First, I have a confession, I was wrong! I told many of you I thought vaccinations would be available to anyone over age 16 by mid to late April. Now several states have already announced that they are making vaccines available for all age groups now!

Under COVID-19 News I report on the trials and tribulations of the AstraZeneca vaccine. Next is the IDSA update on monoclonals followed by some changes in distribution of bamlanivimab based on variants.

Under Journal Review I start with a Science Perspective on the challenges of reducing SARS-CoV-2 transmission in person without symptoms. The next article looks at use of ASA and outcomes. The last article is a nice review on pregnancy, postpartum care, and COVID-19 Vaccination in 2021.

I hope everyone has a wonderful day.

Ed

COVID-19 News

AstraZeneca's Covid-19 Vaccine
The U.S. trial involved 32,449 participants aged 18 and over, with roughly 20% aged 65 or over. The interim trial data showed the vaccine, developed in partnership with the University of Oxford, was 80% effective in participants aged 65 and over, a group previous AstraZeneca trials lacked in large numbers and 79% overall. The vaccine was also found to be 100% effective in preventing serious illness and hospitalization across ages and ethnicities. The summary of the U.S. trial didn't break out efficacy against Covid-19 variants. AstraZeneca said that independent U.S. safety monitors ran a specific review of severe blood clotting, or serious thrombotic events, based on the trial data, including a severe condition known as cerebral venous sinus thrombosis, or CVST, that has been reported to be possibly linked to a very small number of deaths in Europe among people who received the vaccine. They found no increased risk of thrombosis among 21,583 participants who received at least one dose of the vaccine, and no cases of CVST. The interim results have not yet been reviewed by independent researchers and the analysis is being submitted for publication.

Comment: AstraZeneca cannot get its act together! NIAID has been informed by the independent data-monitoring board working with AstraZeneca on the U.S. trials that the drug company might have used out-of-date information in its public disclosure of the vaccine's effectiveness. This is the latest in a series of stumbles by AstraZeneca that has little experience in vaccines.

IDSA Updated Guidelines
Among ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel suggests bamlanivimab/etesevimab rather than no bamlanivimab/etesevimab. (Conditional recommendation, low certainty of evidence)

- Patients with mild to moderate COVID-19 who are at high risk of progression to severe disease admitted to the hospital for reasons other than COVID-19 may also receive bamlanivimab/etesevimab.
- For patients at high risk for progression to severe disease, the data are strongest for bamlanivimab/etesevimab. Bamlanivimab monotherapy or casirivimab/imdevimab may have similar clinical benefit, but data are more limited.

Comment: A press release on the phase III trial assessing casirivimab/imdevimab in non-hospitalized patients reported that the independent data monitoring committee found both the 1200 mg and 2,400 mg dose had clear clinical efficacy on reducing the rate of hospitalizations and death. A trial reviewed a few weeks ago in the Briefing suggested dual monoclonal with bamlanivimab/etesevimab may be better than monotherapy with bamlanivimab. (see below)

