A lot has happened in just a few days!

Today I start with my own Perspective and Reflections over the last year including the breakthrough drug Paxlovid.
In Covid-19 News the announcement of the study on the activity of the Pfizer vaccine against Omicron. Next an interesting lung model comparing Omicron to other Covid-19 strains. Last is a review of what is known about Paxlovid. I believe once approved we will initially have a supply and demand challenge.

Under Journal Review I started with a pre-print article from the UK on effectiveness of the Pfizer vaccine against Omicron. Next an article on use of portable HEPA/UV removal of bioaerosols. Next an updated report of the effectiveness of the Novavax vaccine. Next is a very interesting report on the difference in risk of transmission between infected fully vaccinated persons versus infected unvaccinated. Last an article which confirms that up to 40% of infection persons with Covid-19 at time of testing may be asymptomatic.

Have a good weekend. I will continue to monitor any major new information especially around Omicron and what it means. Will send out updates as they become available.

Ed

VII Perspective and Reflections: Latest Therapeutic Breakthrough

On Tuesday Pfizer announced Paxlovid (see below) reduced risk of hospitalization by almost 90% if taken within 5 days of symptoms. Paxlovid is a protease inhibitor and has activity against Omicron and other variants. Pfizer's study also showed a 10-fold reduction in viral load suggesting it should reduce transmission as well. There appear to be no major safety concerns. This is a game changer and gives us another valuable tool in our toolbox to combat this pandemic. The NIH and the federal government have been slow to invest in oral therapeutics compared to investment in vaccines and monoclonal antibodies (MCA).

Pfizer has submitted data to the FDA for EUA and I hope the FDA will act quickly. Once FDA approved Americans who test positive especially in a high-risk group can receive Paxlovid similar to how we prescribe oseltamivir for influenza. The US has ordered 10 million courses at a cost of 5.3 billion. The cost is ~$530 per treatment. It is unclear how the drug will be distributed or who will pay for the treatment. Manufacturing and supply will need to be ramped up to meet the demands.

There is no question vaccines have been incredibly effective, but we have only 60% of Americans fully vaccinated. [70% of adults and only 27% have received a booster] We have also learned that vaccine protection waned over time and may not be as effective against new variants such as Omicron. (See below) MCA have also been very effective in preventing progression, but recent data indicates that Eli Lilly and Regeneron MCA have lost most of their effectiveness against the Omicron variant. MCA must be administered by either infusion or by the subcutaneous route. Fortunately, Sotrovimab MCA is still effective against the Omicron variant. The addition of an effective oral drug like Paxlovid will hopefully save lives and reduce hospitalizations.

This week is the anniversary of when vaccines became available to the public. I received my first Covid-19 vaccination on December 17, 2020, and I remember the feeling of hope that perhaps we were

turning the corning on this pandemic. We have come a long way in the last year. We now have 3 vaccines, 4 MCA products, improved therapeutics and diagnostics, and better genomic surveillance, but tragically we have witnessed too many preventable deaths. The pandemic reminds us how dependent we are on one another. We must all do our share. A few reflections as we will soon begin year 3 of the pandemic: (1) be credible, (2) express empathy, (3) show respect, (4) be transparent and communicate uncertainty, (5) learn from mistakes, (6) encourage community engagement, (7) follow the science, (8) multistakeholder coordination, and (9) humility! The value of preserving individual and community health is one of the most important goals of public health. Vaccination including a booster if eligible is still the most effective strategy to end the pandemic and to blunt the Omicron wave.

