First I want to wish all of you a joyous and safe holiday season. Below is a quote from an adult education text I find helpful during challenging times.

"In a values narrative, we must see each other for what we can become. The conversation is not about embracing and accepting what is, but rather about building a common vision of what ought to be. In a relationship build on shared values, we will invariably face disappointments, as we confront realities which are not commensurate with our aspirations. These disappointments, however, cannot be allowed to lead to disillusionment and disengagement. Indeed, it is at moments of failure that true commitment is expressed, as one partner reminds the other of who they can be, resolving to work together to fulfill their greatest potential."

I started the COVID-19 Briefing in March 2020. Little did I know I would still be at it! Your response has been overwhelming positive and inspiring. What started out as a local "publication" is now distributed to hundreds of people internationally. I hope this will be the final Brief until after Christmas.

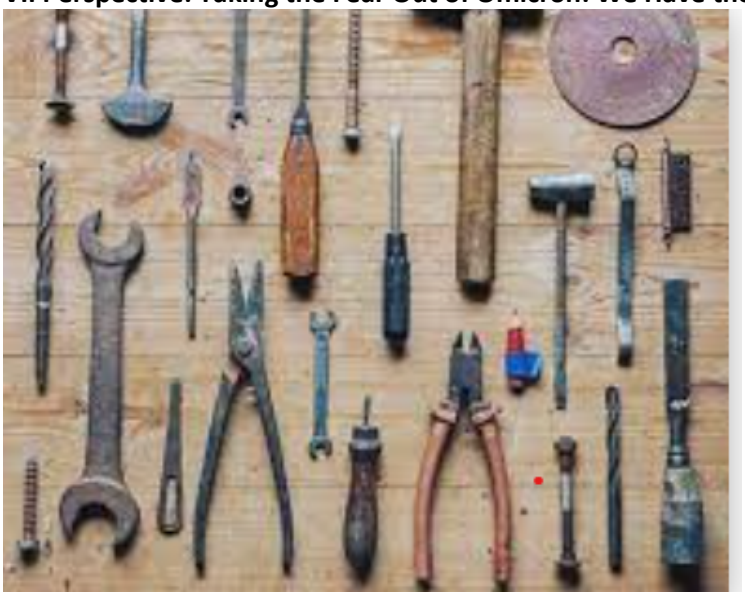
Today I start with a perspective on taking the fear out of Omicron. I hope you find this useful. Under Covid-19 News an update on Omicron in the US, followed by the CDC guidance on self-testing before the holidays[I guess no one told the CDC there is a serious shortage] Next is the latest numbers of death due to SARS-CoV-2 in the US. Europe has approved the Novavax vaccine. On the influenzas front we are beginning to see an uptick in cases mostly H3N2. It appears we may have a mismatch compared to vaccine.

Under Journal Review, an encouraging article on variant cross neutralization after breakthrough infection. The second article compares the risk of myocarditis between the Moderna and Pfizer vaccine. The next two articles look at molnupiravir activity, one for outpatient and one for inpatient. The last article looks at use of CP in the outpatient setting.

Let us continue to work together to fight this pandemic and reach our greatest potential.

Ed

VII Perspective: Taking the Fear Out of Omicron: We Have the Tools



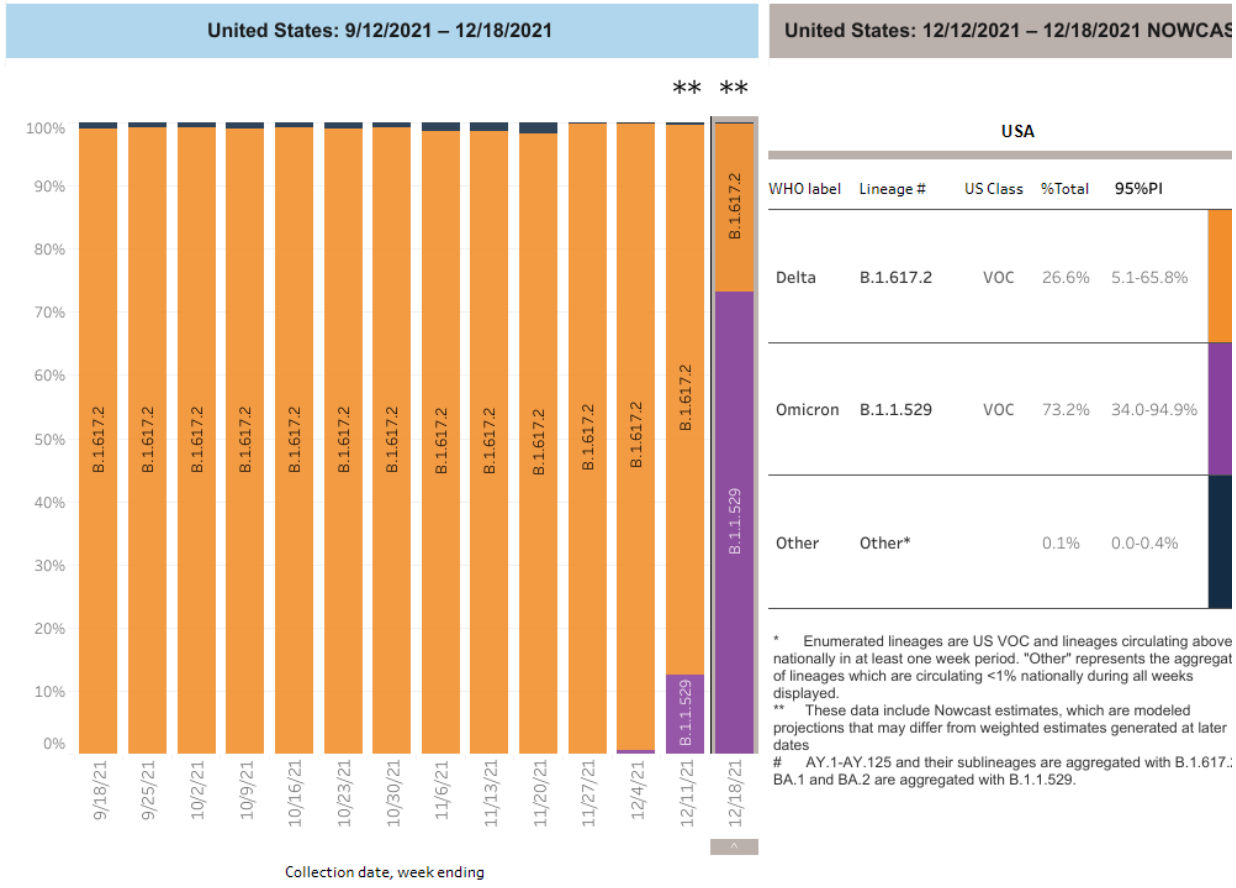
There is uncertainty whether record number of Omicron infections will translate into record number of hospitalizations and deaths, however, initial data shows decoupling between the number of positive cases and hospitalizations. Statement like the unvaccinated were "looking at a winter of severe illness and death" does not help. However, I was pleased with the President's tone yesterday saying this is no time to panic. While Omicron means increased number of infections, vaccines should blunt large number of hospitalizations and deaths. In fact, many countries now put more weight on hospitalizations rather than case counts. Next CDC should redefine "fully vaccinated" to include a booster for all eligible persons. The message should be clear: being fully vaccinated may not totally prevent infection, but it will protect you from becoming severely ill and requiring hospitalization. This will preserve critical hospital beds. One of the greatest challenges with this wave could be staffing. Across the US and elsewhere, HCWs are exhausted and demoralized. Many hospitals were already understaffed before Omicron. The problem will be exacerbated if vaccinated HCWs become infected and are unable to work. This will impact patient safety and outcomes.

