PINNACLECARE

Medical Intelligence Report

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Topic: COVID-19 Research Update

Overview of COVID-19 Surge in the United States

By the end of July, eight in ten cases of SARS-CoV-2 in the United States were caused by the Delta variant (Soucheray, 2021).

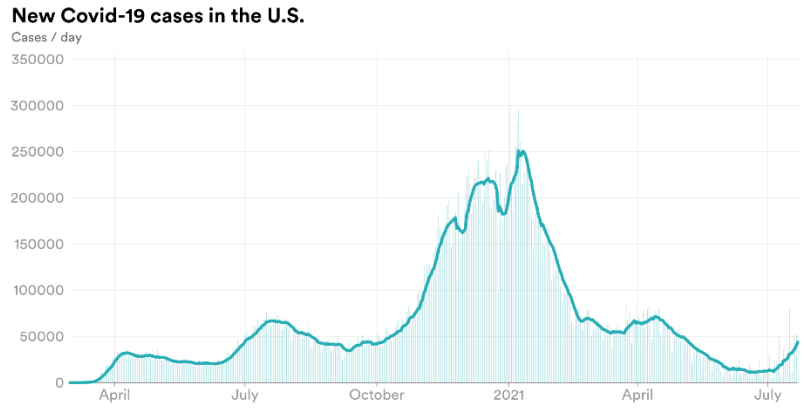
Based on data collected from states by the CDC, COVID-19 cases increased by 300% between June 19 and July 23 due to the spread of the Delta variant.

The overall magnitude of the new cases and deaths is still small compared to the surge that occurred in the fall of 2020 and winter of 2021 due to vaccination of large numbers of vulnerable members of the population, but the rate at which new cases are increasing now is faster than that from the spring and summer of 2020 when vaccines were not available (Parker, 2021). In certain hot spots where the local level of vaccination is low, the number of hospitalizations and deaths are also increasing. For example, Texas reported 4,320 COVID19-related hospitalizations on July 24, which is a level last reached in the state on March, 2021, and the governor of Arkansas has reported that there were only eight intensive care beds available statewide (Soucheray, 2021 and Riess, 2021). The increased rate of new cases can be visualized in Figure 1 below.

It has been found that the rate at which cases increase is a reasonable indicator of how intense that wave might be and how long it might last.

The case acceleration rates for each state and major territory in the U.S indicates that the number of cases is increasing the fastest in Louisiana, Florida, Arkansas, Missouri, Mississippi, Alaska, and Alabama, which are also the areas with the lowest level of vaccinations. The five states where cases are accelerating the fastest all have vaccination rates below the national average.

A.



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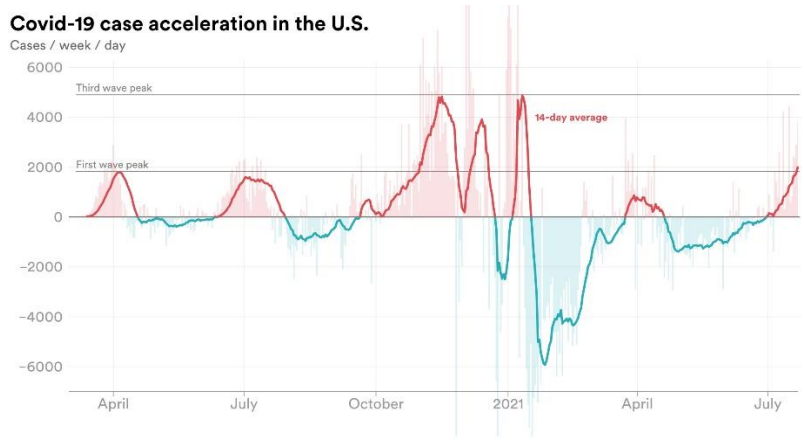

Figure 1. A. The weekly average of new cases in the United States in 2020 and 2021, which allows for a representation of the magnitude of cases. B. The graph of the rate of weekly case acceleration allows for a visualization of how quickly the weekly average of new cases is changing. Increasing cases are shown in red, and decreasing cases are shown in blue. (Adapted from Parker, 2021)

For example, in the weeks starting July 12 and July 19, the new case counts in Louisiana accelerated the fastest of any state in the United States at an average rate of 444 cases per week per day with only 36% of the state's residents vaccinated.

