I hope everyone had a relaxing weekend. Lots to share today so let's get started.

By now everyone has heard the FDA and now the CDC has approved the J&J vaccine for EUA. Please see my comment below. Next good news on the monoclonal front-combination (not monotherapy) monoclonals for the treatment of outpatients with mild-to-moderate COVID-19 who are at high risk for clinical progression work!

Under journal review two articles on transmission in fitness facilities. The next article is a systematic review and meta-analysis of RCTs on the use of convalescent plasma and outcomes. The last two articles look at interleukin-6 receptor antagonists with different results, however I urge everyone to read my comments since the two studies have some key differences.

Have a wonderful Monday

Ed

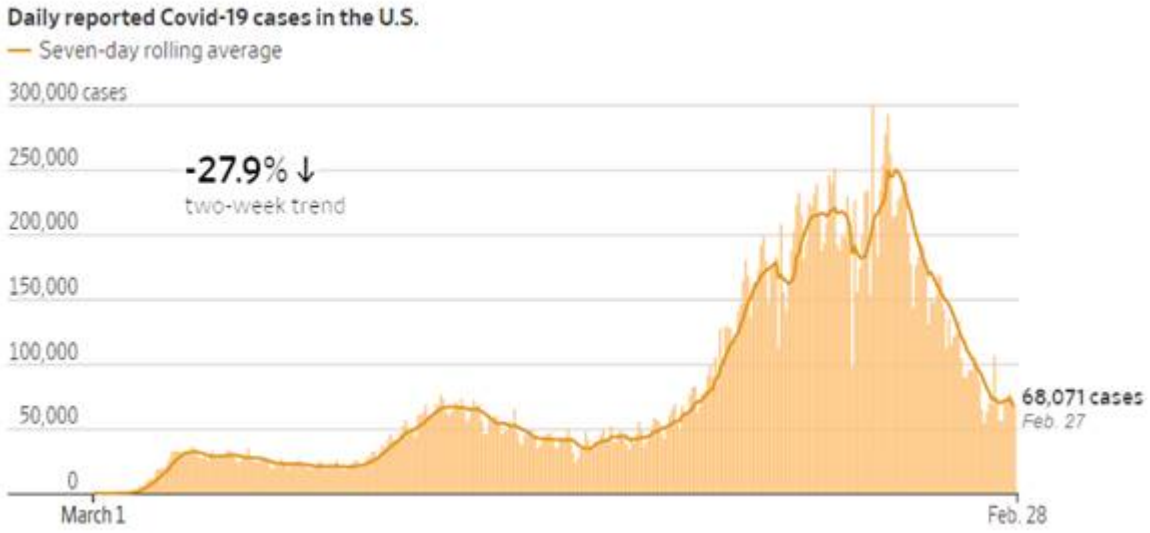
COVID-19 News

FDA and CDC Action on J&J Vaccine
The FDA Saturday issued an EUA for the Johnson & Johnson COVID-19 vaccine, giving the United States a third vaccine to fight the pandemic—one that offers an easier, one-dose option. The vaccine is the first adenovirus-based COVID-19 vaccine to be approved for emergency use in the United States and the first to be given as a single dose. It can also be stored at normal refrigeration temperatures, which eases shipping and storage. Johnson & Johnson has said it expects to produce 100 million doses for the US market in the first half of the year, starting with about 2 million doses allocated to states next week and increasing to 20 million doses by the end of March.

The CDC's ACIP panel Sunday voted to recommend the single-dose Johnson & Johnson COVID-19 vaccine with 12 in favor and 1 recusal for use in people ages 18 and older, based on the FDA's EUA. Members of the committee generally had favorable comments about the vaccine, but some expressed concerns. One concern was that in the large clinical trial, J&J's vaccine appeared to be less effective among people age 60 and older who had certain medical conditions such as diabetes and hypertension. J&J commented the results should be interpreted with caution because they are based on a relatively small number of Covid-19 cases in that subgroup. Committee members also began to wrestle with the potentially difficult task of comparing the three authorized vaccines and giving guidance about whether people should choose one over the others. The question has arisen partly because the overall efficacy of J&J's vaccine in a large trial was lower than that for Pfizer's and Moderna's from separate trials. However, ACIP members emphasized that, owing to differences in research protocols and settings, it is inappropriate to compare efficacy.

