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## Medical Intelligence Report

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# Topic: COVID-19 Research Update



## Overview of the Current Status of the Pandemic

The WHO's COVID-19 Emergency Committee met on July 14, 2021 to assess pandemic developments (Schnirring, 2021). The group unanimously agreed that a designation of pandemic is still warranted and that "the pandemic is nowhere near finished with new variants continuing to evolve along with the threat of newer and possibly more dangerous ones." The Delta variant itself already has produced two sub-lineages with additional mutations that have been associated with an increased ability to avoid immune detection.

A research group from the WHO published an assessment of the transmissibility and global spread of the SARS-CoV-2 variants of concern (VOC) identified as of June 2021 (Campbell et al., 2021).

**The Delta variant (also known as B.1.617.2), was found to have an increased transmissibility that was 97% higher than the original strains of SARS-CoV-2 first identified from Wuhan, China.**

For comparison sake, the Alpha variant was found to have a 29% increase in transmissibility compared to initial strains. When more transmissible strains are spreading, control of transmission through public health interventions, such as mask wearing, can still be effective, but require an increase in the duration and/or stringency in order to achieve the same level of reduction achieved before the new strain was introduced. Additionally, it would be expected that more people would need to be immune, through natural infection or vaccination, before the susceptible population was low enough to stop the virus from spreading, or so-called herd immunity was reached. Vaccinating more people means that it will take longer to reach this immunity threshold, and in this time, it is highly likely that additional mutations will develop, and the authors state "the degree of protection offered by the different vaccines against future VOC/VOI [variants of concern/variants of interest] remains unclear."

The director of the CDC, Rochelle Walensky, has stated that 97% of hospitalizations for COVID-19 are among those who are unvaccinated, and almost all deaths are in people who were not vaccinated. Four states were responsible for more than 40% of the cases of COVID-19 in the

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United States during the week of July 12, Florida, Missouri, Arkansas, and Louisiana (Abutaleb and Sellers, 2021). As seen in a previous outbreak of the Delta variant in Scotland and Canada, the individuals being affected in the United States are younger than previously observed, with the greatest increase in patients between the ages of 30 and 50, and an increase in the severity of symptoms leading to an increase in the number of people requiring hospitalization for treatment (Sheikh et al., 2021 and Fisman et al., 2021). Dr. Steppe Mette, the chief executive of the Little Rock hospital, reported that more people with COVID-19 have required treatment in the hospital than in previous surges in the pandemic, and individuals in the hospital now require a higher level of care despite being younger than previous patients.

Public health officials in Toronto investigated 211,197 individuals who tested positive for COVID-19 between February 7 and June 22, 2021 when variants of concern were spreading and displacing the initial strain of the virus (Fisman et al., 2021). The first variants of concern detected in the area were Alpha, Beta, and Gamma, which all include the mutation N501Y. The elevation in risk associated with N501Y-positive variants was 59% for hospitalization; 105% for intensive care admission; and 61% for death. The increased risk associated with the Delta variant was more pronounced: 120% for hospitalization; 287% for intensive care admission; and 137% for death.

**Based on the results of the analysis, the authors concluded that “The progressive increase in transmissibility and virulence of SARS-CoV-2 VOCs will result in a significantly larger, and more deadly, pandemic than would have occurred in the absence of VOC emergence.”**

## How Will the Pandemic End?

There are two general ways that most pandemics can “end.” In the first, the oft mentioned “herd immunity” scenario, a population reaches a threshold of individuals who are immune, either through vaccination or natural infection, so that there are not enough people to sustain transmission. Measles is a disease that can be controlled through this process because vaccination for measles produces sterilizing immunity in which vaccinated individuals can no longer be infected by the virus. There are a number of experts that have suggested that the length of immunity against SARS-CoV-2 is most likely not long-lasting enough to allow for sterilizing immunity and complete control of the virus (Branswell, 2021).

In the second scenario, infections from the virus (e.g. SARS-CoV-2) continue, but hospitalizations and deaths from the disease caused by the virus (e.g. COVID-19) decline. In this scenario, the outcomes from viral infection are reduced. The reduction can occur through vaccination or mutations in the virus that lead to a weakened variant. Influenza virus is an example of this scenario, where there are yearly outbreaks of flu, but most people have a mild illness from infection. Viruses with this type of cycle are called endemic.

There is already evidence of the second scenario starting to occur. Even in countries where there are areas with high vaccination levels, the infection rates are going up due to the Delta variant. However, the hospitalization and death rate remain low. For example, the Johns Hopkins Center for Health Security stated in their COVID Situation Report that the CDC has reported only 3,554 hospitalized breakthrough cases and 733 deaths out of more than 157

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million fully vaccinated individuals in the United States (JHCHS, 2021). There are also rising case numbers in 20 European countries and the United Kingdom. In the Netherlands, new COVID-19 cases increased by 500% over the week of July 12 after remaining distancing restrictions were lifted (Corder, 2021). Infections among people ages 18 to 24 surged by 262%, and infections rose by 191% in 25 to 29 year-olds. However, hospital admission increased by only 11% in the Netherlands. In Europe, the impact on health systems has been minimal in most countries with the number of people hospitalized or requiring treatment in the intensive care unit remaining stable, most likely due to high levels of vaccination in older individuals.

