First, I hope everyone had a wonderful Christmas weekend.

Good evening. Just finished the Monday edition and lots to share. Depending on events I may or may not send another COVID-19 Briefing this year. As you recall stating in 2022 the name will become "Infectious Diseases Watch" which will include some general ID articles as well as Covid.

I covered the updated CDC Interim Guidance for Managing HCP with SARS-CoV-2 Infection or Exposure to SARS-CoV-2 last Thursday. I want to reiterate one of my major concerns, the update should have been for the general population not just HCWs. Think about other workers such as teachers and keeping schools open just as an example.

Today under Covid-19 News I start with reviewing oral antivirals just approved by the FDA for EUA. Next Novavax announced their vaccine shows protection against Omicron. Next a report from South Africa ending quarantines and contact tracing as well as the most recent numbers from South Africa. I included a summary of the December 23rd UK technical briefing. Next given the limited access to testing, I attempted to provide guidance of when to test. Last Covid-19 by the numbers.

Under Journal Review, an article of SARS-CoV-2 viral dynamics vaccinated versus unvaccinated. Next a follow-up on the outbreak from Norway. The third article is from Israel and the impact of the Pfizer booster across age groups. Finally, the now peer reviewed study on use of RDV to prevent progression of Covid-19 in outpatients.

Have a wonderful week. I will keep an eye out on new developments and provide updates as appropriate.

Ed

COVID-19 News

Oral Antivirals
The FDA on Thursday authorized a second antiviral pill for Covid, molnupiravir, for adults who are vulnerable to becoming severely ill from Covid-19 and for whom alternative Covid treatment options authorized by the FDA are "not accessible or clinically appropriate." The FDA's decision in part reflects concerns that molnupiravir is only modestly effective (30-50%) while also carrying the possible risk of causing reproductive harm. Older people and those who have conditions like obesity, diabetes and heart disease would be eligible to get a prescription for molnupiravir if they get sick from SARS-CoV-2 and cannot get treatments such as Pfizer's newly authorized pills or effective monoclonal antibody treatments. Both vaccinated and unvaccinated people will be eligible. The treatment — to be taken as 40 pills over five days.

Comment: Despite the good news, it is estimated that less than 3% of Pfizer pills ordered by White House will be available in January. Molnupiravir is expected to be in greater supply sooner than Pfizer's. By the end of January, Merck is expected to make available to the federal government enough pills for 3.1 million people, at a cost of about $700 a person. The first 378,000 treatment courses are expected about two weeks after authorization.

Pfizer is expected to supply before the end of January enough Paxlovid, for 265,000 people in the United

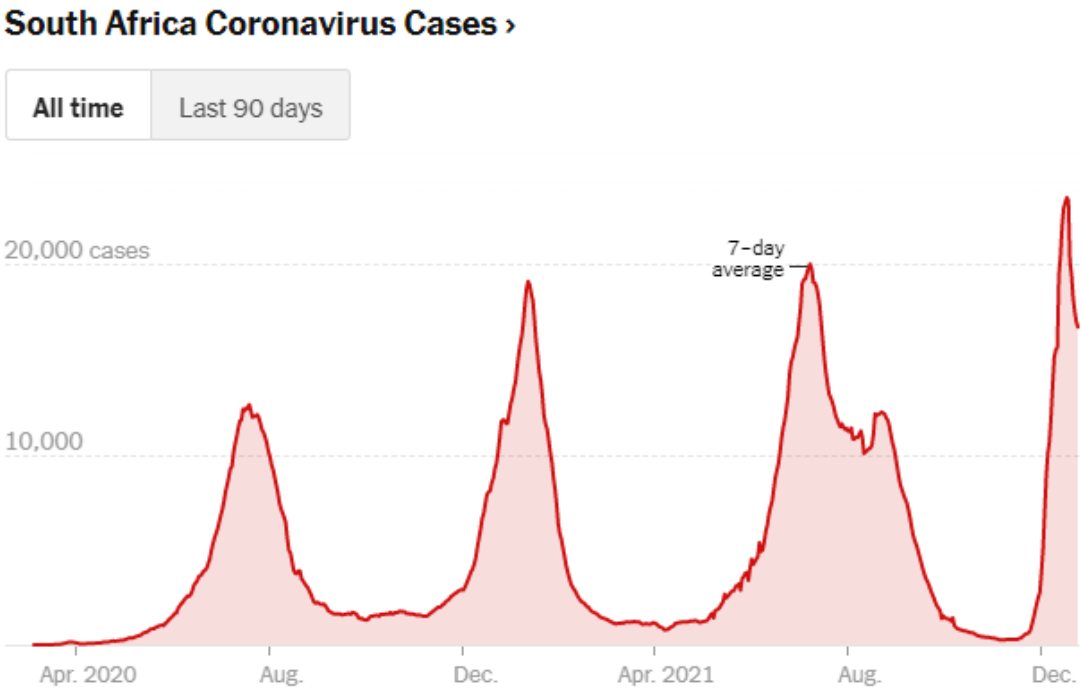
States.Initial supplies are expected in the next few days but will be very limited. Bottom line both drugs will make living with Covid-19 easier, but they are likely to be rationed the next several months and unlikely to impact current wave. Vaccines have saved more than a million lives, but many more would be saved if oral treatments like Paxlovid and Molnupiravir were available sooner. One recommendation to consider moving forward- since these medications are time sensitive, I think we should leverage telemedicine to facilitate more timely interventions and at the same time make testing more readily available with rapid TAT. The approval of these oral medications represents a success of Big Pharma who put their own capital at risk for trials and production.

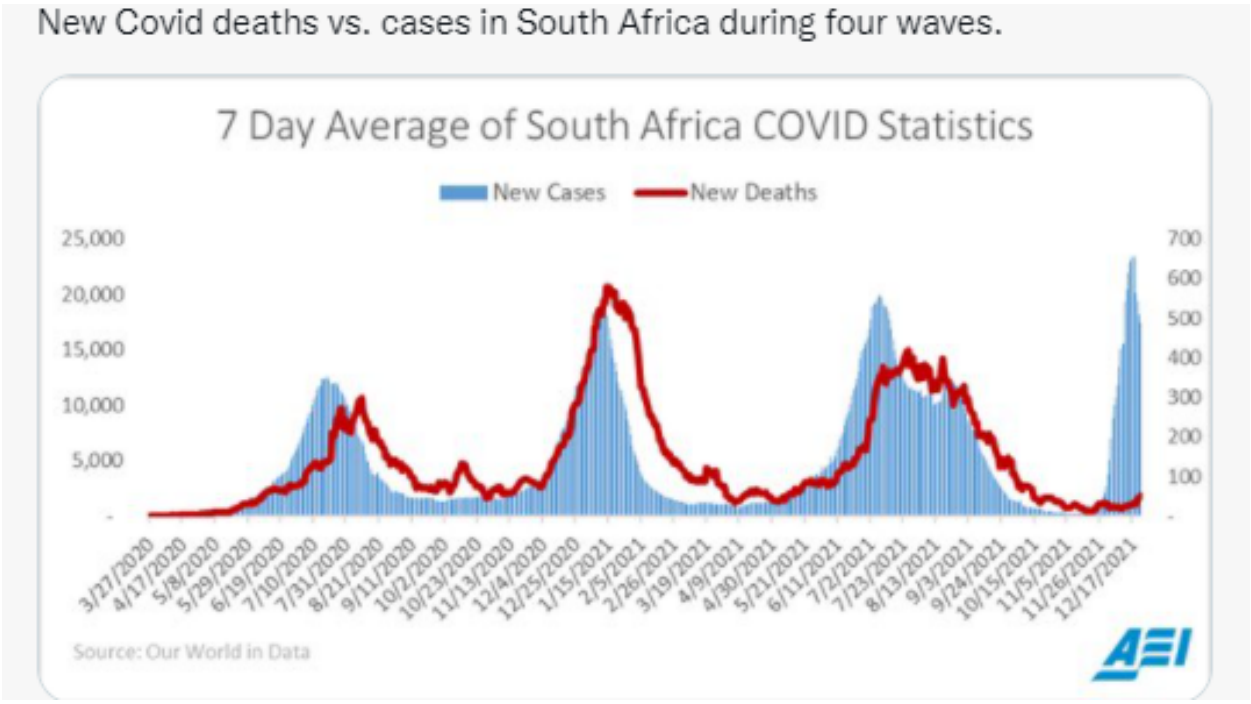
Novavax Says Early Data Shows Covid-19 Vaccine Protects Against Omicron
This is good news and I hope this vaccine will become available in the first quarter of next year.

