AAMC Coronavirus Update
August 27, 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: 214,890,686 confirmed cases (4,478,754 total deaths)
- United States: 38,406,617 confirmed cases (633,761 total deaths)
  - 1,087,938 new cases this week (new daily reported cases rose 11.2% in the past week)
  - 8,444 deaths this week (new daily reported deaths rose 40.9% in the past week)
  - COVID-19-related hospitalizations rose 6.6% in the past week

- U.S. Hot Spots
  - Florida: 22,556 average daily new cases in the last 7 days (+10% change in daily cases in the last 7 days)
  - Texas: 17,125 (+4%)
  - California: 12,329 (-5%)
  - Georgia: 8,763 (+18%)
  - North Carolina: 6,330 (+18%)

- U.S. COVID-19 Vaccine Distribution and Administration
  - Total doses delivered: 434,582,185
  - Total doses administered: 365,767,674
  - People fully vaccinated: 172.2M

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
On Monday, Aug. 23, the Food and Drug Administration (FDA) announced they were approving the full biologics license for the vaccine created by Pfizer and its German partner BioNTech, BNT162b2, which is now brand-named “Comirnaty.” The approval is for individuals age 16 and up, and the vaccine remains available by emergency use authorization (EUA) for adolescents 12-15 years old. The third dose for immunocompromised individuals is also by EUA. The full approval was based on the data that supported the EUA, along with additional long-term follow-up information provided to the FDA. [Editor’s comment: The full approval has been long awaited. The main ramifications of the biologics license application will be that more entities (institutions and corporations) are likely to mandate COVID-19 vaccination. And while an oft-cited rationalization for not being vaccinated has been removed, I have strong doubts that approval will influence the rationalizations of the hesitant. Mandates, however, will make a difference.]

The CDC has been prospectively following recruited groups of front-line workers, the HEROES-RECOVER cohorts, to evaluate the effectiveness of SARS-CoV-2 vaccination. They reported the latest update on these cohorts in the Morbidity and Mortality Weekly Report (MMWR) on Aug. 24. Between Dec. 14, 2020, and April 10, 2021, both mRNA vaccines (Pfizer and Moderna) were 90% effective in preventing symptomatic and asymptomatic infections with SARS-CoV-2 in real-world conditions. Since April 10, the Delta variant has become predominant, so this report focuses on whether vaccine efficacy has changed. There were 4,217 participants, 3,483 of whom were vaccinated. 2,278 (65%) received Pfizer, 1,138 (33%) received Moderna, and only 67 (2%) received Johnson & Johnson (J&J). During the 35-week study period, 4,136 previously SARS-CoV-2 naive participants contributed a median of 20 unvaccinated days, during which time 194 SARS-CoV-2 infections were identified (89.7% were symptomatic). 2,976 participants contributed a median of 177 fully vaccinated days with 34 infections, 80.6% of which were symptomatic. The vaccine efficacy was 85% for those in whom less than 20 days had elapsed since full vaccination, while it was 73% for those in whom greater than or equal to 150 days had elapsed. During Delta-predominant weeks (obviously later in the study), 488 unvaccinated individuals contributed a median of 43 days of follow-up with 19 SARS-CoV-2 infections, 94.7% of which were symptomatic. 2,352 fully vaccinated individuals were followed for a median of 49 days with 24 infections. The adjusted vaccine efficacy in the Delta period was 66% (in comparison to the earlier 91%). [Editor’s comment: Delta has obviously had a major effect on SARS-CoV-2 transmission. This study is unable to separate how much of the change in vaccine efficacy from 91% to 66% is time since immunization versus the effects of Delta. I would judge that both play a meaningful role. This study made no comment on hospitalizations or more serious illness but rather focused on symptomatic and asymptomatic infections — the mild end of the COVID-19 spectrum. Fundamentally, vaccines have retained good efficacy through the study period.]