Comment: For now, all three are generally safe and effective. The best vaccine is the one you can access. Only ~15% of the US population has received one dose but this will accelerate as J&J is added to Pfizer and Moderna and vaccination campaigns are getting more shots into people's arms. I am truly cautiously optimistic, but we still need to be vigilant. Covid-19 cases, hospitalizations and deaths have all sharply dropped in recent weeks (see below) as the country comes down from its worst surge yet. Covid-19 cases in the U.S. have declined for the past several weeks, with the seven-day average dropping 74% since the Jan. 11 peak. Average daily hospital admissions, now 6,500 a day, have dropped

60% and are at their lowest point since the fall. Case counts however are still too high and might be plateauing; current levels of immunity are not enough to reach herd immunity and variants may gain a foothold in the U.S. In the end I agree with Dr. Rochelle Walensky, now is not the time to rapidly relax safety measures.



Monoclonals
The NIH now recommends the combination of bamlanivimab (700 mg) plus etesevimab (1400 mg) for the treatment of outpatients with mild-to-moderate COVID-19 who are at high risk for clinical progression. High-risk patients include those with a BMI at or above 35, diabetes, chronic kidney disease, or an immunocompromising condition; adults 65 and older; and those aged 12-17 years with sickle cell disease or congenital heart disease. The NIH recommends against use of bamlanivimab plus etesevimab in patients hospitalized for COVID-19.

Regeneron Pharmaceuticals said on Thursday that an independent panel found the company's COVID-19 monoclonal product had clear evidence in reducing the rates of hospitalization and deaths in patients. The monoclonal which is a combination of two antibodies casirivimab and imdevimab, was authorized in November for emergency use by the FDA. Independent Data Monitoring Committee found that both 1,200 mg and 2,400 mg doses of the monoclonal had reduced the rate of hospitalization and deaths compared with placebo, according to the company. The panel has recommended that Regeneron should stop enrolling patients in the placebo group for its ongoing late-stage trial. The company will share details of unblinded data later this month.

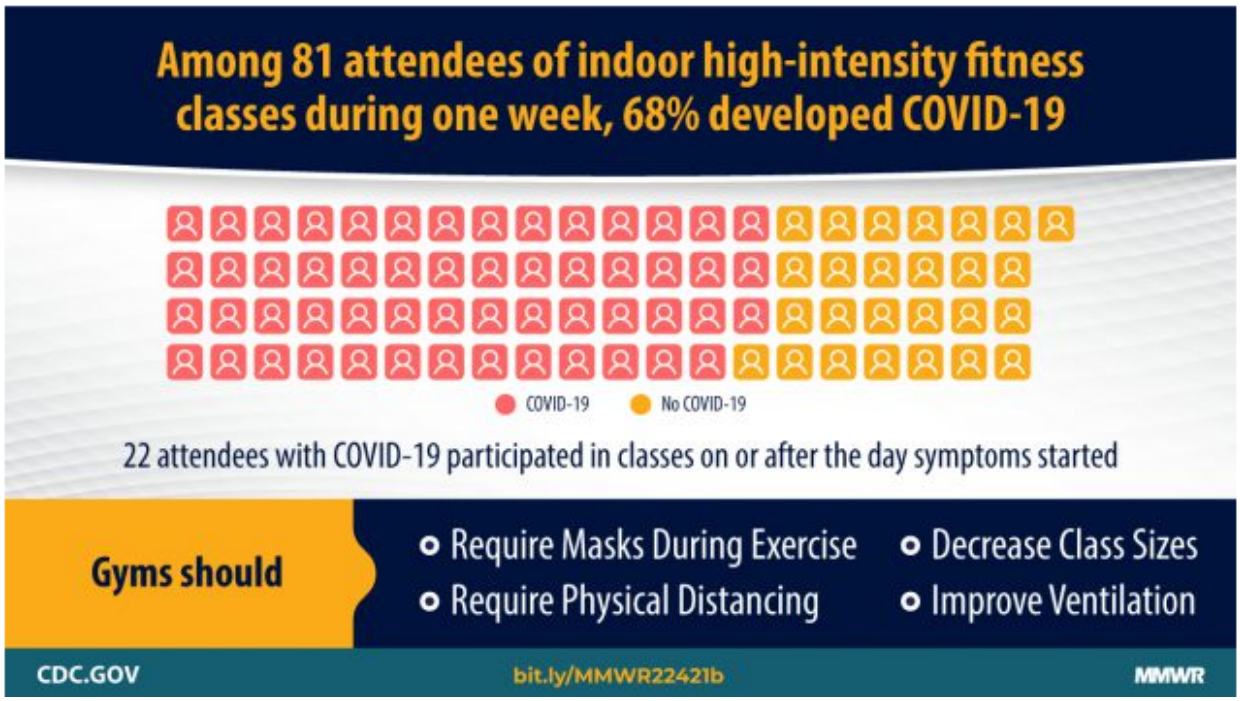
Comment: In the Daily Briefing on January 22, 2021, I reviewed a paper in *JAMA* comparing monotherapy with bamlanivimab vs placebo (June 17 -August 21) versus combination therapy with etesevimab and bamlanivimab vs placebo (August 22-September 3). Treatment with bamlanivimab and etesevimab combination therapy, but not bamlanivimab monotherapy, resulted in a reduction in SARS-CoV-2 log viral load at day 11 in patients with mild to moderate COVID-19. Hospitalization and ED visits appeared to be lower in the treatment group. What seems to have emerged is that combination monoclonals are better than monotherapy and treatment of outpatients with mild-to-moderate COVID-19 who are at high risk for clinical progression seems to be the optimal use of monoclonals.

