There is so much going on, I decided to send this out early.

Under COVID-19 News the Pfizer claim that two doses may not be adequate against Omicron, but if you receive a booster the vaccine may provide better protection. The FDA has approved the AZ MCA for EUA. The last is the EMA recommendations on heterologous vaccination courses against COVID-19.

Under Journal Review I have put together several articles on heterologous vaccinations, an interesting genetic analysis of Omicron and other common cold viruses, the impact of the booster dose in Israel and mortality, and safety and immunogenicity of seven COVID-19 vaccines as a third dose.

Ed

COVID-19 News

Pfizer Says its Booster Offers Significant Protection Against Omicron
Pfizer said Wednesday that laboratory tests suggest that three doses of their coronavirus vaccine offer significant protection against the fast-spreading Omicron variant.

The company said that tests of blood from individuals who received only two doses found more than a 25-fold reduction in antibody levels against the Omicron variant compared to an earlier version of the virus. That finding indicates that two doses alone “may not be sufficient to protect against infection” by the new variant, the companies said.

But the blood samples obtained from people one month after they had received a booster shot showed neutralizing antibodies against the Omicron variant comparable to the levels of antibodies against a previous version of the virus after two doses, the company said in a statement.

At the same time, the tests suggested that the mutations in Omicron do not appear to significantly affect T cells — another critical part of the immune system’s response. That suggests “vaccinated individuals may still be protected against severe forms of the disease” after only two doses, the company said.

Comment: Preliminary reports like this support the broader recommendation for boosters announced by CDC last week. Because of the fear of Omicron, vaccinations are again increasing.

FDA Authorizes Use of AstraZeneca COVID-19 MCA
AstraZeneca's therapy, given in two sequential injections, is designed to last several months to a year. The combination treatment tixagevimab and cilgavimab (Evusheld) is only authorized for adults and adolescents who are not currently infected with SARS-CoV-2 and have not recently been exposed to an infected individual.

Comment: This adds another therapeutic in our toolkit with prolonged activity.

EMA and ECDC Recommendations on Heterologous Vaccination Courses Against COVID-19
Following the analysis of the available evidence, EMA and ECDC have issued the following technical recommendations and advice.

For heterologous primary vaccination

- The currently available evidence consistently points towards an acceptable tolerability and enhanced immune responses with the sequential heterologous regimen of vector vaccine/mRNA vaccine versus the homologous vector vaccine regimen.
- Some studies have reported higher reactogenicity (e.g., pain, fever, headache, fatigue) of heterologous vaccination but results are not consistent. With respect to infrequently occurring adverse reactions, there is insufficient data to draw conclusions.
- Regarding immunogenicity, studies are consistent in showing the heterologous regimen is able to induce significantly increased immune responses, including improved memory B cells, compared with a homologous viral vector regimen. A slight increase in humoral immune responses with respect to homologous mRNA vaccination is sometimes seen, but not consistently, overall supporting a similar antibody response.
- The increased immunogenicity appears consistent with the increased vaccine effectiveness against SARS-CoV-2 symptomatic infection of the heterologous vector-mRNA regimen as compared to homologous vector immunization based on several good quality observational studies;
- Preliminary but consistent evidence indicates that the heterologous regimen is able to induce an expanded breadth of immune responses, with improved humoral and cell mediated cross-reactivity against various variants of concerns, which would translate into improved effectiveness based on the studies seen so far.
- Overall, the data presented support the use of mixed vector/mRNA schedules. Based on the evidence seen so far and on existing clinical knowledge, giving a second dose of mRNA vaccine to previous recipients of a single dose of vector vaccines is a vaccination strategy that is beneficial from an immunological perspective with a positive impact on the achieved level of protection from infection and disease. There is less evidence about heterologous mRNA vaccination regimens, but enough to indicate that such an approach could be used as well when flexibility or acceleration in the vaccination campaigns is needed. Safety data after such heterologous mRNA regimens are currently under investigation to determine if there is an increased risk of myocarditis.
- Giving an adenoviral vector vaccine as second dose after a mRNA vaccine might be considered if there is a problem with availability of mRNA vaccines, but based on the limited data available it may be less advantageous from an immunological point of view than the opposite sequence.
- Long term protection data after heterologous or homologous primary vaccination is limited, but a few studies suggest a decline in protection against symptomatic infection from 6 months after heterologous vaccination. Some of these studies also show that waning of effectiveness is greater and faster for Vaxzevria than other regimens and that waning is overall faster among older frail individuals, and individuals with comorbidities.
- More research is needed to investigate use of heterologous regimens in immunosuppressed individuals.