Public health officials in Los Angeles County, California, have been monitoring SARS-CoV-2 infections as the wave of Delta infections washed upon the county’s shores. They analyzed case data for infections between May 1 and July 25 and included the vaccine status of the affected individuals and sequencing to determine the variant mix. The results were published in the MMWR. There were 43,127 SARS-CoV-2 infections: 10,895 (25.3%) in fully vaccinated individuals, 1,431 (3.3%) in partially vaccinated people, and
30,801 (71.4%) in unvaccinated people. The clinical courses for vaccinated and unvaccinated people were very different. Lower percentages of vaccinated people were hospitalized (3.2% vaccinated vs. 7.6% unvaccinated), were admitted to an intensive care unit (ICU) (0.5% vs 1.5%), were mechanically ventilated (0.2% vs 0.5%), or died (0.2% vs. 0.6%). Of the 24 vaccinated people who died, six had immunocompromising conditions, and the median age was 78 years old as opposed to the median age of death of 63 in the unvaccinated population. At the start of the May to July period, Delta was about 8% of the isolates — by the end, it was roughly 90%. In the beginning of the period, viral loads were lower in the vaccinated individuals, but by the end of the period, that was no longer true and viral loads for vaccinated and unvaccinated people were the same — an apparent characteristic of Delta. On July 25 (the end of the sampling), infection rates were 4.9 times higher in unvaccinated people than in those who were vaccinated, and hospitalization rates were 29.2 times higher. [Editor’s comment: The fact that vaccines work is evident, but it’s true that Delta seems to be infecting more vaccinated people. That said, the protective effects of vaccines against infection are real, if not perfect, and the beneficial effects regarding hospitalization and death are unequivocal. This study added more depth to our understanding of breakthrough infections, as compared to infections not modified by vaccines, and should further reassure people that getting vaccinated is a very good thing.]

Popular folklore has it that a strong reaction after one of the mRNA COVID-19 vaccines is evidence of the immune system working. Investigators at Johns Hopkins evaluated whether symptoms following vaccination were reflected in higher antibody titers in health care workers who had known status regarding previous infection with SARS-CoV-2. The results were published in *JAMA Internal Medicine*. A questionnaire and a serum sample were taken from 954 health care workers 14 or more days after their second vaccine dose. Significant symptoms were reported by 52 out of 954 individuals after dose 1 (5%) and 407 out of 954 individuals after dose 2 (43%). After adjusting for several variables, the odds of significant symptoms were higher for people who received the Moderna vaccine than those who received Pfizer (dose 1 odds ratio: 1.83; dose 2 odds ratio: 2.43). A history of prior SARS-CoV-2 infection was associated with more symptoms after dose 1 but not after dose 2 after controlling for vaccine type, age, and sex. Regardless of symptoms, nearly everyone (953 out of 954) developed anti-spike IgG antibodies as detected by enzyme-linked immunosorbent assay (ELISA). Reported symptoms, an age of less than 60 years, female sex, use of Moderna vaccine, and prior SARS-CoV-2 exposure were all associated with higher antibody titers. [Editor’s comment: The good news is that whether the participant had symptoms or not, they developed good IgG anti-spike antibody titers. However, there does seem to be some truth to the folk wisdom since people with more symptoms had higher anti-spike antibody titers.]

In one of those stories that sadly didn’t have a happy ending, convalescent plasma obtained from people who recovered from COVID-19 demonstrated no significant benefits in a randomized controlled clinical trial of patients seen in emergency departments. The results were published in the *New England Journal of Medicine (NEJM)*. 511 patients seen in emergency rooms for COVID-19 symptoms were treated with one unit of convalescent plasma or placebo. All patients were age 50 or older (with a median of 54 years) or had at least one risk factor for disease progression. Patients had to present within seven days of the onset of symptoms (with a median of four days) and were clinically stable. The endpoints were progression within 15 days, as measured by hospitalization, seeking emergency or urgent care, or death without hospitalization. Disease progression occurred in 77 patients who received convalescent plasma (30.0%) and 81 patients who received placebo (31.9%). Five patients in the plasma group died and one in the placebo cohort died. [Editor’s comment: Early in the pandemic, great hopes were placed on convalescent plasma, so much so that more than half a million patients were treated with it without any meaningful evidence. This study, like several before, points out that the urge to do something — anything — just because it seems to make sense isn’t an ideal strategy. Now that the evidence is in, we can move on in our approach to treatment of COVID-19.]
J&J used a press release to announce that a vaccine booster given six months after initial dosing, using their adenovirus-based vaccine, elevated antibody concentrations ninefold in comparison to the antibody titers 28 days after their single-dose regimen. The company noted that while the original vaccine was still protective months after its initial dose, higher antibody levels from boosting might be beneficial. [Editor’s comment: The results were submitted to medRxiv but were not available at the time of newsletter production.]

