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

Delta and the Variants

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This update features the chronology and physiology of Delta, currently the most prominent variant of coronavirus disease 2019 (COVID-19). We offer a template for further appreciation of the ongoing evolution of the COVID-19 variants.

Variants

Lauring AS, Malani PN. Variants of SARS-CoV-2. *JAMA*. 2021;326:880.

Li H, Liu T, Wang L, et al. SARS-CoV-2 Delta variant infects ACE2 primary bronchial epithelial cells more efficiently than other variants [e-pub ahead of print]. *J Med Virol*. doi:10.1002/jmv.27372, accessed 12-21-21.

As viruses spread, they constantly change through mutations to their genetic code. Most mutations in the COVID-19 genome do not affect the function of the virus. However, mutations in the spike protein of COVID-19, which binds to receptors on cells lining the upper respiratory tract in man, may make the virus easier to spread or affect how well vaccines protect recipients. Other mutations may lead to a reduced response of a variant to treatments.

The Centers for Disease Control and Prevention (CDC) classifies a *variant of concern* as a variant with 1 or more mutations that allow the virus to more readily infect subjects or spread from person to person more readily, making the virus less responsive to treatment or affecting how well vaccines work against the virus. The CDC finds a *variant of high consequence* as one for which there is clear evidence that medical countermeasures have reduced effectiveness relative to previous viral variants. At present, no variants of high consequence have been identified for COVID-19.

Four variants of concern have been identified for COVID-19. Alpha was the first major variant of concern identified. This variant was found in the United Kingdom in the fall of 2020 and spreads approximately 50% faster than the original COVID-19 virus. There is some evidence that the Alpha variant may cause more severe disease. Current vaccines and monoclonal antibody therapies appear to be effective against this variant.

The Beta and Gamma variants were first identified in South Africa and Brazil, respectively. Both of these variants demonstrated increased transmissibility but not at the level of the Alpha variant. Some of the current monoclonal antibodies are less effective against the Beta and Gamma variants. There is a small decrease in the effectiveness of current vaccines against these variants.

Delta is currently the most prevalent variant in the United States. Early data suggest that the Delta variant spreads almost twice as rapidly as the original virus. The Delta variant may not be neutralized as well by antibodies in vaccinated people. Individuals who received only a single dose of a 2-dose vaccine regimen receive far less protection against the Delta variant. Individuals without vaccination are at high risk of infection with the Delta variant. Complete vaccination remains the most effective way to prevent severe disease with the Delta variant.

An intriguing preclinical study comes from a Chinese investigative team. These investigators developed cell cultures of human bronchial epithelial cells from specimens obtained at the upper airway of healthy nonsmokers during bronchoscopy. Airway epithelial cell cultures were exposed to viral particles bearing the spike protein of the original Wuhan viral isolate along with the Alpha, Beta, Gamma, and Delta variants. Pseudovirus particles were produced by transfection of cell lines where harvested supernatants contained the spike protein of each viral variant. Infectivity of viral particles bearing spike proteins of all variants was positively correlated with ACE2 receptor presence in the epithelial cell lines. Viral particles bearing the Delta variant spike protein displayed infectivity that was 3-fold higher than that of the Alpha variant and 5 times higher than that of the Beta and Gamma variants. These investigators suggest that the Delta variant spike protein does not necessarily possess higher affinity toward human ACE2 and may have other mechanisms to gain more effective entry into the respiratory epithelium.

Background Information on the Delta Variant

Liu Y, Gayle AA, Wilder-Smith A, et al. The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J Travel Med*. 2020;27:taaa021.

Liu Y, Rocklöv J. The reproductive number of the Delta variant of SARS-CoV-2 is far higher compared to the ancestral SARS-CoV-2 virus. *J Travel Med*. 2021;28:taab124.

Mishra B, Ranjan J, Purushotham P, et al. High proportion of low cycle threshold value as an early indicator of COVID-19 surge. *J Med Virol*. 2022;94:240-245.