Considerations for Heterologous Booster Vaccination

- The evidence available so far with different types of authorized vaccines indicates that a heterologous booster appears as good as or better in terms of immune responses than a homologous booster. Among the heterologous booster combinations, boosting with an mRNA after a vector primary series is more immunogenic than the reverse. In addition, the safety profile of heterologous and homologous booster combinations remains comparable based on the data available.

- A heterologous booster vaccination strategy can thus be considered as an alternative strategy, e.g., to improve protection that can be achieved with some vaccines, to allow more flexibility in case of issues with vaccine acceptance, supply or availability. Data currently available support safe and effective administration of a booster dose as early as 3 months from completion of the primary vaccination should such a short interval be desirable from a public health perspective, notwithstanding current recommendations to administer booster preferably after 6 months.
- Safety data provide limited but reassuring information with respect to short term reactogenicity for any booster combination. A heterologous booster dose of viral vector vaccine or Spikevax tend to give more adverse events related to local or systemic reactogenicity. Large observational studies will provide additional evidence with respect to occurrence of rare adverse events, such as myocarditis, with either homologous or heterologous boosters.
- While it would be expected that higher immune response will translate into increased protection against infection and disease, including from different variants of concern, due to the lack of established correlates of protections it cannot be precisely defined at this stage to what extent such an improved immunogenicity would translate into higher effectiveness. However emerging effectiveness data show increased protection from symptomatic disease after heterologous boosting with an mRNA vaccine during spread of the Delta variant.
- Administration of booster doses, whether homologous or heterologous, needs to consider waning of protection over time and optimal interval for an efficient immune response. At the moment there are no data in immunosuppressed individuals to support a recommendation for heterologous boosting.

Comment: According to the EMA, evidence from studies on heterologous vaccination suggests that the combination of viral vector vaccines and mRNA vaccines produces good levels of antibodies against SARS-CoV-2 and a higher T-cell response than using the homologous vaccination whether in a primary or booster regimen. The agency added that the heterologous regimens were generally well tolerated. See articles below.

Journal Review

Omicron Variant of SARS-CoV-2 Harbors a Unique Insertion Mutation of Putative Viral or Human Genomic Origin
OSF published online December 2021
The Omicron variant is likely to have acquired at least one of its mutations by picking up a snippet of genetic material from another virus – possibly one that causes the common cold – present in the same infected cells, according to investigators in this pre-publication.

