Good morning and TGIF

Today I have divided the Briefing into COVID-19 News and Literature Review.

For Covid-19 news, many of you may have seen the report on SARS-CoV-2 infections in HCWs at Mayo Clinic in Rochester. The key was the source of infections and it was not direct patient care in the vast majority of cases. The second report is the announcement of the first FDA approved home test for SARS-CoV-2. [do not get your hopes up since there will be very limited supply until next Spring] The next is the NIH Guidelines Panel recommendation for bamlanivimab. The last entry is the updated WHO recommendation on Remdesivir.

The section of Literature review starts with a Danish study on masks. Please read the comment section to put this study in proper context. The next article reviews the successful Duke University SARS-CoV-2 mitigation program for the fall semester outlining the interventions and testing strategies. The last article is a fascinating prepublication study looking at immunological memory.

Have a wonderful weekend.

Ed

COVID-19 News

Mayo Clinic HCW COVID-19 Infections

More than 900 Mayo Clinic staff have contracted COVID-19 in the past two weeks. Most of the staff who have contracted the virus — 93 percent — did so in the community. Most of those who contracted COVID-19 at work did so while eating in the break room without wearing a mask not direct patient care.

The 905 newly diagnosed workers make up about one-third of the 2,981 Mayo staff in the Midwest who have been diagnosed with the virus since March. Across the Midwest, the system is experiencing a stable shortage of 1,500 staff, including 1,000 in Rochester, according to the report.

Comment: This report highlights the importance of community behavior and spread of COVID-19. Breaks rooms have also been recognized as a source for transmission as well. This impacts our ability to care for patients everywhere and the need for everyone in the communities to do their part to limit the spread of COVID-19. This is the same story concerning school. Transmission in schools have been very low-the overwhelming number of students and staff infected are infected in the community not the schools.

FDA Clears First Covid-19 Test Performed Fully at Home

The US Food and Drug Administration (FDA) issued an emergency use authorization for the first at-home COVID-19 diagnostic test, which provides results in 30 minutes or less. The All-In-One Test Kit (Lucira Health) is a molecular, single-use test that detects SARS-CoV-2 using self-collected nasal swab samples in people aged 14 years and older who are suspected of having COVID-19 by their healthcare provider. The test uses a technology, known by the acronym LAMP. LAMP searches for and amplifies the virus's

genetic material to detect it. LAMP, however, involves a slightly different process that can be done at a single temperature, allowing tests to be faster and more portable. Lucira said the test can correctly flag an infection 94.1% of the time and identify a negative result 98% of the time, when compared with a PCR test. Antigen tests, which look for viral proteins, can identify the virus 84% to 97.6% of the time compared with PCR tests when used within five to seven days after a person develops symptoms.

Comment: Initial supplies unfortunately will be limited. The test is relatively expensive and will require a physician order. It is expected to be first available at Sutter Health in Northern California and at Cleveland Clinic Florida in Miami-Ft. Lauderdale, followed by a national rollout by early spring 2021. Lucira said it expects its test to cost around $50 apiece.

