Good morning. I hope your week is going well.

Today I start with vaccine news starting with a comment about the role of vaccinations in public health. I report on a revision on use of tocilizumab from IDSA.

Under journal review I start with the single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AstraZeneca). The next article reminds us on the role of ASP in managing patients with severe COVID-19. We must get back to basics! The last article looks at sequalae of COVID-19 after 6 months.

Have a wonderful day

Ed

VII Comment:
The real-world experience in the UK and Israel shows that vaccinations significantly lower hospitalizations and deaths. -repeated below- This gives me cautious optimism that as more people are immunized, we should see continued decline in cases, hospitalizations, and deaths and real community control of COVID-19. To be clear, the vaccines will not mean zero COVID. To put into perspective, based on the Israeli experience only 3.5 per 100,000 vaccinated have required hospitalization with COVID-19. However, during a typical influenza season ~150 per 100,000 people are hospitalized. Yet the seasonal flu does not bring life to a standstill. I am old enough to remember lining up to receive the Salk vaccine which stopped the polio epidemic but did not provide sterilizing immunity. The COVID vaccines are truly remarkable. Like the Salk vaccine in the 1950s, we should remind ourselves the transformative power of vaccines to prevent disease without eliminating infection. The sooner we reduce spread and protect as many people as possible through vaccination the sooner we will be able to relax the NPI.

COVID-19 News

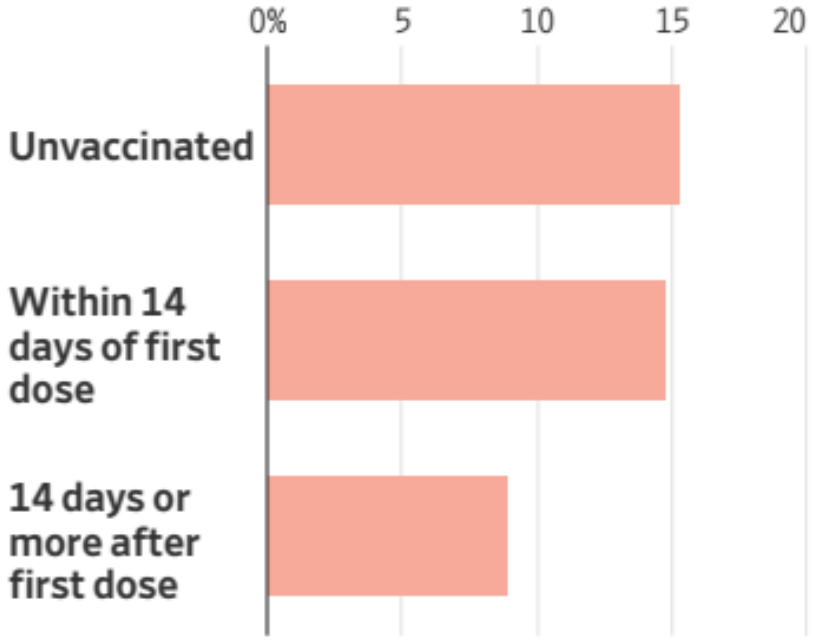
Vaccine News
Two UK studies released Monday showed that COVID-19 vaccination programs are contributing to a sharp drop in hospitalizations, boosting hopes that the shots will work as well in the real world as they have in carefully controlled studies. See below.

Preliminary results from a study in Scotland found that the Pfizer vaccine reduced hospital admissions by up to 85% four weeks after the first dose, while the Oxford-AstraZeneca shot cut admissions by up to 94%. In England, preliminary data from a study of healthcare workers showed that the Pfizer vaccine reduced the risk of catching COVID-19 by 70% after one dose, a figure that rose to 85% after the second.