What can we do now to alleviate fear? First, we must continue to focus on vaccinations as the best single way to save lives and preserve our healthcare system from further stress. Next, I think the CDC should consider shortening isolation periods for vaccinated persons who test positive and are either asymptomatic or no longer have symptoms from 10 days to closer to 5 days especially with a negative test. Initial studies demonstrate levels of virus rapidly decline in vaccinated persons. This will help people with breakthrough infections able to return to their normal lives if they continue wear a mask. "Test-to-stay" should be considered for unvaccinated people who have close contact with an infected person. Instead of requiring staying home and quarantine they could be allowed to return to work or school if they do not have symptoms and test negative initially and periodically for the next 7 days and wear a mask.

Beyond vaccination, we should add layers of protection such as greater access to testing including use of rapid tests before gatherings, wearing high quality masks, and improving ventilation. To increase testing, we need to encourage and increase access to rapid tests at home. The announcement yesterday to distribute at-home testing cannot be executed for weeks raising doubts about how much this will help in the short term. This testing plan may be too little too late. Experts have been calling for months to ramp up testing. Next, a priority should be accelerating the approval and production of therapies and vaccines to cope with new variants. Monoclonal antibodies were rationed even before the current surge, and now the Regeneron and Eli Lilly treatments that the US has relied on do not work against Omicron. SKG's monoclonal sotrovimab has activity against Omicron, but we have only about 50,000 total doses on hand. Pfizer has applied for EUA for its antiviral pill, Paxlovid, which was found to cut the risk of hospitalization by about 90% in high-risk patients if taken within five days of symptom onset. The FDA should approve it ASAP. [word on the street the FDA may approve both Paxlovid and Molnupiravir as soon as this week] Ramping up production and distribution will be the challenge. The Administration could also recommend off-label use of the anti-depressant fluvoxamine, which has proven highly effective in preventing hospitalizations in two randomized control trials. [see last Briefing]

In summary we have the tools to fight the fear of Omicron: (1) Vaccination and get boosted! Remember vaccines do not save lives, vaccinations do (2) approve Paxlovid and expand access to therapeutics such as fluvoxamine, (3) increase access to testing, and (4) add layers of protection such as masking in public areas. We must learn to live with SARS-CoV-2 which has crippled so many physically and emotionally. The reality is that the virus will eventually become endemic, like many other pathogens that we have learned to live with. If we do our part, we can flatten the curve and save lives!