Ong SWX, Chiew CJ, Ang LW, et al. Clinical and virological features of SARS-CoV-2 variants of concern: a retrospective cohort study comparing B.1.1.7 (Alpha), B.1.315 (Beta), and B.1.617.2 (Delta) [e-pub ahead of print]. *Clin Infect Dis*. doi:10.1093/cid/ciab721, accessed 12-21-21.

Planas D, Veyer D, Baidaliuk A, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. *Nature*. 2021;596:276-280.

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Edara VV, Pinsky BA, Suthar MS, et al. Infection and vaccine-induced neutralizing-antibody responses to the SARS-CoV-2 B.1.617 variants. *N Engl J Med*. 2021; 385:664-666.

The Delta variant (B.1.617.2) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in late 2020 in India. It is currently the predominant variant in the United States and is the variant responsible for the fourth surge that began to engulf the United States in the summer of 2021. This variant has mutations in the genes that encode the spike protein, and these mutations have enabled this variant to be more transmissible than previous variants. A key measure of transmissibility is R_0, which is the average number of infections caused by an infected individual in a nonimmunized population. With the original SARS-CoV-2 strain, Liu et al compiled a review of 14 estimates of R_0, and they reported a median R_0 of 2.79 with estimates ranging from 1.4 to 6.49. A subsequent review by Liu et al of R_0 estimates of the Delta variant yielded a median of 5.08 with a range from 3.2 to 8. Accordingly, the CDC released updated recommendations in late July 2021 in which masks were once again recommended for all individuals regardless of vaccination status when indoors in public settings in areas of substantial or high transmission.

Subsequent studies further highlight the transmissibility of the Delta variant. Mishra and coworkers examined cases of SARS-CoV-2 infections in India during the second wave of the pandemic, which began in April 2021, of which the Delta variant was the predominant member. The second wave was compared with the first wave in India during 2020. This study used cycle threshold (Ct), which refers to the number of amplification cycles of the viral genetic material to reach a detectable level, to serve as a surrogate for viral load and transmissibility; lower values suggest higher viral loads and transmissibility. The authors reported a median Ct (interquartile range [IQR]) value of 29 (IQR = 22-32) in 2020 compared with 23 (IQR = 18-29) in 2021. The percentage of Ct values ≤ 25 was 35.7% in 2020 and 60% in 2021 ($P < .001$). Likewise, the median Ct value across sex and all age groups was significantly lower in 2021 compared with 2020 ($P < .001$). Outcomes of patients infected with SARS-CoV-2 variants of concern have been examined and compared with patients infected with the original strain of SARS-CoV-2. Findings from these studies confirm that the Delta variant is associated with higher viral loads and duration of viral shedding, leading to increased transmissibility.

Antibody neutralization studies further underscore the significance of the Delta variant. Planas et al examined the sensitivity of the Delta variant to monoclonal antibodies, antibodies in sera from individuals convalescent from COVID-19, and vaccinated individuals. In monoclonal antibody studies, the Delta variant demonstrated resistance to neutralization by some antibodies due to reduced binding with the spike protein. Sera from individuals convalescent from COVID-19 were less potent against the Delta variant compared with the Alpha variant of SARS-CoV-2. Finally, 2 doses of the Pfizer or AstraZeneca vaccines generated an adequate neutralizing antibody titer response against the Delta variant, but this response was weaker relative to the response generated against the Alpha variant. These findings seem to correlate with another recent trial that examined the neutralizing activity of individuals convalescent from SARS-CoV-2 infection and individuals vaccinated with the Pfizer or Moderna vaccines. Compared with the early WA1/2020 variant of SARS-CoV-2, the Delta variant was less susceptible to neutralization by antibodies from previously infected and vaccinated individuals. Notably, detectable neutralizing activity against the Delta variant was still noted 3 months after infection or the second dose of a vaccine.

