Lots to share today – many articles in the queue including recent articles on HAIs during the pandemic (next issue).

Today under Covid News I start with a comment about the ACIP/FDA regarding boosters, vaccinations, and what are the hard questions we should be asking about our goals. Next is the CDC guidance for Labor Day and the start of school. Next the most recent WHO report on Covid-19 since this is a true global pandemic. I finish this section with an update on the Mu variant.

Under Journal Review the first article presents data suggesting that antibody protection in Pfizer vaccine recipients wanes at a higher rate than in COVID-19 survivors. The next article demonstrates increasing the interval up to 45 weeks results in increased antibody titers after the second dose, offering flexibility in current vaccination schedules. The third article suggests that the risk of long COVID is reduced in individuals who are fully vaccinated. The last article study shows that casirivimab-imdevimab treatment of mild to moderate COVID-19 was associated with a statistically significant decrease in the rate of all-cause hospitalization during the first 28 days after infusion.

I hope everyone has a wonderful Labor Day weekend.

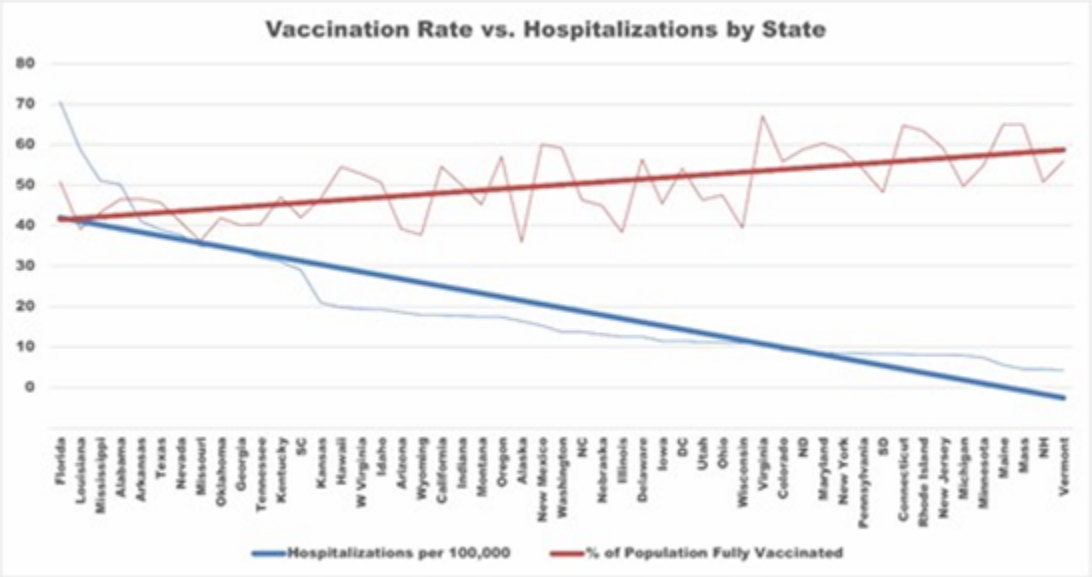
Ed

COVID-19 News Updates

VII Comment: Many of us were disappointed that ACIP did not reach consensus on booster doses this past week. (See below) People are already going out and receiving their dose since proof of immunosuppression is not required to receive a third dose. Data from Israel reviewed in the last Briefing support a third dose for persons over age 60 after 6 months as well as the immunosuppressed. I do agree with CDC that fully vaccinated healthy adults are still protected at preventing severe disease, hospitalizations, and deaths. Some researchers still believe the evidence is insufficient for a third dose at this time. I think the President's announcement of boosters after September 20th was premature. [another example of injecting politics into the pandemic] If you are healthy and fully vaccinated, you are still highly protected from severe disease and death. To put into perspective: From February 1, 2021, to August 18, 2021, ~1400 vaccinated people have died from Covid-19. 3960 persons die of drowning/year; 38,000 persons die of traffic related injuries/year; and over 39,000 persons die of gun related violence/year. In the end I do believe certain groups will be offered a third dose.