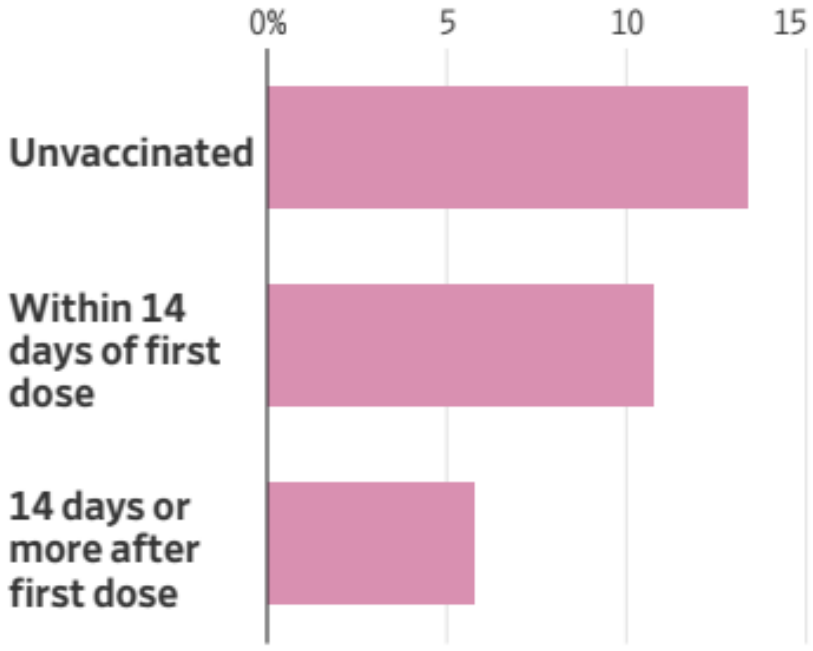
Broader testing in the overall population showed that the Pfizer vaccine was 57% effective in preventing symptomatic illness in people over 80 three to four weeks after the first dose. That rose to more than 85% after the second dose. Overall, hospitalizations and death should be reduced by over 75% after one dose of the vaccine.

In addition, both AstraZeneca and Pfizer vaccines are effective against the UK variant. Preliminary data from Novavax is promising as well with interim analysis showing 89% efficacy in the UK including the B.1.1.3 variant. The vaccine was not as effective against the South African variant.

Risk of hospitalization among those over 80



Risk of death among those over 80



Source: Public Health England

A study published Feb. 14 by Clalit, Israel's largest healthcare provider, recorded 94% fewer symptomatic Covid-19 infections among 600,000 people who received two doses of Pfizer vaccine compared with an unvaccinated group the same size. The vaccinated group was also 92% less likely to develop severe illness from the disease.

Comment: As we learn more, the real-world experience supports the UK strategy and that vaccinations significantly lower hospitalizations and deaths. This gives me cautious optimism that as more people are immunized, we should see continued decline in cases and deaths and real community control of COVID-19. To be clear, the vaccines will not mean zero COVID. To put into perspective, based on the Israeli experience only 3.5 per 100,000 vaccinated have required hospitalization with COVID-19. However, during a typical influenza season ~150 per 100,000 people are hospitalized. Yet the seasonal flu does not bring life to standstill. I am old enough to remember lining up to receive the Salk vaccine which stopped the polio epidemic but did not provide sterilizing immunity. The COVID vaccines are truly remarkable. Like the Salk vaccine in the 1950s, we should remind ourselves the transformative power of vaccines to prevent disease without eliminating infection. The sooner we reduce spread and protect as many people as possible through vaccination the sooner we will be able to relax the NPI.

IDSA Revision on Tocilizumab February 17, 2021
Recommendation 7: Among hospitalized adults with progressive severe* or critical** COVID-19 who have elevated markers of systemic inflammation, the IDSA guideline panel suggests tocilizumab in addition to standard of care (i.e., steroids) rather than standard of care alone. (Conditional recommendation, Low certainty of evidence)

Comment: NIH, NHS, and now IDSA have changed guidance based on recent two studies. Both RECOVERY and REMAP CAP (the two tocilizumab trials that reported a benefit) initiated treatment early (randomization at median of two days of hospitalization in RECOVERY; <24 hours in the ICU for REMAP-CAP), suggesting tocilizumab may be more beneficial in people with early rapidly progressive disease.

