AAMC Coronavirus Update
February 4, 2022

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**: 388,686, 859 confirmed cases (5,714,792 total deaths)
- **United States**: 75,994, 966 confirmed cases (897,377 total deaths)
  - 2,479,478 new cases this week (new daily reported cases fell 40% in the past week)
  - 17,664 deaths this week (new daily reported deaths rose 4% in the past week)
  - COVID-19-related hospitalizations fell 15% in the past week
- **U.S. Hot Spots**
  - California: 57,137 average daily new cases in the last 7 days (-43% change in daily cases in the last 7 days)
  - Texas: 32,140 (-33%)
  - Florida: 20,297 (-31%)
  - Washington: 19,490 (-2%)
  - North Carolina: 15,069 (-43%)
- **U.S. COVID-19 Vaccine Distribution and Administration**
  - Total doses delivered: 669,540,355
  - Total doses administered: 541,410,847
  - People fully vaccinated: 212,336,183 (64%)
  - People received a booster dose: 88,983,833 (41.9%)

For the most up-to-date data, refer to the Johns Hopkins COVID-19 Map. Details of other
Lead News

After the last few months of Omicron, findings of another new variant are bound to provoke attention. The next problematic variant is a subvariant of Omicron, labeled BA.2 (the current widespread Omicron variant is BA.1). The two variants are actually quite distinct. The sequence of BA.2 lacks the deletion in BA.1 that gives the latter a quickly identified PCR signature. Investigators in Denmark have exploited the fact that both variants are present in their country, although it appears that BA.2 is in the process of replacing BA.1. They performed a study of the dynamics of household transmission of both variants that they published as a non-peer reviewed preprint in MedRxiv. They evaluated 8,541 primary household cases, 2,122 of which were caused by BA.2. They identified 5,702 secondary cases out of 17,945 contacts during a follow-up period of one to seven days. The secondary attack rate for BA.1 was 29%, and for BA.2 it was 39%. Compared to BA.1, BA.2 was associated with increased susceptibility in unvaccinated individuals with an odds ratio of 2.19, 2.45 for vaccinated individuals, and 2.99 for vaccinated-boosted individuals. BA.2 was more contagious than BA.1 within a household if the primary case was unvaccinated (compared to vaccinated, an odds ratio of 2.62), but not if the index case was a vaccinated or vaccinated-boosted breakthrough case. [Editor’s comment: BA.2 appears to be more contagious than BA.1, based both on the fact that it’s replacing BA.1 in Denmark and the data contained in this article on household spread. Fortunately, based on preliminary information published by the U.K. Health Security Agency, the current vaccines work as well against BA.2 as BA.1 — which is to say they aren’t perfect (see below) but they’re still likely to be quite effective, especially against severe disease. Vaccine efficacy for symptomatic disease was 63% two weeks after a booster dose for BA.1 and 70% for BA.2. The sample size is still small, so this finding warrants validation.]

Clinical and Treatment News

The Centers for Disease Control and Prevention (CDC) used the Morbidity and Mortality Weekly Report to put out a series of articles related to SARS-CoV-2 vaccination. There were so many published during the last two weeks that we have distilled the key messages down to a few sentences for each article, but the links are available for greater detail if desired.

Real-world evidence regarding the vaccine efficacy (VE) for two and three doses of mRNA vaccines in both the Delta and Omicron eras: The study evaluated 222,772...
emergency department and urgent care encounters and 87,904 hospitalizations, stratifying for the date when Omicron became predominant in that community. During Delta’s predominance, VE for emergency department and urgent care encounters was 86% 14 to 179 days after dose 2 of vaccine, 76% greater than or equal to 180 days after dose 2, and 94% more than four days after dose 3. In contrast, throughout Omicron’s predominance, the VE during the same intervals was 52%, 38%, and 82%. Protection against hospitalization was better, as shown in the same intervals: for Delta the VE was 90%, 81%, and 94%, and for the Omicron era, 81%, 57%, and 90%.

