Good morning

Lots to share today. Under COVID-19 Updates, first updated survey on vaccine hesitancy and what may motivate the unvaccinated to get vaccinated. Next the FDA has expanded the EUA for Casirivimab and Imdevimab (REGEN-COV). The FDA also revised the EUA for baricitinib (JAK inhibitor) now authorizing baricitinib "alone" for the treatment of COVID-19 in hospitalized. Prior EUA was with RDV.

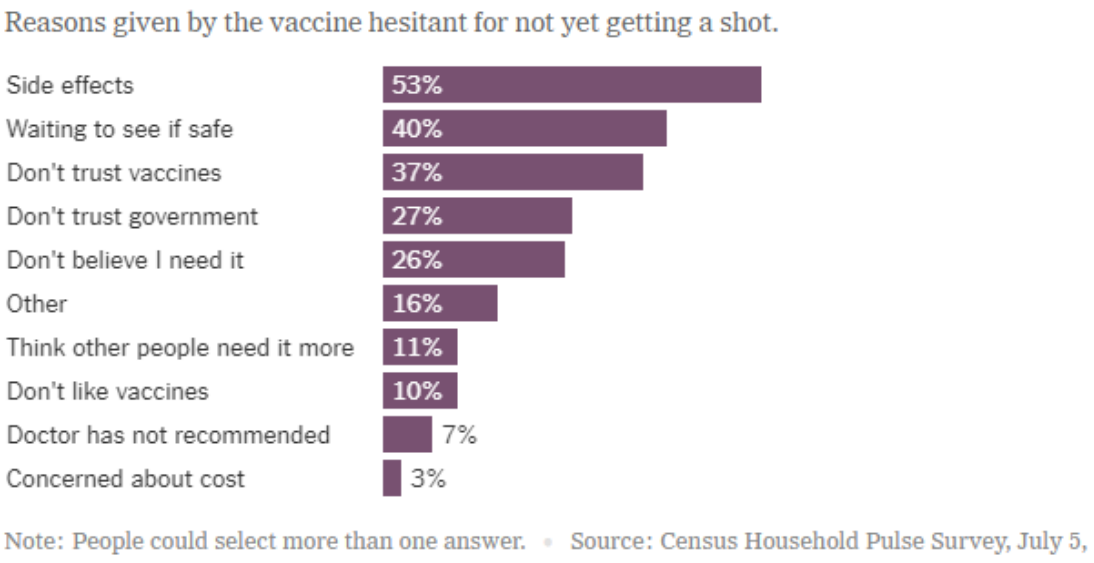
Under Journal Review I start with the outbreak on Cape Cod which in part drove a change in CDC policy around masking. I provide an expanded comment section on this article to help put it into perspective. Next an important article on the virological kinetics of Delta vaccine breakthroughs. Last a census bureau's survey of U.S. households. They estimated the prevalence of vaccine hesitancy across states and nationally and assessed the predictors of vaccine hesitancy and vaccine rejection. This ties in with the survey reviewed under Covid-19 News.

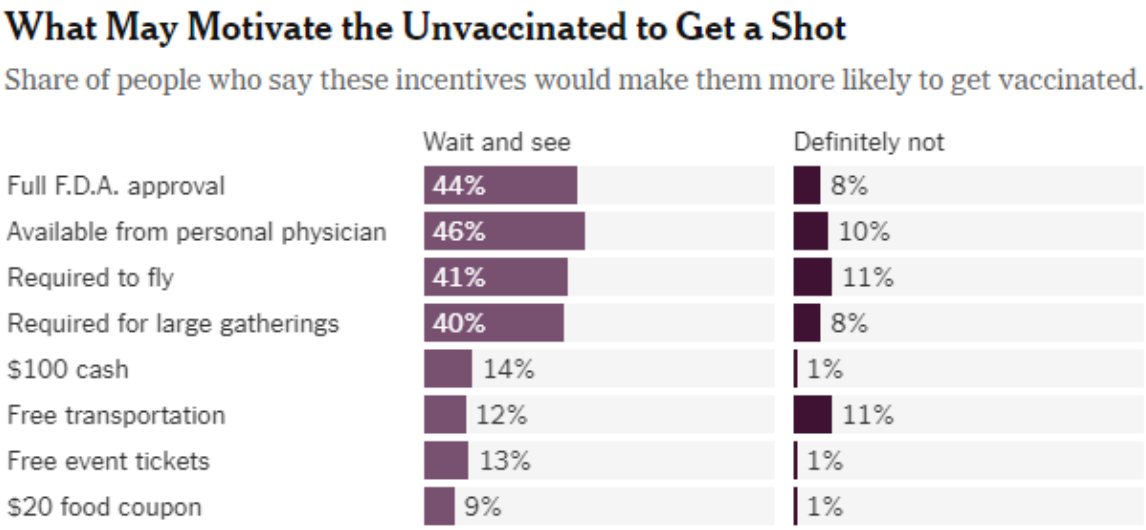
I know SARS-CoV-2 infections are increasing in most locations which has added to our stress and burnout. I hope all of you remain safe and healthy as we weather this surge of the unvaccinated.