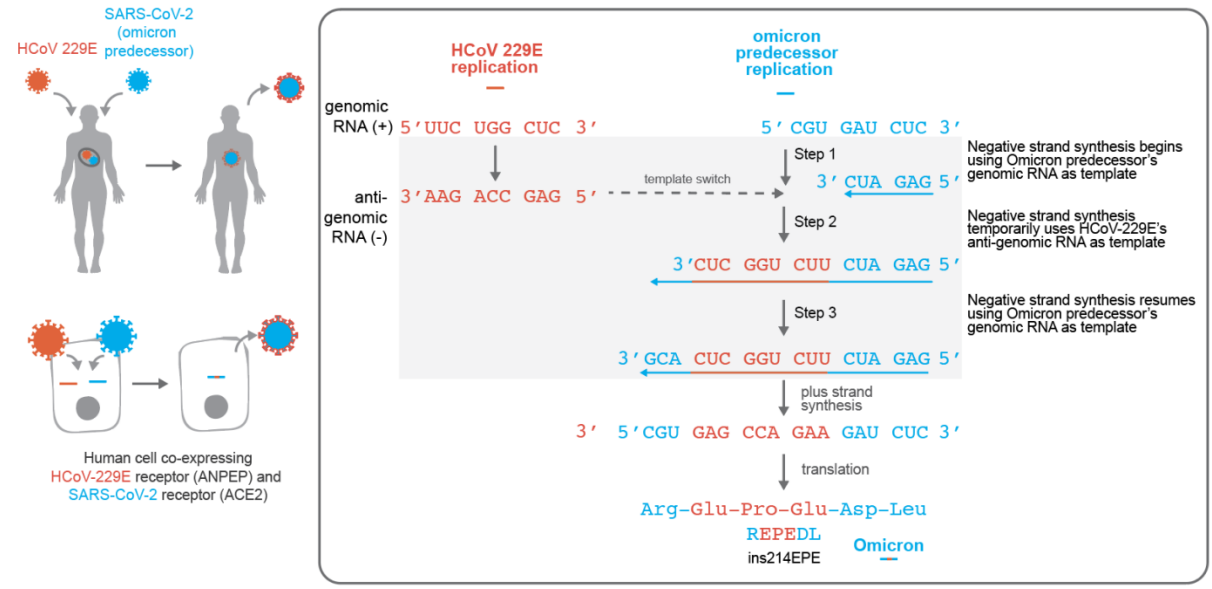
This genetic sequence does not appear in any earlier versions of SARS-CoV-2 but is ubiquitous in many other viruses including those that cause the common cold. This could mean the virus transmits more easily, while only causing mild or asymptomatic disease. Cells in the lungs and in the gastrointestinal system can harbor SARS-CoV-2 and common-cold coronaviruses simultaneously, according to earlier studies. Such co-infection sets the scene for viral recombination, a process in which two different viruses in the same host cell interact while making copies of themselves, generating new copies that have some genetic material from both "parents."

This new mutation could have first occurred in a person infected with both pathogens when a version of SARS-CoV-2 picked up the genetic sequence from the other virus. The same genetic sequence appears

many times in one of the coronaviruses that causes colds in people – known as HCoV-229E [coronavirus]. This genetic sequence does not appear in any earlier versions of SARS-CoV-2 but is ubiquitous in many other viruses including those that cause the common cold, many coronaviruses.

Omicron's Spike protein has 26 amino acid mutations (23 substitutions, two deletions and one insertion) that are distinct compared to other variants of concern. Whereas the substitution and deletion mutations have appeared in previous SARS-CoV-2 lineages, the insertion mutation (ins214EPE) has not been previously observed in any SARS-CoV-2 lineage other than Omicron. The nucleotide sequence encoding for ins214EPE could have been acquired by template switching involving the genomes of other viruses that infect the same host cells as SARS-CoV-2 or the human transcriptome of host cells infected with SARS-CoV-2.

a. Potential mechanism of template switching leading to the generation of the ins214EPE in Omicron



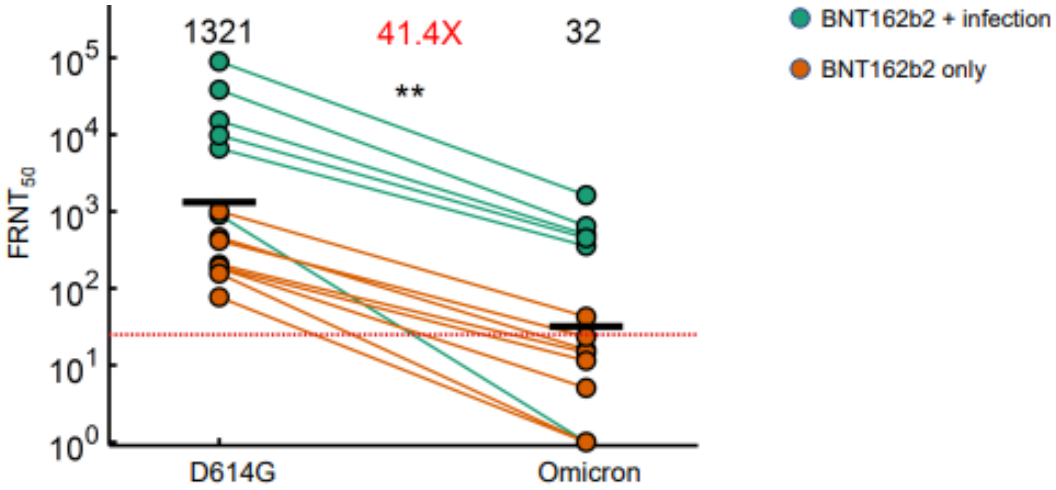
Comment: I found this pre-publication very interesting, but needs further study and confirmation. Scientists do not yet know whether Omicron is more infectious than other variants [but may be], whether it causes more severe disease [seems less likely], or whether it will overtake Delta as the most prevalent variant. It will take several more weeks to get answers to these questions.

