AAMC Coronavirus Update
April 21, 2021

To help filter through the large volume of news about the coronavirus, Ross McKinney Jr., MD, AAMC chief scientific officer, with assistance from his team in the Scientific Affairs unit at the AAMC, has initiated this science-focused newsletter.

This newsletter will be published twice a month on alternating Wednesdays.

Opt-in to receive future updates.

Contact AAMC Senior Science Policy Specialist Julia Omotade, PhD, with any other questions or requests.

To access the latest AAMC updates and resources on COVID-19, visit aamc.org/coronavirus. For resources on COVID-19 medical research, read more here.

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Today's Numbers

- World: 143,257,146 confirmed cases (3,049,638 deaths)
  - 5,511,969 new cases this week (5,028,468 cases last week)
- United States: 31,820,518 confirmed cases (568,733 deaths)
  - 455,153 new cases this week (498,637 cases last week)
  - 5,212 deaths this week (5,359 deaths last week)
  - 419,722,893 total tests
- U.S. Hot Spots
  - Michigan: 48,238 new cases in last 7 days (-12% change in daily cases)
  - Florida: 43,869 (0%)
  - New York: 41,831 (-14%)
  - Pennsylvania: 30,678 (-8%)
  - New Jersey: 23,866 (-6%)
- U.S. COVID-19 Vaccine Distribution and Administration
  - Total doses delivered: 277,938,875
  - Total doses administered: 215,951,909

For the most up-to-date data, refer to the Johns Hopkins COVID-19 Map. Details of other U.S. hot spots can be found at the Washington Post's coronavirus data webpage. Overall U.S. COVID-19 vaccine distribution and administration data can be found at the Centers for Disease Control and Prevention (CDC) COVID Data Tracker.

The Institute for Health Metrics and Evaluation at the University of Washington Medicine is projecting hospital resource use in the United States based on COVID-19 deaths.
Lead News

The issue of blood clots and thrombocytopenia after vaccination with the AstraZeneca and Johnson & Johnson (J&J) adenovirus-based vaccines has provoked a rush of theories and new evidence. The theories were well-reviewed in an article in the Atlantic. One of the early cases of vaccine-induced thrombotic thrombocytopenia (VITT) after the J&J vaccine was described in a correspondence to the New England Journal of Medicine (NEJM). The patient was a previously healthy 48-year-old woman who developed splanchic vein and cerebral venous sinus thrombosis and thrombocytopenia 14 days after vaccination. Scientists at J&J/Janssen responded, noting that there have been six cases of possible VITT following J&J vaccine administration, although they argue that the low incidence (six cases per 7.2 million doses) makes establishing causality difficult. They also point out several differences between the AstraZeneca vaccine and theirs, including the use of different adenoviruses that attach to different cellular receptors and a distinct spike protein configuration. The CDC’s Advisory Committee on Immunization Practices put the J&J vaccine on “pause,” although the Food and Drug Administration (FDA) did not change its emergency use authorization (EUA), and will further evaluate the situation this Friday, April 23. Regarding the AstraZeneca vaccine, European investigators described 23 cases of VITT in the NEJM and included the finding that 22 out of 23 had detectable antibodies to platelet factor 4 (PF4). Only 61% of the cohort were female. [Editor’s comment: If the adverse event rate really is 1 in 1 million, that’s uncommon enough that it seems reasonable to resume use of the J&J vaccine. For people who are not comfortable with even that low event rate, there remains the Pfizer and Moderna mRNA options. And the mechanism for the AstraZeneca vaccine-associated VITT appears to be anti-PF4 antibodies, which suggests that treatment should focus on intravenous immunoglobulin and nonheparin anticoagulants.]