Omicron Variant Accounts for 73% of U.S. Covid-19 Cases

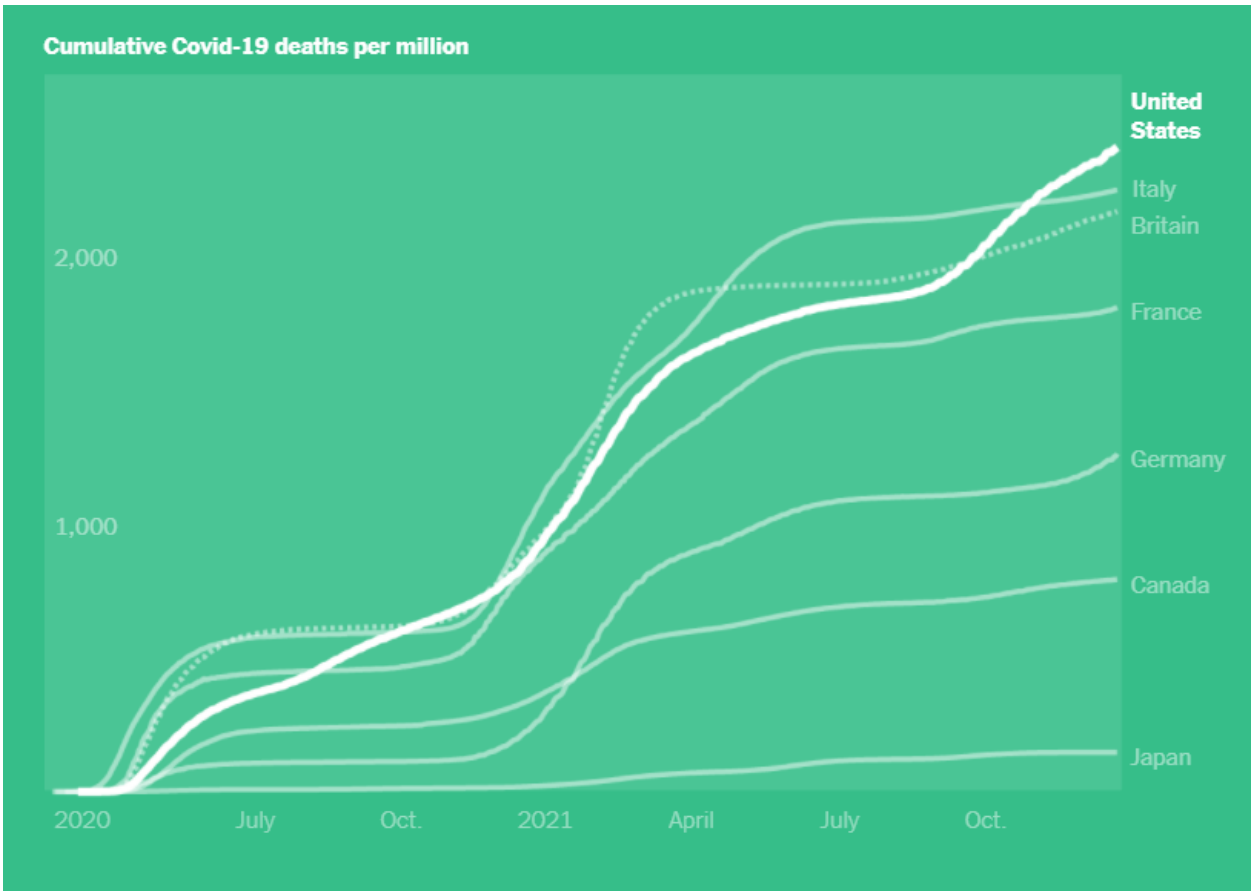


Comment: The CDC said Monday that Omicron had overtaken the Delta variant of the coronavirus in the U.S. and accounted for an estimated 73% of infections for the week ending December 18th up from 13% the week before. The Omicron variant is causing Covid-19 cases to double every 1.5 to 3 days in places with community transmission. This spread is unprecedented.

CDC Recommends COVID-19 Self-testing Before Holiday Gatherings

CDC says you should consider recommending people perform COVID-19 rapid antigen self-tests and encourage their guests to do the same, before indoor holiday gatherings. Along with vaccination, masking, and physical distancing, self-tests help reduce the chance of spreading SARS-CoV-2. Self-tests can also help protect unvaccinated children, older individuals, those who are immunocompromised, or individuals at risk of severe disease.
Comment: This is a reasonable suggestion, but currently trying to find a rapid home test is challenging and lines to be tested are very long. There seems to be a disconnect between CDC and Main Street.

Sobering Fact NY Times December 22, 2021



Comment: The US thought 2020 would be the worst year, but we were wrong. The death toll this year is even worse with over 450,000 deaths compared to ~350,000 deaths in 2020.

