Good morning. I did not get a response on the article on RDV. Question to all of you, do you still find the Covid-19 Briefing of value to your work and education?

In today's Briefing under Covid-19 News I start out with the FDA's panel deliberation on the Pfizer application to immunize children ages 5-11. Next is a CDC update Monday regarding vaccinations for some immunocompromised people.

Under Journal Review an important RCT on the use of fluvoxamine for early SARS-CoV-2 infections in persons with a known risk factor for progression to severe disease. Next an RCT on use of the MCA sotrovimab also for early infection in persons with risk for severe disease. The last article examines the mortality rates within the general population of vaccinated and unvaccinated persons.

Have a great weekend.

Ed

COVID-19 News

FDA Advisors Recommend Pfizer Vaccine for Children 5-11
Tuesday the expert panel, called the Vaccines and Related Biological Products Advisory Committee, reviewed scientific data about the vaccine's safety and effectiveness in children. In a study of 2,268 children 5 to 11 years, the vaccine was generally well-tolerated and generated levels of neutralizing antibodies comparable with those seen in subjects who were 16 to 25 years. Subjects got 10-microgram dose three weeks apart. No cases of myocarditis were found in the children's study, though it was too small to detect the potential risk. After the FDA approval, the CDC's ACIP will review the data and recommend guidance on who should get vaccinated.

Comment: Children initially had a relatively low risk of severe disease and death from Covid-19, but more have been hospitalized than earlier in the pandemic due to the Delta variant. Severe pediatric Covid-19 is still not as common as in adults, but it is not insignificant with ~600 children dying of Covid-19. In addition, more than 8,300 children ages 5 to 11 have been hospitalized, and roughly one-third of them were admitted to the ICU. At least 94 children in this age group have died. Experts hope vaccinating children is important to protect not only them, but people around them. Some members said they had concerns about myocarditis and other potential side effects, but wanted to ensure that the vaccine was available to those children who are at highest risk of becoming severely ill such as patients with obesity, cardiac and pulmonary conditions, immunocompromised children etc. Data presented from the CDC found that up to 40% of children between 5 and 11 years old have already been infected many without symptoms. [some experts believe the number is lower] The panel questioned whether all kids needed two doses and whether children previously infected might need just one dose or no dose at all. With Covid-19 rates decreasing and most children are not at risk for severe disease and concern over safety with only 2268 children in the trial, it will be interesting to see the recommendation from ACIP next week. Vaccinating children will help slow the spread of the disease to the unvaccinated and to more at-risk adults. Parents and other family members can also protect their children by getting vaccinated themselves.

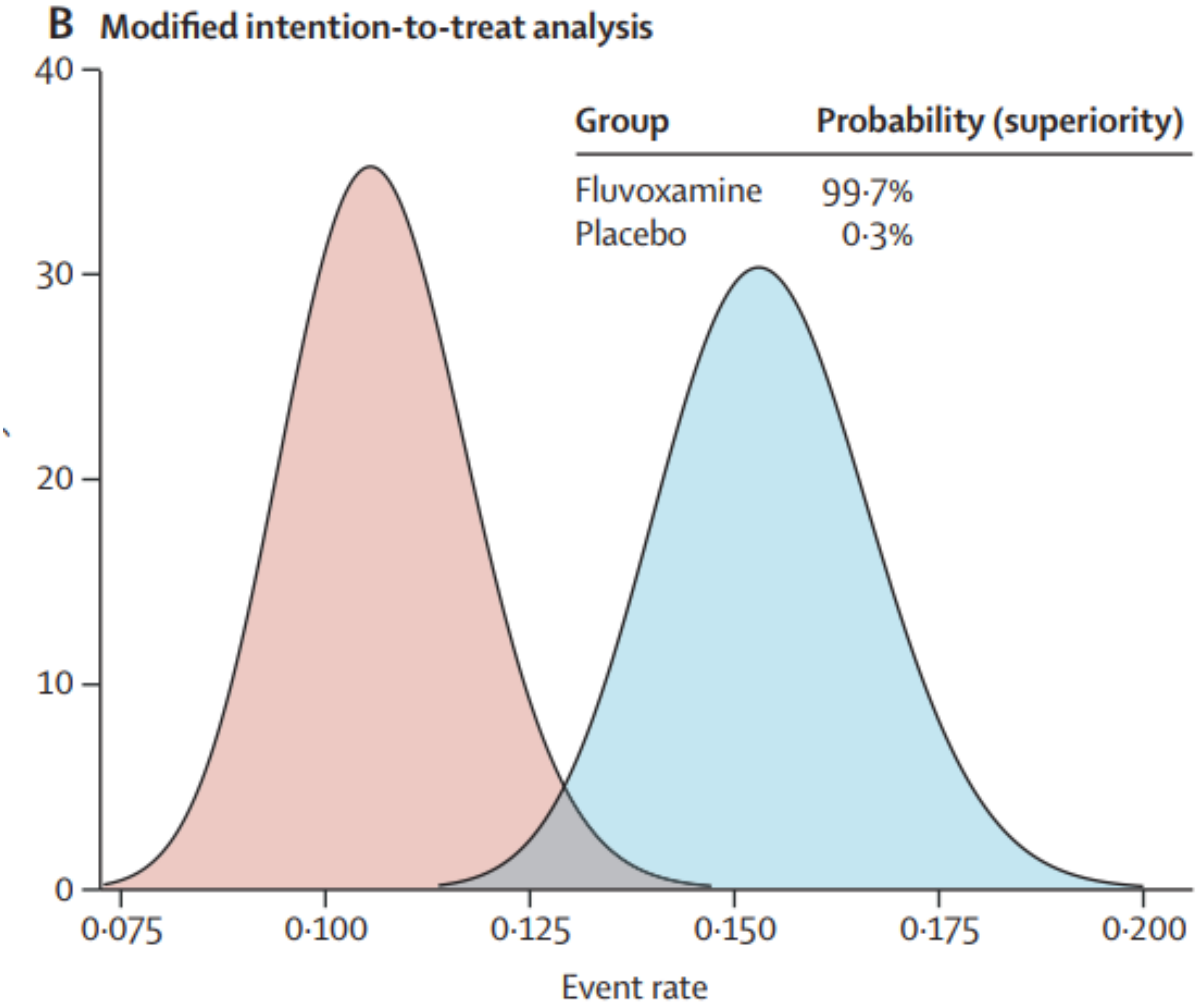
Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States

