TGIF!!!

Under COVID-19 News I review the upcoming CDC requirements for international travelers coming to the US and REMAP-Cap Trial announcement on use of convalescent plasma.

Under Journal Reviews, the first is the final Mayo Clinic findings on the use of convalescent plasma. The second paper looks at COVID-19 trends in persons ages 0-24. The last paper is the phase 1/2 findings on the J&J vaccine.

Have a "delightful" weekend.

Ed

COVID-19 News

New CDC Testing Requirement for International Travelers
All travelers boarding international flights to the U.S. must now have evidence of a negative COVID-19 test within 3 days before their flight or have documentation of recovery from COVID-19, the CDC announced on Tuesday. The agency recommends that passengers get tested again 3 to 5 days after their arrival in the U.S. and stay home for a week after traveling. This will start in <2 weeks.

Comment: I am not sure a single negative test will really prevent spread from overseas. I am not sure how the repeat testing and 1 week quarantine will be enforced. There is nothing in the current guidance about proof of immunization.

REMAP-Cap Trial Announcement on Use of Convalescent Plasma
Earlier this week an international trial testing convalescent blood plasma on COVID-19 patients with moderate and severe illness has halted enrolment of severely ill COVID-19 patients requiring intensive care after it found no benefit. The decision by the REMAP-CAP trial leaders came after an initial analysis of more than 900 severely ill trial participants in intensive care showed that treatment with convalescent plasma taken from people who have recovered from the pandemic disease - did not improve outcomes.

Comment: I would like to see details of this trial and eligibility. From announcement patients were in the ICU, but eligibility was for moderate to severe illness. The Mayo Clinic trial was just published (see below) confirming the prepublication results.

Journal Review

Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19
N Engl J Med published online January 13, 2021
DOI: 10.1056/NEJMoa2031893
This is a retrospective study based on a U.S. national registry, [Mayo Clinic] to determine the impact of anti-SARS-CoV-2 IgG antibody levels in convalescent plasma used to treat hospitalized adults with Covid-19. The primary outcome was death within 30 days after plasma transfusion. Patients who were enrolled through July 4, 2020, and for whom data on anti-SARS-CoV-2 antibody levels in plasma transfusions and on 30-day mortality were available were included in the analysis. Signal-to-cutoff ratios

for anti-SARS-CoV-2 IgG antibody levels were categorized as low (<4.62), medium (4.26-18.45), or high (>18.45).

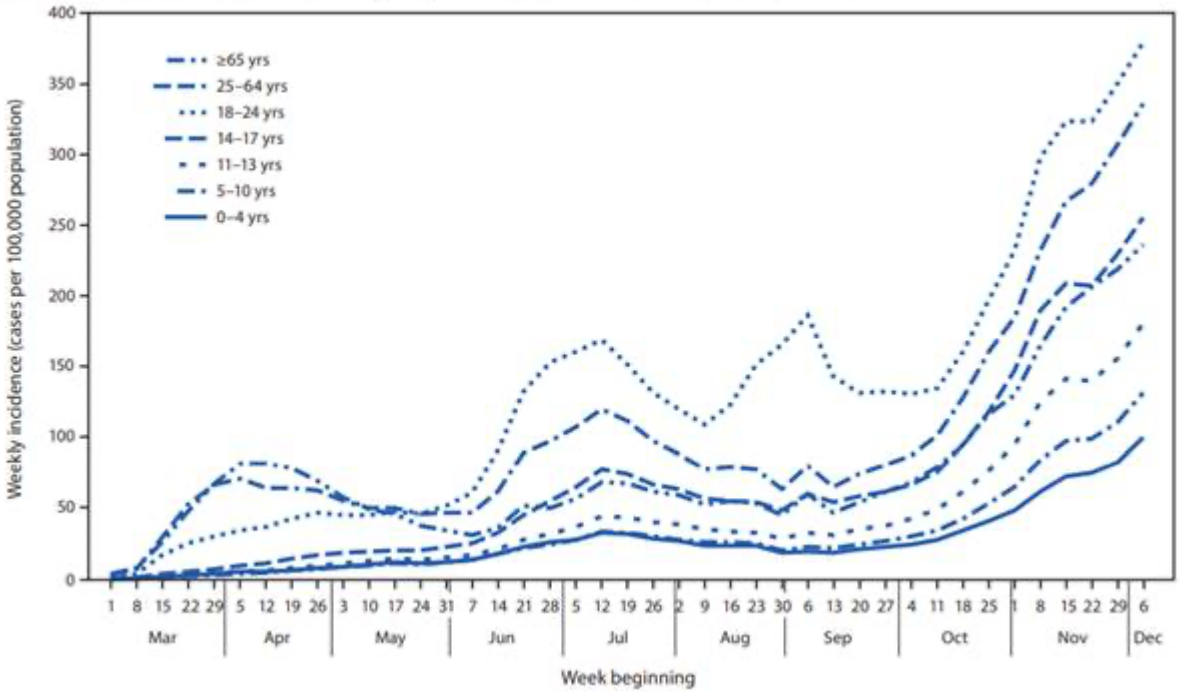
Of the 3082 patients included in this analysis, death within 30 days after plasma transfusion occurred in 115 of 515 patients (22.3%) in the high-titer group, 549 of 2006 patients (27.4%) in the medium-titer group, and 166 of 561 patients (29.6%) in the low-titer group. A lower risk of death within 30 days in the high-titer group than in the low-titer group was observed among patients who had not received mechanical ventilation before transfusion (relative risk, 0.66; 95% confidence interval [CI], 0.48 to 0.91), and no effect on the risk of death was observed among patients who had received mechanical ventilation (relative risk, 1.02; 95% CI, 0.78 to 1.32). In addition, patients who received plasma within 3 days after receiving a diagnosis of Covid-19 had a lower risk of death than those who received transfusions later in the disease course.