The question of waning immunity after vaccinations is critical. Investigators in the United Kingdom evaluated several aspects of follow-up after single and multiple doses of the Pfizer, Moderna, and AstraZeneca vaccines. Results were published as a preprint in Nature with a simultaneous summary in the main journal. The investigators used the results of 2,580,021 polymerase chain reaction (PCR) tests from 384,543 adults between Dec. 1, 2020, and May 16, 2021 — when the Alpha variant was dominant — and 811,624 test results from 358,983 adults between May 17 and Aug. 1, 2021, when the Delta variant was more prevalent. They found, as others have, that the vaccines were generally less effective against Delta than previous variants, both in regard to symptomatic infections and infections with high viral loads. The dynamics of immunity were different after a two-dose Pfizer regimen than a two-dose AstraZeneca regimen. Looking at prevention of high-viral load positive PCRs, the Pfizer vaccine was 92% effective 14 days after the second vaccine dose but only 78% effective after 90 days. The AstraZeneca vaccine went from 69% to 61%. Single doses of either vaccine were much less effective than two-dose regimens, especially in the Delta-dominant period. [Editor’s comment: It is clearly much harder to protect against Delta than Alpha using vaccines, although the general efficacy remains very high. The use of booster doses as a strategy will unfold over the next few months.]

Delta virus infection is marked by its rapid spread. Certain characteristics of its behavior affect the epidemiology. A study published as a preprint in medRxiv started with 167 patients in Guangdong Province, China, who were identified as Delta-infected. Data was obtained from the affected individuals and their close contacts. The median age was 47 years, with 13.2% of cases under 15 years old and 26.3% over the age of 65. From the 101 individuals with sufficient data, the mean estimate for the latent period (time from contact with an infected person before onset of virus shedding) was 4.0 days, while the median incubation time (contact to symptom onset) was 5.8 days. The 95th percentile for incubation was 11.5 days. The secondary attack rate for close contacts of a patient was only 1.4%, and 73% of the transmissions occurred before the onset of symptoms. Index cases who were unvaccinated or partially vaccinated were more likely to transmit to contacts. However, the household secondary attack rate was 22%, which was higher than the 12.4% seen in the same region with the wild-type variant in 2020. Viral loads with Delta were higher than had historically been the case with wild-type SARS-CoV-2. [Editor’s comment: This is a fascinating study made possible by the close monitoring of the Chinese population. Delta becomes contagious quickly, it’s infectious before symptoms arise, and vaccines make a difference. The 95th percentile for incubation of 11.5 days suggests a quarantine of two weeks after Delta exposure will be necessary, although the low secondary attack rate in nonhousehold settings is a mitigating factor.]

Despite somewhat reassuring early studies, pregnant women with COVID-19 are at high risk of complications, including death. In a study published in JAMA Network, 869,079 pregnant women followed by 499 academic medical centers between March 2020 and February 2021 were evaluated. 18,715 (2%) had COVID-19. Women with COVID-19 were more likely to have preterm birth (16.4% vs. 11.5%). Those giving birth with COVID-19 were more likely to be admitted to an ICU (5.2% vs 0.9%), more likely to be intubated (1.5% vs 0.1%), and more likely to die in the hospital (0.1% vs. less than 0.01%). [Editor’s comment: This simple study shows that the risks of COVID-19 during pregnancy are real and significant. Given that there are no adverse consequences of vaccination, this is all the more incentive for pregnant women to get vaccinated against SARS-CoV-2 infection.]
In a tidy study from Israel, published as a preprint in medRxiv, antibody titers were followed for two mutually exclusive groups: people who had received two doses of the Pfizer vaccine and had no history of SARS-CoV-2 infection and people who had a history of SARS-CoV-2 infection and no history of vaccination. Samples were obtained between Jan. 31 and July 31, 2021, from 2,653 individuals who had been vaccinated and 4,361 people who had been infected with SARS-CoV-2. Higher titers were seen in the vaccinated individuals (1,581 antibody units [AU]/mL vs. 355.3 AU/mL). However, antibody titers decreased by 40% per month in vaccinated individuals and less than 5% per month in convalescent individuals. Six months after vaccination, 16.1% of vaccinated individuals were below the threshold of 50 AU/mL, while only 10.8% of convalescent patients were. [Editor’s comment: The rate of fall in antibody titers is impressive, but work like this requires replication. Quite a few studies have shown better durability of antibody titers after vaccination.]