Novavax's Covid Vaccine Is Authorized in Europe

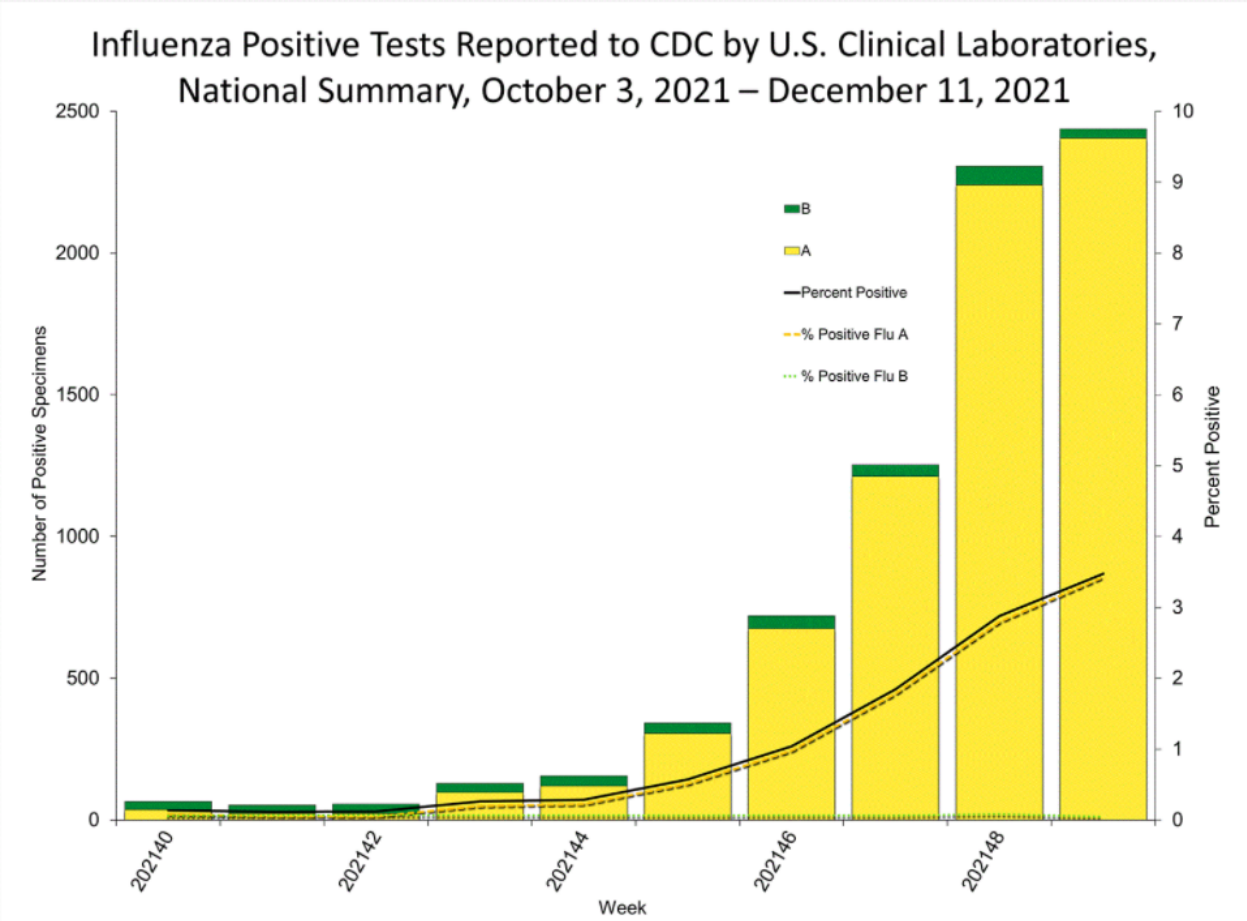
The European Commission on Monday authorized a Covid-19 vaccine made by Novavax, making it the fifth vaccine available in the 27 nations of the European Union. It's not yet clear how well the vaccine will work against the Omicron variant. In a report published last week in NEJM [review in the last Briefing] investigators found that Novavax was 90 percent effective against symptomatic infection and 100 percent effective against moderate to severe disease.

Comment: Protein-based vaccines have been used for decades and generally have a strong track record of safety and mild side effects. Novavax side effects are usually mild or moderate and clear up within a couple days.

Weekly U.S. Influenza Surveillance Report Week ending December 11th

- Influenza activity is increasing, with the eastern and central parts of the country seeing the largest increases and the western part of the country reporting lower levels of influenza virus circulation currently.
- The majority of influenza viruses detected are A(H3N2). Most influenza A(H3N2) infections have occurred among children and young adults ages 5-24 years; however, the proportion of infections occurring among adults aged 25 years and older has been increasing.
- Hospitalizations for influenza are starting to increase.

- The percentage of outpatient visits due to respiratory illness has trended upwards in recent weeks and is now above the national baseline. Influenza is contributing to levels of respiratory illness, but other respiratory viruses are also circulating including RSV and adenovirus



Comment: Influenza viruses have circulated at very low levels during the COVID-19 pandemic, and population immunity against these viruses is now low. Influenza virus cases have been increasing in the Northern Hemisphere involving an H3N2 strain (3C.2a1b.2a2) with a hemagglutinin (HA) that has several substitutions relative to the 2021-2022 H3N2 vaccine strain. Scientists found that antibodies elicited by the 2021-2022 Northern Hemisphere influenza vaccine poorly neutralize the new H3N2 strain. Together, these data indicate that 3C.2a1b.2a2 H3N2 viruses efficiently replicate in human cells and could potentially cause an antigenic mismatch if they continue to circulate at high levels during the 2021-2022 influenza season. This may complicate the respiratory/influenza season which usually peaks on average in February.

Journal Review

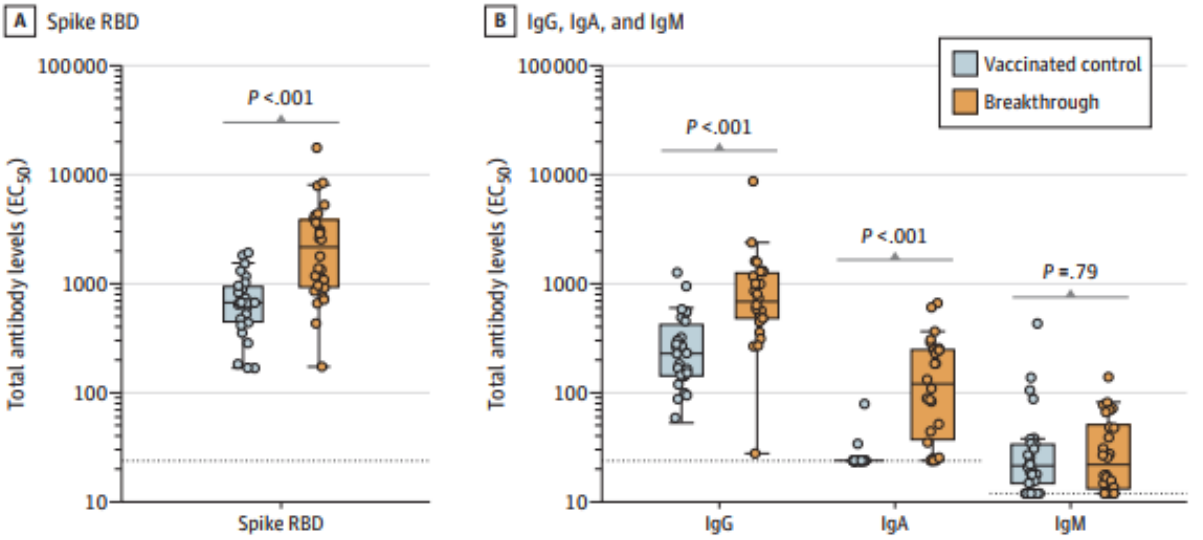
Antibody Response and Variant Cross-Neutralization After SARS-CoV-2 Breakthrough Infection JAMA published online December 16, 2021