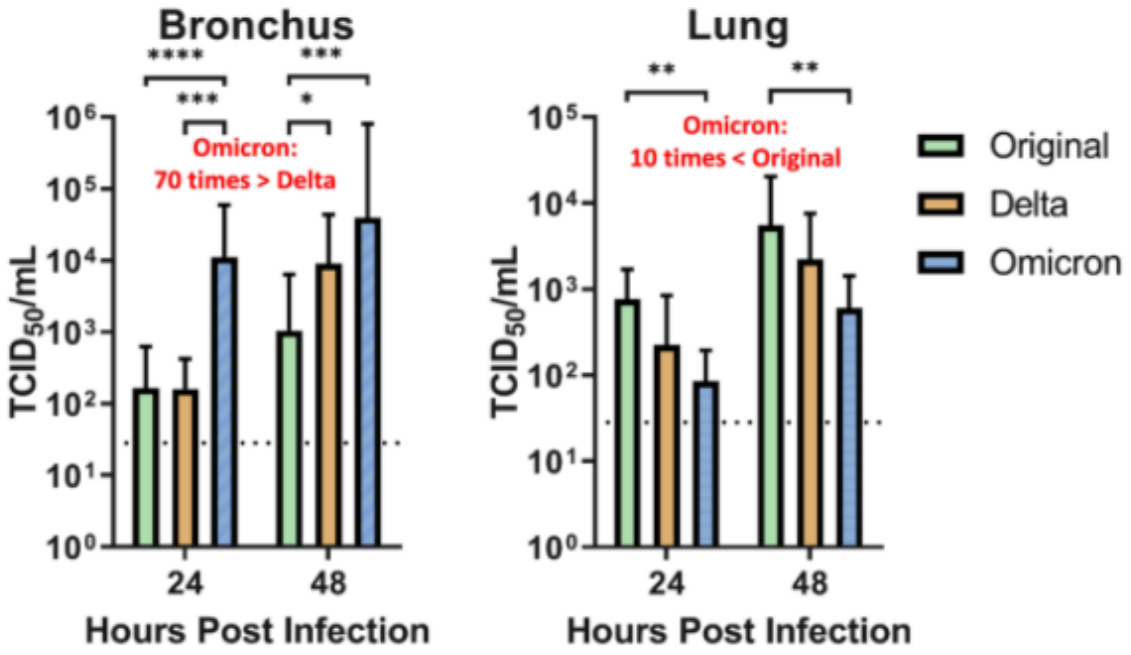
COVID-19 News

Study Finds Two Pfizer Vaccine Doses Offer Less Protection Against Omicron Than Against Delta WSJ December 14, 2021
The study, by South Africa's largest private health insurer Discovery Ltd., found that while Omicron reduced vaccine effectiveness against infection to 33% from 80% for Delta, its effect on protection against hospitalization was less marked, falling to 70% from 93%. [results similar to UK-See below]
Comment: The study—the largest to provide clues about how the vaccines hold up against Omicron in the real world—suggests that although the new strain can easily infect people who have been fully vaccinated, it is still much less likely to cause serious illness when it does. This is supported by the fact that despite Omicron's many mutations, most of the protein fragments recognized by T cells are identical to those of other variants. The research hasn't yet been published or peer-reviewed in a scientific journal.

Omicron and Lung Tissue Study

Hong Kong University investigators used lung tissue samples to compare infection with the recent Omicron variant compared with Delta and the original virus from 2020.

At 24 hours after infection, Omicron replication was 70 times higher than the other two viruses. However, they found that Omicron replication was less efficient in deeper lung tissue—more than 10 times lower than the original virus. This study is under peer review for publication.



Comment: Virus replication isn't the only driver of disease severity and that host immune response can also play a role, such as the immune system dysregulation that leads to cytokine storm. This is obviously more complex than this model suggests but nonetheless this study may provide some clues.

Paxlovid

Pfizer also said Tuesday that a final analysis of late-stage study results confirmed the drug, named Paxlovid, was 89% effective at reducing the risk of hospitalization and death in adults at high risk of severe Covid-19. The company also said that laboratory experiments indicated that the drug will attack a key protein in the Omicron variant, which is surging in South Africa and Europe and is expected to dominate U.S. cases in the weeks ahead. The data comes from a phase 2/3 trial involving 2,246 adults.

Pfizer said that in its final analysis, 0.7 percent of patients who received Paxlovid were hospitalized within 28 days of entering the trial, and none died. By contrast, 6.5 percent of patients who received a placebo were hospitalized or had died.

Pfizer also released preliminary data from a separate trial looking at people with a lower risk. These volunteers included vaccinated people who carried a risk factor for severe disease, as well as unvaccinated patients with no risk factors. Among this group of 662 volunteers, Paxlovid reduced the risk of hospitalization and death by 70 percent.

The study also showed that the amount of virus, or viral load, in subjects who received the drug was significantly less than in the placebo group. This should translate to lower transmission of the virus.

Pfizer's treatment is meant to be taken as 30 pills over five days. Patients will take three pills at a time: two of Pfizer's new pills and one ritonavir, which helps Pfizer's drug remain active in the body longer. [similar to HIV]

The positive results come as the FDA reviews whether to give EUA of Paxlovid in high-risk adults, a decision that could come as early as the end of the year. However, there are logistical obstacles that could limit the Pfizer treatment's promise. To be eligible, patients are expected to need a positive Covid-19 test and a prescription from a health care provider, all within five days after developing symptoms. Those challenges could be especially pronounced among the people most vulnerable to becoming severely ill from Covid. The federal government has ordered enough of Pfizer's pills to cover 10 million people, at a cost of about $530 per patient. Pfizer will have about 180,000 treatment courses ready by the time it receives its expected authorization this month, but some of those will most likely go to countries other than the United States. The company is expected to deliver only enough of its pills to cover 300,000 Americans before the end of February, and then sharply increase the pace of its deliveries.