Ed

COVID-19 News

Vaccine Hesitancy





Comment: A few things come through in this updated survey: Side effects and full FDA approval matter. The good news is an uptick in vaccinations in the last few weeks. Hopefully FDA will act soon – appears September or October. See article below Clin Infect Dis article under Journal Review.

FDA Expands Authorization Use of Casirivimab and Imdevimab (REGEN-COV)
The authorization now includes post-exposure prophylaxis in people at high risk for progression to severe COVID-19, who are not fully vaccinated or are not expected to mount an adequate response to vaccination and have been exposed to a SARS-CoV-2 infected individual, or who are at high risk of exposure to an infected individual because of infection occurring in the same institutional setting (such as in nursing homes or prisons). In those who require repeat dosing for ongoing exposure, REGEN-COV can also now be administered monthly. This new indication in people aged 12 and older is in addition to the previously granted authorization to treat non-hospitalized patients. REGEN-COV is not a substitute for vaccination against COVID-19 and is not authorized for pre-exposure prophylaxis to prevent COVID-19.

A pivotal Phase 3 trial jointly run with the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), assessed REGEN-COV for post-exposure prophylaxis of COVID-19 in household contacts of individuals infected with SARS-CoV-2 (index case). REGEN-COV was found to:

- Reduce the risk of symptomatic infections by 81% in those who were not infected when they entered the trial ($p<0.0001$).
    - There were 1,505 participants (753 REGEN-COV, 752 placebo) who were not infected (seronegative with a negative PCR test) when they entered the trial.
    - In a post-hoc analysis in the subgroup of participants who met the criteria for high risk for progression to severe COVID-19 (570 REGEN-COV, 567 placebo), there was a 76% risk reduction in COVID-19 with REGEN-COV treatment compared to placebo ($p<0.0001$).

- Reduced the risk of symptomatic infections by 62% in a broader group of asymptomatic participants, regardless of infection status, based on a post-hoc analysis ($p<0.0001$).

- There were 2,378 participants who were asymptomatic when they entered the trial, regardless of serology (1,201 REGEN-COV, 1,177 placebo).

Limitations of Authorized Use (Treatment):

- REGEN-COV is not authorized for use in patients:
  - who are hospitalized due to COVID-19, OR
  - who require oxygen therapy due to COVID-19, OR
  - who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity

- Monoclonal antibodies, such as REGEN-COV, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high-flow oxygen or mechanical ventilation

Post-Exposure Prophylaxis:

REGEN-COV is authorized in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications) **and**
  - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC) **or**
  - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of COVID-19 infection in other individuals in the same institutional setting (for example, nursing homes, prisons)

Comment: Post-exposure prophylaxis with REGEN-COV is not a substitute for vaccination against COVID-19. REGEN-COV is not authorized for pre-exposure prophylaxis for prevention of COVID-19.

