AAMC Coronavirus Update
May 5, 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.

Please share/forward this newsletter freely.

Today's Numbers

- World: 154,534,328 confirmed cases (3,231,397 deaths)
  - 5,642,661 new cases this week (5,511,969 cases 14 days ago)
- United States: 32,534,179 confirmed cases (578,925 deaths)
  - 337,209 new cases this week (455,153 cases 14 days ago)
  - 5,062 deaths this week (5,212 deaths 14 days ago)
  - 438,358,030 total tests
- U.S. Hot Spots
  - Florida: 4,483 average daily new cases in the last 7 days (-18% change in daily cases in the last 7 days)
  - Michigan: 3,627 (-25%)
  - Texas: 3,120 (-5%)
  - New York: 3,050 (-21%)
  - Pennsylvania: 3,020 (-14%)
- U.S. COVID-19 Vaccine Distribution and Administration
  - Total doses delivered: 321,549,335
  - Total doses administered: 249,566,820

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

On April 13, the CDC and Food and Drug Administration (FDA) recommended a well-publicized pause in the use of the Janssen (Johnson & Johnson) vaccine, Ad26.CoV2.S, after six cases of cerebral venous sinus thrombosis (CVST) with thrombocytopenia. By the time the CDC’s Advisory Committee on Immunization Practices (ACIP) met to reconsider the pause on April 23, the syndrome had been renamed “thrombosis with thrombocytopenia syndrome” (TTS). By April 21, there were 15 recognized and confirmed cases of TTS among 8 million doses of Ad26.CoV2.S, all of whom were female. 13 cases were in individuals ages 18-49 and two cases were in people ages 50 or older. The highest incidence was in women ages 30-39. The median time of onset was eight days. 12 patients had CVST and 11 had thrombosis in some other location. The pathogenesis seemed similar to heparin-induced thrombosis with thrombocytopenia, and the heparin-induced thrombocytopenia testing frequently noted a positive platelet factor 4 antibody assay. Weighing the risk information, the ACIP decided the benefits of the vaccine exceeded the extremely rare but serious cases of TTS, and the pause was lifted. [Editor's comment: The Ad26.CoV2.S vaccine is clearly effective, and the risks are vanishingly small but measurable. If the mRNA vaccines were not available, this would have been an even shorter debate. The fact that an adverse event could be found in 15 people among 8 million doses is actually pretty remarkable and a testament to the adverse event reporting system for immunizations. There appears to be no issues for males, and even for women ages 18-60, the vaccine looks to be safe. If someone develops a headache or other symptoms concerning for TTS, it is extremely important to remember that the treatment should not include heparin, which would likely make the condition worse.]

Treatment News

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial has been a clever protocol design used by the National Health Service in the United Kingdom to explore various treatment options in patients hospitalized with COVID-19. The study adds treatment arms and randomized comparisons to the ongoing use of a defined standard of care. On May 1, results of a randomized controlled trial of tocilizumab as treatment for oxygen-dependent patients hospitalized with COVID-19 was published in the Lancet. The study randomized 4,116 eligible adults out of the 21,550 enrolled in RECOVERY. The primary outcome measure was mortality within 28 days. 621 (31%) of the 2,022 patients allocated to tocilizumab died, while 729 (35%) of the 2,094 assigned to placebo died. Patients assigned to tocilizumab were also more likely to be discharged from the hospital within 28 days (57% vs 51%). Among those patients not originally on mechanical ventilation, the probability of a composite endpoint of mechanical ventilation or death favored tocilizumab (35% vs. 42%). [Editor's comment: Once again, RECOVERY demonstrates how a well-organized study with a simple, consistent design can answer important questions quickly. Tocilizumab is an anti-IL6 receptor monoclonal antibody that has been used as a treatment for rheumatoid arthritis, and studies of its use have vacillated in the degree of effect they demonstrated. In my view, while the results in this study weren't a giant home run, the incremental benefits are clear enough that tocilizumab should now be considered for most patients hospitalized with COVID-19 and an oxygen requirement.]

