What a week!

Under COVID-19 News I report on the J&J second dose response. The next item is related to the dueling opinions between FDA, ACIP, and Rochelle Walensky. In all my years in ID and public health I have never seen such a spectacle. Why do we need multiple expert panels? The politics around this pandemic have hurt the very people we are trying to help. I have tried my best in the Briefing to report the science and keep everyone up-to-date and be honest about what we do not know as the science evolved. I have no control over the messaging and politics at a national level, but we need a deep debriefing after this pandemic is behind us so we do not repeat the mistakes around Covid-19.

Under Journal Review I have selected 3 very different articles. First the report on the real-world effectiveness of the vaccines at preventing symptomatic illness in HCW. Next a meta-analysis on the use of steroids in non-oxygen dependent Covid-19 patients. The last article draws attention to delirium in Covid-19 patients admitted to the ICU.

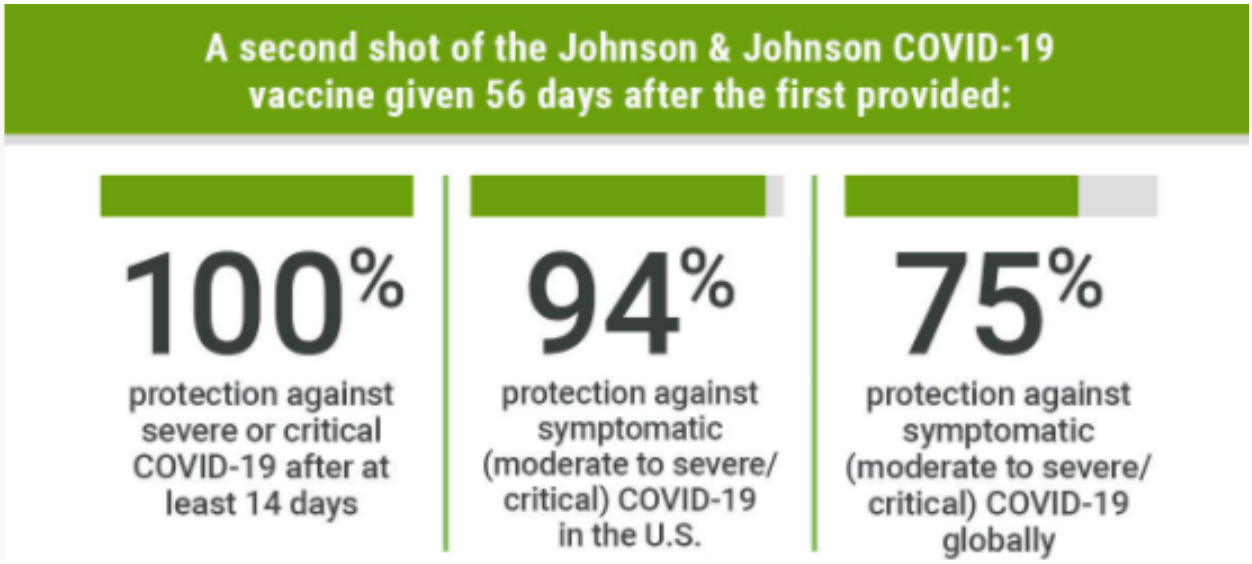
I hope every is able to relax this weekend and enjoy the start of Fall.

Ed

## COVID-19 News

**J&J Says Covid-19 Vaccine Booster Two Months After First Shot Increases Protection**
Data released Tuesday from a late-stage clinical trial showed that study participants in 10 countries including the U.S. who received a second dose of the company's vaccine two months after the first had 75% protection against symptomatic Covid-19. Participants in the U.S. had 94% protection against the illness. J&J didn't explain the reason for the difference in efficacy rates.

A double dose of the vaccine provided participants with 100% protection against severe or critical Covid-19 at least two weeks after the second shot. J&J said Tuesday that an extra shot given two months after the first boosted antibody levels four to six times higher than observed after the single shot. It said a booster administered six months after the first shot initially increased antibody levels ninefold and continued to climb to 12-fold higher four weeks after the second shot. J&J released some of the six-month boosting data in August. Side effects with two doses were comparable to those seen in studies with the single-dose vaccine.