FDA Authorizes Baricitinib Alone as Treatment for COVID-19
July 28, 2021
The FDA revised the EUA for baricitinib (JAK inhibitor) now authorizing baricitinib alone for the treatment of COVID-19 in hospitalized adults and pediatric patients two years of age or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). Under the revised EUA, baricitinib is no longer required to be administered with remdesivir. Baricitinib is not yet FDA-approved as a treatment for COVID-19.

The change was based on a randomized, double-blind, placebo-controlled clinical trial (COV-BARRIER, NCT04421027) of hospitalized adults with confirmed SARS-CoV-2 infection compared to treatment with baricitinib 4mg once daily (n=764) with placebo (n=761). Patients could remain on background standard of care (SOC), as defined per local guidelines, including antimalarials, antivirals, corticosteroids, and/or azithromycin. The most frequently used therapies were corticosteroids (79% of patients, mostly dexamethasone) and/or remdesivir (19% of patients). They found that patients on baricitinib were less

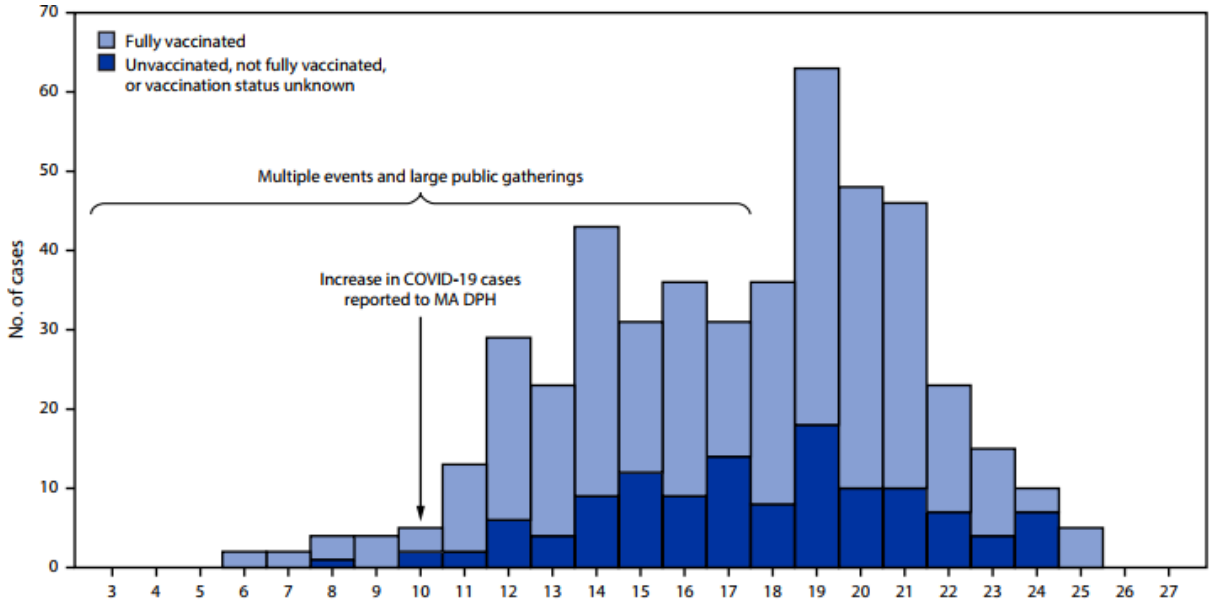
likely to progress to MV or death (OR=0.85;95% CI, 0.67-1.08) [did not reach statistical significance], but addition of baricitinib to SOC was associated with a 39% reduction for death at day 28.

Comment: Although the EUA now says alone, most patients were on steroids.

