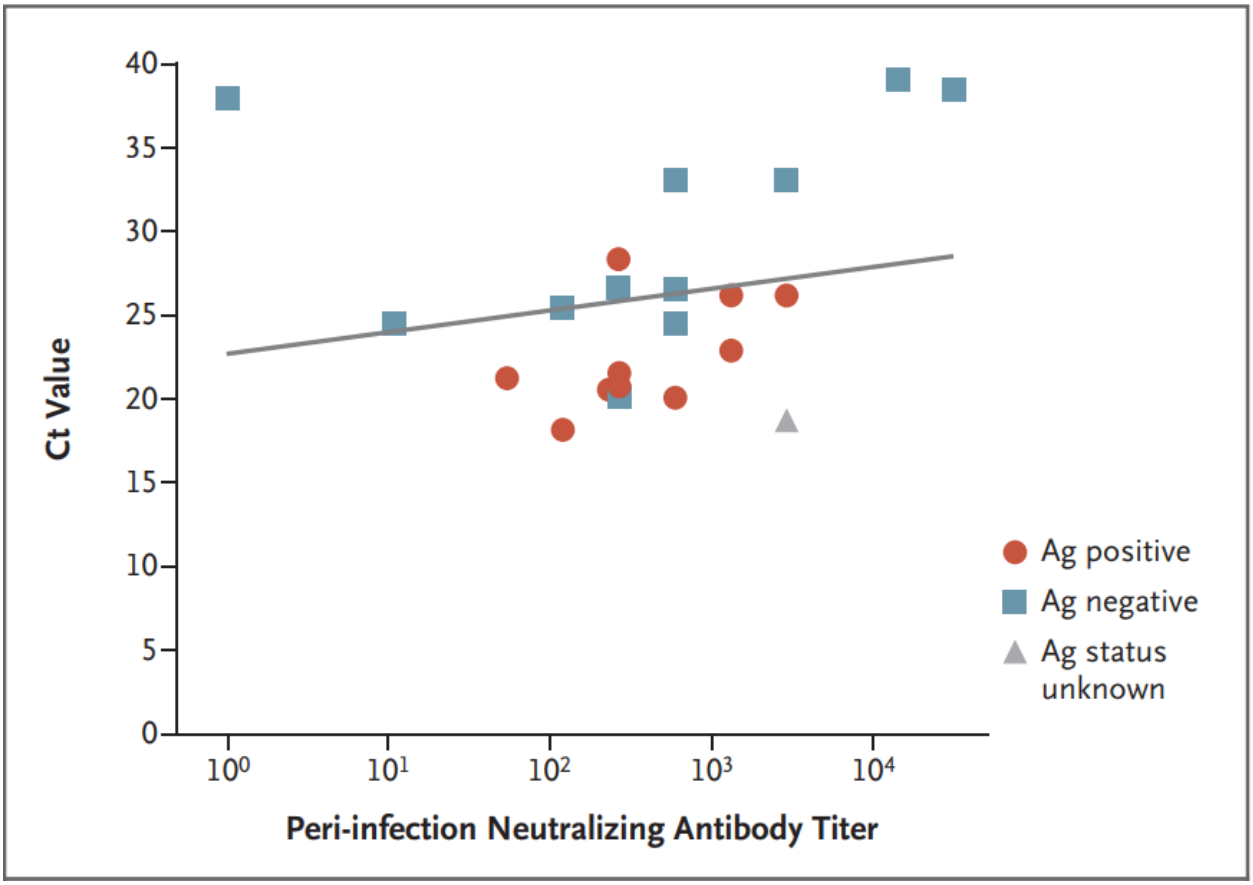
Their analysis confirms substantial differences in antibody persistence by assay, with the Abbott assay showing a marked decline both in antibody titers and seropositivity over a seven-month period. Conversely, the antibodies detected by DiaSorin and Roche appear to remain at high levels for at least nine months. The observed difference in antibody decay between the Abbott and Roche assays, which target the same (N) antigen, is in agreement with previous findings and could be due to partial differences in the employed antigens and to the fact that the range of N epitopes recognized by sera might change with time.

Comment: The investigators found that antibody levels remain high for at least 9 months after an infection with SARS-CoV-2, no matter if the individual was symptomatic or asymptomatic. However, their study does shows that antibody levels vary, sometimes markedly, depending on the test used. This means that caution is needed when comparing estimates of infection levels in a population obtained in different parts of the world with different tests and at different times.