SARS-CoV-2 Omicron has Extensive but Incomplete Escape of Pfizer BNT162b2 Elicited Neutralization and Requires ACE2 for Infection

medRxiv published online December 8, 2021

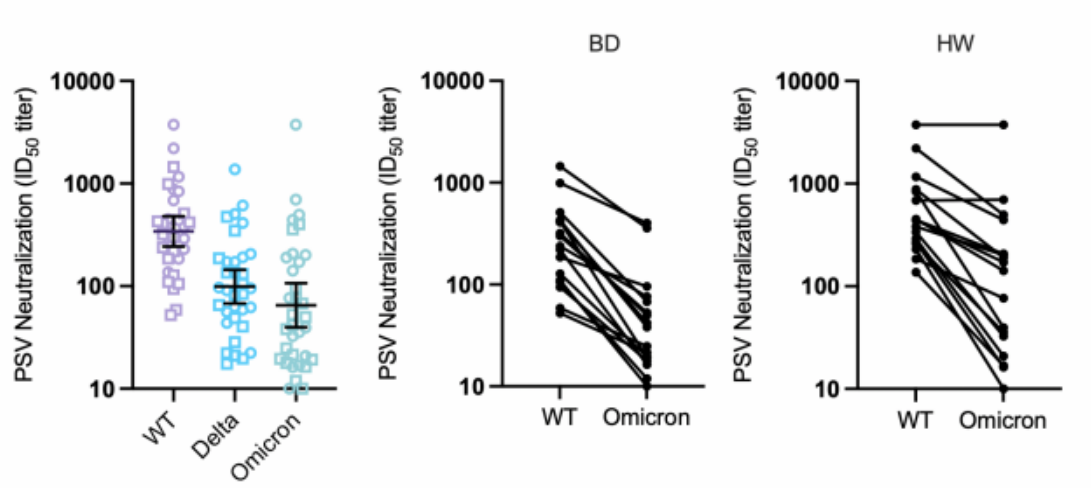
The authors investigated whether Omicron escapes antibody neutralization elicited by the Pfizer vaccine and whether the virus still requires binding to the ACE2 receptor to infect cells. They used an early passage of isolated and sequence confirmed live Omicron virus isolated in South Africa. They used a human lung cell line clone (H1299-ACE2) engineered to express the ACE2 receptor to both isolate the virus and test neutralization. They also tested growth in the parental H1299 which do not overexpress ACE2 and are not appreciably infectable with SARS-CoV-2. The H1299-ACE2 cells were similar to Vero-E6 in titer dependent focus formation but were considerably more sensitive. They observed that Omicron infected the ACE2-expressing cells in a concentration dependent manner but did not infect the parental H1299 cells, indicating that ACE2 is required for Omicron entry. They then tested the ability of plasma

from Pfizer vaccinated participants to neutralize Omicron versus ancestral D614G virus in a live virus neutralization assay. They tested 14 plasma samples from 12 participants, with 6 having no previous record of SARS-CoV-2 infection nor detectable nucleocapsid antibodies indicative of previous infection. For two of these participants, the investigators used samples from two timepoints. The remaining 6 participants had a record of previous infection in the first SARS-CoV-2 infection wave in South Africa where infection was with ancestral D614G virus. Geometric mean titer (GMT) FRNT50 (inverse of the plasma dilution required for 50% reduction in infection foci number) was 1321 for D614G. These samples therefore had very strong neutralization of D614G virus, consistent with sampling soon after vaccination. GMT FRNT50 for the same samples was 32 for Omicron, a 41-fold decline. However, the escape was incomplete, with 5 of the participants, all previously infected, showing relatively high neutralization titers with Omicron. The results presented here with Omicron show much more extensive escape than with the ancestral strain as well as the beta variant. However, escape was incomplete in participants with higher FRNT50 due to previous infection.



