Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Critical Care Update

Vaccination

David J. Dries, MSE, MD [1]

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Hilty MP, Keiser S, Wendel Garcia PD, et al. mRNA-based SARS-CoV-2 vaccination is associated with reduced ICU admission rate and disease severity in critically ill COVID-19 patients treated in Switzerland. *Intensive Care Med*. 2022;48:362-365.

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Some Good News

The available data have consistently shown high levels of short-term protection by vaccines against coronavirus disease 2019 (COVID-19). Protection has also been demonstrated with respect to severe outcomes, including hospitalization and death. The duration of protection and the need for further doses remain unclear.

A variety of studies also suggested that the operative variant causing COVID-19 infection has an impact on vaccine effectiveness. For example, limited data indicate that the Delta variant has increased effectiveness even in vaccinated patients. Data from Qatar, for example, suggest limited protection against infection at 20 weeks or more after some vaccination programs. The extent to which reduced vaccine effectiveness is a result of a new variant or waning immunity remains unclear. A major trial in the United Kingdom examined the impact of COVID-19 as confirmed by a polymerase chain reaction (PCR) test in patients who had been immunized. The prominent variant in the United Kingdom varied during the course of this study. For example, before May 2021, the Alpha variant was the main viral variant in the United Kingdom. After this time, the Delta variant was dominant. Data from the National Health Service were used to examine major outcomes including death.

In general, vaccine effectiveness was higher with the messenger RNA (mRNA) vaccines against symptomatic infection from the Alpha variant compared with the Delta variant and among younger persons compared with older persons. Vaccine effectiveness against symptomatic disease due to the Delta variant peaked in the early weeks after receipt of the second dose of vaccine and then decreased at 20 weeks. Weaning of vaccine effectiveness was greater in persons 65 years of age or older than in persons 40 to 64 years of age. Data on vaccine effectiveness was limited in persons younger than 40 years of age. Limited weaning of vaccine effectiveness was noted with regard to protection against hospitalization. For example, weaning of vaccine effectiveness against hospitalization with the Delta variant ranged from 80% to 91.7% at 20 weeks or more after vaccination. Limited weaning of vaccine effectiveness was noted against death due to the Delta variant as well. Lower vaccine effectiveness against hospitalization was noted in the oldest age group, except in the first 20 weeks after vaccination.

Data from this important trial along with findings from other countries raise important questions about the timing of a third dose of vaccine in adults who remain protected against hospitalization and death for at least 5 months after receipt of the first 2 doses. Israel began to employ a third dose of vaccine in older adults in July 2021. This third dose was associated with a large reduction in the incidence of COVID-19 infection within 1 week of vaccination with greater reductions after the second week. However, the duration of protection offered by the third dose remains unclear. Another technical question is the interval between doses of vaccine. Additional data from the United Kingdom suggest that an extended interval of vaccine dosing from 8 to 12 weeks between doses provides greater serologic response and increased vaccine effectiveness than the licensed interval of 3 to 4 weeks for mRNA vaccines. The impact of this change in practice on subsequent outcomes and policy in other countries remains to be seen.

A related trial examining the impact of a booster dose of vaccine was performed in Israel. This was a study of health care workers investigated at a single center in Israel. Subjects had previously received 2 doses of mRNA vaccine. Seventy percent of approximately 2,000 subjects were women. They were followed symptomatically and with PCR testing. Use of the booster dose was significantly associated with lower rates of symptomatic and asymptomatic COVID-19 infection compared with the protection provided by a 2-dose vaccine regimen. A strength of the study was significant exposure to COVID-19 in the study population of health care workers. A limitation was the relatively small number of subjects and a lack of adequate data to specifically examine the impact of vaccination on severe illness and hospitalization. The short duration of data collection did not allow conclusions to be drawn about the long-term effects of a booster dose. Finally, these observations were made before the Omicron variant emerged as the dominant variant of COVID-19. With the mean follow-up limited to 39 days, ongoing surveillance was proposed.

[1] David J. Dries, MSE, MD is a Senior Fellow in the HealthPartners Institute and an adjunct clinical professor of emergency medicine at the University of Minnesota in St. Paul, MN, and can be reached at david.j.dries@healthpartners.com.