Covid-19 Breakthrough Infections in Vaccinated Health Care Workers
N Engl J Med published online July 28, 2021
DOI: 10.1056/NEJMoa2109072
At the largest medical center in Israel, the investigators identified breakthrough infections by performing extensive evaluations of health care workers who were symptomatic (including mild symptoms) or had known exposure. These evaluations included epidemiologic investigations, repeat RT-PCR assays, antigen-detecting rapid diagnostic testing (Ag-RDT), serologic assays, and genomic sequencing. Correlates of breakthrough infection were assessed in a case-control analysis. We matched patients with breakthrough infection who had antibody titers obtained within a week before SARS-CoV-2 detection (peri-infection period) with four to five uninfected controls and used generalized estimating equations to predict the geometric mean titers among cases and controls and the ratio between the titers in the two groups. We also assessed the correlation between neutralizing antibody titers and N gene cycle threshold (Ct) values with respect to infectivity.

Among 1497 fully vaccinated health care workers for whom PCR data were available, 39 SARS-CoV-2 breakthrough infections were documented. (2.6%) Neutralizing antibody titers in case patients during the peri-infection period were lower than those in matched uninfected controls (case-to-control ratio, 0.361; 95% confidence interval, 0.165 to 0.787). Higher peri-infection neutralizing antibody titers were associated with lower infectivity (higher Ct values). Most breakthrough cases were mild or asymptomatic, although 19% had persistent symptoms (>6 weeks). The most common symptom that was reported was upper respiratory congestion (36%), followed by myalgia (28%) and loss of smell or taste (28%), while fever or rigors were reported in 21%. The Alpha variant was found in 85% of samples tested. A total of 74% of case patients had a high viral load (Ct value, <30) at some point during their infection; however, of these patients, only 17 (59%) had a positive result on concurrent Ag-RDT. No secondary infections were documented. A total of 29 case patients (74%) had a high viral load (Ct value,

<30) at some point during their infection suggesting contagiousness. However, no secondary infections were documented through epidemiologic investigations of data regarding in-hospital contact tracing of the 39 primary infections. This suggests that the infected workers despite high Ct values were less contagious than their unvaccinated peers.



Comment: Overall the investigators found a low rate of breakthrough infection (0.4%). They also found that low titers of neutralizing antibody and S-specific IgG antibody may serve as markers of breakthrough infection. Identifying immune correlates of protection from SARS-CoV-2 is essential to predicting how the expected antibody decay will affect clinical outcomes, if and when a booster dose will be needed, and whether vaccinated persons are protected. This study was pre-Delta. In addition, this cohort represents mostly young and healthy persons, and all breakthrough infections were mild and did not require hospitalization. Thus, they could not determine the correlate of protection from severe infection or infection in vulnerable populations of older persons with coexisting illnesses or persons with immunological issues.

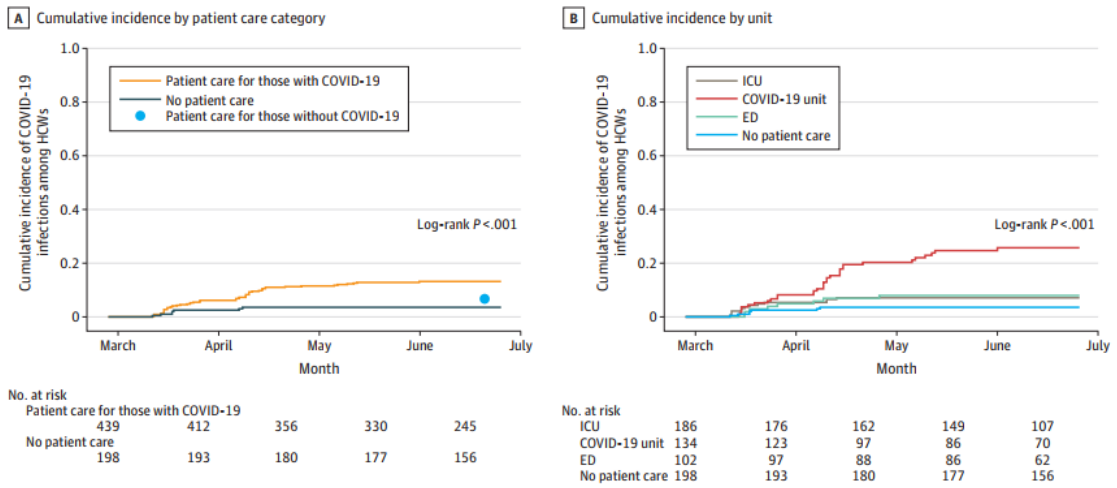
Serologic Surveillance and Phylogenetic Analysis of SARS-CoV-2 Infection Among Hospital Health Care Workers

