AAMC Coronavirus Update

November 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 Fridays.

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: 256,395,565 confirmed cases (5,136,960 total deaths)
- United States: 47,542,749 confirmed cases (768,836 total deaths)
  - 673,695 new cases this week (new daily reported cases rose 31% in the past week)
  - 10,866 deaths this week (new daily reported deaths fell 4% in the past week)
  - COVID-19-related hospitalizations rose 3% in the past week
- U.S. Hot Spots
  - Michigan: 8,407 average daily new cases in the last 7 days (+86% change in daily cases in the last 7 days)
  - New York: 5,891 (+23%)
  - California: 5,529 (-2%)
  - Pennsylvania: 5,363 (+14%)
  - Ohio: 5,180 (+20%)
- U.S. COVID-19 Vaccine Distribution and Administration
  - Total doses delivered: 561,149,025
  - Total doses administered: 446,250,342
  - People fully vaccinated: 195,713,107 (58.9% of US population)

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

Are vaccinated people who catch the Delta variant actually contagious? This has been an important question with real significance as the Thanksgiving and Christmas seasons approach and families swap photos of their vaccination cards. Dutch investigators published a relevant study as a non-peer reviewed preprint in *MedRxiv*, in which they evaluated the effectiveness of vaccination in Dutch households between Aug. 9 and Sept. 24. The setting was a time when Delta was the predominant variant (97%), requirements for non-pharmacologic interventions like masks were being relaxed, and a major eruption of SARS-CoV-2 infections occurred, particularly in unvaccinated individuals. Their dataset, based on contact tracing, included 7,771 contacts of 4,921 index cases (infected people subject to contact tracing). Of the index cases, 33.5% were fully vaccinated and 12% were partially vaccinated. Of the contacts, 4,189 (54%) were fully vaccinated, and 641 (8.2%) were partially vaccinated. In the Netherlands 71% of adults were fully vaccinated at the time of the study, so the high proportion of index cases who were unvaccinated is by itself informative. There were important behavioral correlations in the study population. For unvaccinated index cases, 59.1% of household contacts were also unvaccinated, while for vaccinated index cases, only 11.6% of household contacts were unvaccinated. The crude transmission rate to unvaccinated household contacts was 22% for unvaccinated index cases and 13% for fully vaccinated index cases. Transmission to vaccinated contacts was not affected by the index case's vaccine status, at 11-12%, probably because of the vaccine's protective effects on those contacts. [Editor's comment: Good news, bad news. Vaccination of the index cases meant they were less likely to transmit within their household, but the rate wasn't zero. So, vaccinated people can transmit. But most significantly, vaccinated people made up a minority of the index cases despite their comprising 71% of the population. What about the holidays? Be sensible. And while it may be painful, I'd recommend deferring get-togethers that include unvaccinated family members — they're too much of a risk to everyone else.]

Policy News

As reported in a Nov. 19 press release, the Food and Drug Administration (FDA) has "amended the emergency use authorizations (EUA) for both the Moderna and Pfizer-BioNTech COVID-19 vaccines, authorizing use of a single booster dose for all individuals 18 years of age and older after completion of primary vaccination with any FDA-authorized or approved COVID-19 vaccine." It is important to note that the two-step process that has been previously utilized still applies: the Centers for Disease Control and Prevention (CDC) must greenlight this decision before it's official. The CDC Advisory Committee on Immunization Practices met earlier today to discuss further clinical recommendations. As reported by *Politico*, the panel voted 11-0 in favor of recommending that all adults in all age groups be made eligible for getting a booster shot, and also voted 11-0 in favor of recommending that every adult age 50 and over should receive a booster.

