I hope everyone had a wonderful weekend. A lot to share today.

Under Covid-19 News I start with the FDA vaccine advisory group (VRBPAC) recommending a 2nd J&J dose. FDA is also reviewing myocarditis and mixing vaccine. Next the CDC revised their holiday guidance. Last the IDSA updated their guidance for use of baricitinib.

Under Journal Review I review two articles discussing natural immunity and vaccine immunity. After the second article I attempt to sum up the current science on the topic. Comments on your take on this important topic are appreciated. The next article reviews COVID-19 hospital prevalence as a risk factor for mortality from Ascension. The last article supports masking as an NPI to reduce SARS-CoV-2 transmission.

Have a great week.

Ed

COVID-19 News

FDA Advisors Approve J&J COVID Vaccine Boosters
October 15, 2021
The FDA vaccine advisory group (VRBPAC) today voted unanimously to approve a booster dose of J&J vaccine for all Americans 18 years old and older who received a single dose. Unlike the booster recommendation for the two mRNA vaccines (Moderna and Pfizer), which targets those at highest risk, today's booster recommendation includes anyone who got the J&J vaccine. The booster should be given at least 2 months after the primary, or initial dose. The company applied to the FDA to amend its EUA, based on data it provided showing that a booster increases effectiveness to 94%. At one dose, the vaccine is 71% protective. VRBPAC members said the J&J vaccine should be considered a two-dose product. VRBPAC also discussed data from recent findings on mixed doses from the NIH study (see Briefing October 15, 2021) which found a benefit for all booster combinations, but that J&J recipients had a stronger immune response after getting an mRNA booster. No action was taken.

Comment: In other news the FDA also delayed a decision on authorizing Moderna vaccine for adolescents to assess whether the vaccine may lead to heightened risk of myocarditis, a rare side effect. An Israeli study of health records of about two million people 16 years old or older, published last month in the New Engl J Med [N Engl J Med 2021; 385:1078-1090 (reviewed in the Briefing)] found that Covid-19 is much more likely to cause myocarditis than the Pfizer. Israel is almost exclusively using the Pfizer vaccine. Preliminary information from the US health-claims data sources, which an FDA official presented Thursday to VRBPAC members, indicated the incidence rates of myocarditis and pericarditis, were highest among males ages 18 to 25 years old after the second dose of an mRNA vaccine. Unlike the Israeli study, the FDA analysis didn't find a significant difference in myocarditis incidence rates between the Pfizer and Moderna vaccines.

The FDA is moving to soon allow people to receive booster shots that are different from their first Covid-19 vaccine doses. [see Briefing from last Friday]

CDC Updates Holiday Gathering Guidance
October 15, 2021

1. CDC still recommends delaying travel until you are fully vaccinated.

2. People who are not fully vaccinated should wear masks in indoor public settings.

3. In communities with substantial to high COVID-19 transmission, masks should be worn in public indoor settings, regardless of vaccination status.

4. Outdoor gatherings are generally safer than indoors, and crowded, poorly ventilated spaces should generally be avoided.

5. People who are sick or experiencing COVID-19 symptoms should not attend or host a gathering.

6. People taking medications or who have a condition that weakens their immune system should wear masks, regardless of vaccination status.

7. Additional precautions such as getting tested in advance and avoiding crowded spaces before travel should be taken if attending a gathering with guests from different parts of the country.

8. Masks should not be placed on children younger than 2 years old. Instead, the best way to protect young children is ensuring all other guests who are eligible have been vaccinated.

Updates IDSA Guidelines Bariticinib
October 11, 2021
Among hospitalized adults with severe COVID-19 [Severe illness is defined as patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen, oxygen through a high-flow device, or non-invasive ventilation] **having elevated inflammatory markers, the IDSA panel suggests baricitinib rather than no baricitinib. (Conditional recommendation, Moderate certainty of evidence)**

- Remarks:
    - Baricitinib 4 mg per day (or appropriate renal dosing) up to 14 days or until discharge from hospital.
    - Baricitinib appears to demonstrate the most benefit in those with severe COVID-19 on high-flow oxygen/non-invasive ventilation at baseline.
    - Limited additional data suggest a mortality reduction even among patients requiring mechanical ventilation.
    - Patients who receive baricitinib for treatment of COVID-19 should not receive tocilizumab or other IL-6 inhibitors.