JAMA Netw Open published online July 28, 2021
doi:10.1001/jamanetworkopen.2021.18554

This cohort study comprised 4 weekly measurements of SARS-CoV-2-specific antibodies and collection of questionnaires from March 23 to June 25, 2020, combined with phylogenetic and epidemiologic transmission analyses at 2 university hospitals in the Netherlands. Included individuals were HCWs

working in patient care for those with COVID-19, HCWs working in patient care for those without COVID-19, and HCWs not working in patient care. Data were analyzed from August through December 2020.

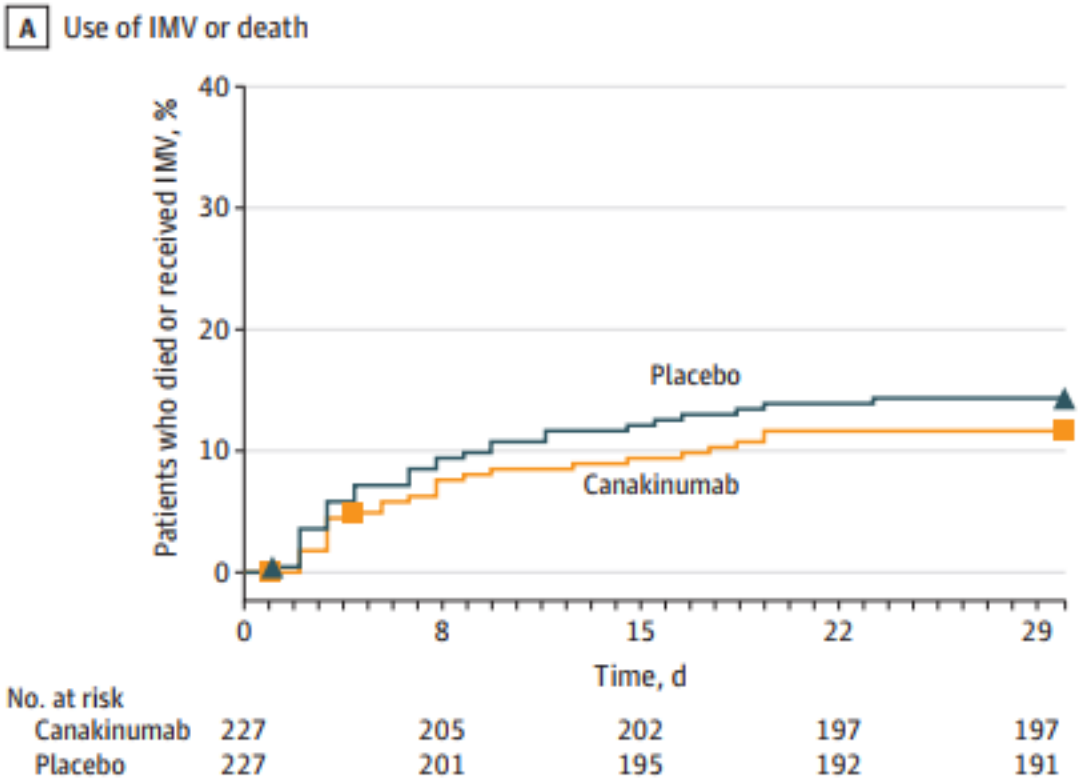
In this cohort study of 801 hospital health care workers (HCWs), the risk of getting infected with SARS-CoV-2 was nearly 4-fold higher among HCWs on COVID-19 wards compared with HCWs not in patient care. Combined phylogenetic and epidemiological analyses found no patient-to-HCW transmission but several occurrences of HCW-to-HCW transmission. Epidemiologic data combined with phylogenetic analyses on COVID-19 wards identified 3 potential HCW-to-HCW transmission clusters. Contact with an individual from the community (including the household) with COVID-19 (HR, 2.60; 95% CI, 1.55-4.35) and contact with a coworker with COVID-19 (HR, 2.02; 95% CI, 1.26-3.24) were associated with increased risk of COVID-19 infection. Among 72 HCWs with SARS-CoV-2 infection, 61 HCWs (84.7%) reported at least 1 symptom suggestive of COVID-19 (i.e., cough, headache, sore throat, fever, dyspnea, chest pain, anosmia, cold, diarrhea) compared with 630 of 729 participants (86.4%) without infection. After adjustment for other symptoms, anosmia was associated with increased risk of infection: 39 of 72 participants who were seropositive (70.8%; 95% CI, 53.4%-81.7%) compared with 14 of 729 participants who were negative (4.5%; 95% CI, 3.0%-6.1%) (adjusted HR, 2.95; 95%, CI 13.71-45.41).