Local Case Reports

Brown CM, Vostok J, Johnson H, et al. Outbreak of SARS-CoV-2 infections, including COVID-19 vaccine breakthrough infections, associated with large public gatherings — Barnstable County, Massachusetts, July 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:1059-1062.

Lam-Hine T, McCurdy SA, Santora L, et al. Outbreak associated with SARS-CoV-2 B.1.617.2 (Delta) variant in an elementary school — Marin County, California, May –June 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:1214-1219.

Some well-publicized case reports further underscored the significance of the Delta variant. In July 2021, 469 cases of COVID-19 were linked to large public events in Barnstable County, MA. There were 346 (74%) cases that occurred in fully vaccinated individuals, and 274 (79%) of these patients experienced symptoms. Genomic sequencing in 133 patients revealed that the Delta variant was found in 119 (89%) patients. When examining Ct values, the median Ct in 127 fully vaccinated patients was 22.77, which was similar to the median Ct (21.54) in 84 patients who were unvaccinated, not fully vaccinated, or with unknown vaccination status. At the conclusion of this report, the authors suggested that communities may consider implementing prevention strategies, such as indoor masking in public settings regardless of vaccination status, even in areas with low rates of COVID-19 transmission. Another case report described an outbreak in the classroom of an elementary school in Marin County, CA, in May 2021. An unvaccinated teacher contracted COVID-19, and of the 24 students in her class, 22 students (ineligible for vaccination due to age) were tested for SARS-CoV-2; 12 students tested positive. Of the students who tested positive, 8 students were in the first 2 rows closest to the teacher's desk (10 total students in the first 2 rows, attack rate = 80%), and 4 students were in the last 3 rows farthest from the desk (14 total students in the last 3 rows, attack rate = 29%). Including these 12 students and the teacher, there were a total of 27 cases from this outbreak. Genomic sequencing occurred in 18 specimens, and the Delta variant was identified from all of the specimens. The authors of this report concluded that the Delta variant increased the risk of transmission among unvaccinated individuals in schools. Accordingly, recommendations to avoid outbreaks in schools included vaccination of adults and eligible children, masking, frequent testing, adequate ventilation, and not coming to school when feeling ill.

International Experience

Sheikh A, McMenamin J, Taylor B, et al. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. *Lancet*. 2021;397: 2461-2462.

Ong SWX, Chiew CJ, Ang LW, et al. Clinical and virological features of SARS-CoV-2 variants of concern: a retrospective cohort study comparing B.1.1.7 (Alpha), B.1.315 (Beta), and B.1.617.2 (Delta) [e-pub ahead of print]. *Clin Infect Dis*. doi:10.1093/cid/ciab721; accessed 12-21-21.

Li B, Deng A, Kuibiao L, et al. Viral infection and transmission in a large, well-traced outbreak caused by the SARS-CoV-2 Delta variant. Available at: https://doi.org/10.1101/2021.07.07.21260122. Accessed 12-21-21.

Studies from other countries highlight the international experience with the Delta variant. A recent trial from Scotland examined 19,543 cases of SARS-CoV-2 infections between April 1, 2021, and June 6, 2021. Of these cases, 7,723 cases and 134 hospital admissions were S gene (which encodes the spike protein) positive; 97% of S gene–positive cases in Scotland were the Delta variant. Furthermore, S gene–positive cases were associated with an increased risk of COVID-19 hospital admission, with a hazard ratio of

1.85 (95% confidence interval [CI], 1.39-2.47), compared with S gene–negative cases where S gene–negative cases corresponded to the Alpha variant. Based on these findings, the risk of hospital admission was higher with the Delta variant compared with the Alpha variant. A study from Singapore provided additional outcomes of patients infected with the Alpha, Beta, and Delta variants. Using a sample of 967 patients and a composite outcome of oxygen requirement, intensive care unit admission, or death, the Delta variant was associated with a higher adjusted odds ratio (aOR) for this composite outcome (aOR = 4.90; 95% CI, 1.43-30.78) compared with the Alpha variant (aOR = 1.88; 95% CI, 0.30-14.76) and the Beta variant (aOR = 1.69; 95% CI, 0.19-14.69). When further examining a subsample of 157 admitted patients, the Delta variant was also associated with a higher aOR of developing pneumonia compared with the Alpha and Beta variants. With these findings, the authors suggest that although their sample size was small, the Delta variant may be associated with increased COVID-19 disease severity.