Fourth Dose of mRNA
Israel announced that a fourth dose of COVID-19 mRNA vaccine will be made available to help control an Omicron wave of infection. The initial focus will be persons over age 60, health care workers and those who are immunocompromised. Only 3 months will be required since the third dose.

Comment: Some scientists warned that the plan could backfire, because too many shots might cause a sort of immune system fatigue, compromising the body's ability to fight SARS-CoV-2 or respond to repeated doses of vaccine. There is early discussion in the US about offering a fourth dose to HCWs, but I think this is premature and needs additional data.

South Africa Ends Quarantines and Contact Tracing and Authorizes Booster Shots
NY Times 12.25.21
South Africa dropped quarantine restrictions for all but symptomatic people. That includes allowing people who have tested positive but show no symptoms to gather with others, so long as they wear a mask and social distance. A top health official explained that since the variant spreads so quickly, there are likely many infected people socializing with others and it no longer made sense to quarantine only those who have tested themselves. The revisions were based on data showing that immunity resulting from previous infections was as high as 80 percent. That, coupled with a vaccination rate of nearly 45 percent among adults in the country, has kept hospitalizations lower than previous surges. A high proportion of cases in South Africa have been asymptomatic, so quarantine measures have been skewed toward those with symptoms. That has been particularly true in the recent wave of infections driven by the Omicron variant, during which cases increased steeply, but just over 5 percent led to hospital admissions. Under the new guidance, people who test positive but are asymptomatic will no longer need to quarantine. People showing mild symptoms like fever, cough and loss of taste or smell are still required to isolate for eight days. Covid-19 testing will be required if a person has symptoms. Anyone who came in contact with someone who tested positive would not need to quarantine and must instead do "self-observation" for five to seven days and avoid crowded gatherings.

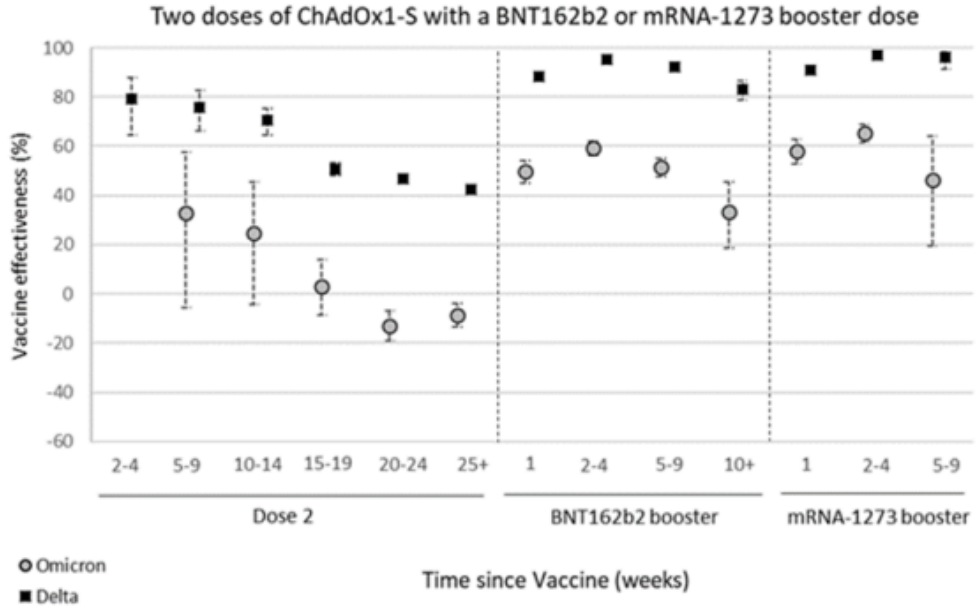


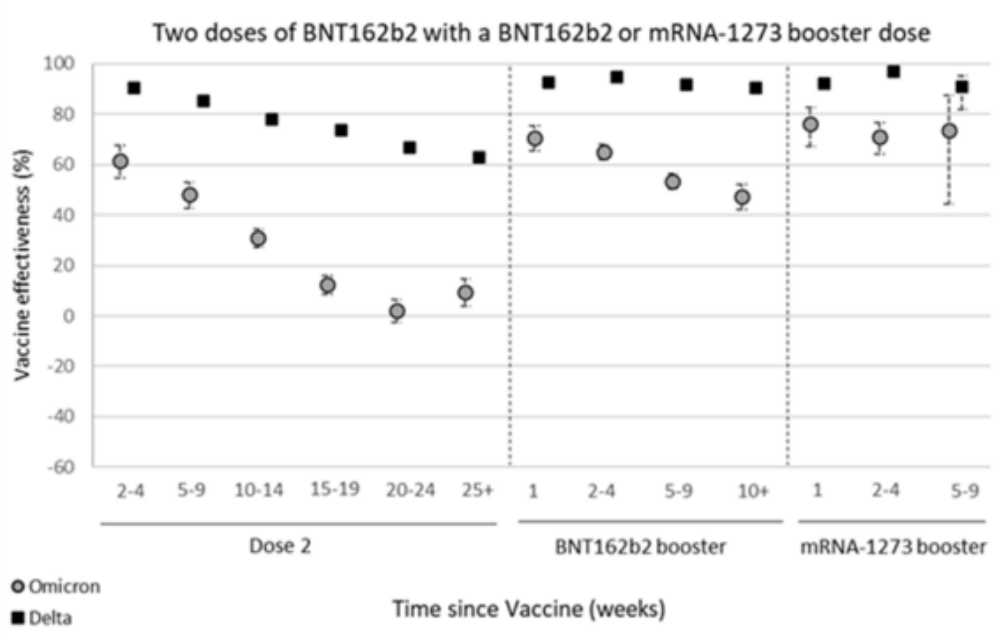


Comment: From above a steep increase, but now a steep decrease in a matter of weeks and low new deaths! The South African experience reflects the reality of Omicron, highly contagious and fewer hospitalizations in a fairly high immune population. I hope the US experience mirrors South Africa.