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A related Swiss study examined the effect of vaccination on the use of critical care resources in approximately 1,000 patients treated in critical care units in Switzerland. Vaccinated patients were approximately 7 years older and had more comorbidities, particularly immunosuppression, than patients who were not vaccinated. Vaccinated patients had lower initial illness acuity scores including sequential organ failure assessment components, a reduced length of stay by approximately 6 days in survivors, and similar intensive care unit (ICU) mortality compared with unvaccinated patients. Other important results demonstrate that less than 4% of COVID-19 patients admitted to the ICU in the first 9 months of the vaccination program in Switzerland were vaccinated. Despite older age and a higher risk profile, vaccinated ICU patients had less severe lung and systemic organ failure, a reduced need for mechanical ventilation, and shorter ICU length of stay. These findings appeared to persist despite the appearance of different COVID-19 variants. Specific chronologic data on the involved variants in this study were not provided.

Breakthrough . . . and More

Kuhlmann C, Mayer CK, Claassen M, et al. Breakthrough infections with SARS-CoV-2 omicron despite mRNA vaccine booster dose. *Lancet*. 2022;399:625-626.

Bates TA, McBride SK, Winders B, et al. Antibody response and variant cross-neutralization after SARS-CoV-2 breakthrough infection. *JAMA*. 2022;327:179-181.

Jabagi MJ, Botton J, Bertrand M, et al. Myocardial infarction, stroke, and pulmonary embolism after BNT162b2 mRNA COVID-19 vaccine in people aged 75 years or older. *JAMA*. 2022;327:80-82.

Oster ME, Shay DK, Su JR, et al. Myocarditis cases reported after mRNA-based COVID-19 vaccination in the US from December 2020 to August 2021. *JAMA*. 2022;327:331-340.

Levy M, Recher M, Hubert H, et al. Multisystem inflammatory syndrome in children by COVID-19 vaccination status of adolescents in France. *JAMA*. 2022;327:281-283.

The anatomy of a cluster of breakthrough cases secondary to the Omicron variant of COVID-19 despite mRNA booster dosing comes in a recent online report. These cases, reported in *The Lancet*, arose in a group of visitors to South Africa in late 2021. This was a young group with average age less than 30 years. Several individuals were participating in clinical training at different hospitals in Cape Town. During a COVID-19 surge in South Africa, this group reported respiratory symptoms consistent with COVID-19 and were diagnosed using molecular assays. These were some of the first documented breakthrough infections with the Omicron variant in fully vaccinated individuals after receipt of booster vaccine doses.

Specific immune cell responses were detected in all subjects at least 2 weeks after the onset of symptoms. Patients pursued a mild to moderate course of illness, suggesting that full vaccination followed by a booster dose provided good protection against severe disease. Long-term sequelae of COVID-19 could not be ruled out by these data. Obviously, COVID-19 variants are able to evade immunity induced by mRNA vaccines in vivo. This experience led to further calls for additional booster vaccine dosing with growing prominence of the Omicron variant. Even with full vaccination, nonpharmaceutical measures were recommended in appropriate situations.

A second study to characterize the breakthrough infection behavior of COVID-19 comes from the United States. Fully vaccinated health care workers who developed symptoms consistent with COVID-19 and were positive on a PCR test were recruited into a comparative study versus controls who were fully vaccinated without evidence of breakthrough infection and matched for age, sex, time between vaccine doses, and timing of test sample collection. Notably, COVID-19 variants including Alpha, Beta, Gamma, and Delta were included. Substantial boosting of humoral immunity was identified with breakthrough infection despite predominantly mild clinical disease in the affected patients. Boosting was most notable for immunoglobulin A, possibly because of the difference in the route of immune exposure between vaccination and natural infection. The pattern of immune response suggested that the development of boosters specific to individual variants could be helpful. This study was limited by the small number of subjects involved, whereas the quality of the laboratory data appeared to be good.

Other recent reports discuss specific complications of vaccination. One recent letter describes the incidence of cardiovascular complications including myocardial infarction, stroke, and pulmonary embolism after mRNA COVID-19 vaccine administration in subjects 75 years of age and older. It is important to note that the vaccine studied had no increase in cardiovascular events in phase 3 trials. This follow-up evaluation took place because older patients were underrepresented in the trials for vaccine approval. Clinical data were obtained from the French National Health Data System linked to the national COVID-19 vaccination database. Clinical events were followed for the first 14 days after vaccine administration. Events occurring within 14 days of either vaccine dose were identified. There was no evidence of an increase in the incidence of acute myocardial infarction, stroke, or pulmonary embolism within 14 days of vaccination in this study, which is consistent with the data reported by the United States and Israel. Additional data from younger subjects are not presented in this report.