The FDA has now announced that its Vaccines and Related Biological Products Advisory Committee (VRBAC) will meet on Sep 17 to discuss COVID-19 vaccine third doses and specifically address the Pfizer supplemental Biologics License Application for administration of a third dose of that vaccine. The FDA is also considering whether to authorize a lower dose of Moderna for boosters. Moderna is asking the FDA to authorize a 50-microgram dose as a booster, half of the current vaccine. One possible benefit of a lower dose may be fewer side effects.

As I have stated several times in the Briefing the issue of third doses and masking mandates have detracted from focusing on the 40 million eligible persons who have not been vaccinated at all. There is a clear correlation by state, the higher your vaccination rate, the lower hospitalizations. (See below)



While the availability of vaccines refocused the U.S. response to the pandemic, many policy questions remain. What exactly are our goals? If the goal is zero spread, this is not realistic. Should vaccinated people get boosters? Does everyone need to wear a mask and for how long? Are unvaccinated children safe in schools? In the end I think much of the confusion and disagreement among scientists and politicians alike comes down to undefined and sometimes conflicting goals in responding to the pandemic. I think the heart of the problem in the US is not just the CDC, politicians, etc., but everyone — including us public health "experts" — who do not always connect our recommendations to clear goals and communicate these goals honestly with the public. We need to have an honest conversation with the public about what our goals really are and how together we can achieve them. Is the goal getting to zero infections or to make this virus more like the seasonal flu – keeping rates low, protecting the vulnerable, and learning to live with the virus? Let us continue to work together to reduce fear and provide hope.

ACIP Follow-Up

August 30th meeting

A risk-based booster dose strategy for COVID-19 vaccines could target populations at risk of severe disease and those critical to the public health infrastructure, CDC staff said at a meeting of CDC's ACIP on Monday.

Though FDA has not reviewed data on booster doses for COVID-19 vaccines among the general population yet, CDC staff presented a preliminary framework to determine those who might need it most, including older adults, long-term care facility residents [seeing outbreaks in NH again], and healthcare workers.

CDC staff presented limited data that showed that vaccines remain effective at preventing hospitalization and severe disease but could be less effective at preventing infection or milder symptomatic illness. [assume related to Delta variant]

There is limited data on vaccine effectiveness among frontline workers -- including healthcare professionals which showed declines against the Delta variant, but differences were not significant compared with a pre-Delta period. However, recent data showed lower vaccine effectiveness against infection among long-term care facility residents since the Delta variant gained prominence in the U.S. Preliminary vaccine effectiveness estimates found that among adults ages 65 and older, vaccine effectiveness decreased against hospitalization, but overall VE remains fairly good against severe disease and death for those >65.

ACIP members disagreed about the need for booster doses, with some arguing that ensuring the unvaccinated receive the primary vaccination series should be the highest priority.

CDC Press Briefing by White House COVID-19 Response Team and Public Health Officials
August 31, 2021
Seven-day average of cases is about 129,000 cases per day. Seven-day average of hospital admissions is about 11,500 cases per day. And seven-day average of daily deaths has increased to 896 per day.

After Labor Day many of our children will return to school. [Many have already returned] CDC has strong and detailed guidelines that should be implemented to promote our children's safety in the classroom. Below is what Dr. Walensky discussed:

1. CDC recommends that everyone eligible for vaccination be vaccinated before school starts. If you or your vaccine-eligible child is not yet vaccinated, it is never too late to begin your vaccine series.

2. Next, universal masking is critically important in schools for students, teachers, staff, and visitors, regardless of vaccination status.

3. CDC also recommends schools employ additional key strategies in school to keep kids safe, including improved ventilation, physical distancing, and establishing screening programs for students and teachers. Parents should encourage their children to wear masks when in public indoor settings.

