First thanks to everyone who responded. The overwhelming response has been you find the Briefing of value – thank you – it has been a labor of love.

Today I start with a comment on hybrid immunity and current US policy.

Under Covid-19 News lots to share. First an updated CDC report on breakthrough cases. Next, I report on the FDA formal approval of the Pfizer vaccine for children ages 5-11. Next the announcement of a delay in approving Moderna vaccine for ages 12-17. Last is IDSA update on fluvoxamine.

Under Journal Review CDC publication on laboratory-confirmed COVID-19 among adults hospitalized with COVID-19-like illness with infection-induced or mRNA vaccine-induced SARS-CoV-2 immunity. Next a report on community transmission and viral load kinetics of the SARS-CoV-2 Delta variant in vaccinated and unvaccinated individuals. The last article is another important article on managing Covid-19 vaccination in persons with allergies.

Have a great day.

Ed

VII: "Hybrid Immunity."
First let me define hybrid immunity: natural immunity acquired by people who have had Covid-19 plus the protection gained when such people also get vaccinated. Natural immunity has often been misused by anti-vaxxers, and people who oppose mandatory vaccinations, but we should be open to the evidence. Should vaccine mandates and passports make accommodations for people who have already had Covid-19? Should people who have been infected receive two vaccine doses when they may only need one dose for optimal protection? People with hybrid immunity also don't appear to gain much more immunity from a second dose and not receiving the second dose may decrease side effects like myocarditis. To be clear vaccination is extraordinary protection against severe disease and death and is the best option for returning to a more normal life.

Immunity by infection may be different from vaccination. Vaccination stimulates a specific part of the virus, mainly the spike protein. When people are infected with SARS-CoV-2, their immune system is exposed to the whole virus which may provide a broader immune response compared to vaccine alone. In both situations, memory B cells and memory T cells are produced.

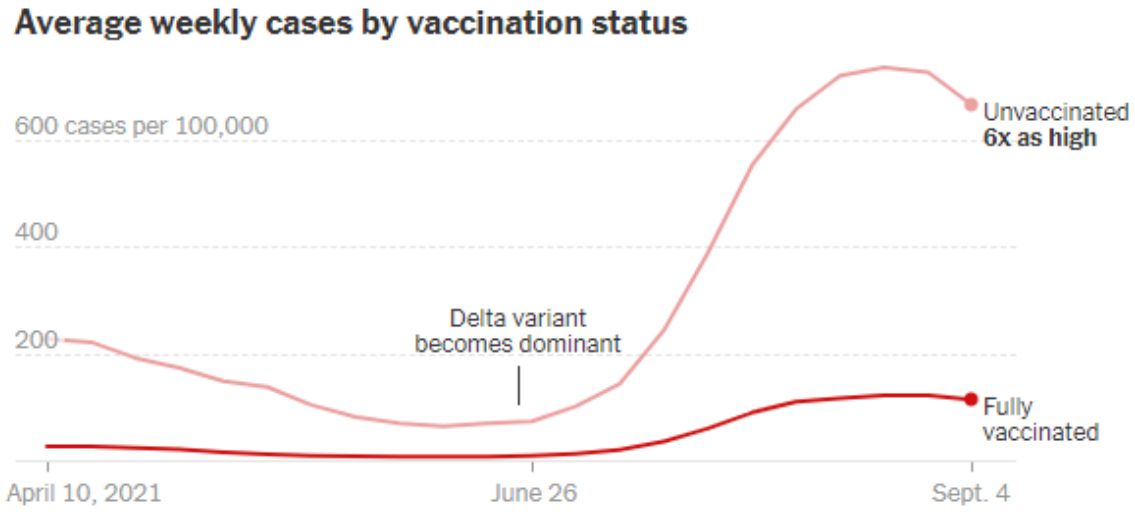
The rationale for vaccination regardless of history of natural infection is based on the current science that not everyone mounts a strong immune response after natural infection. [See article below] And data shows that while so-called natural immunity can last a long time — possibly up to a year — the duration varies based on factors such as a person's age, medical conditions, and disease severity.