Journal Review

COVID-19 Outbreak Among Attendees of an Exercise Facility — Chicago, Illinois, August–September 2020
MMWR published online February 24, 2021

Community Transmission of SARS-CoV-2 at Three Fitness Facilities — Hawaii, June–July 2020
MMWR published online February 24, 2021

Two articles in *MMWR* just published highlight the potential for high risk for COVID-19 transmission at indoor fitness centers. In the first, two thirds of 81 people who attended indoor classes at a Chicago gym during the last week of August 2020 developed COVID-19. Of these cases, three fourths attended classes during their infectious period, including some who were symptomatic! Many said they infrequently wore masks (less than 60% of the time). In the second article, researchers report on 21 COVID-19 cases linked to a fitness instructor at Hawaii exercise facilities. The instructor had taught classes before he developed symptoms. Of note, when the instructor wore a mask for a yoga class, none of the unmasked attendees developed COVID-19. When he did not wear a mask for other classes, the COVID-19 attack rate was as high as 100%. The authors of the first article note that "the increased respiratory exertion that occurs in the enclosed spaces of indoor exercise facilities facilitates transmission of SARS-CoV-2."

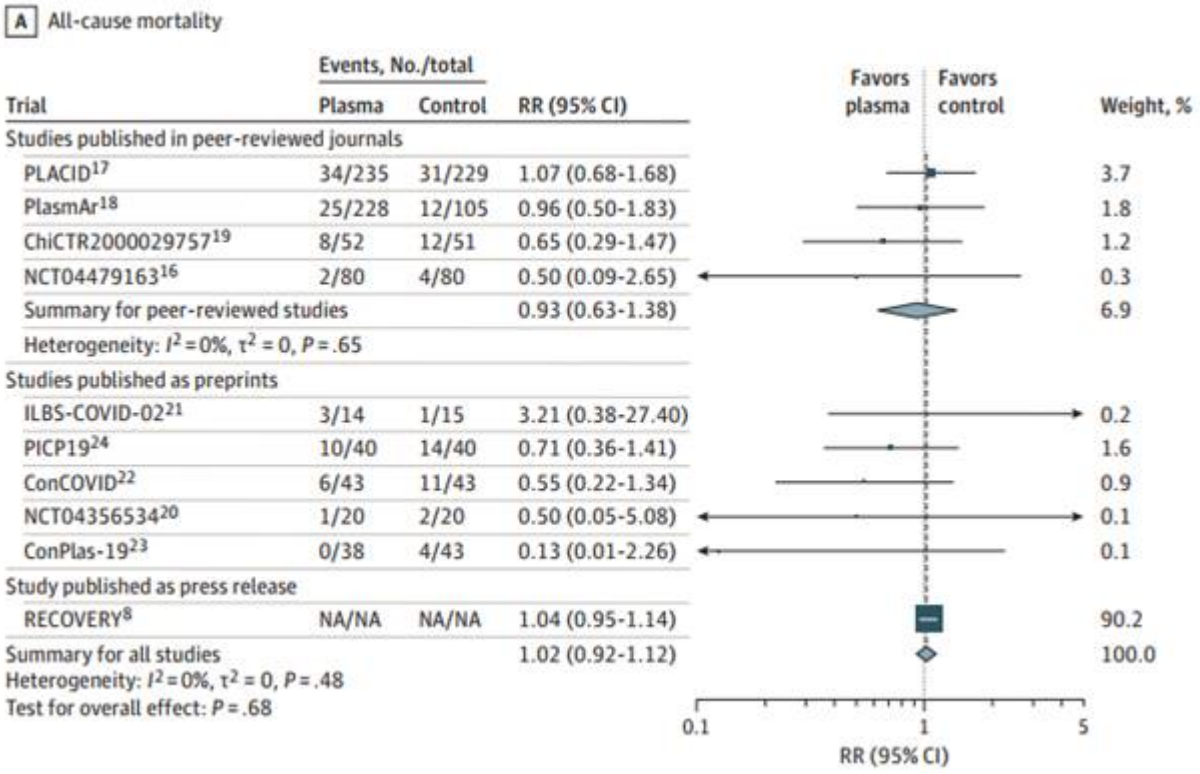


Comment: To reduce SARS-CoV-2 transmission in fitness facilities, staff members and participants should wear a mask, and facilities should enforce consistent and correct mask use (including during high-intensity activities) and physical distancing, improve ventilation, and remind participants and staff members to stay home when ill. Exercising outdoors or virtually could further reduce SARS-CoV-2 transmission risk. Face shields are not a substitute for masks! Facilities who have improved ventilation, enforce social distancing, limit size of exercised classes, require masks for most activities, and screen members have been able to open safely.

