Good morning

Lots to report in terms of COVID-19 News. First the FDA has revoked EUA that allowed for the investigational monoclonal antibody therapy bamlanivimab, when administered alone. Next, The European Medicines Agency concluded the overall benefits of J&J COVID-19 Vaccine in preventing COVID-19 outweigh the risks of side effects and that a warning about unusual blood clots with low blood platelets should be added to the product information. Lastly the CDC has updated its travel advisory this week and said it will boost its "Do Not Travel" guidance to about 80% of countries worldwide.

Under Journal Review the first article is a very good article on the incidence of acute allergic reactions to the mRNA vaccines. The next article looks at SARS-CoV-2 transmission in a school district in GA. Indoor sports posed the greatest risk for transmission. The last article demonstrates that reinfection is not more likely in the presence of the B.1.1.7 variant suggesting that immunity developed from infection with pre-existing variants is likely to protect against B.1.1.7.

Have a wonderful Wednesday

Ed

## COVID-19 News

**FDA Update: Bamlanivimab**
April 19, 2021
The FDA has revoked EUA that allowed for the investigational monoclonal antibody therapy bamlanivimab, when administered alone, to be used for the treatment of mild or moderate coronavirus disease 2019 (COVID-19) in adults and certain pediatric patients.

Based on its ongoing analysis of emerging scientific data, specifically the sustained increase of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral variants that are resistant to bamlanivimab alone resulting in the increased risk for treatment failure, the FDA has determined that the known and potential benefits of bamlanivimab, when administered alone, no longer outweigh the known and potential risks for its authorized use. Therefore, the agency determined that the criteria for issuance of an authorization are no longer met and has revoked the EUA.

Alternative monoclonal antibody therapies remain available under EUA, including the combination of casirivimab and imdevimab (REGEN-COV), and the combination of bamlanivimab and etesevimab (Lilly).

**Comment:** This is consistent with recent NIH revision on monoclonals reviewed recently in the Daily Briefing.

**European Medicines Agency's (EMA) J&J Vaccine**
At their meeting on April 20, 2021, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has concluded that a warning about unusual blood clots with low blood platelets should be added to the product information for COVID-19 Vaccine Janssen. In addition, the PRAC also concluded that these events should be listed as very rare side effects of the vaccine.

According to the EMA, in reaching its conclusion, the committee took into consideration all currently available evidence, including eight cases of thrombosis in combination with thrombocytopenia in people who received Janssen's COVID-19 vaccine in the US, one of which had a fatal outcome. All cases occurred in people under 60 years of age within three weeks after vaccination, the majority in women.

The PRAC noted that these very rare types of thrombosis included venous thrombosis mostly in unusual sites such as cerebral venous sinus thrombosis and splanchnic vein thrombosis, as well as arterial thrombosis, together with thrombocytopenia and sometimes bleeding. The committee also added that the cases reviewed were remarkably similar to the cases that occurred with the COVID-19 vaccine developed by AstraZeneca.

Based on the currently available evidence, the agency said that specific risk factors have not been confirmed. It also urged healthcare professionals and people who will receive the vaccine to be aware of the possibility of very rare cases of blood clots combined with low levels of blood platelets occurring within three weeks of vaccination. Particularly, the agency advised that healthcare professionals should inform people receiving the vaccine that they must seek medical attention if they develop:

- symptoms of blood clots such as shortness of breath, chest pain, leg swelling, persistent abdominal pain
- neurological symptoms such as severe and persistent headaches and blurred vision
- petechiae beyond the site of vaccination after a few days.

"By recognizing the signs of blood clots and low blood platelets and treating them early, healthcare professionals can help those affected in their recovery and avoid complications," the EMA added.

They conclude the overall benefits of J&J COVID-19 Vaccine in preventing COVID-19 outweigh the risks of side effects.

**Comment:** I think the EMA reached the correct decision based on the rarity of this side effect and the substantial benefit of vaccination. The J&J vaccine does not require cold storage, is less expensive, is 1 dose, and except for this very rare complication has fewer side effects than the mRNA vaccines. This vaccine can make an enormous difference in low to middle income countries, and vaccination of people who cannot easily return for a second dose.