An early outbreak of the Delta variant in China occurred in Guangdong, China, in May and June 2021. There were 167 infections in this outbreak, and the time interval between exposure and the first positive test was 4 days (IQR = 3-5 days). In comparison, with previous strains from the early stages of the pandemic in 2020, the time interval was 6 days (IQR = 5-8 days). Viral load measurements were made at the same time when a positive test occurred, and viral loads from individuals infected with the Delta variant were found to be 1,260 times higher than viral loads from individuals infected early in the pandemic in 2020. Accordingly, Ct values were lower for the patients infected with the Delta variant compared with earlier strains from 2020. This report is still a preprint, so the findings still need to undergo peer review. Nonetheless, the results described by Li et al are consistent with published data demonstrating the greater infectiousness of the Delta variant compared with earlier strains of SARS-CoV-2.

Vaccine Effectiveness

Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (Delta) variant. *N Engl J Med*. 2021;385:585-594.

Barouch DH, Stephenson KE, Sadoff J, et al. Durable humoral and cellular immune responses 8 months after Ad26.COV2.S vaccination. *N Engl J Med*. 2021; 385:951-953.

Nasreen S, Chung H, He S, et al. Effectiveness of mRNA and ChAdOx1 COVID-19 vaccines against symptomatic SARS-CoV-2 infection and severe outcomes with variants of concern in Ontario. Available at: https://doi.org/10.1101/2021.06.28.21259420. Accessed 12-21-21.

Fowlkes A, Gaglani M, Groover K, et al. Effectiveness of COVID-19 vaccines in preventing SARS-CoV-2 infection among frontline workers before and during B.1.617.2 (Delta) variant predominance — eight U.S. locations, December 2020 –August 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:1167-1169.

Scobie HM, Johnson AG, Suthar AB, et al. Monitoring incidence of COVID-19 cases, hospitalizations, and deaths, by vaccination status — 13 U.S. jurisdictions, April 4 –July 17, 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70;1284-1290.

Talic S, Shah S, Wild H, et al. Effectiveness of public health measures in reducing the incidence of covid-19, SARS-CoV-2 transmission, and covid-19 mortality: systematic review and meta-analysis. *BMJ*. 2021;375:e068302.

Recent studies have examined the effectiveness of vaccines against the Delta variant. Lopez Bernal and coworkers examined the effectiveness of the Pfizer and AstraZeneca vaccines against the Delta variant compared with the Alpha variant. First, when examining individuals who had received either vaccine, effectiveness was higher after the first dose in individuals with the Alpha variant (48.7%) compared with the Delta variant (30.7%). This difference narrowed when examining individuals who received both doses, with 87.5% for the Alpha variant and 79.6% for the Delta variant. When examining each vaccine individually, for the Pfizer vaccine, the effectiveness of 2 doses was reported as 93.7% for the Alpha variant and 88.0% for the Delta variant. For the AstraZeneca vaccine, the effectiveness of 2 doses was 74.5% for the Alpha variant and 67.0% for the Delta variant. Based on these findings, the authors concluded that both vaccines had high levels of effectiveness after 2 doses. Furthermore, compared with the Alpha variant, the effectiveness of the vaccines against the Delta variant appeared to be similar or only slightly lower compared with the Alpha variant. The effectiveness of the vaccines increased markedly after the second dose, which underscored the importance of obtaining both doses of these vaccines.

