PINNACLECARE

Medical Intelligence Report

Date: February 17, 2021

Topic: Update on Coronavirus Variants

Coronavirus Variants

A number of new variants of SARS-CoV-2 have been identified around the world. The first case was observed in the United Kingdom, but due to limited testing of the genetic sequence in other parts of the world, including the United States, it is difficult to determine the timing of the emergence of the different variants. Researchers have indicated that the newer versions of SARS-CoV-2 have evolved independently rather than a single new variant spreading around the world. Therefore, while there are some of the same mutations in each variant, there are also mutations that are unique in each one.

Summary of Key Facts

- There are three variants that are widespread in different regions around the world that are known to be more easily spread from sick individuals, called B.1.1.7, B.1.351, and P.1.
- Cases of all three variants have been detected in the United States.
- B.1.1.7 is currently the most prevalent in the United States, and several independent research groups have estimated that it will become the dominant form of SARS-CoV-2 by March, 2021.
- The number of cases of B.1.351 and P.1 are still small, but the level of surveillance is low, and therefore information on the prevalence is incomplete.
- An increase in transmission can lead to a much higher number of cases of COVID-19, which would also result in a higher number of deaths and poor outcomes from the disease.
- Transmission can be prevented using the same mitigation strategies previously recommended by the CDC, including mask use, social distancing, and avoidance of indoor or outdoor gatherings.
- An immune response from a previous case of COVID-19 will not necessarily prevent an infection from the B.1.1.7, B.1.351, or P.1 SARS-CoV-2 variants.
- There is evidence of re-infection from all three variants.
- The risk of re-infection seems largest from B.1.351 and P.1 based on the contribution from the E484K mutation.

- Binding of commercial antibody treatment from Eli Lilly and Regeneron was reduced for the B.1.351 variant, but not for B.1.1.7.
- Most studies and laboratory experiments suggest that currently available vaccines will have a similar efficacy to B.1.1.7 as that seen with original versions of SARS-CoV-2.
- All available vaccines had a lower response to the variant B.1.351, but direct evidence of a reduced efficacy is only available for the Johnson & Johnson, Novavax, and AstraZeneca-Oxford vaccines.
- Indirect evidence from laboratory experiments indicates a lower neutralizing activity from the Moderna and Pfizer-BioNTech vaccines toward B.1.351, but it is not known if the reduction is sufficient to cause a change in efficacy of the vaccine.
- The Johnson & Johnson vaccine is the only vaccine with direct information about the efficacy for the P.1 variant, and it is less effective for P.1 than with the original version of SARS-CoV-2.
- The Johnson & Johnson vaccine had a lower efficacy for prevention of infection from B.1.351 and P.1, but the vaccine was able to prevent 85% of cases with severe symptoms regardless of the variant.
- **No one** who was vaccinated with the Johnson & Johnson vaccine **died or required medical interventions**, such as hospitalization, ICU admission, mechanical ventilation, extracorporeal membrane oxygenation (ECMO), even though a large number of those with COVID-19 in the clinical trials were infected with B.1.351 or P.1.
- Vaccination with the Novavax vaccine provided a larger protection from re-infection with B.1.351 than natural immunity from a previous infection.

Overview of Genes and Proteins

In order to discuss how mutations occur and affect a virus, there are some terms that can aid in understanding the process.

Gene- In living organisms, a gene is the specific pattern of genetic material, or nucleotides, which denotes a particular protein. A gene is a made up of DNA and is used to store instructions on how to make a protein. DNA is a stable molecule that is resistant to changes, or mutations.

DNA- Deoxyribonucleic acid, or DNA, is the molecule used by cells to store genetic material. There are four smaller units, called nucleotides, that are strung together to make a strand of DNA.

Nucleotides- Nucleotides are the units that are attached together, as in a chain. There are four different nucleotides, and the order of the nucleotides determines the genetic sequence that is used to produce functional proteins. The names of the nucleotides are adenine (A), thymine (T), guanine (G), cytosine (C).

