TGIF

Today a few short items under Covid-19 News. First EMA Approves Booster Shot of Pfizer COVID-19 Vaccine for those 18 and older. Second AstraZeneca has asked the FDA to authorize another antibody treatment to prevent Covid-19. Last as expected Pfizer has submitted application to FDA for vaccines for ages 5-11.

Under Journal Review I have two themes. The first two articles look at incidence of myocarditis with mRNA vaccines. The next three articles report on waning immunity associated with the Pfizer vaccine.

Have a great weekend.

Ed

COVID-19 News

EMA Approves Booster Shot of Pfizer-BioNTech COVID-19 Vaccine for Those 18 and Older
Booster shot of the Pfizer vaccine can be given to healthy adults at least six months after the second dose. "The EMA [Europe FDA] is still assessing booster shots of the Moderna vaccine."

The EMA said on Monday people with weakened immune systems should get a third dose of a COVID-19 vaccine from Pfizer or Moderna

AstraZeneca Asks the FDA to Authorize an Antibody Treatment to Prevent Covid-19
AstraZeneca said on Tuesday that it had asked the FDA to grant emergency authorization for a long-acting antibody treatment to prevent Covid-19 in people who are at high risk of the disease. If authorized, it would become the first such preventive treatment to be available in the US. The company said in a statement that the treatment had reduced the risk of symptomatic Covid-19 by 77 percent (P<.001) versus placebo in a trial in which most participants either had other medical conditions that placed them at greater risk of severe illness or were not producing sufficient antibodies after vaccination. It said the treatment could be used in conjunction with vaccines in people with weaker immune systems. Other antibody treatments in use in the United States, including one developed by the drug maker Regeneron, have mainly been used to treat people who are already infected with the coronavirus. The AstraZeneca treatment is designed to stay in the body for much longer than the available antibody treatments for Covid

Comment: Vulnerable populations such as the immunocompromised often can't mount a protective response following vaccination and who continue to be at risk of developing Covid-19 may benefit from this product. The treatment could be used in conjunction with vaccines in people with weaker immune systems who may not mount a robust response to current vaccines.

Pfizer Asks FDA to Authorize Covid-19 Vaccine in Young Children
The companies said Thursday that they submitted the application for authorization with the FDA. There are more than 28 million children ages 5 to 11 in the US. Children would get two injections of the Pfizer vaccine, three weeks apart, just like adolescents and adults do but at a lower dosage. (10 micrograms) There also were no cases of myocarditis, an inflammatory heart condition, so far. Pfizer enrolled about 2,268 subjects 5 to 11 years. Two-thirds of the subjects got two doses of the vaccine, three weeks apart,

with the rest getting a placebo. Medical sites won't be able to vaccinate the children with existing supply on hand because doses for children are smaller and prepared differently than for adults.

