Good morning everyone

Today under news I start with a Delta Update – please take a moment to read and circulate if you think this will help mobilize people who have not been vaccinated. Next, the FDA has given EUA for use of tocilizumab for treatment of severe Covid-19. The FDA also paused distribution of the Lilly monoclonals because data has shown they are not effective against variants of concern.

Under Journal Review, I have focused on items relating to vaccination. The first two articles review the incidence of Bell's Palsy with Covid-19 vaccination. The next article looks at impact of the first dose of either AZ vaccine or Pfizer vaccine in LTC. The next article demonstrates one dose of either Pfizer or AZ resulted in substantial risk reductions of COVID-19-related hospitalization in people aged at least 80 years old. The next article looks at adding a third dose of mRNA vaccine to improve response in SOT patients. Finally, the last articles explore the safety and efficacy of a heterologous vaccination regimen.

Have a wonderful day

Ed

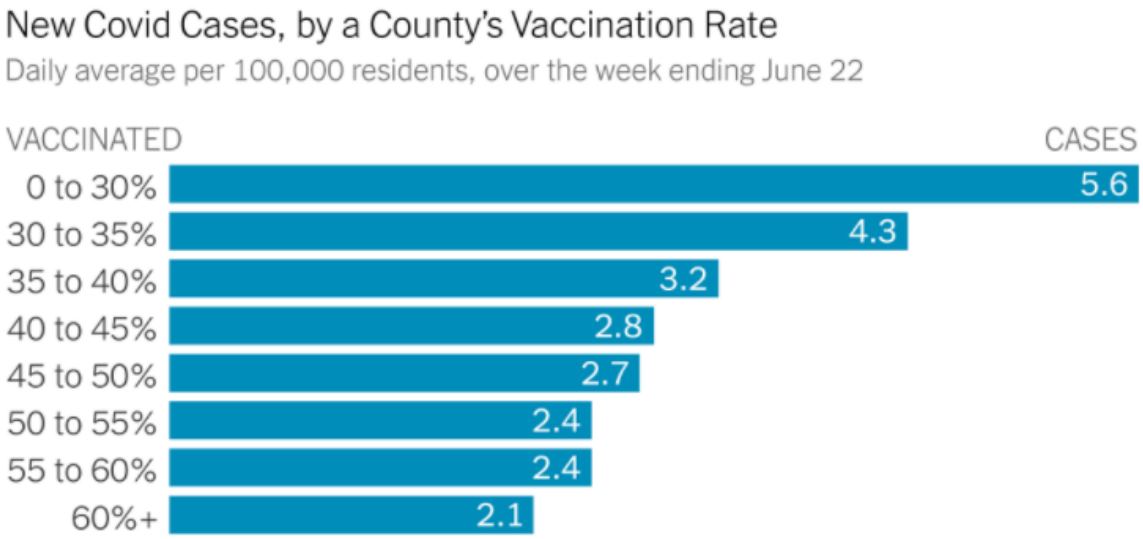
COVID-19 News

COVID Delta Spread
Public Health England said the end of last week in its weekly update that the Delta variant now makes up 95% of sequenced cases, with its case numbers rising 46% over the past week. Of about 35,000 Delta variant cases reported last week, 42 were the Delta Plus sublineage. The majority of people hospitalized in the last week were unvaccinated. As reported last week Israel, which had recently driven its daily cases down into the single digits, reimposed its indoor mask order, with more than 200 new cases reported, the most since early April. Most of these cases were in unvaccinated people. The health ministry also signaled that it may reimpose limits on gatherings if cases continue to rise. Australia's outbreak in Sydney—also driven by the Delta variant—rose to 60 cases last week, and officials announced a week-long lockdown for downtown Sydney and its eastern suburbs. Indonesia recently reported a record daily high of more than 20,000 cases, with the Delta variant spreading in the wake of Ramadan holiday travel.

