Most of us think of Memorial Day weekend as a holiday weekend that is officially the start of summer. However, this is the day we pay respect to all those who didn't come home. It is a day of solemn contemplation over the cost of freedom we all now enjoy. I also think of all of our colleagues who lost their lives fighting Covid-19, a different kind of war.

In today's Briefing under COVID-19 News, I start with a topic I have tried to avoid, but given the news of the past week I felt the need to share a few thoughts about the ongoing investigation of the origins of SARS-CoV-2. Next the FDA stated they are against antibody testing for SARS-CoV-2 to determine immunity or protection from COVID-19, especially among those who are vaccinated. Lastly, FDA has just issued an EUA for the investigational monoclonal antibody therapy sotrovimab which retains activity against most variants.

Under Journal Review I start with two articles that demonstrate persistent cellular immunity against SARS-CoV-2 for at least a year. Last is the peer reviewed article on the efficacy and safety of Pfizer vaccine in adolescents ages 12-15.

Have a safe and meaningful weekend. Remember the Daily Briefing will be published on Tuesday and Friday starting next week.

Ed

COVID-19 News

Biden Orders Intelligence Inquiry into Origins of Virus

VII Comment: I have been trying to avoid this story, but it has become front and center. Last Monday the WSJ reported on an illness in November 2019 involving 3 scientists associated with the Wuhan lab. In January 2020, international media began reporting about a serious virus spreading in Wuhan identified as a unique beta-coronavirus genetically like SARS. At that time, it was reasonable to think that this coronavirus most likely came from an animal reservoir much like SARS and MERS. The other theory was a potential leak from the Wuhan lab, China's only biosafety level 4 lab. In February, the South China University posted a paper later withdrawn suggesting the virus may have originated in the Wuhan lab. Also in February 2020, the Lancet published a statement condemning "conspiracy theories". Donald Trump also came out suggesting the virus came from the Wuhan lab, but he was accused of trying to distract from the administration's response to the pandemic. In January 2021 before Trump left office, they disclosed that they had evidence of researchers inside the Wuhan lab who became ill in November 2019. [reported in the WSJ article last Monday] In addition, to date no one has found a natural origin for SARS-CoV-2. Taken together it is now impossible to discount the possibility of a lab leak. Unfortunately, when the WHO visited Wuhan, they were not given access to vital information, so they left with little new information. Even the WHO director-general Tedreos Ghebreyesus called for further investigation. Earlier this month in Science, a group of investigators noted that "theories of accidental release from a lab and zoonotic spillover both remain viable." Most virologists still lean towards the theory that animals spread Covid-19 outside of a lab, but at least the possibility of a lab leak should be explored.

I am personally not sure of the origin of SARS-CoV-2 to date, but what I do know is the origin of SARS-CoV-2 is critical to our understanding how to prevent the next pandemic. We need transparency, honesty, and a strong and independent WHO.

Antibody Testing Not Useful to Prove Immunity Among Vaccinated: FDA
May 19, 2021
The FDA in a Safety Communication stated they are against antibody testing for SARS-CoV-2 to determine immunity or protection from COVID-19, especially among those who are vaccinated.
The FDA is reminding the public of the limitations of COVID-19 antibody, or serology, testing and providing additional recommendations about the use of antibody tests in people who received a COVID-19 vaccination. Antibody tests can play an important role in identifying individuals who may have been exposed to the SARS-CoV-2 virus and may have developed an adaptive immune response. However, antibody tests should not be used at this time to determine immunity or protection against COVID-19 at any time, and especially after a person has received a COVID-19 vaccination. The agency explained that antibodies from prior SARS-CoV-2 infection [nucleocapsid] differ from antibodies induced by the COVID-19 vaccines. [anti-spike] Therefore, testing for prior infection antibodies would not identify people with antibody protection from immunization. SARS-CoV-2 antibody tests should be ordered only by healthcare professionals who are familiar with the use and limitations of the test, the agency notes.

Comment: This is an important reminder to clinicians and supports prior IDSA guidance.

FDA Issues EUA for Monoclonal Antibody Therapy Sotrovimab for Treatment of Mild-to-Moderate COVID-19
May 27, 2021
FDA has issued an EUA for the investigational monoclonal antibody therapy sotrovimab [also known as VIR-7831 and GSK4182136] for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kilograms) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death.