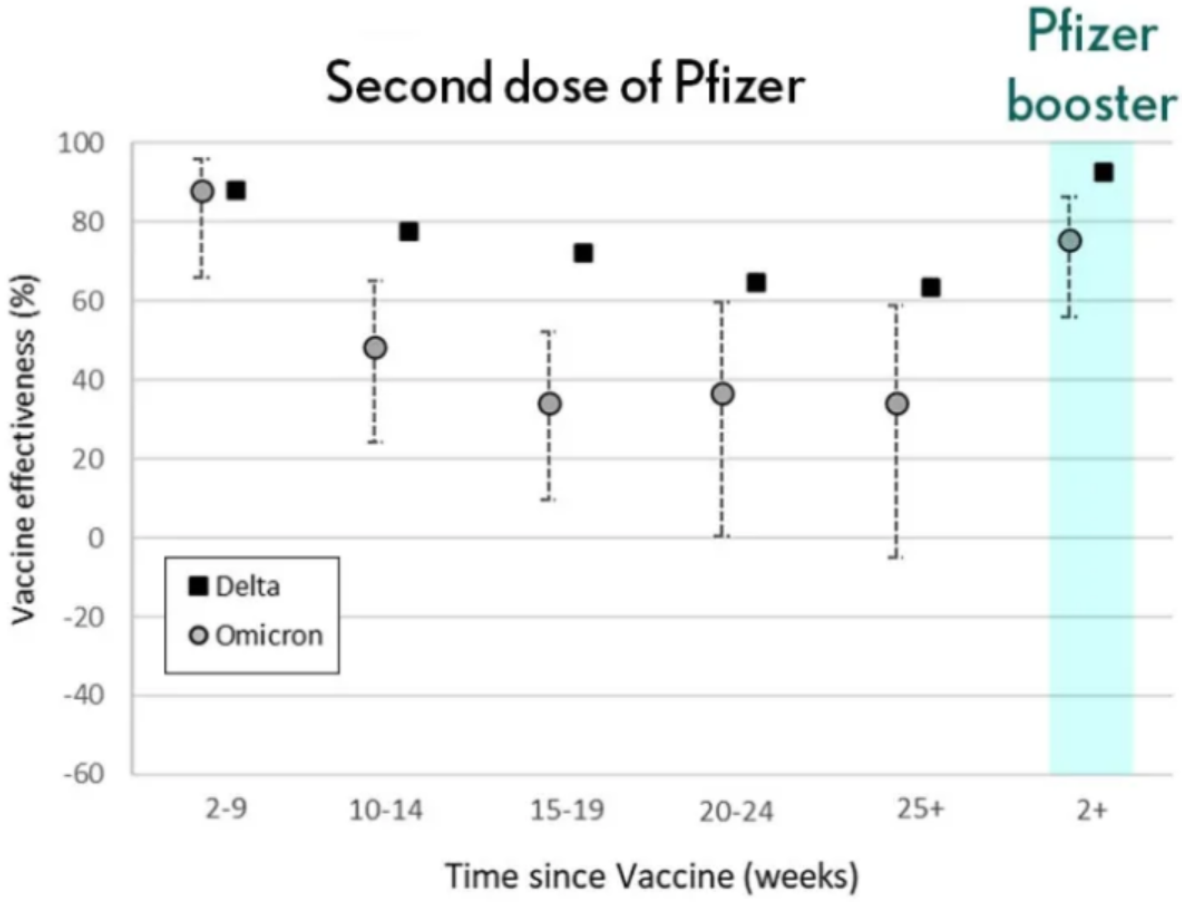
Comment: Pfizer's good news comes as its rival, Merck, awaited word on authorization of its own antiviral pill for Covid, molnupiravir. In October, Merck announced that preliminary data showed the pill reduced the risk of hospitalization and death from Covid-19 by 50 percent, if taken within five days of the onset of symptoms, however, final analysis on all their data, showed molnupiravir' s effectiveness dropped to 30 percent. At an FDA advisory committee meeting last month, several experts were not enthusiastic with only a 30% effectiveness, especially given some concerns about the safety of the pill in pregnancy. The FDA has yet to vote to authorize EUA for molnupiravir. France has turned down the application for molnupiravir, but the UK approved the use of molnupiravir.