Journal Review

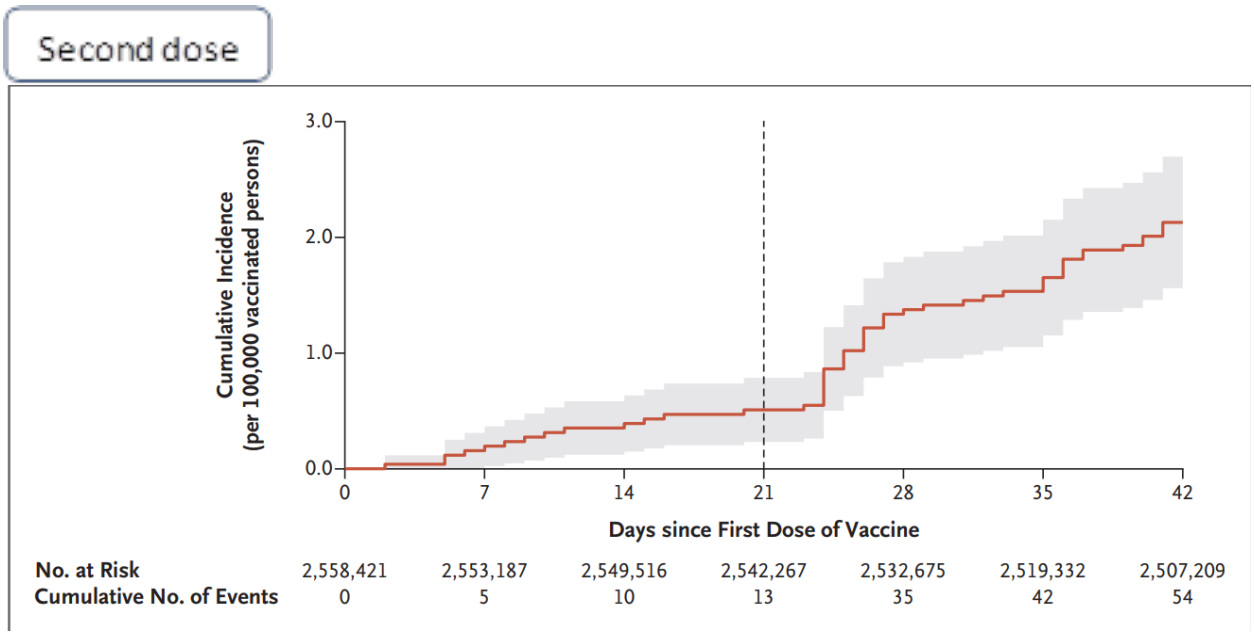
Acute Myocarditis Following COVID-19 mRNA Vaccination in Adults Aged 18 Years or Older
JAMA Intern Med published online October 4, 2021
doi:10.1001/jamainternmed.2021.5511
This study included Kaiser Permanente Southern California (KPSC) members aged 18 years or older who received at least 1 dose of the Pfizer or Moderna vaccine between December 14, 2020, and July 20, 2021. Potential cases of post vaccine myocarditis were identified based on reports from clinicians to the KPSC Regional Immunization Practice Committee and by identifying hospitalization within 10 days of vaccine administration with a discharge diagnosis of myocarditis. All cases were independently adjudicated by at least 2 cardiologists.

The absolute risk of myocarditis remains extremely low. Specifically, after a second dose, men average age 25 years were found to have 5.8 cases per million while after a first dose, there were 0.8 cases per million. All were men, with a median (IQR) age of 25 (20-32) years. Among unexposed individuals, there were 75 cases of myocarditis during the study period, with 39 (52%) men and median (IQR) age of 52 (32-59) years.

Comment: Limitations of this study include the observational design. See next review.

Myocarditis after Covid-19 Vaccination in a Large Health Care Organization
N Engl J Med published online October 6, 2021
DOI: 10.1056/NEJMoa2110737
The investigators searched the database of Clalit Health Services, the largest health care organization in Israel, for diagnoses of myocarditis in patients who had received at least one dose of the Pfizer vaccine. The diagnosis of myocarditis was adjudicated by cardiologists using the case definition used by the CDC

Among more than 2.5 million vaccinated members who were 16 years of age or older, 54 cases met the criteria for myocarditis. The estimated incidence per 100,000 persons who had received at least one dose of vaccine was 2.13 cases (95% confidence interval [CI], 1.56 to 2.70). The highest incidence of myocarditis (10.69 cases per 100,000 persons; 95% CI, 6.93 to 14.46) was reported in male patients between the ages of 16 and 29 years. The risk increased after the second dose.



Comment: Among patients in a large Israeli health care system who had received at least one dose of the Pfizer vaccine, the estimated incidence of myocarditis was 2.13 cases per 100,000 persons; the highest incidence was among male patients between the ages of 16 and 29 years. The results of these two articles are essentially the same. Myocarditis, a rare side effect, occurs mostly after the second dose as both these studiers report. So, in some countries, officials are trying out single doses for children. Even as parents in the US struggle with difficult questions over vaccinating their children, families in other countries have been offered an option: giving children just one dose of the vaccine. Officials in Hong Kong as well as in Britain, Norway and other countries have recommended a single dose of the vaccine for children ages 12 and older — providing partial protection from the virus, but without the potential harms occasionally observed after two doses. On Wednesday, Sweden and Denmark joined the ranks, announcing that adolescents should get only one dose of the Moderna vaccine. Public health officials in those countries are particularly worried about increasing data suggesting that myocarditis appears to be more common among adolescents and young adults after vaccination than had been originally thought. To be clear the risk remains very small, and significant only after the second dose of an mRNA vaccine. But the numbers may have changed the risk benefit calculus in countries where new infections are mostly lower than in the US. The risk was negligible in females of any age. Myocarditis was among the concerns that led the FDA to ask vaccine makers this summer to increase the number of children in clinical trials. The chance of getting severe Covid in a healthy 12- to 15-year-old is very low so you have to make sure that the vaccine that you're giving is extremely safe. The issue is likely to be the focus of serious discussion when agency advisers meet next week to review the evidence for vaccinations of children ages 5 to 11. One last consideration: What would you recommend to a male age 16-30 who has proof of natural immunity since reports demonstrate higher SARS-CoV-2 antibody levels in previously infected individuals after 1 dose of Pfizer compared with infection-naive individuals after 2 doses? [JAMA Netw Open 2021;4(8):e2119741] What if this male was an athlete? If the risk appears primarily after the second dose, should we advise only one dose of vaccine for persons with natural immunity? The mechanism of vaccine-induced myocarditis is not known but may be related to the active component of the vaccine, the mRNA sequence that codes for the spike protein SARS-CoV-2, or to the immune response that follows vaccination.