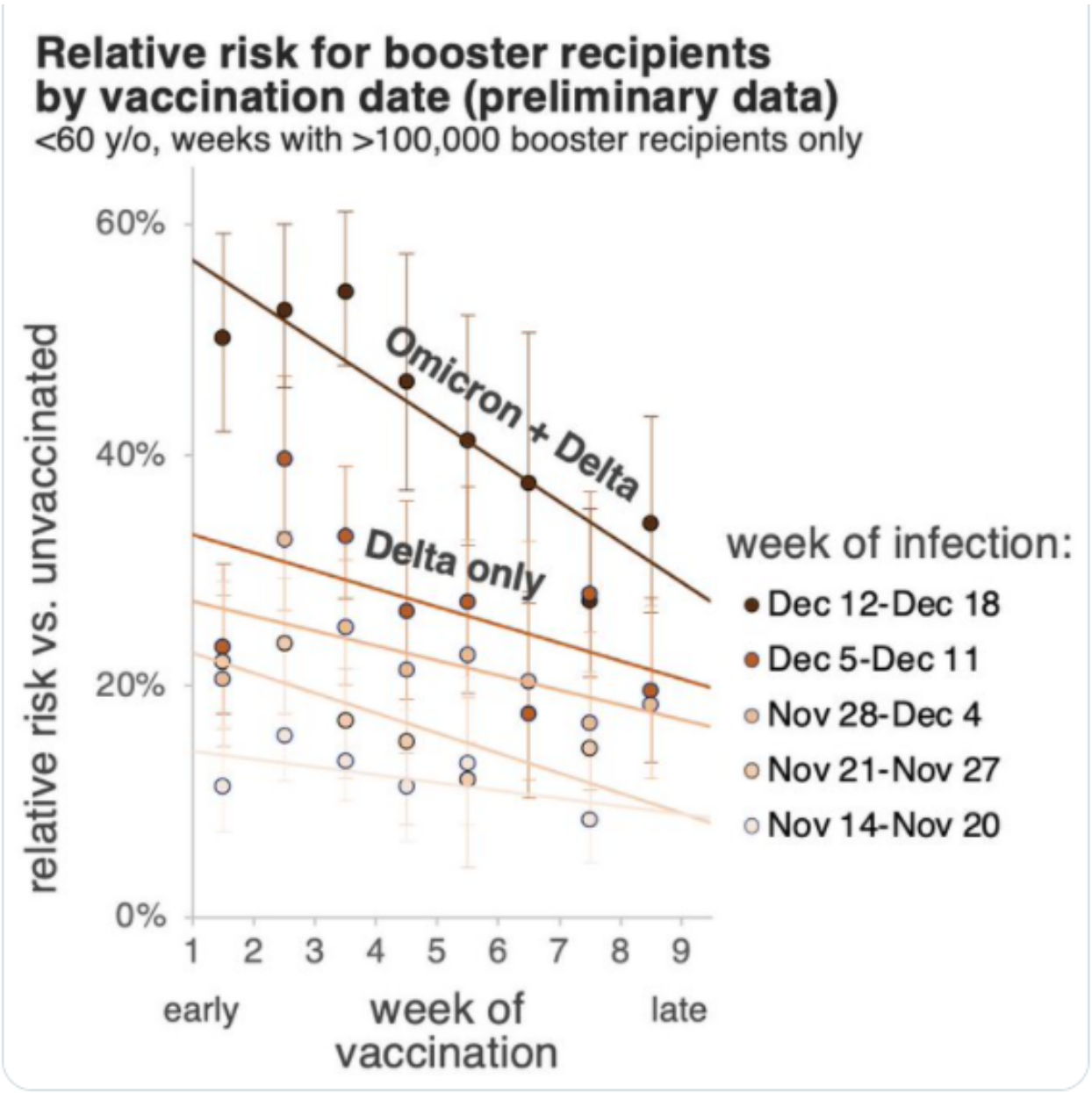
SARS-CoV-2 Variants of Concern and Variants Under Investigation in England Technical Briefing 33; 23 December 2021

Vaccine effectiveness was estimated by period after dose 2 and dose 3. The final analysis included 147,597 Delta and 68,489 Omicron cases. Vaccine effectiveness against symptomatic disease by period after dose 2 and dose 3 is shown who received a primary course of the AstraZeneca vaccine, Pfizer or Moderna. Booster estimates are separated for Pfizer and Moderna boosters. In all periods, effectiveness was lower for Omicron compared to Delta.





A “very” preliminary analysis may imply a faster waning of booster effectiveness against Omicron in Israel. (See below)



When to Test for SARS-CoV-2

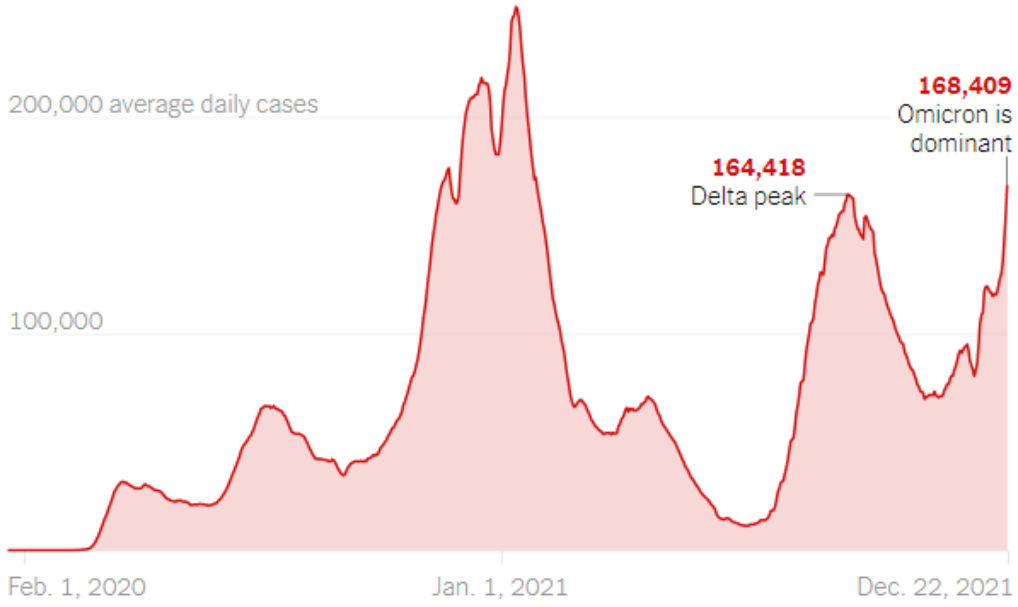
First contracts to purchase tests could be signed as soon as this week, but relief could be weeks away for people trying to buy the hard-to-find tests. Therefore, I have come up with some guidance on who should be tested.