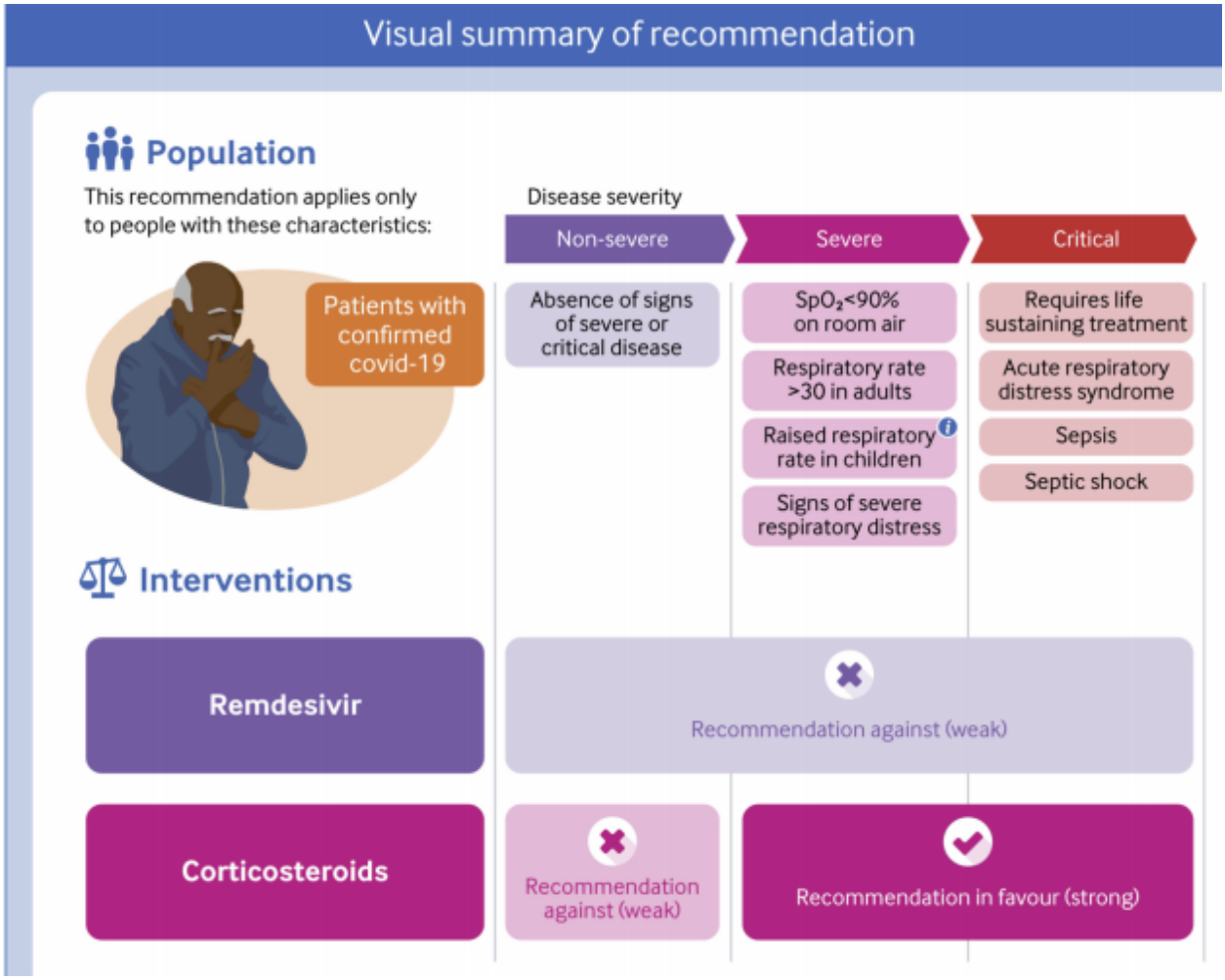
NIH Guidelines on Bamlanivimab

The National Institutes of Health's COVID-19 Treatment Guidelines Panel says there is not enough evidence to recommend for or against use of bamlanivimab in outpatients with mild-to-moderate COVID-19. The treatment was granted emergency use authorization on Nov. 9. The treatment should not be the standard of care for infected patients, and it should not be administered to hospitalized patients outside a clinical trial, the panel said. Patients at highest risk for COVID-19 progression should be prioritized to receive bamlanivimab.

Comment: As stated in Monday's Daily Briefing it was my opinion that monoclonals probably have a role in mild infections in high-risk persons to prevent progression in the outpatient setting. Another potential role would be use prophylactically in high-risk persons who have had close contacts with a person with a documented infection with SARS-CoV-2.

