Good evening. I just finished the Briefing I was going to send out in AM, so I thought I would get it out so you have it when you open your email in AM. So much going on and my vision for the Briefing has been to provide all of you with relevant and timely information to help all of us navigate this continuing and challenging pandemic. I had hoped to decrease the number of issues as the holiday approaches, but as you know, no one told Omicron it is the holiday season. ☹

For this issue I initially tried to summarize what we know about Omicron and what steps we can take to reduce infection and burden on the healthcare system. Under Covid-19 News: A review from CDC on current Covid numbers as of end of last week. Next is a preliminary report from Norway and an outbreak from a party in a restaurant in Oslo highlighting how contagious Omicron can be. Next is a disappointing report from Pfizer on initial vaccine trials on children under age 5. Next is CDC recommendation for test-to- stay in schools K-12. I included a figure on the relationship between percent immunity and Ro for Omicron and Delta based on modeling. I thought the figure may be useful in future presentations. The next section starts with a report showing that Evusheld the AZ MCA has activity against Omicron like sotrovimab. I then comment on antiviral alternatives and a discussion started by Paul Sax's tweet. I thought the chart on oral antiviral drugs against SARS-CoV-2 would be a good reference. Last, the CDC decided last week to make the recommendation to state a preference for the mRNA vaccines over those from J&J after hearing a safety update on cases of thrombosis with thrombocytopenia syndrome (TTS).

Under Journal Review a report that two doses of Moderna was found less effective against the new Omicron variant, but a booster shot of the Moderna vaccine increased antibodies that were highly effective at blocking Omicron. The last two articles were from the CDC report, one from Ill and one from LA showing test-to-stay programs are safe and keep students in class.

I hope things slow up, but I will do my best to update all of you during this holiday season.

Ed

COVID-19 News

VII: Omicron: The Current Science
Omicron's increased transmissibility appears to be a combination of several factors. [see study on an Oslo Christmas Party below] (1) It seems able to more easily blind to human respiratory cells; (2) it appears to replicate faster; and (3) it can evade the immunity gained from past infection and/or vaccination. Among Omicron's roughly 50 mutations, at least 30 are on the spike protein, the structure that facilitates the virus binding to respiratory cells; the main target of vaccines. Modeling recently published by the Imperial College London estimates the risk of reinfection with Omicron is 5.4 times greater than with Delta, suggesting limited protection from prior infection and or vaccination. There are signs the variant is associated with less severe disease than Delta, however, severity may vary from place to place depending on factors including levels of immunity and population characteristics. Even if Omicron proves less virulent, its ease of transmission means Omicron could still cause significant waves of infection which in unvaccinated or immunosuppressed people can still lead to severe disease and death.

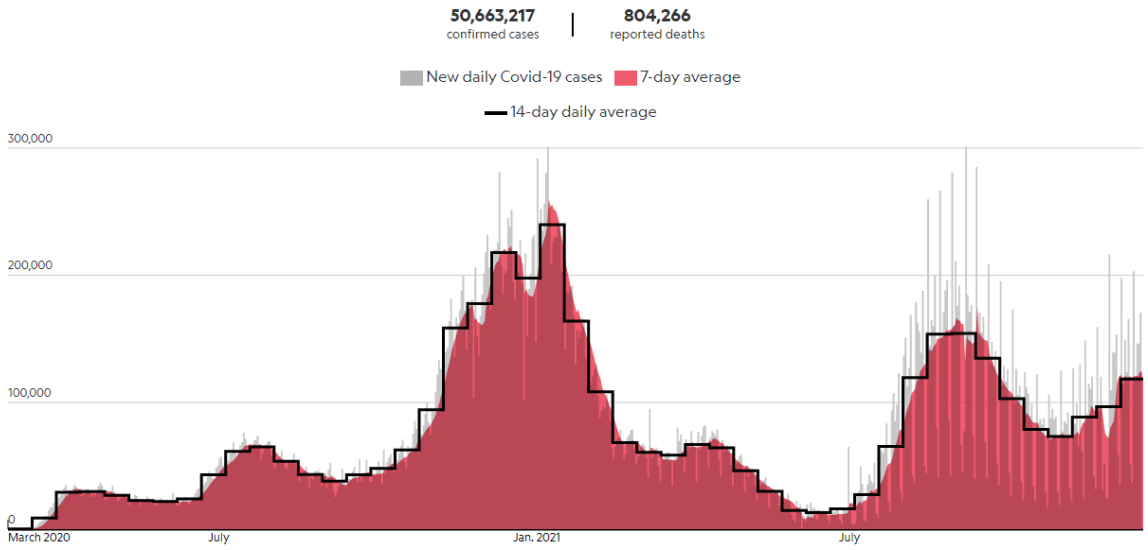
In the UK, Omicron has displaced Delta as the dominant variant of coronavirus in England and Scotland in less than a month and it is only days behind doing the same in Denmark. It is already the dominant variant in Ontario, Canada, accounting for 51% of new cases. British health data suggest Omicron cases