doi:10.1001/jama.2021.22898

Fully vaccinated health care workers subsequently diagnosed with SARS-CoV-2 breakthrough infection based on a positive PCR test result were recruited between January 31, 2021, and August 18, 2021. Only those with no history of previous infection whose test results were negative for nucleocapsid antibodies were included. Controls were fully vaccinated individuals without a breakthrough infection matched on sex, age, time between vaccine doses, and time between sample collection and most recent antigen exposure. Full length viral genomic sequencing was used to determine SARS-CoV-2 variant identity. Enzyme-linked immunosorbent assays were used to determine serum dilution titers with a 50% effective concentration (EC50) of IgG, IgA, and IgM antibodies specific to the SARS-CoV-2 spike receptor-binding domain.

Results of this study showed substantial boosting of humoral immunity after breakthrough infection, despite predominantly mild disease. Boosting was most notable for IgA, possibly due to the differences in route of exposure between vaccination and natural infection. In addition, breakthrough sera demonstrated improved variant cross neutralization, and Delta breakthrough infections exhibited improved potency against Delta vs ancestral strain, suggesting that the protective immune response may be broadened through development of variant boosters with antigenic inserts matching the emerging SARS-CoV-2 variants.

Figure 1. SARS-CoV-2 Spike Receptor-Binding Domain (RBD)–Specific Antibody Levels After Vaccination and Breakthrough Infection



Comment: Omicron clearly evades vaccine-based immunity against infection, with breakthroughs increasingly common. Thankfully, it does not seem to evade vaccine-based protection against severe disease and death. In fact, suggests that a breakthrough infection in a vaccinated person might even be a good thing — it seems that most cases are quite mild and they act a bit like a booster vaccine, with the added benefit of increasing IgA which may be necessary to prevent even mild infection by stopping the virus from binding to nasal and bronchial epithelial cells. As a colleague remarked, getting Omicron is like getting a nasal live attenuated vaccine.

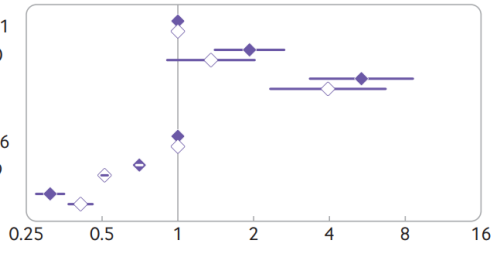
SARS-CoV-2 vaccination and myocarditis or myopericarditis: population based cohort study
BMJ 2021;375:e068665

doi.org/10.1136/ bmj-2021-068665

The purpose of this study was to investigate the association between SARS-CoV-2 vaccination and myocarditis or myopericarditis after vaccination. After vaccination, 269 participants developed myocarditis or myopericarditis, of whom 108 (40%)
were 12-39 years old and 196 (73%) were male. Of 3 482 295 individuals vaccinated with Pfizer, 48 developed myocarditis or myopericarditis within 28 days from the vaccination date compared with unvaccinated individuals (adjusted hazard ratio 1.34 (95% confidence interval 0.90 to 2.00); absolute rate 1.4 per 100 000 vaccinated individuals within 28 days of vaccination (95% confidence interval 1.0 to 1.8)). Adjusted hazard ratios among female participants only and male participants only were 3.73 (1.82 to 7.65) and 0.82 (0.50 to 1.34), respectively, with corresponding absolute rates of 1.3 (0.8 to 1.9) and 1.5 (1.0 to 2.2) per 100 000 vaccinated individuals within 28 days of vaccination, respectively. The adjusted hazard ratio among 12–39-year-olds was 1.48 (0.74 to 2.98) and the absolute rate was 1.6 (1.0 to 2.6) per 100 000 vaccinated individuals within 28 days of vaccination.

Among 498 814 individuals vaccinated with Moderna, 21 developed myocarditis or myopericarditis within 28 days from vaccination date (adjusted hazard ratio 3.92 (2.30 to 6.68); absolute rate 4.2 per 100 000 vaccinated individuals within 28 days of vaccination (2.6 to 6.4)). Adjusted hazard ratios among women only and men only were 6.33 (2.11 to 18.96) and 3.22 (1.75 to 5.93), respectively, with corresponding absolute rates of 2.0 (0.7 to 4.8) and 6.3 (3.6 to 10.2) per 100 000 vaccinated individuals within 28 days of vaccination, respectively. The adjusted hazard ratio among 12–39-year-olds was 5.24 (2.47 to 11.12) and the absolute rate was 5.7 (3.3 to 9.3) per 100 000 vaccinated individuals within 28 days.