**medRxiv**: Delta Variant and mRNA COVID-19 Vaccines Effectiveness: Higher Odds of Vaccine Infection Breakthroughs

**Science**: Autoantibodies Neutralizing Type I IFNs Are Present in ~4% of Uninfected Individuals Over 70 Years Old and Account for ~20% of COVID-19 Death

**NEJM**: Pan-Sarbecovirus Neutralizing Antibodies in BNT162b2-Immunized SARS-CoV-1 Survivors

**JAMA Pediatrics**: Association of Age and Pediatric Household Transmission of SARS-CoV-2 Infection

**medRxiv**: Virological Characteristics of SARS-CoV-2 Vaccine Breakthrough Infections in Health Care Workers

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**Policy News**

On Aug. 11, the CDC released a statement affirming the safety of the COVID-19 vaccines in pregnant people. The “CDC encourages all pregnant people or people who are thinking about becoming pregnant and those breastfeeding to get vaccinated to protect themselves from COVID-19,” said CDC Director Rochelle Walensky, MD, MPH. “The vaccines are safe and effective, and it has never been more urgent to increase vaccinations as we face the highly transmissible Delta variant and see severe outcomes from COVID-19 among unvaccinated pregnant people.”

On Aug. 18, the CDC and the U.S. Department of Health and Human Services released a joint statement on the administration’s plan for COVID-19 booster shots in the United States. According to the statement, booster shots will begin the week of Sept. 20 and eight months after an individual’s second dose. Those fully vaccinated earliest in the rollout will likely be given their booster shot during the early phases of the booster rollout. Officials also stated that they anticipate booster shots will be needed for people who received the J&J vaccine. According to the statement, “Recognizing that many vaccines are associated with a reduction in protection over time and acknowledging that additional vaccine doses could be needed to provide long lasting protection, we have been analyzing the scientific data closely from the United States and around the world to understand how long this protection will last and how we might maximize this protection. The available data make very clear that protection against SARS-CoV-2 infection begins to decrease over time following the initial doses of vaccination, and in association with the dominance of the Delta variant, we are starting to see evidence of reduced protection against mild and
moderate disease. Based on our latest assessment, the current protection against severe disease, hospitalization, and death could diminish in the months ahead, especially among those who are at higher risk or were vaccinated during the earlier phases of the vaccination rollout. For that reason, we conclude that a booster shot will be needed to maximize vaccine-induced protection and prolong its durability.

**Coronavirus and Health Equity**

A new [NBC News poll](https://www.nbcnews.com/health/healthcare/a-new-nbc-news-poll-assessed-the-demographic-breakdown-of-whos-vaccinated-in-the-united-states-2026368) assessed the demographic breakdown of who’s vaccinated in the United States. While 69% of all adults report that they are vaccinated, variations exist by race (with fewer White respondents [66%] than Black [76%] or Latino [71%] respondents reporting vaccination), age (people who are 35-49 years old are the least likely to be vaccinated, at 58%), geography (nearly 8 in 10 urban residents report vaccination but only 5 in 10 rural residents report the same), political affiliation, and other factors.


**Research News**

It has been established that children and infants have reduced SARS-CoV-2 infection rates when compared with adults. Moreover, research has shown that children are at a substantially lower risk for developing COVID-19 compared with adults. What is happening on the cellular level and the molecular level that accounts for this difference? On Aug. 18, researchers published a manuscript in *Nature Biotechnology* that shed some light on why younger age groups have relatively superior protection from SARS-CoV-2 infection. For this study, investigators characterized the “single-cell transcriptional landscape” in the upper airways of SARS-CoV-2 negative and positive children and adults, spanning an age range of 4 weeks to 77 years old. Investigators chose the upper airway (nose) as a location to examine because this region has been shown to have high susceptibility for SARS-CoV-2 infection. For the study design, the authors chose to focus on early infections, so only mild and/or moderate COVID-19 cases were considered for the study. What did the investigators find? When using single-cell RNA sequencing data to compare the cellular composition in the upper respiratory tract of children and adults, the authors found “striking” differences between pediatric and adult study participants — including the number and type of cells found in each cohort. “While immune cells were rarely detected in nasal samples from healthy adults, samples from SARS-CoV-2-negative children contained high amounts of almost each immune cell subset, with an overall dominance of neutrophils,” the authors noted. Secondly, the cellular and molecular events after SARS-CoV-2 infection differed between the two cohorts. In adults, “SARS-CoV-2 infection was associated with immune cell influx, while the proportion of immune and epithelial cells remained nearly stable in children.” Notably, children had significantly higher basal expression of genes encoding proteins that promote response to viral infections and viral sensing. [Editor’s comment: This study used a dataset of over 265,000 cells to map out the differences in gene expression and cell composition in SARS-CoV-2 negative and positive children vs. adults. The data convincingly show that, compared to adults, the epithelial and immune cells of the upper airways of children are so-called “pre-activated and primed for virus sensing.” The authors believe that this is likely a general feature of children’s mucosal immune response and accounts for the relatively low rates of SARS-CoV-2 infection in children. As for a nascent pathway, the authors hypothesize that “primed virus sensing and a pre-activated innate immune response” in children leads to efficient early production of interferon — a family of proteins involved in alerting the cellular immune system to viral infection of host cells — in the infected airways. This in turn might cause a reduction in virus replication and faster clearance of SARS-CoV-2. The
authors propose that their data may provide a mechanism that explains “why children are better able to control early-stage infection as compared to adults and therefore have a lower risk of developing severe COVID-19.” As vaccines are still not authorized for children younger than 12, this data is encouraging, to say the least. As stated below, various nonpharmaceutical interventions have been shown to be highly effective and will make a big difference during this upcoming school season.