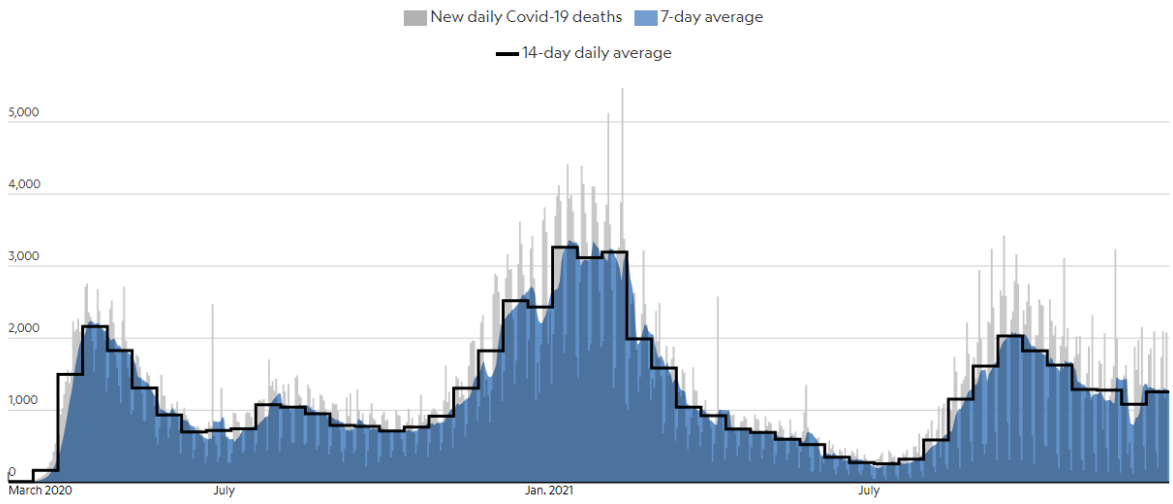
are doubling through much of the country in less than two days! Areas in the US experiencing Omicron are seeing rapid doubling times as well. In Houston, Omicron is expected to be the dominant variant as early as Christmas.