**Comment:** The data are supportive of giving a second shot of the J&J vaccine, anywhere from two months onwards. The longer you wait, the better the boost will likely be which is what we have learned about the mRNA vaccines.

**Following FDA, ACIP Recommends COVID-19 Booster Shots [With Some Differences]**
Americans aged 65 and older who received the two-dose Pfizer vaccine should get a third booster dose of that vaccine if it has been at least 6 months since completing their vaccination series.

That was the recommendation the FDA made Wednesday, and it was echoed Thursday during a meeting of the CDC's ACIP.

In addition to those 65 and older, the FDA authorized booster doses of the Pfizer vaccine for people 18 through 64 who are at high risk of severe COVID-19 or whose institutional or occupational exposure puts them at high risk of severe COVID-19. ACIP agreed with recommending a booster for the first group but not the second. [see below] The FDA amended the guidance [this is under EUA] for the Pfizer COVID-19 vaccine to allow for a booster dose in certain populations such as health care workers, teachers and day care staff, grocery workers, and those in homeless shelters or prisons, among others. [see ACIP below]

ACIP voted on four questions. They agreed that vaccine boosters should be used for those 65 and older, and for those 50 to 64 who have underlying medical conditions that make them at risk for severe COVID-19. The third recommendation the committee considered was a booster for those 18 to 49 based on individual benefit and risk given underlying medical conditions. The third recommendation passed 9-6. The fourth and final consideration was for those 18 and older who worked in an occupational setting that put them at more risk for COVID-19 infections, including HCWs, people who live in congregate settings, and caregivers for the immunocompromised. The fourth did not pass, by a 6-9 vote. Those who voted nay said these terms were too broad and allowed for too much gray area in who should get a booster.

**Comment:** The ACIP left out HCWs, a group many expected would be first in line for third doses for those at risk. This is a departure from the FDA's authorization, which included boosters for those 65 and over and for those aged 18-64 who are at high risk for severe illness from SARS-CoV-2 infection,

*including* essential workers — such as those in healthcare — whose jobs increase their risk for infection. Confused ☹ We are now entering the booster confusional state. We now have different recommendations from FDA and CDC!!! Just when I thought it couldn't get any worse.

I am not finished yet! CDC Director Dr. Rochelle Walensky late yesterday signed off on a series of recommendations from the panel, saying boosters should be offered to people 65 and over as well as those 50 to 64 years with underlying medical conditions. But one of Dr. Walensky's endorsements went against the panel's recommendation. She said people should be offered boosters if they are ages 18 to 64 years and are HCWs or have another job that puts them at increased risk of being exposed to the virus. [I actually agree with Walensky to an extent – other than HCWs, prisons etc., which jobs clearly puts them at increased risk of exposure?]

The FDA is still considering Moderna's application to market booster doses. J&J hasn't yet applied to the FDA for permission to offer second doses in the US.