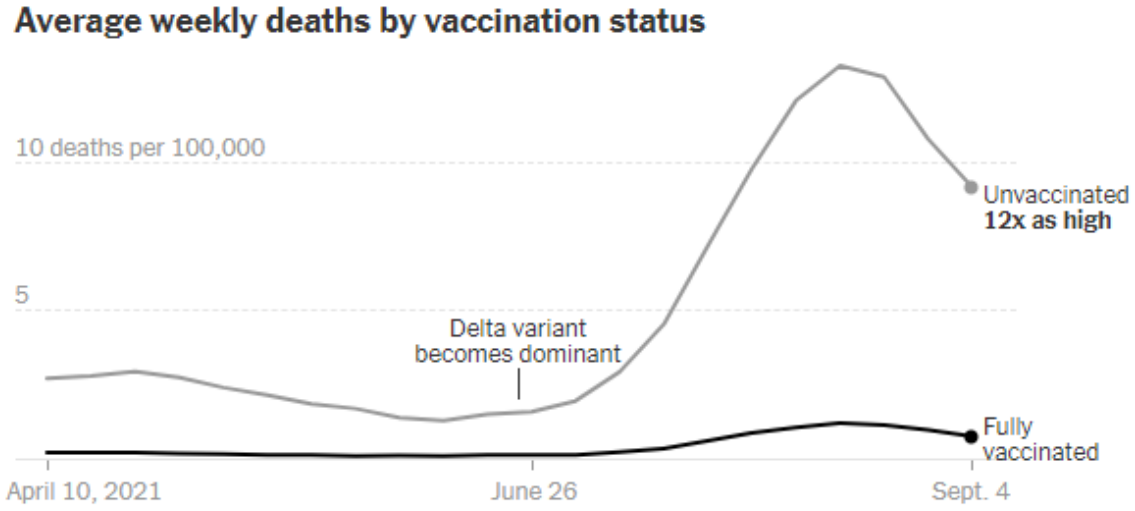
Currently 14 European countries — including France, Germany, Italy and Spain — recommend that people without underlying health conditions who have already been infected receive one dose of a vaccine (for vaccines with a two-dose schedule). Israel offers a temporary "green pass," an immunity passport, to people who have recovered from Covid-19 within the last six months regardless of their vaccination status. They only recommend one dose of vaccine if person had natural infection just like the European countries. The European Union allows travel between member states if citizens or residents have a positive PCR test showing they've recovered from Covid-19 in the past 180 days. The UK also accepts proof of a positive Covid-19 test result within 180 days for its Covid-19 Pass.

Current US guidance should address that a single dose may be sufficient for those with a prior infection. I believe failure to take natural immunity into account favoring a one-size fits all approach has contributed to vaccine hesitancy.

COVID-19 News

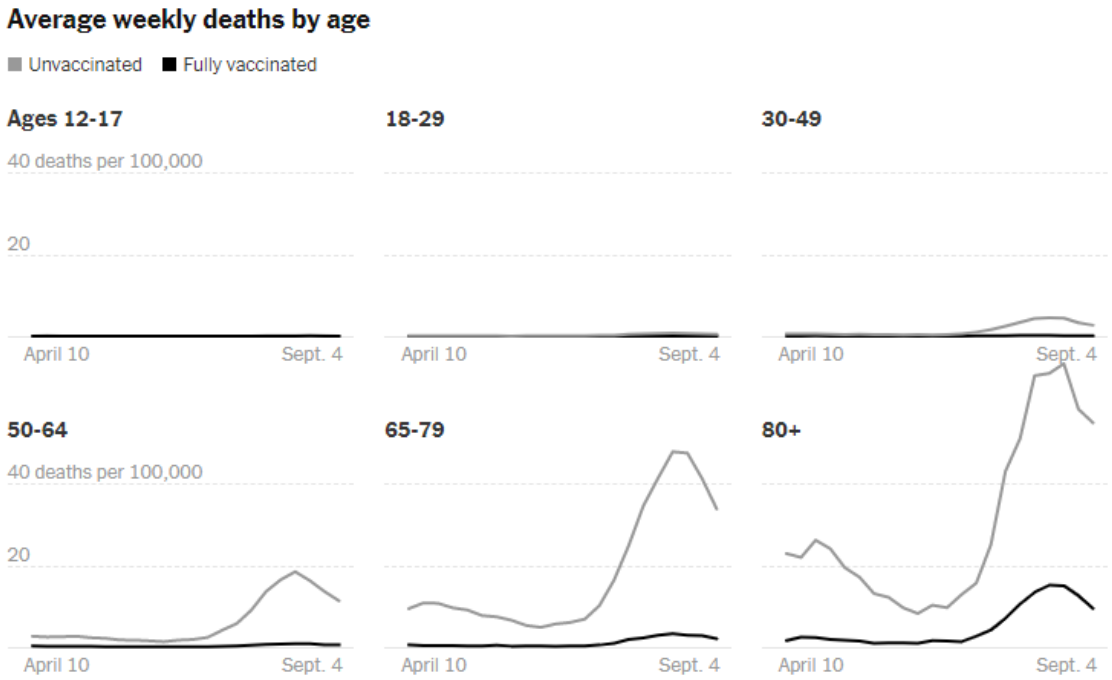
Covid-19 Vaccine Breakthrough Cases CDC
The data, from the CDC, is based on health department records from 14 states and two cities. Compared with the unvaccinated, fully vaccinated people overall had a much lower chance of testing positive for the virus or dying from it, even though the summer's Delta surge and the relaxation of pandemic restrictions in many parts of the country.