Journal Review

Outbreak of SARS-CoV-2 Infections, Including COVID-19 Vaccine Breakthrough Infections, Associated with Large Public Gatherings — Barnstable County, Massachusetts, July 2021
MMWR published online July 30, 2021

- 469 cases linked to multiple summer events and large summer gatherings in a small town, 346 (74%) occurred in fully vaccinated people, and almost 80% of those cases were symptomatic There were only five hospitalizations, four among fully vaccinated people, and no deaths.
- Of 133 cases with sequence information available, 89% were from the Delta variant.
- The authors compared RT-PCR cycle threshold (Ct) values in 127 vaccinated people with breakthrough cases to 84 unvaccinated people or those with unknown vaccination status and found them to be comparable (median 22.77 and 21.54, respectively).
- They described "multiple summer events and large public gatherings" from July 3 to 17, where those with COVID-19 reported "attending densely packed indoor and outdoor events at venues that included bars, restaurants, guest houses, and rental homes." The events attracted thousands of tourists from across the United States.
- On July 3, MA DPH had reported a 14-day average COVID-19 incidence of zero cases per 100,000 persons per day in residents of the town in Barnstable County; by July 17, the 14-day average incidence increased to 177 cases per 100,000 persons per day in residents of the town
- Among persons with breakthrough infection, 274 (79%) reported signs or symptoms, with the most common being cough, headache, sore throat, myalgia, and fever.



Comment: This is one of the key studies that contributed to the revised CDC guidance on masking. This was a unique event and may not reflect real world experience. See the key points in report:

- As population-level vaccination coverage increases, vaccinated persons are likely to represent a larger proportion of COVID-19 cases.
- Asymptomatic breakthrough infections might be underrepresented because of detection bias.
- Demographics of cases likely reflect those of attendees at the public gatherings, as events were marketed to adult male participants; further study is underway to identify other population characteristics among cases, such as additional demographic characteristics and underlying health conditions including immunocompromising conditions – this is a key weakness of the publication at present.
- This is not a controlled study. This is a report from a period of time when over 60,000 men descended on a resort town to pack themselves into poorly ventilated bars and clubs every day for several days. Virtually no one was wearing a face mask.
- The assay used in this investigation was not validated to provide quantitative results, however, there was no significant difference between the Ct values of samples collected from breakthrough cases and the other cases. This might mean that the viral load of vaccinated and unvaccinated persons infected with SARS-CoV-2 is also similar. However, microbiological studies are required to confirm these findings such as culturing for viable virus capable in transmitting virus. Ct values can also vary based on how samples were collected, stored, and transported, and because of that variation, there's no universally accepted conversion between a given Ct value and a specific amount of virus present in the sample.
- Bottom line: This was a unique set of circumstances and does not resemble real world experience. If you are vaccinated you are still well-protected, especially if you are among other vaccinated people. The focus should be that vaccines remain effective and highly protective against severe disease and death even against the Delta variant. Yes, masks can protect transmission to those most at risk, but the message has created confusion. What we need is a consistent and clear message. Vaccination should be the priority.

See next article.

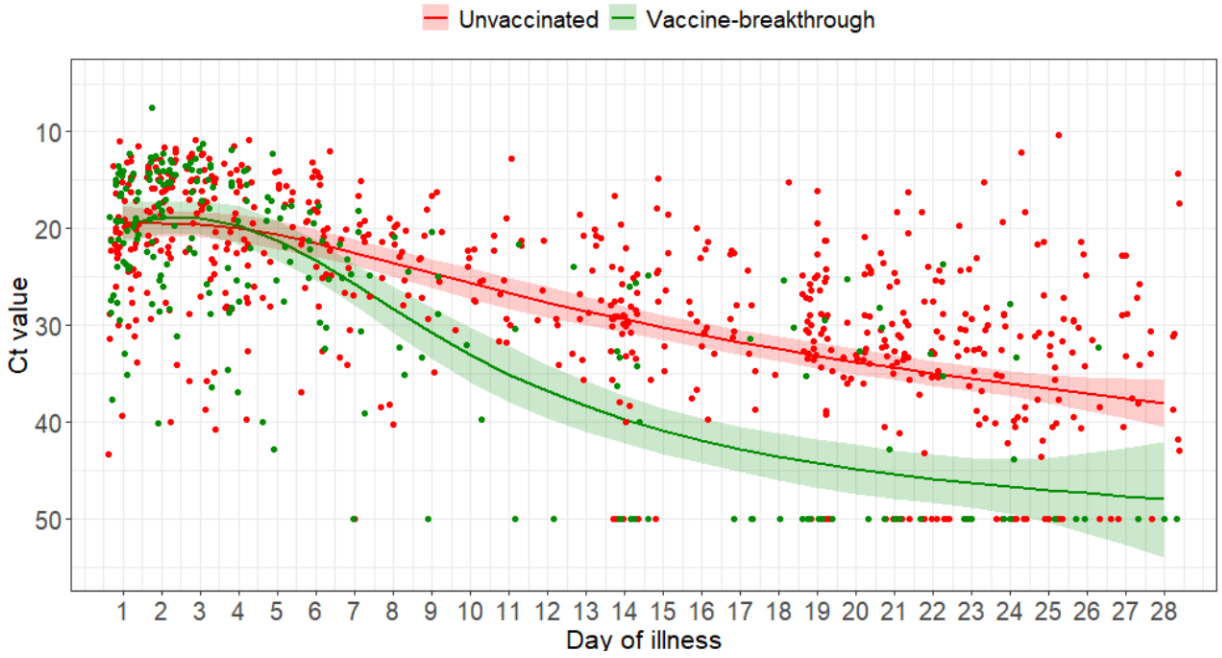
Virological and Serological Kinetics of SARS-CoV-2 Delta Variant Vaccine-Breakthrough Infections: A Multi-Center Cohort Study

