Good evening

This issue of the Briefing starts with Covid-19 News. First the FDA EUA for the AZ MCA. Next a sobering update on deaths in US from Covid-19 as we approach 800,000.

Under Journal Review a very nice comment from colleague Sanjat Kanjilal on the article from December 10th on Omicron variant of SARS-CoV-2 harboring a unique insertion mutation of putative viral or human genomic origin. Next outcomes of pregnancy comparing vaccinated with unvaccinated patients. Next a possible explanation why obesity is associated with more severe disease. The last article is an important article on the emotional impact of Covid-19 on HCPs.

Have a wonderful week.

Ed

FDA EUA Tixagevimab with Cilgavimab (AZ) MCA
FDA has issued an EUA for Evusheld (tixagevimab with cilgavimab) for the pre-exposure prophylaxis of COVID-19 in certain individuals 12 years of age and older weighing at least 40kg.

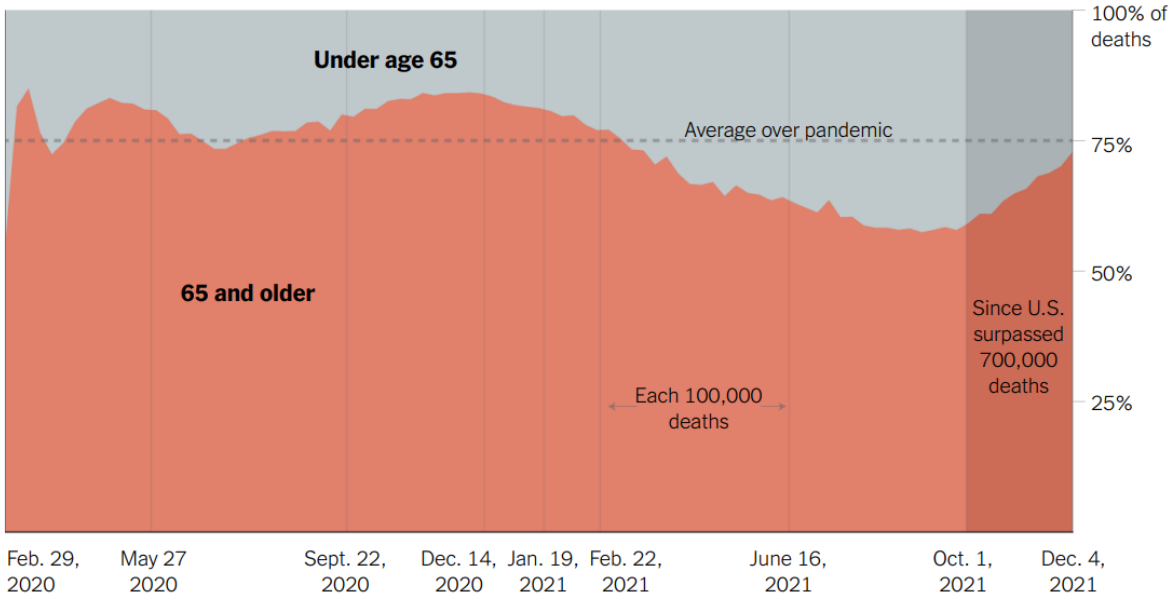
Evusheld is a combination of 2 long-acting monoclonal antibodies designed to bind to distinct sites on the SARS-CoV-2 spike protein. The product is authorized for individuals who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2, and:

- Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination; or
- For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).