CDC October 25, 2021
CDC issued updated guidance Monday saying some immunocompromised people can get a fourth COVID-19 vaccine dose for additional protection. Some US adults with weakened immune systems who have received a third dose of either the Pfizer or Moderna vaccine may become eligible for a fourth shot as a booster next year. The earliest people will be eligible for a fourth shot as a booster would be February. The CDC updated its guidelines on Monday, adding the possibility of a fourth booster dose for many immunocompromised people, including those undergoing chemotherapy, recovering from a solid organ transplant, or facing certain other medical issues, like infection with H.I.V.

Comment: This was released without much fanfare. Since SARS-Co-2 is not going away and will become endemic for the foreseeable future the need to booster doses needs to be studied beyond the immunocompromised.

Journal Review

Effect of Early Treatment with Fluvoxamine on Risk of Emergency Care and Hospitalisation among Patients with COVID-19: The TOGETHER Randomised, Platform Clinical Trial
Lancet Glob Health published online October 27, 2021
doi.org/10.1016/S2214-109X(21)00448-4
This is a placebo-controlled, randomized, adaptive platform trial done among high-risk symptomatic adults confirmed positive for SARS-CoV-2 including eligible patients with a known risk factor for progression to severe disease. Patients were randomly assigned (1:1) to either fluvoxamine (100 mg twice daily for 10 days) or placebo. The trial was initiated on June 2, 2020, with the current protocol reporting randomization to fluvoxamine from Jan 20 to Aug 5, 2021, when the trial arms were stopped for superiority. 741 patients were allocated to fluvoxamine and 756 to placebo. The mean age of participants was 50 years (range 18-102 years); 58% were female. The proportion of patients observed in a COVID-19 emergency setting for more than 6 hr or transferred to a tertiary hospital due to COVID-19 was lower for the fluvoxamine group compared with placebo (79 [11%] of 741 *vs* 119 [16%] of 756); relative risk [RR] 0·68; 95% Bayesian credible interval [95% BCI]: 0·52–0·88), with a probability of superiority of 99·8% surpassing the prespecified superiority threshold of 97·6% (risk difference 5·0%). Of the composite primary outcome events, 87% were hospitalizations. Findings for the primary outcome were similar for the modified intention-to-treat analysis (RR 0·69, 95% BCI 0·53–0·90) and larger in the per-protocol analysis (RR 0·34, 95% BCI, 0·21–0·54). There were 17 deaths in the fluvoxamine group and 25 deaths in the placebo group in the primary intention-to-treat analysis (odds ratio [OR] 0·68, 95% CI: 0·36–1·27). There was only one death in the fluvoxamine group and 12 in the placebo group for the perprotocol population (OR 0·09; 95% CI 0·01–0·47). They found no significant differences in number of treatment adverse events among patients in the fluvoxamine and placebo groups.



Comment: Fluvoxamine belongs to a class of antidepressants called selective serotonin reuptake inhibitors, or SSRIs. The investigators found that patients who received fluvoxamine were 32% less likely to be hospitalized than those in the placebo group. Among patients who were compliant to the regimen and reported taking the drug or placebo for at least eight days of the 10-day course, there was an even bigger difference—a 66% reduction in hospitalization and 91% reduction in death rates.