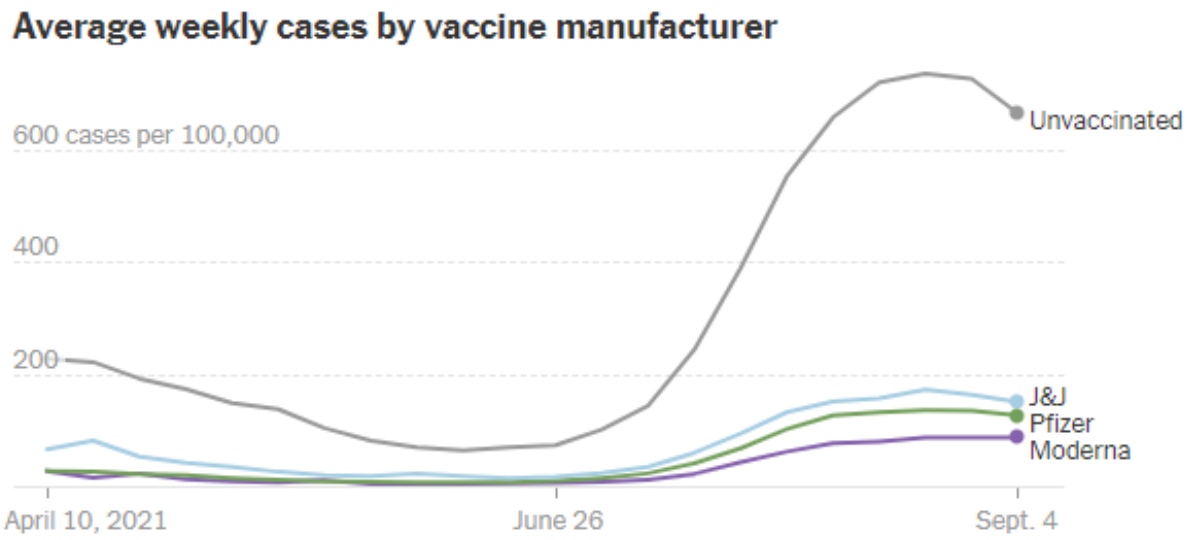


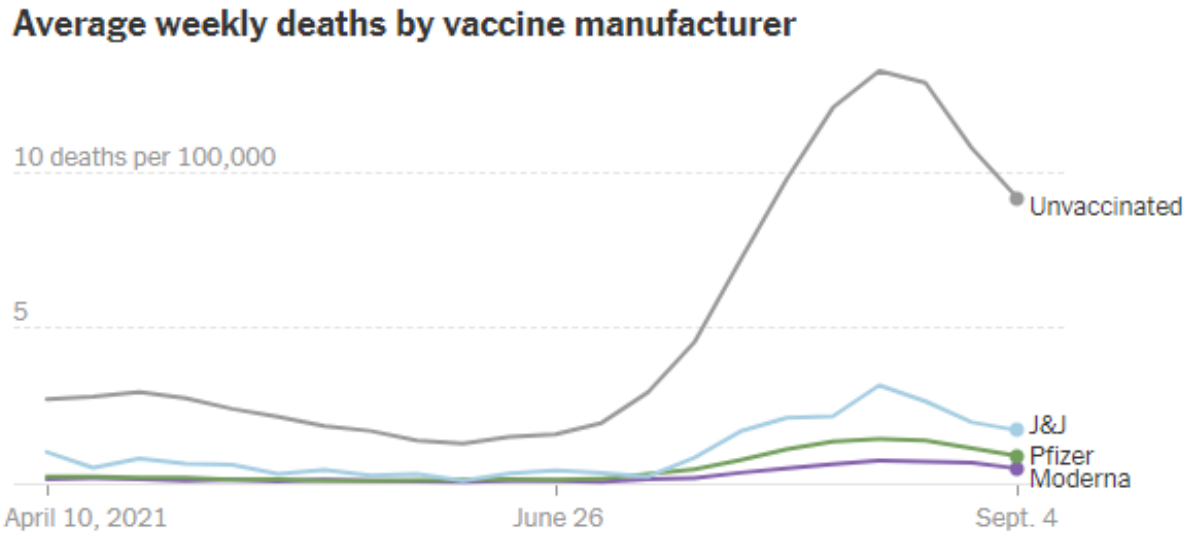
But the data indicates that immunity against infection may be slowly waning for some vaccinated people, even as the vaccines continue to be strongly protective against severe illness and death. While

every age group had similar rates of breakthrough cases, death rates varied significantly by age. Unvaccinated seniors were the most likely to die from Covid of any group. In addition, vaccinated people 80 and older had higher death rates than unvaccinated people under 50.



Among those vaccinated, J&J recipients had slightly higher rates of breakthrough cases and related deaths. And Pfizer recipients had slightly higher rates than those who got Moderna.





Comment: No matter how you look at this data, VE remains very high against severe disease and death. Age is the top risk factor for vaccine breakthrough deaths which is thought to be due to immunesenescence. Hopefully the booster dose for ages 65 years and older will address that issue.

FDA Approval for Children 5-11
As expected on Friday, the full FDA gave approval to vaccinate children 5-11. Today the CDC's ACIP is meeting to issue final recommendations.

Comment: The US has acquired enough vaccine for 28 million children. However, a recent Kaiser Foundation survey found only 27% of parents would immunize their children immediately, while 33% said they would wait and see and 30% they would definitely not vaccinate their children. Although the risk of COVID-19 in children is lower it is not insignificant especially in the Delta era. The risk of infection in vaccinated children is far less with a VE of 90%.

FDA Delaying Moderna's Vaccine in Adolescents to Review Myocarditis Risk
