AAMC Coronavirus Update
December 3, 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.

Please share/forward this newsletter freely.

Today’s Numbers

- **World:** 264,438,500 confirmed cases (5,238,702 total deaths)
- **United States:** 48,883,401 confirmed cases (785,916 total deaths)
  - 686,583 new cases this week (new daily reported cases rose 15% in the past week)
  - 7,485 deaths this week (new daily reported deaths fell 3% in the past week)
  - COVID-19-related hospitalizations rose 12% in the past week
- **U.S. Hot Spots**
  - New York: 7,057 average daily new cases in the last 7 days (+3% change in daily cases in the last 7 days)
  - Ohio: 6,880 (+21%)
  - Michigan: 6,818 (-20%)
  - Pennsylvania: 6,742 (+12%)
  - Illinois: 6,088 (+32%)
- **U.S. COVID-19 Vaccine Distribution and Administration**
  - Total doses delivered: 578,263,565
  - Total doses administered: 464,445,580
  - People fully vaccinated: 197,838,728 (59.6% 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

While we usually lead off this newsletter with a study that interests us, this week the lead news will be about the Omicron variant. (It’s pronounced OH-mik-ron or AH-mik-ron, not omni-cron.) What we don’t know about Omicron yet far exceeds what we do know, and that lack of knowledge seems to have produced confusion and concern across the community. The Omicron variant was first recognized in Botswana and South Africa, adjacent countries in southern Africa. The variant had actually been detected in the Netherlands several days before the report from South Africa, but the significance of the Dutch isolates became clearer when the South African government reported a rapid rise in the incidence of COVID-19 in Gauteng Province. Gauteng contains major cities Johannesburg and Pretoria. Once the World Health Organization declared Omicron (aka B.1.1.529) a “variant of concern,” countries began to limit international travel.

What is known about Omicron?

- Omicron has a large number of mutations, 30 or so in the spike region, relative to the original SARS-CoV-2 virus that originated in Wuhan. What is not yet known is what these mutations mean.
- The new variant appears to be quite contagious.
- Omicron seems to be able to infect people who have recovered from prior COVID-19 infections and some vaccinated people.
- The genetic sequence is known, and Pfizer has said they have created a DNA template the company could use to synthesize mRNA for an Omicron-specific vaccine.
- Omicron is characterized by an "s-gene dropout" similar to Alpha (B.1.1.7) and Beta (B.1.351), and distinct from Delta (B.1.617.2). What this means is that the standard PCR tests, which look for three SARS-CoV-2 gene sequences, find only two in people infected with this variant. The s-gene, one of the targets for the test, is modified in such a way that the PCR test doesn’t create a copy. That two-out-of-three signature is distinctive and a quick way to identify suspect isolates.

What do we still need to know?

- Relative to Delta, how contagious is Omicron? Will vaccinated people with breakthrough infections shed infectious Omicron as copiously as they shed infectious Delta? How does the duration of viral shedding in vaccinated breakthroughs compared to Delta?
- How well protected will people be using the currently available vaccines?
- Does a history of prior infection with SARS-CoV-2 offer some protection, and does the variant of the primary infection (Alpha, Delta, etc.) matter?
- How pathogenic is the virus? Will the age effects (i.e., more serious disease in older individuals) seen with other variants of SARS-CoV-2 also be present with Omicron?
- Will monoclonal antibodies be effective as treatment? (Regeneron has already expressed concern.)
- Will the new oral antivirals from Merck/Ridgeback and Pfizer work to prevent serious disease from Omicron?

[Editor’s comment: What to do? For now, it’s important to wait for more data. Don’t panic. And if you aren’t yet vaccinated, get vaccinated as quickly as possible.]
On Nov. 29, The Food and Drug Administration’s (FDA’s) scientific advisors, the Vaccines and Related Biological Products Advisory Committee (VRBPAC), recommended by a slim margin the authorization of an antiviral pill for COVID-19. The experts voted 13-10 in favor of authorization, with committee members in opposition expressing concerns about insufficient levels of efficacy and safety data. Even those who supported the drug’s authorization urged that it should not be used by pregnant people and should be limited to older adults. The FDA, which is not bound by the VRBPAC’s recommendation, is expected to take action on the drug soon. This drug is the first of its kind, potentially allowing for early treatment of people at high risk of severe disease but not yet hospitalized. The indications for its use would be similar to those for existing monoclonal antibody treatments, but uptake of those treatments have been moderate, likely because they require an hour-long infusion at a health care facility. Molnupiravir, made by Merck, was the first to come before the FDA. A second pill with a different mechanism of action has been developed by Pfizer, which has already applied for emergency use authorization. The committee’s discussion followed what some saw as disappointing final results in the reported 30% reduction of hospitalization and death, significantly lower than published interim reports. For further discussion of new study outcomes for molnupiravir, see the Clinical and Treatment News section below.