Comment: With shortages of tocilizumab, bariticinib has been the go-to anti-inflammatory agent on high flow heated oxygen administered early in the inflammatory phase.

Journal Review

Anti-SARS-CoV-2 Receptor Binding Domain Antibody Evolution After mRNA Vaccination
Nature published online
doi.org/10.1038/s41586-021-04060-7

Recent studies have suggested that antibodies wane within 5 to 6 months of receiving a vaccine or recovering from a natural infection; however, memory B cells remain available. Investigators studied if there are any differences in memory B cell evolution by comparing blood samples from convalescent COVID-19 patients to those from mRNA-vaccinated individuals who did not have natural infection.

Vaccination and natural infection both elicited similar numbers of memory B cells. Memory B cells rapidly evolved between the first and second dose of the Pfizer and Moderna vaccines, but after 2 months, progress leveled off. The memory B cells were present in large numbers and expressed potent antibodies, but the antibodies were not getting any stronger. Also, although some of these antibodies were able to neutralize Delta and other variants, there was no overall improvement in breadth of response.

With convalescent patients, on the other hand, memory B cells continued to evolve and improve up to 1 year after infection. More potent and more broadly neutralizing memory antibodies were coming out with every memory B cell update.

Comment: Natural infection stimulates memory B cells that continue to evolve over several months, producing highly potent antibodies adept at eliminating even viral variants. There are several potential reasons that memory B cells produced by natural infection might be expected to outperform those produced by mRNA vaccines. First, it is possible that the body responds differently to viruses that enter through the respiratory tract than those that are injected into muscle. Or perhaps an intact virus stimulates the immune system in a way that the lone spike protein represented by the vaccines simply cannot. Lastly, since the virus persists in the naturally infected for weeks, this may give the body more time to mount a more robust response. These results suggest that boosting vaccinated individuals with currently available mRNA vaccines will increase plasma neutralizing activity but may not produce antibodies with equivalent breadth to those obtained by vaccinating convalescent individuals. See next article.

A Systematic Review of the Protective Effect of Prior SARS-CoV-2 Infection on Repeat Infection
Eval Health Prof published online September 30, 2021
doi.org/10.1177/01632787211047932
The authors did a systematic review of studies to estimate the risk of SARS-CoV-2 reinfection among those previously infected with SARS-CoV-2. For this systematic review, they searched scientific publications on PubMed and MedRxiv, through August 18, 2021. To identify relevant studies with appropriate control groups, they developed the following criteria for studies to be included in the systematic analysis: (1) baseline polymerase chain reaction (PCR) testing, (2) an uninfected comparison group, (3) longitudinal follow-up, (4) a cohort of human participants, i.e. not a case report or case series, and (5) outcome determined by PCR. The review was conducted following PRISMA guidelines.

10 studies were eligible for systematic review. The weighted average risk reduction against reinfection was 90.4% with a standard deviation of 7.7% (*p*-value: 0.01). Protection against SARS-CoV-2 reinfection was observed for up to 10 months. Studies had potential information, selection, and analysis biases.

Comments: In this analysis the protective effect of prior SARS-CoV-2 infection on re-infection is high and similar to the protective effect of vaccination. It is not clear how long natural protection after infection will last. However, many of the studies including in this review followed people infected with SARS-CoV-2 earlier in the pandemic when infection was most likely with the original ancestral strain of SARS-CoV-2 before the development of variant strains. [see Israeli and UK studies] Biological studies have found