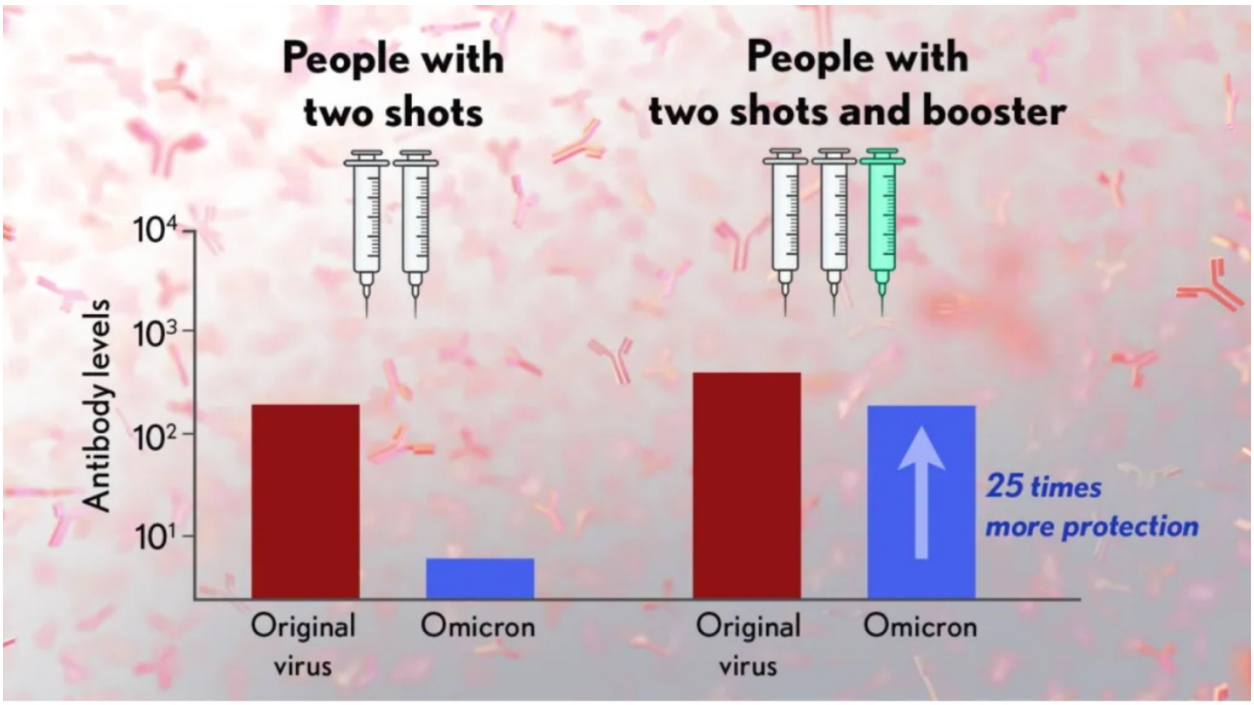
Realistically, Paxlovid may not be readily available a month from now for the average patient. In the meantime, vaccination including a booster if eligible will be critical to blunt the Omicron wave along with NPI especially in areas with high levels of transmission.

Journal Review

Effectiveness of COVID-19 vaccines against the Omicron (B.1.1.529) variant of concern KHub.net preprint. December 10, 2021.
A test negative case control design was used to estimate vaccine effectiveness against symptomatic COVID-19 with the Omicron variant compared to the Delta variant. The odds of vaccination in PCR positive cases is compared to the odds of vaccination in those who test negative. The National Immunization Management System (NIMS) contains demographic information on the whole population of England who are registered with a GP in England and is used to record all COVID-19 vaccinations. Sequencing is undertaken at a network of laboratories, including the Wellcome Sanger Institute, and whole-genome sequences are assigned to UKHSA definitions of variants based on mutations. Analyses were stratified by which primary doses had been received (ChAdOx1-S[AZ] or Pfizer). Any mixed primary courses were excluded. Vaccine effectiveness was assessed for each primary course in intervals of 2-9, 10-14, 15-19, 20-24 and 25+ weeks post dose 2. Vaccine effectiveness was also assessed for both primary courses followed by a Pfizer booster for the period 1 week and at least 2 weeks post vaccination. Comparison was to unvaccinated individuals to estimate the absolute effectiveness of vaccination against Omicron and Delta variants.