The cases in Louisiana are currently increasing faster than they did at the start of last winter's wave.

A similar pattern in the acceleration in new cases has been seen in Florida where 48% of residents are fully vaccinated. However, in Massachusetts where 63% of the population is fully vaccinated, the rate at which cases are accelerating is much lower than for any of the previous waves of infection and below the national average for case acceleration.

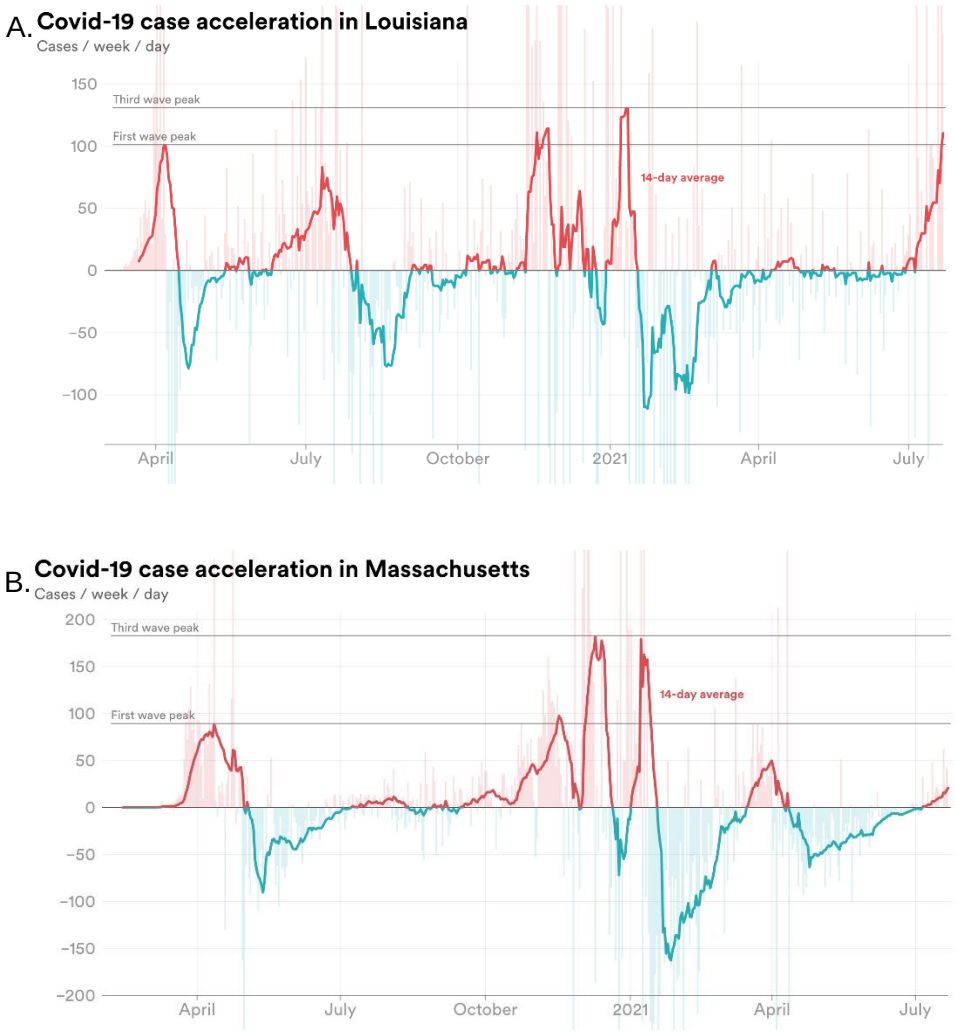

Figure 2. A. The visualization of the acceleration of cases in Louisiana shows that it is near the same levels seen during the winter surge. B. In Massachusetts where vaccination levels are higher, the acceleration of new cases is much lower even though the number of cases is increasing. (Adapted from Parker, 2021)

Reporters from the news section of *Science* interviewed several experts who have been studying the pandemic since its start to find out what they expect to see happening in the United States from the surge in cases from the Delta variant (Wadman, 2021). Natalie Dean, a biostatistician at Emory University stated that there is currently a large amount of uncertainty, making it difficult to predict how bad the current surge will be or how long it will last. Many models currently predict the surge will peak in mid-August to early September with a peak of 450,000 daily cases. More conservative models predict the peak of daily case counts to be around 29,000 and 176,000. The predictions have been difficult due to uncertainty in the response to mask and vaccination recommendations by individuals who live in areas where virus transmission is high.