Comment: I chose to update Delta spread to make sure we keep our eye on the ball and get as many people vaccinated as fast as we can now since everyone is traveling for vacation and non-pharmacological interventions are being relaxed. In the US, Delta is up to 20% and spreading rapidly. Vaccines still work very well against all variants. The Delta variant is unlikely to pose much risk to people who have been fully vaccinated. According to a recent study, the Pfizer vaccine was 88 percent effective at protecting against symptomatic disease caused by Delta, nearly matching its 93 percent effectiveness against the Alpha variant. But a single dose of the vaccine was just 33 percent effective against Delta. Vaccination rates have been uneven and are lower in certain states and demographic groups**.** Many have not returned for their second dose.

The pandemic is not over. Covid-19 remains a serious threat to unvaccinated adults, especially those middle-aged or older. And now the surprising trends from the spring may be coming to an end: Cases have begun to rise more rapidly in communities with lower vaccination rates. See below. It is too early

to know whether the recent trends will continue, but further increases do seem a likely scenario, based on the experience with Delta in other countries**.**



Bottom line: Vaccination is how this pandemic ends-Get vaccinated.

FDA Approves Tocilizumab for Emergency Use Against Severe COVID-19
June 24, 2021
The FDA said on Thursday it had issued an EUA for tocilizumab to treat adults and pediatric patients hospitalized with COVID-19. The EUA is based on results from four randomized, controlled studies that evaluated tocilizumab for the treatment of COVID-19 in more than 5,500 hospitalized patients. [All reviewed in the Covid-19 Briefings over the last 3 months]

Comment: Evolving evidence suggests combination dexamethasone plus an anti-inflammatory agent (JAK or IL6 inhibitor) administered early in hospitalized patients with severe Covid-19 on high flow heated oxygen or noninvasive ventilation who have evidence of clinical progression or increased inflammatory markers improves outcomes.

FDA has Paused Distribution of Bamlanivimab and Etesevimab (Lilly Monoclonals)
Last week the FDA paused distribution of the Lilly monoclonals because data has shown they are not effective against variants of concern which are becoming more common. Regeneron remains active and a new monoclonal has received EUA which is active against new variants (sotrovimab). FDA has also approved Regeneron's monoclonal to be administered by SC injection.

Comment: The good news is we still have alternative monoclonals that remain active against new variants.

Journal Review

Incidence of Bell's Palsy (BP) in Patients With COVID-19
JAMA Otolaryngol Head Neck Surg published online June 24, 2021
doi:10.1001/jamaoto.2021.1266

These data were collected from 41 health care organizations worldwide and accessed through TriNetX, a global federated research network. [the value of data sharing] Queries were made on April 7, 2021, to identify patients diagnosed with COVID-19 (January 1, 2020, to December 31, 2020) with or without a diagnosis code of BP within 8 weeks of the COVID-19 diagnosis. Among these patients, we identified those with a history of BP. To account for vaccination, the queries were restricted from January 1, 2021, to March 31, 2021. Using TriNetX to evaluate BP as our outcome, we matched 63,551 non-vaccinated patients with COVID-19 to those who were vaccinated against COVID-19 and had no history of COVID-19 infection.

A total of 348,088 patients with COVID-19 were identified in this study. Of these patients, 284 (0.08%) were diagnosed with BP within 8 weeks of the initial COVID-19 diagnosis. 153 of these patients (53.9%) had no history of BP, whereas 131 (46.1%) had a history of BP. Overall, 1525 patients (0.44%) had a history of BP before receiving the COVID-19 diagnosis, which translates to an 8.6% BP recurrence rate within 8 weeks of COVID-19 diagnosis. After matching patients with COVID-19 to vaccinated individuals (n = 63 551), there was an increased relative risk of 6.8 (95% CI = 3.5-13 206.0, *P* < .001) of a diagnosis of BP in those with COVID-19 compared with those who were vaccinated. This analysis found a statistically significant higher risk of BP in patients with COVID-19 compared with those who were vaccinated against the disease. See below.