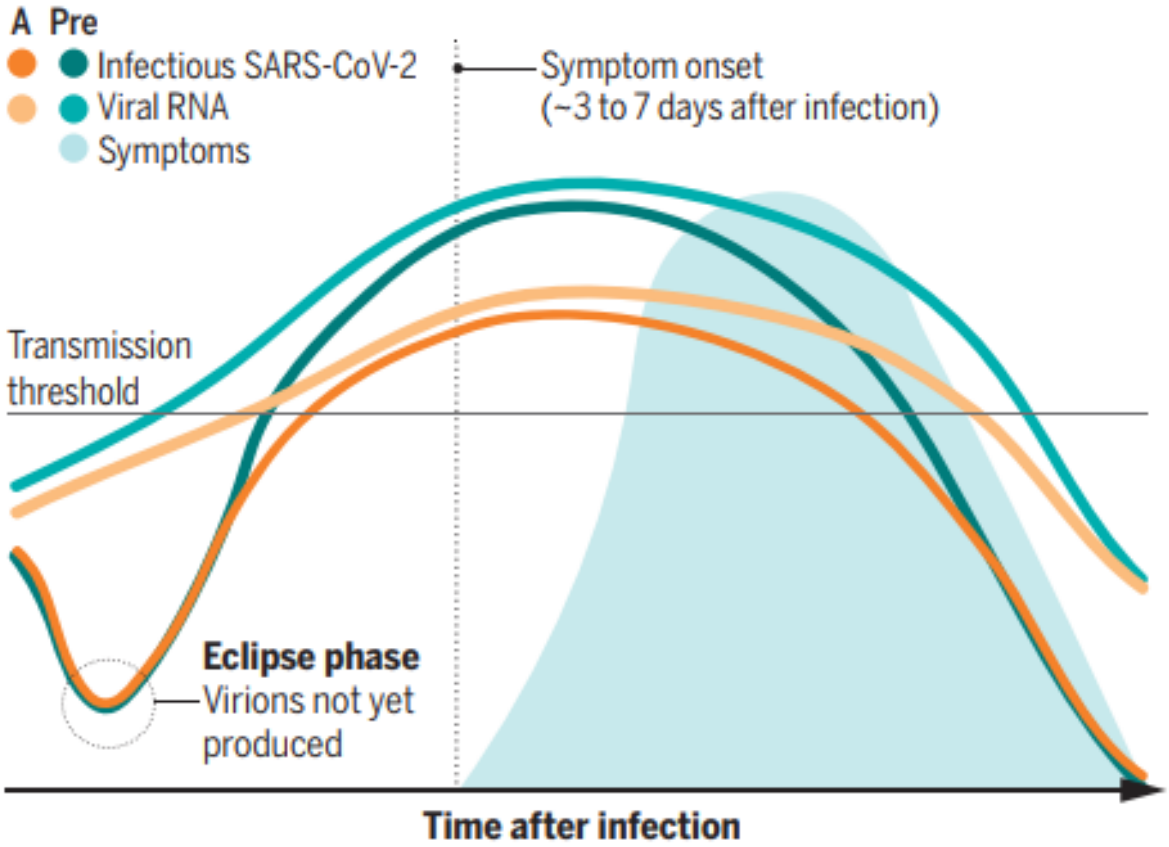
Outpatient Monoclonal Antibody Treatment for COVID-19 Made Available under Emergency Use Authorization: Bamlanivimab
March 10, 2021
The US Government is evaluating recommendations for use of bamlanivimab in regions where the SARS-CoV2 mutation L452R found in B.1.429/B.1.427 lineages (a.k.a. 20C/CAL.20C) is circulating in high numbers given concerns that the clinical activity of bamlanivimab is impacted by this variant. ASPR will limit distribution to these regions of the country by stopping direct ordering for bamlanivimab while evaluations are ongoing.

Currently, this action will only affect the states of California, Arizona, and Nevada. The other two authorized products, bamlanivimab/etesevimab and casirivimab/imdevimab, do not appear to be affected and will continue to be available for direct ordering in these states.

ASPR is working with the CDC, NIH, and FDA on any recommendations for treatment and will continue to work closely with these agencies on surveillance of this and other variants that may impact the use of the monoclonal antibodies authorized under emergency use. We will update our stakeholders with any new recommendations.

Journal Review

SARS-CoV-2 Transmission Without Symptoms
Science published online March 18, 2021
Doi:10.1126/science.abf9569
Even as vaccines are becoming more readily available in the U.S., protecting against the asymptomatic and pre-symptomatic spread of the virus (SARS-CoV-2) that causes COVID-19 is a key to ending the pandemic. In their Perspective the authors make the case that symptomless transmission silently drives viral spread and is key to ending the pandemic. The authors state that from a biological perspective, it would be unlikely that a vaccine that protects well against disease would not protect against infection, but just like the vaccines don't offer a hundred percent protection against symptomatic infection, they are unlikely to be hundred percent in preventing transmission. They also point out that while vaccines reportedly will become widely available in the U.S. by summer, that is not the case in the rest of the world where the pandemic continues unabated. They conclude “until there is widespread implementation of robust surveillance and epidemiological measures that allow us to put out these smokeless fires, the COVID-19 pandemic cannot be fully extinguished."