The number of new deaths nationwide is still expected to be lower than previous peaks due to the high vaccination rates in vulnerable groups, such as those over the age of 70.

The range of new deaths from COVID-19 predicted by the Institute for Health Metrics and Evaluation (IHME) at the University of Washington by November 1, 2021 is 76,000 or 27,000 if 95% of all the people in the United States wore masks. However, regions with low levels of vaccination may see high local numbers of new deaths associated with the surge of infections.

Overview of Delta Worldwide

In the United Kingdom, the surge associated with the arrival of the Delta variant has apparently recently declined sharply, but experts are unsure as to why the number of new cases have gone down so suddenly (Ball, 2021). Approximately 70% of the adult population has been fully vaccinated, but there are still too many susceptible individuals for the drop to be due to herd immunity according to John Edmunds at the London School of Hygiene & Tropical Medicine. When herd immunity occurs, it is observed in different regions at different times as a local population goes over the threshold where new infections are no longer sustainable. However, the change in the United Kingdom occurred throughout the nation at about the same time, which is a scenario that is more commonly observed after a lockdown-like event where the change happens all at once.

There were several societal changes that recently occurred in the country that could have influenced a change. For example, the Euro 2020 football tournament was held leading to congregation of people in pubs, bars, private homes, and stadiums, and the school term ended. The combination may have led to the large spike of new cases after the tournament, followed by a period of quarantining combined with reduced interaction in school-aged individuals that together lowered the rate of new infections. Currently, the United Kingdom has decided not to vaccinate most people under the age of 18 to concentrate efforts on older individuals, and the highest proportion of infections is occurring in people aged 16 to 24 years.

There is also evidence of a reduction in the number of test results being reported, suggesting that people may be avoiding getting tested to avoid the consequences of a positive test, such as required isolation or the need to cancel summer plans. While the number of tests being reported has dropped, the proportion of tests that are positive has risen.

Worldwide the number of cases has doubled in the last four weeks with the number of new infections increasing by 80% in five of the six regions designated by the WHO (Schnirring, 2021). With continued low levels of testing in low-income countries, officials have voiced concerns about not knowing where the virus is moving and how it might be evolving.

Two analyses were recently released that warned of the high likelihood of the evolution of a vaccine-resistant strain of SARS-CoV-2. The first was a peer-reviewed publication in Nature Scientific Reports (Rella et al., 2021). The researchers used modeling based on realistic transmission of SARS-CoV-2 to determine the probability of the emergence of a vaccine-resistant strain.

They found that the highest probability of establishment of a resistant strain occurs when a large fraction of the population has already been vaccinated, but the transmission of the virus is not controlled.

Similar situations have been observed during influenza epidemics. The timing of the emergence of several variants that have high rates of transmission (specifically Alpha and Delta) at the same time that vaccination campaigns began may lead to such a scenario in the current pandemic. In the United States, the increase in vaccinated individuals has led to a relaxation of public health measures to control transmission. This has led to uncontrolled transmission in areas where there are still low levels of vaccination, and the virus has many opportunities to develop mutations that may circumvent the protections provided by current vaccines.

The Scientific Advisory Group for Emergencies (SAGE) in the United Kingdom is a group of experts that provides scientific and technical advice to support government decision makers during emergencies. They recently compiled a report describing the possible role of variants in the pandemic in the near and long-term as well as possible strategies that could be instigated to reduce the impact of variants on populations around the world (SAGE, 2021).

As has been stated by other experts, the report suggests that the eradication of SARS-CoV-2 is unlikely, and that new variants will continue to develop.