Neutralizing antibody titers were examined in individuals who had received the Johnson & Johnson vaccine against several strains of SARS-CoV-2, including the Delta variant. Barouch and several authors found that the Johnson & Johnson vaccine was able to elicit a durable humoral and cellular immune response at least 8 months after vaccination. Moreover, after 8 months, there was increased neutralizing antibody responses to the other variants, including the Delta variant. Finally, the efficacy of several vaccines against Delta and other variants was examined in a Canadian study available as a preprint by Nasreen et al. For the Delta variant, effectiveness after 1 vaccine dose against symptomatic infection was reported as 70% for the Moderna vaccine, 68% for the AstraZeneca vaccine, and 57% for the Pfizer vaccine. After 2 doses, effectiveness increased for all 3 vaccines, with 95% for the Moderna vaccine, 87% for the AstraZeneca vaccine, and 92% for the Pfizer vaccine. Against hospitalization or death, all 3 vaccines were > 80% effective after 1 dose and > 90% effective after 2 doses. Accordingly, the authors concluded that the vaccines were effective at preventing symptomatic infection, hospitalization, and death. Although both doses of the vaccine provide the best protection and are recommended for all individuals, even a single dose of these vaccines provides significant protection; this finding is particularly relevant to regions of the world where vaccine supply limitations may impede timely administration of the second dose.

Finally, 2 recent *Morbidity and Mortality Weekly Report* studies provided updates on vaccine effectiveness after the Delta variant had become the predominant strain in the United States. One report from Fowlkes et al provided an interim analysis of SARS-CoV-2 infections in vaccinated and unvaccinated frontline workers, including health care personnel, first responders, and other essential workers. In the period before the Delta variant became the predominant strain, vaccine effectiveness was reported to be 91%. However, vaccine effectiveness decreased to 66% with predominance of the Delta variant. In a subsequent report from Scobie et al, the incidence rate ratio (IRR) for cases of SARS-CoV-2 infections among not fully vaccinated and fully vaccinated individuals was compared during periods of low and high Delta variant prevalence. The IRR was calculated by dividing the incidence of SARS-CoV-2 infections in not fully vaccinated individuals by the incidence in fully vaccinated individuals. This parameter can be used to monitor breakthrough cases and vaccine effectiveness where smaller numbers suggest more breakthrough cases and decreased vaccine effectiveness. During the period of low Delta variant prevalence, the IRR was 11.1, but the IRR decreased to 4.6 when the prevalence of the Delta variant was higher. Furthermore, IRRs for hospitalizations and deaths also decreased when comparing the periods of

low and high Delta variant prevalence, from 13.3 to 10.4 for hospitalizations and 16.6 to 11.3 for deaths. Based on these findings, there is a reduction in vaccine effectiveness in preventing infection with SARS-CoV-2. However, there is less reduction in vaccine effectiveness in preventing hospitalization and death, suggesting that vaccines continue to provide robust protection against these severe outcomes. There are limitations when interpreting these findings because there are multiple reasons to explain the apparent decline in the vaccine effectiveness. Ultimately, the findings from these reports underscore and emphasize that immunity obtained from vaccines, although durable and still effective in preventing severe COVID-19 disease from the currently circulating variants, may not last forever, and ongoing research is needed to better understand how long immunity truly lasts. In the interim, given the increased transmissibility of the Delta variant and the declining effectiveness of vaccines, continued adherence to nonpharmaceutical interventions will be important. A recent systematic review and meta-analysis comprehensively examined the effectiveness of some of these interventions in mitigating the spread of COVID-19. Talic et al examined the utility of several nonpharmaceutical interventions in reducing the incidence of SARS-CoV-2 infections. Simple interventions such as mask wearing and physical distancing resulted in a significant reduction in the incidence of SARS-CoV-2 infections. Handwashing also trended toward significance in reducing the incidence of infections. Other interventions that were examined, including disinfectant use, stay-at-home/isolation measures, lockdowns, school/business closures, and travel restrictions, frequently were effective but could also be more disruptive to the economic and social well-being of communities. The authors concluded by suggesting that until herd immunity is achieved, a combination of effective pharmacologic and nonpharmacologic interventions will likely be needed to control the COVID-19 pandemic.