Effectiveness of mRNA BNT162b2 COVID-19 Vaccine up to 6 Months in a Large Integrated Health System in the USA: A Retrospective Cohort Study

Lancet published online October 4, 2021
doi.org/10.1016/ S0140-6736(21)02183-8

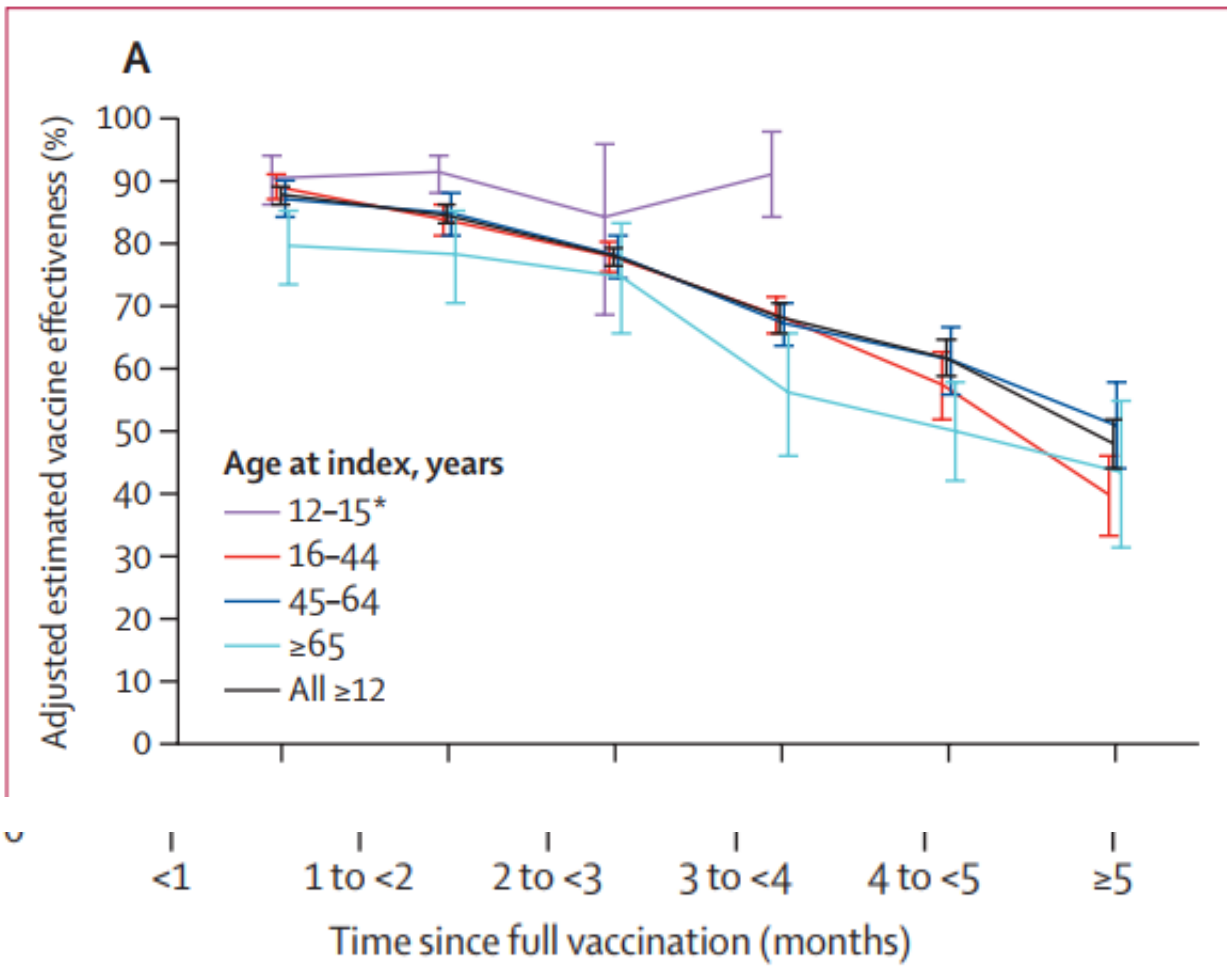
Investigators retrospectively mined 3.4 million electronic health records of patients 12 years and older from Kaiser Permanente Southern California from Dec 4, 2020, to Aug 8, 2021. Roughly 1.1 million patients had received at least one dose of the Pfizer COVID-19 vaccine, 91% of whom were fully vaccinated, and 6.6% of whom were partially vaccinated. Among vaccinated cohort members, an average of 3.4 months had elapsed since their second Pfizer dose.

