AAMC Coronavirus Update
May 19, 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: 164,387,580 confirmed cases (3,407,915 deaths)
  - 4,543,419 new cases this week (5,642,661 cases 14 days ago)
- United States: 33,008,319 confirmed cases (587,493 total deaths)
  - 220,369 new cases this week (337,209 cases 14 days ago)
  - 4,287 deaths this week (5,062 deaths 14 days ago)
  - 454,120,086 total tests
- U.S. Hot Spots
  - Florida: 3,007 average daily new cases in the last 7 days (-15% change in daily cases in the last 7 days)
  - Texas: 2,041 (-11%)
  - Michigan: 1,834 (-32%)
  - New York: 1,661 (-24%)
  - Pennsylvania: 1,550 (-28%)
- U.S. COVID-19 Vaccine Distribution and Administration
  - Total doses delivered: 349,210,095
  - Total doses administered: 277,290,173

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 work is still early, but progress is being made on a pancoronavirus vaccine. A large multi-institutional group led by investigators at Duke published in *Nature* the result of inoculation of macaques with a multimeric SARS-CoV-2 receptor-binding domain nanoparticle adjuvanted with 3M-052/Alum. The resulting sera was able to neutralize multiple variants of SARS-CoV-2, including B.1.1.7, B.1.351 (first isolated in South Africa), and P-1 (first isolated in Brazil). The sera was also able to cross-neutralize betacoronaviruses, including SARS-CoV-1, and several bat and pangolin coronavirus species. While the titers were lower against many of the viruses other than SARS-CoV-2, the authors felt that the potential exists for vaccines like the one they modeled to have utility in protection against future coronavirus epidemics. [Editor’s comment: This is early work, but the fact that some level of blockage of the receptor-binding domain carried from one betacoronavirus type to another bodes well for attempts to prevent future pandemics. Coronaviruses seem to be particularly problematic, and finding a significant chink in their armor is reason for optimism.]

Treatment News

They seem to be very late to the party, but Sanofi and GSK now have Phase 2 data that their candidate SARS-CoV-2 vaccine effectively produces neutralizing antibody responses. Their first candidate failed during preliminary clinical trials in 2020, so the companies can be admired for their persistence. The vaccine is a combination of a recombinant spike protein produced using insect cells (Sanofi’s technology) and GSK’s adjuvant. The study results, announced in a press release, involved 722 volunteers age 18 or older and three different dosage sizes (5, 10, and 15 micrograms of antigen). There was 95%-100% seroconversion after a two-dose regimen regardless of dosage. Antibody titers were higher in younger individuals (18-59 years old), and there were very good antibody levels after a single injection in people who had been previously infected with SARS-CoV-2, which suggested to the company that the vaccine has potential as an immune booster. The press release did not have many details regarding the actual neutralizing antibody titers — nor the relative *in vitro* effects against different mutants. The companies are now planning a 35,000-participant Phase 3 study using the 10-microgram dosage. According to *STAT*, that Phase 3 study will test two different versions of the spike protein: one based on the original virus isolated in Wuhan, and another based on the B.1.351 variant identified in South Africa. [Editor’s comment: Both companies, Sanofi and GSK, have long made vaccines, so the failure of their first vaccine version was particularly disappointing. Studying new versions of the vaccine based on B.1.351 may give Sanofi and GSK important therapeutic benefits that could allow them to define a different niche than existing vaccines.]

Demonstrating that hope never dies, Quebec-based Medicago also announced the results of a Phase 2 study for a SARS-CoV-2 vaccine that combines their antigen and a GSK-developed adjuvant. Study results were published as a non-peer reviewed preprint on *medRxiv*. The Medicago vaccine is a virus-like particle produced by plants and administered in combination with GSK’s adjuvant AS03. The vaccine is an assembly of trimers of recombinant spike protein in a lipid droplet. The study evaluated 42-day safety and immunogenicity, including both neutralizing antibodies and cell-mediated immunity. Adverse events were described as “mild or moderate and of transient duration.” Older adults (age 65 and up) had fewer adverse events than younger adults. Muscle ache, fatigue, and/or headache was seen in approximately 60% of participants. Both cohorts, younger and older, produced antibody responses after two doses that were roughly tenfold higher than the titers of patients recovered from COVID-19. [Editor’s comment: Vaccine developers clearly have hope that there will be a market for booster vaccines —
or that vaccines will still be needed in parts of the world beyond the United States. This vaccine seems most similar to the Sanofi-GSK vaccine, noted above, and the Novavax vaccine, which is also a recombinant protein-adjuvant combination.]