Incidence rates and death rates for vaccinated and unvaccinated people compared for four periods in 2021 defined by which variant was dominant: The four eras studied were pre-Delta (April-May), Delta emergent (June), Delta predominant (July-November), and Omicron emergent (December). The study used average incidence rate ratios (cases in an average week for unvaccinated people compared to the rate for vaccinated people). The ratios of diagnosed COVID-19 cases in relation to those periods were 13.9, 8.7, 5.1, and 3.1 (i.e., in April-May unvaccinated people were 13.9 times more likely to be diagnosed with COVID-19). The death rate ratios were 21.9, 16.4, 16.3, and TBD.

Effectiveness of a booster dose of mRNA vaccine against hospitalization in immunocompromised and immunocompetent adults: In a study of 2,952 hospitalized patients between Aug. 15 and Dec. 15, 2021 (which included 1,385 COVID-19 case patients and 1,567 COVID-19-negative controls) 1,875 were not immunocompromised, while 1,077 were immunocompromised. Among those not immunocompromised, VE against hospitalization was 97% for those who had received a booster dose and 82% for those who had only two doses of vaccine. Among those with an immunocompromising condition, VE against hospitalization was 88% for three-dose recipients and 69% for two dose recipients.

The effect of prior COVID-19 infection on subsequent protection against infection and hospitalization: This study used medical record information from California and New York and considered week-by-week rates in vaccinated and unvaccinated individuals between May 30 and Nov. 20, 2021, some of whom had a history of COVID-19. Case rates were available in both states, while hospitalization rates were only available from California. The results were quite complicated, in part because of which variant was circulating. The timing of the study was pre-Omicron, and generally most people had not been boosted. In the early (Alpha variant) periods, the lowest COVID-19 incidence rates were in those who had been vaccinated without previous COVID-19 diagnosis. In the early Delta periods, both vaccinated and unvaccinated people who had a history of COVID-19 had lower incidences than those who had only been vaccinated. Both vaccination and prior infection were protective against hospitalization as compared to unvaccinated people.

During the transition from Delta to Omicron predominance, a comparison of vaccinated, vaccinated-boosted, and unvaccinated adults in Los Angeles showed the striking effects of Omicron: During the last week of Delta predominance (the period
ending Dec. 11, 2021), unvaccinated people had an incidence of COVID-19 3.8 times higher than two-dose vaccinated people and their hospitalization rate was 12.9 times higher. **Unvaccinated people compared to vaccinated-boosted individuals had 12.3-fold higher incidence and an 83-fold higher hospitalization rate.** In the Omicron-dominant week ending Jan. 8, the incidence rate was twofold higher for unvaccinated people and the hospitalization rate was 5.3-fold higher than those with two-doses of vaccine. Vaccinated-boosted individuals did better, their unvaccinated counterparts having 3.6- and 23-fold higher incidence and hospitalization, respectively. But while protection rates were impressive, there was clearly less vaccine protection from Omicron than there had been against Delta.

[Editor’s comment: after all those studies, the bottom line is the most effective protection against infection and severe disease is for people to be vaccinated and boosted. It’s really simple. And having had past infection as well as vaccination is probably a protective advantage against subsequent infection, but not enough to justify the risk of infection.]

**MMWR: COVID-19 Incidence and Death Rates Among Unvaccinated and Fully Vaccinated Adults With and Without Booster Doses During Periods of Delta and Omicron Variant Emergence — 25 U.S. Jurisdictions, April 4-December 25, 2021**

**MMWR: Trends in Disease Severity and Health Care Utilization During the Early Omicron Variant Period Compared With Previous SARS-CoV-2 High Transmission Periods — United States, December 2020-January 2022**