4. And finally, and perhaps most importantly, parents can protect their children by getting vaccinated themselves. This will create a protective bubble around their children who are not yet eligible for their own vaccine.

CDC recommendations to be safe over Labor Day weekend:

1. If gathering with family and friends, remember that spending time outside with others who are not vaccinated will help to prevent transmission. Throughout the pandemic, we have seen that the vast majority of transmission takes place among unvaccinated people in closed, indoor settings.

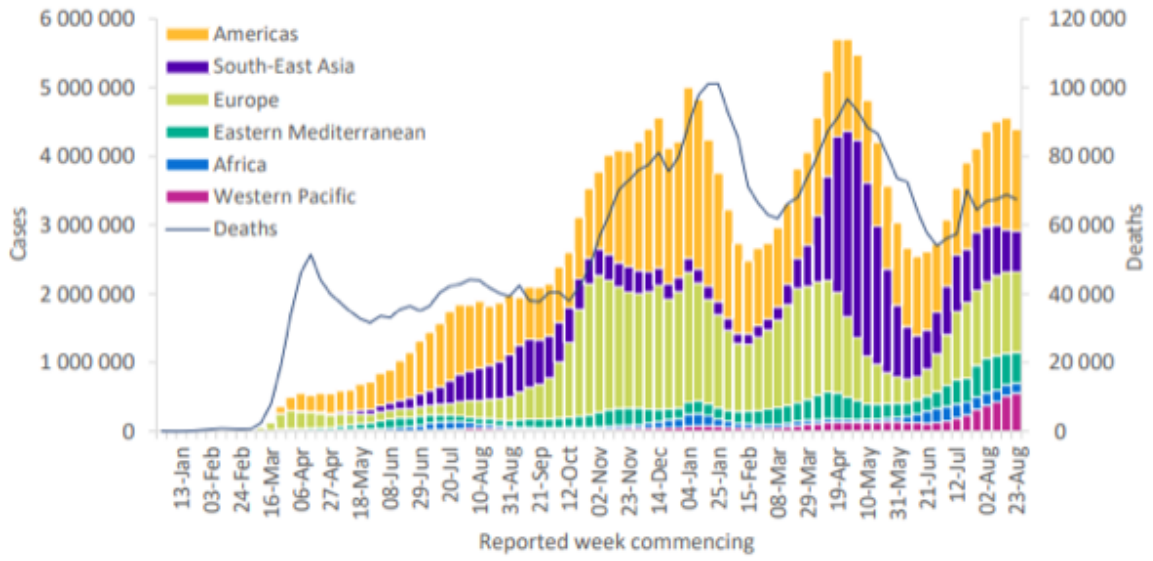
2. When in public indoor settings, please wear a mask — vaccinated or unvaccinated. Given the high transmissibility of the Delta variant and the significant community transmission in this country, wearing a mask is the easiest way for anyone, regardless of your vaccination status, to slow the spread of disease.

3. Talk with family and friends who are still unvaccinated about the benefits of the vaccine and consider taking them to get vaccinated over the long holiday weekend.

4. If you are unvaccinated, CDC recommends **not** traveling.

WHO COVID-19 Weekly Epidemiological Update
August 31, 2021
With just under 4.4 million new cases reported this week (23-29 August), the number of new cases reported globally remains similar to the previous week after having increased for nearly two months (see below). The highest numbers of new cases were reported from the US (938,014 new cases; 8% decrease), India (270,796 new cases; 17% increase), the Islamic Republic of Iran (254,753 new cases; similar to the previous week), the United Kingdom (237,556 new cases; 8% increase), and Brazil (175,807 new cases; 16% decrease).