persistent reservoirs of immunologically active and antibody producing cells for up to 10 months or longer. [Cell Reports Medicine, 2(7), 100354. doi.org/10.1016/j.xcrm.2021.100354] A recent CDC investigation conducted in Kentucky among persons with prior COVID-19 found that vaccination was associated with enhanced protection of those with prior infection. [MMWR. doi.org/10.15585/mmwr.mm7032e1] At the Cleveland Clinic, none of 1,359 health care workers who remained unvaccinated after having Covid-19 tested positive for the virus over many months. [medRxiv published online June 2021]. The clinic tested only people who were visibly ill and may have missed asymptomatic reinfections. The participants were 39 years old on average, so the results may not apply to older adults. Investigators in Israel found that natural immunity confers longer lasting and stronger protection against infection, symptomatic disease, and hospitalization caused by the Delta variant of SARS-CoV-2, compared to the Pfizer two-dose vaccine-induced immunity. Individuals who were both previously infected with SARS-CoV-2 and given a single dose of the vaccine gained additional protection against Delta. [medRxiv August 2021] Investigators in Boston compared antibody durability and breadth after SARS-CoV-2 infection and vaccination. [bioRxiv September 2021] While vaccination delivered robust initial virus-specific antibodies with some cross variant coverage, pre-variant SARS-CoV-2 infection-induced antibodies, while modest in magnitude, showed highly stable long-term antibody dynamics. Vaccination after infection induced maximal antibody magnitudes with enhanced longitudinal stability while infection-naïve vaccinee antibodies fell with time to post-infection-alone levels. The composition of antibody neutralizing activity to variant relative to original virus also differed between groups, with infection-induced antibodies demonstrating greater relative breadth. Lastly, a recent study conducted in the UK found among persons infected during a period of nearly exclusive Delta SARS-CoV-2 transmission, found those fully vaccinated with Pfizer and AZ had similar levels of protection (82% and 67%, respectively) as those with previous infection (73%) [Nuffield Department of Medicine. 2021 doi.org/10.1101/2021.08.18.2126223]

So how do we interpret the current science? Clearly natural infection counts for something, but vaccination after infection induced maximal antibody magnitudes with enhanced protection over time. The last question, does a person who has had natural infection need two doses vs a single dose.

COVID-19 Hospital Prevalence as a Risk Factor for Mortality: An Observational Study of a Multistate Cohort of 62 Hospitals

BMJ Qual Saf 2021;0:1–9 article provided and reviewed by Mohamad Fakih
doi:10.1136/ bmjqs-2021-013721

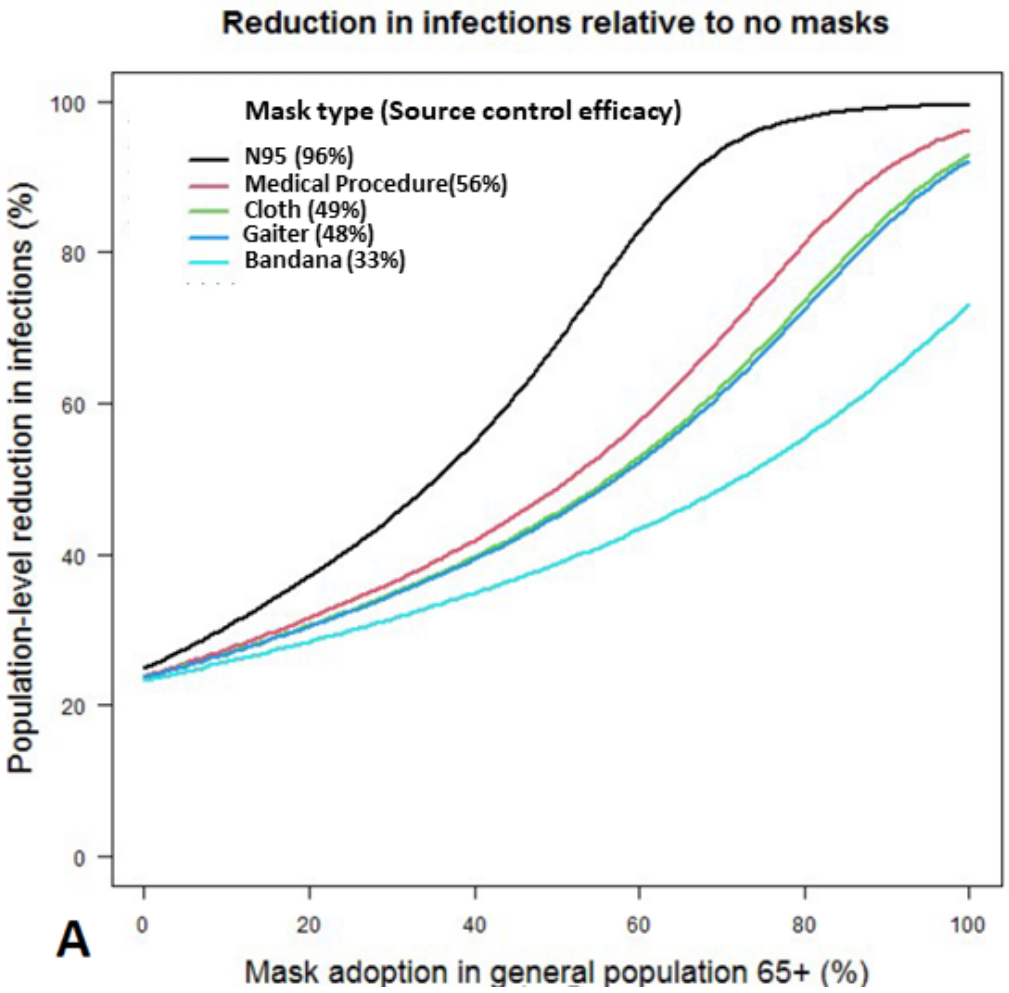
The study evaluates Ascension's experience in caring for COVID-19 patients during the pandemic. We have witnessed a sharp decline in mortality compared to the early pandemic period, with the implementation of standardized management protocols. However, we have also found an association between COVID-19 hospital prevalence and COVID-19 mortality. COVID-19 infected patients' mortality increased by 25% when the COVID-19 hospital prevalence increased to 10%-25% compared to <10%. The impact of surges was even more noticeable with higher COVID-19 hospital prevalence, with prevalence of >25%, the mortality had a relative increase by 41%. High COVID-19 hospital prevalence was associated with absolute contribution to probability of death of 2%-3%, close to the impact of some chronic diseases.