Comment: This is the final report from the Mayo Clinic trial initially posted in medRxiv. Among patients hospitalized with Covid-19 who did not require mechanical ventilation, transfusion of plasma with higher anti-SARS-CoV-2 IgG antibody levels was associated with a lower risk of death than transfusion of plasma with lower antibody levels. The Infectious Diseases Society of America and the AABB (formerly known as the American Association of Blood Banks) recommend that the use of convalescent plasma be limited to clinical trials, that critically ill patients and those in the intensive care unit (ICU) are unlikely to benefit from transfusions of convalescent plasma, and that convalescent plasma should be used as early as possible in the course of infection (preferably within 3 days after diagnosis) in order to achieve the best outcomes. This sounds remarkably similar to the RDV story.

COVID-19 Trends Among Persons Aged 0–24 Years — United States, March 1–December 12, 2020
MMWR published online January 13, 2021
Children, adolescents, and young adults were stratified into five age groups: 0–4, 5–10, 11–13, 14–17, and 18–24 years to align with educational groupings (i.e., pre-, elementary, middle, and high schools, and institutions of higher education), and trends in these groups were compared with those in adults aged ≥25 years. Confirmed COVID-19 cases, defined as positive-PCR test results for SARS-CoV-2.

During March 1–December 12, 2020, a total of 2,871,828 laboratory-confirmed cases of COVID-19 in children, adolescents, and young adults aged 0–24 years were reported in the United States. Among these cases, the majority (57.4%) occurred among young adults aged 18–24 years; children and adolescents aged 14–17 years accounted for 16.3% of cases, those 11–13 years for 7.9%, those 5–10 years for 10.9%, and those 0–4 years for 7.4%. Among persons aged 0–24 years, weekly incidence was higher in each successively increasing age group; weekly incidence among adults aged 25–64 years and ≥65 years exceeded that among children and adolescents aged 0–13 years throughout the review period. Among children, adolescents, and young adults with available data for these outcomes, 30,229 (2.5%) were hospitalized, 1,973 (0.8%) required ICU admission, and 654 (compared with 16.6%, 8.6%, and 5.0% among adults aged ≥25 years, respectively.

FIGURE 1. COVID-19 weekly incidence,*,† by age group — United States, March 1–December 12, 2020§



Comment: In general, trends in incidence and percentage of positive test results among preschool-aged children (0–4 years) and school-aged children and adolescents (5–17 years) paralleled those among adults throughout the summer and fall, including during the months that some schools were reopening or open for in-person education. In addition, reported incidence among children, adolescents, and young adults increased with age; among children aged 0–10 years, incidence and percentage of positive test results were consistently lower than they were among older age groups. Lower incidence among younger children and evidence from available studies suggest that the risk for COVID-19 introduction and transmission among children associated with reopening childcare centers and elementary schools might be lower than that for reopening high schools and institutions of higher education. As recent studies have indicated, schools who maintain mitigation strategies can operate safely. CDC recommends that K–12 schools be the last settings to close after all other mitigation measures have been employed and the first to reopen when they can do so safely. Lastly, in a study reported from the UK, they found children under 10 were half as likely as adults to spread the variant. Adolescents and teenagers between ages 10 and 19 were more likely than younger children to spread the variant, but not as likely as adults. The schools in US that closely adhered to the guidelines have not seen many infections, even when the virus was circulating at high levels in the community.