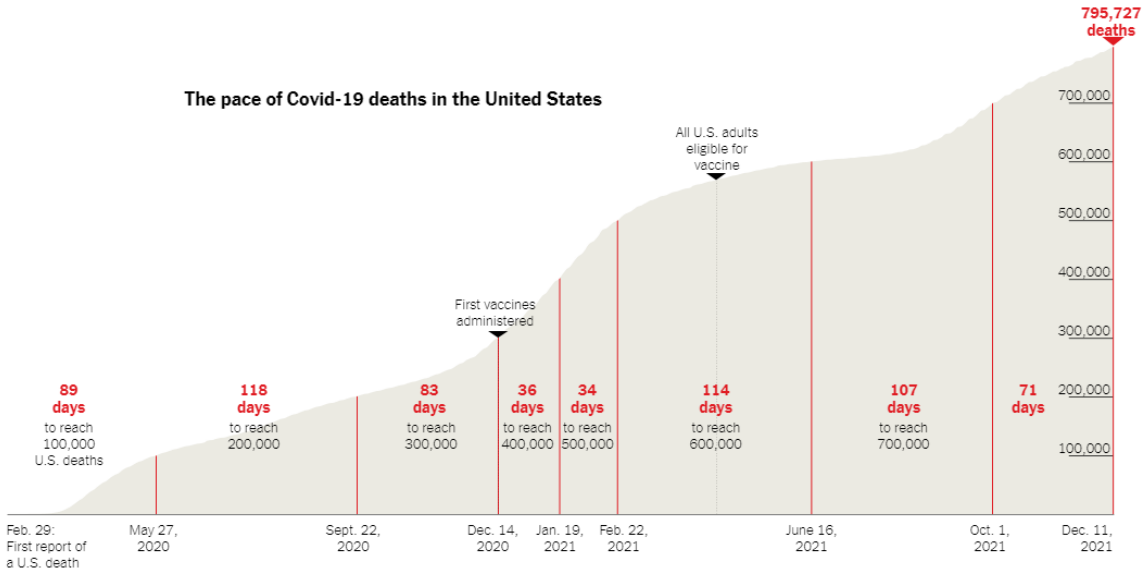
For pre-exposure prophylaxis, the authorized dose of Evusheld is 150mg of tixagevimab and 150mg of cilgavimab administered as 2 separate consecutive intramuscular injections. Evusheld is not authorized for use in individuals for the treatment of COVID-19, or for postexposure prophylaxis of COVID-19.

Comment: Pre-exposure prophylaxis with Evusheld is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended. In individuals who have received a COVID-19 vaccine, Evusheld should be administered at least 2 weeks after vaccination.

US COVID-19 Deaths
The United States is just about to surpass 800,000 deaths from SARS-CoV-2. People 65 and older make up about three-quarters of the nation's coronavirus death toll or about 600,000 of the nearly 800,000 who have died have been 65 or older. One in 100 older Americans has died from the virus. For people younger than 65, that ratio is closer to 1 in 1,400.



Source: Centers for Disease Control and Prevention ▪ Note: The number of deaths reported by age for the most recent weeks is provisional because of delays in reporting.



Source: New York Times database of reports from state and local health agencies

Comment: Covid-19 has become the third leading cause of death among Americans 65 and older, after heart disease and cancer. It is responsible for about 13 percent of all deaths in that age group since the beginning of 2020, more than diabetes, accidents, Alzheimer's disease, or dementia. Older Americans are now the most vaccinated age group in the country: 87 percent of people 65 and older have been "fully" vaccinated. The most recent available CDC data on deaths among vaccinated people, which does not include those in the past 10 weeks, shows breakthrough deaths to be a small fraction of the nation's toll. But there is no doubt that breakthrough infections in older people have resulted in some deaths.

Journal Review

Omicron Variant of SARS-CoV-2 Harbors a Unique Insertion Mutation of Putative Viral or Human Genomic Origin

OSF published online December 2021 **Comment by Sanjat Kanjilal**

Sanjat Kanjilal (a colleague from Boston) commented on the conclusions made by the authors of the OSF paper from Cambridge, MA in the December 10th Briefing. He believes the data analytics are not based on solid evidence. The methods themselves are ok, but the conclusion they drew is much more in the realm of speculation than evidence.

The authors assert on the basis of just 3 amino acids (not even nucleotides, which are a more robust marker for recombination), that SARS-CoV-2 has undergone recombination with endemic CoVs and/or HIV. Dr. Kanjilal is on a discussion thread with a group of highly accomplished virologists, epidemiologists, immunologists, and diagnosticians and this claim was thoroughly criticized. The reason is that the smaller the window of analysis (3 amino acids is trivially small), the more likely you'll see evidence for that sequence in other life forms. It does not mean recombination happened.