A real-world study from Israel that was published in JAMA demonstrated the effectiveness of the Pfizer SARS-CoV-2 vaccine (BNT-162b2) in the prevention of both asymptomatic and symptomatic infection in health care workers. 6,710 participants were periodically tested for SARS-CoV-2. The adjusted incidence rate ratio for vaccinated individuals was 0.03 for symptomatic infection and 0.14 for asymptomatic infection (compared to unvaccinated individuals). The study took place between Dec. 20, 2020, and Feb. 25, 2021. 5,953 (88.7%) health care workers had received at least one dose of the BNT-162b2 vaccine, 5,517 received two doses (82.2%), and 757 (11.3%) were unvaccinated. Symptomatic COVID-19 occurred in eight fully vaccinated individuals (seven or more days after their second dose) in comparison to 38 unvaccinated health care workers. The rates were 4.7 per 100,000 person-days and 149.8 per 100,000 person-days in the two cohorts. Asymptomatic infection was detected in 19 vaccinated people and 17 unvaccinated, for rates of 11.3 versus 67 cases per 100,000 patient days. Thus, the vaccine was effective against both symptomatic and asymptomatic infections. There were changes in the polymerase chain reaction (PCR) testing schedule over time that required adjustment. From Dec. 20 to Jan. 2, health care workers were screened biweekly or monthly by risk. From Jan. 3-14, all health care workers were screened. From Jan. 15 to the study’s conclusion, health care workers with medium to high exposure risk and all unvaccinated individuals were screened weekly-to-monthly. All participants had access to PCR testing at their own discretion. [Editor’s comment: There are some issues with how testing was carried out, since unvaccinated individuals were more likely to be tested, but there can be little doubt that there was an enormous rate differential between those who were vaccinated and those who were not. Five cases of symptomatic disease in 100,000 person-days is a remarkably low rate of infection. Masks were probably in use, so this shouldn’t be used a justification to drop masks, but it is nice evidence that vaccines make an enormous difference.]

Using a press release, Moderna announced preliminary results from a Phase 2/3 study of their SARS-CoV-2 vaccine (mRNA-1273) in adolescents 12-17 years old that was called “TeenCOVE.” The study completed enrollment with 3,235 volunteers who were randomized 2:1 to the vaccine. The vaccine was 96% effective in participants who had received at least one vaccine dose. There were 12 cases of symptomatic disease that occurred at least 14 days after the first dose of vaccine. Symptomatic disease was defined as any one COVID-19 symptom combined with a positive PCR test. The company noted that the low incidence of serious disease in adolescents meant that they needed to study milder disease than the case definitions they used for their primary licensure study in individuals age 18 and older. The company is continuing follow-up and states that they plan to discuss filing for an extension to their emergency use authorization (EUA) with the Food and Drug Administration (FDA).

The rapid spread of the B.1.617.1 variant first identified in India has led to concerns regarding the potential effectiveness of the Pfizer and Moderna vaccines against that variant. Investigators in the United States evaluated post-vaccine and convalescent sera using live virus neutralization assays and published the results as a non-peer reviewed pre-print in bioRxiv. They found that B.1.617.1 is 6.8fold more resistant to sera in both groups — convalescent and post-vaccine — than the original wild-type virus had been. However, the sera were still well above the levels of antibody needed to effectively neutralize the virus.

The FDA extended the EUA for the Pfizer vaccine to 12- to 15-year-olds, and the CDC’s Advisory Committee for Immunization Practices recommended that it be used in that population.
Clinical News

The United Kingdom’s RECOVERY Trial has been a leader in defining better treatment options for hospitalized patients with COVID-19. The study is a randomized, controlled, open-label trial that compares the addition of an experimental treatment to standard care to the outcomes of people receiving standard care alone. In results published in the *Lancet*, investigators evaluated the effect of the addition of convalescent plasma on 28-day mortality. 11,558 patients were eligible for the study and were randomized to standard care or standard care plus convalescent plasma. The outcomes were that convalescent plasma made no clinical difference in any subset, including people who lacked a positive antibody titer at the time of randomization. The results were similar whether mortality rates or the proportion of patients discharged within 28 days were used. [Editor’s comment: Sadly, convalescent plasma does not seem to have a beneficial effect as a COVID-19 therapeutic in hospitalized patients, so its use as an anti-COVID-19 treatment in patients with established disease can now be dropped. There may still be a role for convalescent plasma in patients with compromised immune systems, but the niche is much smaller than had been hoped. RECOVERY was a much better way to answer this therapeutic question than the immediate use of this product in nearly 100,000 United States patients with virtually no evidence.]

Policy News

On May 13, the CDC updated their public health recommendations for fully vaccinated people in non-health care settings. Key updates included the following modifications regarding mask wearing and testing: “[F]ully vaccinated people no longer need to wear a mask or physically distance in any setting, except where required by federal, local, tribal, or territorial laws, rules, and regulations, including local business and workplace guidance.” Moreover, “fully vaccinated people can refrain from testing following a known exposure unless they are residents or employees of a correctional or detention facility or a homeless shelter.”