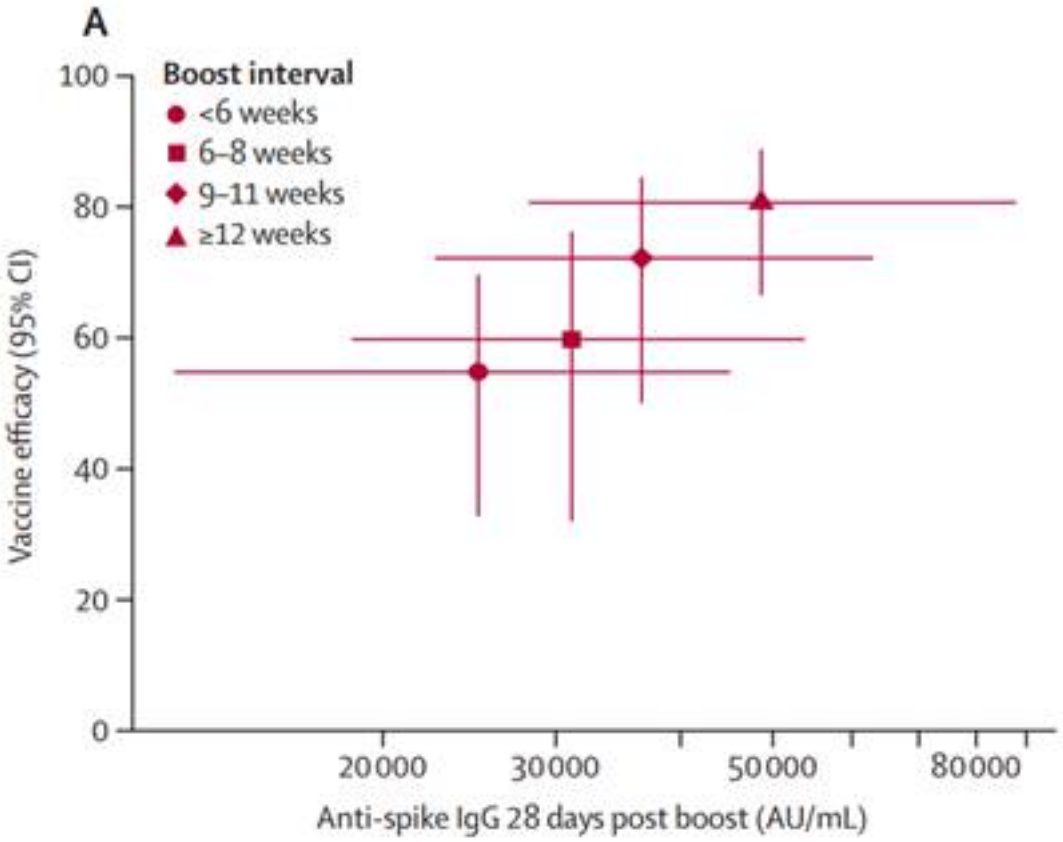
Journal Review

Single-Dose Administration and the Influence of the Timing of the Booster Dose on Immunogenicity and Efficacy of ChAdOx1 nCoV-19 (AZD1222) Vaccine: A Pooled Analysis of Four Randomised Trials
Lancet published online February 19, 2021
doi.org/10.1016/ S0140-6736(21)00432-3
The ChAdOx1 nCoV-19 (AZD1222) vaccine has been approved for emergency use by the UK regulatory authority, Medicines and Healthcare products Regulatory Agency, with a regimen of two standard doses given with an interval of 4-12 weeks. The planned roll-out in the UK will involve vaccinating people in high-risk categories with their first dose immediately and delivering the second dose 12 weeks later. The pooled post-hoc exploratory analysis of four randomized, controlled trials led by researchers from Oxford University involved 17,178 adults in the United Kingdom, Brazil, and South Africa from Apr 23 to Dec 6, 2020. The study also examined the effect of one versus two doses of the vaccine in reducing community spread of COVID-19 and the protection conferred by a low dose followed by a standard dose versus two standard doses.

Participants who received two vaccine doses at least 3 months apart were estimated to have 81% protection against SARS-CoV-2, with 8 COVID-19 cases among 1,293 vaccinees, compared with 45 of

1,356 in the placebo group. In contrast, those given their doses less than 6 weeks apart were 55% protected, based on 35 of 3,890 COVID-19 cases, compared with 76 of 3,856 in the control group.