Treatment News

The National Institutes of Health (NIH) has been coordinating a series of studies of treatment strategies to evaluate the safety and efficacy of novel therapeutic agents in hospitalized adults diagnosed with COVID-19, which is the mission of the Adaptive COVID-19 Treatment Trial (ACTT). The National Institute of Allergy and Infectious Diseases announced this week that the fourth iteration of the trial, ACTT-4, was closing to enrollment because the study met criteria for futility, where the enrollment of additional patients would be unlikely to show a demonstrable beneficial effect. ACTT-4 evaluated two strategies for treating patients hospitalized with SARS-CoV-2 infection — baricitinib plus remdesivir or dexamethasone plus remdesivir — with a primary endpoint of preventing progression from a supplemental oxygen requirement to mechanical ventilation or death. Baricitinib is an anti-inflammatory drug approved for rheumatoid arthritis, known by its brand name Olumiant, that acts as a Janus kinase inhibitor. ACTT-4 enrolled more than 1,000 of its planned 1,500 participants, but on reviewing the data so far, the Data Safety Monitoring Board found that further enrollments were unlikely to demonstrate a difference between the two regimens. [Editor’s comment: Good news, bad news. We know that dexamethasone saves lives, so the fact that baricitinib performed similarly suggests it might have a niche as an option, although dexamethasone is relatively inexpensive and well known. We’ll know more when the full results of the study are published, but the consequences are not likely to be earth-shaking.]

The FDA has revoked the EUA for one of the monoclonal antibodies against SARS-CoV-2, bamlanivimab. Bamlanivimab, from Eli Lilly and Co., was initially authorized as a single agent for early COVID-19. Given the pattern of mutations with currently circulating variants, resistance rates to bamlanivimab have been rising, so the FDA now recommends using one of the monoclonal antibody cocktails — either bamlanivimab plus
etesevimab administered together or Regeneron’s REGEN-COV (casirivimab and imdevimab). [Editor’s comment: The tight specificity of monoclonal antibodies is both a strength and weakness. Small changes to the virus may change the attachment site for the monoclonal, making it less effective. The use of combinations of monoclonals substantially decreases the risk of resistance mutations. As a positive note for corporate responsibility, Eli Lilly made the request to the FDA for withdrawal of the EUA.]

Clinical News

Antiviral therapeutics for SARS-CoV-2 infection continue to advance slowly. Merck and Ridgeback Biotherapeutics announced that the use of molnupiravir (aka MK-4482 or EIDD-2801) in hospitalized patients failed to provide significant benefit in a clinical trial. The companies will continue to evaluate whether molnupiravir, which is given orally, can provide benefit early in infection. Researchers at the NIH's Rocky Mountain Laboratories published their study of molnupiravir in hamsters in Nature Communications, where they were able to demonstrate that the use of molnupiravir after high-risk exposures resulted in lower levels of SARS-CoV-2 replication and decreased lung pathology.

Merck announced that they were suspending their development work on MK-7110 (aka CD24Fc), an immunomodulator that had been studied for hospitalized COVID-19 patients. The developmental timeline on the drug was such that it wouldn’t be available until mid-2022, which seemed too late given the pace of vaccination.

Coronavirus and Health Equity


New preprint research has indicated that there has been lower vaccine delivery relative to risk of infection in economically under-resourced communities and communities with larger Black and Latinx populations in Massachussets. These disparities are greater than those previously seen using county-level data, demonstrating the importance of surveillance and interventions targeting smaller geographies to ensure equitable distribution of vaccines.