Clinical and Treatment News

A group in London evaluated the vaccine efficacy of a booster dose of the Pfizer/BioNTech SARS-CoV-2 vaccine. Their results were published as a preprint on the Knowledge Hub and the data came from the National Immunisation Management System on Nov. 1. The study used a test-negative, case-control design enrolling people over the age of 50 who had received either the Pfizer or AstraZeneca (AZ) SARS-CoV-2 vaccine as their primary immunization. The test-negative comparison was between individuals with

symptoms and a positive PCR test for SARS-CoV-2 and individuals with symptoms and a negative test. Pfizer booster doses were given 140 or more days after the second dose in the primary series and after Sept. 13 (which means the outcomes are very short term). Data from a total of 271,747 symptomatic people were evaluated. There were 149,434 symptomatic people tested with a PCR who received the AZ vaccine and no booster, 84,506 who received the Pfizer vaccine with no booster, and 13,569 unvaccinated people. Looking at symptomatic patients 14 days or later post-boost, there were 1,266 people primarily immunized with AZ and a Pfizer booster and 5,905 people who had a Pfizer primary series and Pfizer boost. The effectiveness of the AZ-Pfizer sequence was 93.1% compared to unvaccinated individuals, followed by Pfizer at 94%. [Editor's comment: The data is very short term, but the Pfizer booster was clearly beneficial whether the primary vaccination was AZ or Pfizer. Of course, what we really want to know is how long the booster retains its benefit, and it will be months before we know that.]

In one of those useful studies with a straightforward design, a research group from Mongolia and Stanford University compared the antibody responses of four different vaccines against nine different SARS-CoV-2 variants. The study involved samples from 196 Mongolian participants who received a full series from one of four vaccines: Pfizer, AZ, Sputnik V (Russia), or Sinopharm (China). The study evaluated receptor-binding antibody concentrations post-vaccination. The results were published as a preprint in *Cell Host & Microbe*. Individuals were selected so that there was a roughly even distribution of vaccine type (47, 50, 45, and 54, respectively), and balance for age, sex, and time since second vaccine dose. The investigators found striking differences between the four vaccines. Pfizer induced the highest antibody concentrations, followed by AZ, Sputnik, and then Sinopharm. The pattern was the same for all variants, although in some cases AZ and Sputnik were similar. Testing for antibodies to nucleocapsid antibodies (an antigen not present in the Pfizer, AZ, or Sputnik vaccines) found a small number of people who probably had a history of COVID-19 infection of which they were not aware. The authors concluded that there were meaningful differences in the ability of the vaccines to produce SARS-CoV-2 antibodies among these four vaccines, and that those differences were large enough that they might correspond with clinical efficacy (which they did not assess in this paper). [Editor's comment: Examining the antibody titer figures in this manuscript makes very clear that there are real differences in vaccines. The Pfizer vaccine is significantly more potent than the other three, and Sinopharm's inactivated virus vaccine looks seriously less effective. As the world tries to protect its population from COVID-19, studies like this one can be very useful.]

An important logistical question for health care providers (and you and me) is whether it's safe and appropriate to administer a SARS-CoV-2 vaccine and influenza vaccine at the same time. Investigators in the U.K. pursued this question and published the result of their study in the *Lancet*. The study randomized individuals receiving their second COVID-19 vaccine dose 1-to-1 to administration of their influenza vaccine concurrently or three weeks later. The study was placebo controlled, so all enrollees received two shots the first week and one shot at week three. Participants were evaluated for symptoms and for their antibody titers to both vaccines. The SARS-CoV-2 vaccines studied were from Pfizer and AZ, while the influenza vaccines were either trivalent or quadrivalent. There were basically no differences in outcomes between groups, and influenza vaccine did not cause more serious systemic symptoms than the SARS-CoV-2 vaccines alone. [Editor's comment: It's time to get your flu shot, and you might as well do it at the same time as your SARS-CoV-2 booster.]