**CDC Travel Advisory**

The U.S. State Department this week said it will boost its "Do Not Travel" guidance to about 80% of countries worldwide, citing "unprecedented risk to travelers" from the COVID-19 pandemic. "This update will result in a significant increase in the number of countries at Level 4: Do Not Travel, to approximately 80% of countries worldwide," the department said in a statement. The State Department already listed 34 out of about 200 countries as "Level 4: Do Not Travel," including places like Chad, Kosovo, Kenya, Brazil, Argentina, Haiti, Mozambique, Russia, and Tanzania. Getting to 80% would imply adding nearly 130 countries. Most Americans were already prevented from traveling to much of Europe because of COVID-19 restrictions. Washington has barred nearly all non-U.S. citizens who have recently been in most of Europe, China, Brazil, Iran, and South Africa.

**Comment:** Earlier this month, the CDC said people who are fully vaccinated against COVID-19 can safely travel within the United States at "low risk" but CDC Director Rochelle Walensky then said she discouraged Americans from doing so because of high coronavirus cases nationwide. [confused!] I think

in general if you are fully vaccinated travel within the US is generally low risk [perhaps except to Detroit!], but international travel carries a much higher risk.

## Journal Review

**Acute Allergic Reactions to mRNA COVID-19 Vaccines**
JAMA 2021; 325:1562-1565
doi:10.1001/jama.2021.3976
The investigators prospectively studied Mass General Brigham (MGB) employees who received their first dose of an mRNA COVID-19 vaccine (12/16/2020-2/12/2021, with follow-up through 2/18/2021). For 3 days after vaccination, employees completed symptom surveys through a multipronged approach including email, text message, phone, and smartphone application links. Acute allergic reaction symptoms solicited included itching, rash, hives, swelling, and/or respiratory symptoms.

To identify anaphylaxis, allergists/immunologists reviewed the electronic health records of employees (1) reporting 2 or more allergy symptoms, (2) described as having an allergic reaction in MGB safety reports, (3) logged by the on-call MGB allergy/immunology team supporting employee vaccination, and (4) referred to MGB allergy/immunology. They described characteristics and outcomes of identified anaphylaxis cases. They calculated incidence rates and 95% CIs of self-reported acute allergic reactions and confirmed anaphylaxis, using vaccine administrations as the denominator.

Of 64,900 employees who received their first dose of a COVID-19 vaccine, 25,929 (40%) received the Pfizer vaccine and 38,971 (60%) received the Moderna vaccine. At least 1 symptom survey was completed by 52,805 (81%). Acute allergic reactions were reported by 1,365 employees overall (2.10% [95% CI, 1.99%-2.22%]), more frequently with the Moderna vaccine compared with Pfizer (2.20% [95% CI, 2.06%-2.35%] vs 1.95% [95% CI, 1.79%-2.13%]; *P* = .03). Anaphylaxis was confirmed in 16 employees (0.025% [95% CI, 0.014%-0.040%]): 7 cases from the Pfizer vaccine (0.027% [95% CI, 0.011%-0.056%]) and 9 cases from the Moderna vaccine (0.023% [95% CI, 0.011%-0.044%]) (*P* = .76).

Individuals with anaphylaxis were a mean age of 41 years, and 15 (94%) were female; 10 (63%) had an allergy history and 5 (31%) had an anaphylaxis history. Mean time to anaphylaxis onset was 17 (SD, 28; range, 1-120) minutes. One patient was admitted to intensive care, 9 (56%) received intramuscular epinephrine, and all recovered. Three employees, with prior anaphylaxis history, did not seek care.