He goes on to say, to be fair, the potential for recombination exists for SARS-CoV-2, but there is no evidence of that in the data presented in this paper. Other experienced groups are also looking into this topic and he is looking forward to seeing more robust analyses being published in the near future.

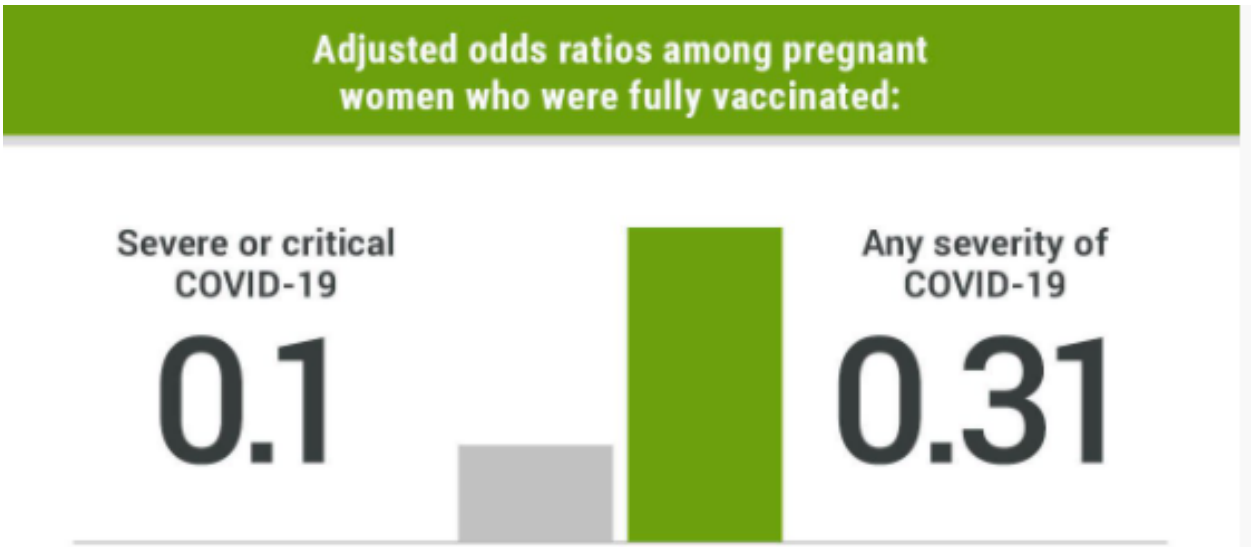
Maternal Outcomes After Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Vaccinated Compared with Unvaccinated Pregnant Patients

Obstet Gynecol published online October 13, 2021

DOI: 10.1097/AOG.0000000000004621

This is a retrospective cohort study of all active pregnancies in the Ochsner Health System between June 15, 2021, and August 20, 2021. Patients were compared according to vaccination status. The vaccinated group included patients who were fully vaccinated 2 weeks before the start of the study period. Vaccine status was confirmed objectively using LINKS, a statewide immunization reporting network that can be accessed only by health care professionals. Race was included in our demographic comparison to identify potential disparities in vaccine access and acceptance. The primary outcome was development of severe or critical COVID-19. Severe illness is defined as SpO_2 less than 94% on room air, PaO_2/FiO_2 ratio less than 300 mm Hg, respiratory rate greater than 30 breaths per minute, or lung infiltrates greater than 50%. Critical illness is defined as respiratory failure, septic shock, or multiple organ failure. Secondary outcomes included SARS-CoV-2 infection, supplemental oxygen requirement, intensive care unit admission, and use of adjunctive medical therapy. A secondary analysis of the cohort was performed, including those who were partially vaccinated.

This study confirms an association between SARS-CoV-2 vaccination and lower odds of severe or critical COVID-19 and COVID-19 of any severity in pregnant patients during the Delta variant-predominant fourth surge of SARS-CoV-2. A possible limitation of our study is the lack of data on positive SARS-CoV-2 test results or treatment of SARS-CoV-2 infection performed outside of Ochsner Health. This study also identified a low vaccination rate among pregnant patients (13.2%); unvaccinated status was associated with younger age, current smoking, lower BMI, and race.