medRxiv published online July 28, 2021
Article provide by Josh Septimus
doi.org/10.1101/2021.07.28.21261295

The investigators conducted a multi-center retrospective cohort study of patients in Singapore who had received a licensed mRNA vaccine and been admitted to hospital with Delta SARS-CoV-2 infection. They compared the clinical features, virological, and serological kinetics (anti-nucleocapsid, anti-spike, and surrogate virus neutralization titers) between fully vaccinated and unvaccinated individuals. Vaccines used were mRNA vaccines, Pfizer and Moderna. As of 19 July 2021, 6,837,200 vaccine doses had been administered and ~2,792,430 individuals (47% of the total population) had completed the vaccination course. In May 2021, Delta became the dominant circulating variant based on local sequencing data. Vaccine-breakthrough infection was defined as PCR-confirmed COVID-19 with symptom onset or first positive PCR (whichever was earlier) ≥14 days following a second dose of Pfizer or Moderna vaccine. Incomplete vaccination was defined as receipt of one dose of these vaccines ≥14 days prior to symptom onset or first positive PCR.

Of 218 individuals with Delta infection, 84 had received an mRNA vaccine of which 71 were fully vaccinated, 130 were unvaccinated, and 4 received a non-mRNA vaccine. Despite significantly older age in the vaccine breakthrough group, the odds of severe COVID-19 requiring oxygen supplementation

was significantly lower following vaccination (adjusted odds ratio 0.07 95%CI: 0.015-0.335, p=0.001). PCR cycle threshold (Ct) values were similar between both vaccinated and unvaccinated groups at diagnosis, but viral loads decreased faster in vaccinated individuals. Early, robust boosting of anti-spike protein antibodies was observed in vaccinated patients; however, these titers were significantly lower against Delta as compared with the wildtype vaccine strain.



Comment: The mRNA vaccines are highly effective at preventing both symptomatic and severe COVID-19 associated with Alpha infection. Vaccination is associated with faster decline in viral RNA load and a robust serological response with Delta. While initial Ct values were similar; the effect of vaccination with a more rapid decline in viral load (and hence shorter duration of viral shedding) has implications on transmissibility and infection control policy. They did not evaluate vaccine efficacy against asymptomatic infection. Ct values are only a surrogate measure of viral load and shedding. They did not evaluate viability of shed virus via viral culture. Vaccination remains the most important strategy for control of COVID-19 pandemic.