Hospitals experienced surge periods where rapid escalation of admissions occurred. More than 75% of patients were cared for in periods with higher hospital COVID-19 prevalence. Acute surges in patients infected with COVID-19 may overwhelm clinicians and disrupt standard operations, especially in high-demand areas, such as the critical care environment. In addition, some processes may have been altered during the pandemic to reduce potential exposure of frontline workers to COVID-19-infected patients.

Comment: There are important quality of care and national policy implications.
1. Need to reconsider how we best support the care for patients in times of increased volume and complexity, such as those experienced during COVID-19 surges.
2. A reevaluation of the healthcare workforce structure and its needs is essential. A national plan may be necessary to deploy resources—physically and virtually— to weather large disruptive events. There is a substantial opportunity to build partnerships among government, local entities, and health systems.
3. The value of investing in quality and infection prevention, coupled with a robust analytics infrastructure, have surfaced as essential elements to identify acute changes in processes and associated adverse outcomes.
4. National physician, nursing, and specialty societies should re-examine our current state and whether we are ready to support workforce challenges in the future.

Evaluation of Different Types of Face Masks to Limit the Spread of SARS-CoV-2 – A Modeling Study
medRxiv published online September 30, 2021
doi.org/10.1101/2021.04.21.21255889
The investigators use a previously published SARS-CoV-2 transmission model adapted to include updated laboratory-derived source control and wearer protection efficacy estimates for a variety of face coverings including N95 respirators. The impact of mask wearing on COVID-19 incidence in the United States was estimated.

Based on modeling, face masks reduce cumulative infections (cloth: 69%; medical procedure mask: 78%) when the basic reproductive number (R_0) is 2.5 and face masks are worn by 80% of persons aged ≥65 years and by 60% of persons <65 years. Increasing cloth or medical procedure mask efficacies by 30% (by improving mask fit) could reduce the effective reproductive number to 2.3.



Comment: This model supports that mask can substantially reduce SARS-CoV-2 transmission. For highly contagious variants such as Delta, mask wearing and other prevention strategies (e.g., vaccination, ventilation, and physical distancing) are needed even more to limit spread. Delta R_0 is estimated to be 6-8.