I hope everyone had a good weekend and enjoyed the Super Bowl.

Under COVID-19 News I report on the revised FDA stance on Convalescent Plasma and the AstraZeneca vaccine trial in South Africa.

Under Journal Reviews I report on a retrospective trial on adding methylprednisolone to intravenous immunoglobulins in multisystem inflammatory syndrome in children (MIS-C). The next article looks at single dose AstraZeneca vaccine.

Have a wonderful day

Ed

COVID-19 News

FDA Limits Use of Convalescent Plasma as Covid-19 Treatment
February 4, 2021
The FDA is scaling back its authorization of the use of convalescent blood-plasma (CP) for Covid-19 patients in an effort to guide physicians who have faced a confusing data about the therapy's effectiveness. FDA revised to limit CP to patients early in the course of the disease and hospitalized patients with a medical condition that impairs their ability to make antibodies. Patients will be allowed to receive only plasma containing high concentrations of antibodies. The FDA update is meant so convalescent plasma can best be used on those who will benefit. The FDA reached its decision after evaluating results from several recent studies. Some showed benefits from CP while others showed no benefit. Two clinical trials of convalescent plasma for hospitalized patients shut down last month after investigators said there appeared to be no benefit. Three trials involving hospitalized patients recently reported some benefit for the plasma, but only when given to patients soon after admission. Still another trial showed that elderly outpatients given plasma shortly after showing symptoms were less likely to develop serious disease. [reviewed in Daily Briefing in last few weeks] Last month researchers at Mayo published data from 3,000 of those patients and reported an apparent survival benefit among hospitalized patients not on mechanical ventilation who received plasma containing high concentrations of antibodies early in their hospitalization. [NEJM reviewed in Daily Briefing last month]

Comment: Despite these findings, CP remains in demand. I think this is a step forward. This helps define, for the first time, guidance on when to use it and how to use CP. IDSA guideline panel recommends COVID-19 CP only in the context of a clinical trial. (Knowledge gap) NIH guidelines state there are insufficient data for the COVID-19 Treatment Guidelines Panel to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19.

AstraZeneca Vaccine Halted in South Africa
South Africa on Sunday halted use of the AstraZeneca vaccine after clinical trial evidence indicated that it did not protect against mild-to-moderate COVID-19 caused by B.1.351 the predominant variant in South Africa. Whether the vaccine protects against severe disease caused by B.1.351 is unclear. See comment.

Comment: The clinical trial participants who were evaluated were relatively young and unlikely to become severely ill, making it impossible for the scientists to determine whether the variant interfered

with the AstraZeneca vaccine's ability to protect against severe Covid-19, hospitalizations, or deaths. However, based on the immune responses detected in blood samples from people who were given the vaccine, investigators said they believed that the vaccine could yet protect against more severe cases. Pfizer and Moderna have both said that preliminary laboratory studies indicate that their vaccines, while still protective, are less effective against B.1.351. Novavax and Johnson & Johnson have also sequenced test samples from their clinical trial participants in South Africa, where the variant caused most cases — and both reported lower efficacy there than in the United States. Novavax said its vaccine was just under 50 percent effective in preventing Covid-19 in its South Africa trial. Johnson & Johnson reported that its single-shot vaccine was 57 percent effective in preventing moderate to severe Covid-19 in South Africa. B1.351 is now the dominant variant in South Africa and has been found in over 20 countries and a small number of cases have been reported in South Carolina, Maryland, and Virginia. Moderna has also begun developing a new form of its vaccine that could be used as a booster shot against the variant in South Africa.

Now for some good news: the variant known as B.1.1.7 and first identified in the UK, does not appear to interfere with vaccines. All five of the leading vaccines, and most recently AstraZeneca's product, have been found to offer similar levels of protection against B.1.1.7 compared to earlier lineages of the virus. Bottom line: vaccination is still our best tool to turning this pandemic into an endemic disease.

Journal Reviews

Association of Intravenous Immunoglobulins Plus Methylprednisolone vs Immunoglobulins Alone with Course of Fever in Multisystem Inflammatory Syndrome in Children
JAMA published online February 1, 2021
doi:10.1001/jama.2021.0694
This is a retrospective cohort study drawn from a national surveillance system with propensity score–matched analysis. All cases with suspected MIS-C were reported to the French National Public Health Agency. Confirmed MIS-C cases fulfilling the World Health Organization definition were included. The study started on April 1, 2020, and follow-up ended on January 6, 2021.