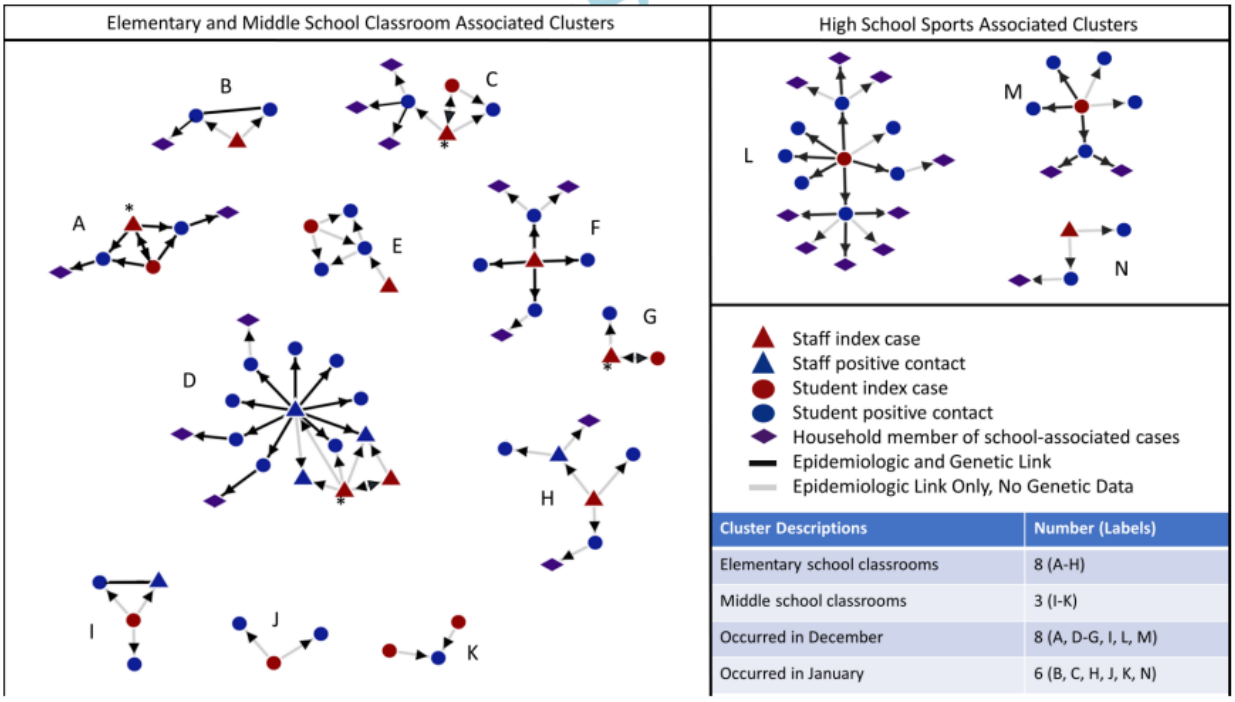
**Comment:** Overall 2% reported some allergic symptoms; however, severe reactions consistent with anaphylaxis occurred at a rate of 2.47 per 10,000 vaccinations. All individuals with anaphylaxis recovered without shock or endotracheal intubation. The incidence rate of confirmed anaphylaxis in this study is higher than that reported by CDC based on a more passive reporting method (0.025-0.11 per 10 000 vaccinations). [JAMA. Published online February 12, 2021] However, the overall risk of anaphylaxis to an mRNA COVID-19 vaccine remains extremely low. The mechanism of these reactions is still unknown.

**SARS-CoV-2 Transmission in a Georgia School District — United States, December 2020-January 2021**
Clin Infect Dis published online April 17, 2021
doi/10.1093/cid/ciab332/623210
This study tracked COVID-19 cases and case contacts from Dec 11, 2020, through Jan 22, 2021, in a district that included eight elementary schools, two middle schools, and one high school. Students were

in-person 4 days per week and wore masks, and desks were spaced 3 to 6 feet apart. The district serves approximately 8,500 students and employs approximately 1,400 staff members. The student body is racially, ethnically, and socioeconomically diverse; 38% of students are Hispanic, 36% are non-Hispanic Black, 20% are non-Hispanic White, and 60% qualify for the free or reduced meal program.