1. Test when you have symptoms. If you have symptoms already, test right away. If the test is negative and you still have symptoms a few days later, follow up with another test especially if initial test was a rapid test, although rapid test has a good sensitivity if you have symptoms.
2. Test when you know you have been exposed to Covid-19. If you don't have symptoms after the exposure and vaccinated, doctors recommend an initial test at day 2 and a second test at day 5-7. A rapid test is acceptable. You do not need to quarantine if fully vaccinated.
3. Test to screen yourself before getting together with friends or family in a setting, say, indoors and maskless, in which you are at higher risk of transmitting the virus. Test yourself as close to

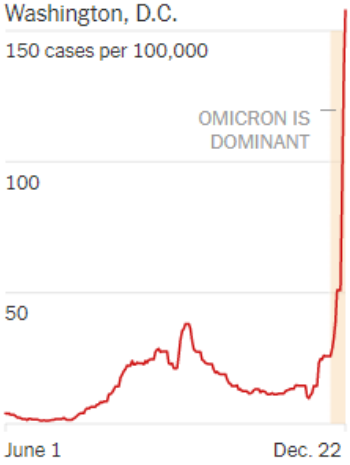
the start of the event as possible. The rapid test does the best job of quickly letting you know whether you are contagious the moment you test yourself. Rapid antigen tests—which give results in about 15 minutes—are a good gauge of infectiousness. However, rapid tests aren't as sensitive as PCR tests. The PCR test is better at detecting whether you are incubating Covid-19 or asymptomatic.

4. If you plan to travel, the CDC recommends you test one to three days before and again after your travel if you aren't vaccinated. All travelers should test themselves if they develop symptoms, the CDC says.

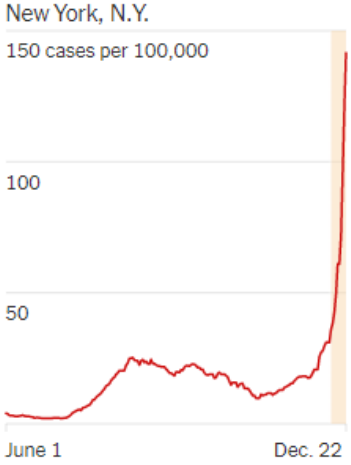
Covid-19 by the Numbers
Omicron Drives U.S. Virus Cases Past Delta's Peak



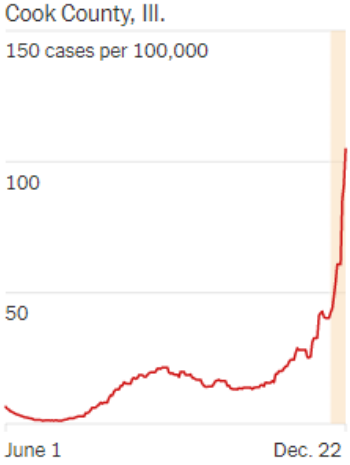
Washington, D.C.
Washington, D.C.



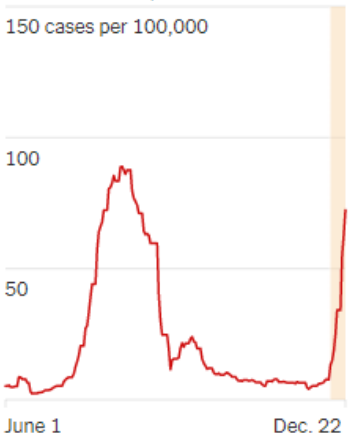
New York City
New York, N.Y.



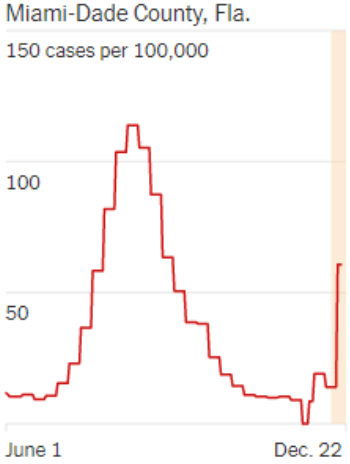
Chicago
Cook County, Ill.



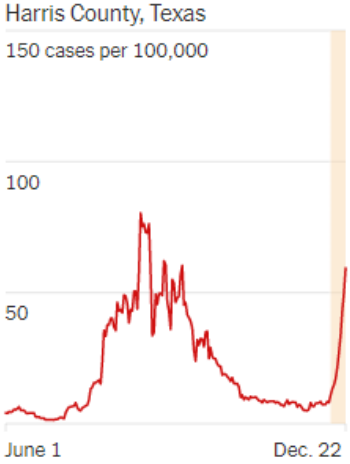
New Orleans
Orleans Parish, La.



Miami
Miami-Dade County, Fla.

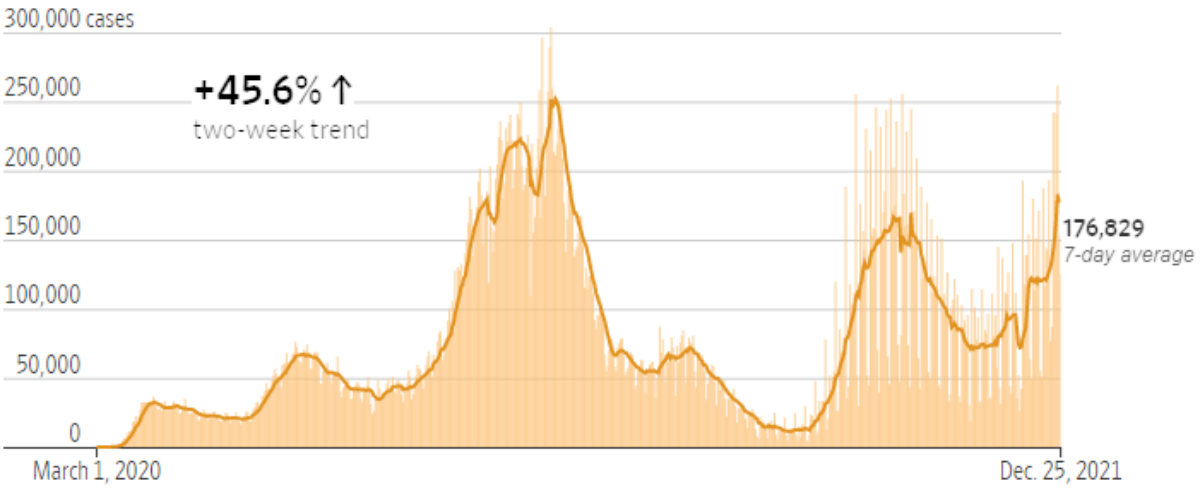


Houston
Harris County, Texas



Daily reported Covid-19 cases in the U.S.