The National Institutes of Health funded a study that compared SARS-CoV-2 vaccine boosting using the same (homologous) vaccine compared to a different (heterologous) vaccine to boost a primary series. The results were published in the *New England Journal of Medicine*. 458 individuals enrolled in the trial, all of whom had received a primary series of two Pfizer/BioNTech doses, two Moderna doses, or one dose of the Johnson & Johnson (J&J) vaccine. Volunteers were randomized as to which booster they received. Endpoints included reactogenicity, neutralizing antibody titers against the D614G strain, and spike-specific T-cell responses using stimulation and intracellular cytokine staining. Homologous boosting raised neutralizing antibody titers by 4 to 20 times, while heterologous boosters were generally more effective: 6- to 73-fold. Boosting raised spike T-cell responses in all but the J&J homologous booster cohort. However, J&J-primed individuals had more durable T-cell responses, and the J&J vaccine “substantially increased” spike-specific CD8 cell responses. [Editor’s comment: By and large, boosters work. The least effective in terms of neutralizing antibody was homologous boosting of J&J, which may reflect the immune response to dosing a second time with the same vaccine, effectively attenuating the response to the vaccine as a whole.]

A large investigative team looked at biological factors associated with post-acute sequelae of COVID-19 (PASC, aka long COVID-19). The results were published in *Cell*. They performed a longitudinal analysis of 209 COVID-19 patients from diagnosis through convalescence, obtaining a large number of samples and in-depth medical history from each individual. They also followed 457 healthy controls. The team found four factors
associated with increased risks for PASC: preexisting Type 2 diabetes, SARS-CoV-2 RNAemia, Epstein-Barr virus viremia, and specific autoantibodies. [Editor's comment: An interesting start to understanding the pathogenesis of PASC. These investigators looked carefully, deeply, and prospectively at a defined cohort. The associations are interesting, and they lay a foundation for potential interventions long term.]

*Nature: Long-COVID Symptoms Less Likely in Vaccinated People, Israeli Data Say*


*Canadian Medical Association Journal: Remdesivir for the treatment of patients in hospital with COVID-19 in Canada: a randomized controlled trial: Ten days of remdesivir in hospitalized patients led to lower mortality, less need for mechanical ventilation, and fewer days requiring oxygen or ventilation.*

*New England Journal of Medicine: Remdesivir for the Treatment of Patients in Hospital With Covid-19 in Canada: A Randomized Controlled Trial: The report from the NIH ACTT-1 randomized, controlled trial. Remdesivir shortened the time to recovery in hospitalized adults with COVID-19 respiratory disease compared to placebo treatment.*

*Lancet: Hyperimmune Immunoglobulin For Hospitalized Patients With COVID-19 (ITAC): A Double-Blind, Placebo-Controlled, Phase 3, Randomized Trial: Hyperimmune immunoglobulin provided no advantage over standard of care including remdesivir in this study of 593 hospitalized patients with COVID-19.*

*Nature: Where Did Omicron Come From? Three Key Theories*

*Science: Omicron, Its Mutations, and the Antibody Response*

*JAMA Internal Medicine: APOL1 Risk Variants, Acute Kidney Injury, and Death in Participants With African Ancestry Hospitalized With COVID-19 From the Million Veteran Program*

*Nature Scientific Reports: COVID-19 Reinfections Among Naturally Infected and Vaccinated Individuals*

*Nature: Memory B Cell Repertoire From Triple Vaccinees Against Diverse SARS-CoV-2 Variants*

*Nature Medicine: Three Exposures to the Spike Protein of SARS-CoV-2 by Either Infection or Vaccination Elicit Superior Neutralizing Immunity to All Variants of Concern*

**Policy News**

As stated in a U.S. Food and Drug Administration (FDA) press release from Jan. 31, the
FDA approved the Moderna COVID-19 vaccine for the prevention of COVID-19 in individuals 18 years of age and older. The approved vaccine, which was first authorized for use in individuals 18 and older on Dec. 18, 2020, is now marketed as Spikevax. “The FDA’s approval of Spikevax is a significant step in the fight against the COVID-19 pandemic, marking the second vaccine approved to prevent COVID-19. The public can be assured that Spikevax meets the FDA’s high standards for safety, effectiveness and manufacturing quality required of any vaccine approved for use in the United States,” said Acting FDA Commissioner Janet Woodcock, MD.