The FDA notified Moderna on Friday that an analysis may not be completed until January of next year while the agency reviews recent international data on the risk of myocarditis after vaccination on Moderna's application for authorization in 12- to 17-year-olds after several Nordic countries limited use due to myocarditis reports. Moderna also said it would delay asking the FDA to authorize use of a lower dose of its shot in even younger children, ages 6 to 11, while the agency continues to review its request to clear the shots in adolescents.

Comment: This is a small setback, but the delay may help sort out the risk of myocarditis in this age group. For now, we have the Pfizer vaccine which may or may not have a slightly lower risk of myocarditis. I will remind everyone, the risk of myocarditis from disease is far greater and more severe that from mRNA vaccines.

IDSA Guidelines on the Treatment and Management of Patients with COVID-19 – Fluvoxamine
October 27, 2021
Among ambulatory patients with COVID-19, the IDSA guideline panel recommends fluvoxamine only in the context of a clinical trial (Knowledge gap).

The IDSA Panel search identified two RCTs (including pre-prints – one has now been published – see below) that reported on ambulatory patients with SARS-CoV-2 infection. Patients in these studies were randomized to fluvoxamine or placebo/usual care. Both trials included symptomatic outpatients who tested positive for SARS-CoV-2 infection within seven days. Reis included patients who were at high risk for severe infection and utilized a composite primary outcome of hospitalization or emergency room visit lasting greater than six hours. [This trial has now gone through peer review and has been published after this guideline was written – see Briefing October 28, 2021] Additional outcomes reported in the two trials included mortality, hospitalization, emergency room visit lasting >6 hours, progression to oxygen saturation <92%, viral clearance, and serious adverse events.