Information regarding the frequency and characteristics of Long-COVID-19, aka post-acute sequelae of COVID-19 (PASC), are becoming available. Researchers used U.K. data from 81 million patients with electronic health records to identify 273,618 survivors of COVID-19. Results were published in *PLOS Medicine*. The authors looked for key COVID-19-related symptoms during the entire six months following diagnosis (including acute

disease), and during the period between three and six months after diagnosis. For comparison, they also looked at patients who had experienced influenza. 57% had one or more COVID-19-related symptom during the six-month span, 36.6% during the 90-180-day period. Notable symptoms included difficulty breathing (18.7% within six months, 7.9% within 90-180 days), fatigue/malaise (12.8% / 5.9%), chest/throat pain (12.6% / 5.7%), headache (8.7% / 4.3%), other pain (11.6% / 7.2%), abdominal symptoms (15.6% / 8.3%), cognitive symptoms (7.9% / 4%), and anxiety/depression (22.8% / 15.5%). [Editor's comment: What impressed me most was the fact that 37% of patients were still symptomatic three to six months after their acute COVID-19 diagnosis. Even if the mortality wasn't so high, the threat of Long-COVID-19 should encourage those who still remain unvaccinated to get immunized.]

Nature: Burdens of Post-acute Sequelae of COVID-19 by Severity of Acute Infection, Demographics and Health Status

Coronavirus and Health Equity

This brief from Kaiser Family Foundation outlines the current state of race and ethnicity data collection for COVID-19 booster shots. The CDC and most states are not currently reporting race and ethnicity data of booster recipients — a significant barrier to assessing inequities in booster shot distribution. Community health centers, which do collect this data for their booster doses, report rates representative of their overall patient populations, which are 62% people of color. Limited data from five states suggests that White people are more likely to have received a booster as compared to other groups.

Time: Biden's Health Equity Task Force Highlights Progress in Addressing Disparities

JAMA: Disparities in COVID-19 Outcomes by Race, Ethnicity, and Socioeconomic Status

Research News

Throughout the COVID-19 pandemic, polypeptides have been front and center of scientific inquiry — and it's easy to see why. SARS-CoV-2 initiates infection of human cells by the binding of its spike protein via the receptor-binding domain (RBD) to angiotensin-converting enzyme 2 (ACE2), a protein found on the surface of many cells. Though this protein-protein interaction is a crucial step in SARS-CoV-2 infection, lipids — which form the structural basis of the membrane bilayer of various cells and organelles— also play a critical role in COVID-19 pathogenesis. To accomplish viral entry, viruses have been known to exploit carbohydrates, known as glycans, that are attached to protein and lipid carriers on host epithelial cells. A Nov. 9 *Nature* article published by Nguyen et al. presents convincing data that the RBD of the SARS-CoV-2 spike protein recognizes *distinct* oligosaccharides containing sialic acid. These so-called sialoglycans are densely displayed on the surface of mammalian cells. Understanding the binding of viral proteins to host membrane complexes containing oligosaccharides is a crucial step in unraveling the pathogenesis of many viruses, such as orthomyxoviruses, paramyxoviruses, picornaviruses, reoviruses, polyomaviruses, and adenoviruses to name a few. In their investigation, Nguyen et al. analyzed the binding of a library of glycans to the SARS-CoV-2 RBD and found that the RBD prefers monosialylated gangliosides. Using complementary loss-of-function analyses in cell-based studies, the authors found that "RBD binding and SARS-CoV-2 pseudotyped virus entry in ACE2-expressing cells is decreased following depletion of Sia levels on cells pharmacologically, genetically or enzymatically."

[Editor's comment: An accompanying *Nature* perspective covering the original manuscript by Nguyen et al. nicely distills the novel role of glycolipids in SARS-CoV-2 infection, as well as provides context for the importance of these findings. "The discovery of sialylated glycans, especially glycolipids, as a key host factor for viral infection provides an important insight into the virus life cycle and unlocks the potential for new antiviral treatments." For good reason, the study of science for investigative purposes breaks down whole entities into traceable pieces that have similar properties. For example, we study protein-protein interaction, protein-DNA interactions, lipids, vesicles, membranes, the nucleus, and a host of other cellular organelles and molecules as distinct entities. The challenge is then to bring these pieces back together to answer the question: how do these distinct pieces work in concert, generating the complexity that underlies health and disease? This paper is a wonderful example of how the examination of glycans and lipids — using both *in vitro* and *in vivo* techniques — sheds light on the functionality of proteins, which in turn expands our knowledge on SARS-CoV-2 infection and pathogenesis. It is important to remember that work on a specific virus — in this case SARS-CoV-2 — leads to techniques, extrapolations, and potential treatments that may be applied to a range of other viruses.]