A related risk with COVID-19 and mRNA vaccination is myocarditis. A recent report from the Centers for Disease Control and Prevention (CDC) examines the incidence of this complication after vaccination. When national vaccination was introduced in the United States, the CDC begin monitoring for adverse events of special interest, including myocarditis and pericarditis in the Vaccine Adverse Event Reporting System, a long-standing national spontaneous reporting system. Data collected here came from a collaboration between academic medical centers and the CDC, including infectious disease specialists and cardiologists, combined with data from other countries. Approximately 2,000 reports of myocarditis were examined. Of the reports meeting the CDC definition of myocarditis, 73% of cases were younger than 30 years of age, and 33% were younger than 18 years of age. The median age was 21 years. When dose information was available, 82% of myocarditis cases occurred after the second vaccination dose. The median time from vaccination to symptom development, when available, was 3 days after the first vaccination dose, and 74% of myocarditis cases occurred within 7 days. Eighty-two percent of cases of myocarditis were in males. White persons had the largest proportion of myocarditis cases. Among persons younger than 30 years of age, there was no report of death associated with myocarditis after mRNA-based COVID-19 vaccination without another identifiable cause. The reporting rate for myocarditis in females was lower than that in males across all ages younger than 50 years. The reporting rate of myocarditis was highest after the second vaccination dose in adolescent females aged 12 to 15 years and in females aged 17 to 18 years.

Among nearly 1,400 reports of myocarditis in patients younger than 30 years of age, symptoms included chest pain, chest pressure, or chest discomfort in association with shortness of breath. Troponin levels were elevated in 98% of subjects. Electrocardiogram results were typically abnormal. When treatment data were available, many patients received nonsteroidal anti-inflammatory drugs. Other immune-modulating treatments were used infrequently. Intensive therapies including vasoactive drugs and mechanical ventilation were rare.

Compared with cases of myocarditis not associated with vaccine administration, the acute clinical course was mild, which may have contributed to slow identification of cases. In addition, vaccination of younger individuals was popularized later than in adults. The onset of myocarditis symptoms after exposure to an immunologic trigger was shorter for COVID-19 vaccine-associated cases than is typical for myocarditis cases diagnosed after a viral illness. Cases of myocarditis reported after COVID-19 vaccination were typically identified within days of vaccination, whereas typical viral myocarditis can pursue an indolent course with symptoms absent for weeks to months after the trigger if the cause is ever identified. Major presenting symptoms appeared to resolve faster in cases of myocarditis after COVID-19 vaccination than in typical viral cases of myocarditis. In general, myocarditis after vaccination required only pain management. Evaluation for myocarditis usually included the measurement of troponin levels, electrocardiography, and echocardiography. Cardiac magnetic resonance imaging was also sometimes used. Long-term outcome data are not yet available for COVID-19 vaccine–associated myocarditis. This ultimately will reflect events over 3 to 6 months after diagnosis. Finally, a prominent limitation of this report is passive rather than mandatory reporting of cases to the CDC. Thus, myocarditis may be underrepresented.

The impact of mRNA vaccination against COVID-19 in the young was evaluated in a French review of multisystem inflammatory syndrome in children (MIS-C). This was an early attempt to describe the effect of vaccination on this important pediatric complication. Vaccinated patients reviewed were 12 years of age and older, and data collection took place during the Delta variant surge in France during late 2021. All pediatric patients diagnosed with MIS-C according to the World Health Organization and admitted to a French pediatric intensive care unit during September and October 2021 were reviewed.

In this French trial, most adolescents with MIS-C for whom vaccination was indicated had not yet been vaccinated. Thus, it appears that COVID-19 vaccination did not increase the rate of MIS-C in adolescents. In addition, the reported median of 25 days between a single vaccine dose and MIS-C onset compared with a mean 28-day delay between COVID-19 diagnosis and MIS-C onset suggests that in most cases COVID-19 infection had occurred before or shortly after vaccine injection when the immune response was incomplete. In all, a small number of patients were available for study, and the inability to control for individual risks of MIS-C was acknowledged. These writers do recommend that the association between mRNA vaccination with MIS-C in younger children should be evaluated as vaccines are approved for use in children aged 5 to 11 years. The investigators also acknowledged concerns regarding myocarditis reported previously.

The Big Picture

Morens DM, Taubenberger JK, Fauci AS. Universal coronavirus vaccines - an urgent need.

N Engl J Med. 2022;386:297-299.

