Good morning everyone. I hope your week is going well.

Today under COVID-19 News I report on the preliminary Pfizer report on children ages 12-16 and efficacy of their vaccine. Next is the controversial WHO report on the origin of SARS-CoV-2. The final selection is Lilly's announcement from the randomized, double-blind, placebo-controlled BLAZE-1 Phase 3 study, demonstrating bamlanivimab (LY-CoV555) 700 mg and etesevimab (LY-CoV016) 1400 mg together significantly reduced COVID-19 related hospitalizations and deaths.

Under Journal Review I start with sensitivity of infectious SARS-CoV-2 B.1.1.7 and B.1.351 variants to neutralizing antibodies. The next article explores escape of SARS-CoV-2 501Y.V2 from neutralization by convalescent plasma. The third article is a powerful report from CDC on interim estimates of vaccine effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines in preventing SARS-CoV-2 infection among HCPs, first responders, and other essential and frontline workers. The last article is another in the series I have been reviewing on the "long-haulers".

I hope everyone has a great day.

Ed

COVID-19 News

Pfizer Vaccine Ages 12-16
Preliminary report shows 100% efficacy for children ages 12-16. Pfizer will file report with the FDA.

Comment: This is welcomed news which may facilitate children ages 12-16 being able to be vaccinated soon.

Origins of the SARS-CoV-2 Virus
WHO March 30, 2021
The most probable origin of the SARS-CoV-2 virus was an intermediary animal host, states a joint report from the World Health Organization and experts from China and 10 other countries. They said intermediary hosts were "likely to very likely" to have transmitted the virus to humans. They report similar viruses have been found in bats and pangolins, but since these animals rarely come into close contact with humans, the authorities say there may have been amplifying by other animal hosts. They suggest for instance, farm animals. [no proof] The joint committee also considered other possible sources: direct zoonotic transmission (possible to likely), cold/food chain products (possible), and laboratory origin (extremely unlikely).

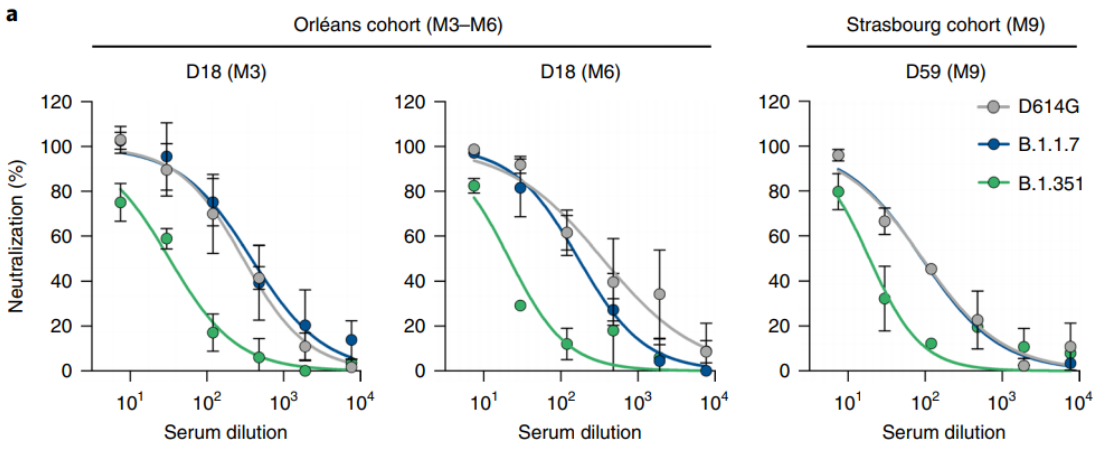
Comment: The expert team offered further recommendations for additional research, but it is unclear whether China, which has hindered the WHO investigation, will cooperate. The U.S. and 13 other governments released a statement Tuesday expressing "shared concerns" that the WHO study "was significantly delayed and lacked access to complete, original data and samples. Dr. Robert Redfield, the former chief of the CDC, said last week that "I still think the most likely etiology of this pathogen in Wuhan was from a laboratory." Dr. Redfield added that virus transfer to a lab worker is not unusual in such research. Although he was short on details the WHO team concluded although a laboratory leak is the least likely hypothesis, they held open that this requires further investigation.

