Good Morning

I hope everyone had a safe and relaxing Thanksgiving weekend.

In COVID-19 news I update vaccines and the hope the CDC will be revising their quarantine/isolation guidance this week.

Under publications, there are 2 articles reviewing national seroprevalence levels before the recent widespread spikes seen across the US this month, but bottom line, we are a long way from herd immunity. The next article is a RCT on CP which does not show benefit even though trial ensured that more than 95% of the transfused convalescent plasma units had a total anti–SARS-CoV-2 antibody titer of at least 1:800. The last article is a small study that reviews the impact of sufficient control group (glycated hemoglobin [HbA1c] <6.5%) and insufficient control group (HbA1c ≥6.5%).

Take a deep breath, December will be wild ride, but vaccinations will begin! ACIP will be finalizing its recommendation on how to prioritize vaccinations this week.

Ed

COVID-19 News

CDC Finalizing Recommendation to Shorten Covid-19 Quarantines
CDC officials are finalizing recommendations for a new quarantine period that would likely be between seven and 10 days and include a test to ensure a person is negative for Covid-19. [which test has not been specified yet] About 50% of people who develop symptoms on average do so between five and six days after infection, while only 9% develop symptoms after 10 days. France has already reduced time for quarantine to 7 days. In the study reviewed last Wednesday from *Lancet Microbe* also suggest shorter quarantine periods can be safe. In this review and a paper reviewed months ago in the Daily Briefing found that most patients do not transmit SARS-CoV-2 after 5-6 days from onset of symptoms. In addition, studies show you cannot culture live virus after day 8 in most cases.

Moderna Vaccine
Moderna will apply for EUA today. This will be reviewed on December 17th at the FDA. If granted it is estimated vaccinations could be begin as early as December 21st. Moderna said it can produce 20 million doses by the end of December, and 500 million to a billion in 2021. Each person requires two doses, administered a month apart, so 20 million doses will be enough for 10 million people. The vaccine is 94.1 percent effective in phase 3 trials and new data also showed that the vaccine was 100 percent effective at preventing severe disease from the coronavirus.

AstraZeneca Vaccine Update
AstraZeneca has acknowledged a key dosing error. The study participants in whom the vaccine was 90 percent effective had mistakenly been given a half dose of the vaccine, followed a month later by a full dose. Among those who received two full doses, the effectiveness dropped to 62 percent. And the people who received the smaller dosing regimen were 55 years old or younger, making it difficult to know if the more promising results would hold among older people, who are especially vulnerable to Covid-19. The biggest questions were, why was there such a large variation in the effectiveness of the

vaccine at different doses, and why did a smaller initial dose appear to produce much better results? AstraZeneca and Oxford researchers said they did not know.

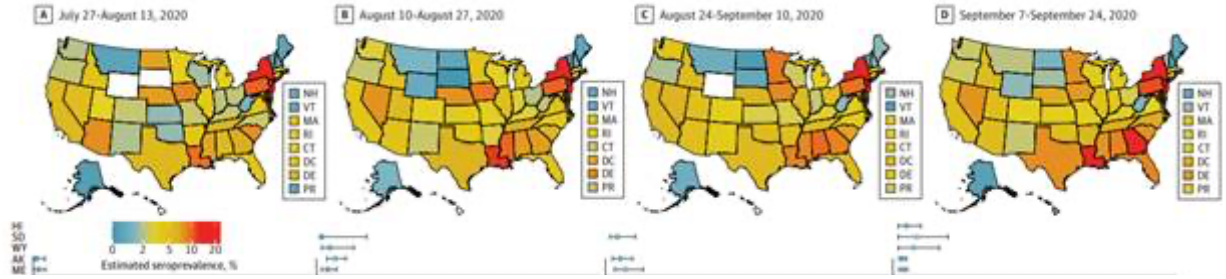
On the positive side, the vaccine is inexpensive — only a few dollars per dose — and easy to mass-produce. Requires 2 doses 4 weeks apart. Unlike Pfizer and Moderna's vaccines, AstraZeneca's could be stored for months in normal refrigerators. The company has estimated it will be able to produce some three billion doses next year, enough to vaccinate nearly one-fifth of the global population.