In France, roughly 100 children with confirmed MIS-C who were treated with IVIG and methylprednisolone were compared with similar children who received only IVIG as first-line treatment. Those who received dual therapy had significantly lower risk for treatment failure (i.e., persistence of fever for 2 days after starting treatment or fever recurrence within 7 days) than those who only received IVIG (9% vs. 38%). IVIG and methylprednisolone therapy vs IVIG alone was also significantly associated with lower risk of use of second-line therapy (absolute risk difference, -0.22 [95% CI, -0.40 to -0.04]; OR, 0.19 [95% CI, 0.06 to 0.61]; *P* = .004), hemodynamic support (absolute risk difference, -0.17 [95% CI, -0.34 to -0.004]; OR, 0.21 [95% CI, 0.06 to 0.76]), acute left ventricular dysfunction occurring after initial therapy (absolute risk difference, -0.18 [95% CI, -0.35 to -0.01]; OR, 0.20 [95% CI, 0.06 to 0.66]), and duration of stay in the pediatric intensive care unit (median, 4 vs 6 days; difference in days, -2.4 [95% CI, -4.0 to -0.7]).

Table 2. Primary and Secondary Analyses in the Propensity Score–Matched Cohorts

Outcomes	After propensity score matching				
	No. (%)		Absolute risk difference between groups (95% CI) [reference: IVIG alone]	Odds ratio (95% CI) [reference: IVIG alone]	*P* value
	IVIG and methylprednisolone (n = 32)	IVIG alone (n = 64)			
Primary outcome					
Treatment failure[a]	3 (9)	24 (38)	−0.28 (−0.48 to −0.08)	0.25 (0.09 to 0.70)	.008
Secondary outcomes					
Second-line treatment[b]	3 (9)	20 (31)	−0.22 (−0.40 to −0.04)	0.19 (0.06 to 0.61)	.004
Hemodynamic support[c,d]	2 (6)	15 (23)	−0.17 (−0.34 to −0.004)	0.21 (0.06 to 0.76)	.01
LVEF <55%[c]	2/12 (17)	14/40 (35)	−0.18 (−0.35 to −0.01)	0.20 (0.06 to 0.66)	.007
Duration of PICU stay, median (IQR), d	4 (2 to 5)	6 (4 to 8.5)	Reduction of days: −2.4 (−4.0 to −0.7)		.005

Comment: Adding methylprednisolone to intravenous immunoglobulins (IVIG) was associated with better outcomes in multisystem inflammatory syndrome in children (MIS-C). I was surprised JAMA published a retrospective propensity matched study. It was not a randomized trial. There was variation in the dosage and routes of steroid treatment used among the 34 children who received IVIG and methylprednisolone as first-line therapy, and the study design did not allow for comparing regimens. Despite propensity match, there may be confounders not considered. Lastly due to the rarity of this syndrome, the numbers were relatively small.

Single Dose Administration, and the Influence of the Timing of the Booster Dose on Immunogenicity and Efficacy of ChAdOx1 nCoV-19 (AZD1222) Vaccine