Final Thoughts

Twohig KA, Nyberg T, Zaidi A, et al. Hospital admission and emergency care attendance risk for SARS-Co-V-2 delta (B.1.617.2) compared with alpha (B1.1.7) variants of concern: a cohort study. *Lancet Infect Dis*. 2022;22:35-42.

Khadri SS, Simpson SQ. Potential implications of SARS-CoV-2 delta variant surges for rural areas and hospitals. *JAMA*. 2021; 326:1003-1004.

Sonnabend R, Whittles LK, Imai N et al. Non-pharmaceutical interventions, vaccination, and the SARS-CoV-2 delta variant in England: a mathematical modelling study. *Lancet*. 2021;398:1825-1835.

Torgeson I. Covid-19: Omicron may be more transmissible than other variants and partly resistant to existing vaccines, scientists fear. *BMJ*. 2021;375:n2943

Four recent reports add new perspective on the impact of the Delta variant on health care systems in the Western world. Twohig and coworkers, consistent with other reports, point out that new COVID-19 infections in England are increasingly due to the Delta variant. The latest data in this study indicate that approximately 75% of new cases reflect the Delta variant. Patients with the Delta variant had more than twice the risk of hospital admission compared with patients with the Alpha variant. Emergency care attendance combined with hospital admission was also higher for patients with the Delta variant, demonstrating increased use of emergency care services along with inpatient hospitalization. Results were similar for the subgroup of unvaccinated patients when comparing risks of both hospital care outcomes between the Alpha and Delta variants. This study did suggest that vaccination resulted in similar relative risk reduction for hospitalization in patients exposed to the Delta or the Alpha variants. The rising risk of appearance for the Delta variant in England allows comparison with India where the impact of the Delta variant has been significant. High infection incidence, overwhelming hospital burden, shortage of supplies, and inadequate amount of lifesaving equipment were reported in India. Findings from the study in England support the importance of considering the Delta variant in resource planning and policy decisions to reduce the impact of the Delta variant in countries where the rapid spread could occur.

A second important dichotomy is the difference between rural and urban locations. For example, a recent comment from the National Institutes of Health points out that many rural counties report that less than 25% of residents are fully vaccinated, increasing the likelihood of a localized surge in these areas. Rural health systems in the United States have unique organizational, clinical, financial, and social vulnerabilities that make it more difficult for hospitals to withstand a surge of COVID cases. These vulnerabilities could compromise care quality, delivery, and financial stability.

In the United States, 35% of hospitals are designated as rural. These hospitals are spread across 97% of the United States land area but account for only 1% of all intensive care unit beds. This contradiction requires ultraregionalized critical care. Patients with COVID-19 may deteriorate rapidly, stressing available personnel, clinical resources, and capabilities creating a need for long-distance transfer between centers. When referral centers are overburdened with COVID-19 cases, smaller hospitals must care for patients they would normally transfer. Small rural hospitals generally maintain a low census. Rapid expansion of patient volume, particularly with critical illness, could pose challenges and risks for rural hospitals. Rural hospitals frequently have staffing shortages complicating the provision of care. Excess mortality in rural areas has been observed before the COVID-19 pandemic. This mortality difference has increased in recent years. For example, obesity and poverty are more common in rural populations. Chronic diseases that worsen outcomes from COVID-19 are common. The COVID-19 death rate peaks at higher levels in rural versus metropolitan areas. A recent review including rural and metropolitan hospitals reported that 1 in 4 COVID-19 deaths was associated with hospitals strained by surge caseloads.