An ongoing issue for the mRNA COVID-19 vaccines has been their use in pregnant women. The CDC used data from their V-safe registry to evaluate safety-related outcomes and published the results in the New England Journal of Medicine (NEJM). The investigators had responses available from 35,691 pregnant women and were able to compare to the larger cohort of nonpregnant women. Injection site pain was reported more frequently (by a few percentage points), while headache, myalgia, chills, and fever were
less common in pregnant women. The study team attempted to contact 5,230 of the women vaccinated while pregnant by phone to evaluate outcomes. They ultimately enrolled 3,958, of whom 3,719 identified as health care personnel (health care personnel had been prioritized in the study). 827 completed their pregnancy during the study period, of whom 115 (13.9%) reported a pregnancy loss and 712 (86.1%) reported a live birth. 9.4% of births were preterm and 3.25% were small for gestational age. There were no neonatal deaths. These outcomes are similar to studies completed in the pre-COVID-19 era. [Editor’s comment: The good news is the lack of difference between this study and the baseline rates of problems during pregnancy. The surprise for me is the frequency of pregnancy loss, but that reflects a lack of appreciation of pre-COVID-19 norms. The authors cite 12 studies in establishing those pre-COVID-19 rates.]

Swedish investigators evaluated the effect of maternal SARS-CoV-2 infection during pregnancy on neonatal outcomes and published the results in *JAMA*. Given a national medical record system, they were able to evaluate 92% of all pregnancy outcomes in Sweden between March 11, 2020, and Jan. 31, 2021. There were 88,159 newborns in that period, including 2,323 who were born to women who had a positive test for SARS-CoV-2. The mean gestational age for the infants born to SARS-CoV-2-infected women was 39.2 weeks vs. 39.6 weeks for uninfected women. The proportion of preterm births (with a gestational age of less than 37 weeks) was higher in the infected women (8.8% vs. 5.5%, or 205/2,323 vs. 4,719/85,836). Mortality did not differ in the groups, but the infants born to infected women were more likely to require admission for neonatal care (11.7% vs 8.4%), to have respiratory distress syndrome (1.2% vs 0.5%), and to have hyperbilirubinemia (3.6% vs 2.5%). [Editor’s comment: While differences could be detected in pregnancy outcomes when women were infected with SARS-CoV-2 during pregnancy, the differences in outcomes for the babies were fairly subtle.]

**The CDC performed a real-world evaluation of the efficacy of the mRNA COVID-19 vaccines in people ages 65 or older.** They found both mRNA vaccines were 94% effective against COVID-19 hospitalization after two doses and 64% effective in the period greater than or equal to 14 days after the first vaccine dose and less than 14 days after the second dose.

*Science: Clear Link Emerges Between COVID-19 and Pregnancy Complications*

*NEJM: Vaccine Breakthrough Infections with SARS-Cov-2 Variants*

**Clinical News**

Post-acute sequelae of COVID-19 (PASC) is a syndrome that has been drawing increasing attention. Investigators associated with the VA St. Louis Health Care System evaluated a database of post-COVID-19 patients cared for by the Veterans Affairs (VA) system and published the results in *Nature*. Data were evaluated for the six months after the initial diagnosis of SARS-CoV-2 infection in patients who had not been hospitalized and who had survived at least 30 days after their diagnosis. 73,435 patients were included. The comparison group was 4,990,835 VA users who did not have COVID-19. Beyond the first 30 days of illness, post-COVID-19 patients had a higher risk of mortality (with a hazard ratio of 1.59), equal to 8.39 excess deaths/1,000 COVID-19 patients during that six-month interval. Respiratory problems were frequent. The excess burden for respiratory signs and symptoms was 28.5/1,000 relative to the control group, with higher rates of respiratory failure, respiratory arrest, and lower respiratory disease. Neurological diseases were common, with an excess burden of 14.32 per 1,000 COVID-19 patients. Other problems included disorders of sleep, mental health, lipid metabolism, fatigue and malaise, hypertension, cardiac dysrhythmias, chest pain, and heart failure. A comparison
was made of disease sequelae between patients hospitalized with COVID-19 and those hospitalized with influenza. Patients with COVID-19 did far worse, with more pulmonary problems, neurological diagnoses, neurocognitive problems, and a variety of other issues. [Editor’s comment: PASC is very real and very significant. The damage done by COVID-19, even in nonhospitalized patients, is evident in this study. All the more reason to push hard to vaccinate as many people as possible.]