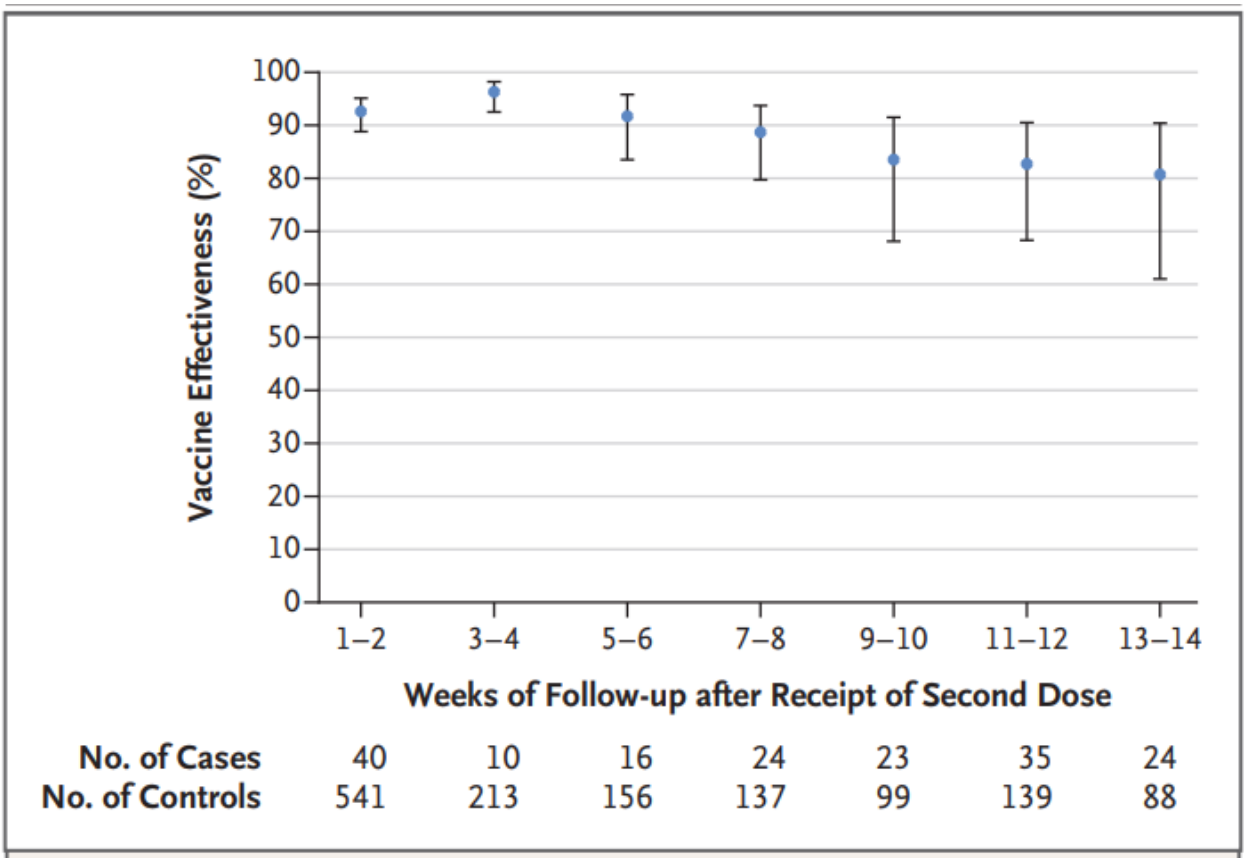
The CDC COVID Data Tracker shows only 54.9% of Americans are fully vaccinated, and 64% have received at least one dose of COVID-19 vaccine. [many have received one dose and not come back for their second dose] The discussion of how and if to implement boosters comes as CDC data show that the US last week had its slowest week of first-dose vaccinations since mid-July.

I am very concerned that the back-and-forth over who should get the extra doses has confused people and could potentially deter some who would benefit from the additional dose or who are vaccine hesitant. **I have said this multiple times, we need to focus on the unvaccinated.**

## Journal Review

**Effectiveness of mRNA Covid-19 Vaccine among U.S. Health Care Personnel**
N Engl J Med published online September 22, 2021
DOI: 10.1056/NEJMoa2106599
The investigators conducted a test-negative case-control study involving health care personnel across 25 U.S. states. Cases were defined based on a positive PCR or antigen-based test for SARS-CoV-2 and at least one Covid-19-like symptom. Controls were defined on the basis of a negative PCR test for SARS-CoV-2, regardless of symptoms, and were matched to cases according to the week of the test date and site. Using conditional logistic regression with adjustment for age, race and ethnic group, underlying conditions, and exposures to persons with Covid-19, we estimated vaccine effectiveness for partial vaccination (assessed 14 days after receipt of the first dose through 6 days after receipt of the second dose) and complete vaccination (assessed ≥7 days after receipt of the second dose)

Vaccine effectiveness for partial vaccination was 77.6% (95% confidence interval [CI], 70.9 to 82.7) with the Pfizer vaccine and 88.9% (95% CI, 78.7 to 94.2) with the Moderna vaccine. For complete vaccination, vaccine effectiveness was 88.8% (95% CI, 84.6 to 91.8) and 96.3% (95% CI, 91.3 to 98.4), respectively. Vaccine effectiveness was similar in subgroups defined according to age (<50 years or ≥50 years), race and ethnic group, presence of underlying conditions, and level of patient contact. Estimates of vaccine effectiveness were lower during weeks 9 through 14 than during weeks 3 through 8 after receipt of the second dose, but confidence intervals overlapped widely.