According to the FDA, the data supporting the EUA for sotrovimab are based on an interim analysis from a Phase I/II/III randomized, double-blind, placebo-controlled clinical trial in 583 non-hospitalized adults with mild-to-moderate COVID-19 symptoms and a positive SARS-CoV-2 test result. Of these patients, 291 received sotrovimab and 292 received a placebo within five days of onset of COVID-19 symptoms. The primary endpoint was progression of COVID-19 (defined as hospitalization for greater than 24 hours for acute management of any illness or death from any cause) through day 29. Hospitalization or death occurred in 21 (7%) patients who received placebo compared to 3 (1%) patients treated with sotrovimab, indicating an 85% reduction. Potential side effects of sotrovimab include anaphylaxis and infusion-related reactions, rash, and diarrhea.

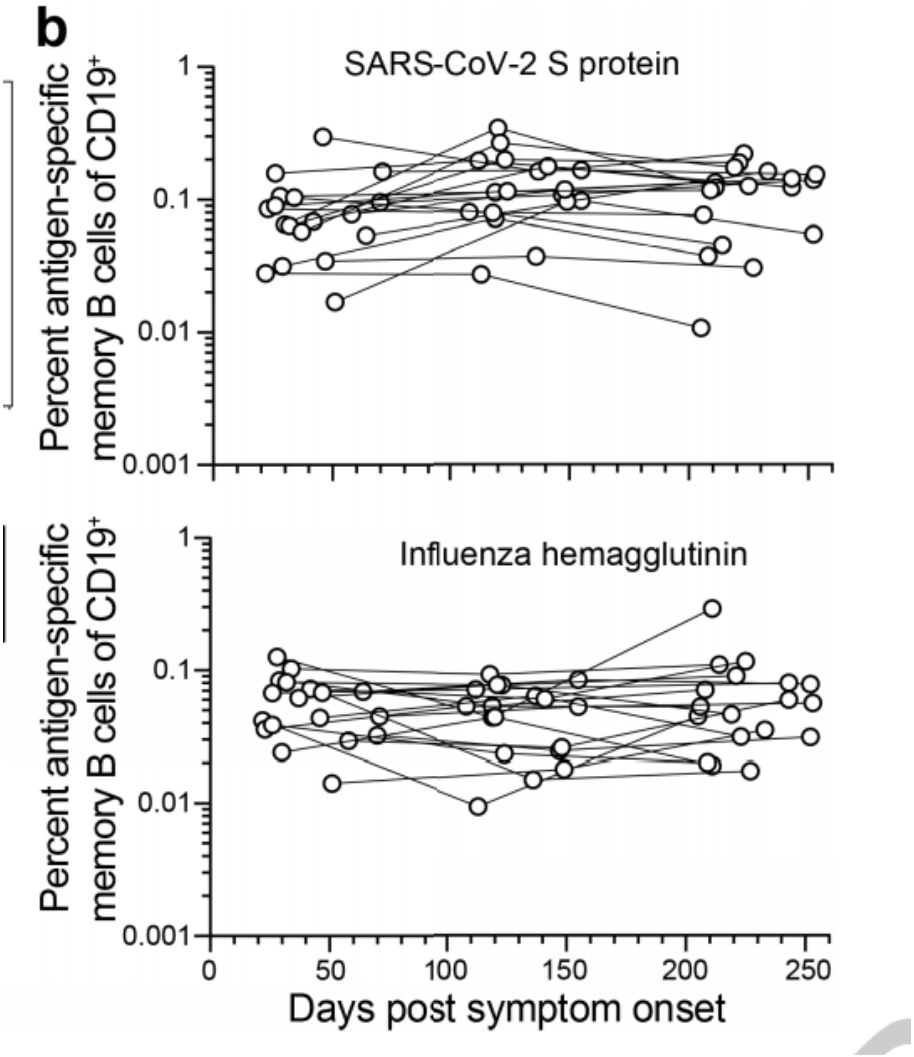
Comment: We now have 3 choices for monoclonals. This monoclonal in laboratory tests neutralized six important variants including UK, India, and South African strains. This monoclonal provides another option to keep high-risk patients with early Covid-19 out of the hospital.