One surprisingly useful cohort of observational research subjects was the group of NBA players who worked in an isolation “bubble” during the 2020 season. The cohort was notable for the fact that players were tested by PCR for SARS-CoV-2 infection on a daily basis. 3,648 people participated in the study, which was published in JAMA Internal Medicine, and 36 of these individuals were persistently PCR-positive after the end of their acute COVID-19 infection. All were asymptomatic, and despite at least 1,480 patient-days of exposure to other players, there were no secondary transmissions. This affirms the CDC’s guidance to end isolation based on time rather than negative PCR tests.

**Lancet:** COVID-19-Associated Coagulopathy and Antithrombotic Agents—Lessons After 1 Year

**Lancet:** Safety and Immunogenicity of One Versus Two Doses of the COVID-19 Vaccine BNT162b2 for Patients With Cancer: Interim Analysis of a Prospective Observational Study

**JAMA Network:** Association of Cancer Screening Deficit in the United States With the COVID-19 Pandemic

---

**Policy News**

Yesterday, the Biden administration released a statement and fact sheet announcing the goal to “administer at least one vaccine shot to 70% of the U.S. adult population by July 4th.” The administration’s blueprint for curbing the pandemic also included hopes for “160 million U.S. adults to be fully vaccinated by July 4th so that life can start to look closer to normal.” The next phase of the administration’s vaccination campaign also includes measures aimed at boosting the general public’s confidence in vaccines; increasing walk-in appointments for thousands of pharmacies in the federal pharmacy program; “redirecting Federal Emergency Management Agency (FEMA) resources to support more pop-up clinics, smaller community vaccination sites, and more mobile clinics; shipping new allocations of the vaccine to rural health clinics across the country; and providing additional funding to help communities do outreach and engagement to help get people vaccinated.” In the ongoing battle to mitigate the effects of the gaping health disparities in the United States, the plan also included additional measures to support “underserved communities with the tools needed to get vaccinated.” As authorization for adolescent vaccinations becomes ever more imminent, the fact sheet also alluded to a plan to “get the nation’s adolescents vaccinated as soon as possible” — assuming authorization by the FDA and recommendation for use by the CDC.

On April 27 and April 29, the CDC updated its “Interim Public Health Recommendations for Fully Vaccinated People” and also provided “Updated Healthcare Infection Prevention and Control Recommendations in Response to COVID-19 Vaccination.” The updated public health recommendations note that “fully vaccinated people no longer need to wear a mask outdoors, except in certain crowded settings and venues,” and that “fully vaccinated residents of non-healthcare congregate settings no longer need to quarantine following a known exposure.” The updated health care infection prevention recommendations also include “updated visitation guidance to include recommendations
for acute care facilities and to describe circumstances when source control and physical distancing are not required during visitation.”

## Coronavirus and Health Equity

Results of a retrospective case-control study based in Massachusetts and published in *Pediatrics* found that lower socioeconomic status, neighborhood social vulnerability, Latinx ethnicity, and Black race independently increased risk for multisystem inflammatory syndrome in children.

a. According to new research published in *EClinicalMedicine*, residential segregation may “play a role in the capacity of Blacks in segregated areas to successfully carry out the distancing required to prevent COVID-19 spread.” Specifically, once COVID-19 stay-at-home restrictions were lifted, data showed “an elevated mobility increase in segregated counties, as longer commutes from segregated areas were required to perform work outside of segregated living areas,” thereby increasing risk of exposure.

A new paper in the *Journal of Racial and Ethnic Health Disparities* recalculated the “Black-White disparity in COVID-19 mortality rates across 35 states using direct age standardization” and found that the crude death rates typically used result in a “substantial underestimation of the true magnitude of the Black-White disparity in COVID-19 mortality rates.” The authors also explored the relationship between the magnitude of these disparities and a measure of structural racism and found that each “standard deviation increase in the racism index was associated with an increase of 0.26 in the ratio of COVID-19 mortality rates among the Black compared to the White population.”