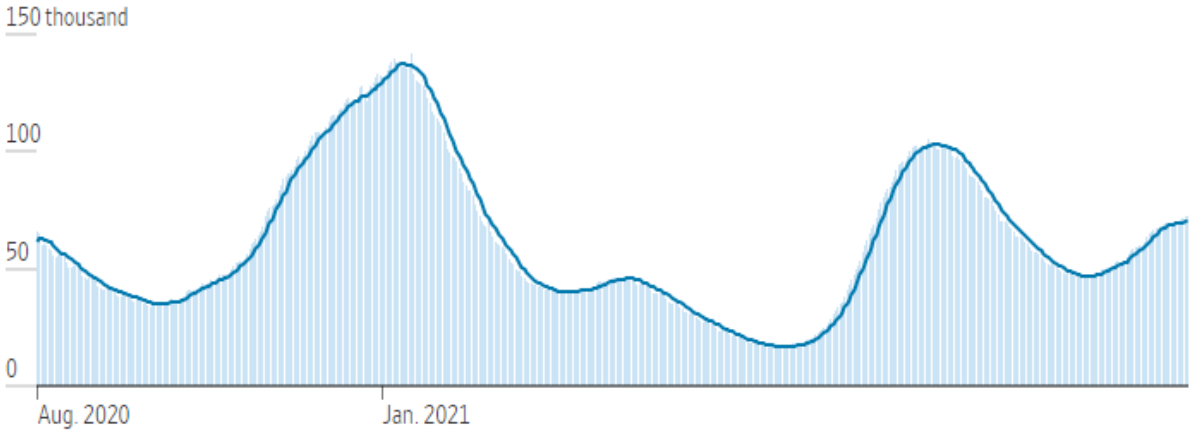
— Seven-day rolling average



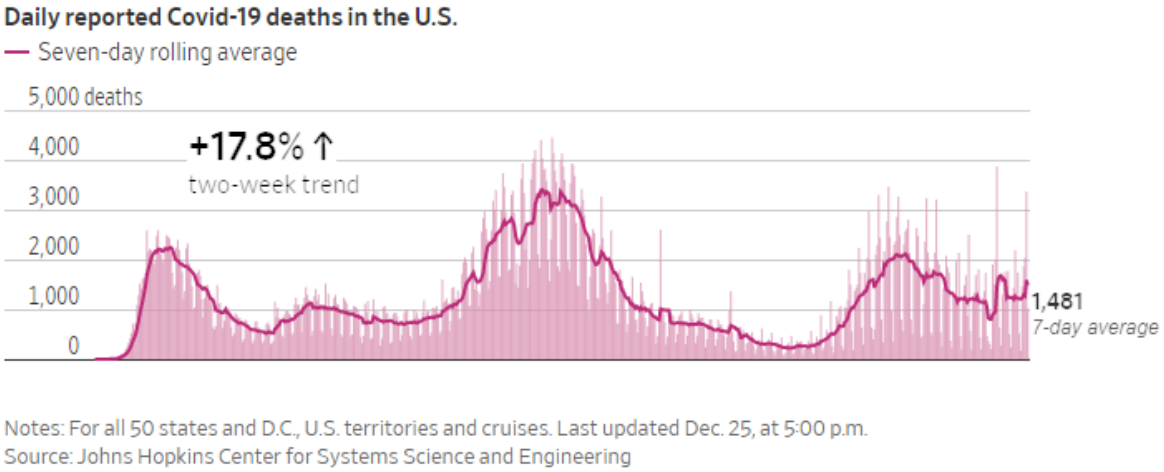
Note: For all 50 states and D.C., U.S. territories and cruises. Last updated Dec. 25, at 5:00 p.m.
Source: Johns Hopkins Center for Systems Science and Engineering

Number of Covid-19 patients hospitalized in the U.S.

■ Seven-day rolling average

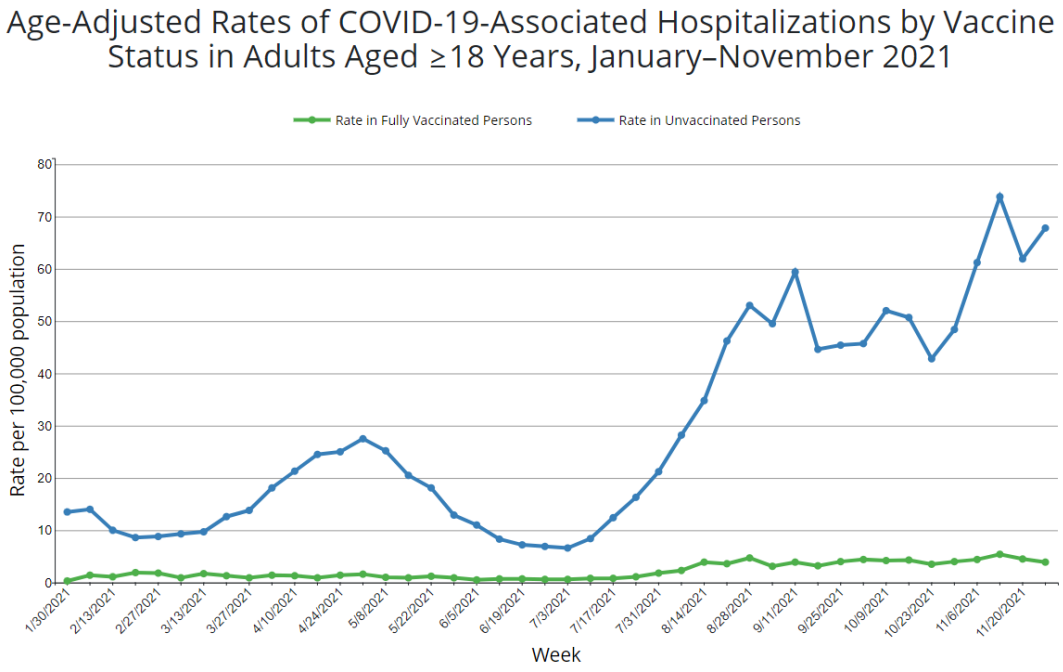


Note: Last updated Dec. 24
Source: U.S. Department of Health & Human Services



Comment: Even if these early results hold and Omicron does cause mostly mild illness, the sheer magnitude of cases it causes could still escalate hospitalizations at a time when many medical centers are already full especially among the unvaccinated. Hospital administrators say that their nurses and doctors are overwhelmed and exhausted, and that staffing shortages are making matters worse. Almost 20% of HCWs have retired since the pandemic.

Hospitalization by Vaccine Status

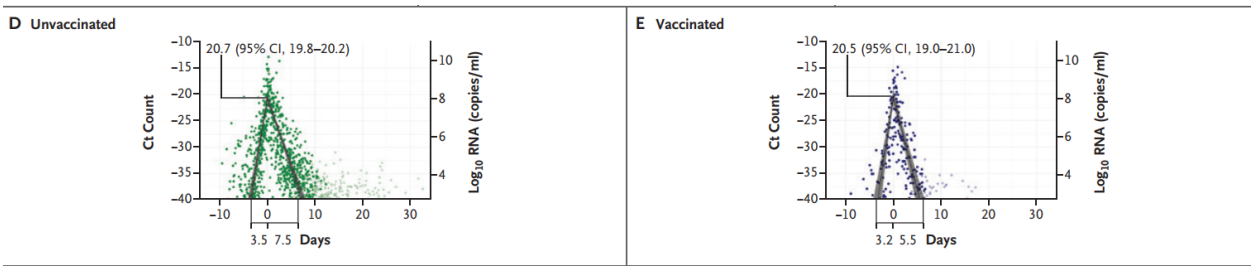


Comment: Updated data from CDC last week shows rate of hospitalization among unvaccinated 67.8/100K & rate among vaccinated 3.9/100K (typical flu hospitalization rate 20-40/100K). Influenza is already here so make sure you get vaccinated for influenzas as well as Covid.