Figure 1. COVID-19 cases reported weekly by WHO Region, and global deaths, as of 29 August 2021**



Mu: VOI
Since its first identification in Colombia in January 2021, there have been a few sporadic reports of cases of the Mu variant and some larger outbreaks have been reported from other countries in South America and in Europe. B.1.621 was classified as a VOI on 30 August 2021 and given the WHO label “Mu”. This includes the descendent Pango lineage B.1.621.1. This variant is known as 21H in Next strain nomenclature. The Mu variant has a constellation of mutations that indicate potential properties of immune escape. Although the global prevalence of the Mu variant among sequenced cases has declined and is currently below 0.1%, the prevalence in Colombia (39%) and Ecuador (13%) has consistently increased. It's not yet known whether Mu is more transmissible or if it causes more severe illness. The epidemiology of the Mu variant in South America, particularly with the co-circulation of the Delta variant, will be carefully monitored for changes.

Journal Review

Large-Scale Study of Antibody Titer Decay Following BNT162b2 mRNA Vaccine or SARS-CoV-2 Infection
medRxiv published online August 19, 2021
doi.org/10.1101/2021.08.19.21262111
The research team tracked antibody levels in 2,653 adults who received two doses of the Pfizer vaccine

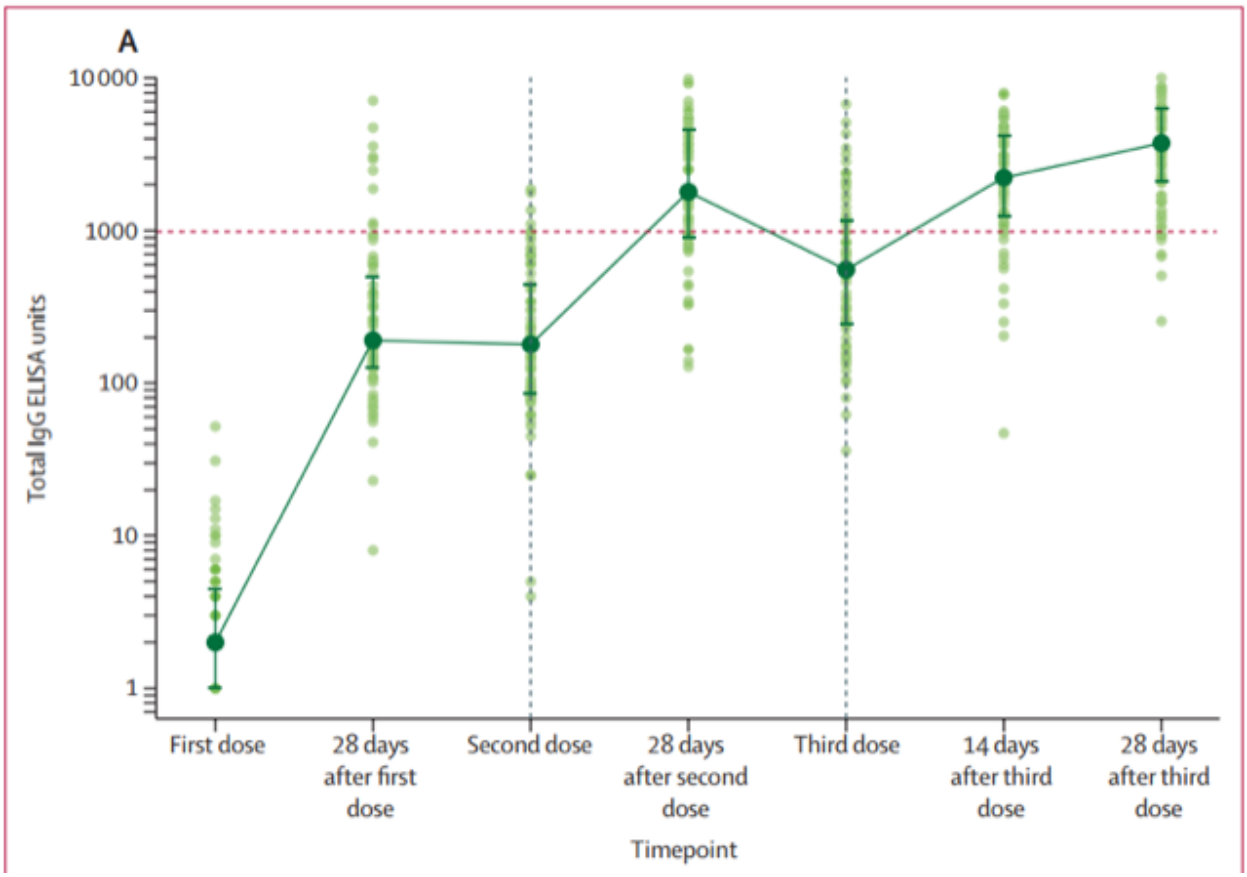
and in 4,361 COVID-19 survivors who were never vaccinated. Serum samples were run on the SARS-CoV-2 IgG lab-based serology blood test on the Abbot Alinity™ i system following the manufacturer's instructions. In this antibody test, the SARS-CoV-2 antigen-coated paramagnetic microparticles bind to the IgG antibodies that attach to the SARS-CoV-2 spike protein (SP) in patients' serum and plasma sample.