Association of Convalescent Plasma Treatment with Clinical Outcomes in Patients With COVID-19 A Systematic Review and Meta-Analysis

JAMA published online February 26, 2021
doi:10.1001/jama.2021.2747

The authors performed a meta-analysis of randomized clinical trials (RCTs) of convalescent plasma for the treatment of patients with COVID-19. Based on an analysis of 1060 patients from 4 RCTs published in peer-reviewed journals and 10 722 patients from 6 RCTs (5 published as preprints and 1 as a press release), the authors found that treatment with convalescent plasma vs placebo or standard of care was not associated with a significant decrease in all-cause mortality (risk ratio, 0.93 [95% CI, 0.63-1.38] for the 4 peer-reviewed RCTs; risk ratio, 1.0 [95% CI, 0.92-1.12] for all 10 RCTs) or with benefit for other clinical outcomes, including length of hospital stay, mechanical ventilation use, and clinical improvement or deterioration.



Comment: Of interest even though more than 100,000 patients have been treated in the US, none of the RCT were performed in the US. The conclusion of this analysis differs from the publication in *Mayo Cl Proc* reviewed last week in the Daily Briefing. The authors in that paper aggregated patient outcome data from 10 RCTs, 20 matched-control studies, two dose response studies, and 96 case-reports or case-series. Their analysis showed that early transfusion (within 3 days of hospital admission) of higher-titer plasma was associated with lower patient mortality.