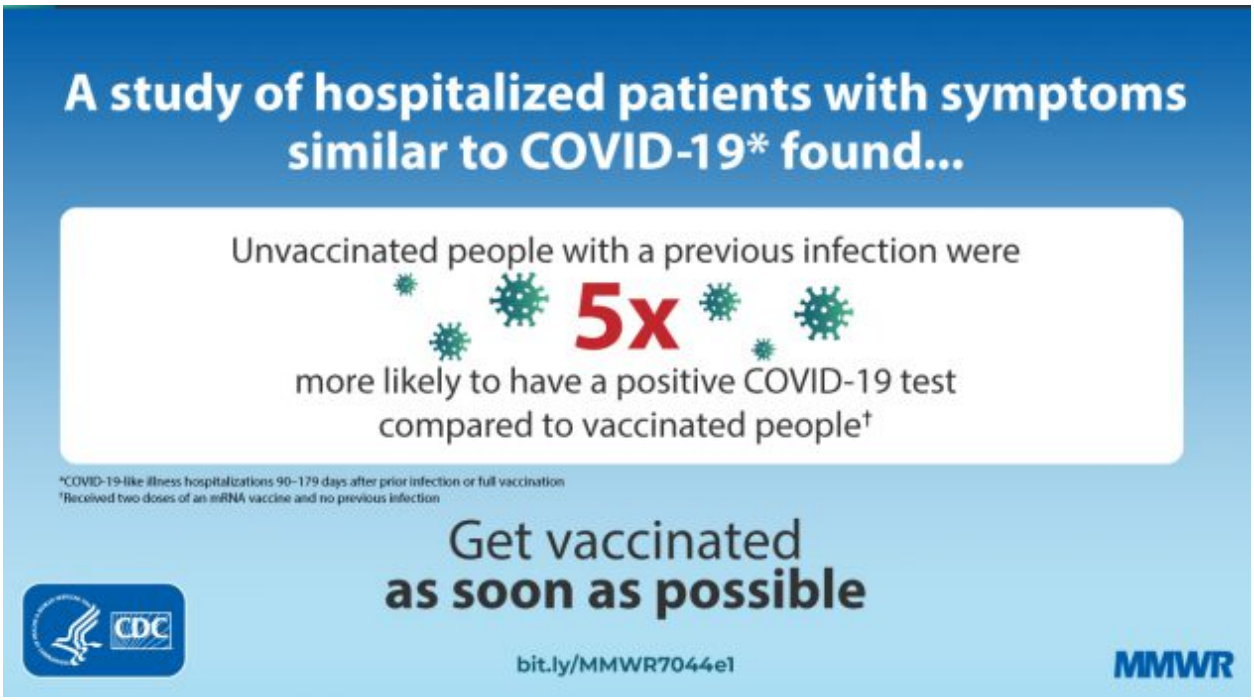
Comment: The panel agreed overall that the certainty of evidence was low given the scarcity in mortality data and because upper boundary of the 95% confidence interval failed to exclude the risk of possible harms. The panel also had concerns about the generalizability/indirectness in the results surrounding hospitalization and emergency room visit >6 hours in the Reis study was partially conducted in patients with extended stays in emergency settings (mobile hospitals) to inform the primary endpoint, and it is unclear if resource constraints (possible contingency setting) may have affected the total number of events (i.e., emergency room stays and rates of hospitalization). I think the panel brings up some concerns, but the availability, cost, and PO etc. make fluvoxamine an attractive possible therapeutic, but I agree larger trials maybe be needed to confirm the Reis study. Hopefully the NIH trial may help clarify fluvoxamine's effectiveness.

Journal Review

Laboratory-Confirmed COVID-19 Among Adults Hospitalized with COVID-19-Like Illness with Infection-Induced or mRNA Vaccine-Induced SARS-CoV-2 Immunity — Nine States, January-September 2021
MMWR October 29, 2021

CDC used data from the VISION Network to examine hospitalizations in adults with COVID-19-like illness and compared the odds of receiving a positive SARS-CoV-2 test result, and thus having laboratory-confirmed COVID-19, between unvaccinated patients with a previous SARS-CoV-2 infection occurring 90-179 days before COVID-19-like illness hospitalization, and patients who were fully vaccinated with an mRNA COVID-19 vaccine 90-179 days before hospitalization with no previous documented SARS-CoV-2 infection. Among patients hospitalized with COVID-19-like illness whose previous infection or completion of vaccination occurred 90-179 days earlier, the odds of laboratory-confirmed COVID-19 were compared between previously infected persons and fully vaccinated mRNA COVID-19 vaccine recipients. aORs and 95% CIs were calculated using multivariable logistic regression, adjusted for age, geographic region, calendar time (days from January 1 to hospitalization), and local virus circulation, and weighted based on propensity to be in the vaccinated category.