The Atlantic: The Rural Pandemic Isn’t Ending


Research News

According to the CDC, over 213 million vaccines have been administered in the United States, just over a quarter of Americans are fully vaccinated, and 40% of the population has received at least one dose. Coupled with the wide divergence in global vaccination efforts, these numbers reveal the dire need — and great potential — for scientific studies to shed light on how real-life vaccination campaigns can affect pandemic dynamics. With a highly effective national vaccination campaign, Israel has achieved “one of the highest rates of vaccinated individuals per capita.” As of Feb. 24, 2021, “68.7%, 48% and 8% of the population have received the first or the second vaccine dose or have recovered from COVID-19, respectively.” These figures come from a study published this past Monday in
**Nature**, which reported data from a retrospective study conducted between Aug. 28, 2020, and Feb. 24, 2021. The goal of the study was to investigate the effect of the national Pfizer vaccination campaign, initiated in Israel on Dec. 20, 2020, on the number of new COVID-19 cases and hospitalizations. According to the authors, “a little over 2 months after the initiation of the vaccination campaign, with 85% of individuals older than 60 years already vaccinated with two doses (24 February 2021), there was an approximately 77% drop in cases, a 45% drop in positive test percentage, a 68% drop in hospitalizations and a 67% drop in severe hospitalizations compared to peak values.” Though these findings are preliminary, they provide “large-scale, real-world data demonstrating real-life effectiveness of a national vaccination campaign.” Another study published over the weekend in *Cell* likewise examined the effects of “massive RT-PCR testing” — one of three national programs used in Israel’s pandemic response efforts — on the spread of COVID-19. The authors analyzed data from approximately 300,000 RT-PCR samples collected from Dec. 6, 2020, to Feb. 10, 2021, and reported that “RT-PCR testing and prioritized vaccination programs were capable of preventing the spread of the B.1.1.7 variant (shown to be 45% more transmissible) in the elderly” population. From their results, the authors extrapolate three major conclusions: “Active surveillance markedly reduces the transmission of B.1.1.7 in nursing homes,” “[p]rioritized vaccination prevents B.1.1.7-associated infections in the elderly,” and “[p]roactive surveillance combined with prioritized vaccination are achievable” — reducing “severe illness and subsequent death.” [Editor’s comment regarding the *Nature* paper: Though much work has been done to characterize the efficacy of vaccines in clinical trial settings, the real-world data from this study sheds light on the logistics of a “rapid [vaccine] deployment campaign” and “heterogenous and population dependent” factors that determine vaccine effectiveness in populations (e.g., deterioration of immune function in older individuals). Equally as important as the results themselves, the authors noted several considerations and limitations of their study. Among those was the consideration that various other factors besides vaccination may very well have contributed to the observed results. The authors made several observations that they believe “suggest that [the patterns] are likely to be driven, to a considerable degree, by the vaccines.”]

A scientific hallmark in this phase of the ongoing pandemic is the emergence of studies dedicated to examining the range of clinical manifestations caused by SARS-CoV-2 infection. To date, at least two major conditions have been reported: post-acute sequelae of SARS-CoV-2 infection — a myriad of symptoms that emerge or persist after the initial recovery from COVID-19 (also referred to as “Long COVID” or “Post-acute COVID-19”) — and multisystem inflammatory syndrome in children (MIS-C), which is a “life-threatening post-infectious complication occurring unpredictably weeks after mild or asymptomatic SARS-CoV-2 infection.” MIS-C primarily occurs in a proportion of pediatric patients with COVID-19, and although the precise etiology of MIS-C is unknown, the CDC has noted that “many children with MIS-C had the virus that causes COVID-19, or had been around someone with COVID-19” — spurring researchers to investigate the link between SARS-CoV-2 infection and MIS-C. As stated in our April 14 issue of the *Coronavirus Update*, our understanding of the long-term effects of MIS-C is in its infancy, and the investigation of MIS-C will prove to be a critical topic. A range of studies have characterized the clinical manifestations of MIS-C, and a recent study in *Cell* used a multidisciplinary approach consisting of single-cell RNA sequencing, flow cytometry, antigen receptor repertoire analysis, and unbiased serum proteomics to analyze samples of MIS-C patients. Through this many-pronged experimental approach, the authors identified an immunopathological signature in MIS-C patients that correlated with disease severity. As the authors noted, “the determinants of whether a child with MIS-C develops moderate or severe disease is still currently unknown,” and these studies might inform diagnostic and prognostic testing.

As more Americans get vaccinated and begin to adopt components of pre-pandemic life (e.g., gatherings, travel), ongoing data on how to best reduce SARS-CoV-2 transmission in congregations — particularly indoor settings — will be critical in guiding public health recommendations and policies. Three recent articles published in the *Lancet*, *JAMA*, and
the *Proceedings of the National Academy of Sciences* highlighted 10 “streams of evidence that collectively support the hypothesis that SARS-CoV-2 is transmitted primarily by the airborne route,” examined air filtration and ventilation standards fundamental to pandemic risk reduction strategies, and quantified “the extent to which transmission risk is reduced” by nonpharmaceutical interventions such as large rooms with high air exchange rates and the use of face masks. These ongoing studies will be important to optimize the role of nonpharmaceutical interventions as a compliment to the global vaccination strategy.