Hospitals in rural counties have financial challenges as well. Most of these facilities are small, low-occupancy centers lacking parent corporations that absorb losses, so rural centers depend on government funding for operations. The pandemic has contributed to financial problems in rural hospitals with temporary suspension of elective procedures and added cost for personal protective equipment, testing, and additional staff. Government funding has provided some support, but a clear pattern of rural hospital recovery has not been noted. Increased emphasis on vaccination and emergency personnel support along with focused financial aid are considered potential solutions.

An intriguing study examines the use of mathematical modeling in decisions regarding the use of nonpharmaceutical interventions and lockdown approaches, which have been used by many governments. One such model used by the British includes 4 tests: continued success of vaccination, evidence of effectiveness of vaccines against the need for hospitalization, no risk of overwhelming the hospital system, and new variants of concern do not change the risk assessment. The emergence of the Delta variant in the United Kingdom in April 2021 drove a rapid increase in cases and hospitalizations across all areas of the country. Daily case numbers increased from May 2021 and grew exponentially from June to July with a peak of over 56,000 cases daily. The model framework reported was developed to provide epidemiologic insight to the British government. During initial application of the mathematical model, the British were largely successful at keeping hospital admissions and deaths at manageable levels. Unfortunately, with additional

data showing the high transmissibility of the Delta variant, inconsistent vaccine effectiveness, and future increases in contact rates, modeling consultants identified a significant risk of increased transmission in coming months, which might not be controlled by simple vaccination. A need to return to aggressive use of nonpharmaceutical interventions was identified. Emergence of the Delta variant affected data feeding the mathematical model and identified the benefit of delaying complete reopening and continued emphasis on caution due to the increased risk posed by Delta and the associated increased transmission of this variant.

In support of the biology of COVID-19 reviewed, the medical literature now reports the identification of an additional variant—Omicron. The first cases with this variant appeared in South Africa but now seem to be rapidly spreading around the world. Omicron is thought to be the most heavily mutated variant of concern to emerge thus far and carries mutations similar to changes seen in previous variants of concern associated with enhanced transmissibility and partial resistance to immunity induced by vaccines.

The first cases featuring this variant were confirmed in Belgium on the European continent in late November 2021. In the United States, the first case was reported in California on December 1, 2021. In the subsequent weeks, dozens of countries in multiple continents began reporting cases of infections with the Omicron variant. At the rate at which it is spreading, the Omicron variant is expected to replace the Delta variant as the predominant strain of SARS-CoV-2. Countries are beginning to reinforce the mask mandates and other nonpharmaceutical interventions against this pathogen.

The Omicron variant of COVID-19 carries many of the changes found in other variants but never altogether in 1 virus. In all, the Omicron variant genome has approximately 50 mutations, including more than 30 in the spike protein that interacts with human cells. A particular concern is the risk that the Omicron variant may be more easily spread than the Delta variant.

Summary Points

- The Delta variant of COVID-19 is now the predominant mutation of this virus in the United States and in multiple sites of the world. A variety of assays, both demographic and laboratory tests, document increased aggressive spread of this pathogen. The source of this uptick of spread for the Delta variant is thought to be related to mutation in the spike protein that it carries.
- Reproduction data and numerical case spread studies also support the increased infection rates associated with the Delta variant. A variety of reports are suggesting a return to more aggressive mask use, social distancing, and changes in social behaviors as seen in earlier months of the pandemic.
- Available vaccines effectively reduce hospitalization and improve mortality outcomes with all variants of COVID-19 including Delta. Although support for vaccination is clearly seen, the preponderance of data suggests decreased effectiveness of vaccination against the Delta variant. Additional need for nonpharmaceutical interventions is also identified in these data.
- The Delta variant dramatically increases the pressure on smaller and rural health care systems to manage a rapidly spreading pathogen with limited critical care resources. Demands on the medical transportation industry may also increase.
- With continued rapid mutation leading to further spread of COVID-19, new variants selected by the effectiveness of aggressive clinical behavior are likely to appear in the near future. One such variant, Omicron, is attracting attention at present. For this variant, data are limited at present.

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