Association of COVID-19 Vaccination and Facial Nerve Palsy
JAMA Otolaryngol Head Neck Surg published online June 24, 2021
doi:10.1001/jamaoto.2021.1259
This is a case-control study performed from January 1 to February 28, 2021, at the ED of a tertiary referral center in Israel. Patients admitted for facial nerve palsy were matched by age, sex, and date of admission with control patients admitted for other reasons. Adjusted odds ratio for recent exposure to the Pfizer vaccine among patients with acute-onset peripheral facial nerve palsy. The proportion of patients with Bell's palsy exposed to the Pfizer vaccine was compared between groups, and raw and adjusted odds ratios for exposure to the vaccine were calculated. A secondary comparison with the overall number of patients with facial nerve palsy in preceding years was performed.

Thirty-seven patients were admitted for facial nerve palsy during the study period. Among recently vaccinated patients (21 [56.7%]), the mean (SD) time from vaccination to occurrence of palsy was 9.3 (4.2 [range, 3-14]) days from the first dose and 14.0 (12.6 [range, 1-23]) days from the second dose. Among 74 matched controls (2:1 ratio) with identical age, sex, and admittance date, a similar proportion were vaccinated recently (44 [59.5%]). The adjusted odds ratio for exposure was 0.84 (95% CI, 0.37-1.90; *P* = .67). Furthermore, analysis of the number of admissions for facial nerve palsy during the same period in preceding years (2015-2020) revealed a relatively stable trend (mean [SD], 26.8 [5.8]; median, 27.5 [range, 17-35]). These outcomes suggest that recent vaccination with the Pfizer vaccine is not associated with an increased risk of facial nerve palsy.

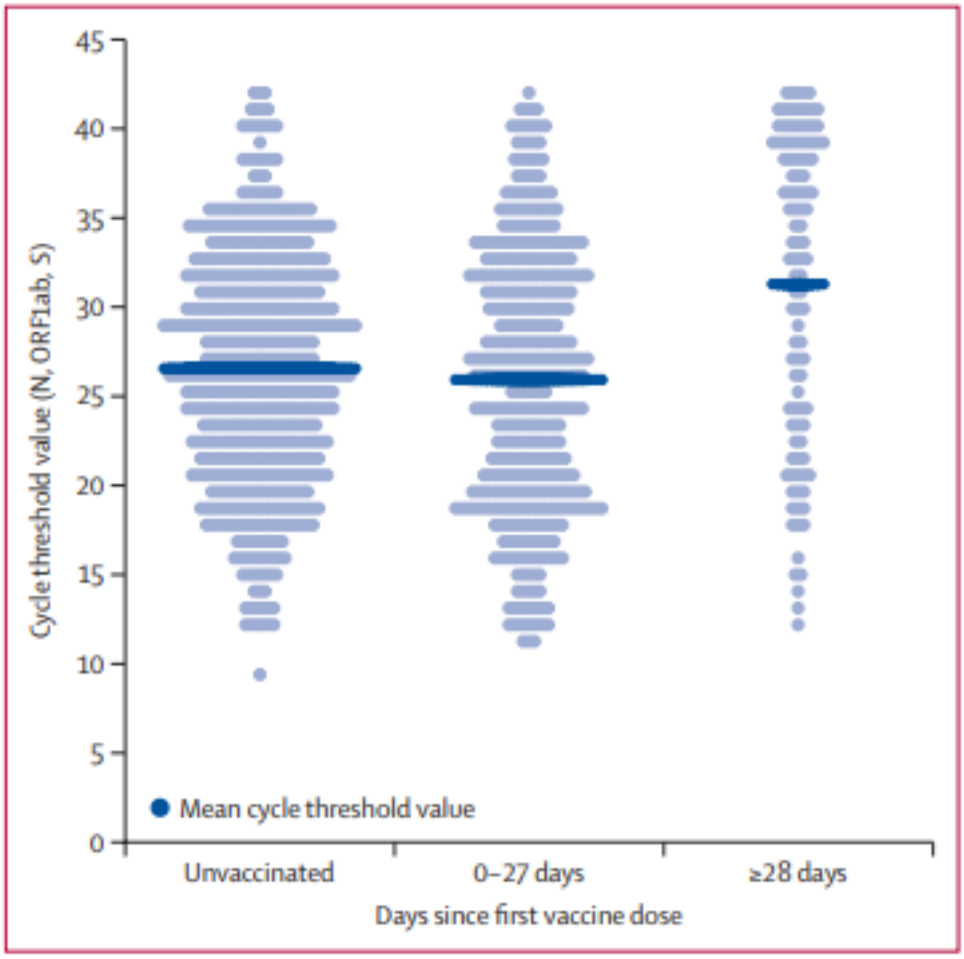
Comment: Linking the vaccine with an adverse event requires accurate estimation of event incidence in association with the vaccine, comparison with a nonvaccinated group, and understanding of the background incidence in the community. In the first article of 348,088 identified patients with COVID-19, 284 had a diagnosis of BP within 8 weeks of COVID-19 diagnosis: 153 patients had new-onset BP, whereas 131 had recurrent BP. The investigators translate this to an 8-week incidence of 82 per 100,000 patients with COVID-19. However, if using a crude analysis and assuming a prepandemic rate of 40 per 100,000 person-years and no seasonality, BP would be expected to naturally occur in only 21 of 348,088