Bamlanivimab and Etesevimab Together Reduced Hospitalizations and Death in Phase 3 Trial for Early COVID-19
Lilly press release
Lilly announced new data from the randomized, double-blind, placebo-controlled BLAZE-1 Phase 3 study, demonstrating bamlanivimab (LY-CoV555) 700 mg and etesevimab (LY-CoV016) 1400 mg together significantly reduced COVID-19 related hospitalizations and deaths ("events") in high-risk patients recently diagnosed with COVID-19. This new Phase 3 cohort of BLAZE-1 included 769 high-risk patients, aged 12 and older with mild to moderate COVID-19 (therapy: n=511; placebo: n=258). There were four events in patients taking bamlanivimab with etesevimab and 15 events in patients taking placebo, representing an 87 percent risk reduction (p<0.0001).

Comment: This announcement is good news along with similar report on Regeneron. These monoclonals are preventing progression, hospitalization, and deaths.

Journal Review

Sensitivity of Infectious SARS-CoV-2 B.1.1.7 and B.1.351 Variants to Neutralizing Antibodies
Nat Med published online March 26, 2021
doi.org/10.1038/s41591-021-01318-5



Researchers at Institute Pasteur in Paris isolated infectious B117, the variant first identified in the United Kingdom, and B1351, first discovered in South Africa, from the nasal swabs of symptomatic COVID-19 patients. Like some other emerging variants, B117 and B1351 are more infectious than previously dominant varieties, leading to fears that they could evade natural and vaccine-induced immunity.

The researchers tested the variants' susceptibility to SARS-CoV-2 antibodies from serum samples from 58 patients infected with the previously circulating D614G reference strain (pseudovirus) and 19 people who had received two doses of the Pfizer mRNA COVID-19 vaccine within the previous 6 weeks. Antibodies from patients who had recovered from the virus within the previous 9 months neutralized B117 as well as D614G. Samples collected after 9 months, however, showed a sixfold reduction in antibody concentrations, with 40% of the samples unable to neutralize B1351. Similarly, antibodies from people fully vaccinated against COVID-19 were also able to defend against B117 but less so against B1351, compared with D614G. While antibody levels rose overall after the second shot, anti-B1351

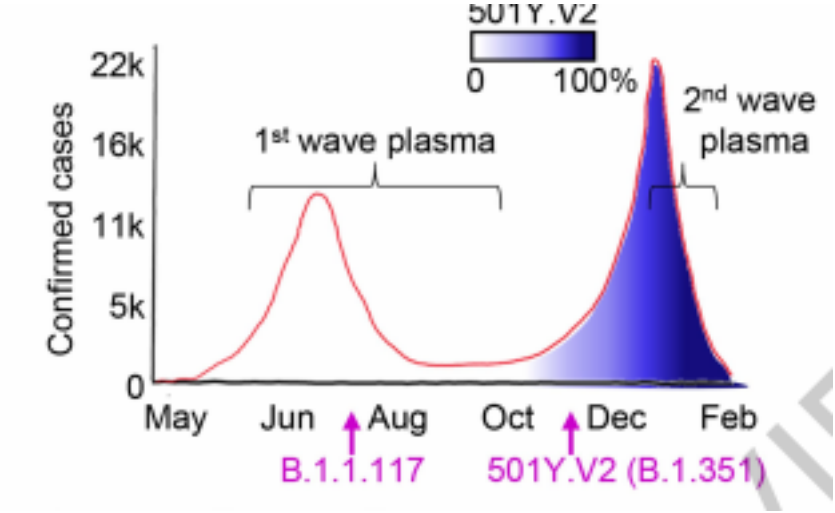
antibodies remained 14 times lower than those against D614G. SARS-CoV-2 antibodies were rarely observed in nasal swabs obtained from vaccinees.

Comment: The authors noted that previous studies have shown that the Moderna mRNA COVID-19 vaccine also prevented infection against virus variants but that its efficacy is 5 to 10 times lower against B1351, compared with D614G. This study also highlights the importance of the second dose of the Pfizer vaccine, which was associated with a strong increase of neutralizing antibody titers and a widening of strain cross-reactive antibody responses.

Escape of SARS-CoV-2 501Y.V2 from Neutralization by Convalescent Plasma
Nature published online March 29, 2021
doi.org/10.1038/s41586-021-03471-w
This study was led by researchers at the University of KwaZulu-Natal in Durban, South Africa, and just published today in *Nature*, used plasma from hospitalized adult COVID-19 patients to compare antibody responses to live B1351 virus and a reference SARS-CoV-2 strain from the first and second pandemic waves 1 month after symptom onset in July 2020 and January 2021, respectively. B1351 is now the dominant strain in South Africa.