Specifically, they state “we have high confidence in stating that there will always be variants.” However, they do believe that the number of variants that develop can be limited by controlling the transmission of the virus though deployment of public health measures, including both vaccination and non-pharmaceutical measures such as universal masking, physical distancing, etc. Whether communities and officials will be able to get the support to implement these proven methods is unclear.

There are several scenarios that the SAGE group outlined for consideration, and they also provided their expert opinion of the likelihood of each scenario occurring. These scenarios and their details are listed in Table 1.

The group provided considerations for reducing the impact of variants, including continuing to proactively support a strategy of worldwide effective vaccination in order to drive down global viral load to reduce the likelihood of dangerous variants emerging in other parts of the world. Continued research for better vaccines that limit transmission as well as disease was also suggested as well as continuing to rapidly obtain and share viral sequences to allow for rapid study and evaluation of the threat posed by novel variants.

Table 1. Potential scenarios of SARS-CoV-2 evolution

	Details	Likelihood
Scenario 1	A variant that causes severe disease in a greater proportion of the population, e.g. more similar to the level of disease from SARS-CoV-1 (10% fatality) and MERS-CoV (35% fatality). This could occur due to mutations in individual genes or large genetic swaps between different existing variants.	The likelihood of genetic changes in the virus was deemed **likely** while the circulation is still high and the likelihood of increased severity is a **realistic possibility**. The impact from such an occurrence would be **high** even *without* failure of current vaccines because breakthrough disease is possible
Scenario 2	A variant evades current vaccines. A change in the spike protein of the virus could occur that incorporates an entirely new protein or swaps out an existing spike protein from a currently circulating coronavirus, such as those that lead to yearly cold symptoms.	The likelihood of this scenario was deemed a **realistic possibility**, and the impact would be **high** if a completely new spike protein is incorporated because new vaccines would be needed. The mRNA platforms allow for relatively quick development. The impact would be **medium or low** if a spike protein from a seasonal coronavirus was inserted because most people have a certain level of immunity to these viruses already.
Long-term Scenario 2	SARS-CoV-2 infects an animal reservoir that allows for evolution outside of humans and could re-emerge later with changes that have not been accounted for in vaccines	This scenario is a **realistic possibility**, and the impact would be expected to be **medium**.
Long-term Scenario 2	The gradual accumulation of genetic changes leads to failure of the current vaccines with the potential of reduced response from next-generation vaccines due to complex immune system responses.	The likelihood of the scenario is considered to be **almost certain**. The impact is expected to be **medium**.
Scenario 3	Emergence of a drug resistant variant after anti-viral strategies.	This scenario is considered **likely** unless the drugs are used correctly, but as vaccines are effective, the impact would only be **medium** unless the drugs become more widely needed.
Scenario 4	SARS-CoV-2 follows an evolutionary trajectory with an increased transmissibility but decreased virulence, becoming an endemic infection similar to the flu.	This scenario is considered **unlikely in the short term**, but a **realistic** possibility in the long term.

Transmission of SARS-CoV-2 and Changes in Mask Recommendations

The CDC recently changed their recommendations for vaccinated individuals to suggest that all individuals, regardless of vaccination state, should wear a mask when indoors. This change is based in large part on information from an outbreak that occurred in Barnstable County, Massachusetts in July, 2021 (Soucheray, 2021). The details of the outbreak were reported by public health officials in a publication in the *Morbidity and Mortality Weekly Report* for July 30, 2021 (Brown et al., 2021).

Between July 10 and July 26, a cluster of COVID-19 cases was identified among Massachusetts residents that were associated with travel to or residence in a town in Barnstable County. July 3, 2021 coincides with the start of a summer event that included large public gatherings in the area.

> **The statewide immunization coverage at the time was high (69%), and a large number of breakthrough cases were associated with the event, leading the state official to investigate the outbreak more thoroughly.**

Based on evaluation of 469 cases, 74% occurred in fully vaccinated persons, which was defined as those who had completed a two-dose course of an mRNA vaccine or had received a single dose of the Johnson & Johnson vaccine more than 14 days before exposure. Based on genomic sequencing of positive cases, 89% were found to be the Delta variant. Additionally, 79% of those with breakthrough infections were symptomatic. There were five individuals hospitalized, and four had been fully vaccinated. There were no deaths associated with this outbreak. Additional reporting from 22 states suggests there are additional cases from people who traveled further, but analysis of this information is still ongoing.