No participants were hospitalized in the 22 days after they received their first vaccine dose, while 15 in the control group were admitted. Tests of immune response in vaccinees aged 18 to 55 years also found that antibody concentrations were more than twice as high in the group given doses 3 months apart than in those under the 6-week dosing regimen. Participants who chose to have just one vaccine dose showed sustained 76% protection and antibody response from 22 days to 3 months later (17 COVID-19 cases among 9,257), versus 71 of 9,237 cases in the control group. When the data were broken down by dose amount, participants given two standard doses had a vaccine efficacy of 63% (74 COVID-19 cases among 7,201), versus 197 of 7,179 in the placebo group. In contrast, those who received a low dose followed by a standard dose saw 81% protection (10 of 1,396), versus 51 of 1,402 in the placebo group.



Comment: The primary analysis supports the findings reported in the interim analysis that the vaccine is efficacious and safe. Exploratory analyses show that higher vaccine efficacy is obtained with a longer prime-boost interval, and that a single dose of vaccine is efficacious in the first 90 days, providing further evidence for current policy. The investigators said that the duration of protection conferred by a single vaccine dose is unknown because the study had only a 3-month follow-up period. The studies were not designed to establish whether vaccine efficacy differed by dose interval and the presence of data of varying intervals arose because of the logistics of running large-scale clinical trials in a pandemic setting.

Two UK studies released Monday showed that COVID-19 vaccination programs are contributing to a sharp drop in hospitalizations, boosting hopes that the shots will work as well in the real world as they have in carefully controlled studies. Preliminary results from a study in Scotland found that the Pfizer vaccine reduced hospital admissions by up to 85% four weeks after the first dose, while the Oxford-AstraZeneca shot cut admissions by up to 94%. In England, preliminary data from a study of healthcare workers showed that the Pfizer vaccine reduced the risk of catching COVID-19 by 70% after one dose, a figure that rose to 85% after the second. Broader testing in the overall population showed that the Pfizer vaccine was 57% effective in preventing symptomatic illness in people over 80 three to four weeks after the first dose. That rose to more than 85% after the second dose. Overall, hospitalizations and death should be reduced by over 75% after one dose of the vaccine.

Bacterial Superinfections Among Persons with Coronavirus Disease 2019: A Comprehensive Review of Data from Postmortem Studies
Open Forum Infect Dis published online February 4, 2021
doi/10.1093/ofid/ofab065/6128788
They reviewed postmortem studies of patients with COVID-19 published in English through 26 September 2020 for histopathologic findings consistent with bacterial lung infections.

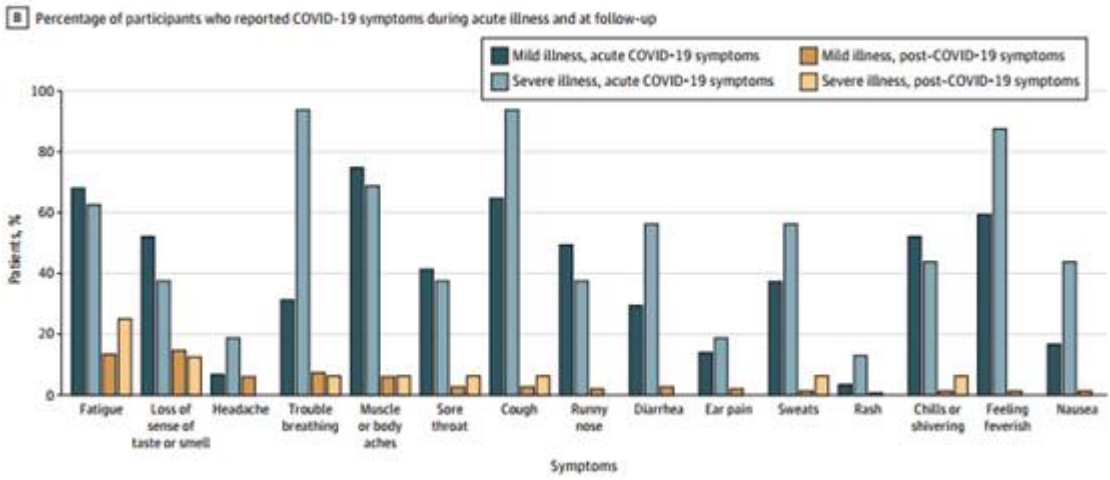
621 patients from 75 studies were included. Histopathology consistent with potential superinfection was seen in 32% of patients, mostly pneumonias. Seventy-three percent of pneumonias were focal rather than diffuse. Predominant histopathologic findings were intra-alveolar neutrophilic infiltrations that were distinct from those typical of COVID-19-associated diffuse alveolar damage. In studies with available data, 79% of patients received antimicrobial treatment; most common agents were beta-lactam/beta-lactamase inhibitors (48%), macrolides (16%), cephalosporins (12%), and carbapenems (6%). Superinfections were proven by direct visualization or recovery of bacteria in only 25.5% (51/200) of potential cases, and 8% of all patients in postmortem studies. In rank order, pathogens included *Acinetobacter baumannii, Staphylococcus aureus, Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. Lung superinfections were causes of death in 16% of potential cases, and 3% of all patients with COVID-19.