patients during an 8-week period. This suggests that COVID-19 could be a risk factor for BP. They then compared matched COVID-19-vaccinated patients (without a known history of COVID-19) with COVID-19-positive patients and found that vaccinated patients had a lower incidence of BP. The data suggest that the risk of acquiring BP with COVID-19 is greater than the risk of BP associated with the vaccine.

In the second paper the investigators report their evaluation of the Pfizer vaccine and BP. An analysis of ED admission data was reviewed at a major medical center. This review revealed 37 patients who were admitted for BP, 21 of whom had received the vaccine. Compared with matched controls who were admitted for other reasons, there was no difference in vaccination rates. The authors also reviewed the crude incidence rate of BP during the same calendar period in the preceding 5 years and did not find significant differences.

Looking at the Vaccine safety Datalink as of February 13, 2021, data are available from 629,523 vaccinated individuals. The Vaccine Safety Datalink reported 21 cases of BP in vaccinated individuals. This finding is comparable to the 20.3 adjusted expected events among the unvaccinated comparators, thus indicating no increased risk. As of May 15, 2021, a similar reporting tool maintained by the CDC found 1743 events of BP and/or facial paralysis after about approximately 270 million COVID-19 vaccine doses administered among 156 million individuals who have received at least 1 dose. No matter how you look at these two publications regarding the incidence of BP, the rate does not come close to the incidence of COVID-19 infection, hospitalizations, and deaths.

Vaccine Effectiveness of the First Dose of ChAdOx1 nCoV-19 and BNT162b2 Against SARS-CoV-2 Infection in Residents of Long-Term Care Facilities in England (VIVALDI): A Prospective Cohort Study
Lancet Infect Dis published online June 23, 2021
doi.org/10.1016/ S1473-3099(21)00224-3
In this prospective cohort study in 10,412 residents aged 65 years and older from 310 long-term care facilities across England, the investigators estimated vaccine effectiveness to be 56% (95% CI 19-76) at 28-34 days and 62% (23-81) at 35-48 days after a single dose of AZ or Pfizer. This suggests that the risk of SARS-CoV-2 infection is substantially reduced from 28 days after the first dose of either vaccine and this effect is maintained up to at least 7 weeks after vaccination, with similar protection offered by both vaccines. They also found that PCR Ct was significantly higher in infections occurring at 28 days or longer after vaccination than in infections that occurred during the unvaccinated period, suggesting that vaccination might reduce transmission of SARS-CoV-2 from individuals with breakthrough infections. Alpha variant was the most common during this study.



Comment: These findings add to the growing body of evidence on the protective effect of both Pfizer and AZ vaccines in residents in long-term care facilities. The higher Ct values in the vaccinated group that experience breakthrough infection hopefully indicates transmission is less likely in infected vaccinated residents. They also remind us that the risk of infection is not eliminated with either vaccine, emphasizing the need for some targeted non-pharmaceutical interventions in long-term care facilities. See next study.