RNA- Ribonucleic acid, or RNA, is a molecule that is used to transport the genetic code from DNA to the protein-making machinery outside of the nucleus

of the cell. RNA is a transient molecule that is made up of a slightly different set of nucleotides, adenine (A), cytosine (C), guanine (G), and uracil (U).

In many organisms, including humans, the DNA in a cell is encased inside a compartment, called the **nucleus**, to protect it from other components in the cell and to allow for better control of which genes are activated at a specific time. To make proteins from the genetic code stored in DNA, there needs to be a molecule that moves across the nucleus and into the main part of the cell where cellular machinery that makes proteins is located. Because RNA carries the genetic sequence from the DNA to the cellular machinery, it is sometimes called **messenger RNA**, or **mRNA**.

Protein- A protein is a molecule made up of a string of units called **amino acids**. The order of the amino acids determines the three-dimensional shape of the protein and provide the specific chemical groups that allow for a protein to perform its function in the cell.

Amino Acid- An amino acid is a component of a protein that is strung together in a chain. There are 20 specific amino acids used to make proteins in organisms. The order of the nucleotides in a gene specify which amino acid will be added next to a growing protein. A list of the 20 amino acids can be accessed at https://www.ncbi.nlm.nih.gov/books/NBK557845/

Mutation- A mutation is a change in the genetic code of an organism. A mutation can lead to a switch in the type of amino acid inserted in the protein, cause a section of the protein to be removed (or deleted), or add amino acids that were not previously in the gene.

Because cellular organisms store their genetic material as DNA in the nucleus of the cell and incorporate numerous editing mechanisms, mutations are rare. Viruses do not have many of these processes to protect their genetic code from changes, and therefore, mistakes are often made when copying the genetic code for the new virus.

When a mutation occurs in a virus, they happen randomly due to a mistake in copying the genetic material.

Nomenclature of Mutations

- A substitution of an amino acid is signified by the amino acid originally found followed by the position in the protein and the new amino acid. For example, a change from histidine (H) at position 45 to a proline would be called H45P.
- If an amino acid is deleted, the Greek letter delta (Δ) is followed by the position of the amino acid. For example, if histidine 45 was removed, it would be called ΔH45.

The result of the changed proteins from a mutation varies greatly based on where the changes have occurred. Amino acids that end up on the inside of a protein when it adopts its three-

dimensional form are often important because different sized amino acids can affect how well the protein fits together in its shape. Amino acids on the surface of the protein can often be changed without disturbing the shape, leading to a mutation that has no effect on the protein. However, the amino acids on the outside are also the areas of the protein that interact with other molecules in order to perform its function. If an amino acid necessary for the function of the protein is changed, it can function better, function worse, or cease to function all together.

Because viruses replicate quickly, with numerous generations within a single day, and because they have no procedure for proofreading the new genomes that are produced, mutations occur frequently. If a mutation leads to a protein that does not function, the virus with the mutation will not be able to reproduce correctly, and it will not infect new cells and/or produce new virus.

If a mutation leads to a protein with an improved function, that virus will be able to more easily infect cells and/or produce new virus, and more copies of the mutated virus will be available.

More copies will then lead to more people infected and further the spread of the virus. The environment the virus is in when a mutation occurs can influence which mutations are advantageous. For example, early in the pandemic, there were few people with immunity due to infection with the virus, and therefore, there is not an advantage to being able to re-infect a person. As a pandemic proceeds, more people will become immune, and mutations that allow a virus to infect someone who has previously been infected will allow the virus to continue to reproduce (Joseph, 2021b).

There are a number of factors that influence how often a virus incorporates mutations into its genome, but this subject becomes increasingly complicated and is beyond the scope of this report. Nevertheless, some viruses, such as influenza, mutate frequently, leading to a large number of variants, and other viruses, such as measles, mutate very slowly, leading to a small number of variants.

Coronaviruses seem to be in the middle of these representative viruses, and currently the speed of mutation for SARS-CoV-2 has been observed to be about one mutation that is stably passed on every few months.