**National Institutes of Health (NIH): NIH to Invest $29 Million to Address COVID-19 Disparities**

**Kaiser Family Foundation: What Could the U.S. Do to Help Improve Global COVID-19 Vaccine Equity?**


**CNN: Navajo Nation Vaccinates More Than Half of Its Adult Population, Outpacing US National Rate**

**NPR: Why Black And Latino People Still Lag On COVID Vaccines — And How To Fix It**

**NPR: The Pandemic Imperiled Non-English Speakers In A Hospital**

**Nature: Inequality’s Deadly Toll**

## Research News

2020 placed the biomedical community in an expeditious race to characterize the physical symptoms of COVID-19 and search for parallel efforts to thwart clinical disease and death. We know that “[r]espiratory failure is the leading cause of death in patients with severe SARS-CoV-2 infection, yet the host response at the lung-tissue level is poorly understood.” In a preprint published on April 29 in *Nature*, researchers created a “lung atlas” of lethal COVID-19: performing “single-nucleus RNA-sequencing of ~116,000 nuclei of lungs from 19 COVID-19 decedents who underwent rapid autopsy and 7 control lungs.”
A reservoir of clues that can account for the devastating pulmonary consequences of COVID-19 were detected: “Integrated analyses revealed significant alterations in cellular composition, transcriptional cell states, and cell-to-cell interactions.” Specifically, COVID-19 lungs were “highly inflamed with dense infiltration of aberrantly activated … macrophages” and “demonstrated impaired T cell responses” — a signature distinct from other “viral and bacterial causes of pneumonia.” The authors also found impaired lung regeneration and pulmonary fibrosis in COVID-19. This so-called atlas “enables dissection of lethal COVID-19, may inform our understanding of long-term complications of COVID-19 survivors, and provides an important resource for therapeutic development.” A related piece in SciTechDaily detailed the implications of these scientific findings.

When discussing COVID-19, an organ that receives much spotlight (for good reason) is the lung. What is now clear to the biomedical community is that COVID-19 is not simply a pulmonary disease but rather a disease that leads to a plethora of symptoms (sometimes occurring after the initial infection) that involve a host of other organs. These “symptoms, which can include fatigue, shortness of breath, ‘brain fog’, sleep disorders, fevers, gastrointestinal symptoms, anxiety, and depression, can persist for months and can range from mild to incapacitating.” Collectively referred to as “Long COVID” or PASC, these constellation of symptoms have initiated novel funding mechanisms and initiatives from the NIH and engendered studies attempting to characterize the wide range of symptoms and pinpoint underlying mechanisms. Importantly, in parallel with scientific progress, mainstream media outlets have been disseminating information, leading to greater public awareness and understanding of PASC. Scientific studies are now beginning to usher in a new phase of COVID-19 biomedical research that explores COVID-19 pathology in a range of organs and cellular structures and processes. Though “many COVID-19 patients display gastroenteritis symptoms [and] mounting evidence suggests that SARS-CoV-2 infects the human gut,” many outstanding questions remain. For example, “whether gastrointestinal symptoms are associated with the direct replication of SARS-CoV-2 in the GI tract or are a consequence of the strong pro-inflammatory response is unknown. Likewise, little is known about the antiviral programs triggered in this organ.” To address this gap, a paper published on April 27 in Molecular Systems Biology reported data in which researchers performed single-cell transcriptomics of SARS-CoV-2-infected intestinal organoids,” identifying a subpopulation of enterocytes (a type of intestinal cell) as a “prime target of SARS-CoV-2.” As the authors noted, “SARS-CoV-2 is a member of the betacoronavirus genus, which initiates its lifecycle by exploiting the cellular receptor angiotensin-converting enzyme 2 (ACE2) to enter and infect host cells.” Interestingly, the authors found that “[h]igh expression levels of ACE2 does not correlate with higher infectability of cells by SARS-CoV-2,” “ACE2 expression is downregulated upon SARS-CoV-2 infection of human intestinal epithelial cells,” and “[i]nfected cells show a high pro-inflammatory response and little to no interferon-mediated response as the result of a SARS-CoV-2-mediated inhibition of interferon signaling.” As we begin to grasp the wide pathology of COVID-19, these findings “reveal that SARS-CoV-2 curtails the immune response and highlights the gut as a pro-inflammatory reservoir that should be considered to fully understand SARS-CoV-2 pathogenesis.”