For both primary courses, the booster dose given was Pfizer. Apart from 2-9 weeks post dose 2 for Pfizer, effectiveness was lower for Omicron compared to Delta post vaccination at all time interval investigated. Among those who had received 2 doses of AZ, there was no protective effect of vaccination against symptomatic disease with Omicron from 15 weeks after the second dose. Among those who had received 2 doses of Pfizer, vaccine effectiveness was 88.0% (95%CI: 65.9 to 95.8%) 2-9 weeks after dose 2, dropping to 48.5% (95%CI: 24.3 to 65.0%) at 10- 14 weeks post dose 2 and dropping further to between 34 and 37% from 15 weeks post dose 2. Among those who received AZ as the primary course, from 2 weeks after a Pfizer booster dose, vaccine effectiveness increased to 71.4% (95%CI: 41.8 to 86.0%). Vaccine effectiveness increased to 75.5% (95%CI: 56.1 to 86.3%) after the booster among those who had received Pfizer as the primary course. With the Delta variant, effectiveness drops from 76.2% (95%CI: 63.7 to 84.4%) 2-9 weeks after dose 2 down to 41.8% (95%CI: 39.4-44.1%) at 25+ weeks after dose 2 with a AZ primary course. Effectiveness increases to 93.8% (95%CI: 93.2-94.3%) 2 weeks after a Pfizer booster. With a Pfizer primary course, effectiveness drops from 88.2% (95%CI: 86.7 to 89.5%) 2-9 weeks after dose 2 down to 63.5% (95%CI: 61.4 to 65.5%) 25+ weeks after dose 2, increasing to 92.6% (95%CI: 92.0-93.1%) 2 weeks after the booster.





Credit: Adapted from Pfizer, Dec. 8, 2021

Comment: The key is a booster substantially raised that vaccine effectiveness to about 80 percent. That's not quite as high as for Delta, but certainly an encouraging result. Once again, these data show that boosting the immune system produces enhanced immunity against new viral variants, even though the booster was designed from the ancestral strain. It is also worth reminding everyone that the Omicron variant doesn't have mutations in portions of its genome that are the targets of other aspects of vaccine-induced immunity, including T cells. These cells are part of the body's second line of defense and are generally harder for viruses to escape. While T cells can't prevent infection, they help protect against more severe illness and death. Despite Omicron's many mutations, most of the protein fragments recognized by T cells are identical to those of other variants; therefore, the T cell response is largely preserved.

The removal of airborne SARS-CoV-2 and other microbial bioaerosols by air filtration on COVID-19 surge units Clin Infect Dis published online October 30, 2021
doi.org/10.1093/cid/ciab933

Investigators in the U.K. demonstrated that portable systems combining high-efficiency particulate air (HEPA) filtration with ultraviolet (UV) light could provide additional safety by removing viral particles from the air. They studied two multi-bed units dedicated to patients with COVID-19. Nucleic acids were extracted from air samples in medium (1–4 µm) and large (>4µm)–sized particulate fractions and from the filter (<1 µm), and RT-PCR was performed to identify viruses, bacteria, and fungi.

In a six-bed room with the air system off, SARS-CoV-2 RNA was detected in medium and large aerosol fractions every day of testing for 1 week. When a portable HEPA/UV system was turned on in the same room for the second week, no SARS-CoV-2 RNA was detected. In a four-bed room in an intensive care unit, limited evidence of SARS-CoV-2 RNA was seen during the first week (when the system was off), but SARS-CoV-2 RNA was detected in a single sample during the week when the system was on. For both

units, the total number of bioaerosol detections when the system was off was significantly higher than when it was on.

Comment: This study demonstrated that adding a portable HRPA/UV system could reduce total bioaerosols, including SARS-CoV-2, in the hospital environment. However, the study was not designed to evaluate reduction of SARS-CoV-2 transmission. If transmission in fact was reduced, these systems could serve as an adjunct to standard PPE in preventing the spread of Covid-19. The results may also have implications in schools, restaurants, and offices.

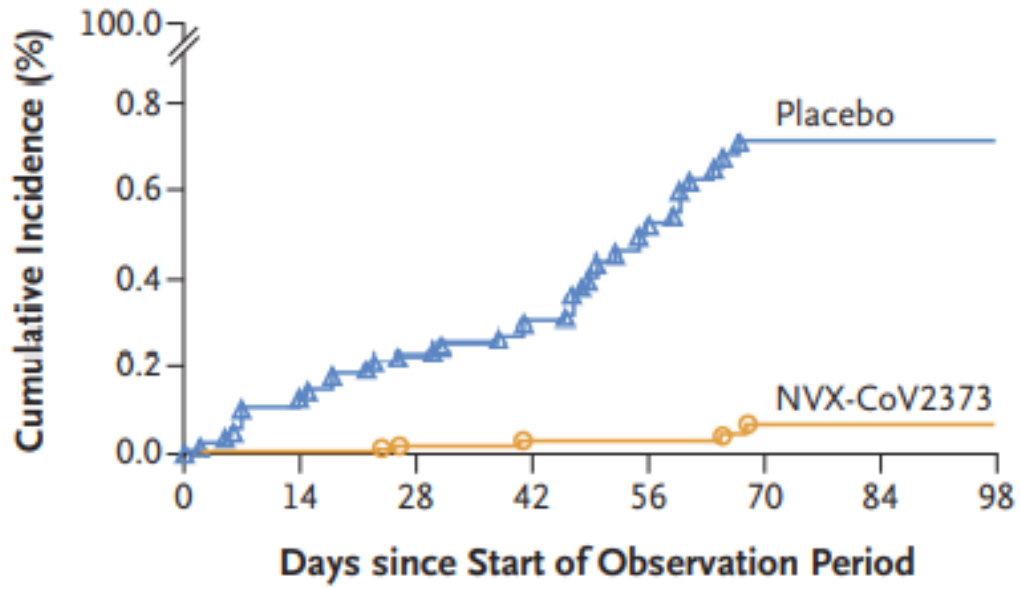
Efficacy and Safety of NVX-CoV2373 in Adults in the United States and Mexico N Engl J Med published online December 15, 2021