Novavax announced on Feb. 1 that it had submitted an application for emergency use authorization (EUA) to the FDA for its vaccine. If granted EUA status, it would be the fourth available vaccine in the United States to protect against COVID-19. The two studies on which the EUA application are based were conducted in the United States, the U.K., and Mexico, and showed approximately 90% efficacy in the 45,000 participants, according to a statement from the company. The Novavax vaccine candidate, unlike the currently available mRNA and viral vector COVID-19 vaccines, is based on a purified spike protein technology. The mechanism for this vaccine has been used for decades to prevent viral infections and was explained in a November 2021 Nature news article.

Rounding out a busy week for FDA vaccine related news, on Feb. 1, Pfizer and BioNTech announced that the companies had asked the FDA to authorize two doses of their vaccine for children between 6 months and 5 years old in a rolling application, with an expectation that data supporting a third dose as part of the primary series will be submitted to the FDA in the next several months. The FDA is expected to have its external experts, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) discuss the clinical trial data and the merits of the FDA's authorization of a two-dose regimen for this age group on Feb. 15. [Editor’s comment: This unusual regulatory approach to ask for authorization for two doses (which early clinical trial results suggested were insufficient for broad protection) is likely in response to the significant pressure on the companies and the FDA to have a vaccine available for young children. While it’s likely that three doses will be required to give adequate protection, this action suggests that the FDA is being encouraged to allow the first two doses to begin being administered three weeks apart while the data from the third dose are being prepared for submission. Pfizer has suggested that the third dose would be administered eight weeks after the second. This is an understandable but risky move. If the FDA does authorize two doses despite its relatively limited effect but then does not authorize the third dose within 11 weeks of the EUA decision, children would be left with having two doses of uncertain effectiveness. It is our prediction that the VRBPAC will be very concerned about this strategy, while recognizing the need to vaccinate younger children.]

We thank our colleague Heather Pierce, JD, MPH, for her contribution to this item.

**Coronavirus and Health Equity**

This Feb. 1 story in the Washington Post offers a potential explanation for the paradox
that some seemingly underprepared countries, like Vietnam, fared much better during the COVID-19 pandemic than high-income countries like the United States. A peer-reviewed study in the *Lancet* revealed that the strongest predictor of better outcomes among those tested was trust in government and other citizens.

A Jan. 21 paper in *JAMA Network Open* measured the change in COVID-19 vaccine hesitancy among Black and White adults since vaccines became publicly available in December 2020. Black and White people had about the same rates of intention to get vaccinated in December 2020, but by March 2021, the vaccine intention level of Black participants surpassed that of White participants. These results coupled with the fact that vaccination rate inequities persist in Black communities as compared to White ones, could mean that this inequity is due to accessibility or other social factors, rather than vaccine hesitancy.

*American Journal of Preventive Medicine: Vaccinating Veterans for COVID-19 at the U.S. Department of Veterans Affairs*

*JAMA: Disruptions in Care for Medicare Beneficiaries With Severe Mental Illness During the COVID-19 Pandemic*

*JAMA: Racial, Ethnic Disparities Found in Receiving Monoclonal Antibodies for COVID-19*

*Journal of Community Health: Strategies That Promote Equity in COVID-19 Vaccine Uptake for Undocumented Immigrants: A Review*

*Morehouse School of Medicine: Research Finds COVID Pandemic Worsened Health Equity Gap*

**Research News**

**Of Structure and Function; Liposomes and Macaques**

A nicely done paper published on Jan. 23 in Cell demonstrates that *immunization with synthetic SARS-CoV-2 S glycoprotein virus-like particles protects macaques from infection*. But before we dive headfirst into this paper, let’s take a step back:

As we discuss often in this newsletter, an important correlate of protection from antiviral vaccines is the generation of neutralizing antibodies. As popularly discussed, spike glycoprotein (S) is the main SARS-CoV-2 target for inducing neutralizing antibodies. The old adage in the study of biological systems is true: structure equals function. The same is true of the infamous spike protein. Spike is a heavily glycosylated, type I membrane protein that forms a trimer that is anchored to the viral membrane via a transmembrane segment. The large ectodomain of the protein decorates the virion surface. What is the overall structure of S protein? We know that S is a compact heterotrimer (for you visual learners, here is an excellent review with schematics) and that the 1,273 amino acid, full-length origin SARS-CoV-2 has an S1 domain for receptor binding (with an N terminal
domain, receptor binding domain, and C terminal domains) and S2 domain for fusion (which consists of a transmembrane segment and a cytoplasmic tail, among other regions and domains). [Editor’s comment: Herein lies the wonder of foundational research: Decades worth of studies have been synthesized into this paragraph. These studies account for the generation of clinical and medical therapeutic products (e.g., antibodies) that are saving lives today.]