**The timeframe for this type of scenario progressing so that COVID-19 becomes an illness with a mildness similar to the flu is dependent on the timing of vaccination of large sectors of the world population compared to evolution of new variants that can circumvent the available vaccines.**

Most of the research on pandemic cycles involves studies on the influenza virus (Branswell, 2021). However, influenza virus has some key differences from SARS-CoV-2. Importantly, the infection and transmission times differ, and the incubation time, or time from exposure until the illness starts, is longer for SARS-CoV-2 than influenza virus. Because of the short incubation time, influenza outbreaks have very abrupt endings, with transmission dying out at a location within a couple of weeks. However, the COVID-19 pandemic has had multiple waves that occur in the same location, unlike influenza outbreaks. Marc Lipsitch, an infectious diseases epidemiologist at Harvard's T.H. Chan School of Public Health, said in an interview with *STAT News* that he is a bit concerned by the fact that after a whole year "still there's no real evidence that it's ending on its own in any country."

As mentioned above, most experts believe that the pandemic is far from over. While there are positive signs in countries that have access to vaccines, most of the people in the world remain unvaccinated. In the continent of Africa, the overall vaccination rate is only 2%, and the infection rate is rising by 25% each week (Schnirring, 2021). There are also continuing surges in South America. Brazil has the highest seven-day average for cases in the world and the outbreak is accelerating. Officials currently estimate that 12% of the country is fully vaccinated. With the high level of transmission that is still occurring around the world, including in the United States, it is likely that mutations in the virus will continue to occur, leading to additional variants that will have unknown properties.

## COVID-19 in Children

Three groups of researchers published preprints of comprehensive reports of the immediate effects of SARS-CoV-2 infection in people under the age of 18, who have generally been found to be less affected by the virus.

In the first, researchers performed a systematic review of the published literature throughout the first year of the pandemic in order to identify if there were patterns that suggest risk factors for severe COVID-19 and to better determine the outcomes of COVID-19 in young individuals (Harwood et al., 2021). A systematic review is a specific type of search of available scientific databases that include all of the publications available. The authors limited their search to publications between January 1, 2020 and January 29, 2021 and those that were published in

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English. The search terms used included COVID-19, SARS-CoV-2, or variations of MIS-C (the inflammatory condition that occurs after the infection in some individuals) and were further narrowed to those relating to people under 18. The initial search returned 23,050 reports. The first group of reports was evaluated, and studies that did not relate to the topic and duplicated entries were removed.

**After this process, there were 81 studies included in the review, and 57 of these were used in a statistical evaluation called a meta-analysis that allows for compilation of the results.**

As a group, the 57 reports used in the meta-analysis included information on 21,412 children. There were studies from countries around the world with nine studies from Asia, fifteen from Europe, one from Africa, twenty-one from North America, and eight from South America.

Based on the information in the collected reports, the researchers were able to determine demographic risk factors for admission to critical care and death. Sex was not associated with the risk of needing critical care, unlike in adults. Compared with children aged one to four years, infants had increased odds of admission to critical care or death. The risk of death was also two times larger in the groups of children aged ten to 14 and 14 and over.

**Similar to early studies, published reports suggest that the most risk for severe symptoms from COVID-19 requiring critical care or leading to death occur in infants under the age of one year and in those over the age of ten years.**

Based on age, children between the ages of one and nine are the least likely to have severe symptoms or die from COVID-19.

There was also an association with chronic conditions and severe symptoms as has been observed in adults with COVID-19. In children, neurological and cardiac conditions were associated with the greatest increase in odds of severe disease or death. Additionally, there was an increased risk for individuals with two or more chronic conditions and those who are obese.

**The researchers determined that while there was an increase in the odds of severe symptoms or death for certain individuals, the magnitude of the increase is small when compared to children without underlying conditions.**

Another group was able to utilize anonymous health records from the public health system in England to evaluate all of the inpatient hospital admissions in England between March 1, 2015 and February 28, 2021 (Ward et al., 2021). With this information, they examined the associations between pediatric intensive care unit admission and death based on sociodemographic factors and chronic conditions.

During the study period, there were 6,338 hospital admissions, 259 pediatric intensive care unit admissions, and 8 deaths from COVID-19, and 712 hospital admissions, 312 pediatric intensive care unit admissions, and less than 5 deaths from MIS-C. This represents 1.3% of all secondary care (hospital) admissions in the pandemic year and less than 5% of non-traumatic emergency pediatric intensive care unit admissions.