Prevention measures implemented to reduce the spread of SARS-CoV-2 in the school district included mandatory mask use on campus (except during indoor or outdoor sports participation). Physical distancing was implemented where possible; in general, distance between student desks was 3-6 feet in the middle and high schools but was <3 feet in elementary school. Prevention measures also included three-sided plastic shields on all desks, hand hygiene promotion, increased frequency of facility cleaning and disinfection, advising community members to perform self-screening for symptoms and remain home if symptomatic, and contact tracing for staff or students who tested positive for SARS-CoV-2 infection. Measures to improve ventilation, including opening windows in classrooms and buses, were implemented where possible. Outside air intake was increased from 15-30%, they used MERS-10 filters [not medical grade] and they installed ionization devices.

All cases were confirmed by polymerase chain reaction testing. Secondary attack rate (SAR)—which is the percent of case contacts who become infected—was calculated by setting (classroom, bus, indoor sports), index case roll (student or staff), symptom status (asymptomatic or symptomatic), and time of exposure. Eighty-six primary cases were included in the analysis, involving 33 staff and 53 students, who generated 1,119 contacts (112 staff and 1,007 students). Among contacts, 9.8% tested positive. The overall SAR was 8.7% (95% confidence interval [CI], 6.8% to 10.9%). SAR was highest in indoor sports settings (including basketball, wrestling, and cheerleading) (23.8%; 95% CI, 12.7%–33.3%), interactions among staff (group lunches, staff meetings) (18.2%; 95% CI, 4.5%–31.8%), and in elementary school classrooms (9.5%; 95% CI, 6.5%–12.5%). Symptomatic index cases had a higher SAR than asymptomatic cases—10.9% versus 3.0%. Most positive high school student contacts and all high school clusters were associated with indoor, high-contact sports rather than high school classrooms.




| Cluster Descriptions | Number (Labels) |
|---|---|
| Elementary school classrooms | 8 (A-H) |
| Middle school classrooms | 3 (I-K) |
| Occurred in December | 8 (A, D-G, I, L, M) |
| Occurred in January | 6 (B, C, H, J, K, N) |

**Comment:** In-school transmission seen in this investigation was higher than reported in recent studies from those in the United States. Indoor sports posed the highest risk for SAR. AAP recommends masks be worn during most indoor sporting events. Despite the use of in-depth epidemiologic investigation, it was challenging to definitively determine whether a person became infected in school versus the community [high community rates] and to know from which index case a positive contact might have become infected in settings with >1 index case. Inadequate mask use in specific instances and distancing <3 feet probably contributed as well. Compliance with mask use and the choice of masks and how well they fit were not included. Preventing infection in staff members, through measures that include COVID-19 vaccination, is critical to reducing in-school transmission. Because many positive contacts were asymptomatic, contact tracing should be paired with testing, regardless of symptoms.

**Changes in Symptomatology, Reinfection, and Transmissibility Associated with the SARS-CoV-2 Variant B.1.1.7: An Ecological Study**

Lancet Public Health published online April 12, 2021

doi.org/10.1016/ S2468-2667(21)00055-4

The investigators conducted an ecological study examining associations between the proportion of infections with the SARS-CoV-2 B.1.1.7 variant and reported symptoms, disease course, rates of reinfection, and transmissibility. Data on symptoms was acquired from the COVID Symptom Study app users reporting a positive COVID test between September and December 2020. During the study period, 36,920 app users reported positive tests. No associations were found between the B.1.1.7 variant and reported symptoms or disease duration. The study found no evidence to indicate that reinfection was higher for the B.1.1.7 variant, suggesting that vaccines are likely to remain effective against this variant. They also found a multiplicative increase in the effective reproduction number, Rt, of the B.1.1.7 variant by a factor of 1·35 (95% CI 1·02–1·69) compared with pre-existing variants.

**Comment:** The finding that reinfection is not more likely in the presence of the B.1.1.7 variant suggests that immunity developed from infection with pre-existing variants is likely to protect against the B.1.1.7 variant, and that vaccines will probably remain effective against this new variant. The results add to the emerging consensus that the B.1.1.7 variant has increased transmissibility.