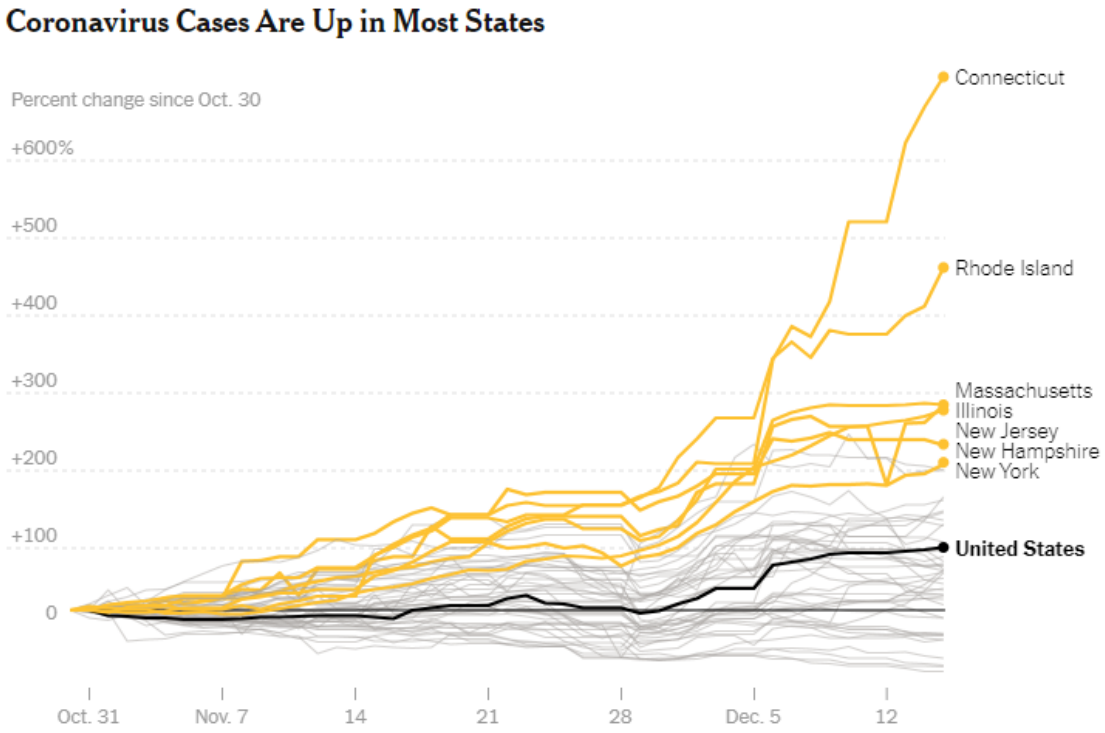
Furthermore, if the virus multiplies faster, it may be able to transmit earlier. UK public health officials say Omicron's advantages mean the interval between a newly infected person becoming infectious to others appears shorter with Omicron, perhaps three days compared with a mean of 5-6 days with Delta. UK Health estimates the current Rt value of Omicron to be between 3 and 5. The overall Rt (not Ro) value for the epidemic in the U.K. had been around 1 to 1.2. Booster shots have been shown to increase protection against infection. Researchers are broadly optimistic that if fully vaccinated (including booster) this will blunt severe disease and death due to Omicron.

My current recommendations: (1) get a booster now if you are eligible; (2) increase testing; (3) FDA approval of Paxlovid; (4) make sotrovimab widely available; (5) in areas with substantial or high transmission re-enforce NPI including masking in public areas; and (6) do not panic!

COVID-19 by the Numbers December 18, 2021







1. The nation's current seven-day reported case average is 122,297, a 1.5 percent increase from the previous week's average.
2. The current seven-day hospitalization average for Dec. 8-14 is 7,814, a 4.4 percent increase from the previous week's average.
3. About 240.3 million people — 72.4 percent of the total U.S. population — have received at least one dose of the COVID-19 vaccine, and more than 203.2 million people, or 61.2 percent of the population, have received both doses.
4. About 57.1 million booster doses in fully vaccinated people have been reported. ~30% of eligible people

5. The seven-day average number of vaccines administered daily was nearly 1.8 million as of Dec. 16, a 3 percent decrease from the previous week.
6. The current seven-day death average is 1,180, up 8.2 percent from the previous week's average.
7. The seven-day average for percent positivity from tests is 7.2 percent, down 0.13 percent from the previous week.
8. The nation's seven-day average test volume for the week of Dec. 3-9 was about 1.5 million, up 12.6 percent from the prior week's average.
9. In communities with Omicron, the doubling time is every 2-3 days. If this continues, Omicron will replace Delta in the next few weeks.

Preliminary Findings from Study after Christmas Party in Oslo
Norwegian Institute of Public Health (NIPH) report December 9, 2021. Provided by John Butler
As of 8 December, around 70% of just over 100 participants at a Christmas party held on 26 November at a restaurant in Oslo have been subsequently diagnosed with SARS-CoV-2. Of those who are infected, 17 are confirmed as being infected with the Omicron variant. It is assumed that the majority of cases without sequencing results available at this time were also infected with the same variant. In addition, more than 60 people who visited the restaurant the same evening as the Christmas party have been confirmed as infected with SARS-CoV-2. Over 70% of cases reported cough, lethargy, headache, sore throat and over half of them reported fever. No hospital admissions have been reported.

All the participants at the Christmas party were asked to take a rapid antigen test before the party. Everyone reported a negative result (PCR test or rapid antigen test) 1-3 days before the Christmas party. Most of the participants were aged between 30 and 50 years and had received their second vaccine dose between May and November 2021. In addition, infection has been detected among more than 60 people who visited the restaurant on the same evening as the party.