Increased Rate of SARS-CoV-2 Mutations

Due to the normally slow rate of mutations in coronaviruses, the number of SARS-CoV-2 viruses with stable changes to their genomes that have recently been detected throughout the world was considered noteworthy by researchers. The variant called B.1.1.7, which was identified in the United Kingdom, has 23 total mutations compared to previous SARS-CoV-2 variants. There are mutations in the spike protein of the B.1.1.7 variant that both change the amino acids making up the protein and delete sections of the protein. Seventeen of the changes emerged in a single evolutionary step. This large number of mutations occurring in a small amount of time is remarkable for viral evolution, and scientists who investigate viral genomes stated that they have not seen such a vast change in so little time before (Kupferschmidt, 2020).

The sudden increase in the rate of mutations observed for SARS-CoV-2 is not thought to be due to a change in the virus' characteristics. Instead, researchers have proposed that a quickly evolving strain, or strains, was produced in immunocompromised individuals who become infected with SARS-CoV-2 and remain infectious for months.

A person with a prolonged, active infection gives the virus an ideal environment to acquire multiple mutations, allowing for the virus to change faster than the typical rate of one to two mutations a month.

If the virus is then transmitted to others late in the infection cycle of the immunocompromised individual, the situation allows for transmission of a highly mutated form of the virus. This type of accelerated mutation rate has also been documented in influenza with mutations from immunocompromised individuals eventually spreading globally.

Researchers have published a report describing the emergence of some of the mutations found in the B.1.1.7 variant arising in an individual in England who was immunocompromised from a previous treatment for lymphoma (Kemp et al., 2021 and EurekaAlert, 2021). The individual shed infectious virus for 101 days after diagnosis with COVID-19. After being treated with two courses of convalescent plasma on days 66 and 82 of his illness, the researchers found that new, stable forms of the virus were detectable in samples from the patient that had not been present before. The new forms made up a large proportion of the viruses recovered from testing samples.

Specifically, viruses with two mutations in the spike protein, a change from aspartate to histidine at position 796 (called D796H) and deletions of the amino acids 69 and 70 (referred to as ΔH69/ΔV70), became the dominant form of the virus recovered. The mutation ΔH69/ΔV70 is one of the mutations that is present in the B.1.1.7 variant, but this case was the first time that researchers had observed the ΔH69/ΔV70 mutation develop naturally in a person with SARS-CoV-2. Further testing indicated that the ΔH69/ΔV70 mutation led to a two-fold increase in infectivity compared to the original SARS-CoV-2. Spike proteins from the virus with D796H were less sensitive to neutralization by antibodies contained in the convalescent plasma. In viruses with both of the mutations, there was a two-fold reduction in the response to convalescent plasma.

With the high number of cases of SARS-CoV-2 around the world, instances such as this are more likely to happen, where the virus encounters an environment where chronic infection allows for selection of viruses with multiple mutations that are more effective at replicating in humans. Additionally, as more people in an area become resistant to a virus, through infection or vaccination, only viruses that can evade the immune system will continue to reproduce at high levels, which can also promote the emergence of new variants of a virus (Joseph, 2021c). For example, there were areas in Brazil and South Africa where high levels of transmission were occurring, leading to 40% to 50% of people being infected in populations living in crowded conditions. This situation can lead to emergence of variants that can spread despite existing immunity from a previous infection (Mahase, 2021).

Mutations that become stable in a virus genome typically remain present because they confer an advantage to the virus (Zhang, 2021). The variants of SARS-CoV-2 that have been identified

are thought to have evolved independently from each other, in areas that are geographically separate.

The fact that multiple variants have arisen that contain some of the same mutations suggests that these mutations provide a sizable advantage to the virus that allows it to reproduce more effectively.

Variants of SARS-CoV-2 that have been Identified

New variants are being reported at a high rate currently, and new variants are being identified in all parts of the world.