DOI: 10.1056/NEJMoa2116185

NVX-CoV2373(Novavax) is an adjuvanted, recombinant spike protein nanoparticle vaccine. The investigators conducted a phase 3, randomized, observer-blinded, placebo-controlled trial in the United States and Mexico during the first half of 2021 to evaluate the efficacy and safety of NVX-CoV2373 in adults (≥18 years of age) who had not had SARS-CoV-2 infection. Participants were randomly assigned in a 2:1 ratio to receive two doses of NVX-CoV2373 or placebo 21 days apart. The primary objective was to determine vaccine efficacy against PCR–confirmed Covid-19 occurring at least 7 days after the second dose. Vaccine efficacy against moderate-to-severe disease and against different variants was also assessed.

Of the 29,949 participants who underwent randomization between December 27, 2020, and February 18, 2021, a total of 29,582 (median age, 47 years; 12.6% ≥65 years of age) received at least one dose: 19,714 received vaccine and 9868 placebo. Over a period of 3 months, 77 cases of Covid-19 were noted — 14 among vaccine recipients and 63 among placebo recipients (vaccine efficacy, 90.4%; 95% confidence interval [CI], 82.9 to 94.6; P <0.001) Ten moderate and 4 severe cases occurred, all in placebo recipients, yielding vaccine efficacy against moderate-to-severe disease of 100% (95% CI, 87.0 to 100). Most sequenced viral genomes (48 of 61, 79%) were variants of concern or interest — largely Alpha) (31 of the 35 genomes for variants of concern, 89%). Vaccine efficacy against any variant of concern or interest was 92.6% (95% CI, 83.6 to 96.7). Reactogenicity was mostly mild to moderate and transient but was more frequent among NVX-CoV2373 recipients than among placebo recipients and was more frequent after the second dose than after the first dose.

E Analysis of Covid-19 Due to VOC or VOI (Per-Protocol Efficacy Analysis Population)



No. at Risk								
Placebo	8,140	7,619	6,989	6,349	4,627	2803	1055	220
NVX-CoV2373	17,312	16,782	16,166	15,330	11,458	6951	2447	379
No. of Events								
Placebo	0	10	17	22	34	41	41	41
NVX-CoV2373	0	0	2	4	4	7	7	7

Comment: NVX-CoV2373 is a new adjuvanted recombinant protein vaccine that can be added to the portfolio of vaccines that are safe and highly protective against contemporary SARS-CoV-2 strains and that have an acceptable side-effect profile. The extended stability and easy storage requirements (up to 6 months at refrigerator temperatures). Because case accrual for this analysis occurred during the first half of 2021, vaccine efficacy against delta and other newer variants could not be established. Nonetheless NVX vaccine appears to be a very effective and safe vaccine and if approved by the FDA will be the 4th approved vaccine in the US.