preprinted in Lancet-has not gone through peer review

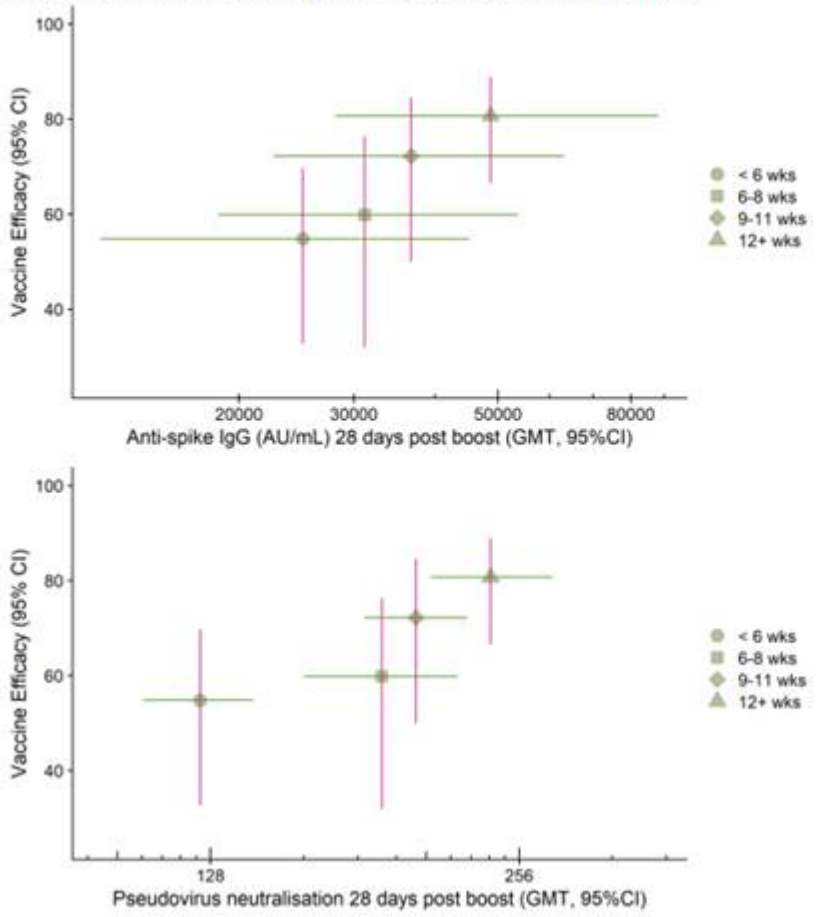
The primary analysis of the Phase III clinical trials from the UK, Brazil and South Africa, was published in a preprint form in Lancet. The primary analysis for efficacy was based on 17,177 participants accruing 332 symptomatic cases from the Phase III UK (COV002), Brazil (COV003) and South Africa (COV005) trials led by Oxford University and AstraZeneca, a further 201 cases than previously reported. As previously described, individuals over 18 years of age were randomized 1:1 to receive two standard doses (SD) of ChAdOx1 nCoV-19 (5x1010 viral particles) or a control vaccine/saline placebo. In the UK trial efficacy cohort, a subset of participants received a lower dose (LD, 2.2x1010 viral particles) of the ChAdOx1 nCoV-19 for the first dose.

Results demonstrated vaccine efficacy of 76% (CI: 59% to 86%) after a first dose, with protection maintained to the second dose. With an inter-dose interval of 12 weeks or more, vaccine efficacy increased to 82% (CI: 63%, 92%). Antibody levels were maintained during this period with minimal waning by day 90 (GMR 0.66, 95% CI 0.59, 0.74). In the SD/SD group, after the second dose, efficacy was higher with a longer prime-boost interval: VE 82.4% 95%CI 62.7%, 91.7% at 12+ weeks, compared with VE 54.9%, 95%CI 32.7%, 69.7% at <6 weeks. These observations are supported by immunogenicity data which showed binding antibody responses more than 2-fold higher after an interval of 12 or more weeks

compared with an interval of less than 6 weeks GMR 2.19 (2.12, 2.26) in those who were 18-55 years of age.

The analysis also showed the potential for the vaccine to reduce asymptomatic transmission of the virus, based on weekly swabs obtained from volunteers in the UK trial. The data showed that PCR positive readings were reduced by 67% (CI: 49%, 78%) after a single dose, and 50% (CI: 38% to 59%) after the two-dose regimen, supporting a substantial impact on asymptomatic transmission of the virus.

Figure 4 Relationship between binding and neutralising antibody 28 days post second dose, and vaccine efficacy against primary symptomatic COVID-19



Comment: The trial confirmed the AstraZeneca vaccine is safe and effective at preventing COVID-19, with no severe cases and no hospitalizations, more than 22 days after the first dose. The reduction in asymptomatic spread is great news. [not 100%] In addition, ChAdOx1 nCoV-19 vaccination programs aimed at vaccinating a large proportion of the population with a single dose, with a second dose given after a 3-month period may be an effective strategy for reducing disease and may be the optimal for rollout of a pandemic vaccine when supplies are limited in the short term. I believe the US should reconsider the current strategy and consider using a single dose strategy to immunize more people as long as supplies are limited. Efficacy estimates now include data from all four studies of the vaccine from 3 countries, and a breakdown by the interval between the two doses. Recent report

from South Africa and limited efficacy against B.1.351 variant needs to be considered. In the US very few cases have been reported but we are seeing increased cases due to the B.1.1.7 where all vaccines work.