Literature Review

Estimated SARS-CoV-2 Seroprevalence in the US as of September 2020
JAMA Intern Med published online November 24, 2020
doi:10.1001/jamainternmed2020.7976
This is a cross-sectional study conducted across all 50 states, the District of Columbia, and Puerto Rico used a convenience sample of residual serum specimens provided by persons of all ages that were originally submitted for routine screening or clinical management from 2 private clinical commercial laboratories. Samples were obtained during 4 collection periods: July 27 to August 13, August 10 to August 27, August 24 to September 10, and September 7 to September 24, 2020.

Overall, 177,919 residual sera specimens were collected during the four periods, of which 58.3% were from women, 15% from children, 26.7% from people 65 and older, and 14.8% from people in non-metropolitan areas. The results over the four periods showed a wide variance in seroprevalence estimates between regions and metropolitan and non-metropolitan areas, and generally reflect the trajectory of the pandemic. Two of the states at the epicenter of the pandemic in the spring—New York and New Jersey—had the highest seroprevalence in each testing period. In New York, seroprevalence was as high as 23% in the first testing period. South Dakota, meanwhile, had a seroprevalence of 0% in the second testing period. [this has probably changed with recent surge] Estimates in southern states, where infections began to surge in the summer, were as high as 13%. But they were less than 10% in the Midwest and West.

This report found that most people in the US did not have evidence of previous SARS-CoV-2. This is consistent with other large-scale seroprevalence surveys conducted in the US, as well as population-based surveys in the United Kingdom, Spain, and Geneva that were conducted over periods with substantial SARS-CoV-2 community transmission.



Comment: This study provides an accurate snapshot of national seroprevalence levels because it used serum sent to laboratories for routine testing, rather than from patients suspected of having COVID-19. Based on this finding, herd immunity is a long way off. A vaccine could not come fast enough. See below.

Estimated Incidence of COVID-19 Illness and Hospitalization — United States, February-September 2020

Clin Infect Dis published online November 25, 2020
doi:10.1093/cid/cica1780/6000389

The investigators estimated the cumulative incidence SARS-CoV-2 infections, symptomatic illnesses, and hospitalizations, by adapting a simple probabilistic multiplier model. Laboratory-confirmed case counts that were reported nationally were adjusted for sources of under-detection based on testing practices in inpatient and outpatient settings and assay sensitivity from February to September 2020.

They estimated that through the end of September, 1 of every 2.5 (95% Uncertainty Interval (UI): 2.0–3.1) hospitalized infections and 1 of every 7.1 (95% UI: 5.8–9.0) non-hospitalized illnesses may have been nationally reported. Applying these multipliers to reported SARS-CoV-2 cases along with data on the prevalence of asymptomatic infection from published systematic reviews, they estimate that 2.4 million hospitalizations, 44.8 million symptomatic illnesses, and 52.9 million total infections may have occurred in the U.S. population from February 27-September 30, 2020.

Comment: The availability and use of testing for SARS-CoV-2 has changed rapidly since the pandemic began; therefore, data on the proportion of persons who are tested for COVID-19 and how this varies across all the previously described factors remains limited. Although data on testing by time, healthcare setting, and age was available, it lacked the granularity to allow for geographic-specific model inputs. These data limitations could have resulted in overestimation of cases from areas with higher testing rates, including some hospitals that are performing universal testing, or have more outpatient testing facilities and active contact tracing. In addition, their model may have underestimated the rate in areas with lower testing and contact tracing. Additionally, some infections, such as those among healthcare workers or from outbreaks in congregate residential settings, may be more likely to be tested and nationally reported compared with the general population, and could overestimate non-hospitalized cases and infections. Despite these limitations, I believe their model provides a relatively simple approach to illustrate why there are more persons who have SARS-CoV-2 than reported. Based on their estimate this indicates that 84% of the U.S. population has not yet been infected and thus most of the country remains at risk, despite already high rates of hospitalization. This article plus the article reviewed above confirm we have a long way to go before we achieve herd immunity even in areas hard hit by COVID-19. Neither of these two articles account for the widespread rates of SARS-CoV-2 we are currently experiencing.