We thank AAMC Senior Director of Science Policy and Regulatory Counsel Heather Pierce, JD, MPH, for her contribution to the item above.

Clinical and Treatment News

Investigators at the University of Wisconsin and the Center for Disease Control and Prevention (CDC) did a tidy study comparing the amount of Delta variant shed by infected vaccinated people compared to unvaccinated people. Their results were published as a non-peer reviewed preprint in MedRxiv. Two methods were used to quantitate the virus: RT-PCR cycle threshold (CT) and plaque assays. The RT-PCR threshold count indicates the amount of viral RNA present, while the plaque assays count viable viral particles and were only used when the cycle count was less than 25. Enrolled in the trial were 699 PCR-positive individuals, 310 who had been vaccinated, 389 who had not. Low counts (less than 25 CT, indicating high levels of virus) were observed in 212 out of 310 (68%) vaccinated people and 246 out of 389 (63%) unvaccinated enrollees. Plaque assays were performed on 48 samples, and there was no difference between vaccinated and unvaccinated individuals. [Editor’s comment: While it’s been clear for a while that vaccinated breakthrough cases and unvaccinated COVID-19 cases shed similar amounts of virus, there have been discussions whether vaccinated people might be less infectious through some mechanism like coating virus with antibodies. The answer? Sadly, the plaque assays demonstrate vaccinated breakthrough cases are just as infectious as unvaccinated cases. There are just more unvaccinated cases.]

Molnupiravir, a nucleoside analog that targets the SARS-CoV-2 RNA-dependent RNA polymerase, may soon be authorized by the FDA based on its advisory committee's recommendation (see Policy News above). Preliminary results from the key study, MOVe-OUT, had been released in early October. The study enrolled non-hospitalized adults with COVID-19 who were randomized to take molnupiravir or a placebo. At the time of an Oct. 1 press release, 53 of 377 (14.1%) patients in the placebo group were hospitalized or died, while the treatment group had 28 out of 385 (7.3%) individuals who were hospitalized or died. This was heralded as a 50% reduction in progression to severe disease. A subsequent analysis was used for the FDA review, by which point 68 of 699 (9.7%) enrollees in the placebo group and 48 out of 709 (6.8%) of the enrollees in the molnupiravir group had progressed to hospitalization or death. The absolute reduction in hospitalization and death endpoints was 3%, and the relative risk reduction was 30%. There were nine deaths in the placebo group and one in the treatment group. [Editor’s
In a study that gives hope for the direction of the SARS-CoV-2 pandemic, investigators in Qatar evaluated the course of primary infections in comparison to reinfections. Results were published as a correspondence in the New England Journal of Medicine. From March through June 2020, Qatar experienced a wave of COVID-19 after which 40% of the population had antibodies to SARS-CoV-2. From January to May of 2021, Qatar suffered back-to-back waves caused by the Alpha and Beta variants. The country has a national database for COVID-19-related data, so the investigators were able to evaluate the clinical course of reinfections. There were 1,300 reinfections, which were matched 1-to-5 with people with primary infections by sex, age group, nationality, and the calendar week of the PCR test. Four out of 1,300 people with reinfection had severe disease, compared with 158 of 6,095 primary infections (an odds ratio of 0.12). There were no cases of critical (ICU admission) or fatal disease in the reinfection cohort, while there were 28 of 6,095 critical cases and 7 of 6,095 fatal cases in the primary infection cohort. The risk of severe disease from reinfection was judged to be approximately 1% of the risk of severe disease from primary infection. [Editor’s comment: The study is pre-Delta, but a history of previous SARS-CoV-2 infection appears to go a long way toward attenuating the risk of severe COVID-19. However, Delta complicates the situation, and this study could not address that issue.]