Comment: This report confirms if people are gathered closely together indoors with poor ventilation without masks, plus high noise levels, talking loudly and singing you will increase the risk. Add a highly transmissible variant and you can have a large outbreak.

Pfizer Extends COVID-19 Vaccine Clinical Trials for Children Under 5
On Friday, Pfizer announced that it is extending its clinical trials among this age group to test the efficacy of three doses rather than two. (3 micrograms) The company said that an analysis of its ongoing study found that two doses of the vaccine did not produce a similarly robust immune response in children ages two to five as it did with older age groups. The vaccine did, however, produce an adequate immune response in children younger than two. There were also no safety concerns identified.

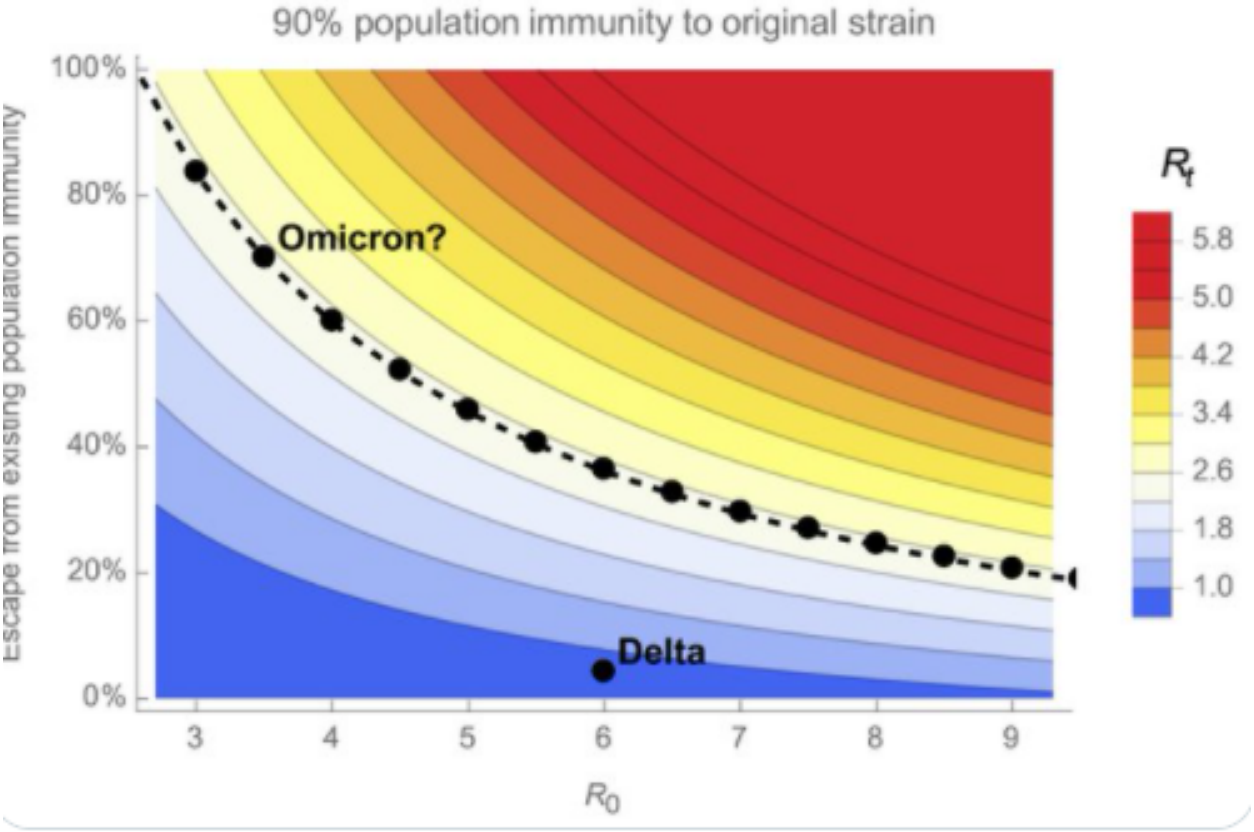
Comment: Pfizer said it expects to submit data to federal regulators for EUA of vaccines for children ages six months to five years in the first half of 2022. It will also test the efficacy of a third dose for older children. For parents anxious to vaccinate their children < age 5, they will need to wait a little longer.