Back-to-school season is fully underway and a keen understanding of the SARS-CoV-2 aerosol transmission in schools is of utmost importance. An Aug. 20 preprint published in medRxiv reported on the effectiveness of different interventions on SARS-CoV-2 spread. Using a previously developed aerosol transmission model, the investigators found that the most effective, single intervention for SARS-CoV-2 spread was natural ventilation through the full opening of windows all day during the winter, followed by the universal use of surgical face masks. Interestingly, the authors stated that in the spring and summer, natural ventilation was only effective when windows were fully open all day. By contrast, in winter, partly opening two windows all day or fully opening six windows at the end of each class was found to be effective, though opening windows during recess and lunch breaks only had minimal effect. Of note, the authors stated that combined interventions (i.e., natural ventilation, masks, and HEPA filtration) remained highly effective in the presence of a superspreader, with over a thirtyfold decrease in transmission. [Editor’s comment: Given that schools primarily contain young children that are in close proximity and largely unvaccinated, it is critical to not only understand but also implement emerging and established data that demonstrate feasible ways to protect children from SARS-CoV-2 infection and COVID-19.]

We know that the Delta variant is more effective at spreading and infecting hosts. But why? What signatures of this variant account for its ability to spread like wildfire? A handful of research articles published in the last month or so have beautifully revealed molecular hallmarks of the Delta variant that account for its increased pathogenicity. A very digestible news piece published on Aug. 20 in Nature breaks down key findings. Below are some of the key primary research articles that help uncover the strategies that Delta employs to be a “superspreader”:

An Aug. 13 publication in bioRxiv used a series of in vitro experiments to determine that the Delta spike mutation, P681R, plays a pivotal role in driving the global replacement of Alpha by Delta. Experiments from this study showed that the Delta variant “efficiently outcompeted the Alpha variant in human lung epithelial cells and primary human airway tissues” and that a fabricated version of Delta that bears the Alpha-spike glycoprotein “replicated less efficiently than the wild-type Delta variant.” [Editor’s comment: Though the results of this study indicated that P681R is a critical mutation that enhances Delta variant replication and fitness over Alpha, it is likely that other mutations, in concert with P681R, account for Delta’s enhanced pathogenicity.]

In mid-July, researchers published an article in bioRxiv showing that the P681R mutation in the Delta variant confers enhanced and accelerated viral fusion. On Aug. 17, another bioRxiv manuscript investigated the structure, function, and antigenicity of Delta's full-length spike trimer, compared with that of other variants — Gamma, Kappa, Alpha, and Beta. The results from this study indicate that Delta’s spike protein can not only fuse membranes more efficiently but also do so at lower levels of ACE2, the cellular receptor required for spike binding. [Editor’s comment: Cumulatively, results such as these — characterized as “foundational” or “basic” research — are critical for advancing our understanding of the distinct molecular properties of SARS-CoV-2 variants. From this knowledge comes the promise of future intervention strategies and therapeutics.]

bioRxiv: The Neutralization Potency of Anti-SARS-CoV-2 Therapeutic Human Monoclonal Antibodies Is Retained Against Novel Viral Variants
### Other COVID-19 News

*Health Affairs:* Vaccinations Against COVID-19 May Have Averted Up To 140,000 Deaths In The United States

*Nature:* A Glycan Gate Controls Opening of the SARS-CoV-2 Spike Protein

*Science:* Evolving Threat

*Nature:* Lipid Nanoparticles for mRNA Delivery

### For All Things Delta Variant

*Nature:* How the Delta Variant Achieves Its Ultrafast Spread

*Nature:* Delta Threatens Rural Regions That Dodged Earlier COVID Waves

*Nature:* How Do Vaccinated People Spread Delta? What the Science Says

*Nature:* COVID Vaccines Slash Viral Spread — But Delta Is an Unknowns

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