Comment: What is beginning to emerge is that previous infection, followed by vaccination or booster is likely to increase the neutralization level and likely confer protection from severe disease in Omicron infection. For vaccinated people (no prior infection), the third dose or booster appears to also increase protection against the Omicron variant. (See above)

Preliminary Report – Early Release, Subject to Modification Quantification of the Neutralization Resistance of the Omicron Variant of Concern
published December 7, 2021
A team based at Sweden's Karolinska Institute found a sevenfold reduction in blood samples from random donors and a fivefold reduction in samples from those who had earlier COVID-19 infections.



Comment: This report and the one above point to partial escape of protection against the Omicron variant. On the positive side, Pfizer's announcement that people who receive a booster probably have better protection against Omicron compared to people who have received standard two-dose vaccination. (See above)

Previous Infection Combined with Vaccination Produces Neutralizing Antibodies with Potency Against SARS-CoV-2 Variants
mBio**;** 2021; 12: e02656-21
doi.org/10.1128/mBio.02656-21
The investigators evaluated how antibodies act against a panel of seven spike variant combinations of five mutations. They studied people shortly after they recovered from a mild case of COVID-19. They then compared this group with people never infected who were evaluated shortly after vaccination.

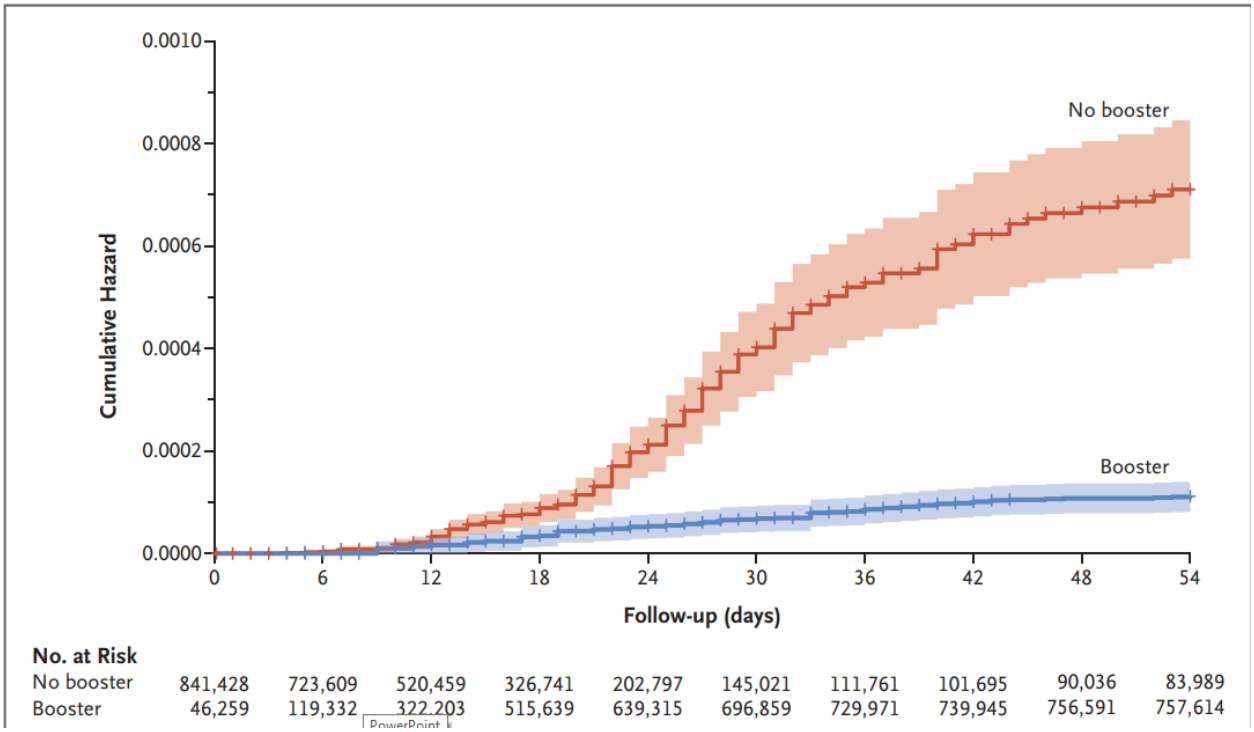
They found that people who had had COVID and then got vaccinated developed not only more antibodies to the virus but a higher quality of antibodies, more equipped to take on variants.
The antibodies produced by either just getting COVID-19 or by getting vaccinated without having had COVID had decreased protection against certain variants. When they looked at the combination of the two — people who had had COVID and who also got vaccinated after they'd had COVID — they developed much more effective antibodies that could deal with all the spike variants that they tested.