The adjusted odds of laboratory confirmed COVID-19 among unvaccinated adults with previous SARS-CoV-2 infection were 5.49-fold higher than the odds among fully vaccinated recipients of an mRNA COVID-19 vaccine who had no previous documented infection (95% confidence interval = 2.75–10.99). The benefit of vaccination compared with infection without vaccination appeared to be higher for recipients of Moderna than Pfizer vaccine, which is consistent with a recent study that found higher vaccine effectiveness against COVID-19 hospitalizations for Moderna vaccine recipients than for Pfizer vaccine recipients. [see CDC updates above under COVID-19 News]



Comment: In this multistate analysis of hospitalizations for COVID-19-like illness among adults aged ≥18 years during January-September 2021 whose previous infection or vaccination occurred 90-179 days earlier, the adjusted odds of laboratory-confirmed COVID-19 were higher among unvaccinated and previously infected patients than among those who were fully vaccinated with 2 doses of an mRNA COVID-19 vaccine without previous documentation of a SARS-CoV-2 infection. Secondary analyses that did not adjust for time since infection or vaccination or adjusted time since infection or vaccination differently as well as before and during Delta variant predominance produced similar results.

These findings differ from those of a retrospective records-based cohort study in Israel, which did not find higher protection for vaccinated adults compared with those with previous infection during a period of Delta variant circulation. This variation is possibly related to differences in the outcome of interest and restrictions on the timing of vaccination. The Israeli cohort study assessed any positive SARS-CoV-2 test result, whereas this study examined laboratory-confirmed COVID-19 among hospitalized patients. The Israeli cohort study also only examined vaccinations that had occurred 6 months earlier, so the benefit of more recent vaccination was not examined. The aOR could not be further stratified by time since infection or vaccination because of sparse data and limited ability to control for residual confounding that could be magnified within shorter intervals. The aOR that did not adjust for time might also be subject to residual confounding, particularly related to waning of both types of immunity. Residual confounding might exist because the study did not measure or adjust for behavioral differences between the comparison groups that could modify the risk of the outcome. Finally, this study focused on hospitalized patients only and may not apply to those not hospitalized. It is important to understand what happens to those who are not hospitalized as they fare with reinfection. Does infection confer protection against future hospitalization and how does that compare against vaccinated and unvaccinated. In this last issue in JID, an article the Briefing reviewed back in June 2021 showed that immunological memory is acquired in most individuals infected with SARS-CoV-2 and is sustained in a majority of patients for up to 11 months after recovery; however, 25% of donors had neutralizing levels that dropped to an undetectable titer over time. [J Infect Dis 2021; 224:1294–304] Nonetheless it is becoming clear that that those with prior infection can benefit with a single dose of vaccine to boost immunity that they have already acquired naturally. US guidance has not addressed the issue of hybrid immunity. [see comments above under hybrid immunity]

Community Transmission and Viral Load Kinetics of the SARS-CoV-2 Delta (B.1.617.2) Variant in Vaccinated and Unvaccinated Individuals in the UK: A Prospective, Longitudinal, Cohort Study
Lancet Infect Dis published online October 28, 2021
doi.org/10.1016/S1473-3099(21)00648-4
Between September 13, 2020, and September 15, 2021, 602 community contacts of 471 UK COVID-19 index cases were recruited to the Assessment of Transmission and Contagiousness of COVID-19 in Contacts cohort study and contributed 8,145 upper respiratory tract samples from daily sampling for up to 20 days. All participants had non-severe ambulatory illness or were asymptomatic. SARS-CoV-2 quantitative RT-PCR, conversion of ORF1ab and envelope (E-gene) cycle threshold values to viral genome copies, whole-genome sequencing, and lineage assignments were used.