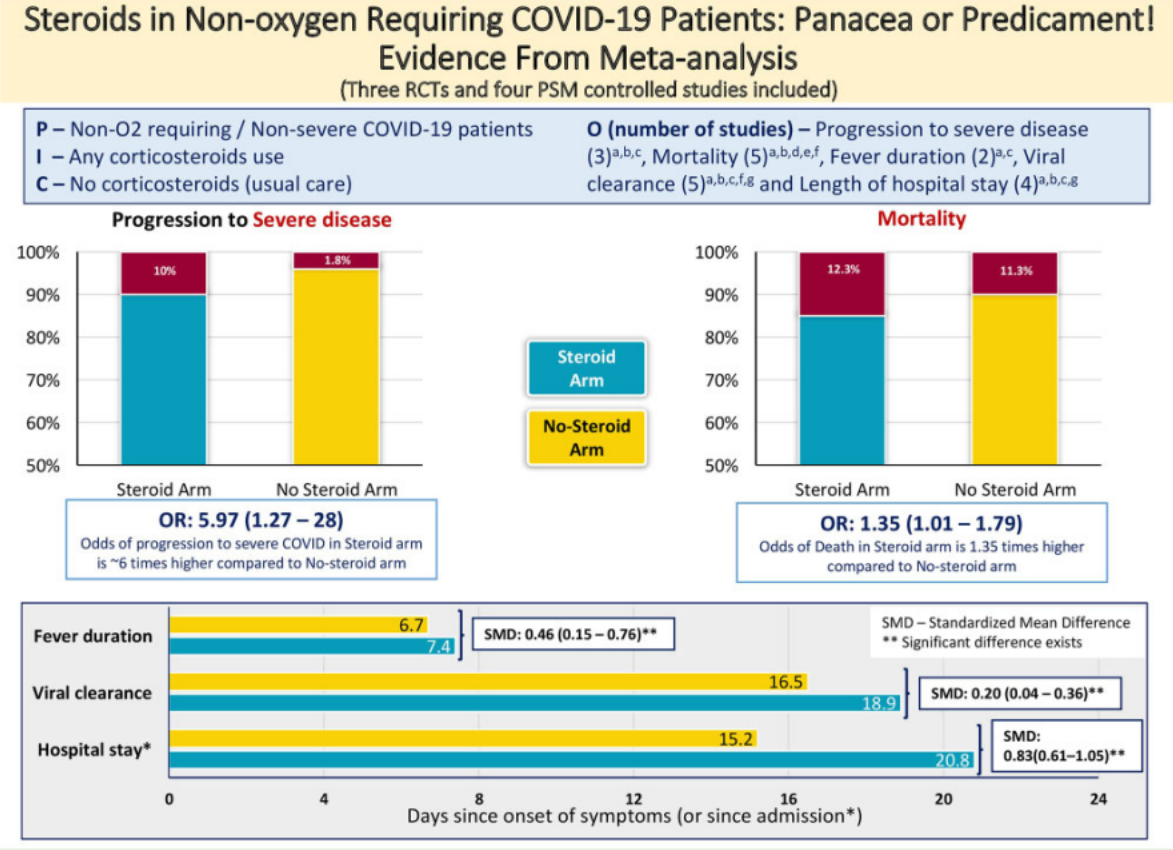



**Comment:** The investigators evaluated the real-world effectiveness of the vaccines at preventing symptomatic illness in about 5,000 health care workers in 25 states. The study found that the Pfizer vaccine had an effectiveness of 88.8 percent, compared with Moderna's 96.3 percent. Research published on Friday by the CDC found that the efficacy of the Pfizer vaccine against hospitalization fell from 91 percent to 77 percent after a four-month period following the second shot. The Moderna vaccine showed no decline over the same period. [Briefing September 21, 2021] A lot has been made of a slight difference between Pfizer and Moderna, but both vaccines are highly effective. J&J is still a good vaccine but underperforms with one dose. I hope with the new J&J data (see above) that the FDA will approve a second dose.