Comment: Boosters were not available at the time of the study, but preliminary data predicts that they should behave similarly. This all suggests that if we get boosters, the additional exposure from the vaccine will not only increase the number of antibodies but will also improve the quality of those antibodies. These studies further support the push to offer boosters to all persons over age 18 after 6 months. See next two articles.

BNT162b2 Vaccine Booster and Mortality Due to Covid-19
N Engl J Med published online December 8, 2021
DOI: 10.1056/NEJMoa2115624
The investigators obtained data for all members of Clalit Health Services [largest health system in Israel] who were 50 years of age or older at the start of the study and had received two doses of BNT162b2 (Pfizer) at least 5 months earlier. The mortality due to Covid-19 among participants who received the booster during the study period (booster group) was compared with that among participants who did

not receive the booster (nonbooster group). A Cox proportional-hazards regression model with time-dependent covariates was used to estimate the association of booster status with death due to Covid-19, with adjustment for sociodemographic factors and coexisting conditions.

Death due to Covid-19 occurred in 65 participants in the booster group (0.16 per 100,000 persons per day) and in 137 participants in the nonbooster group (2.98 per 100,000 persons per day). The adjusted hazard ratio for death due to Covid-19 in the booster group, as compared with the nonbooster group, was 0.10 (95% confidence interval, 0.07 to 0.14; P<0.001).



Comment: Participants who received a booster at least 5 months after a second dose of Pfizer vaccine had 90% lower mortality due to Covid-19 than participants who did not receive a booster. This study and the emergence of the Omicron variant support the CDC policy of boosters.

Safety and Immunogenicity of Seven COVID-19 Vaccines as a Third Dose (Booster) Following Two Doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): A Blinded, Multicentre, Randomised, Controlled, Phase 2 Trial
Lancet published online December 2, 2021
doi.org/10.1016/ S0140-6736(21)02717-3
COV-BOOST is a multicenter, phase 2 RCT, of third dose booster vaccination against COVID-19. Participants were aged older than 30 years and were at least 70 days post two doses of AstraZeneca(AZ) or at least 84 days post two doses of Pfizer primary COVID-19 immunization course, with no history of laboratory-confirmed SARS-CoV-2 infection. 18 sites were split into three groups (A, B, and C). Within each site group (A, B, or C), participants were randomly assigned to an experimental vaccine or control. Group A received NVX (Novavax); a half dose of NVX, AZ, or quadrivalent meningococcal conjugate vaccine (MenACWY) control (1:1:1:1). Group B received Pfizer, VLA2001 (Valneva (VLA), a half dose of VLA, Ad26(J&J). COV2.S or MenACWY (1:1:1:1:1). Group C received Moderna; CVnCov (CureVac; (CVn), a

half dose of Pfizer, or MenACWY (1:1:1:1). Participants and all investigatory staff were blinded to treatment allocation. Coprimary outcomes were safety and reactogenicity and immunogenicity of anti-spike IgG measured by ELISA. The primary analysis for immunogenicity was on a modified intention-to-treat basis; safety and reactogenicity were assessed in the intention-to-treat population. Secondary outcomes included assessment of viral neutralization and cellular responses.

This trial has demonstrated the potential of all vaccines tested (AZ, Pfizer, Moderna, NVX, J&J, CVn, and Valneva) to boost immunity after an initial course of AZ/AZ and of six vaccines (AZ, Pfizer, Moderna, NVX, J&J, and CVn) after an initial course of Pfizer/Pfizer. All vaccines showed acceptable side-effect profiles, although some schedules were more reactogenic than others.