Michaels D, Emanuel EJ, Bright RA. A national strategy for COVID-19: testing, surveillance, and mitigation strategies. *JAMA*. 2022;327:213-214.

Del Rio C, Omer SB, Malani PN. Winter of Omicron-the evolving COVID-19 pandemic. *JAMA*. 2022;327:319-320.

Recent coronavirus outbreaks (ie, severe acute respiratory syndrome, Middle East respiratory syndrome, and now COVID-19) provide evidence of the ecologic reality that coronavirus disease will emerge again in the future, potentially posing a new health threat. Viruses causing these epidemics are globally distributed in various species of bat. The full extent of this reservoir is unknown; however, it has been increasingly spilling over into humans and other mammals. Because of genetic and structural receptor conservation among mammalian species, many of these coronaviruses are well equipped for infecting humans by binding to angiotensin-converting-enzyme 2 receptors, facilitating viral transmission. Infection control experts suggest the need to characterize the coronavirus universe along with the natural history and pathogenesis of coronavirus in laboratory animals and in humans, allowing application of this information to develop universal vaccines protecting against all of the coronavirus species.

At present, we have limited understanding of the universe of endemic and potentially emerging coronaviruses. The most important hot spots are in Southeast Asia and the adjacent areas of Southern and Southwest China. Studies of bat vectors in this area reveal rapid evolution and enormous viral complexity. Generation of new genomes through mixed infection and genetic recombination creates substantial coronavirus genetic diversity analogous to that observed in influenza as spread by wild birds. This genetic variety adds to the urgent need for universal coronavirus vaccines. Although standard nonpharmaceutical public health measures such as social distancing, masking, and isolation of sick and exposed individuals help with infection control, these strategies are not enough. Current COVID-19 vaccines have protection that wanes over time, necessitating booster doses. Vaccination has been unable to prevent breakthrough infections, allowing subsequent transmission to individuals even though vaccines may prevent severe and fatal disease.

Individuals who have been naturally infected with COVID-19 can also be naturally reinfected as has been shown with coronaviruses, influenza, respiratory syncytial virus, and other respiratory viruses. Immunity to COVID-19 after natural infection and vaccine-induced immunity have been unable to prevent the rapid spread of viral variants including Delta and Omicron. These sobering facts suggest that COVID-19 is unlikely to be eliminated. This pathogen will likely continue to circulate indefinitely with periodic outbreaks.

The limitations of current COVID-19 vaccination suggest that a second-generation vaccine is needed that will induce more broadly protective and durable immunity. We must prioritize the development of broadly protective vaccines, such as the universal influenza vaccine that has been under development in recent years. A universal coronavirus vaccine would ideally protect against COVID-19 and the many animal-derived coronaviruses that may cause future outbreaks and pandemics.

The development of a national strategy for COVID-19 requires more than vaccines. Public health experts from George Washington University and the University of Pennsylvania advocate for a geographic genomic surveillance program to detect and track the appearance of COVID-19 variants. Current scattered information produces limited and delayed insight into the emergence of new variants until other countries experience them. Because it appears that COVID-19 will persist and the pandemic will continue for some time, an approach featuring testing, surveillance, and nonpharmaceutical interventions requires additional emphasis.

The CDC could facilitate the collection and dissemination of population-based incidence data on COVID-19 and its variants. This broader data set will reduce reliance on poorly representative sites for information. Comprehensive testing and reporting will enhance our ability to respond to viral respiratory illness. Data from all testing facilities should be reported to the CDC and linked to social and demographic vaccination and clinical outcomes data. Expanded access to low-cost testing with appropriate reporting to a central tracking system will allow identification of the spread of infectious disease.

Recent data from the rapid spread of the Omicron variant have highlighted the need for a comprehensive, nationwide, environmental surveillance system to complement

patient testing. Environmental surveillance may include waste water and air sampling to monitor for potential outbreaks of viral and bacterial illness. Progress has been made toward establishing environmental surveillance for COVID-19, but there is a need to expand to other pathogens and reach rural and other communities that lack appropriate waste water management systems. In addition, a comprehensive genomic surveillance system for variants is needed to provide early indication of immunity escape and the emergence of new variants. This includes the need to sequence vaccine breakthrough cases even if only mild infection is involved. A system organized by the CDC to sequence a far greater and more geographically representative proportion of positive COVID-19 tests is necessary. Surveillance of vaccinated individuals for frequency and severity of adverse effects, postvaccination infections, and waning immunity goes hand in hand with this approach.