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There was no difference in the proportion of males and females admitted for COVID-19, but more male individuals (63.5%) were admitted for treatment of MIS-C. As the age increased, females had lower odds of admission to the pediatric intensive care unit as is seen in adults. Generally, those admitted with COVID-19 and MIS-C were older and more likely to be non-white than in the other demographic groups. As with the previous study, the odds of admission to the pediatric intensive care unit were higher for infants than those aged one to four. There was also a higher odds of pediatric intensive care unit for Black individuals compared to white individuals.

Children with complex medical problems across multiple body systems and those with neurodisabilities were at the highest risk of admission to the pediatric intensive care unit from COVID-19, which is consistent with previous studies. There were too few cases of MIS-C to make clear determinations about the association between chronic conditions and admission to the pediatric intensive care unit.

**Overall the magnitude of the increase in risk of admission to the pediatric intensive care unit in individuals with chronic conditions was low during the study period for a number of infectious diseases: the increase in risk above those without chronic conditions was 2% for COVID-19, 0.75% for all admissions, and 1.3% for influenza.**

The one difference from previous years was the increase in age of those admitted to the hospital. In typical years, younger individuals are more often admitted for complications from influenza, but in this study the COVID-19 pandemic shifted the age of those requiring hospital and pediatric intensive care unit towards older age-groups.

The third group used the National Child Mortality Database from Public Health England to quantify the risk of mortality from COVID-19 in individuals under the age of 18 (Smith et al., 2021). Determining the risk has been difficult due to the large number of individuals with asymptomatic cases, leading to a necessity to differentiate between those who died from an alternative disease but also tested positive for COVID-19.

The authors performed a clinical review of all deaths from March, 2020 to February, 2021 to differentiate those who died of SARS-CoV-2 infection and those who died of an alternative cause, but coincidentally tested positive. There were 61 deaths associated with positive COVID-19 tests out of a total 3105 in individuals under the age of 18 in the first year of the pandemic in England. Based on the evaluation, there were 22 deaths from acute infection and three from MIS-C.

**99.995% of individuals under the age of 18 with a positive SARS-CoV-2 test survived.**

The mortality rate was found to be 2 per million. They also found that older children, or those over ten years old; those of Asian and African descent; and those with chronic conditions were overrepresented compared to other children. This suggests that the apparent protection from severe disease and death begins to wane around the age of ten. Additionally, socioeconomic conditions and systemic racism have been found to contribute to an increased risk of severe disease and death from COVID-19 for both children and adults.

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**Overall, they conclude that SARS-CoV-2 is rarely fatal in children and young people under the age of 18, even in those with underlying, chronic conditions.**

The study was not able to investigate the potential long-term effects SARS-CoV-2 infection might have on children, however. There has not yet been sufficient time to determine the prevalence of long-COVID in children, which is made more difficult by the increased rate of asymptomatic cases (Radtke et al., 2021).

**The level of long-COVID that has been reported in children varies between 0% and 27%.**

In a study recently published in *JAMA* that occurred in Zurich, Switzerland, the spread of asymptomatic COVID-19 was being monitored through assessment of antibodies in school children (Radtke, 2021). The researchers in the study were also able to monitor the long-term symptoms of the participants compared to whether they had previously had COVID-19 based on their antibody status. Out of 1,355 children, 109 tested positive for SARS-CoV-2 antibodies and 1246 were negative. None of the individuals in the study had severe symptoms during the initial infection.

**During the timeframe of October, 2020 and April, 2021, 4% of those who had had COVID-19 reported at least 1 symptom lasting beyond 12 weeks while 2% of those who had not had COVID-19 reported at least 1 symptom lasting beyond 12 weeks.**

The most frequently reported symptoms lasting more than 12 weeks among those who had had COVID-19 were tiredness (3%), difficulty concentrating (2%), and increased need for sleep (2%). Hospitalization was not required for any of the participants with SARS-CoV-2 antibodies during this time.

This study allows for an assessment of the prevalence of long-COVID in children in the general population because it allows for identification of asymptomatic cases. The rate determined was 4%, which is on the low end of the range reported in published studies. The study itself had a small number of participants and there were demographic differences between those who were included in the analysis and those who were not, which could skew the results.

Along with the frequency of occurrence of long-COVID, it is also important to look at the severity of the symptoms experienced by those with the condition, which was not assessed in the Zurich study described above. There are varying levels of impairment that have been observed that range from brain fog to numbness that leaves children unable to walk (Cooney, 2021).

Most individuals with long-COVID are over the age of 12, but there are cases that span from infants to the elderly. In infants and young children, Audrey John, chief of pediatric infectious diseases at the Children's Hospital of Philadelphia, told STAT News that it is too soon to know if long-COVID will lead to developmental delays. In older children, it has shown obvious effects on school attendance. Carlos Oliveira, director of congenital infectious diseases at Yale New Haven Children's Hospital, likens some of the symptoms to the lethargy and fatigue experienced from an out of balance immune system after mononucleosis and Lyme disease. Teens suffering from long-COVID have had to take months off of school. Some have had unexplained hair loss,

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coughs, muscle aches, joint pain, headaches, tingling sensations, and a disrupted sense of smell that makes everything smell foul.

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