Comment: This perspective was written before publications on the impact of vaccines on preventing asymptomatic infection. I am more optimistic than the opinions expressed in this Perspective especially as more people are immunized in the US.

Aspirin Use Is Associated with Decreased Mechanical Ventilation, Intensive Care Unit Admission, and In-Hospital Mortality in Hospitalized Patients with Coronavirus Disease 2019
Anesth Analg 2021;132:930–41
DOI: 10.1213/ANE.0000000000005292
Researchers studied roughly 400 U.S. patients admitted with COVID-19 between March and July 2020; about a quarter received aspirin (median dose, 81 mg) in the 7 days before admission or within 24 hours after admission. The primary outcome — need for mechanical ventilation — occurred in 36% of aspirin recipients versus 48% of those who did not receive aspirin. After multivariable adjustment, aspirin use was associated with a 44% reduced risk for mechanical ventilation. It was also associated with significant, similarly reduced risks for ICU admission and in-hospital mortality. Aspirin users did not show increased risk for major bleeding.

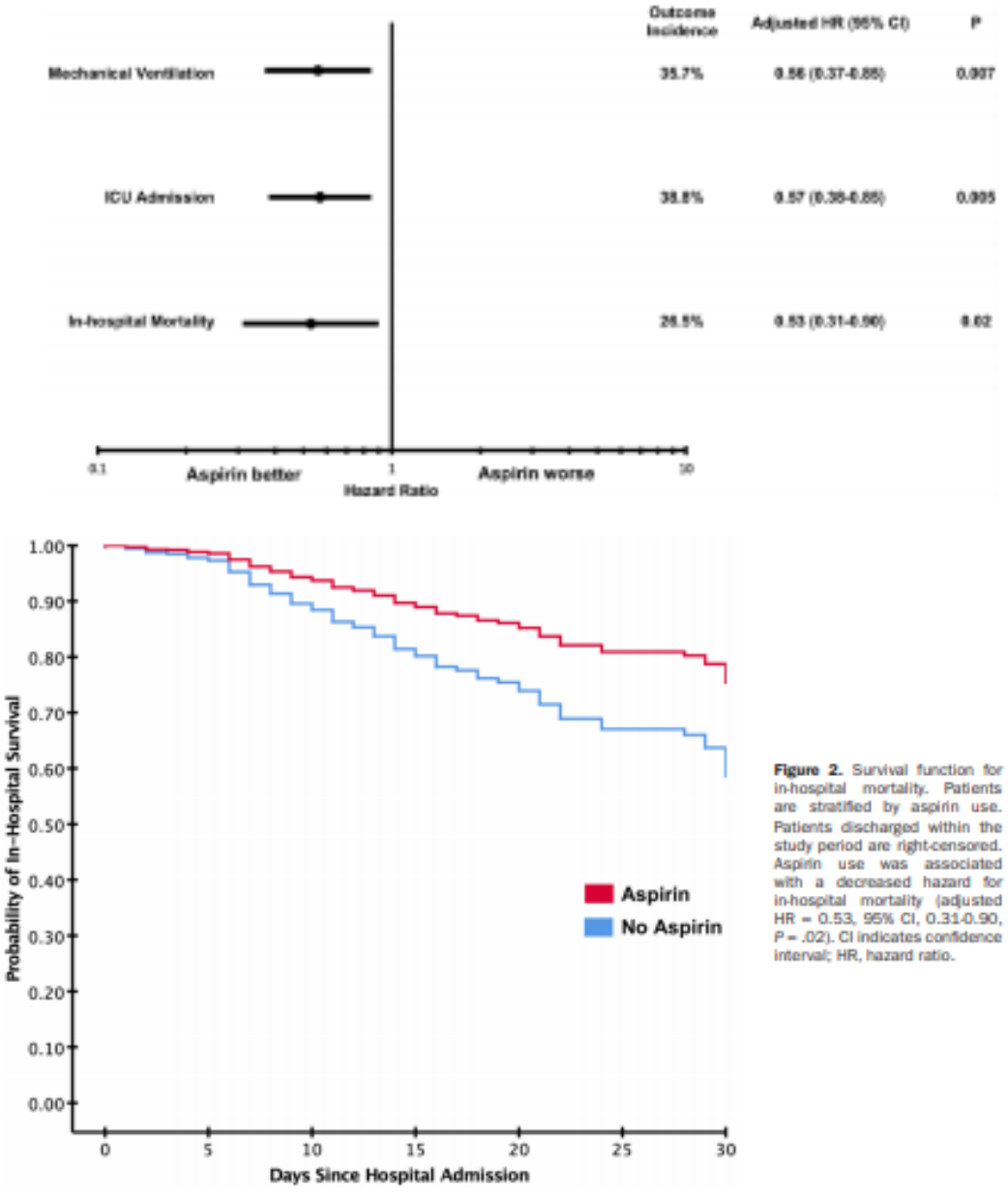


Figure 2. Survival function for in-hospital mortality. Patients are stratified by aspirin use. Patients discharged within the study period are right-censored. Aspirin use was associated with a decreased hazard for in-hospital mortality (adjusted HR = 0.53, 95% CI, 0.31-0.90, *P* = .02). CI indicates confidence interval; HR, hazard ratio.

Comment: The investigators postulated that aspirin can irreversibly inhibit platelet aggregation in the lungs, which could reduce pulmonary microthrombi and subsequent lung injury. Microthrombosis has been well described in autopsies of COVID-19 patients, and excess megakaryocytes have been observed in the heart, lungs, and kidneys of deceased patients. In addition, aspirin's anti-inflammatory properties may also contribute to its lung-protective effects in COVID-19. Aspirin has been shown to decrease the production of interleukin-6 (IL-6), C-reactive protein (CRP), and macrophage colony-stimulating factor in patients with cardiovascular disease, and in COVID-19, these actions could reduce the incidence of cytokine storm. The major limitation of this study is its observational design and modest sample size, which limits its generalizability.