CDC Test and Stay
December 17, 2021
The CDC said on Friday that unvaccinated students exposed to the coronavirus can remain in school if they are tested for the virus at least twice during the seven-day period after an exposure and both tests come back negative. On Friday, the CDC released studies from two counties, one in California and the

other in Illinois, that effectively tested the protocol and found that it worked. (See Journal Review) Vaccinated students with exposures have generally been allowed to remain in school as long as they are asymptomatic and wear a mask and test from day 3-5.

Comment: The studies were conducted before Omicron began spreading in the United States. Scientists are still investigating many basic questions about the variant, including whether it increases the risk of in-school transmission. See reviews of the two studies in MMWR below.

Model Based on Existing Immunity and Strain



Comment: I thought this figure helps explain Ro and immunity of the population. The better the immunity the lower the Ro.

Evusheld
AstraZeneca said "that a lab study of Evusheld, MCA, found that the treatment 'retained neutralizing activity' against Omicron."

Comment: This is good news. Early analyses suggest that sotrovimab (GlaxoSmithKline) is also effective MCA therapy against omicron, but current supplies are limited.

With Paxlovid and molnupiravir not yet available, and the most widely used MCAs lacking activity against Omicron, is it time to consider fluvoxamine at least in the short term since two well-done RCTs

show benefit and Paxlovid supply after approval will be very limited in the first month? This question was raised in a tweet by respected colleague Paul Sax in Boston. See chart below from David Boulware.

	Molnupiravir (Merck)	Paxlovid (Pfizer)	Fluvoxamine
Efficacy in high-risk patients, reduction of hospitalizations/deaths at 28 days	30% 9.7% vs 6.8%	88% 6.5% vs 0.8%	26% 64% if took >80% of medicine
Deaths in placebo vs. drug	9 vs.1	12 vs. 0	12 vs. 1 who took medicine
N	1418 mITT	2085 mITT	2196 ITT
Duration of therapy (twice daily)	5 days	5 days	10 days
Published Double-Blind Randomized Placebo-Controlled Trials	0	0	2
Drug interactions (CYP3A4)	Minimal	Yes, such as statins, blood thinners	Yes, such as caffeine, statins, blood thinners
Repurposed	Yes, Equine encephalitis Planned to test for RSV, influenza, redirected	No, Covid specific New chemical entity adapted from an anti-SARS molecule	Yes, SSRI antidepressant - >25 years of safety data
Mechanism	Nucleoside analog; Induces mutations	Inhibits Mpro, not mutagenic	Anti-inflammatory, sigma-1 receptor.
Given with co-drug to promote half-life	No	Yes, ritonavir	No
Cost	~$710	~$529	$5
Available Today?	No	No	Yes

The most recent trial TOGETHER was published in Lancet Global Health (online October 27, 2021, reviewed in the COVID-19 Briefing). To remind everyone, a total of 1497 participants were randomly allocated to fluvoxamine, 100 mg twice daily, or matching placebo. All included participants had a positive test for SARS-CoV-2 and known risk factors for disease progression (including age ≥50 years, diabetes, hypertension, obesity, smoking, conditions associated with immunosuppression, unvaccinated status, or comorbidities such cancer, cardiovascular, pulmonary, and kidney disorders). The primary endpoint was a composite of COVID-19 emergency setting retention for greater than 6 h or hospitalization. The study found that the proportion of patients reaching the primary endpoint was lower for the fluvoxamine group compared with placebo (11% *vs* 16%; relative risk: 0·68; 95% Bayesian credible interval 0·52–0·88), with a probability of superiority of 99·8%. TOGETHER constitutes the largest randomized trial completed to date aimed at testing the effect of fluvoxamine for outpatients with COVID-19. The definitive answer regarding the effects of fluvoxamine on individual outcomes such as mortality and hospitalizations still need addressing. Fluvoxamine is very inexpensive and well tolerated.

CDC Panel Backs mRNA COVID Vaccines Over J&J Due to Rare Clot Risk

A panel of vaccine experts that advises the CDC on the use of vaccines in the United States said the Pfizer and Moderna mRNA COVID-19 vaccines should be preferred over the use of J&J shot for all adults

because the J&J shot carries the risk for a rare but potentially fatal adverse effect that causes blood clots and bleeding in the brain.