Investigation is underway to characterize if and how previous infection with SARS-CoV-2 affects subsequent SARS-CoV-2 reinfection and vaccination. An April 15 *study in the Lancet* "investigated whether young adults infected with SARS-CoV-2 are at risk for subsequent infection." a. Between May 11, 2020, and Nov 2, 2020, the authors enrolled 3,249 predominantly male, U.S. Marine recruits, aged 18-20, in a study. Through testing, the participants were identified as seronegative or seropositive for SARS-CoV-2. PCR tests were done at weeks 2, 4, and 6 in both seropositive and seronegative groups and the authors found that “among 189 seropositive participants, 10% had at least one positive PCR test for SARS-CoV-2 during the 6-week follow-up, compared to 48% of seronegative participants who subsequently tested positive for SARS-CoV-2.” Notably, the authors found that “among seropositive recruits, infection was more likely with lower baseline full-length spike protein IgG titres than in those with higher baseline full-length spike protein IgG titres.” Though "seropositive young adults had about one-fifth the risk of subsequent infection compared with seronegative individuals," the authors noted that “although antibodies induced by initial infection are largely protective, they do not guarantee effective SARS-CoV-2 neutralization activity or immunity against subsequent infection.” On the other end of the developmental spectrum, a *JAMA article* examined if SARS-CoV-2 seropositive, older adults living in nursing homes (adults previously infected with SARS-CoV-2) may only “require one dose rather than two doses of a messenger RNA vaccine,” which studies have suggested may be the case for younger adults. To investigate this, between March and June 2020, researchers “compared IgG antibody levels after a single dose of the Pfizer vaccine in nursing home residents with or without prior COVID-19.” The authors found that 100% of residents (36/36) “with prior COVID-19 were seropositive for S-protein IgG after 1 vaccine dose vs 49.2% of residents (29/60) without prior COVID-19.” The authors believe that their preliminary result “suggests that a single dose of the Pfizer vaccine may be sufficient to obtain a high level of S-protein IgG antibody in nursing home residents previously diagnosed with COVID-19 based on RT-PCR results.” [Editor's comment: Though some of the limitations of this study include a small sample size and lack of neutralization assays, the authors believe that their results may very well have important implications in vaccine protocols. For example, “measuring S-protein IgG antibody levels just before the second vaccine dose could be useful in determining whether a second dose is required in individuals whose infection history is unknown. This could limit possible adverse effects related to reactogenicity in previously infected patients and spare precious vaccine doses.” In many studies examining immune response to SARS-CoV-2 and various vaccines, a fundamental question is not only who is immunologically protected from infection or the mechanisms underlying such protection; but also, how long immunological protection will persist. Issues such as the size of the pool of memory B cells — which will affect the speed of antibody generation on reinfection — or the number and significance of virus-specific T-cells need to be evaluated over time to understand both their importance and their rate of decay.]

*Science: Distinct Antibody and Memory B Cell Responses in SARS-CoV-2 Naive and Recovered Individuals Following mRNA Vaccination*

*JAMA: Symptoms and Functional Impairment Assessed 8 Months After Mild COVID-19 Among Health Care Workers*

*Cell Reports: SARS-CoV-2 Infection of Primary Human Lung Epithelium for COVID-19*
Other COVID-19 News

*Nature:* The Race for Antiviral Drugs to Beat COVID — and the Next Pandemic

*Science:* The Dream Vaccine

For questions, contact **Julia Omotade**, PhD, AAMC lead science policy specialist.

Ross McKinney Jr., MD  
Chief Scientific Officer  
rmckinney@aamc.org

Julia Omotade, PhD  
Senior Science Policy Specialist  
jomotade@aamc.org

Stephen J. Heinig  
Director, Science Policy  
sheinig@aamc.org

Philip Alberti, PhD  
Senior Director, Health Equity Research & Policy  
palberti@aamc.org