There is currently not an agreed upon convention for naming the variants, leading to multiple names for the same virus (Callaway, 2021). Some of the names, such as B.1.1.7, are based on the classification system used to track evolutionary relationships between viruses. The numbers signify different lineages where the evolution of the virus branched off. The periods between the numbers show the branch points. For example, there is also a B.1.177, which was identified in Spain.

Another naming convention being used incorporates the mutations observed in the new variant. For example, 501Y.V2 refers to the change in the virus spike protein at position 501 where the previous amino acid is replaced by a tyrosine, which is abbreviated Y. The V2 is in reference to the fact that it was the second version of SARS-CoV-2 reported with this specific mutation.

A large consortium of scientists researching the evolution of viruses, including SARS-CoV-2, uses a naming convention where different types of a virus are grouped based on how related they are into groups called clades. The clades identified so far for SARS-CoV-2 are 19A, 19B, 20B, 20C, 20D, 20E (EU1), 20F, 20G, 20H/501Y.V2, 20I/501Y.V1, and 20J/501Y.V3.

A third naming convention uses the date when the variant was first identified. In this system, a variant is called VOC 202012/01, which stands for Variant of Concern with the date of discovery (December 1, 2020). A similar naming convention used Variant Under Investigation, or VUI-202012/01, with the same use of the date of identification.

Below is a short description of the variants that have been reported, and a more in depth discussion follows.

B.1.1.7

This variant is most often referred to as B.1.1.7, but has also been called VOC 202012/01, VUI-202012/01, and 20I/501Y.V1.

In this report, the variant first observed in the United Kingdom will be referred to as B.1.1.7.

Based on genomic studies, researchers estimate that the new variant, B.1.1.7, emerged in September, 2020 and was present at low levels in the population of the United Kingdom until the middle of November, 2020. It was first detected in December in the United Kingdom.

There are 23 total mutations in B.1.1.7 compared to previous forms of SARS-CoV-2, and the mutations lead to both amino acid substitutions as well as deletions of sections of the protein (CDC, 2021). There are three mutations in the spike protein that have been identified as potentially important, including N501Y, P681H, and ΔH69/ΔV70. The three mutations in the spike protein all allow the virus to more easily infect cells. N501Y allows for a tighter interaction between the viral spike protein and the cellular protein when the virus first encounters a human cell, P681H improves the interaction at a site on the spike protein that is cut by an enzyme on human cells in order for it to cross the cell membrane, and ΔH69/ΔV70, as mentioned above, causes a two-fold increase in the infectivity of the virus.

A recent report from COVID-19 Genomics UK (COG-UK) Consortium, a group in the United Kingdom performing viral genome surveillance, suggests that some versions of B.1.1.7 have also acquired the mutation E484K, which is found in the B.1.351 and P.1 variants. This mutant may lead to avoidance of the immune response to COVID-19. In a report from Public Health England, researchers describe that they found 11 COVID-19 samples out of 214,159 total samples of B.1.1.7 that also contained E484K (Wise, 2021)

B.1.351

> **This variant is most often denoted as 501Y.V2, but can also be referred to as B.1.351, 20H/501Y.V2, or 20C/501Y.V2**.

In this report the variant first identified in South Africa will be referred to as B.1.351.

The variant of SARS-CoV-2 reported in South Africa was first observed at the start of a period of high transmission that began in the middle of October.

There are eight mutations that were identified in the viral spike protein of B.1.351, including some that were also seen in B.1.1.7, such as N501Y (CoVariants, 2021). B.1.351 also has a number of different amino acid substitutions from B.1.1.7, and B.1.351 does not contain a deletion at amino acid 69 and 70 (ΔH69/ΔV70 in B.1.1.7).

The mutation of most concern in B1.351 is E484K, which occurs in a key area of the spike protein that has two effects on the virus (Tegally et al., 2021). First, it enhances binding of the spike protein to the human cell, and it also seems to reduce the response of the immune system by interfering with the binding of antibodies to the spike protein. A third mutation on the spike protein, K417N, also has been found to reduce the binding of antibodies to the spike protein, but it does not change the binding of the virus to the cell.