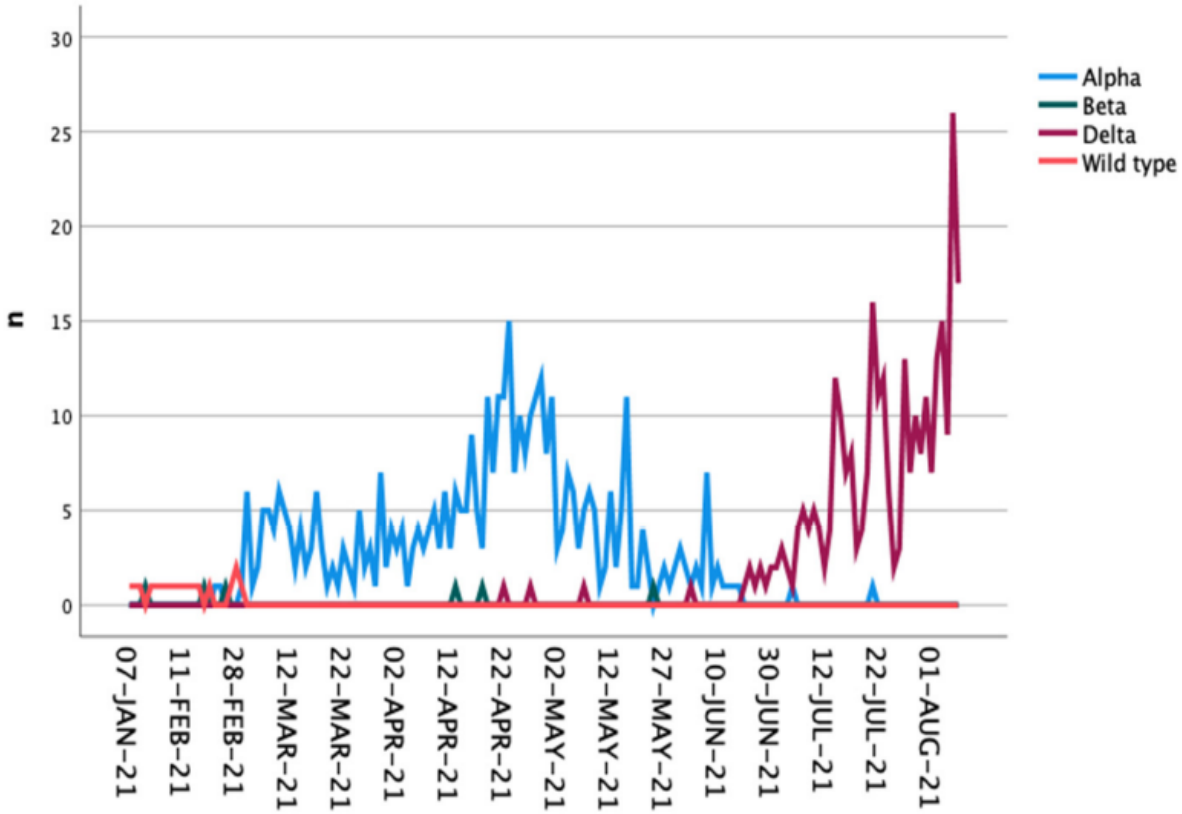
COVID-19 Breakthrough Infections and Transmission Risk: Real-World Data Analyses from Germany's Largest Public Health Department (Cologne) Vaccines published online November 2, 2021

doi.org/10.3390/vaccines9111267

Infections despite vaccination, so-called "breakthrough infections", have been reported. Even though they are more likely to have a milder or even asymptomatic course, the assessment of further transmission is highly relevant for successful infection prevention. Therefore, the investigators calculated the real-world transmission risk from fully vaccinated patients (vaccination group, VG) to their

close contacts (CP) compared with the risk from unvaccinated reference persons matched according to age, sex, and virus type (control group = CG) utilizing data from Cologne's health department.

A total of 357 breakthrough infections occurred among Cologne residents between 27 December 2020 (the date of the first vaccination in Cologne) and 6 August 2021. Of the 979 CPs in VG, 99 (10.1%) became infected. In CG, 303 of 802 CPs (37.8%) became infected. Factors promoting transmission included non-vaccinated status (β = 0.237; p < 0.001), male sex (β = 0.079; p = 0.049), the presence of symptoms (β = −0.125; p = 0.005), and lower cycle threshold(Ct) value (β = −0.125; p = 0.032).