A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia

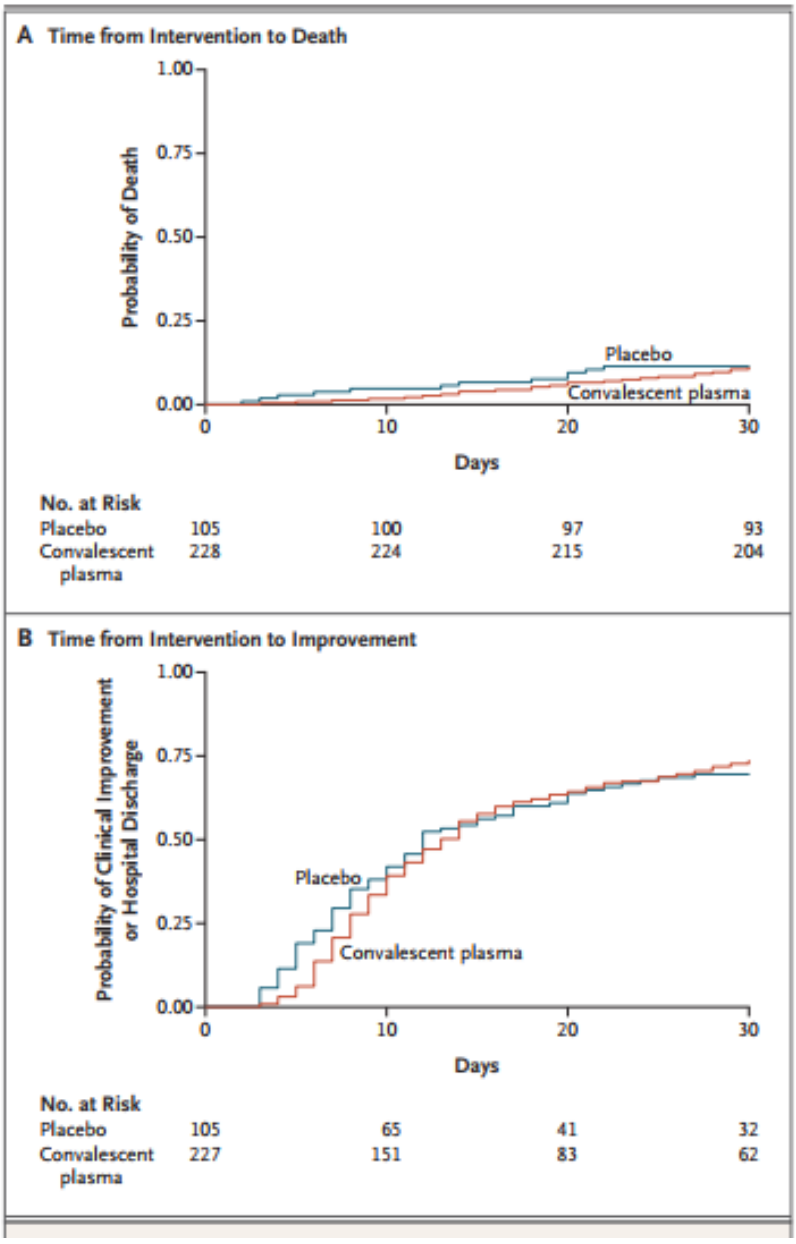
N Engl J Med published online November 24, 2020
doi: 10.1056/NEJMoa2031304

The investigators randomly assigned hospitalized adult patients with severe Covid-19 pneumonia in a 2:1 ratio to receive convalescent plasma or placebo. The primary outcome was the patient's clinical status 30 days after the intervention, as measured on a six-point ordinal scale ranging from total recovery to death.

A total of 228 patients were assigned to receive convalescent plasma and 105 to receive placebo. Criteria for inclusion was a + PCR for SARS-CoV-2, radiologically confirmed pneumonia, and at least one of the following severity criteria: oxygen saturation (SaO2) below 93% on RA at rest, a ratio of the partial pressure of oxygen (PaO 2) to the fraction of inspired oxygen (FiO2) below 300 mm Hg (PaO2:FiO2), or a Sequential Organ Failure Assessment (SOFA) or modified SOFA (mSOFA) score of two or more points above baseline status (scores range from 0 to 24, with higher scores indicating more severe disease).