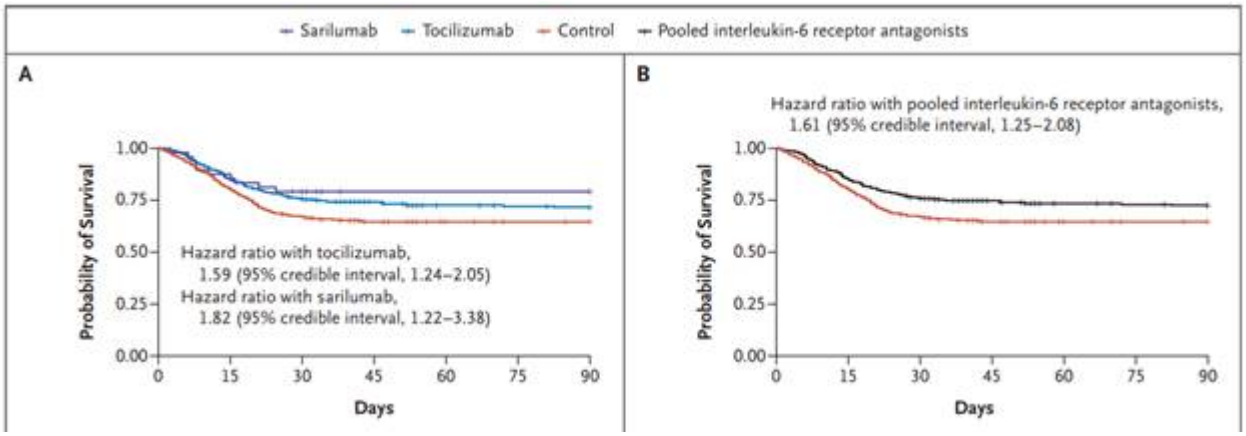
Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19:
Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP)

N Engl J Med published online February 26, 2021

DOI: 10.1056/NEJMoa2100433

The investigators evaluated tocilizumab and sarilumab in an ongoing international, multifactorial, adaptive platform trial. Adult patients with Covid-19, within 24 hours after starting organ support in the intensive care unit (ICU), were randomly assigned to receive tocilizumab (8 mg per kilogram of body weight), sarilumab (400 mg), or standard care (control). The primary outcome was respiratory and cardiovascular organ support-free days, on an ordinal scale combining in-hospital death (assigned a value of -1) and days free of organ support to day 21. The trial uses a Bayesian statistical model with predefined criteria for superiority, efficacy, equivalence, or futility. An odds ratio greater than 1 represented improved survival, more organ support-free days, or both. 353 patients had been assigned to tocilizumab, 48 to sarilumab, and 402 to control.

The investigators found that in critically ill patients with Covid-19, the interleukin-6 receptor antagonists tocilizumab and sarilumab were both effective as compared with the current standard of care, which importantly included glucocorticoids in the majority of patients (>80%) [see next paper]. The benefit was consistent across primary and secondary outcomes and across subgroups and secondary analyses. In particular, they observed both a shorter time to clinical improvement and lower mortality with tocilizumab and with sarilumab than with control. It is important to note that in this trial, patients had to be enrolled within 24 hours after starting organ support in the ICU. This may be an important factor to maximize effectiveness. [see comment after next article] Investigators and others have proposed using CRP (median > 130 with range 71-221) or other inflammatory markers to select patients with a hyperinflammatory state for treatment. There were no significant increases in serious adverse events reported.



Comment: see below after next article

Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia

N Engl J Med published online February 25, 2021

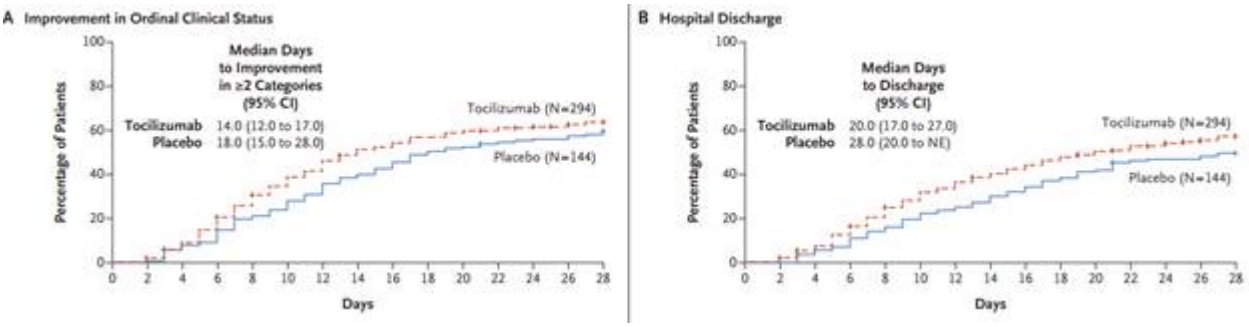
(COVACTA Trial)