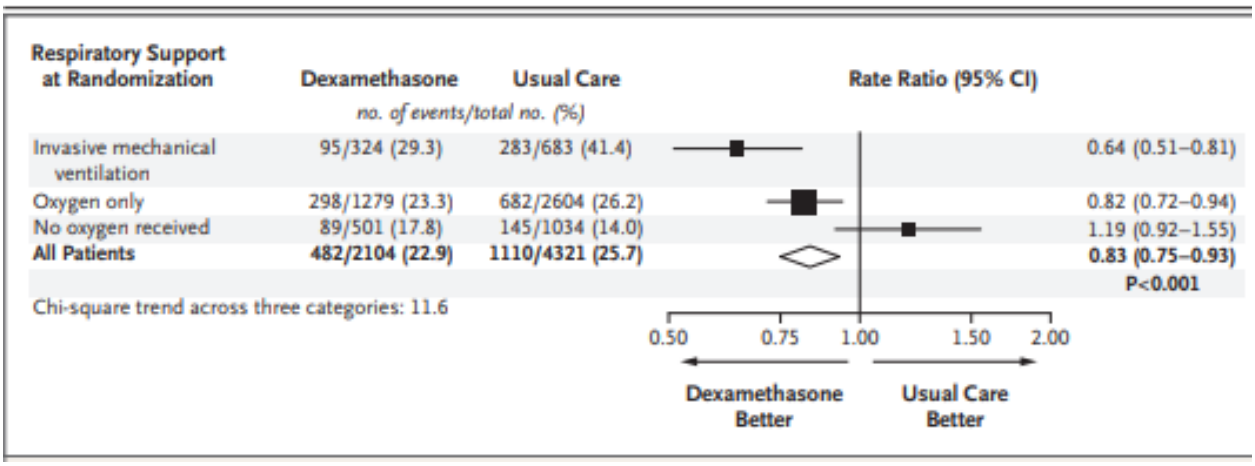
**Steroids Use in Non-Oxygen Requiring COVID-19 Patients: A Systematic Review and Meta-Analysis**
Int J Medicine published online August 4, 2021; article provided by Shivani Patel
doi: 10.1093/qjmed/hcab212
Corticosteroids have become the mainstay treatment in severe COVID-19. However, its role in mild disease is controversial due to lack of robust scientific evidence. The authors looked at PubMed, EMBASE, Web of Science, and medRxiv from 31 December 2019 to 14 May 2021 for studies that reported effectiveness of steroids in non-oxygen requiring COVID-19 patients in terms of progressing to severe disease, mortality, duration of fever, duration of viral clearance and length of hospital stay (LOS). Studies on inhalational steroids, case reports, and reviews were excluded.

A total of 6411 studies were identified, 2990 articles were screened after exclusion. Seven studies which fit the criteria (involving 2214 non-oxygen requiring COVID-19 patients) were included and analyzed. Overall odds of progression to severe disease among the non-oxygen requiring COVID-19 patients

receiving steroids was 5.97 [95% confidence interval (CI): 1.27–27.99, I2 ¼ 0%] and odds of death (OR: 1.35, 95% CI: 1.01–1.79; I2 ¼ 0%) as compared to the patients not receiving steroids. Mean duration of fever (7.4 days), duration to viral clearance (18.9 days) and LOS (20.8 days) were significantly higher in the steroid arm, as compared to that in no-steroid arm (6.7, 16.5 and 15.2 days, respectively).