COVID-19 is spread by aerosols. Public health strategies include masks, distancing, and ventilation controls. Viral disease in these individuals should be identified by systematic access to testing. Another approach to mitigation focuses on upgrades to ventilation and air filtration systems including the intake of outside air using high-efficiency particulate air filters. These systems must be implemented in public places including work and social settings. Finally, the increased use of high-quality filtering face masks such as N95 masks rather than simple cloth or surgical masks will reduce the transmission of respiratory viruses including COVID-19 in crowded indoor settings where community exposure risk is increased.

Vaccines remain the most important tool for controlling COVID-19 by helping to shift the pandemic to the next phase. Unfortunately, suboptimal vaccine acceptance, at least partly associated with misinformation and political division, continues to be a major barrier. Vaccination rates vary geographically with 9 states and Puerto Rico having more than 70% of the population fully vaccinated, whereas 4 states have the proportion vaccinated less than 50%. Infection control consultants recommend expanding vaccination coverage to 80% to 85% of the entire population in the United States.

These comments are particularly important in light of the characteristics of Omicron. It appears that this variant is more transmissible than the Delta variant and is capable of significant immune evasion against vaccines or prior COVID-19 infection. Most current hospitalizations and deaths are among unvaccinated individuals. Breakthrough infections are increasingly being diagnosed among individuals who have been fully vaccinated and even among those who have received booster doses. To date, most of these infections have not resulted in severe disease. Vaccination does not prevent all infections but does provide protection against severe illness, hospitalization, and death.

As the number of breakthrough cases increases due to the spread of the Omicron variant, we must consider whether to count an infection as a vaccine dose. Current CDC recommendations do not support omitting a dose of vaccine in case of a breakthrough or prevaccination infection. Questions have also been raised if the definition of full vaccination should be amended to include 3 doses of a vaccine (primary series plus a booster). How fully vaccinated is defined matters when vaccination status is required for international travel, social events, attendance at university, and participation in sports organizations. Despite new vaccines and therapeutic advances, we are entering a potentially dangerous phase of the pandemic because of multiple respiratory virus threats including Delta, Omicron, and seasonal influenza. In addition to COVID-19 and unlike last year when influenza activity was quite low, this winter could bring a significant influenza season to complement the new challenge posed by the Omicron variant. Efforts to stabilize the vaccine supply and strengthen delivery will be necessary to support the pandemic response in the face of COVID-19 combined with influenza.

Summary Points

- The effectiveness of vaccines against COVID-19 up to 20 weeks after vaccination is suggested by recent data. Whether further improvement can be demonstrated with additional booster doses or altered timing of vaccine administration remains to be seen.
- Critical care resource use with vaccination against COVID-19 is significantly reduced in patients presenting with subsequent COVID infection. Even patients presenting with more severe initial illness see reduced length of stay and the need for various forms of organ system support after vaccination.
- COVID-19 breakthrough cases after vaccination are found in multiple reports from various demographic groups. In general, symptoms are relatively mild compared with other patterns of exposure to COVID-19. COVID-19 variants are clearly able to evade immunity induced by vaccination in various situations. However, outcomes including critical care use and mortality are favorably affected in the presence of vaccine administration.
- Complications including myocarditis have been described in relation to COVID-19 vaccination. In general, involved myocarditis patients are younger than 30 years of age, and disease is confirmed by elevated troponin levels and electrocardiogram results. Fortunately, patients typically have mild symptoms and require only nonsteroidal anti-inflammatory drugs for management.
- Continued vaccination against COVID-19 will require the development of agents designed around the need to treat the ongoing emergence of new coronaviruses. The development of new agents will require collection and dissemination of population-based incidence data on COVID-19 and its variants. A central repository of these data, such as the CDC, is essential.
- Environmental surveillance may include animal populations, waste water, and targeted air sampling to monitor for potential outbreaks of viral illness. Surveillance of vaccinated individuals for breakthrough and the severity of adverse effects after vaccination should also take place.
- As we enter the influenza season, the combined effects of COVID-19 and influenza must be considered because the impact of these 2 pathogens could be complementary, thus requiring vaccine coverage designed to manage both.

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David J. Dries, MSE, MD, is a Senior Fellow in the HealthPartners Institute and a professor of surgery and an adjunct clinical professor of emergency medicine at the University of Minnesota in St Paul, MN, and can be reached at david.j.dries@healthpartners.com.