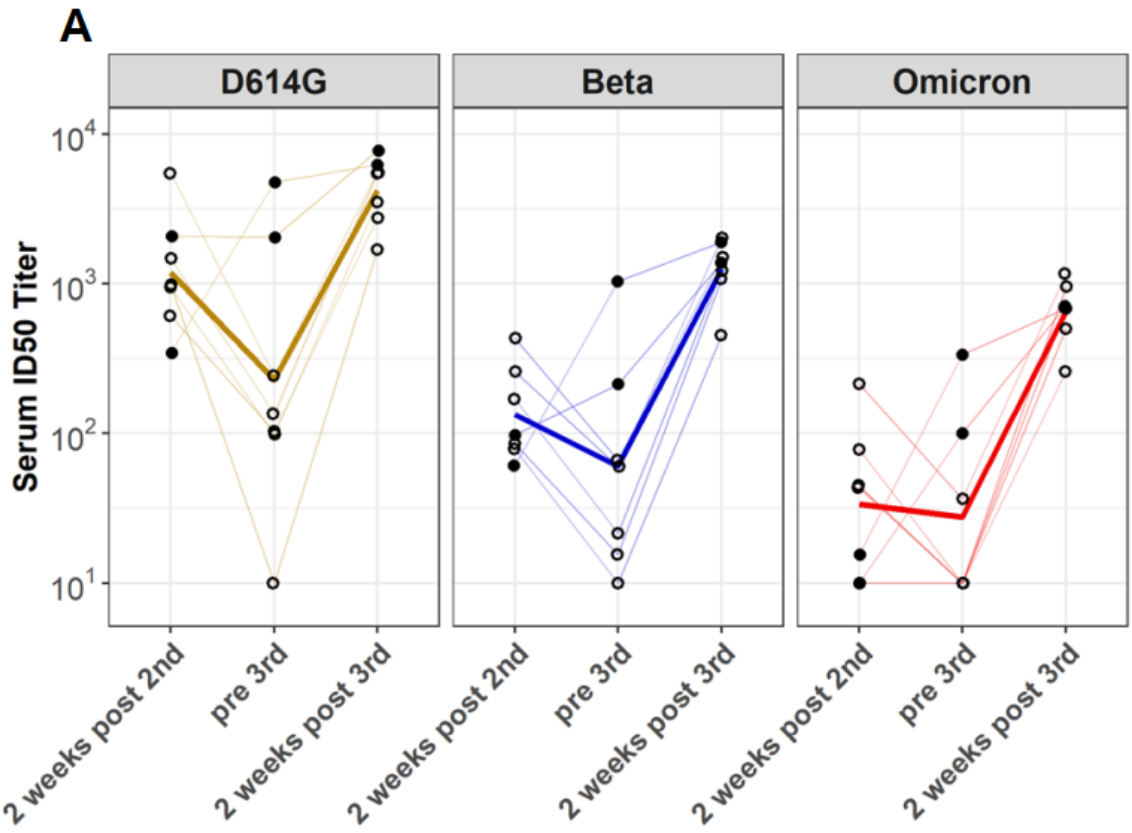
In an emergency meeting on Thursday, the CDC's ACIP voted unanimously (15-0) to state a preference for the mRNA vaccines over those from J&J after hearing a safety update on cases of thrombosis with thrombocytopenia syndrome (TTS). This condition causes large clots that deplete the blood of platelets, resulting in uncontrolled bleeding. The risk for dying of TTS after a J&J shot is extremely rare. There is approximately one death for every 2 million doses of this vaccine given in the general population. That risk is higher for women aged 30 to 49 years, rising to about two deaths for every million doses given in women in this age group.

Comment: There's no question that the J&J shot has saved many more lives than it has taken. For that reason, and because other, safer vaccines are available, the panel decided to make what's called a preferential statement, stating the Pfizer and Moderna mRNA vaccines should be preferred over the J&J vaccine. The statement leaves the J&J vaccine on the market and available to patients who are at risk for a severe allergic reaction to the mRNA vaccines. It also means that people can still choose the J&J vaccine if they still want it after being informed about the risks. About 17 million first doses and 900,000 second doses of the J&J vaccine have been given in the United States. Through the end of August, 54 cases of TTS have occurred in the United States after the J&J shots. Nearly half of those were in women aged 30 to 49 years. There have been nine recorded deaths from TTS after J&J shots. I hope Novavax will apply for EUA soon.