Comment: All study vaccines boosted antibody and neutralizing responses after AZ/AZ initial course and all except one after Pfizer/Pfizer, with no safety concerns. Although neutralizing responses can be predicted from spike IgG concentrations, they found that cellular responses do not correlate as well. The age range (only recruiting people >30 years) limits the generalizability to younger populations, which might be particularly relevant with respect to reactogenicity, which was generally inversely proportional to age. The study also recruited a mostly White population. Due to the group design, not all vaccines were able to be randomized together, limiting the ability to compare vaccines between site groups. Overall, it appears that any FDA approved vaccine can be used as a booster. In US most who received an mRNA vaccine take an mRNA vaccine as a booster. If they received J&J many have opted to taking an mRNA vaccine as a booster. Regardless, for Omicron a booster dose gives better protection than the traditional 2 dose regimen.

Immunogenicity, Safety, and Reactogenicity of Heterologous COVID-19 Primary Vaccination Incorporating mRNA, Viral-Vector, and Protein-Adjuvant Vaccines in the UK (Com-COV2): A Single-Blind, Randomised, Phase 2, Non-Inferiority Trial
Lancet published online December 6, 2021
doi.org/10.1016/ S0140-6736(21)02718-5
Between April 19 and May 14, 2021, 1,072 participants aged 50 years and older were enrolled at a median of 9.4 weeks after receipt of a single dose of AZ (n = 540, 47% female) or Pfizer (n = 532, 40% female). Participants were randomly assigned within these cohorts to receive a second dose intramuscularly with the homologous vaccine, Moderna, or Novavax (NVX).

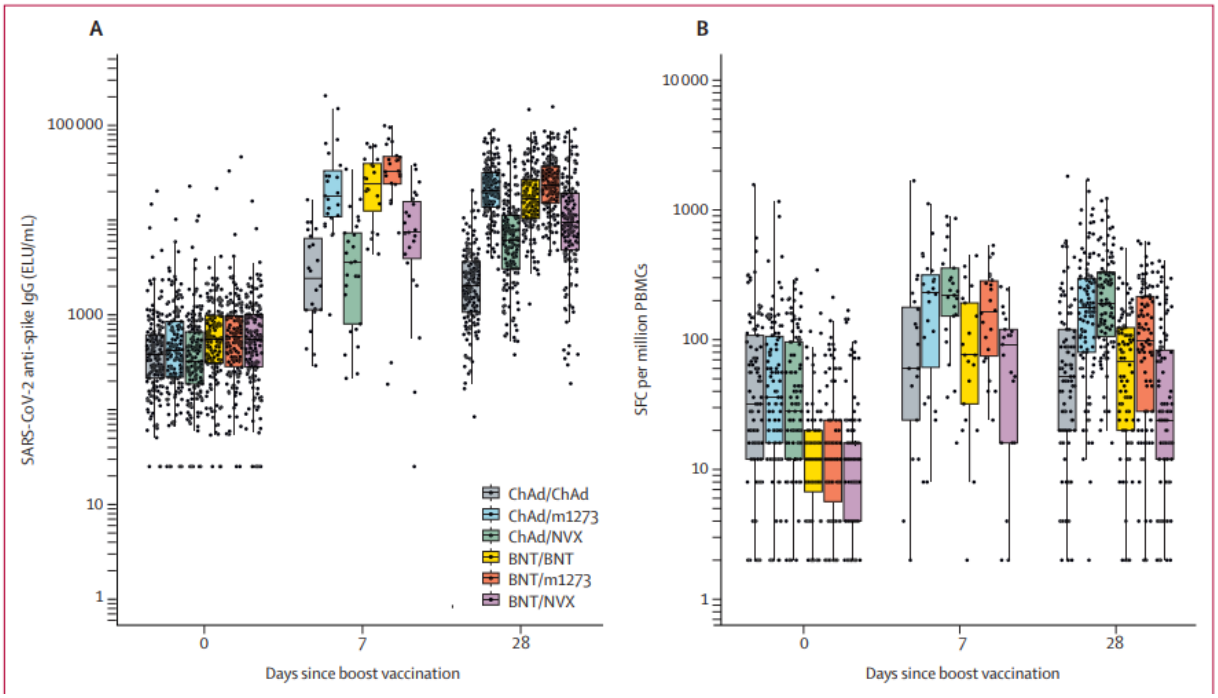
In AZ-primed participants, at 28 days after the second dose, geometric mean concentration (GMC) of SARS-CoV-2 anti-spike immunoglobulin G in recipients of AZ/Moderna (20,114 ELISA laboratory units [ELU]/mL [95% confidence interval (CI) 18,160 to 22,279]) and AZ/NVX (5,597 ELU/mL [4,756 to 6,586]) was non-inferior to that of AZ/AZ recipients (1,971 ELU/mL [1718 to 2262]) with a geometric mean ratio (GMR) of 10.2 (one-sided 98.75% CI 8.4 to ∞) for AZ/Moderna and 2.8 (2.2 to ∞) for AZ/NVX, compared with AZ/AZ.