Journal Review

Viral Dynamics of SARS-CoV-2 Variants in Vaccinated and Unvaccinated Persons
N Engl J Med published online December 23, 2021
DOI: 10.1056/NEJMc2102507
Recent studies suggests that infections with the Delta feature higher peak viral loads than those in other lineages and that vaccine recipients who are infected with SARS-CoV-2 may clear the infection more quickly than unvaccinated persons. [review in the Briefing last month www.medrxiv.org/content/10.1101/2021.07.28.21261295v1] In this study the investigators collected and analyzed a prospective, longitudinal set of 19,941 SARS-CoV-2 viral samples obtained from 173 participants as part of the occupational health program of the NBA between November 28, 2020, and August 11, 2021. The investigators compared SARS-CoV-2 viral dynamics among 36 participants who were infected with the Alpha variant, 36 participants with the Delta) variant, and 41 participants with a variant that was not of current interest or concern, along with 37 vaccinated and 136 unvaccinated participants.

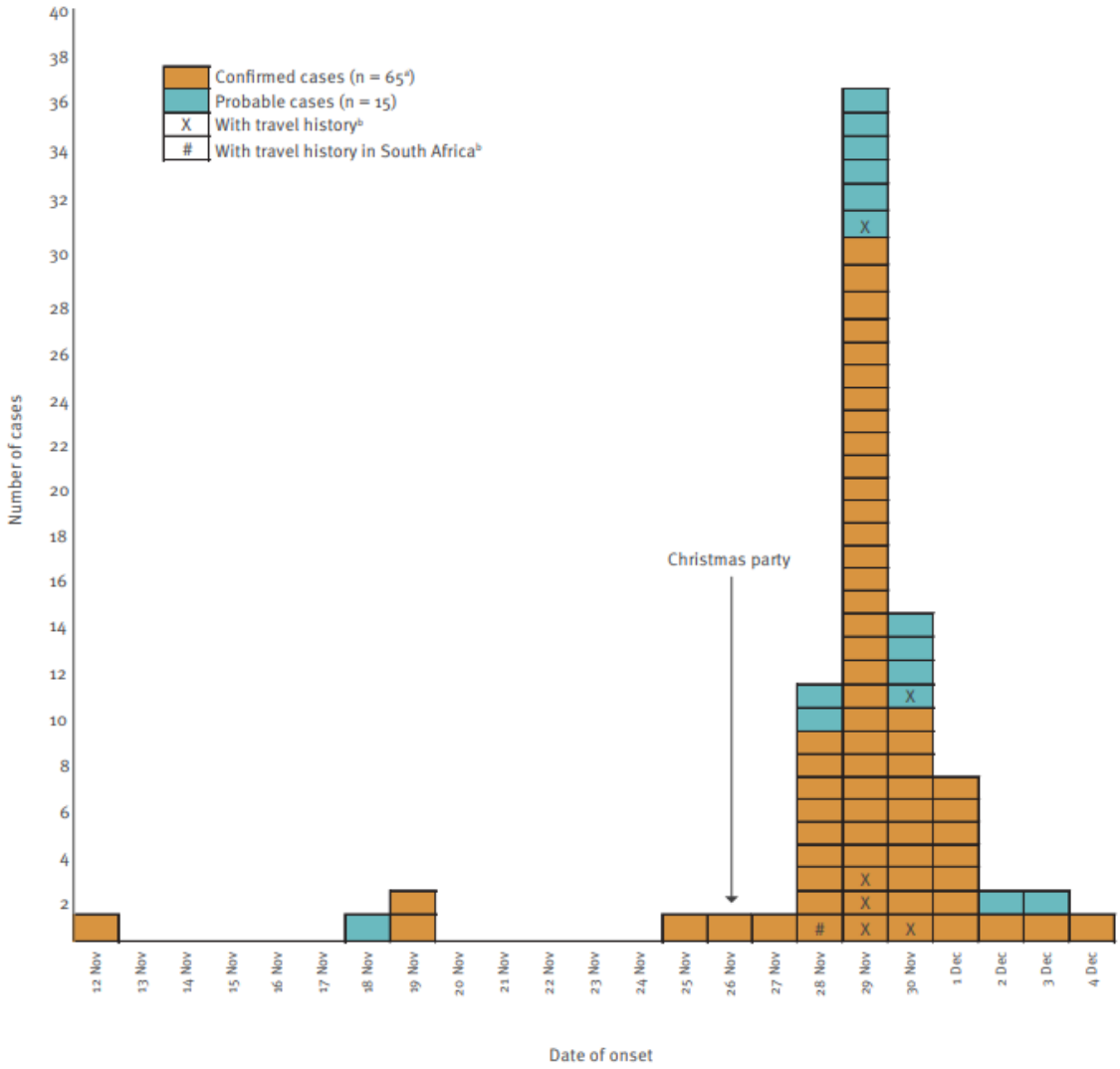
They found no meaningful difference in the mean peak viral load (with a lower peak cycle threshold [Ct] indicating a higher viral load), proliferation duration, clearance duration, or duration of acute infection of either the alpha or the delta variant as compared with variants not of interest or concern. They also found no meaningful difference in the mean peak viral load or proliferation duration between vaccinated and unvaccinated participants. However, breakthrough infections among vaccine recipients were characterized by a faster clearance time than that among unvaccinated participants, with a mean of 5.5 days (95% credible interval, 4.6 to 6.5) and 7.5 days (95% credible interval, 6.8 to 8.2), respectively. The shorter clearance time led to a shorter overall duration of infection among vaccine recipients.



Comments: This is a small sample size with predominantly healthy young men and thus may not be representative of the general population. As you already know, the CDC recommended that fully vaccinated HCWs who are asymptomatic can return to work after seven days with a negative test, adding that isolation time can be cut further if there are staffing shortages. In this study researchers demonstrated the unvaccinated were infectious for up almost eight days, two days longer than the vaccinated.

Outbreak Caused by the SARS-CoV-2 Omicron Variant in Norway, November to December 2021
Eurosurveillance 2021; 26: Issue 50 December 16, 2021
On November 30, 2021, the Norwegian Institute of Public Health (NIPH) was notified by a local laboratory in Oslo of a COVID-19 case with suspected SARS-CoV-2 Omicron variant infections. Following a Christmas party with 117 attendees, 80 were infected with an observed an attack rate of 74% and

most cases developed symptoms. As of December 13th, none have been hospitalized. Most participants were 30–50 years old. Ninety-six percent of them were fully vaccinated.