DOI: 10.1056/NEJMoa2028700

This is a phase 3 trial, that randomly assigned patients who were hospitalized with severe Covid-19 pneumonia in a 2:1 ratio to receive a single intravenous infusion of tocilizumab (at a dose of 8 mg per kilogram of body weight) or placebo. Approximately one quarter of the participants received a second dose of tocilizumab or placebo 8 to 24 hours after the first dose. To be eligible patients needed a confirmed PCR and evidenced by bilateral chest infiltrates on chest radiography or computed tomography. Eligible patients had a blood oxygen saturation of 93% or less or a ratio of the partial

pressure of oxygen to the fraction of inspired oxygen of less than 300 mm Hg. Standard care according to local practice (antiviral treatment, low-dose glucocorticoids, convalescent plasma, and supportive care) was provided. However, concomitant treatment with another investigational agent (except antiviral drugs) or any immunomodulatory agent was prohibited. A lower percentage of patients received glucocorticoids in the tocilizumab group than in the placebo group both at baseline (57 [19.4%] vs. 41 [28.5%]) and during the trial (99 [33.7%] vs. 75 [52.1%]). [see study above] The primary outcome was clinical status at day 28 on an ordinal scale ranging from 1 (discharged or ready for discharge) to 7 (death) in the modified intention-to-treat population, which included all the patients who had received at least one dose of tocilizumab or placebo.

438 (294 in the tocilizumab group and 144 in the placebo group) were included in the primary and secondary analyses. The median value for clinical status on the ordinal scale at day 28 was 1.0 (95% confidence interval [CI], 1.0 to 1.0) in the tocilizumab group and 2.0 (non-ICU hospitalization without supplemental oxygen) (95% CI, 1.0 to 4.0) in the placebo group (between-group difference, -1.0; 95% CI, -2.5 to 0; P=0.31 by the van Elteren test). In the safety population, serious adverse events occurred in 103 of 295 patients (34.9%) in the tocilizumab group and in 55 of 143 patients (38.5%) in the placebo group. Mortality at day 28 was 19.7% in the tocilizumab group and 19.4% in the placebo group (weighted difference, 0.3 percentage points (95% CI, –7.6 to 8.2; nominal P=0.94). Using the ordinal scale for outcome has important limitations, including sensitivity to differences in local clinical practice, lack of proportionality between categories, insensitivity to events before the time point of assessment, and lack of an established minimum clinically important difference for therapeutic effect. The median CRP was ~150 in both groups.



Comments: A recent preprint from the RECOVERY trial showed that, as in REMAP-CAP above, treatment with tocilizumab led to lower death rates across groups with differing disease severity. [reviewed in the Daily Briefing several weeks ago] The results of these recent 2 trials appear contradictory, but a deeper dive I think helps explain the differences. First the timing of treatment may be crucial in understanding responses. Second, the periods of time over which the trials were conducted was different. One particularly significant change has been that patients with severe disease now almost universally receive glucocorticoids since these drugs were shown in July 2020 to reduce mortality. Only a minority of patients in the COVACTA trial were treated with glucocorticoids. Fewer in the group that received tocilizumab (19.4%) than in the group that received placebo (28.5%) also received glucocorticoids. In contrast, 93% and 82% of all patients in REMAP-CAP and the RECOVERY trial, respectively, were receiving glucocorticoid therapy. Subgroup analysis in the RECOVERY trial indicated that those receiving steroids had a survival advantage, which suggest a treatment effect with interleukin-6 inhibition. Interleukin-6 blockade plus glucocorticoids, acting in different ways, may together improve outcomes. For now, I am left with the current evidence that interleukin-6 inhibitors, at least under some circumstances probably improves outcomes if given early. I think the updated IDSA Guidelines got it

right: Among hospitalized adults with progressive severe* or critical COVID-19 who have elevated markers of systemic inflammation, the IDSA guideline panel suggests tocilizumab in addition to standard of care (i.e., steroids) rather than standard of care alone. (Conditional recommendation, Low certainty of evidence)