WHO Guideline Update on Remdesivir

In a COVID-19 drug guideline update, the WHO suggests against using the antiviral remdesivir in patients who are hospitalized with COVID-19. The recommendation, considered "weak or conditional." The WHO panel said there is no evidence that remdesivir improves patient-important outcomes, including mortality, the need for mechanical ventilation, or the time to clinical improvement. The panel also noted that they did not find proof that remdesivir is ineffective. This update was heavily influenced by the result of the Solidarity Trial. The WHO continues to strongly recommend corticosteroids in cases of severe and critical disease.



Comment: There is growing consensus over the limited value of remdesivir. I still think there is some evidence for use early in patients who require oxygen at <15 liters. [at least in time to recovery]

Literature Review

Effectiveness of Adding a Mask Recommendation to Other Public Health Measures to Prevent SARS-CoV-2 Infection in Danish Mask Wearers:
A Randomized Controlled Trial Ann Intern Med published online November 18, 2020
The investigators randomized 6000 adults in Denmark who were outside their homes for at least 3 hours a day to either receive a recommendation to wear a mask when outside the home, along with a supply of surgical masks, or to receive no recommendation. During April to June, mask wearing in Denmark was not common outside healthcare settings, but social distancing measures were in effect. Half were given surgical masks and told to wear them when leaving their homes; the others were told not to wear masks in public. The participants completed weekly surveys as well as antibody tests at 1 month. At that time, 2 percent of the

Danish population was infected — a rate lower than that in many places in the United States and Europe today. Only 46% of the mask group wore the masks as directed. The primary outcome — a COVID-19 hospital diagnosis or positive PCR or antibody test by 1 month — occurred in 1.8% of the mask group and 2.1% of the control group, a difference that did not reach statistical significance.

Comment: First this trial does not address the question about transmission in communities where most people wear masks and does not disprove the effectiveness of widespread mask use. The trial was designed to examine the protective effect of masks not source control (preventing spread from an infected person to others by blocking droplets). CDC recently updated its guidance on masks. They state that masks when worn by all may reduce transmission via both source control and personal protection. It should be noted that this trial took place during the spring of 2020 in Denmark. At the time social distancing was recommended, but masks were not recommended, and infections were modest. This was an RCT in a real-world setting, however, the study only examined the effect of recommending masks not the effect if subjects actually wore them. Observational trials have shown that widespread mask use can decrease transmission. Despite some weaknesses of this trial the findings reinforce the importance of social distancing and hygiene measures and suggest that masks need to be worn by most if not all people to reduce community infection rates.

Implementation of a Pooled Surveillance Testing Program for Asymptomatic SARS-CoV-2 Infections on a College Campus — Duke University, Durham, North Carolina, August 2–October 11, 2020

MMWR November 17, 2020

The Duke campaign relied on a combination of strategies, including a 14-day pre-arrival self-quarantine for all enrolled students and a code-of-conduct pledge to wear masks, follow physical distancing guidelines, and undergo regular COVID-19 testing. Daily symptom monitoring—carried out via a custom smartphone app—was accompanied by contact tracing and quarantine. On-campus students were tested twice a week with self-swab kits collected at strategically located sites on campus. Off-campus students were tested once a week. They used a quantitative, in-house, laboratory-developed, real-time PCR test. The surveillance testing used pooled samples to conserve resources, and the investigators reported positive results with testing samples in batches of five and re-testing individual samples within batches that showed a positive result. The batch method allowed Duke to process 80,000 samples from Aug 2 to Oct 11, including 68,913 specimens from 10,265 graduate and undergraduate students—excluding 781 student-athletes who participated in a separate surveillance program. [athletes are special!]

This surveillance approach resulted in a lower average per-capita infection prevalence among students (0.08%) than in the surrounding community (Durham County, 0.1%), and no large campus outbreaks. There were 84 COVID-19 cases among students, with 51% of the cases occurring among asymptomatic people, highlighting the importance of comprehensive versus symptom-based testing since half of infections were asymptomatic.