Epidemiologists in Germany have evaluated the recent uptick in infections within their country. They published their non-peer reviewed preprint in MedRxiv. Sixty-five percent of the German population is fully vaccinated. In evaluating the rapid increase in cases that began in October 2021, researchers found 41% of cases were breakthroughs in the vaccinated cohort. Only 9%-16% of cases were vaccinated people infecting other vaccinated people. Remarkably, this implies that unvaccinated people are expected to be involved in 80%-90% of new infections, either as the vector or the infected recipient. The investigators modeled interventions and found that reducing contact between vaccinated and unvaccinated people has a similar effect to increasing vaccination rates. They note that the optimum strategy probably involves both increasing immunization rates and decreasing contact with unvaccinated people. [Editor’s comment: Conceptually, reducing contact with unvaccinated people, given their higher likelihood of being a source for infection, makes logical sense. Is it discriminatory? I would argue that deciding not to be vaccinated and being willing to risk harm to others as a result is sufficient reason to justify quarantine. All of us can participate: if someone says they are unvaccinated, it’s reasonable not to invite them to holiday dinner or a New Year’s party.]

NEJM: A Possible Role for Anti-idiotype Antibodies In SARS-Cov-2 Infection and Vaccination

Science: Lung Epithelial and Endothelial Damage, Loss of Tissue Repair, Inhibition of Fibrinolysis, and Cellular Senescence in Fatal COVID-19

Science: Pfizer Antiviral Slashes COVID-19 Hospitalizations

Nature: SARS-Cov-2 Transmission Across Age Groups in France and Implications for Control

BMJ: Elapsed Time Since BNT162b2 Vaccine and Risk of SARS-CoV-2 Infection: Test Negative Design Study
Coronavirus and Health Equity

A [Nov. 29 discussion paper](#) published by the National Academy of Medicine (and co-authored by AAMC President and CEO David J. Skorton, MD) outlines the state of patient, family, and community engagement prior to the pandemic; experiences and inequities that developed or worsened during the pandemic; and the overall impact of COVID-19 on the economic, physical, and mental health of patients, families, and communities, and their relationships to health systems. The paper also includes examples of resiliency and effective engagement and recommends policy changes to improve the health of these populations.

**JAMA:** Variation in COVID-19 Mortality in the U.S. by Race and Ethnicity and Educational Attainment

Research News

Cascades, cascades, cascades. The transition from SARS-CoV-2 infection to the full-blown clinical manifestation of COVID-19 involves an exceptional amount of complex and overlapping cellular cascades — the biology of which researchers are very much still figuring out. A Nov. 19 [manuscript in *iScience*](#) uses complimentary in vivo and in vitro methods to elucidate our understanding of the cellular and molecular machinery underlying viral entry, replication, and pathogenesis. The envelope of SARS-CoV-2 is decorated with the now-infamous surface glycoprotein, Spike (S), and convincing research from 2020 shows that S binds to angiotensin-converting enzyme 2 (ACE-2) on the surface of human cells. What next? How do we get from viral binding to severe disease or even death? Luu et al. show that Pannexin-1 (Panx-1), an oligomeric protein that forms a channel expressed on the plasma membrane, is an important puzzle piece in the pathogenesis of SARS-CoV-2. The phospholipid bilayer of cells is jam-packed with transmembrane, anchored, and accessory proteins, but Panx-1 is unique. This protein contains “one of the largest mammalian pores enabling the release of small ions, nucleotides, lipids, and small RNA into the extracellular space.” In disease states such as stress, HIV, cancer, and neurodegeneration, the normally closed Panx-1 opens to release proinflammatory factors. Here, the investigators find that SARS-CoV-2 binding opens Panx-1 channels “aggressively” and for a prolonged amount of time compared to other viruses. Panx-1 opening is ACE-2, furin, and endocytosis dependent, and in turn releases adenosine triphosphate (ATP), Prostaglandin E2 (PGE2), and interleukin-1 Beta (IL-1β) — proinflammatory biomolecules — into the extracellular space. In vivo analysis of the lungs shows that, when compared to other lung diseases, such as chronic obstructive pulmonary disease (COPD), the levels of ATP, PGE2, and IL-1β are indeed elevated.

[Editor’s comment: While vaccines against SARS-CoV-2 infection were constructed and administered with unprecedented speed, it is important to remember that much remains to be learned about the pathogenesis of SARS-CoV-2 and the progression into COVID-19. This study suggests that the Panx-1 channel contributes to COVID-19 pathogenesis in three primary ways: first, opening of Panx-1 releases ATP and allows viral entry via purinergic receptors; second, “IL-1β release results in a pro-inflammatory response and recruitment of leukocytes into the area of infection; and third, the release of PGE2 into the extracellular matrix induces coagulation and vascular compromise.” The authors propose that the resulting cellular cascades partially account for the inflammatory conditions observed during COVID-19 pathogenesis, “including hypoxia, coagulation, blood pressure,
endothelial permeability, and apoptosis." From this body of work, it appears that targeting Panx-1 and/or the associated purinergic response might be a viable therapeutic target for mitigating COVID-19.