Interim Results of a Phase 1–2a Trial of Ad26.COV2.S Covid-19 Vaccine

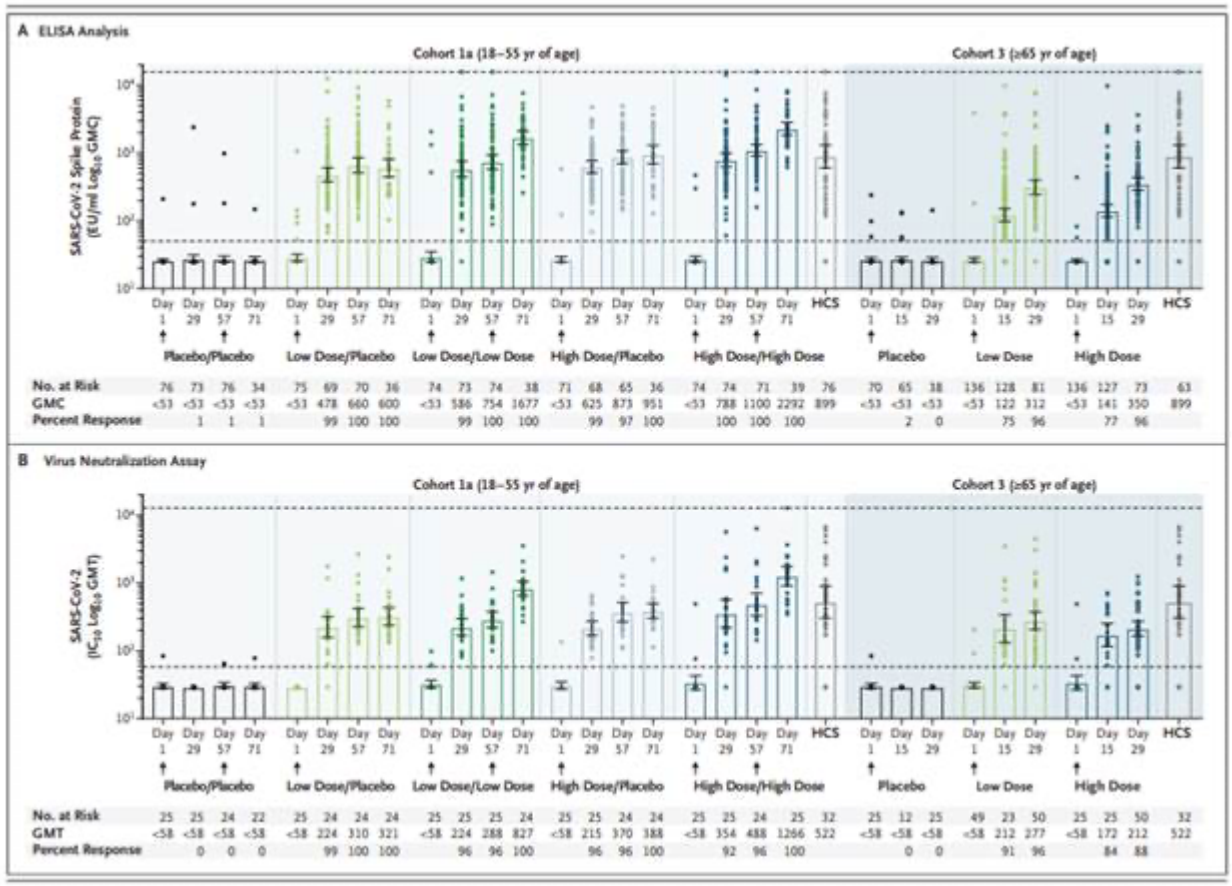
N Engl J Med published online January 13, 2021

DOI: 10.1056/NEJMoa2034201

Ad26.COV2.S, is a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector encoding a full-length and stabilized SARS-CoV-2 spike protein. This is a multicenter, placebo-controlled, phase 1–2a trial, randomly assigned healthy adults between the ages of 18 and 55 years (cohort 1) and those 65 years of age or older (cohort 3) to receive the Ad26.COV2.S vaccine at a dose of 5×10^{10} viral particles (low dose) or 1×10^{11} viral particles (high dose) per milliliter or placebo in a single-dose or two-dose schedule. Longer-term data comparing a single-dose regimen with a two-dose regimen are being

collected in cohort 2; those results were not reported here. The primary end points were the safety and reactogenicity of each dose schedule.

A total of 800 adults aged 18 to 55 or aged 65 and up were randomized to various combinations of low-dose or high-dose vaccines or placebo, given 56 days apart. At day 29 after the first dose, the seroconversion rate was 99% or more in the younger cohort across dosing groups. Older vaccine recipients had a 96% seroconversion rate. At 57 days after the first dose, antibody titers had increased further. Adverse events were common, with fatigue, headache, myalgia, and injection-site pain reported most often. On day 14, CD4+ T-cell responses were detected in 76 to 83% of the participants in cohort 1 and in 60 to 67% of those in cohort 3, with a clear skewing toward type 1 helper T cells. CD8+ T-cell responses were robust overall but lower in cohort 3.



Comment: This interim analysis indicates that vaccine candidate Ad26.COV2.S is safe and immunogenic in both younger and older adults. The potential of only one dose, the lower cost, and easy storage make this vaccine potentially very attractive if phase 3 trials demonstrate high protective efficacy. It is hoped this vaccine will be reviewed by FDA in the next month. The Astra Zeneca vaccine currently approved in the UK should also go before the FDA in the next month. The J&J vaccine could be a game changer.