A Nov. 15 publication in *Nature* summarizes recent data showing that SARS-CoV-2 infection of mothers "can prime the fetal immune response indirectly even when the virus does not infect the fetus." An Oct. 6 *Nature* manuscript by Sarah Gee et al. characterized the immunology of neonates born to mothers with confirmed SARS-CoV-2 infection during pregnancy. The authors found that maternal SARS-CoV-2 infection affects the neonatal immune system by leading to increased percentages of natural killer cells, Vδ2+ γδ T cells, and regulatory T cells in neonates born to mothers with recent or ongoing infection compared with those born to recovered or uninfected mothers. The authors also detected increased plasma cytokine levels evident in neonates and mothers within the recent or ongoing infection group as well as enhanced cytokine functionality in neonates born to SARS-CoV-2-exposed mothers, compared to those born to uninfected mothers. Interestingly, the Nov. 15 accompanying report states, "the increased T cell cytokine functionality noted by Gee et al. was evaluated in a subset of neonates and was found not to be specific for SARS-CoV-2 peptides in seven of eight neonates (88%). These data indicate that fetal immune imprinting due to a maternal SARS-CoV-2 infection during pregnancy is probably not a result of direct exposure to the virus and is instead a result of fetal exposure to an inflammatory environment." Regarding the connection between in utero exposure to environmental factors and the immunology of neonates, the authors conclude that there is indeed an "immunological legacy imprinted on the neonate following maternal SARS-CoV-2 exposure."

Science: Immune Signatures Underlying Post-acute COVID-19 Lung Sequelae

Cell: Using Soft X-Ray Tomography for Rapid Whole-Cell Quantitative Imaging of SARS-CoV-2-Infected Cells

JAMA: Assessment of Prolonged Physiological and Behavioral Changes Associated With COVID-19 Infection

Nature: SARS-CoV-2 Infection and Replication in Human Gastric Organoids

CDC *MMWR:* Effectiveness of 2-Dose Vaccination with mRNA COVID-19 Vaccines

Cell: Identification of a Therapeutic Interfering Particle — A Single-Administration SARS-CoV-2 Antiviral Intervention With a High Barrier to Resistance

The Lancet: One World, One Health, One Virology of the Mysterious Labyrinth of

Coronaviruses: the Canine Coronavirus Affair

Testing News

JAMA: The Flawed Science of Antibody Testing for SARS-CoV-2 Immunity

Other COVID-19 News

The Economist: New Antiviral Drugs Mark a Big Turning Point in the Covid-19 Pandemic

The Lancet: How an Outbreak Became a Pandemic: A Chronological Analysis of Crucial Junctures and International Obligations in the Early Months of the COVID-19 Pandemic

JAMA: The Financial Effects and Consequences of COVID-19: A Gathering Storm

The New York Times: Moderna and U.S. at Odds Over Vaccine Patent Rights

JAMA: Pediatric COVID-19 Vaccines—What Parents, Practitioners, and Policy Makers Need to Know

NIH *Director's Blog:* Early Data Suggest Pfizer Pill May Prevent Severe COVID-19

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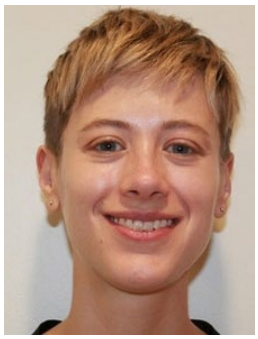

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