Outcome	No	Person years	Hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Myocarditis or myopericarditis				
Unvaccinated (reference)	155	3 213 951	1	1
BNT162b2 (Pfizer-BioNTech)	48	509 590	1.90 (1.37 to 2.64)	1.34 (0.90 to 2.00)
mRNA-1273 (Moderna)	21	74 441	5.35 (3.34 to 8.57)	3.92 (2.30 to 6.68)
Cardiac arrest or death				
Unvaccinated (reference)	25 933	3 214 646	1	1
BNT162b2 (Pfizer-BioNTech)	4438	509 609	0.70 (0.68 to 0.73)	0.51 (0.49 to 0.53)
mRNA-1273 (Moderna)	298	74 461	0.31 (0.27 to 0.35)	0.41 (0.37 to 0.46)



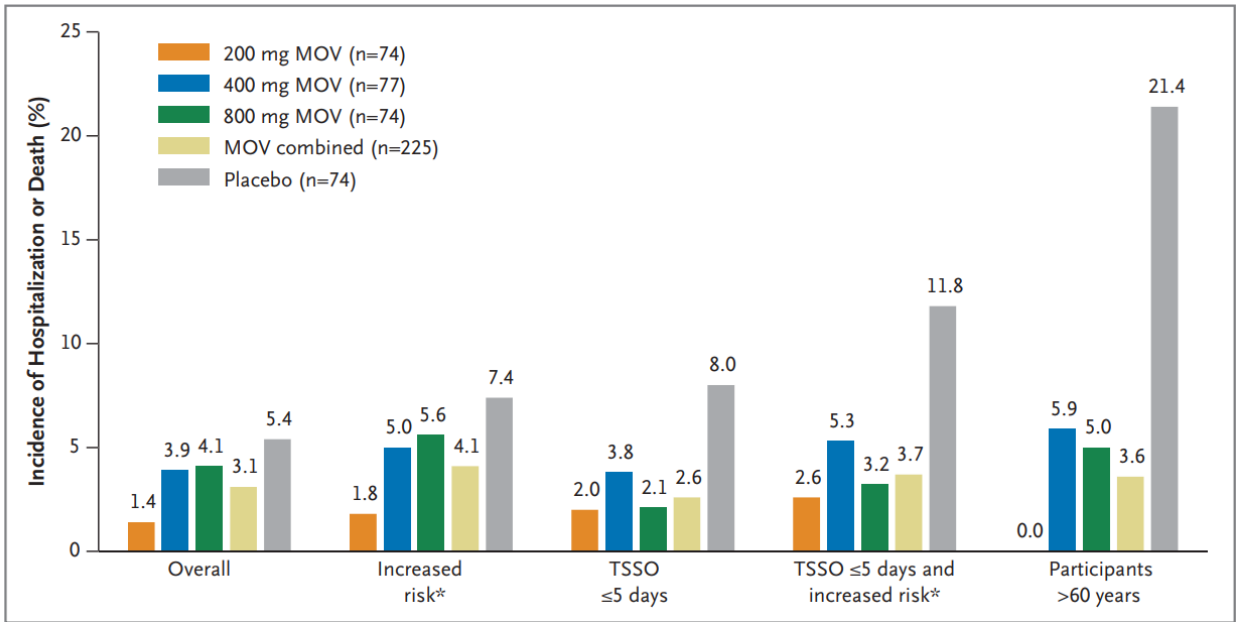
Comment: Moderna's vaccine is up to four times more likely to cause myocarditis compared to the vaccine from Pfizer. Clinical outcomes of myocarditis or myopericarditis were predominantly mild and generally similar between vaccinated and unvaccinated individuals, although the accuracy in describing clinical outcomes was limited owing to few myocarditis or myopericarditis cases. The absolute rate of myocarditis or myopericarditis after Moderna vaccination was low, even in younger age groups. The benefits of vaccination far outweigh the risks.

Phase 2/3 Trial of Molnupiravir for Treatment of Covid-19 in Nonhospitalized Adults N Eng J Med Evidence published online December 16, 2021

DOI: 10.1056/EVIDoa2100043

MOVe-OUT is an ongoing, phase 2/3, randomized, placebo-controlled, double-blind study evaluating the safety, efficacy, and pharmacokinetics of molnupiravir in nonhospitalized adults. In the phase 2 component, participants had mild or moderate, laboratory-confirmed Covid-19 with sign/symptom onset up to (and including) 7 days before randomization. Participants were randomly assigned 1:1:1:1 to receive 200, 400, or 800 mg of molnupiravir or placebo twice daily for 5 days, stratified by time since sign/ symptom onset and by being at increased risk for severe illness from Covid-19. The primary efficacy end point was the proportion of participants who were hospitalized and/or died through day 29. Change from baseline in SARS-CoV-2 RNA titer and the proportion of participants with undetectable SARS-CoV-2 RNA over time were determined by quantitative PCR.
In another subgroup, Molnupiravir was administered orally (800 mg [four tablets] twice daily for 5 days) and compared with a matching placebo. Patients with mild-to-moderate disease and at least one risk factor for progression to severe illness (including age >60 years, obesity, diabetes, or cardiovascular disease) were eligible for enrollment. The primary end point was a composite of hospitalization or death at 29 days. At the planned interim analysis, 775 patients who were infected with SARS-CoV-2 and had symptoms of no more than 5 days' duration were enrolled; 387 patients received molnupiravir and 388 received placebo.

The prespecified interim analysis was performed at approximately 50% of the planned enrollment. In the molnupiravir group, the risk of hospitalization or death was 7.3% (28 of 385 patients), as compared with 14.1% (53 of 377) in the placebo group (P=0.001); no deaths had occurred in the molnupiravir group at the time of this interim analysis. However, the final analysis of these peer-reviewed data shows a more modest effect. In the final data, 1433 infected volunteers were randomly assigned to molnupiravir (716 patients) or placebo (717 patients). A primary end-point event occurred in 48 of 709 molnupiravir recipients (6.8%) and 68 of 699 placebo recipients (9.7%), an absolute difference of approximately 3 percentage points. One death occurred in the treatment group, and nine among placebo recipients. Subgroup analyses suggested lower incidences of hospitalization and/or death in the molnupiravir versus placebo groups in participants older than 60 years of age, those with increased risk for severe illness, those with symptom onset up to (and including) 5 days before randomization, and those with both symptom onset up to (and including) 5 days before randomization and increased risk of severe illness.