In Pfizer-primed participants, non-inferiority was shown for Pfizer/Moderna (GMC 22,978 ELU/mL [95% CI 20,597 to 25,636]) but not for Pfizer/NVX (8,874 ELU/mL [7,391 to 10,654]), compared with Pfizer/Pfizer (16,929 ELU/mL [15,025 to 19,075]) with a GMR of 1.3 (one-sided 98.75% CI 1.1 to ∞) for Pfizer/Moderna compared with Pfizer/Pfizer. Although Pfizer/NVX did not meet the non-inferiority criterion at 0.5 (one-sided 98.75% CI 0.4 to ∞), the researchers pointed out that NVX still induced an 18-fold rise in GMC 28 days after vaccination.

Meanwhile, cellular responses by T-cell ELISpot for AZ community-primed participants were greatest in those boosted with NVX at 190 spot forming cells (SFC) per million peripheral blood mononuclear cells (PBMCs) (95% CI 159–227), with a GMR of 4.8 (3.6–6.6) compared with participants receiving homologous AZ (45 SFC per million PBMCs, 34–61). For those boosted with Moderna these respective values were 148 SFCs per million PBMCs (118–187) and a GMR of 3.5 (2.5–4.8). In Pfizer community-primed groups, cellular responses by T-cell ELISpot were higher in those receiving Moderna at 76 SFC per million PBMCs (95% CI 58–99) than in the homologous boost group at 49 SFC per million PBMCs (39–63); however, the GMC for NVX boost was below that of the homologous boost at 29 SFC per million PBMCs (22–38).

In AZ-primed groups, live virus neutralizing antibody titers (50% focus reduction neutralization titers [$FRNT_{50}$]) were reduced according to point estimates across all groups for beta and delta variants, relative to Victoria, with the greatest decrement noted for beta. However, both heterologous groups maintained numerically higher titers than AZ/AZ, with the highest titers in AZ/Moderna recipients, with GMRs of 15.8 (95% CI 9.6–26.1) against the beta variant and 17.4 (10.2–29.5) against the delta variant. Similarly, in Pfizer-primed groups, live virus neutralizing antibody titers ($FRNT_{50}$) across groups were numerically lower against beta and delta variants than to Victoria. There was no evidence of a difference in neutralizing activity against Victoria, beta, and delta variants between the Pfizer primed groups. Across all groups, little difference was noted in cellular responses to variants.

On the other hand, local and systemic reactions were more frequent after Moderna boost vaccination compared with the homologous boost groups, with feverishness reported by 60 (33%) of 181 recipients of AZ/Moderna compared with 9 (5%) of 176 recipients of AZ/AZ (difference 28%, 95% CI 20–36), and by 39 (22%) of 176 recipients of Pfizer/Moderna, compared with 16 (9%) of 175 recipients of Pfizer/Pfizer (13%, 5–21). By contrast, for NVX recipients, similar patterns were observed in systemic reactogenicity compared with the homologous study schedules. Local reactions were generally less frequent for NVX.



Comment: In this complicated paper heterologous second dosing with Moderna, but not NVX, increased transient systemic reactogenicity compared with homologous schedules. Multiple vaccines are appropriate to complete primary immunization following priming with Pfizer or AZ. This research confirms previous evidence of mixed adenoviral and mRNA schedules as being safe, tolerable, and immunogenic alternatives to homologous schedules when given at an 8–12 weeks interval. Flexibility of schedules should be considered to improve access to COVID-19 vaccination globally. Although not tested in this study I would assume the J&J vaccine would perform close to the AZ vaccine.