One last thing to note before we dive into this paper is that S is a very dynamic protein. It binds to ACE3 on the host cell membrane and undergoes large structural conformational changes to promote membrane fusion. As noted in the Cell manuscript, “the conformation of RBD [receptor binding domain] RBD is in a dynamic equilibrium between either all RBDs in a closed, receptor-inaccessible conformation or one or two RBDs in the ‘up’ [receptor-accessible] conformation. Only the S RBD in the ‘up’ position allows receptor binding.” It should be noted that antibodies targeting the S glycoprotein were identified upon SARS-CoV-2 seroconversion — a general term used to describe the time between exposure to a virus and when antibodies are present in one’s blood. In this state, the RBD that is immunodominant is targeted, and neutralizing antibodies are isolated. Though these antibodies have been shown to confer in vivo protection against SARS-CoV-2 in non-human primates and small animals, as the authors note, “the magnitude of antibody responses to S during natural infection varies greatly and correlates with disease severity and duration.”

A number of animal models, including the macaque model, have demonstrated (1) induction of innate, cellular, and humoral responses upon SARS-CoV-2 infection, and (2) protection elicited by currently licensed vaccine candidates based on S-specific mRNA delivery. In the aforementioned paper published last week, the investigators used synthetic liposomes decorated with the S glycoprotein trimers (also referred to as S-LV=S-coated onto lipid vesicles). Liposomes are not only used to present the antigens, but they also “provide a highly controllable degree of multivalency and stability and a prolonged circulating half-life in vivo.” In their manuscript, Sulbaran et al. used formaldehyde to cross-link S glycoprotein trimers, stabilizing S in its native conversation over a long period of time. Using this technique, the authors find that:

1. “Serum antibody recognition of cross-linked versus non-cross-linked S did not show significant binding differences.
2. A small group of cynomolgus macaques were immunized with S-LVs, which produced high S-specific antibody titers and Th1 CD4+ T cell responses.
3. Potent neutralization of wild-type SARS-CoV2 and of Alpha pseudovirus variants was observed after two immunizations, while Beta and Gamma pseudovirus variants were neutralized at reduced potency.
4. Challenge of the animals with SARS-CoV-2 demonstrated that S-LV immunization protected the animals from infection revealing no detection of genomic RNA upon infection in nasal and tracheal swabs nor in bronchoalveolar lavages, thus suggesting sterilizing immunity.”

[Editor’s comment: This paper is fodder for this cellular and molecular neuroscientist}
editor. First, let’s talk about technique. As the authors pointed out, “liposomes coated with viral glycoproteins such as HIV-1 envelope induced more efficient immune responses than immunization with single glycoprotein trimers.” Based on the results listed above, the authors make a good case for S-LVs as “potential candidates for further clinical development of a safe protein-based SARS CoV-2 vaccine.” Secondly, it is important to point out the utility of model organisms here, without which we could not advance human health. Third, we’ll discuss the ingenuity of scientists which, though commonplace, doesn’t prove any less impressive. The wild-type SARS-CoV-2 glycoprotein has low stability due to its tendency to spontaneously switch into its post-fusion conformation. The workaround? Here, the authors stabilized S protein with two proline mutations and formaldehyde, preserving the native S conformation over extended periods of time. Other factors such as ligand binding, more proline mutations, and disulfide-bond engineering have rendered S more stable for experimental use. I point this out because, as we think about vaccines, doctors, and hospitals, it is critical that we recognize and laud the work of scientists, investigators, and researchers who, through vigorous work, build the foundation of international health. Regarding the conclusions of this paper, the authors note that the S-LVs used in this study induced “robust and potent neutralizing responses in cynomolgus macaques,” leading to high titers after just two immunizations. The absences of clinical signs of COVID-19, including lung damage, should also be noted. Though the authors find that RBD-specific antibodies were prominent after the first and second immunization, they make a case for likewise developing vaccination strategies that consider boosting non-RBD antibodies, given the loss in neutralization of the RBD-targeting antibodies in variants.