Comment: These findings suggest that infection among HCWs deserves more consideration in infection prevention practice. These results mirror the Mayo Clinic experience early in the pandemic where most HCW infection occurred either in the community or in break rooms. Unfortunately, not all nasopharyngeal samples from patients or HCWs collected for SARS-CoV-2 NAAT were available for viral sequencing analyses because they were not stored, or the admitted patients were diagnosed elsewhere. Therefore, there may be missing clusters or missing links in the transmission clusters. Lastly, no systematic data on compliance to infection prevention measures were collected, limiting more precise conclusions.

Effect of Canakinumab vs Placebo on Survival Without Invasive Mechanical Ventilation in Patients Hospitalized with Severe COVID-19 A Randomized Clinical Trial
JAMA 2021;326:230-239
doi:10.1001/jama.2021.9508
Canakinumab is an anti-interleukin-1β antibody. This study evaluated the efficacy of canakinumab in patients hospitalized with severe COVID-19. This was a randomized, double-blind, placebo-controlled phase 3 trial conducted at 39 hospitals in Europe and the United States. A total of 454 hospitalized

patients with COVID-19 pneumonia, hypoxia (not requiring invasive mechanical ventilation [IMV]), and systemic hyperinflammation defined by increased blood concentrations of C-reactive protein or ferritin were enrolled between April 30 and August 17, 2020, with the last assessment of the primary end point on September 22, 2020. Inclusion criteria included a diagnosis of infection with SARS-CoV-2 within 7 days prior to randomization, diagnosis of pneumonia with pulmonary infiltrates on chest x-ray or computed tomographic scan within 5 days prior to randomization. The primary outcome was survival without IMV from day 3 to day 29. Secondary outcomes were COVID-19-related mortality, measurements of biomarkers of systemic hyperinflammation, and safety evaluations. Between days 3 and 29, 198 of 223 patients (88.8%) survived without requiring IMV in the canakinumab group and 191 of 223 (85.7%) in the placebo group, with a rate difference of 3.1% (95% CI, -3.1% to 9.3%) and an odds ratio of 1.39 (95% CI, 0.76 to 2.54; *P* = .29). COVID-19-related mortality occurred in 11 of 223 patients (4.9%) in the canakinumab group vs 16 of 222 (7.2%) in the placebo group, with a rate difference of -2.3% (95% CI, -6.7% to 2.2%) and an odds ratio of 0.67 (95% CI, 0.30 to 1.50). Serious adverse events were observed in 36 of 225 patients (16%) treated with canakinumab vs 46 of 223 (20.6%) who received placebo.



Comment: Unlike the study published in December 2020 in IJID which did show potential benefit, in this study of patients hospitalized with severe COVID-19, treatment with canakinumab, compared with placebo, did not significantly increase the likelihood of survival without IMV at day 29. Only 41% of canakinumab received dexamethasone and only 32% of placebo received dexamethasone. The study was based on the premise that IL-1 inhibition had previously been shown to inhibit inflammatory response in patients with systemic hyperinflammation and cytokine storm in conditions such as macrophage activation syndrome, possibly due to the inhibition of downstream mediators, including IL-6. It was, therefore, hypothesized that IL-1 inhibition would decrease the release of cytokines in patients

with severe COVID-19 pneumonia. The data on tocilizumab indicated that an anti-inflammatory given within 24-48 hours in individuals with progressive disease and high CRP can improve outcomes. The key seems to be early and combined with dexamethasone.