Importantly in regards to the mask mandate, the amount of virus present in testing samples from vaccinated individuals involved in the outbreak was similar to that of those who were not vaccinated. **This measurement is an indication of the level of how infectious a person is.** With previous variants of SARS-CoV-2, vaccinated individuals with breakthrough infections had been found to have **lower** levels of virus in samples taken for testing, suggesting that vaccinated individuals were less infectious than unvaccinated individuals. Therefore, it was not previously necessary for vaccinated individuals to wear a mask because there was little chance they could infect someone else accidently from an asymptomatic infection. In more official terms, vaccinated individuals were not part of, or only minimally part of, transmission chains (Joseph, 2021).

Studies of household transmission are a common approach to evaluating rates of transmission. In these types of studies, researchers evaluate whether the members from a household become ill due to exposure from an individual who is known to have acquired the infection from the community. This measurement is called the **secondary attack rate**.

> **For example, in one study where Alpha was the main variant being transmitted at the time, it was found that the secondary attack rate among household contacts was 11% for those who were vaccinated and 31% for those who were unvaccinated.**

Most of the individuals in the study group that had been vaccinated had received either the AstraZeneca-Oxford or Pfizer-BioNTech vaccine. Evaluation of the household transmission rates indicated that the vaccine effectiveness against transmission for the Alpha variant was 71% between February 1 and May 27, 2021 (deGier et al., 2021).

However, characteristics of the Delta variant are different than the Alpha variant, and vaccinated individuals appear to be as infectious as unvaccinated individuals.

The change in masking recommendation has less to do with a change in the risk of a vaccinated individual being infected while in a public space, and more with an increased risk of someone with a breakthrough infection from the Delta variant making someone else sick.

The vast majority of new infections nationwide are occurring among and from people who are not vaccinated, but as evidenced by the outbreak in Massachusetts, breakthrough infections can cause substantial local events (Joseph, 2021). This would be especially true for mixed groups where there are individuals who cannot be vaccinated due to health concerns or are too young to receive the vaccine yet. Continuing to increase the vaccination level throughout the country will reduce the level of transmission so that breakthrough infections becomes less frequent as well.

The masking recommendations for vaccinated people applies to communities with "substantial" or "high" transmission rates, which the CDC defines as 50 cases or more per 100,000 people over the past seven days.

As of July 27, 2021, nearly two-thirds of counties in the United States fall into those categories with some communities experiencing several hundred new cases per 100,000 people. Overall, breakthrough cases continue to be rare, and those few who have been infected continue to be protected from severe illness and death.

The CDC and the American Academy of Pediatrics have also come out with recommendations that all individuals in schools over the age of two years should wear masks while indoors regardless of vaccination state. While the suggestion for masking in schools is the same as the general recommendation discussed above, both groups felt the need to make a specific recommendation for the school year because a large section of the population at schools, children under the age of 12, are not yet able to be vaccinated. However, children do not need to mask when they are outdoors unless they will be standing in a crowd for long periods of time (CDC, 2021 and AAP, 2021).

Breakthrough Infections

Some epidemiologists have made a distinction between **breakthrough infection** and **breakthrough disease** for COVID-19 vaccines (Tirrell et al., 2021). Breakthrough infections are any infection that occurs after vaccination, but breakthrough disease in the case of COVID-19 describes people with significant symptoms, who are struggling to breathe or require hospitalization for treatment of COVID-19. While there have been reports of breakthrough infections, the reports of breakthrough disease are nearly non-existent, suggesting that vaccines are continuing to protect those who are fully vaccinated. Breakthrough infections are important

to track as well, even if they are not necessarily dangerous to an individual's health, because they may be contributing to transmission, as seen in the outbreak in Massachusetts. They also lead to the emergence of new variants because, in the past, new variants have been found to be more likely to emerge in people who have breakthrough infections.