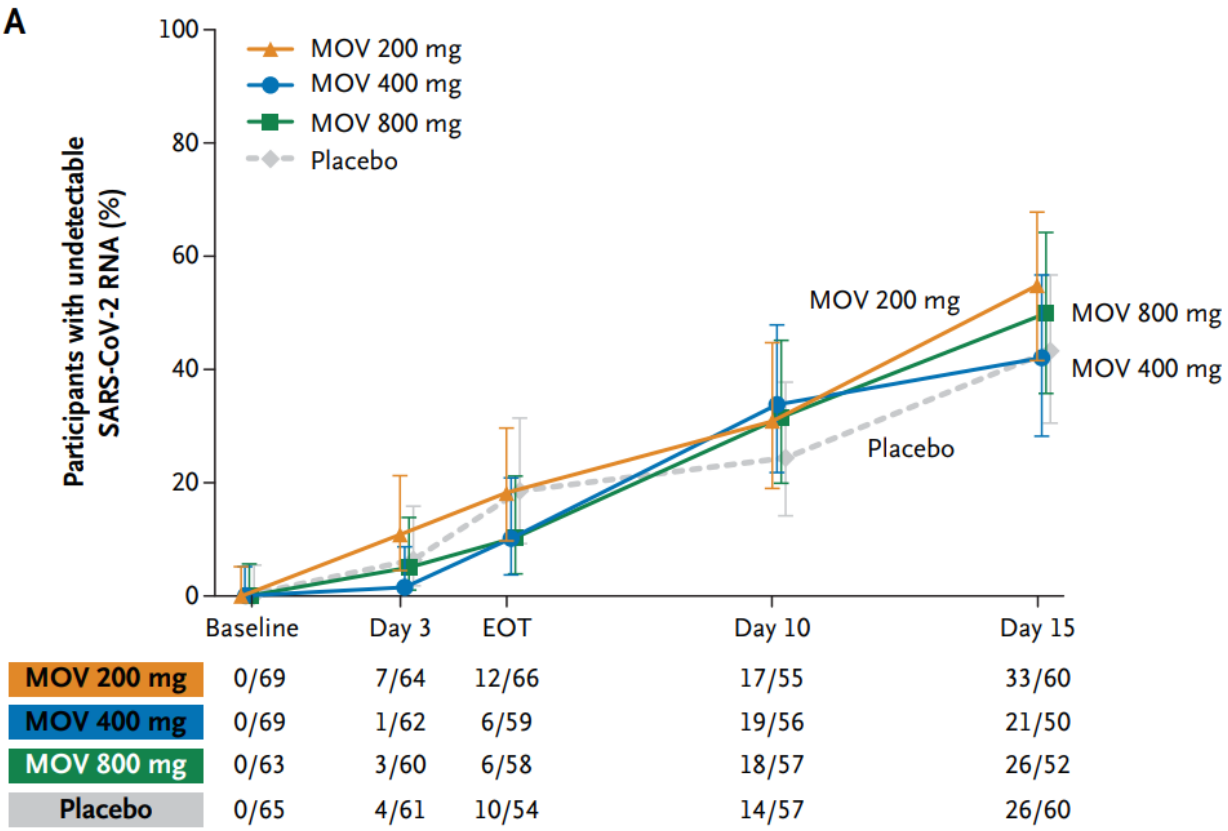
Comment: Numerous potential reasons for the lessening of the drug effect include preexisting SARS-CoV-2 nucleocapsid antibodies, duration of symptoms, and lower viral load at enrollment. First, molnupiravir therapy was initiated within 72 hours after symptom onset in only ~ 50% of patients however, starting therapy within 72 hours in all patients should be our goal similar to studies of influenza. Molnupiravir is less beneficial when administered late in the disease course — namely, after patients have had symptoms for more than 3 to 5 days or after they are hospitalized. [see next article] There is potential mutagenic toxicity has been a concern, since the drug is mutagenic in Chinese hamster ovary cells. Molnupiravir was not recommended for women who are pregnant or breast-feeding or for those who might become pregnant during treatment. Recently concerns were raised that the initial efficacy of Molnupiravir was downgraded to 50% to 30% in preventing progression. Having read this paper, efficacy may be better if Molnupiravir is given sooner in patients older than 60 years of age and those with increased risk for severe illness. Preliminary data on Paxlovid indicated up to 90% efficacy in preventing progression if given within 5 days of symptoms.

Randomized Trial of Molnupiravir or Placebo in Patients Hospitalized with Covid-19 N Engl J Med Evidence published online December 16, 2021

DOI: 10.1056/EVIDoa2100044

This is a randomized, placebo-controlled, double-blind phase 2/3 trial in patients 18 years old and older requiring in-hospital treatment for laboratory confirmed Covid-19 with symptom onset 10 or fewer days before randomization. Participants were randomly assigned to placebo or molnupiravir 200 mg, 400 mg, or 800 mg (1:1:1:1 ratio), twice daily for 5 days. Primary end points were safety and sustained recovery (participant alive and either not hospitalized or medically ready for discharge) through day 29. Of 304 randomly assigned participants, 218 received at least one dose of molnupiravir and 75 of placebo. At baseline, 74.0% had at least one risk factor for severe Covid-19. Change from baseline in SARS-CoV-2 RNA titer and the proportion of participants with undetectable SARS-CoV-2 RNA over time were determined by quantitative PCR.