Pregnancy, Postpartum Care, and COVID-19 Vaccination in 2021

JAMA 2021; 325:1099-1100
doi:10.1001/jama.2021.1683

Highlights

- A large study from the CDC provided data suggesting an increased risk of severe complications from COVID-19. Among more than 450,000 symptomatic women of reproductive age with COVID-19 for whom pregnancy status was known, admission to an intensive care unit, invasive ventilation, ECMO, and death were all more likely among pregnant individuals than among nonpregnant women of reproductive age. [MMWR 2020;69(44):1641-1647] NonHispanic Black individuals accounted for a disproportionate number of deaths.
- Several studies of pregnancy outcomes suggest that preterm birth might occur more often among infants born to individuals with COVID- 19, although findings have been inconsistent. In a systematic review, preterm birth was 3 times more common in individuals with COVID-19 than among those uninfected, with rates of 16% vs 6%, respectively. [*BMJ*. 2020;370:m3320]
- Intrauterine transmission of SARS-CoV-2 has been documented but appears to be rare.
- Data regarding mother-to-infant transmission in the postnatal period have been reassuring when appropriate precautions are taken.
- As often occurs with new medications and vaccines, pregnant individuals were excluded from the clinical trials for these vaccines. Data on pregnancy outcomes of the small number of pregnant individuals inadvertently exposed during the clinical trials are not yet available because pregnancies are ongoing.
- The first 2 authorized COVID-19 vaccines use messenger RNA (mRNA) technology. The mRNA is rapidly degraded in the cell cytoplasm. These mRNA vaccines (and other COVID-19 vaccine candidates) do not contain live virus. Thus, CDC, American College of Obstetricians and Gynecologists (ACOG), and the Society for Maternal-Fetal Medicine (SMFM) state that pregnant individuals who meet criteria for receiving COVID-19 vaccine may choose to be vaccinated. Studies to look at effects of vaccination in pregnancy are in progress.
- Data on the effects of COVID-19 vaccines on the breastfed infant are limited. However, CDC, ACOG, and SMFM are all reassuring about initiating or continuing breastfeeding in a recently vaccinated mother, given the benefits of breastfeeding to the infant and what is known about the safety of other vaccines given during lactation.