A study by the Kaiser Family Foundation of the breakthrough cases, hospitalizations, and deaths in the United States indicates that all three are extremely rare events for individuals who are fully vaccinated (Kates et al, 2021). Not all states report information on breakthrough infections or disease in a way that allows for easy evaluation. Based on their analysis, the Kaiser Family Foundation found that 25 states report some data on COVID-19 breakthrough events, and 15 of these states regularly update these data (on a weekly basis for most). Information from fifteen out of fifty states and Washington D.C. means that there may be a large amount of information that is not accessible. However, the data is generally applicable because a large part of the country's population is represented by the states that do contribute information.

States that report some data on COVID-19 breakthrough events

- Alaska
- Arizona
- Arkansas
- California
- Connecticut
- Delaware
- District of Columbia
- Idaho
- Illinois
- Indiana
- Maine
- Massachusetts
- Michigan
- Montana
- Nebraska
- New Jersey
- New Mexico
- Oklahoma
- Oregon
- Rhode Island
- Tennessee
- Utah
- Vermont
- Virginia
- Washington

The rate of breakthrough cases in fully vaccinated individuals ranges from the lowest level of 0.01% in Connecticut to the highest in Alaska of 0.29%.

The amount of breakthrough disease is even lower than rate of the breakthrough infections and ranges from zero to 0.06%. The actual value of breakthrough disease may even be lower than the reported value because some of the data reported includes information on individuals that are hospitalized for reasons other than COVID-19, but test positive during their stay. Some of the state's reporting methods make it difficult to distinguish these cases.

The rates of death among fully vaccinated people with COVID-19 were even lower, effectively zero in all but two reporting states, Arkansas and Michigan, where they were 0.01%.

Based on the available data, more than nine in ten of all COVID-19 cases, hospitalizations, and deaths have occurred among people who were unvaccinated or not yet fully vaccinated.

Another study of the occurrence of breakthrough infections was published in the *New England Journal of Medicine* and followed healthcare workers in Israel who were vaccinated with the Pfizer-BioNTech vaccine (Bergwerk et al., 2021). The information was collected for 1,487 participants with symptoms or a known exposure to someone who was infectious. Testing for COVID-19 was performed using PCR-based testing to detect breakthrough infections. The level of antibodies produced in response to the vaccine were also measured for those with breakthrough infections, and the levels are compared to healthy, vaccinated individuals at the same institution.

There were 39 breakthrough infections between January 20, 2021 and April 28, 2021, corresponding to a rate of 2.6%. This time period was just after the third, and largest, COVID-19 surge in Israel, which reached its peak on January 14, 2021. In the cases where an infection source could be determined, or 37 out of 39, the vaccinated individual was infected by someone who was not vaccinated, and 57% were a household member. Overall, most breakthrough cases were mild or asymptomatic although 19% had persistent symptoms that lasted more than six weeks.

It was found that individuals with breakthrough infections had lower levels of neutralizing antibodies to COVID-19 when compared to the healthy group.

Additionally, within the group of participants who had breakthrough infections, those with higher levels of virus in their testing samples had lower levels of neutralizing antibodies.

When the participants were also tested using antigen based tests, which are less sensitive than PCR-based tests, only 59% received a positive test. A positive result from many antigen-based tests has been shown to roughly correlate with an infectious case of SARS-CoV-2. Cases that test negative by antigen testing and positive by PCR-based testing have often been found to have too little virus present to be infectious. No secondary infections were documented in this study, which means the individuals in this study did not get anyone else sick.

At the time of this study, 85% of the samples were found to be the Alpha variant.

Due to the increased infectivity of Delta, many of the findings from this study may not be relevant for prevention of transmission of the newer variant. The results from the paper are expected to help for future design of potential vaccines, however, because they allow for an estimation of the correlate of protection (Mallapaty, 2021). This value, the **correlate of protection**, is the threshold level of antibodies needed to provide protection against a specific virus. When it is known, large clinical trials are no longer required to prove a vaccine is efficacious. Instead, vaccines that reach the threshold, or correlate of protection, can move forward in the regulatory process.

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