Comment: A national effort to improve vaccination acceptance is vital. Obstetricians and gynecologists need to educate vulnerable populations on the potential benefits of the SARS-CoV-2 vaccine in preventing severe or critical illness.

SARS-CoV-2 Infects Human Adipose Tissue and Elicits an Inflammatory Response Consistent with Severe COVID-19

bioRxiv published online October 25, 2021
doi.org/10.1101/2021.10.24.465626

In this report, the investigators demonstrate that human adipose tissue from multiple depots is permissive to SARS-CoV-2 infection and that infection elicits an inflammatory response, including the secretion of known inflammatory mediators of severe COVID-19. They identified two cellular targets of SARS-CoV-2 infection in adipose tissue: mature adipocytes and adipose tissue macrophages. Adipose tissue macrophage infection is largely restricted to a highly inflammatory subpopulation of macrophages, present at baseline, that is further activated in response to SARS-CoV-2 infection. Preadipocytes, while not infected, adopt a proinflammatory phenotype. They further demonstrated that SARS-CoV-2 RNA is detectable in adipocytes in COVID-19 autopsy cases and is associated with an inflammatory infiltrate. Taken together these findings suggest that adipose tissue supports SARS-CoV-2 infection and pathogenic inflammation, and which may explain the link between obesity and severe COVID-19.

Comment: Obesity has long been associated with adverse COVID-19 outcomes in both adults and children, but the underlying mechanism is unknown. The investigators provide histologic evidence of inflammation adjacent to viral signals in adipose tissue in an autopsy sample. Together, this in-depth analysis of adipose susceptibility and inflammatory response to SARS-CoV-2 infection suggests that adipose tissue may serve as a potential reservoir for SARS-CoV-2 and potentiator of systemic and regional inflammation, possibly contributing to severe clinical disease observed in obese individuals with Covid-19. The autopsy studies were limited in number, and they were only able to perform confirmatory ISH (*in situ* hybridization) on epicardium, not in the subcutaneous, omental, or pericardial fat due to limited autopsy tissue availability. All experiments were performed with the WA-01 strain of SARS-CoV-2 and no experiments with its variants were performed, and plaque assays to confirm viral production were not performed.

Morally Injurious Experiences and Emotions of Health Care Professionals During the COVID-19 Pandemic Before Vaccine Availability

JAMA Netw Open published online October 24, 2021
doi:10.1001/jamanetworkopen.2021.36150

HCPs were actively recruited to participate in a survey via sampling via email and social media in 2 phases of 5 weeks each: April 24 to May 30, 2020 (phase 1), and October 24 to November 30, 2020 (phase 2). Overall, 1831 respondents answered demographic questions and assessments for moral injury, intrinsic religiosity, and burnout. Of those, 1344 responded to the open-ended questions. Responses to open-ended questions were coded iteratively and thematically analyzed within the framework of moral injury.

There were 335 individuals (109 [32.6%] aged 35-44 years; 288 [86.0%] women; 294 [87.8%] White) in phase 1 and 1009 individuals (384 [38.1%] aged 35-44 years; 913 [90.5%] women; 945 [93.7%] White) in phase 2. In phase 1, the respondents were predominantly nurses (100 [29.9%]), physicians (78 [23.3%]), advanced practice practitioners (APPs) (70 [20.9%]), and chaplains (55 [16.4%]). In phase 2, the respondents were predominantly nurses (589 [58.4%]), physicians (114 [11.3%]), and APPs (104 [10.3%]). HCPs faced numerous stressors, such as fear of contagion, stigmatization, short-staffing, and inadequate personal protective equipment. The emotions experienced were (1) fear in phase 1, then fatigue in phase 2; (2) isolation and alienation; and (3) betrayal.

Comment: These findings suggest that HCPs experienced “moral injury” during the COVID-19 pandemic and it is real. Leadership must identify and address these concerns to effectively support HCPs as COVID-19 continues to strain staff’s physical, mental, and emotional resources. Delta has only made this worse. This important study should serve as a starting point for organizations to engender and enhance organizational and individual recovery, team building, and trust. Healthcare systems have described as “broken” must be mended through initiatives to create environments that are in touch with the new realities and what will likely be long lasting effects of providing care in the pandemic and beyond.