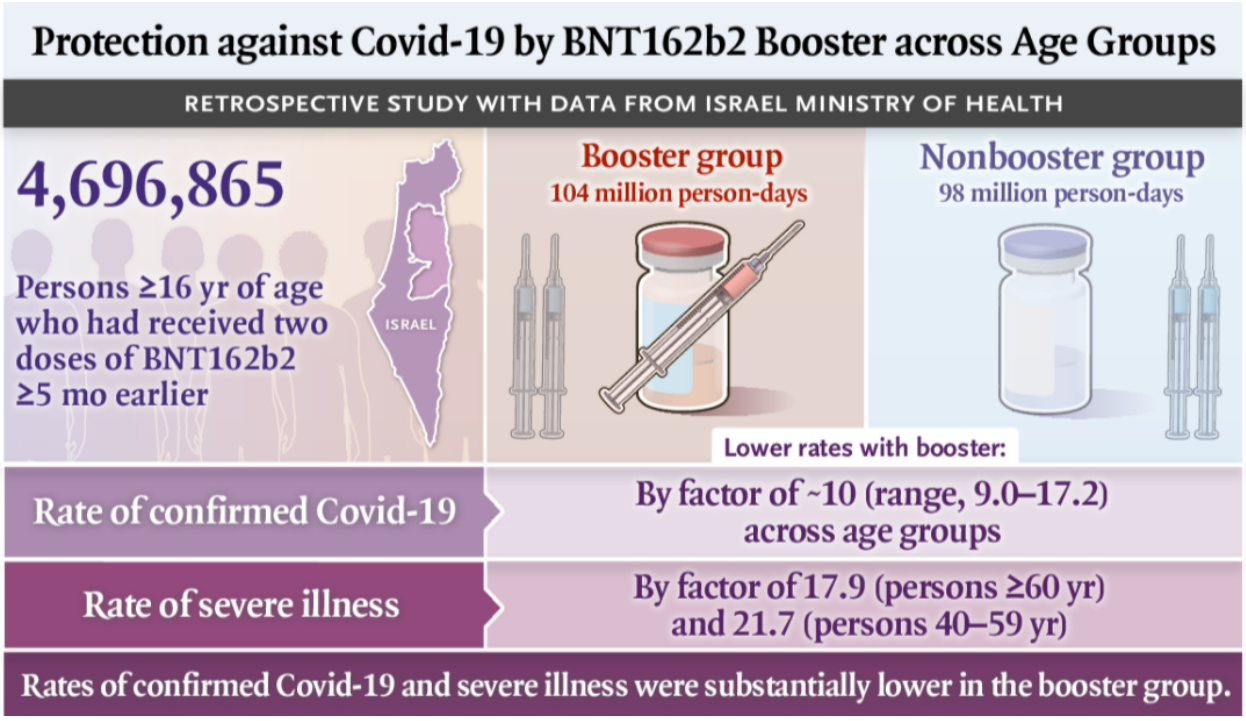


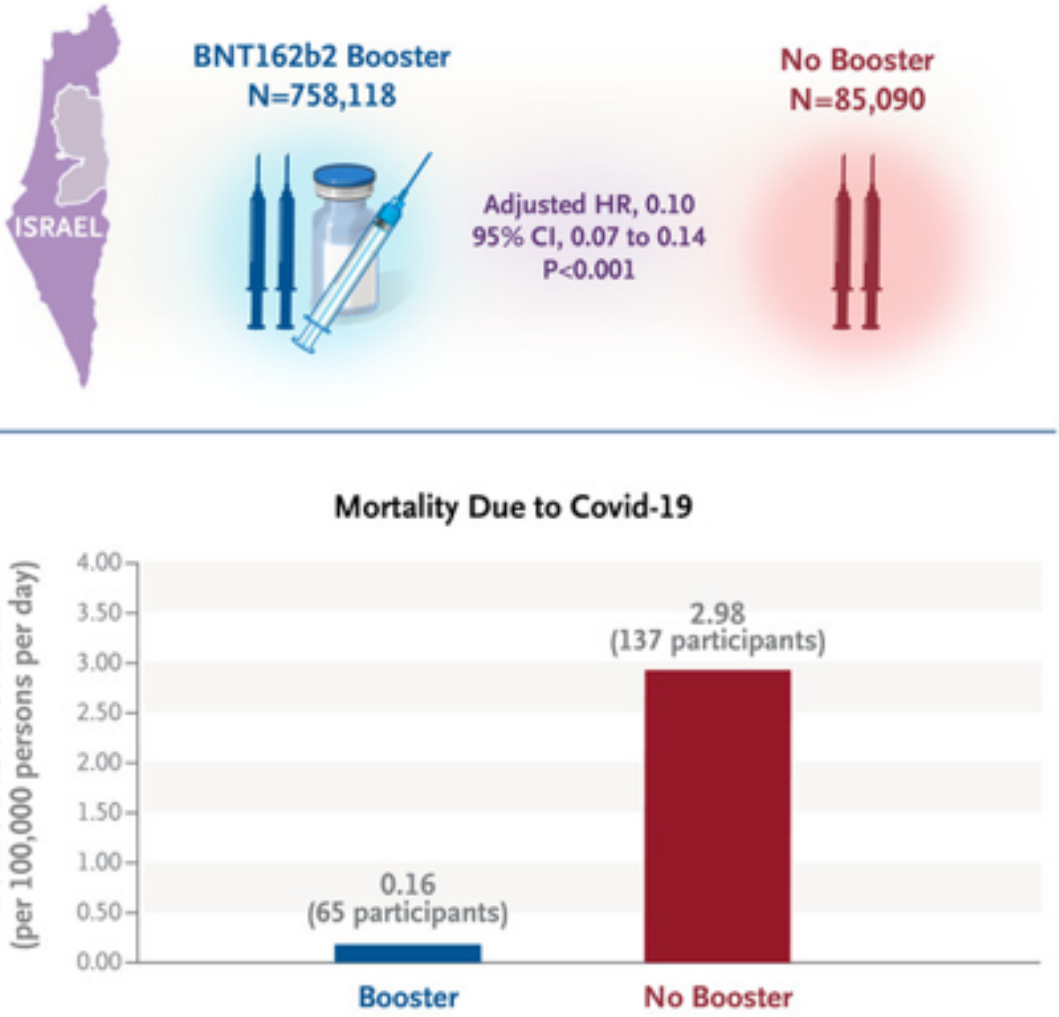
Comment: After the event, symptoms appeared in about three days. The incubation period has been estimated to be about five to six days for the ancestral strain, five days for the alpha variant and four days for delta. Based on this report, the incubation period for Omicron may be as short as 3 days which will also make it harder to control. Incubation periods might differ by vaccination status, underlying health conditions, infection history, age and the amount of viral load people face. The preliminary report was mentioned in the December 20th Briefing.

Protection Against Covid-19 by BNT162b2 Booster Across Age Groups
N Engl J Med published online December 23, 2021
DOI: 10.1056/NEJMoa2115926
The investigators extracted data for the period from July 30 to October 10, 2021, from the Israel Ministry of Health database regarding 4,696,865 persons 16 years of age or older who had received two doses of Pfizer vaccine at least 5 months earlier. In the primary analysis, they compared the rates of confirmed Covid-19, severe illness, and death among those who had received a booster dose at least 12

days earlier (booster group) with the rates among those who had not received a booster (nonbooster group). In a secondary analysis, they compared the rates in the booster group with the rates among those who had received a booster 3 to 7 days earlier (early postbooster group).

The rate of confirmed infection was lower in the booster group than in the nonbooster group by a factor of approximately 10 and was lower in the booster group than in the early postbooster group by a factor of 4.9 to 10.8. The adjusted rate difference ranged from 57.0 to 89.5 infections per 100,000 person-days in the primary analysis and from 34.4 to 38.3 in the secondary analysis. The rates of severe illness in the primary and secondary analyses were lower in the booster group by a factor of 17.9 (95% confidence interval [CI], 15.1 to 21.2) and 6.5 (95% CI, 5.1 to 8.2), respectively, among those 60 years of age or older and by a factor of 21.7 (95% CI, 10.6 to 44.2) and 3.7 (95% CI, 1.3 to 10.2) among those 40 to 59 years of age. The adjusted rate difference in the primary and secondary analyses was 5.4 and 1.9 cases of severe illness per 100,000 person-days among those 60 years of age or older and 0.6 and 0.1 among those 40 to 59 years of age. Among those 60 years of age or older, mortality was lower by a factor of 14.7 (95% CI, 10.0 to 21.4) in the primary analysis and 4.9 (95% CI, 3.1 to 7.9) in the secondary analysis. The adjusted rate difference in the primary and secondary analyses was 2.1 and 0.8 deaths per 100,000 person-days.