Adverse events were reported in 121 of 218 (55.5%) molnupiravir-treated and 46 of 75 (61.3%) placebo-treated participants, with no apparent dose effect on adverse event rates. Of 16 confirmed deaths, most were in participants with severe Covid-19 (75.0%), with underlying comorbidities (87.5%), older than 60 years of age (81.3%), and/or symptom duration longer than 5 days (75.0%) at randomization. Median time to sustained recovery was 9 days in all groups, with similar day 29 recovery rates ranging from 81.5% to 85.2%. Molnupiravir did not significantly change viral load.



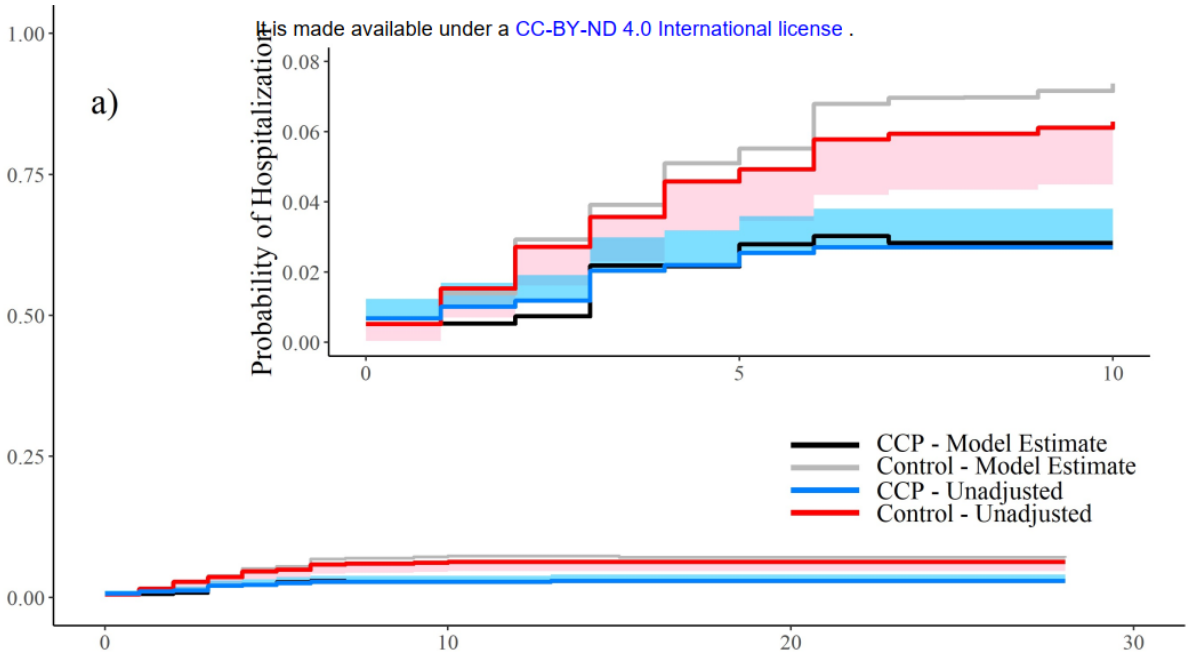
Comment: Patients hospitalized with Covid-19, receiving 5-day course of molnupiravir was not associated with dose-limiting side effects or adverse events, but did not demonstrate clinical benefit. This is consistent with other antiviral therapeutics in hospitalized patients.

Randomized Controlled Trial of Early Outpatient COVID-19 Treatment with High-Titer Convalescent Pl medRxiv published online December 21, 2021

doi.org/10.1101/2021.12.10.21267485

This is a multicenter, double-blind randomized controlled trial compared the efficacy and safety of SARS-CoV-2 high titer convalescent plasma(CP) to placebo control plasma in symptomatic adults >18 years positive for SARS-CoV-2 regardless of risk factors for disease
progression or vaccine status. Participants with symptom onset within 8 days were enrolled, then transfused within the subsequent day. The measured primary outcome was COVID-19-related hospitalization within 28 days of plasma transfusion. The enrollment period was June 3, 2020 to October 1, 2021. [pre-Omicron]

A total of 1225 participants were randomized and 1181 transfused. In the prespecified modified intention-to-treat analysis that excluded those not transfused, the primary endpoint occurred in 37 of 589 (6.3%) who received placebo control plasma and in 17 of 592 (2.9%) participants who received CP (relative risk, 0.46; one-sided 95% upper bound confidence interval 0.733; P=0.004) corresponding to a 54% risk reduction. Examination with a model adjusting for covariates related to the outcome did not change the conclusions.



Comment: Early administration of high titer SARS-CoV-2 CP reduced outpatient hospitalizations by more than 50%. High titer convalescent plasma is an effective early outpatient COVID-19 treatment with the advantages of low cost, availability, and rapid resilience to variant emergence from viral genetic drift in the face of a changing pandemic. Convalescent plasma may be another tool to help prevent SARS-CoV-2 infections sparked by the omicron variant from turning severe if patients receive it soon after developing symptoms. Logistically like MCA, it must be given by infusion. RDV has also been shown to be effective as an outpatient treatment, but it too requires IV access and requires multiple infusions over days. I think the best outpatient option will be oral drugs such as Paxlovid when FDA approved and available and perhaps fluvoxamine which is available now and very inexpensive.