None of the 14 first-wave plasma donors were infected with B1351, which had infected all six second-wave donors. Antibodies from first-wave plasma donors neutralized the SARS-CoV-2 reference strain but had poor efficacy against B1351, with a 15.1-fold fall in neutralization compared with antibodies from second-wave donors.

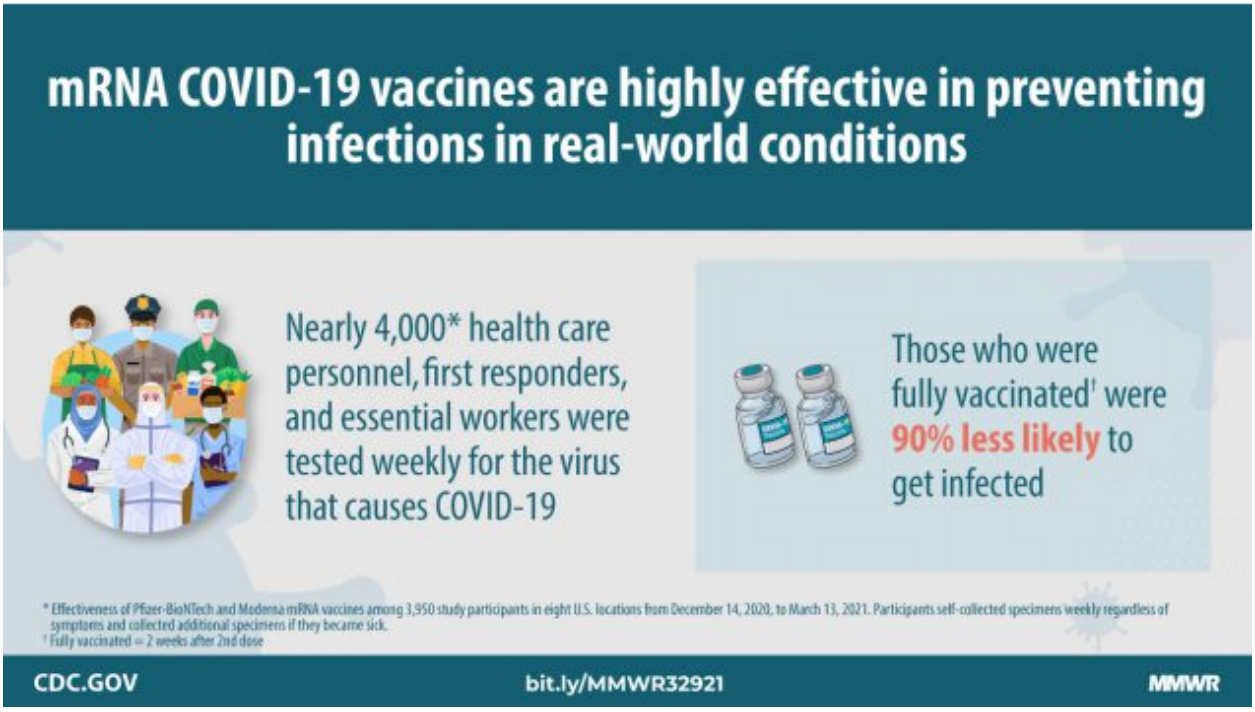
While antibodies from second-wave plasma donors effectively defended against both B1351 and the reference strain, they were 2.3-fold less effective against the reference strain than antibodies from first-wave donors. None of the second-wave donors had been infected with the reference strain during the first wave.



Comment: The observed effective neutralization of first wave virus by [B1351] infection elicited plasma provides preliminary evidence that vaccines based on [variants of concern] sequences could retain activity against other circulating SARS-CoV-2 lineages.

Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers — Eight U.S. Locations, December 2020–March 2021
MMWR published online March 29, 2021
Using prospective cohorts of health care personnel, first responders, and other essential and frontline workers in eight U.S. locations during December 14, 2020–March 13, 2021, CDC routinely tested for SARS-CoV-2 infections every week regardless of symptom status and at the onset of symptoms consistent with COVID-19–associated illness. Among 3,950 participants with no previous laboratory documentation of SARS-CoV-2 infection, 2,479 (62.8%) received both recommended mRNA doses and 477 (12.1%) received only one dose of mRNA vaccine.