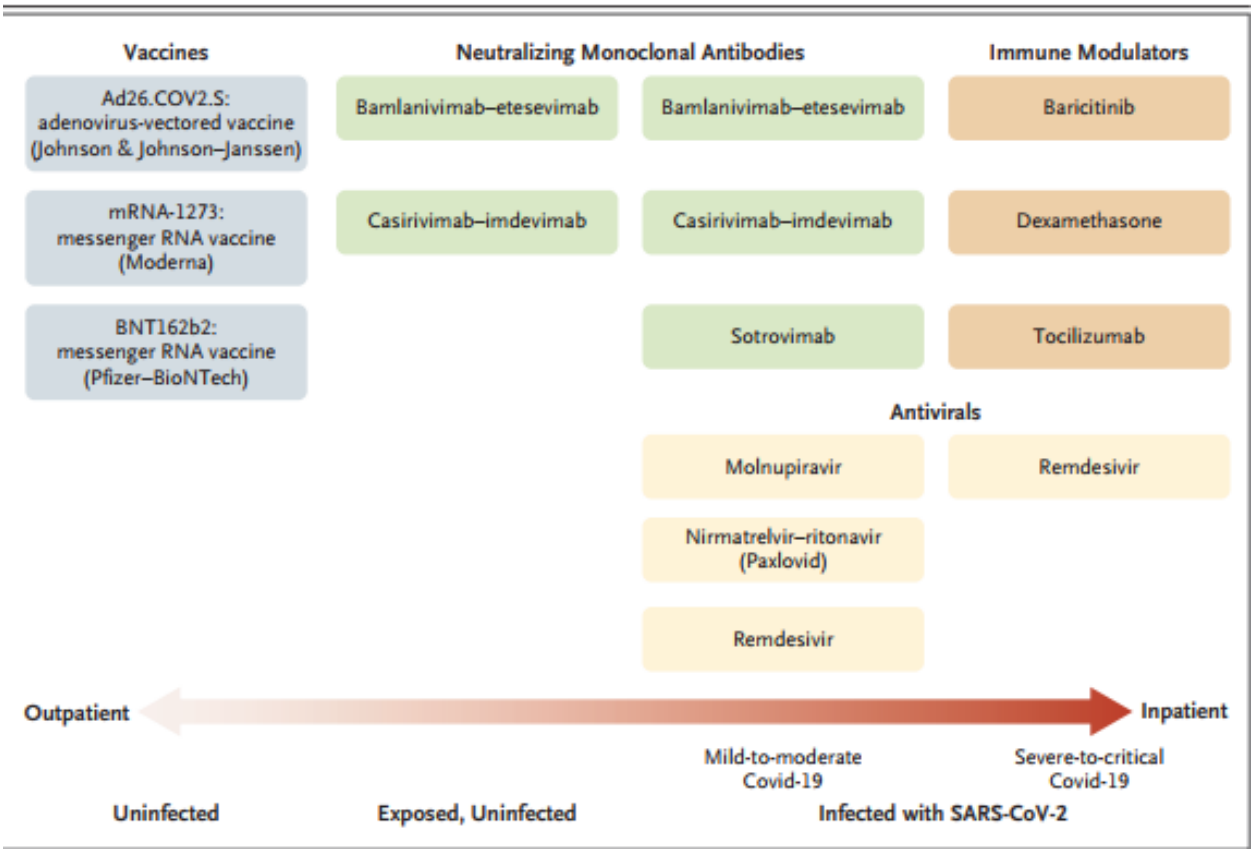


Comment: Across the age groups studied, rates of confirmed Covid-19 and severe illness were substantially lower among participants who received a booster dose of the Pfizer vaccine than among those who did not. Although in their primary analysis they attempted to address confounding and detection bias, some sources of bias may not have been measured or corrected adequately. These biases might include differences between booster recipients and those who chose not to receive the booster with respect to risk-avoidance behaviors and coexisting conditions, neither of which are recorded in the national database. However, there is mounting evidence for a third shot to improve VE.

Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients
N Engl J Med published online December 22, 2021
DOI: 10.1056/NEJMoa2116846
The investigators conducted a randomized, double-blind, placebo-controlled trial involving early outpatient of patients with Covid-19 who had symptom onset within the previous 7 days and who had at least one risk factor for disease progression (age ≥60 years, obesity, or certain coexisting medical conditions). Patients were randomly assigned to receive intravenous remdesivir (200 mg on day 1 and 100 mg on days 2 and 3) or placebo. The primary efficacy end point was a composite of Covid-19–related hospitalization or death from any cause by day 28. The primary safety end point was any adverse

event. A secondary end point was a composite of a Covid-19– related medically attended visit or death from any cause by day 28. Vaccinated people were excluded.

The most common coexisting conditions were diabetes mellitus (61.6%), obesity (55.2%), and hypertension (47.7%). Covid-19–related hospitalization or death from any cause occurred in 2 patients (0.7%) in the remdesivir group and in 15 (5.3%) in the placebo group (hazard ratio, 0.13; 95% confidence interval [CI], 0.03 to 0.59; P=0.008). A total of 4 of 246 patients (1.6%) in the remdesivir group and 21 of 252 (8.3%) in the placebo group had a Covid-19–related medically attended visit by day 28 (hazard ratio, 0.19; 95% CI, 0.07 to 0.56). No patients in either group had died by day 28.



Comment: This article was reviewed last month in Briefing before peer reviewed. Among outpatient patients who were at high risk for Covid-19 progression, a 3-day course of remdesivir resulted in an 87% lower risk of hospitalization or death than placebo. Of interest, no deaths had occurred in either group by day 28. In addition, the change in viral load, determined with the use of nasopharyngeal swabs, from baseline to day 7 in the remdesivir group was similar to that in the placebo group. Although the result of this trial is encouraging, there are some real-world limitations. First, the exclusion of vaccinated patients' limits understanding of early antiviral therapy in vaccinated persons with breakthrough infections which is especially relevant with Omicron. Second, the effect of remdesivir on SARS-CoV-2 viral loads is a surprise. Would remdesivir in fact reduce transmissibility in infected persons (an important consideration in outpatient therapeutics) compared with monoclonal antibodies or new oral antiviral agents, which are both associated with a more rapid decline in viral burden than placebo? Finally, the primary challenge for implementing outpatient remdesivir treatment is the difficulty of administrating a 3-day course of an intravenous agent. Even a single-dose monoclonal antibodies have

been a challenge. The findings of this trial reinforce the need for timely outpatient therapeutics. Rapid emergence of variants with adaptive mutations in the spike protein has resulted in escape from vaccines and monoclonal antibodies, whereas antiviral agents, given the absence of variation in their viral target, are likely to maintain activity, reinforcing the value of antivirals especially the new oral antivirals just given EUA. [see above] Since Covid-19 is here to stay, our focus on prevention through vaccines continues to remain a priority, but therapeutic options to keep vulnerable patients out of the hospital are an important tool in our toolbox. The findings here are based on research that predates the delta variant that surged during the summer and omicron, the variant spreading with great speed globally.