Effectiveness against infection waned. During the study period, 5.4% of patients were infected by SARS-CoV-2. Relative to uninfected patients, a higher proportion of infected patients were younger (median age, 42 vs 45 years), Hispanic (57.7% vs 39.5%), and obese (body mass index of 30 kg/m^2 or higher). Among the 6.6% of infections that resulted in hospitalizations, patients were more likely to be older, male, and have more underlying illnesses and greater healthcare use.

Adjusted vaccine effectiveness (VE) over 6 months was 73% against infection and 90% against hospitalization. While VE against SARS-CoV-2-related hospitalizations remained high, VE against infection with any strain declined, from 88% in the first month after the second dose to 47% after 5 months. The authors said that the results confirm those of earlier reports that showed declines in Pfizer VE against infection about 6 months after the second dose.

VE differences were also seen across age-groups. VE against infection among fully vaccinated patients aged 12 to 15 years was 91%, while it was 61% for those 65 and older. From 1 to 5 months, VE against infection in patients 65 years and older fell from 80% to 43%. VE against hospitalization was 92% for patients 16 to 44 years and 86% for those 65 and older.

Of 5,008 SARS-CoV-2 samples for which a whole-genome sequence could be determined, 28% were the Delta variant. The share of cases caused by Delta rose from 0.6% to nearly 87% from April to July 2021. Lower efficacy against infection with Delta VE against Delta variant infections also fell, from 93% in the first month to 53% after 4 or 5 months, as it did for other variants over the same period (97% to 67%). The investigators noted that over the study period, the rapid spread of Delta coincided with the 6-month post-vaccination mark for many high-risk patients given priority access to the vaccine.



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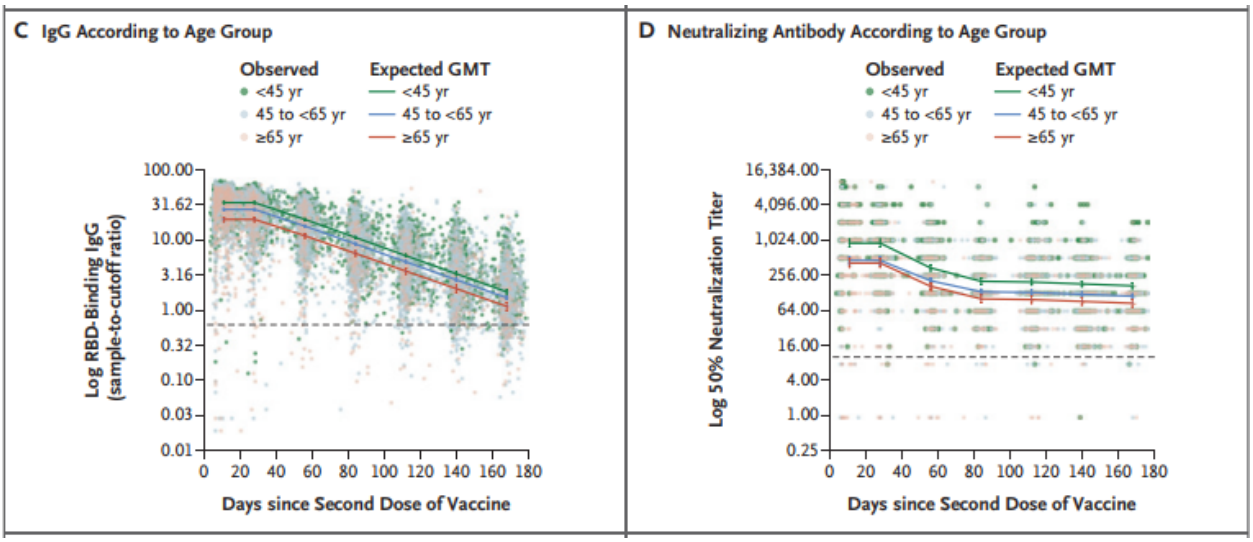
Comment: While VE against hospitalization held steady over the study period, the investigators noted that an unpublished review from the Israel Ministry of Health suggested declining Pfizer VE against hospitalization and severe illness among people 65 and older. Recent update showed significant benefit of a booster in persons > 60 years old. [Briefing October 5, 2021] This finding underscores the importance of monitoring vaccine effectiveness over time and suggest that booster doses will be needed to increase high levels of protection observed early in the vaccination program. These factors are especially important to help control heightened transmission of the delta variant as we enter the upcoming autumn and winter viral respiratory season. [see two articles below]