Comment: Multiple universities began fall 2020 classes using only symptomatic testing. The finding that 51% of SARS-CoV-2 infections in this analysis were asymptomatic suggests that a substantial proportion of infections would be missed with only symptomatic testing. This is a similar approach that other universities are now implementing. The impact of Duke's testing program was assessed within the context of an incidence rate specific to the local Durham community and in the context of multiple strategies for mitigations on campus. The precise findings were likely influenced by multiple factors, such as maintaining students in single rooms on campus and by the level of adherence to campus policies on masks, social distancing, and symptom monitoring by Duke's student populations.

Immunological Memory to SARS-CoV-2 Assessed for Greater than Six Months After Infection
bioRxiv published online November 11, 2020
The investigators analyzed multiple compartments of circulating immune memory to SARS-CoV-2 in 185 COVID-19 cases, including 41 cases at > 6 months post infection. Subjects (43% male, 57% female) represented a range of asymptomatic, mild, moderate, and severe COVID-19 cases, and were recruited from multiple sites throughout the United States. Most subjects had a mild case of COVID-19, not requiring hospitalization. 92% of subjects were never hospitalized for COVID-19; 7% of subjects were hospitalized, some of whom required intensive care unit (ICU) care consistent with the COVID-19 disease severity distribution in the USA. The majority of subjects (97%) reported symptomatic disease. The ages of the subjects ranged from 19 to 81 years old. Most subjects provided a blood sample at a single time point, between 6 days (d) post-symptom onset (PSO) and 240d PSO, with 41 samples at > six months PSO (d178 or longer). Thirty-eight subjects provided longitudinal blood samples over a duration of several months. They performed simultaneous measurement of circulating antibodies, memory B cells, CD8+ T cells, and CD4+ T cells specific for SARS-CoV-2, in a group of subjects with a full range of disease and distributed from short time points PSO out to > 8 months PSO.

Spike IgG was relatively stable over 6+ months. Spike-specific memory B cells were more abundant at 6 months than at 1 month. SARS-CoV-2-specific CD4+ T cells and CD8+ T cells declined with a half-life of 3-5 months. By studying antibody, memory B cell, CD4+ T cell, and CD8+ T cell memory to SARS-CoV-2 in an integrated manner, they observed that each component of SARS-CoV-2 immune memory exhibited distinct kinetics. Notably, memory B cells specific for spike or RBD were detected in almost all COVID-19 cases, with no apparent half-life at 5+ months post-infection. Therefore, eight months after infection, most people who have recovered still have enough immune cells to hopefully provide immunity to the virus and reinfection.

Comment: The findings here are very encouraging and comes as a relief to experts worried that immunity to the virus might be short-lived. This study found a high degree of heterogeneity in the magnitude of adaptive immune responses to SARS-CoV-2. That heterogeneity was observed in this study to be carried on into the immune memory phase to SARS-CoV-2. The source of heterogeneity in immune memory to SARS-CoV-2 is unknown and worth further examination. [we are just beginning to understand the complexity of this unique virus both in clinical presentation and now the immune response] It is possible that some of that heterogeneity is a

result of low cumulative viral load or initial inoculum, essentially resulting in a very minor or transient infection that barely triggered an adaptive immune response in some individuals. Nevertheless, immune memory consisting of at least three immunological compartments was measurable in ~90% of subjects > 5 months PSO, indicating that durable immunity against 2^{o}COVID-19 disease is a possibility in most individuals. This article has not been peer-reviewed, but it is one of the most comprehensive and long-ranging studies of immune memory to SARS-CoV-2 to date. A recent study just published found people who had recovered from COVID-19 still had protective killer immune cells even if antibodies were no longer detectable. (SARS-CoV-2-specific CD8^{+} T cells were detectable in individuals seronegative for anti-SARS-CoV-2) [Nature Med November 12, 2020]