Journal Review

Booster of mRNA-1273 Vaccine Reduces SARS-CoV-2 Omicron Escape from Neutralizing Antibodies
medRXiv published online December 15, 2021
doi.org/10.1101/2021.12.15.21267805
Moderna's two-dose COVID-19 vaccine was found less effective against the new Omicron variant, but a booster shot of the Moderna vaccine increased antibodies that were highly effective at blocking Omicron.

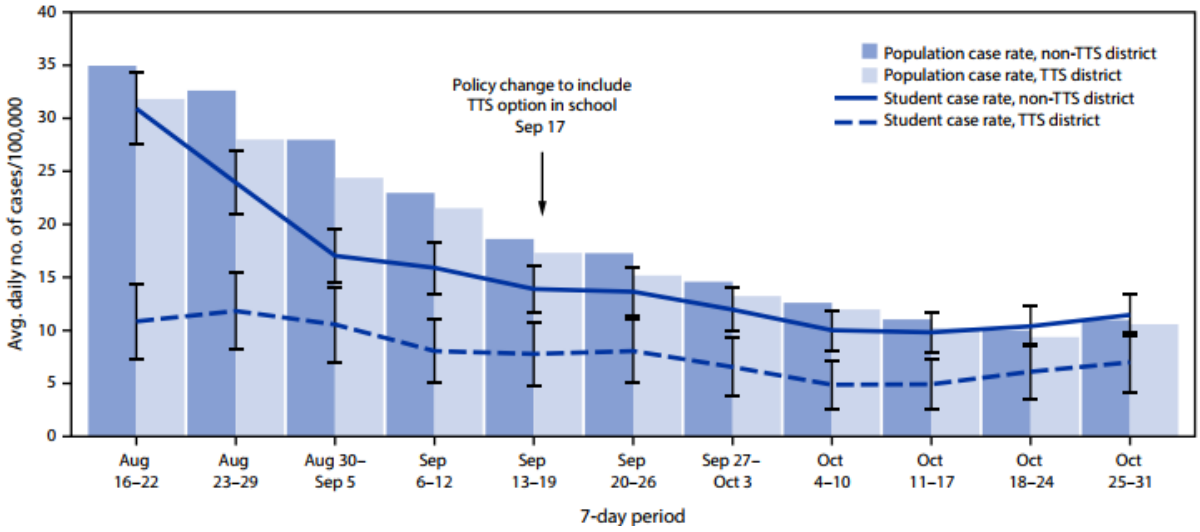
The antibodies that people make after they get the standard two inoculations of the Moderna mRNA vaccines are 50 times less effective against Omicron than they are against the ancestral strain.



Comment: The findings are similar to other studies of blood samples from people who have received Pfizer's COVID-19 vaccine. The two-shot series was less effective against Omicron, but a third shot helped to boost antibodies and reduce infection. These studies support the urgency to get a booster if eligible.

Evaluation of a Test to Stay Strategy in Transitional Kindergarten Through Grade 12 Schools — Los Angeles County, California, August 16-October 31, 2021
MMWR published online December 17, 2021
This study took place in Los Angeles County comparing COVID-19 student case rates (CRs) in 39 school districts that implemented TTS to 39 school districts using traditional quarantine from September 20, 2021-October 31, 2021. For asymptomatic, unvaccinated students under quarantine orders, TTS was permitted during the quarantine period if the exposure occurred in school and the exposed student and infected person both wore masks correctly and consistently during the exposure. During TTS, contacts could continue in-person academic activities during regular school hours if they remained asymptomatic, wore a mask while at school (indoors, outdoors, and on school buses), received testing twice weekly by a certified testing program or health care provider, and agreed to quarantine at home when not at school. Contacts could not participate in extracurricular activities or before- or after-school care during the quarantine period.

The ratio of student COVID-19 case rates in TTS districts compared with non-TTS districts was similar before and after TTS adoption. Schools implementing TTS did not identify tertiary transmission among school-related outbreaks.