Fluvoxamine has been shown to be safe and costs about $4 for a 10-day course. Fluvoxamine's low cost and wide availability make it a compelling alternative to other Covid-19 therapies including monoclonal antibody treatments, which are costly and require an infusion. Another potential treatment molnupiravir, will cost the US government around $700 per course in the US. The result of this trial provides compelling evidence of fluvoxamine's benefit in reducing acute morbidity from COVID-19 illness. The NIH has an ongoing RCT examining the efficacy of fluvoxamine.

Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab
N Engl J Med published online October 27, 2021
DOI: 10.1056/NEJMoa2107934

This is a multicenter, double-blind, phase 3 trial, which randomly assigned, in a 1:1 ratio, nonhospitalized patients with symptomatic Covid-19 ≤5 days after the onset of symptoms and at least one risk factor for disease progression. The patient received either a single infusion of sotrovimab at a dose of 500 mg or placebo. The primary efficacy outcome was hospitalization (for >24 hours) for any cause or death within 29 days after randomization.

This publication used a prespecified interim analysis, which included an intention-to-treat population of 583 patients (291 in the sotrovimab group and 292 in the placebo group). 3 patients (1%) in the sotrovimab group, as compared with 21 patients (7%) in the placebo group, had disease progression leading to hospitalization or death (relative risk reduction, 85%; 97.24% confidence interval, 44 to 96; P=0.002). In the placebo group, 5 patients were admitted to the intensive care unit, including 1 who died by day 29. Safety was assessed in 868 patients (430 in the sotrovimab group and 438 in the placebo group). Adverse events were reported by 17% of the patients in the sotrovimab group and 19% of those in the placebo group; serious adverse events were less common with sotrovimab than with placebo (in 2% and 6% of the patients, respectively).

Comment: The relative risk reduction in hospitalization (for >24 hours) or death between patients who received a single 500-mg dose of sotrovimab and those who received placebo was 85%. Sotrovimab was selected to have an intrinsically higher barrier to resistance because of targeting a pan-sarbecovirus epitope. However, with only three hospitalizations in the sotrovimab group, it was not possible to determine which patient or disease characteristics might be associated with sotrovimab treatment failure. In addition, the number of patients in the sotrovimab group in the safety analysis population was modest (430 patients), and thus a rare adverse event (in <1% of the patients) may not have been observed. Third, the presence of a baseline autologous antibody response to SARS-CoV-2 has not yet been analyzed to determine what effect emerging autologous immunity may have on the safety and efficacy of sotrovimab. Given its in vitro activity against variants of interest and concern I believe sotrovimab has the potential to remain therapeutically useful even as new variants may emerge.

COVID-19 Vaccination and Non-COVID-19 Mortality Risk — Seven Integrated Health Care Organizations, United States, December 14, 2020-July 31, 2021
MMWR October 22, 2021
To date there are no studies comparing mortality rates within the general population of vaccinated and unvaccinated persons. To determine mortality not associated with COVID-19 (non-COVID-19 mortality) after COVID-19 vaccination in a general population setting, a cohort study was conducted during December 2020-July 2021 among approximately 11 million persons enrolled in seven Vaccine Safety Datalink (VSD) sites. After standardizing mortality rates by age and sex, this study found that COVID-19 vaccine recipients had lower non-COVID-19 mortality than did unvaccinated persons. After adjusting for demographic characteristics and VSD site, this study found that adjusted relative risk (aRR) of non-COVID-19 mortality for the Pfizer vaccine was 0.41 (95% confidence interval [CI] = 0.38–0.44) after first dose and 0.34 (95% CI = 0.33–0.36) after second dose. The aRRs of non-COVID-19 mortality for the Moderna vaccine were 0.34 (95% CI = 0.32–0.37) after the first dose and 0.31 (95% CI = 0.30–0.33) after the second dose. The aRR after receipt of the J&J vaccine was 0.54 (95% CI = 0.49–0.59). There is no increased risk for mortality among COVID-19 vaccine recipients. This finding reinforces the safety profile of currently approved COVID-19 vaccines in the US.

Comment: In a cohort of 6.4 million COVID-19 vaccinees and 4.6 million demographically similar unvaccinated persons, recipients of the Pfizer, Moderna, or J&J vaccines had lower non-COVID-19 mortality risk than did the unvaccinated comparison groups. As important, there is no increased risk for

mortality among COVID-19 vaccine recipients. One explanation for lower mortality risk after COVID-19 vaccination suggests substantial healthy vaccinee effects (i.e., vaccinated persons tend to be healthier than unvaccinated persons). Among persons aged 12-17 years, mortality risk did not differ between Pfizer vaccinees and unvaccinated persons. This study was observational, and individual-level confounders that were not adjusted for which might affect mortality risk, including baseline health status, underlying conditions, health care utilization, and socioeconomic status. Although deaths associated with COVID-19 were excluded, causes of death were not assessed. It is possible that the algorithm used might have misclassified some deaths associated with COVID-19. Finally, the findings might not be applicable to the general population since VSD includes approximately 3% of the U.S. population, but it appears representative of the general population with regard to several demographic and socioeconomic characteristics.