**Comment:** Steroids in non-oxygen requiring COVID-19 patients can be more detrimental than beneficial. The previous published studies analyzing the role of steroids in mild COVID showed no significant benefit including the results from the RECOVERY Trial which did not see a benefit in non-oxygen hospitalized patients infected with SARS-CoV-2. [N Engl J Med 2021; 384:693-704]



The use of steroids for short term may be safe, but the potential side effect of developing hyperglycemia and requirement for insulin therapy especially in COVID-19 patients can lead to progression to severe illness and increased in-hospital mortality. The inappropriate use has a risk of tilting the balance in favor of worse outcomes without benefit and may impact viral shedding.

**Delirium and Neuropsychological Outcomes in Critically Ill Patients with COVID-19: A Cohort Study**
BMJ Open 2021;11:e050045
doi:10.1136/bmjopen-2021-050045
Patients (n=148) with COVID-19 admitted to an intensive care unit between 1 March 2020 and 31 May 2020 were eligible for inclusion. Delirium was the primary outcome, assessed via validated chart review method. Secondary outcomes included measures related to delirium, such as delirium duration, antipsychotic use, length of hospital and intensive care unit stay, inflammatory markers and final disposition. Neuroimaging data were also collected. Finally, a telephone survey was conducted between 1 and 2 months after discharge to determine neuropsychological function via the following tests: Family Confusion Assessment Method, Short Blessed Test, Patient-Reported Outcomes Measurement Information System Cognitive Abilities 4a and Patient-Health Questionnaire-9. Delirium prevention strategies, based on the ABCDEF ICU liberation bundle [Wes Ely] were also recorded. CAM screening was conducted every 12 hours by the bedside ICU nurse per hospital protocol.

Delirium was identified in 108/148 (73%) patients, with median (IQR) duration lasting 10 (4-17) days. In the delirium cohort, 50% (54/108) of patients were African American and delirious patients were more likely to be female (76/108, 70%) (absolute standardized differences >0.30). Sedation regimens, inflammation, delirium prevention protocol deviations, and hypoxic ischemic injury were likely contributing factors, and the most common disposition for delirious patients was a skilled care facility (41/108, 38%). Among patients who were delirious during hospitalization, 4/17 (24%) later screened positive for delirium at home based on caretaker assessment, 5/22 (23%) demonstrated signs of questionable cognitive impairment or cognitive impairment consistent with dementia and 3/25 (12%) screened positive for depression within 2 months after discharge.

**Comment:** Patients with COVID-19 commonly experience a prolonged course of delirium in the intensive care unit, likely multifactorial. These results align with previous data demonstrating a high incidence of delirium in critically ill patients with COVID-19. Major neurological complications, such as encephalopathy, strokes, seizures, and ataxia, have all been observed in ICU Covid-19 patients. Delirium appears to be a common complication, with previous investigations demonstrating an incidence of approximately 65%-80% in the ICU. Delirium may occur due to direct SARS-CoV-2 invasion of the central nervous system, and systemic inflammatory responses may further exacerbate neurocognitive impairment. In the ICU, multiple delirium risk factors are often present and can increase risk in an additive manner. Delirium is also associated with prolonged hospitalization, long-term cognitive and functional impairment, and increased mortality. Delirium prevention and management are very challenging for COVID-19 patients. While delirium prevention bundles have been demonstrated to reduce risk, unique challenges posed by COVID-19 patients on MV hinder the implementation of standard prevention practices. Spontaneous awakening and breathing trials, for example, may not have been possible due to illness severity and associated ventilator requirements including the need for proning. Clinicians may have also been limited in terms of sedation regimen. Agitation is common, and nearly 30% of patients required antipsychotics in this cohort. Early mobility was limited given illness severity, and family engagement was not possible due to visitor policy restrictions. Results from this study can now be used to inform future study designs focused on identifying risk factors for delirium in

this population. Delirium was assessed retrospectively for this study, and such retrospective techniques are not equivalent to prospective evaluation. Novel strategies for implementing delirium prevention bundles in this patient population may help to further mitigate risk and should be tested in prospective trial.