Deliberation, Dissent, and Distrust: Understanding Distinct Drivers of COVID-19 Vaccine Hesitancy in the United States

Clin Infect Dis published online July 16, 2021

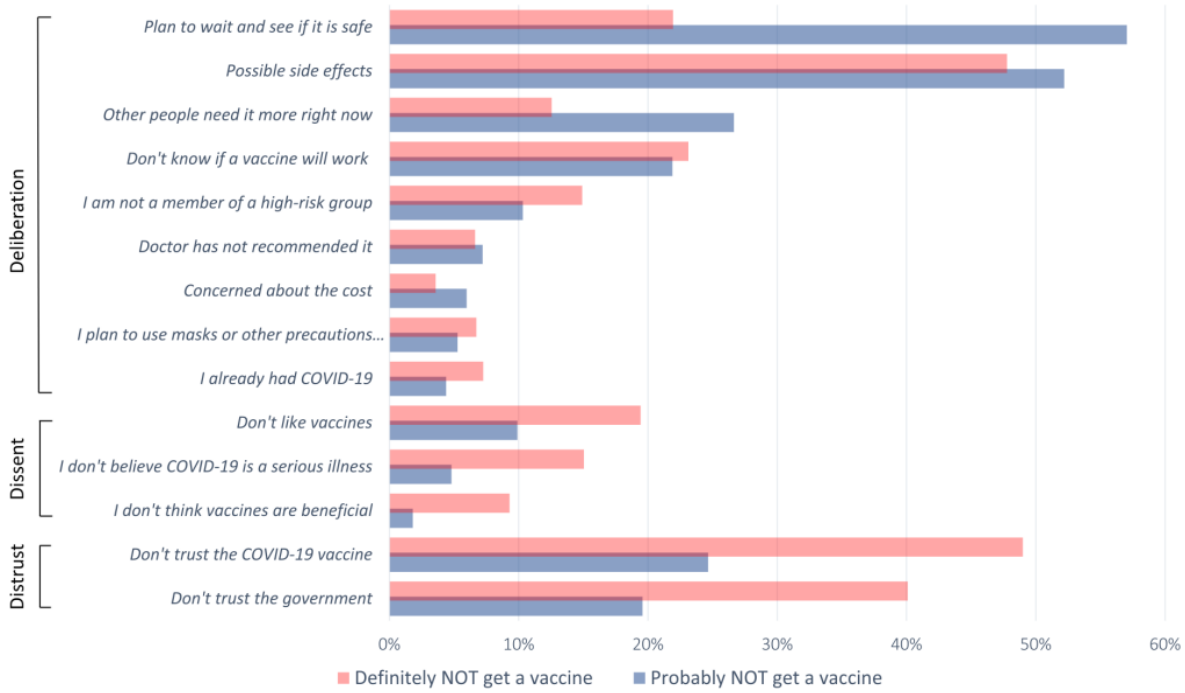
doi/10.1093/cid/ciab633/6323151

In this study, the authors analyzed data from the U.S. Census Bureau's Household Pulse Survey, a biweekly cross-sectional survey of U.S. households. They estimated the prevalence of vaccine hesitancy across states and nationally and assessed the predictors of vaccine hesitancy and vaccine rejection. Additionally, they examined the underlying reasons for vaccine hesitancy, grouped into thematic categories.

A total of 459,235 participants were surveyed from January 6 to March 29, 2021. While vaccine uptake increased from 7.7 to 47 percent, vaccine hesitancy rates remained relatively fixed: overall, 10.2 percent reported that they would probably not get a vaccine, and 8.2 percent would definitely not get a vaccine. Income, education, and state political leaning strongly predicted vaccine hesitancy. However, while both

female sex and Black race were factors predicting hesitancy, among those who were hesitant, these same characteristics predicted vaccine reluctance rather than rejection. Those who expressed reluctance invoked mostly “deliberative” reasons while those who rejected the vaccine were also likely to invoke reasons of “dissent” and “distrust”.

Figure 3. Reasons for Vaccine Hesitancy



Comment: Vaccine hesitancy comprises a sizable proportion of the population and is large enough to threaten achieving herd immunity. Distinct subgroups of hesitancy have distinctive sociodemographic associations as well as cognitive and affective predilections. The response rate was lower than traditional surveys. This analysis was a snapshot in time during a period of rapid change. Whether these associations remain relevant in the coming weeks and months is unclear, but the same reasons for vaccine hesitancy are reflected in the recent survey described above under Covid-19 News. Multipronged public health solutions are needed to target interventions and optimize vaccine uptake.