Higher SARS-CoV-2 IgG antibody titers were observed in vaccinated individuals (median 1581 AU/mL IQR [533.8- 5644.6]) after the second vaccination, than in convalescent individuals (median 355.3 AU/mL IQR [141.2-998.7]; p<0.001). In vaccinated subjects however, antibody titers decreased by up to 40% each subsequent month while in convalescents they decreased by less than 5% per month. Six months after Pfizer vaccination 16.1% subjects had antibody levels below the seropositivity threshold of <50 AU/mL, while only 10.8% of convalescent patients were below <50 AU/mL threshold after 9 months from SARS-CoV-2 infection.

Comment: The data presented here suggests that antibody protection in Pfizer vaccine recipients wanes at a higher rate than in COVID-19 survivors (natural infection). In addition, these investigators had previously reported that breakthrough infection rates increase starting about five months after vaccination. [medRxiv doi:10.1101/2021.08.03.21261496] This additional combined data argues for a booster shot five to six months after the second injection, especially for high-risk individuals. The assay used in this study does not specially measure neutralizing antibody and the observational design, there is potential for unmeasured confounding factors.

Reactogenicity and Immunogenicity after a Late Second Dose or a Third Dose of ChAdOx1 nCoV-19 in the UK: A Substudy of Two Randomised Controlled Trials (COV001 and COV002)
Lancet published online September 1, 2021
doi.org/10.1016/ S0140-6736(21)01699-8
Volunteers aged 18-55 years who were enrolled in the phase 1/2 (COV001) controlled trial in the UK and had received either a single dose or two doses of AZ vaccine were invited back for vaccination. The investigators report the reactogenicity and immunogenicity of a delayed second dose (44-45 weeks after first dose) or a third dose of the vaccine (28-38 weeks after second dose). Data from volunteers aged 18-55 years who were enrolled in either the phase 1/2 (COV001) or phase 2/3 (COV002), single-blinded, randomized controlled trials of AZ vaccine and who had previously received a single dose, or two doses were used for comparison purposes.

The extended interval between the first two doses (44-45 weeks) resulted in higher antibody titers after the second dose than with a shortened interval. A third dose given 28-38 weeks after the primary series increased the antibody titers to above those after a second dose with a shortened interval. Reactogenicity was lower after the second or third dose than after the first dose.