Table. Recommendations for Pregnant or Lactating Individuals Regarding Use of Pfizer-BioNTech and Moderna COVID-19 Vaccines[a]

Pregnancy	Lactation
US Food and Drug Administration (FDA)	
• Available data on COVID-19 vaccine administered to pregnant individuals are insufficient to inform vaccine-associated risks in pregnancy	• Data are not available to assess the effects of COVID-19 vaccine on the breastfed infant or on milk production/excretion
Centers for Disease Control and Prevention (CDC)	
• People who are pregnant and part of a group recommended to receive COVID-19 vaccination, such as health care personnel, may choose to be vaccinated • A conversation between pregnant patients and their clinicians may help them decide whether to receive a vaccine that has been authorized for use under EUA • A conversation with a clinician may be helpful but is not required prior to vaccination • Routine testing for pregnancy before COVID-19 vaccination is not recommended • Persons who are trying to become pregnant do not need to avoid pregnancy after receiving an mRNA COVID-19 vaccine	• There are no data on the safety of COVID-19 vaccines in lactating mothers or on the effects of mRNA vaccines on the breastfed infant or on milk production/excretion • mRNA vaccines are not thought to be a risk to the breastfeeding infant • People who are breastfeeding and are part of a group recommended to receive a COVID-19 vaccine, such as health care personnel, may choose to be vaccinated
American College of Obstetricians and Gynecologists (ACOG)	
• ACOG recommends that COVID-19 vaccines should not be withheld from pregnant individuals who meet criteria for vaccination based on ACIP-recommended priority groups • While a conversation with a clinician may be helpful, it should not be required prior to vaccination because this may cause unnecessary barriers to access • Pregnancy testing should not be a requirement prior to receiving any EUA-approved COVID-19 vaccine • Pregnant patients who decline vaccination should be supported in their decision	• ACOG recommends COVID-19 vaccines be offered to lactating individuals similar to nonlactating individuals when they meet criteria for receipt of the vaccine based on prioritization groups outlined by the ACIP • While lactating mothers were not included in most clinical trials, COVID-19 vaccines should not be withheld from lactating individuals who otherwise meet criteria for vaccination • Theoretical concerns regarding the safety of vaccinating lactating individuals do not outweigh the potential benefits of receiving the vaccine; there is no need to avoid initiation or discontinue breastfeeding in patients who receive a COVID-19 vaccine
Society for Maternal-Fetal Medicine (SMFM)	
• SMFM strongly recommends that pregnant people have access to COVID-19 vaccines and that they discuss potential benefits and unknown risks with their clinicians regarding receipt of vaccine • Counseling should also include the theoretical risk of harm to the fetus; the risk from mRNA vaccines is thought to be low due to the expected degradation of mRNA in the circulation • Individual decision-making needs to balance theoretical risks with risks associated with delayed vaccination and possible maternal SARS-CoV-2 infection	• Vaccination is recommended for lactating persons • Counseling should balance the lack of data on vaccine safety and a person's individual risk for infection and severe disease • The theoretical risks regarding the safety of vaccinating lactating people do not outweigh the potential benefits of the vaccine

Comment: I included this JAMA Insight which I found to be an excellent succinct review of what is known and some commonsense recommendations. Although we have learned a lot about COVID-19 and persons who are pregnant, questions still remain.