Mechanical ventilation was an exclusion. The median time from the onset of symptoms to enrollment in the trial was 8 days (interquartile range, 5 to 10), and hypoxemia was the most frequent severity criterion for enrollment.

The infused convalescent plasma had a median titer of 1:3200 of total SARS-CoV-2 antibodies (interquartile range, 1:800 to 1:3200]. No patients were lost to follow-up. At day 30 day, no significant difference was noted between the convalescent plasma group and the placebo group in the distribution of clinical outcomes according to the ordinal scale (odds ratio, 0.83 (95% confidence interval [CI], 0.52 to 1.35; P=0.46). Overall mortality was 10.96% in the convalescent plasma group and 11.43% in the placebo group, for a risk difference of -0.46 percentage points (95% CI, -7.8 to 6.8). Total SARS-CoV-2 antibody titers tended to be higher in the convalescent plasma group at day 2 after the intervention. Adverse events and serious adverse events were similar in the two groups.



Comment: Although the use of usual therapy was allowed in both groups, it was not standardized among participating sites. Nevertheless, no significant differences were detected in the subgroup analyses performed in this trial. Dexamethasone or other glucocorticoids were heavily used in both trial groups. There was no suggestion for interaction between convalescent plasma and concomitant therapies was found. This trial ensured that more than 95% of the transfused convalescent plasma units had a total anti–SARS-CoV-2 antibody titer of at least 1:800 and that the plasma volume infused had a correction factor according to the participant's weight. I believe the use of convalescent plasma is not a standard of care. Further studies regarding antibody therapy may be best focused on other populations or on earlier in patients with mild to moderate diseases. Monoclonal antibodies may replace uses of convalescent plasma. Based on the Mayo Clinic pre-published data earlier is better with high titer plasma.

Glycemic Control Before Admission is an Important Determinant of Prognosis in Patients with Coronavirus Disease 2019

J Diab Invest published online November 2020
doi: 10.1111/jdi.13431

A total of 77 inpatients were grouped into sufficient control group (glycated hemoglobin [HbA1c] <6.5%, n = 49) and insufficient control group (HbA1c ≥6.5%, n = 28). Regression models were used to analyze the clinical data.

Compared with patients with HbA1c <6.5, patients with HbA1c ≥6.5 showed higher heart rate (101 vs 89, P = 0.012), lower percutaneous oxygen saturation (93 vs 97%, P = 0.001), higher levels of multiple indicators of inflammation, such as white blood cell count (7.9 vs 5.9 9 109/L, P = 0.019), neutrophil count (6.5 vs 4.1 9 109/L, P = 0.001), high-sensitivity CRP (52 vs 30 mg/L, P = 0.025) and serum ferritin (1,287 vs 716 lg/L, P = 0.023), as well as lower levels of lymphocyte count (0.7 vs 0.8 9 109/L, P = 0.049) at hospital admission.

Patients with HbA1c ≥6.5 were more likely to develop secondary respiratory infections (25 [89%] vs 33 [67%], P = 0.032) and acute respiratory distress syndrome (17 [61%] vs 14 [29%], P = 0.006) than patients with HbA1c <6.5, resulting in a higher proportion of critically ill patients (19 [68%] vs 18 [37%], P = 0.009) and non-survivors (13 [46%] vs 11 [22%], P = 0.029). After adjustment for potential risk factors, HbA1c was independently associated with in-hospital death.

Comment: HbA1c was an independent risk factor for poor outcomes in COVID-19 coronavirus patients. This was a retrospective, single-center dataset for analysis and the sample size was limited. This dataset only focused on patients with severe and critical illness. Further validation is required with another larger sample size, multicentered study and, ideally, involving patients of different ethnic origins, and patients with mild and moderate symptoms. I would also have liked to see if different abnormal HcA1c levels impacted outcomes. (e.g. 6.5 vs >10)