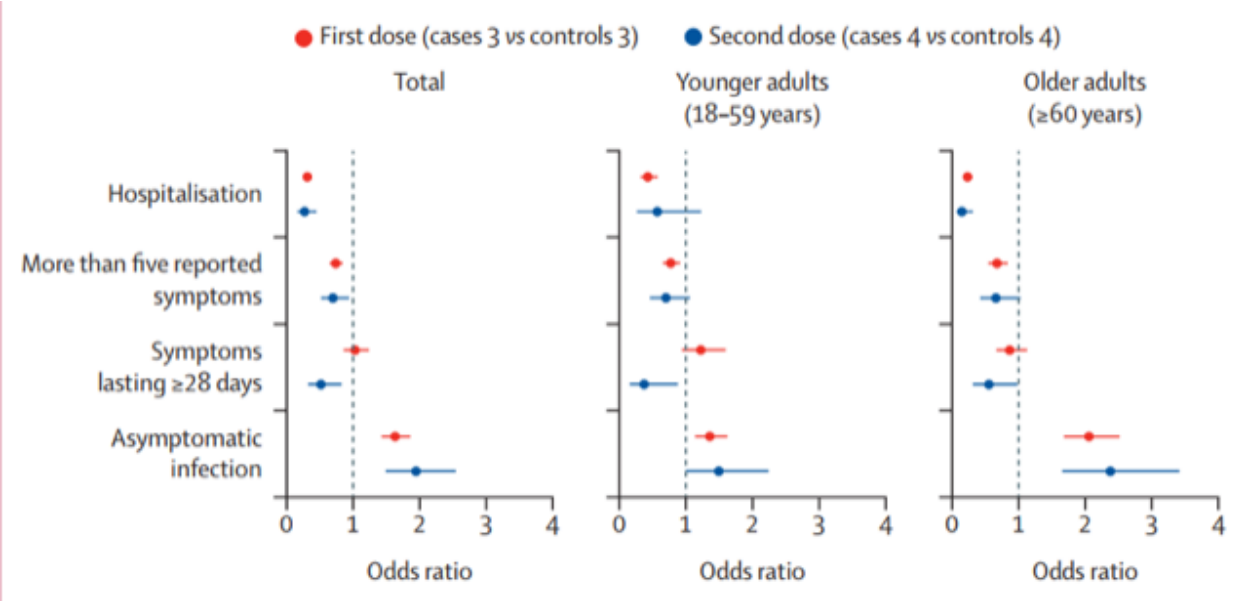


Comment: This study demonstrated increasing the interval up to 45 weeks results in increased antibody titers after the second dose, offering flexibility in current vaccination schedules. A third dose at an extended interval after the second dose resulted in still further increase in antibody titers, mitigating concerns that antibodies raised against the AZ vector would limit repeated use of the vaccine. If booster vaccinations against SARS-CoV-2 will be recommended, perhaps to counter waning immunity or to augment protection against emerging variants, is not yet known. Here, the investigators show that a third dose of AZ is well tolerated and significantly boosts antibody titers above those measured after the second dose to the level associated with 80% vaccine efficacy, or higher, after two vaccine doses [medRxiv 2021; published online June 24. https://doi.org/10.1101/ 2021.06.21.21258528]. Higher titer neutralizing antibodies against alpha, beta, and delta variants of SARS-CoV-2 were induced 28 days after a third dose vaccination than after the second dose. Spike-specific T-cell responses were boosted after a third dose of AZ vaccine and were similar in magnitude to the responses measured after two doses. The discussion on a third dose and boosting immune response reminds me of the hepatitis B vaccine guidance: vaccine at 0, 1, and 6 months. The first two doses prime the immune system and the dose at 6 months provides a significant boost providing better protection and duration.