Effectiveness of BNT162b2 and ChAdOx1 nCoV-19 COVID-19 Vaccination at Preventing Hospitalisations in People Aged at Least 80 Years: A Test-Negative, Case-Control Study
Lancet Infect Dis *2021*; 21: 939–49
doi.org/10.1016/ S1473-3099(21)00224-3
In this study investigators followed patients 80 years or older who had received one COVID-19 vaccine dose at least 14 days prior and who were hospitalized for respiratory symptoms in two National Health Service trusts in the UK. From Dec 18, 2020, to Feb 26, 2021, 18 of 135 with COVID-19 infections (13.3%) and 90 of 269 non-COVID patients (33.5%) had one dose of the Pfizer vaccine, suggesting 71.4% adjusted VE (95% CI, 46.5 to 90.6). In the same time period, 9 of 36 COVID-19 patients (25.0%) and 53 of 90 non-COVID patients (58.9%) had one dose of the AZ vaccine, which translates to an estimated adjusted VE of 80.4% (95% CI, 36.4 to 94.5).

Comment: One dose of either Pfizer or AZ resulted in substantial risk reductions of COVID-19-related hospitalization in people aged at least 80 years. This study highlights the importance of administering two doses, in high-risk populations in whom incidence of severe disease and death from SARS-CoV-2 infection remains high.

Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients

N Engl J Med published online June 23, 2021
DOI: 10.1056/NEJMc2108861

A reduced immune response to two doses of vaccine against SARS-CoV-2 has been reported in recipients of SOT. In this report the investigators measured the humoral response in a group of 101 consecutive SOT recipients (mean [±SD] age, 58±2 years; 69% were men) who were given three doses of the messenger RNA (Pfizer-BioNTech) vaccine. The group included 78 kidney-transplant recipients, 12 liver-transplant recipients, 8 lung-transplant or heart-transplant recipients, and 3 pancreas-transplant recipients. The first two doses were given 1 month apart, and the third dose was administered 61±1 days after the second dose. The time between transplantation and the initiation of vaccination was 97±8 months. Immunosuppression was due to the use of glucocorticoids (in 87% of patients), calcineurin inhibitors (in 79% of patients), mycophenolic acid (in 63% of patients), mammalian target of rapamycin inhibitors (in 30% of patients), and belatacept (in 12% of patients). The levels of antibodies to SARS-CoV-2 spike protein were assessed in all the patients with the use of the Wantai enzyme linked immunosorbent assay.

The prevalence of anti-SARS-CoV-2 antibodies was 0% (95% confidence interval [CI], 0 to 4; 0 of 101 patients) before the first dose, 4% (95% CI, 1 to 10; 4 of 101 patients) before the second dose, 40% (95% CI, 31 to 51; 40 of 99 patients) before the third dose, and 68% (95% CI, 58 to 77; 67 of 99 patients) 4 weeks after the third dose (see below). Among the 59 patients who had been seronegative before the third dose, 26 (44%) were seropositive at 4 weeks after the third dose. All 40 patients who had been seropositive before the third dose were still seropositive 4 weeks later; their antibody titers increased from 36±12 before the third dose to 2676±350 1 month after the third dose ($P<0.001$). Patients who did not have an antibody response were older, had a higher degree of immunosuppression, and had a lower GFR than patients who had an antibody response. No serious adverse events were reported after the administration of the third dose, and no acute rejection episodes occurred.