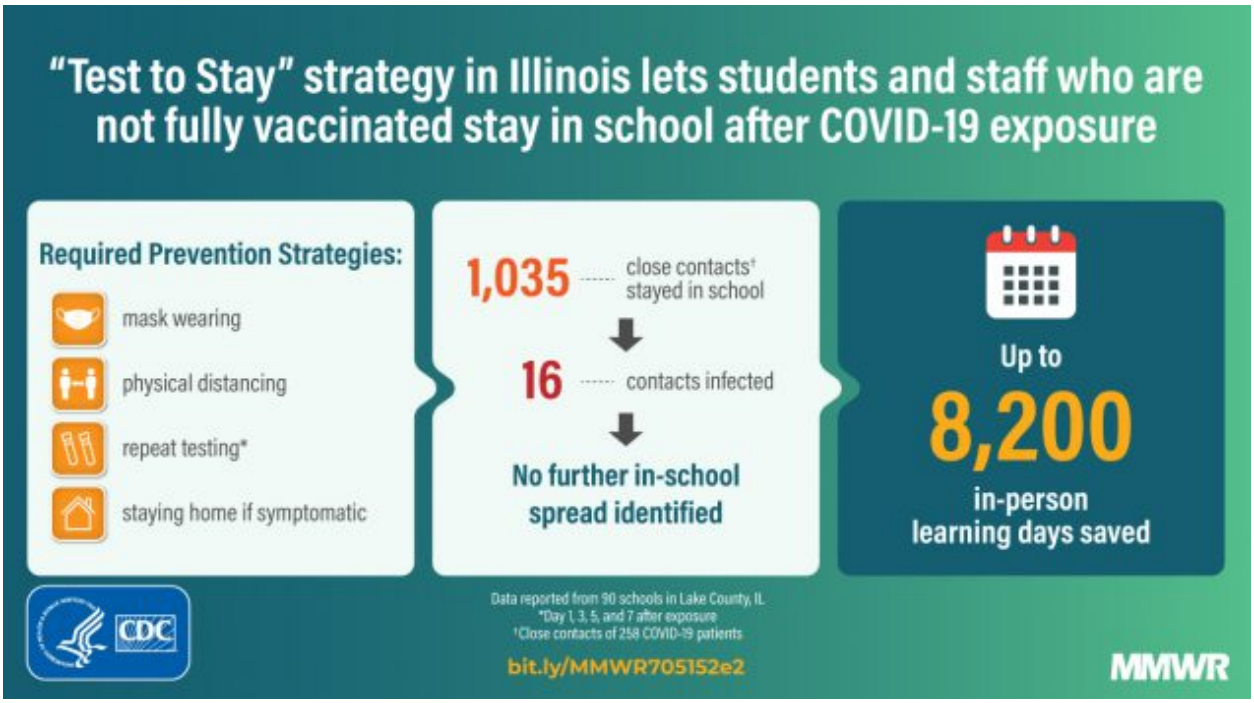
See next report.

Evaluation of Test to Stay Strategy on Secondary and Tertiary Transmission of SARS-CoV-2 in K–12 Schools — Lake County, Illinois, August 9-October 29, 2021

MMWR published online December 17, 2021

In Lake County, Ill., after the Illinois Department of Public Health offered test-to-stay as an option for schools this fall, ninety schools signed up, and about 97% of eligible students who were exposed to a Covid-19 case in school participated. Under most test-to-stay plans in this study, children are tested for Covid-19 daily or every other day after contact with a positive case. Students are sent home only if they develop symptoms or a test comes back positive, rather than having to quarantine.

Out of about 1,000 close contacts who participated, only 16 students ended up testing positive. None appeared to transmit to other in-school contacts, but some did transmit the virus to members of their household, resulting in nine additional cases. Researchers estimated that the program saved more than 8,000 in-person school days. Implementation of TTS in coordination with other concurrent prevention strategies, including masking and physical distancing, allowed transmission of SARS-CoV-2 to remain low among K-12 schools in Lake County, Illinois, and saved up to 8,152 in-person learning days.



Comment: Although vaccination remains the leading recommendation to protect against COVID-19, TTS allows close contacts to remain in the classroom as an alternative to home quarantine. Vaccinated students with exposures have generally been allowed to remain in school as long as they are asymptomatic and wear a mask and get tested between day 3-5. Students unvaccinated participating in test-to-stay programs should be tested at least twice during the seven-day period after an exposure.

These studies were conducted before Omicron variant began spreading in the United States.