In a May 5 statement released by the FDA, the agency provided context surrounding their new report, *Resiliency Roadmap for FDA Inspectional Oversight*. The statement and report outline the mechanisms that the FDA used to respond to the pandemic and the measures that “the agency is taking in order to resume standard operational levels of inspection activities.” According to Acting FDA Commissioner Janet Woodcock, MD, “the FDA experienced unprecedented and unique challenges during the SARS-CoV-2 pandemic. In particular, our inspection, surveillance and compliance activities were significantly impacted. This plan provides the public with a transparent picture of both the successes and challenges we’ve faced in these areas over the past year, as well as our plan moving forward.”

Coronavirus and Health Equity

New research published in *Social Science and Medicine* found a divergence among racial groups when Americans are informed about the inequitable impacts of the pandemic. Specifically, after learning about the disproportionate impact of COVID-19 on communities of color, White Americans who reported “warm” feelings toward Black Americans (as measured on a “feeling thermometer”) endorsed a vigorous public health response — while White people who felt “cool” toward their Black compatriots became less willing to support strong public health measures. The authors noted that their findings present a
dilemma: The same public health information can be interpreted very differently with “opposite effects for different categories of citizens” and suggest more carefully tailored messaging to avoid unintended consequences.

A new ecological cohort study published in *JAMA Network Open* found that there was a significant correlation between county-level income inequality and COVID-19 cases and deaths during the pandemic, particularly during the summer of 2020. The authors suggested that targeted interventions should be focused on such areas going forward.

Findings of a study presented at the American College of Cardiology’s 70th Annual Scientific Session showed that among individuals with a history of heart disease, those with the greatest social adversity (as measured by a combination of “income and financial security, employment, education, health insurance status, food insecurity and neighborhood quality” data) were 46% less likely to report work-from-home flexibility and 31% less likely to be able to follow social distancing guidelines compared to those with the most favorable social risk profile. The study author concluded, “We need to focus on holistic strategies to effectively fight this pandemic and ensure those not afforded the privilege of personal protection, social distancing and work flexibilities are prioritized with vaccine outreach to avoid further compounding existing health inequalities.”


**PatientEngagementHIT: HHS, HUD Urge Community Health Partnership for COVID Health Equity**

**Scientific American: COVID's Outsized Impact on Asian Americans Is Being Ignored**

**New York Times: In Covid Vaccine Data, L.G.B.T.Q. People Fear Invisibility**

**New York Times: Many Unvaccinated Latinos in the U.S. Want the Shot, New Survey Finds**

## Research News

As the COVID-19 pandemic evolves, it is critical to underscore that the nature of investigative research is likewise evolving and mutating. As we highlighted in our last newsletter, the spotlight has moved far beyond the lung, and it is abundantly clear that COVID-19 is not simply a pulmonary disease but rather a disease that leads to a plethora of symptoms that involve a host of other organs. Scientific studies are beginning to usher in a phase of COVID-19 biomedical research that explores COVID-19 pathology in a range of organs and cellular structures and processes; nailing down how SARS-CoV-2 modifies, hijacks, and impairs cellular pathways and signaling. On May 3, researchers published data in *Science* that unveiled the pathophysiology of neurological disorders of COVID-19, which remain poorly understood. In addition to fatigue, memory impairments, and brain fog, olfactory and taste dysfunction are common symptoms of COVID-19. Using “virologic, molecular, and cellular study of the olfactory neuroepithelium of seven patients with COVID-19 presenting with acute loss of smell (anosmia),” researchers found that “the olfactory neuroepithelium may be a major site of SARS-CoV2 infection with multiple cell types, including olfactory sensory neurons, support cells, and immune cells, becoming infected.” Moreover, evidence suggests that “SARS-CoV-2 replication in the olfactory neuroepithelium was associated with local inflammation.” In this study, the researchers used the golden Syrian hamster as a model and found that SARS-CoV-2 infection
“induced acute anosmia and ageusia” in these model organisms, “lasting as long as the virus remained in the olfactory epithelium and the olfactory bulb” — a recapitulation of disease presentations in humans. Regarding timeline, “olfactory mucosa sampling from patients showing long-term persistence of COVID-19-associated anosmia revealed the presence of virus transcripts and of SARS-CoV-2-infected cells, together with protracted inflammation.” These results suggest that “prolonged or relapsing symptoms of COVID-19, such as loss of smell,” is likely caused by “SARS-CoV-2 persistence and associated inflammation in the olfactory neuroepithelium.” [Editor’s comment: Expeditious work has been done in correlating the pathological processes characterizing SARS-CoV-2 infection with the clinical manifestations of COVID-19. Elucidating COVID-19 pathogenesis has and will continue to involve a coordinated and parallel set of biomedical approaches, such as sequencing, clinical trials, patient sample collection, cataloging and characterizing new symptoms, and — as we see from the data above — nailing down the relationship between SARS-CoV-2 infection and cellular processes. The use of in vitro and in vivo studies, coupled with patient samples, will begin to crystallize our understanding of how SARS-CoV-2 viral entry modifies cellular structures and processes in a way that elicits physical symptoms — a key step in driving potential therapeutics.]