A total of 205 household contacts of delta variant index cases were identified, of whom 53 tested positive for COVID-19. Of the 205 contacts, 126 (61%) received two vaccine doses, 39 (19%) had received one vaccine dose, and 40 (20%) were unvaccinated.

Overall, the SAR (secondary attack rate) in household contacts exposed to the delta variant was 25% (95% confidence interval [CI] 18–33) for fully vaccinated individuals compared with 38% (24–53) in unvaccinated individuals. Meanwhile, SAR among household contacts exposed to fully vaccinated index cases was similar to household contacts exposed to unvaccinated index cases (25% [95% CI 15–35] for vaccinated vs 23% [15–31] for unvaccinated). Moreover, 12 (39%) of 31 infections in fully vaccinated household contacts arose from fully vaccinated epidemiologically linked index cases, further confirmed by genomic and virological analysis in three index case-contact pairs. Additionally, viral load trajectories from fully vaccinated individuals with delta infection (n = 29) were compared with unvaccinated individuals with delta (n = 16), alpha n = 39), and pre-alpha (n = 49) infections. Study data demonstrated

that although peak viral load did not differ by vaccination status or variant type, it increased modestly with age (difference of 0.39 [95% credible interval –0.03 to 0.79] in peak log10 viral load per mL between those aged 10 years and 50 years). On the other hand, fully vaccinated individuals with delta variant infection had a faster (posterior probability >0.84) mean rate of viral load decline (0.95 log10 copies per mL per day) than did unvaccinated individuals with pre-alpha (0.69), alpha (0.82), or delta (0.79) variant infections.

Comment: Findings from this a study demonstrated that coronavirus disease 2019 (COVID-19) vaccination reduces the risk of delta variant infection and accelerates viral clearance. Nonetheless, the study finds that fully vaccinated individuals with breakthrough infections have peak viral load similar to unvaccinated cases and can transmit infection in household settings, including to fully vaccinated contacts. In other words, their findings suggest that vaccination is not sufficient to prevent transmission of the delta variant in household settings with prolonged exposures. Index cases were defined as the first household member to have a PCR-positive swab, but they cannot exclude the possibility that another household member might already have been infected and transmitted to the index case. They also did not perform viral culture—which is a better proxy for infectiousness than RT-PCR.

Association of Self-Reported High-Risk Allergy History with Allergy Symptoms After COVID-19 Vaccination

JAMA Netw Open published online October 26, 2021
doi:10.1001/jamanetworkopen.2021.31034

The investigators set out to assess the association between self-reported history of high-risk allergy and self-reported allergic reactions after mRNA COVID-19 vaccination of health care employees. A total of 52,998 health care employees were included in the cohort, of whom 51,706 (97.6%) received 2 doses of an mRNA COVID-19 vaccine and 474 (0.9%) reported a history of high-risk allergy. Individuals with vs without a history of high-risk allergy reported more allergic reactions after receiving dose 1 or 2 of the vaccine (11.6% [n = 55] vs 4.7% [n = 2461]). In the adjusted model, a history of high-risk allergy was associated with an increased risk of allergic reactions (adjusted relative risk [aRR], 2.46; 95% CI, 1.92-3.16), with risk being highest for hives (aRR, 3.81; 95% CI, 2.33-6.22) and angioedema (aRR, 4.36; 95% CI, 2.52-7.54). Most of the reported allergy symptoms, however, did not impede the completion of the 2-dose vaccine protocol.

Comment: The cohort in the present study included 217 employees with a history of a severe allergic reaction to an injectable medication or a vaccine and 9 employees with a history of severe allergic reaction to PEG. By reported history alone, many of these individuals would not be ineligible for an mRNA COVID-19 vaccine, according to many international guidelines. However, following the CDC guidelines, with allergist consultation, risk stratification, and shared decision-making, all employees were able to complete the 2-dose vaccine series. Recent data indicated that, even for individuals who reported immediate and potentially allergic reactions after the first dose of an mRNA COVID-19 vaccine, the second dose can be safely administered. [reviewed in the Briefing a few months ago by same investigators] A self-reported history of high-risk allergy although associated with an increased risk of self-reported allergic reactions after mRNA COVID-19 vaccination, did not impede the completion of the 2-dose mRNA COVID-19 vaccine series. Not everyone has access to an allergist which may make implementation of this study difficult in some locations.