Risk Factors and Disease Profile of Post-Vaccination SARS-CoV-2 Infection in UK Users of the COVID Symptom Study App: A Prospective, Community-Based, Nested, Case-Control Study
Lancet Infect Dis published online September 1, 2021
doi.org/10.1016/S1473-3099(21)00460-6
This is a complicated prospective, community-based, nested, case-control study using self-reported data

(e.g., on demographics, geographical location, health risk factors, and COVID-19 test results, symptoms, and vaccinations) from UK-based, adult (≥18 years) users of the COVID Symptom Study mobile phone app. For the risk factor analysis, cases had received a first or second dose of a COVID-19 vaccine between Dec 8, 2020, and July 4, 2021; had either a positive COVID-19 test at least 14 days after their first vaccination (but before their second; cases 1) or a positive test at least 7 days after their second vaccination (cases 2); and had no positive test before vaccination. Two control groups were selected (who also had not tested positive for SARS-CoV-2 before vaccination): users reporting a negative test at least 14 days after their first vaccination but before their second (controls 1) and users reporting a negative test at least 7 days after their second vaccination (controls 2). Controls 1 and controls 2 were matched (1:1) with cases 1 and cases 2, respectively, by the date of the post-vaccination test, health-care worker status, and sex. In the disease profile analysis, they sub-selected participants from cases 1 and cases 2 who had used the app for at least 14 consecutive days after testing positive for SARS-CoV-2 (cases 3 and cases 4, respectively). Controls 3 and controls 4 were unvaccinated participants reporting a positive SARS-CoV-2 test who had used the app for at least 14 consecutive days after the test and were matched (1:1) with cases 3 and 4, respectively, by the date of the positive test, health-care worker status, sex, body-mass index (BMI), and age. They used univariate logistic regression models (adjusted for age, BMI, and sex) to analyze the associations between risk factors and postvaccination infection, and the associations of individual symptoms, overall disease duration, and disease severity with vaccination status.

The investigators present data on 6030 and 2370 community-based adults in the UK with test-confirmed SARS-CoV-2 infection after their first or second COVID-19 vaccinations, respectively, with Pfizer, AZ, or Moderna. Participants were included if they tested positive for SARS-CoV-2 at least 14 days after their first vaccination or at least 7 days after their second vaccination when immunity had developed and infection was unlikely to be due to exposure around the time of vaccination (e.g., when travelling to the vaccination center). They found that the odds of having symptoms for 28 days or more after post-vaccination infection were approximately halved by having two vaccine doses.