Waning Immune Humoral Response to BNT162b2 Covid-19 Vaccine over 6 Months
N Engl J Med published online October 6, 2021
DOI: 10.1056/NEJMoa2114583
Waning of BNT162b2 Vaccine Protection against SARS-CoV-2 Infection in Qatar
N Engl J Med published online October 6, 2021
DOI: 10.1056/NEJMoa2114114
In the first article, the investigators conducted a 6-month longitudinal prospective study involving vaccinated health care workers who were tested monthly for the presence of anti-spike IgG and neutralizing antibodies. Linear mixed models were used to assess the dynamics of antibody levels and to determine predictors of antibody levels at 6 months. The level of IgG antibodies decreased at a

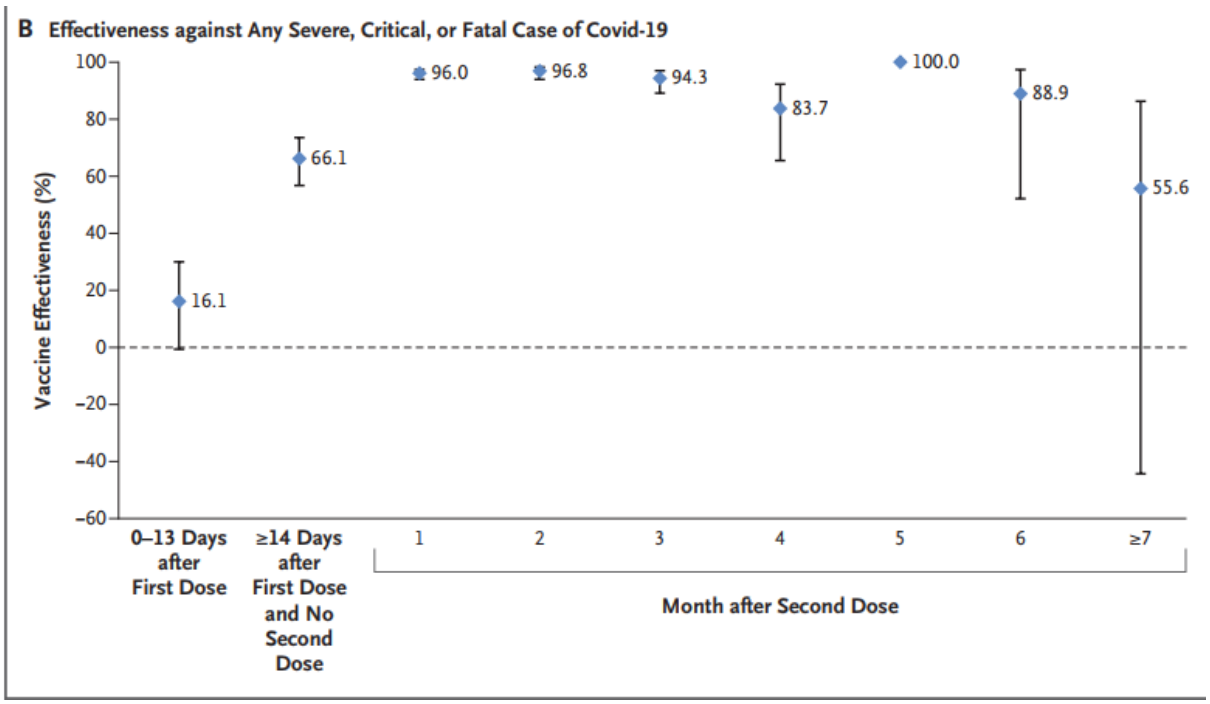
consistent rate, whereas the neutralizing antibody level decreased rapidly for the first 3 months with a relatively slow decrease thereafter. Six months after receipt of the second dose, neutralizing antibody titers were substantially lower among men than among women (ratio of means, 0.64; 95% confidence interval [CI], 0.55 to 0.75), lower among persons 65 years of age or older than among those 18 to less than 45 years of age (ratio of means, 0.58; 95% CI, 0.48 to 0.70), and lower among participants with immunosuppression than among those without immunosuppression (ratio of means, 0.30; 95% CI, 0.20 to 0.46). This study was conducted in a cohort of health care workers, who were mostly healthy persons and therefore may not represent the general population.