More on Structure

Continuing with the theme of structure, a paper released on Jan. 25 in Science makes clear the structural basis of SARS-CoV-2 Omicron immune evasion and receptor engagement. Due to the accumulation of numerous mutations, Omicron has been said to evade antibody mediated immunity that comes from vaccination or infection with earlier variants. In this study, McCallum et al. uses cryo-EM and X-ray crystallography to determine the structures of the spike protein and the receptor editing domain bound to the mAb S309 (the parent mAb of sotrovimab) and to the human ACE2 receptor. With these structures, the investigators demonstrate — with 2.85 angstrom-level detail — that the remodeling of interactions between the Omicron receptor-binding domain and human ACE2 likely accounts for the enhanced affinity for the host receptor relative to the ancestral virus. Other recent works investigating the structure of Omicron likewise do a nice job in using structural tools to understand what we observe at the population level. For example, a Cell paper from Jan. 24 assesses the structural and functional characterization of Omicron infectivity and immune evasion. In their line of investigation, they find that (1) Omicron spike stably maintains an active conformation for ACE2 receptor recognition, (2) the improved stability of Omicron enhances attachment but compromises viral fusion, (3) as we have all guessed, mutations perturb the conformation of antigenic sites recognized by most available antibodies, and (4) “[s]tructurally restrained regions of RBM can be targets for COVID-19 countermeasures.” [Editor’s comment: Any scientist will appreciate that not only the data, but the figures in these manuscripts, are exquisite. We
have reported on enhanced fusogenicity of the Omicron variant, as well as other cellular mechanisms that account for Omicron’s ability to spread like wildfire. As aptly put by the authors of the Jan. 25 Science paper, “this work defines the molecular basis for the broad evasion of humoral immunity exhibited by SARS-CoV-2 Omicron and underscores the SARS-CoV-2 S mutational plasticity and the importance of targeting conserved epitopes in design and development of vaccines and therapeutics.”

**Cell:** Discovery Of Ultrapotent Broadly Neutralizing Antibodies From SARS-Cov-2 Elite Neutralizers

**Virological:** Putative Host Origins of RNA Insertions in SARS-Cov-2 Genomes

**Cell:** Impact of Untreated Diabetes and COVID-19-Related Diabetes on Severe COVID-19

**OSF Preprints:** Omicron Variant of SARS-Cov-2 Harbors A Unique Insertion Mutation of Putative Viral or Human Genomic Origin

**Nature:** Human Genetic and Immunological Determinants of Critical COVID-19 Pneumonia

**Science:** Nervous System Consequences of COVID-19

**BioRxiv:** Omicron and Delta Variant of SARS-Cov-2: A Comparative Computational Study of Spike Protein

**Nature:** An in Silico Analysis Identifies Drugs Potentially Modulating the Cytokine Storm Triggered by SARS-Cov-2 Infection

**Cell:** Immuno-Proteomic Profiling Reveals Aberrant Immune Cell Regulation in the Airways of Individuals With Ongoing Post-COVID-19 Respiratory Disease

**Science:** 4'-Fluorouridine Is an Oral Antiviral That Blocks Respiratory Syncytial Virus And SARS-Cov-2 Replication

**Cell:** Immune Imprinting, Breadth of Variant Recognition and Germinal Center Response in Human SARS-Cov-2 Infection And Vaccination

**NIH Director's Blog:** 'Decoy' Protein Works Against Multiple Coronavirus Variants in Early Study

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**Other COVID-19 News**

**Nature:** Does the World Need An Omicron Vaccine? What Researchers Say

**Nature:** Three, Four or More: What's the Magic Number for Booster Shots?
Lancet: COVID-19 As Culture War

Lancet: COVID-19 Will Continue but the End of the Pandemic Is Near

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