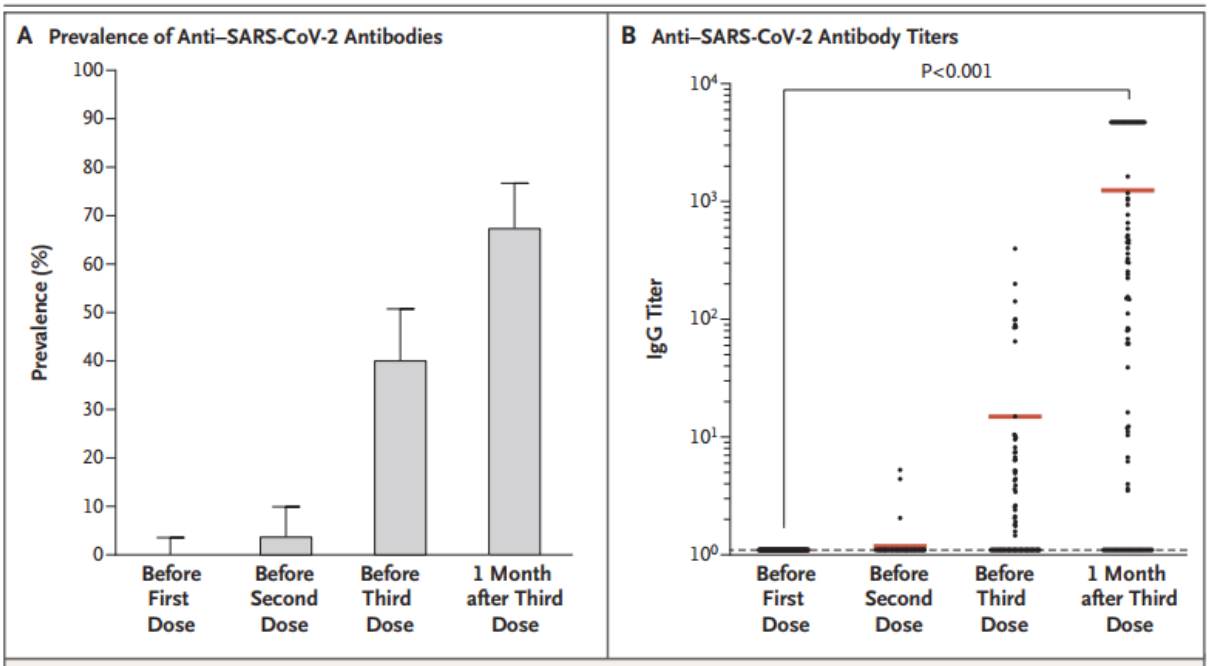


Figure 1. Immunogenicity.

Panel A shows the prevalence of anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies before and after vaccination in the study population. Panel B shows anti–SARS-CoV-2 antibody titers before and after vaccination in the study population.

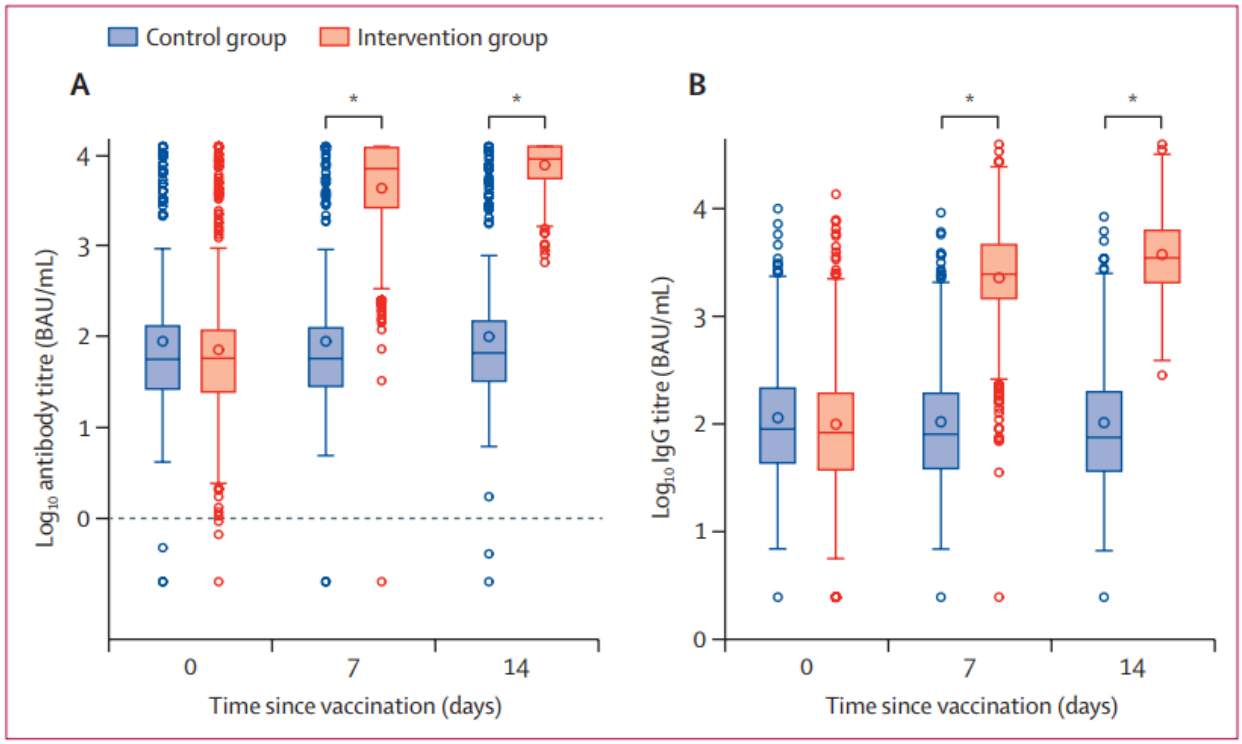
Comment: This study showed that administration of a third dose of the Pfizer vaccine to SOT recipients significantly improved the immunogenicity of the vaccine, with no cases of Covid-19 reported in any of the patients. However, a significant proportion of the patients may remain at risk for Covid-19.