Several studies on the durability of humoral response in persons who have recovered from SARS-CoV-2 infection showed that both IgG and neutralizing antibody levels decrease only modestly at 8 to 10 months after the infection. [Science 2021;371(6529):eabf4063; Cell Host Microbe 2021;29(6):917-929.e4] This striking difference in antibody kinetics between convalescent persons and vaccinated persons may be the reason for the substantially lower incidence of breakthrough infection among previously infected persons than among vaccinated persons. [JAMA Netw Open 2021;4(8):e2119741: They reported higher SARS-CoV-2 antibody levels in previously infected individuals after 1 dose of Pfizer compared with infection-naive individuals after 2 doses.] Overall, the accumulating evidence from our study and others shows that long term humoral response and vaccine effectiveness in previously infected persons were superior to that in recipients of two doses of vaccine.



In the second article the investigators used a matched test-negative, case–control study design to estimate vaccine effectiveness against any SARS-CoV-2 infection and against any severe, critical, or fatal case of Covid-19, from January 1 to September 5, 2021. Estimated Pfizer VE against any SARS-CoV-2 infection was negligible in the first 2 weeks after the first dose. It increased to 36.8% (95% confidence interval [CI], 33.2 to 40.2) in the third week after the first dose and reached its peak at 77.5% (95% CI, 76.4 to 78.6) in the first month after the second dose. VE declined gradually thereafter, with the decline accelerating after the fourth month to reach approximately 20% in months 5 through 7 after the second dose. VE against symptomatic infection was higher than effectiveness against asymptomatic infection but waned similarly. Variant-specific effectiveness waned in the same pattern. VE against any severe, critical, or fatal case of Covid-19 increased rapidly to 66.1% (95% CI, 56.8 to 73.5) by the third week after the first dose and reached 96% or higher in the first 2 months after the second dose; VE against severe disease persisted at approximately this level for 6 months except possibly in the seventh month after

the second dose when there was a hint of a decline, but the case numbers were small. [wide CI] Estimated effectiveness against infection with each variant showed a pattern similar to that seen against any SARS-CoV-2 infection. Individual-level data on coexisting conditions were not available; therefore, they could not be explicitly factored into our analysis. With the young population of Qatar, only a small proportion of the study population may have had serious coexisting conditions. Only 9% of the population are 50 years of age or older, and 60% are young, expatriate craft and manual workers involved in mega-development projects. Their findings may not be generalizable to other countries where elderly persons constitute a sizable proportion of the total population.



Comment: These two articles highlight although the protection against asymptomatic infection diminished more quickly than that against symptomatic infection, evidence also found protection against hospitalization and death remained robust — generally at 90% or higher — for 6 months after the second dose. Implications of these findings on infection transmission remain to be studied, but vaccine breakthrough infections were recently found in this same population, to be less infectious than primary infections in unvaccinated persons.
[https://www.medrxiv.org/content/10.1101/2021.07.28.21261086v1: Through matched-cohort analyses of the randomly diagnosed infections, the mean Ct value was higher in all cohorts of breakthrough infections compared to the cohort of primary infections in unvaccinated individuals.] However, as VE wanes over time especially in the elderly and immunocompromised, a booster dose appears to be justified for person over age 60 or 65 and persons with high-risk conditions.