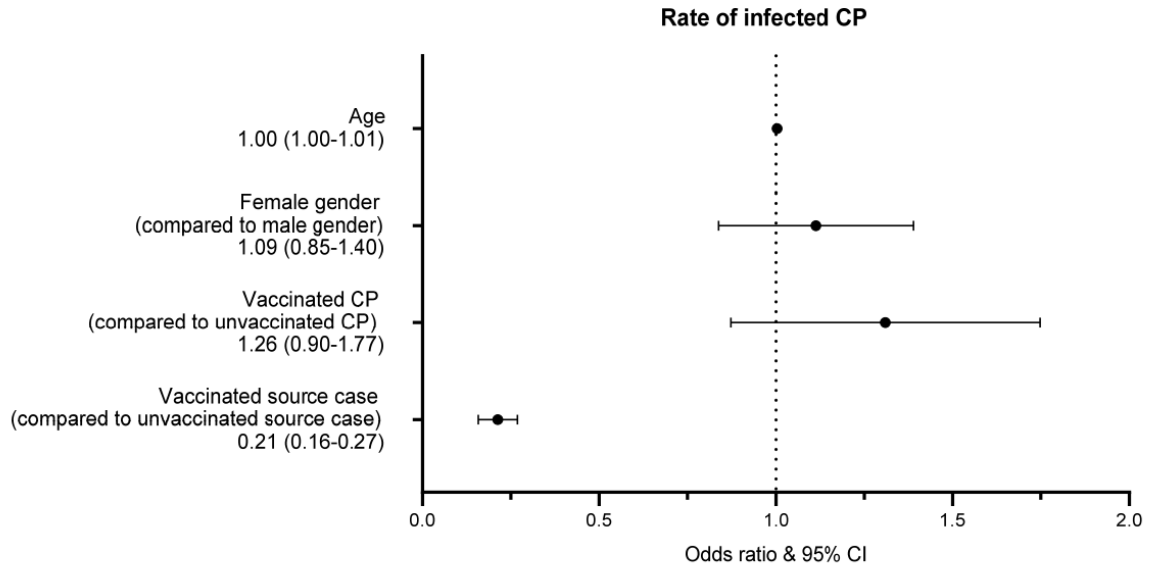


Figure 4. Factors influencing transmission of CPs; binary logistic regression.

Comment: The number of transmissions from unvaccinated controls was three times higher than from fully vaccinated patients. Regression analysis showed that CPs had 79% lower infection risk if the index patient was vaccinated (*P*<0.001). These real-world data underscore the importance of vaccination in not only protecting against infection, but risk of transmission from "breakthrough infection" especially if asymptomatic and higher Ct value. This study was done before the emergence of Omicron variant.

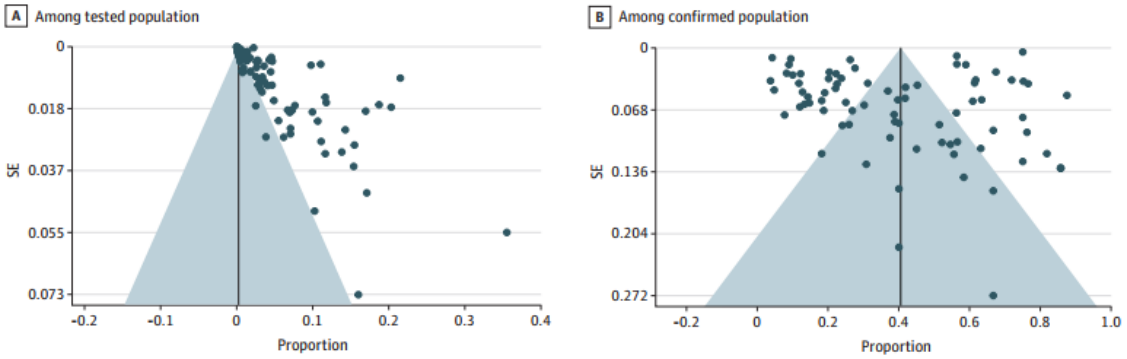
Global Percentage of Asymptomatic SARS-CoV-2 Infections Among the Tested Population and Individuals With Confirmed COVID-19 Diagnosis A Systematic Review and Meta-analysis JAMA Netw Open published online December 14, 2021

doi:10.1001/jamanetworkopen.2021.37257

This paper included cross-sectional studies, cohort studies, case series studies, and case series on transmission reporting the number of asymptomatic infections among the tested and confirmed COVID-19 populations that were published in Chinese or English were included.

Ninety-five unique eligible studies were included, covering 29 776 306 individuals undergoing testing. The pooled percentage of asymptomatic infections among the tested population was 0.25% (95% CI, 0.23%-0.27%), which was higher in nursing home residents or staff (4.52% [95% CI, 4.15%-4.89%]), air or cruise travelers (2.02% [95% CI, 1.66%-2.38%]), and pregnant women (2.34% [95% CI, 1.89%-2.78%]). The pooled percentage of asymptomatic infections among the confirmed population was 40.50% (95% CI, 33.50%-47.50%), which was higher in pregnant women (54.11% [95% CI, 39.16%-69.05%]), air or cruise travelers (52.91% [95% CI, 36.08%-69.73%]), and nursing home residents or staff (47.53% [95% CI, 36.36%-58.70%])

Figure 4. Funnel Plots Based on the Percentage of Asymptomatic Infections



Comment: In this systematic review and meta-analysis of 95 unique studies the pooled percentage of asymptomatic infections was 0.25% among the tested population and 40.50% among the population with confirmed COVID-19. The high percentage of asymptomatic infections from this study highlights the potential transmission risk of asymptomatic infections in communities. Recent studies such as the one reviewed above suggest risk of transmission is much lower if fully vaccinated.