Journal Review

SARS-CoV-2 Infection Induces Long-Lived Bone Marrow Plasma Cells in Humans

Nature published online May 24, 2021
doi.org/10.1038/s41586-021- 03647-4
Researchers took bone marrow samples from 18 out of 77 participants who were already signed up to give blood samples at three-month intervals starting about a month after initial infection. The bone marrow samples were taken between seven and eight months after initial COVID infection. Five of the 18 participants then gave second bone marrow samples four months later. The team compared those samples with bone marrow taken from 11 people who had never been diagnosed with COVID-19.

While antibody levels in the blood of people who had previous infections did drop quickly in the first few months before mostly leveling off, some antibodies were detectable even 11 months after infection. Researchers also found antibody-producing cells specifically targeting SARS-CoV-2 in 15 of the bone marrow samples. The cells were also found in all five of the follow-up samples given four months later.



Comment: Last fall, I reviewed reports that antibodies against SARS-CoV-2 wane quickly after infection. This was interpreted that immunity was not long-lived. It is normal for antibody levels to go down after acute infection, but they do not go down to zero; they plateau. In this publication the investigators found antibody-producing cells in people 11 months after first symptoms. This provides strong evidence

for long-lasting immunity. Consistently, circulating resting memory B cells directed against the S protein were detected in the convalescent individuals. Overall, they show that SARS-CoV-2 infection induces a robust antigen-specific, long-lived humeral immune response. It is not clear if those who have more severe COVID-19 infection would have the same long-lasting protection. See below.

Persistent Cellular Immunity to SARS-CoV-2 Infection
bioRxiv posted online 2021
doi.org/10.1101/2020.12.08.416636
To gain further understanding of the immune response in recovered individuals the investigators measured T cell responses in paired samples obtained an average of 1.3 and 6.1 months after infection from 41 individuals. The data indicate that recovered individuals show persistent polyfunctional SARS-CoV-2 antigen specific memory that could contribute to rapid recall responses. In addition, recovered individuals show enduring immune alterations in relative numbers of CD4+ and CD8+ T cells, expression of activation/exhaustion markers, and cell division. In fact, memory B cells continue to mature and strengthen for at least 12 months after the initial infection.

Comment: These 2 articles are very reassuring. Cellular B cell response has been demonstrated in several studies for up to a year. This helps in determining when and if a booster vaccine will be needed. All vaccines seem to protect from severe disease and death against variants identified to date.

Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents
N Engl J Med published online May 27, 2021
DOI: 10.1056/NEJMoa2107456
This is a placebo-controlled, observer-blinded trial randomly assigned participants in a 1:1 ratio to receive two injections, 21 days apart, of 30 µg of BNT162b2 (Pfizer) or placebo. Noninferiority of the immune response to BNT162b2 in 12-to-15-year-old participants as compared with that in 16-to-25-year-old participants was an immunogenicity objective. Safety (reactogenicity and adverse events) and efficacy against Covid-19; onset, ≥7 days after dose 2 in the 12-to-15-year-old cohort were assessed. Overall, 2260 adolescents 12 to 15 years of age received injections; 1131 received BNT162b2, and 1129 received placebo. The geometric mean ratio of SARS-CoV-2 50% neutralizing titers after dose 2 in 12-to-15-year-old participants relative to 16-to-25-year-old participants was 1.76 (95% confidence interval [CI], 1.47 to 2.10), which met the noninferiority criterion. Among participants without evidence of previous SARS-CoV-2 infection, no Covid-19 cases with an onset of 7 or more days after dose 2 were noted among BNT162b2 recipients, and 16 cases occurred among placebo recipients. The observed vaccine efficacy was 100% (95% CI, 75.3 to 100). BNT162b2 had a favorable safety and side-effect profile, with mainly transient mild-to-moderate reactogenicity (predominantly injection-site pain [in 79 to 86% of participants], fatigue [in 60 to 66%], and headache [in 55 to 65%]); there were no vaccine related serious adverse events and few overall severe adverse events.

Table 2. SARS-CoV-2 Serum Neutralization Assay Results 1 Month after Dose 2 of BNT162b2 among Participants without Evidence of Infection.*

Age Group	No. of Participants	Geometric Mean 50% Neutralizing Titer (95% CI)†	Geometric Mean Ratio (95% CI), 12 to 15 Yr vs. 16 to 25 Yr‡
12–15 yr	190	1239.5 (1095.5–1402.5)	1.76 (1.47–2.10)
16–25 yr	170	705.1 (621.4–800.2)	—

Comment: This article confirms what has been reported: Pfizer vaccine is safe and efficacious in 12-15-year-olds.