Comment: Potential bacterial lung superinfections were evident at postmortem examination in 32% of persons who died with COVID-19 (proven, 8%; possible, 24%), but they were uncommonly the cause of death. Multiple studies have now been published demonstrating <5% of COVID-19 patients have bacterial infections on admission, but most patients are still receiving antimicrobial therapy. In this study 79% of patients were on antimicrobial therapy, but 1/3 actually had possible bacterial superinfection. Antimicrobial stewardship should be a priority, as antibacterial use in SARS-CoV-2-infected patients is likely to remain in excess of documented bacterial superinfections leading to increased antimicrobial resistance which has been reported. Postmortem studies face potential biases and may over-represent severe pathology and descriptions of histopathologic and microbiologic patterns that may differ from those observed in disease survivors.

Sequelae in Adults at 6 Months After COVID-19 Infection
JAMA Network Open published online February 19, 2021
doi:10.1001/jamanetworkopen.2021.0830
This longitudinal prospective cohort of adults with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was enrolled with a concurrent cohort of healthy patients in a control group. COVID-19 symptom data were obtained at the time of acute illness or retrospectively recounted at a 30-day enrollment visit. A total of 234 participants with COVID-19 were

contacted between August and November 2020 to complete a single follow-up questionnaire between 3 and 9 months after illness onset.

Overall, 11 (6.2%) were asymptomatic, 150 (84.7%) were outpatients with mild illness, and 16 (9.0%) had moderate or severe disease requiring hospitalization. Among participants with COVID-19, persistent symptoms were reported by 17 of 64 patients (26.6%) aged 18 to 39 years, 25 of 83 patients (30.1%) aged 40 to 64 years, and 13 of 30 patients (43.3%) aged 65 years and older. Overall, 49 of 150 outpatients (32.7%), 5 of 16 hospitalized patients (31.3%), and 1 of 21 healthy participants (4.8%) in the control group reported at least 1 persistent symptom. Of 31 patients with hypertension or diabetes, 11 (35.5%) experienced ongoing symptoms. The most common persistent symptoms were fatigue (24 of 177 patients [13.6%]) and loss of sense of smell or taste (24 patients [13.6%]). Overall, 23 patients (13.0%) reported other symptoms, including brain fog (4 [2.3%]). A total of 51 outpatients and hospitalized patients (30.7%) reported worse HRQoL compared with baseline vs 4 healthy participants and asymptomatic patients (12.5%); 14 patients (7.9%) reported negative impacts on at least 1 activity of daily living (ADL), the most common being household chores.



Comment: This study had a small sample size and potential bias from self-reported symptoms during illness episode, and loss to follow-up of 57 participants. However, to my knowledge, this study presents the longest follow-up symptom assessment after COVID-19 infection. As we suspected research indicates that the health consequences of COVID-19 extend far beyond acute infection, even among those who experience mild illness. Long-term investigations will be necessary to fully understand the pathophysiology and possible treatments.