It is known that that adults with certain medical conditions — including cancer, chronic lung diseases, dementia, heart conditions, HIV infections, and Type 1 or Type 2 diabetes — can be “more likely to get severely ill from COVID-19.” These important observations have informed vaccine distribution protocols, but countless critical questions remain. Researchers are just beginning to decipher the cellular and molecular mechanisms by which SARS-CoV-2 modifies and disrupts physiological processes and exacerbates the pathological progression or worsening of preexisting diseases, such as cancer. Given that “emerging clinical reports have noted a significant increase in new-onset hyperglycemia, diabetic, ketoacidosis (DKA), and diabetes in patients with COVID-19,” it is crucial to investigate how SARS-CoV-2 affects normal functioning of the pancreas — “an urgent unmet need with fundamental healthcare implications.” In a recent paper published this week in Cell, researchers investigated the “intricate relationship between COVID-19 and diabetes,” noting that “while pre-existing diabetes is associated with severe COVID-19, it is unclear if COVID-19 severity is a cause or consequence of diabetes.” To parse out this question and “mechanistically link COVID-19 to diabetes,” researchers used in vitro and ex vivo techniques to test whether “insulin-producing pancreatic β-cells (beta) can be infected by SARS-CoV-2 and cause β-cell depletion.” Significant findings of the study were that SARS-CoV-2 preferentially infects beta cells in vitro as well as beta cells in patients with COVID-19. Moreover, “SARS-CoV2 spike protein and viral infection” induced apoptotic kinases and elicited beta cell death. Though limitations of this study exist (e.g., “small sample size of pancreas samples of patients with COVID-19”) and many details are still unclear (e.g., “how the virus migrates to the pancreas in patients with severe COVID-19”), the authors believe that their “key observations support a mechanism through which SARS-CoV-2 can directly drive beta cell damage to cause clinical type 1 diabetes linked to hyperglycemia.”

“Through patient interactions and community exposure, health care personnel (HCP) are at high risk for exposure to SARS-CoV-2.” An advantage of the early distribution of vaccines to this group is that it “provided an opportunity to examine vaccine effectiveness in a real-world setting.” On May 14, the CDC released an early MMWR detailing the results from distribution of two vaccines, Pfizer and Moderna, to HCP. For the study, HCP were enrolled in 33 sites across 25 states, and interim analysis, which was collected from January to March 2021, found that “a single dose of Pfizer-BioNTech or Moderna COVID-19 vaccines to be 82% effective against symptomatic COVID-19 and 2 doses to be 94% effective.” [Editor’s comment: As the administration expands (e.g., the 12- to 15-year-old subgroup) and amplifies its vaccination goals (e.g., the hope that at least 70% of the U.S. adult population will have one dose by July 4), real-world evidence demonstrating the effectiveness of the vaccines will continue to be important.]
Lancet: Post-Acute Effects of SARS-CoV-2 Infection in Individuals Not Requiring Hospital Admission: A Danish Population-based Cohort Study


JAMA: Feasibility of Face Covering in School-Aged Children With Autism Spectrum Disorders and Attention-Deficit/Hyperactivity Disorder

Science: Clonal Analysis of Immunodominance and Cross-reactivity of the CD4 T Cell Response to SARS-Cov-2

JAMA: Perinatal Outcomes During the COVID-19 Pandemic in Ontario, Canada

CDC MMWR: Rapid Emergence and Epidemiologic Characteristics of the SARS-CoV-2 B.1.526 Variant — New York City, New York, January 1–April 5, 2021

Other COVID-19 News

Nature Human Behavior: Trust in Science, Social Consensus and Vaccine Confidence

JAMA: Digital Health Passes in the Age of COVID-19 — Are “Vaccine Passports” Lawful and Ethical?

JAMA: COVID-19 Vaccines in Patients With Cancer—A Welcome Addition, but There Is Need for Optimization

Nature: Pfizer COVID Vaccine Protects Against Worrying Coronavirus Variants

Wall Street Journal: Covid-19 Hospital Patients Tend to Be Younger Now

JAMA: Precision Medicine for COVID-19 — Phenotype Anarchy or Promise Realized?

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