Among unvaccinated participants, 1.38 SARS-CoV-2 infections were confirmed by PCR per 1,000 person-days. In contrast, among fully immunized (≥14 days after second dose) persons, 0.04 infections per 1,000 person-days were reported, and among partially immunized (≥14 days after first dose and before second dose) persons, 0.19 infections per 1,000 person days were reported. Estimated mRNA vaccine effectiveness for prevention of infection, adjusted for study site, was 90% for full immunization and 80% for partial immunization. Of interest, 58% of infections were detected before people had symptoms, but just 10% of infected people remained asymptomatic. These findings indicate that authorized mRNA COVID-19 vaccines are effective for preventing SARS-CoV-2 infection, regardless of symptom status, among working-age adults in real-world conditions.



Comment: These interim vaccine effectiveness findings for both Pfizer and Moderna's mRNA vaccines in real-world conditions complement and expand upon the vaccine effectiveness estimates from other recent studies and demonstrate the importance of vaccination in controlling the pandemic. There are a few states that have seen an increase in cases mostly in younger people, but deaths have dropped 29% yet the headlines continue to emphasize the negative. On the same day that this MMWR report was published Dr. Walensky said we have "so much reason for hope" and then turned around and said she

was scared saying she had “the recurring feeling of impending doom”. I have a great deal of respect for Dr. Walensky, but I found her comments to be inappropriate based on the current science and impact of vaccination. Yes, we still need to be cautious, but there is real optimism given the effectiveness of vaccines. There does seem to be an uncoupling between new cases and deaths. We need strategies to encourage everyone to be vaccinated who are eligible. 1 in 4 are still reluctant to be vaccinated. Take this number and add to the ~22% of children <16 who are not eligible for vaccine yet and you can see it may take longer to achieve the “herd immunity”. [we may be closer than we think-at least I hope!]

Persistent Neurologic Symptoms and Cognitive Dysfunction in Non-Hospitalized Covid-19 “Long Haulers”

Ann Cl Trans Neurol published online March 23, 2021
doi:10.1002/acn3.51350

This is a prospective study of the first 100 consecutive patients (50 SARS-CoV-2 laboratory-positive (SARS-CoV-2^+) and 50 laboratory-negative (SARS-CoV-2^-) individuals) presenting to the Neuro-Covid-19 clinic between May and November 2020. Due to early pandemic testing limitations, patients were included if they met IDSA’s symptoms of Covid-19, were never hospitalized for pneumonia or hypoxemia, and had neurologic symptoms lasting over 6 weeks. They recorded the frequency of neurologic symptoms and analyzed patient-reported quality of life measures and standardized cognitive assessments. Long COVID-19 was defined as symptoms persisting for more than 6 weeks, with the consensus that most patients fully recover from COVID-19 in 4 to 6 weeks.

Mean age was 43.2 ± 11.3 years, 70% were female, and 48% were evaluated in televisits. The most frequent comorbidities were depression/anxiety (42%) and autoimmune disease (16%). The main neurologic manifestations were: cognitive dysfunction “brain fog” (81%), headache (68%), numbness/tingling (60%), dysgeusia (59%), anosmia (55%), and myalgias (55%), with only anosmia being more frequent in SARS-CoV-2^+ than SARS-CoV-2^- patients (37/50 [74%] vs. 18/50 [36%]; $p < 0.001$). Moreover, 85% also experienced fatigue. There was no correlation between time from disease onset and subjective impression of recovery. Both groups exhibited impaired quality of life in cognitive and fatigue domains. SARS-CoV-2^+ patients performed worse in attention and working memory cognitive tasks compared to a demographic-matched US population (T-score 41.5 [37, 48.25] and 43 [37.5, 48.75], respectively; both $p < 0.01$).

Comment: Further studies are needed to elucidate the pathogenesis of SARS-CoV-2 in the nervous system. Whereas hypoxemia, systemic inflammation, coagulopathy, and neuroinvasion have been implicated in hospitalized Covid-19 patients who develop encephalopathy, it appears more likely that post-infectious, autoimmune mechanisms may be at play in “long Covid.” The long-term impact of “long Covid” on quality of life and potential return to normalcy, through lost productivity and lingering cognitive dysfunction, may be substantial as the pandemic continues to escalate. Future longitudinal studies are needed to evaluate the cognitive effect of SARS-CoV-2 infection on non-hospitalized individuals, as they comprise the majority of Covid-19 patients and may significantly impact workforce productivity. The idea that the long-haul symptoms might be an autoimmune response, maybe similar to some other post-infection syndromes. Anecdotal reports recently suggest vaccinating “long-haulers” may improve symptoms.