Neurological symptoms of COVID-19, such as memory disturbances and brain fog, have been widely reported; however, as the biomedical community transitions from characterizing clinical symptoms and striving to optimize lifesaving measures, studies are now unearthing the underlying molecular and cellular processes that account for these neurological phenomena. An April 27 paper in Cell reports data in which researchers performed single cell RNA-sequencing and cytokine analyses of cerebrospinal fluid (CSF) and blood from COVID-19 patients with neurological symptoms. In doing so, the researchers “identified both innate and adaptive anti-viral immune responses, as well as humoral autoimmunity that appears to be unique to the CNS.” The “immune survey” that led to these findings are significant because it highlights a distinct and compartmentalized immune response in the central nervous system (CNS) of COVID-19 patients, which likely
contributes to neuropathology (as opposed to, say, “systemic multi-organ dysfunction” that simply results in neurologic complications in a COVID-19 patients). As we dig deeper into understanding the underlying drivers of COVID-19-induced neurological pathology, these authors believe that their data suggest “a role for autoimmunity in neurologic sequelae of COVID-19.”

**Science:** COVID-19-Related Anosmia Is Associated With Viral Persistence and Inflammation in Human Olfactory Epithelium and Brain Infection in Hamsters

**Cell Host & Microbe:** Kinetics and Correlates of the Neutralizing Antibody Response to SARS-CoV-2 Infection in Humans

**Science:** Prevalent, Protective, and Convergent IgG Recognition of SARS-CoV-2 Non-RBD Spike Epitopes

**CDC Morbidity and Mortality Weekly Report:** Effectiveness of Pfizer-BioNTech and Moderna Vaccines Against COVID-19 Among Hospitalized Adults Aged ≥ 65 Years — United States, January–March 2021

**Nature:** Impact of Vaccination on Household Transmission of SARS-COV-2 in England

---

### Testing News

As reported in the April 14 edition of the AAMC Coronavirus Update, emerging data continues to broaden and deepen our understanding of the optimal mechanisms for COVID-19 testing. Though nasal swab tests have been the gold standard for detecting SARS-CoV-2 infection during the pandemic, a recent preprint in *medRxiv* analyzed the sensitivity of conventional nasal swab versus saliva samples for detecting early SARS-CoV-2 infections and found that “high-sensitivity tests that use saliva can detect SARS-CoV-2 infection days earlier than low-sensitivity tests that use nasal swabs.” Moreover, the authors found that it “was possible to observe a high ... viral load in saliva samples while the paired nasal swab was either negative or had low ... viral load.” What we can glean from this and other burgeoning studies is that both the site of sampling and test sensitivity are important parameters that should be considered to ensure early detection of SARS-CoV-2 infection. Adding to the story regarding testing sampling sites, a *JAMA* article published on April 29 highlights reports and clinical observations of severe complications that have arisen from nasopharyngeal sampling (nasal swab tests), which can potentially impact “adjacent vital structures (e.g, orbit, skull base, rich vasculature”). Summarizing more than a year’s worth of data, studies, and public health measures, an in-depth review published yesterday in *Nature* captures and contextualizes the nuances and evolution of COVID-19 testing. This review “details how test sensitivity, specificity and disease prevalence influence the interpretation of test results.” The review also describes the changing role of testing during the COVID-19 pandemic, including the use of genomic surveillance to track SARS-CoV-2 transmission around the world, the use of contact tracing to contain disease outbreaks and testing for the presence of the virus circulating in the environment.” [Editor’s comment: Given that the COVID-19 pandemic will likely not be the last of its kind, what we can extract as lessons and solid data from this current pandemic — which has elicited the “largest global testing programme in history” — will be vital for informing future testing efforts in emergency situations.]

---

### Other COVID-19 News
As the devastating COVID-19 crisis in India — which has been the subject of ongoing media coverage — continues to unfold, a recent Nature article published last Friday commented on an open letter that was written by India's leading scientists to Prime Minister Narendra Modi. In this letter, the scientists urged the government to adopt rapid and systematic changes that can mitigate the onslaught of SARS-CoV-2 infections and related deaths.

*Nature*: One Million Coronavirus Sequences: Popular Genome Site Hits Mega Milestone

*Science*: Household COVID-19 Risk and In-Person Schooling

*NIIH Director's Blog*: A Real-World Look at COVID-19 Vaccines Versus New Variants

*BMJ*: Should Masks Be Worn Outdoors?

*Lancet*: Symptom Study App Provides Real-World Data on COVID-19 Vaccines

*Science*: How SARS-CoV-2 First Adapted in Humans

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