About a week ago, new research published in the American Institute of Physics journal, *Physics of Fluids*, provided estimates of the stochasticity of droplet dispersion by a cough. In plain terms, what does this mean, and how does it inform our understanding of COVID-19? In this study, investigators evaluated the distribution of the size and position of the droplets after a cough. Why? A firm understanding of how respiratory droplets move when they are released is critical for informing prevention guidelines enforced by agencies such as the CDC. In this paper, the investigators found that there is high variability of droplet evaporation and movement depending on temperature, humidity, air flow, and velocity of droplet motion. The take-home?: it's not very straightforward. For example, when looking at the trajectories of intermediate-sized droplets, the authors found that while some droplets remained “suspended within the puff,” some droplets travelled horizontal distances of over 2 meters within 60 seconds. Thus, “in the absence of face coverings, an unprotected cough may not be safe at 2 meters away from the emitter, even outdoors.”

[Editor’s comment: The pandemic has been characterized by countless examples of indoor and outdoor events that have contributed to the spread of COVID-19 (e.g., the July outbreak in Barnstable County, Massachusetts). Through it all, there has been a chorus of voices promoting the use of non-pharmaceutical interventions (NPIs) such as masks and social distancing to curb the spread of COVID-19. The results from this study suggest that the large variability of viral movement during short-range transmission makes estimating risk complex. What we do know is that NPIs are effective in mitigating the spread of COVID-19.]

*Medrxiv*: Six-Month Sequelae of Post-vaccination SARS-Cov-2 Infection: A Retrospective Cohort Study of 10,024 Breakthrough Infections


*Science*: Administration of Aerosolized SARS-CoV-2 to K18-hACE2 Mice Uncouples Respiratory Infection from Fatal Neuroinvasion

*Nature*: Immune Dysregulation and Immunopathology Induced by SARS-CoV-2 and Related Coronaviruses — Are We Our Own Worst Enemy?

*Nature*: Structures and Functions of Coronavirus Replication–Transcription Complexes and Their Relevance for SARS-CoV-2 Drug Design

*CDC MMWR*: Risk for Stillbirth Among Women With and Without COVID-19 at Delivery Hospitalization — United States, March 2020–September 2021

*CDC MMWR*: COVID-19-Associated Deaths After SARS-CoV-2 Infection During Pregnancy — Mississippi, March 1, 2020–October 6, 2021

*Cell*: Population Impact of SARS-CoV-2 Variants with Enhanced Transmissibility and/or Partial Immune Escape

*Nature*: Do Vaccines Protect Against Long COVID? What the Data Say

*Nature*: Understanding and Tracking the Impact of Long COVID in the United Kingdom
Testing News

**STAT:** As Vaccination Efforts Falter, the U.S. Must Get Serious About Covid-19 Testing and Reporting

The *Lancet:* SARS-CoV-2 Antigen-Detecting Rapid Tests for the Delta Variant

Other COVID-19 News

The *Lancet:* Concerts and COVID: Can the Beat Go On?

*JAMA:* COVID-19 Vaccine Highly Effective Against Adolescent Hospitalizations

*Wall Street Journal:* How Omicron Variant Rattled the World in One Week

*Science:* ‘Patience is Crucial’: Why We Won't know for Weeks How Dangerous Omicron Is


*JAMA:* Substance Use Disorders and COVID-19 Vaccine Response

We have continued to receive positive feedback from readers of this newsletter since its first publication in March 2020. We hope our readers continue to find value in this science-focused newsletter, and encourage you to connect with the AAMC in other ways to stay up-to-date on important issues in medical research, science, and academic medicine:

- **Follow us on social media**, including **Ross McKinney, MD**, AAMC chief scientific officer
- **Subscribe to AAMC News** for news, features, current trends, and ongoing conversations about topics important to medical schools and teaching hospitals
- **Subscribe to CFAS News** to receive a weekly roundup of the latest news and happenings in academic medicine
- **Subscribe to Washington Highlights** to receive a weekly update on the latest legislative and regulatory activities affecting medical schools and teaching hospitals
- **Join the AAMC Virtual Communities** to connect and continue the conversation (*for AAMC members only; log in required*)

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

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