Immunogenicity and Reactogenicity of BNT162b2 Booster in ChAdOx1-S-Primed Participants (CombiVacS): A Multicentre, Open-Label, Randomised, Controlled, Phase 2 Trial
Lancet published online June 25, 2021
doi.org/10.1016/ S0140-6736(21)01420-3
To date, no immunological data on COVID-19 heterologous vaccination schedules in humans have been reported. The investigators assessed the immunogenicity and reactogenicity of the Pfizer vaccine administered as second dose in participants primed with the AZ vaccine.

This is an open-label, randomized, controlled trial on adults aged 18-60 years, vaccinated with a single dose of AZ 8-12 weeks before screening, and no history of SARS-CoV-2 infection. Participants were randomly assigned (2:1) to receive either Pfizer via a single intramuscular injection (intervention group) or continue observation (control group). The primary outcome was 14-day immunogenicity, measured by immunoassays for SARS-CoV-2 trimeric spike protein and receptor binding domain (RBD).

676 individuals were enrolled and randomly assigned to either the intervention group (n=450) or control group (n=226) (mean age 44 years [SD 9]; 382 [57%] women and 294 [43%] men). 663 (98%) participants (n=441 intervention, n=222 control) completed the study up to day 14. In the intervention group, geometric mean titers of RBD antibodies increased from 71·46 BAU/mL (95% CI 59·84–85·33) at baseline to 7756·68 BAU/mL (7371·53–8161·96) at day 14 (p<0.0001). IgG against trimeric spike protein increased from 98·40 BAU/mL (95% CI 85·69–112·99) to 3684·87 BAU/mL (3429·87–3958·83). The

interventional: control ratio was 77·69 (95% CI 59·57–101·32) for RBD protein and 36·41 (29·31–45·23) for trimeric spike protein IgG. There was strong positive correlation observed between the two immunoassays and the pseudovirus neutralization assay. Immune cellular response 14 days after the booster vaccine also provides support for the effectiveness of the heterologous approach. Reactions were mild (n=1210 [68%]) or moderate (n=530 [30%]), with injection site pain (n=395 [88%]), induration (n=159 [35%]), headache (n=199 [44%]), and myalgia (n=194 [43%]) the most reported adverse events. No serious adverse events were reported.



Comment: Pfizer vaccine given as a second dose in individuals prime vaccinated with the AZ vaccine induced a robust immune response with no serious adverse events. This study confirms preclinical studies and suggestions anticipating that a heterologous vaccination regimen could elicit potent combined antibody and cellular responses, which might lead to mix-and-match COVID-19 vaccine programs such as the Canadian program. A limitation of the study is the absence of a control group completing the homologous AZ scheme. Trials directly comparing full homologous and heterologous vaccination strategies are needed to confirm safety and vaccine effectiveness of heterologous strategies.