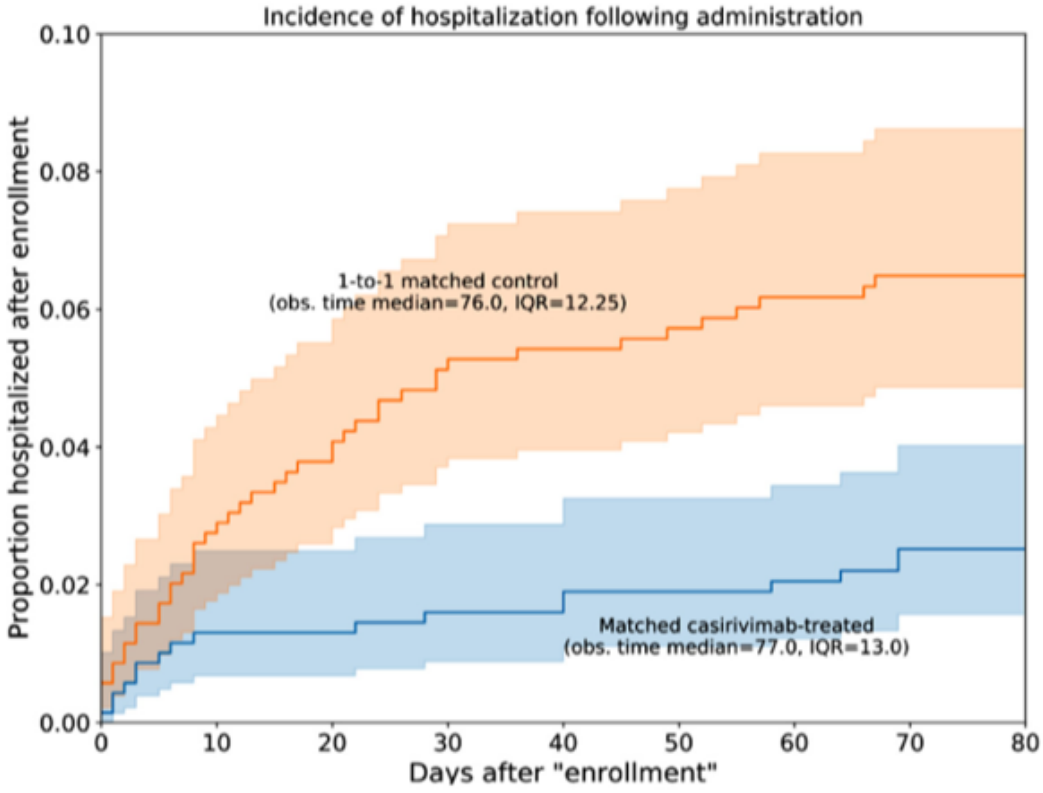


Comment: This result suggests that the risk of long COVID is reduced in individuals who are fully vaccinated. This answers an important question on the risk of long Covid in breakthrough infections and

is another reason to be fully vaccinated. Although they used data from a large population of individuals reporting on a mobile phone app, the sample contained disproportionately more women than men and underrepresented individuals in more deprived areas. Furthermore, they were unable to analyze the impact of ethnicity due to the low number of participants who provided this information. Additionally, the data were self-reported; recording of comorbidities, test results, and vaccination status might not have been completely accurate.

Casirivimab-Imdevimab Treatment is Associated with Reduced Rates of Hospitalization Among High-Risk Patients with Mild to Moderate Coronavirus Disease-19
EClinMed published online August 20, 2021
doi.org/10.1016/j.eclinm.2021.101102
This is a retrospective cohort study of 696 patients who received casirivimab-imdevimab between December 4, 2020 and April 9, 2021 was compared to a propensity-matched control of 696 untreated patients with mild to moderate COVID-19 at Mayo Clinic sites in Arizona, Florida, Minnesota, and Wisconsin. Primary outcome was rate of hospitalization at days 14, 21 and 28 after infusion.

The median age of the antibody-treated cohort was 63 years; 45.5% were 65 years old; 51.4% were female. High-risk characteristics were hypertension (52.4%), body mass index 35 (31.0%), diabetes mellitus (24.6%), chronic lung disease (22.1%), chronic renal disease (11.4%), congestive heart failure (6.6%), and compromised immune function (6.7%). Compared to the propensity matched untreated control, patients who received casirivimab-imdevimab had significantly lower all-cause hospitalization rates at day 14 (1.3% vs 3.3%; Absolute Difference: 2.0%; 95% confidence interval (CI): 0.53.7%), day 21 (1.3% vs 4.2%; Absolute Difference: 2.9%; 95% CI: 1.24.7%), and day 28 (1.6% vs 4.8%; Absolute Difference: 3.2%; 95% CI: 1.45.1%).



Comment: This retrospective study shows that casirivimab-imdevimab treatment of mild to moderate COVID-19 was associated with a statistically significant decrease in the rate of all-cause hospitalization during the first 28 days after infusion. The 1.6% rate of hospitalization at day 28 in our study was comparable to the data from the initial clinical trial that compared casirivimab-imdevimab with placebo. [N Engl J Med 2021;384(3):238-51] This was an observational cohort study, and does not provide the scientific rigor of an RCT, however, to overcome this, propensity score matching was performed to identify a cohort of untreated patients that were matched based on demographic characteristics, medical comorbidities, and risk profiles. This study focused on the combination of casirivimab-imdevimab and did not include patients who received bamlanivimab monotherapy or its combination with etesevimab. Recent study also demonstrated efficacy of monoclonal antibodies in post exposure prophylaxis. Due to emergence of certain variants, casirivimab-imdevimab has become the preferred monoclonal.