P.1

> **This variant is most often referred to as P.1, which is the lineage name, but is also called 501Y.V3, VOC202101/02, or 20J/501Y.V3**.

In this report, the variant first identified in Brazil will be referred to as P.1.

P.1 is also thought to have emerged in late November, and it was first identified in test samples in December 2020. P.1 was first brought to world-wide attention when it was found in individuals traveling from Brazil to Japan.

It has been determined that P.1 has 17 amino acid changes with four of the changes in the spike protein (Faria et al., 2021). There are three mutations in the spike protein that are expected to change functionality of the protein, including N501Y, E484K, and K417N.

P.2

A second variant has been observed in Brazil, called **P.2, 20B/S.484K, or B.1.1.28**.

P.2 has five new mutations not observed in other variants, and it also has the E484K substitution. P.2 does **not** have the N501Y change. Both P.1 and P.2 are thought to have emerged from the same lineage of B.1.1.28, but P.1 has moved farther away and is no longer part of that lineage. The P.2 variant is thought to have emerged in late July of 2020 and was first detected in late October, 2020 (Voloch et al, 2020).

Other Possible Variants

There are a number of newly emerging variants with very limited information currently available. The investigation of their properties is ongoing. Some of these newly identified variants will most likely turn out to be highly prevalent in an area, but not cause a change in transmissibility or severity of COVID-19.

Researchers in Columbus, Ohio detected two variants that quickly increased in prevalence in the area around December, 2020. Both were from the 20G clade. They have a number of mutations that have not been observed as stable changes in other SARS-CoV-2 variants, and one also contains the N501Y mutation (called **COH.20G/501Y**) (Tu et al., 2021).

Another variant was reported in Southern California that was first detected in July, but during a period of high transmission, it increased in prevalence until it accounted for 24% of cases by December. This variant is currently called **CAL.20C**. There are five mutations that have been identified in CAL.20C, and three of the mutations occur in the spike protein (Zhang et al., 2021). None of the mutations are found in other variants.

A similar variant in the 20C lineage was detected in Illinois and is called **20C-US or B1.2**. The variant was identified in the late spring and early summer of 2020. There are five mutations identified that occur in a number of different proteins of the virus, including one in the spike protein (Pater et al., 2021).

Prevalence of Variants

Cases of all three emerging variants, B1.1.7, B.1.351, and P.1, have all been detected in the United States, and the number of new cases is increasing daily. B.1.1.7 is currently the most prevalent variant in the United States, and estimates from the CDC suggest that it will be the predominant strain in the United States by March (Galloway et al., 2021).

This model from the CDC of the prevalence takes into consideration the increasing levels of immunization from vaccination efforts in the United States and finds that at the current level, vaccination will not change the trajectory of the transmission of B.1.1.7 any time soon.

While vaccination rates are not yet high enough to alter the transmission, the authors suggest that use of the other mitigation strategies that have been, and are currently being, used, including social distancing, mask use, and avoidance of gatherings both indoors and outside, will allow more time for ongoing vaccination to achieve higher population-level immunity.

When the study was published, on January 15, 2021, B.1.1.7 had been detected in 12 states. As of February 9, 2021, there were 932 cases of B.1.1.7 reported in 34 states (CDC, 2021).

A separate study evaluating the prevalence and spread of B.1.1.7 in the United States showed that the variant is behaving as previously observed in other countries (Washington et al., 2021). By sequencing the genomes of a representative sample in an area, the researchers were able to partially trace how B.1.1.7 has traveled in the United States, and they found that there were multiple introductions of the variant during November of 2020.

Since that time, local transmission is occurring, and the number of cases of B.1.1.7 in the United States is doubling in about ten days.

Based on the increased number of cases they have detected, the researchers estimate that the transmission rate of B.1.1.7 has increased by 35% to 45% compared to the earlier versions of the virus, which is similar to the value estimated previously by other research groups. It was determined that by the last week of January, 2021, B.1.1.7 made up an average of around 2.1% of the COVID-19 cases in the United States. On a state level, about 2.0% of all COVID-19 cases in California and about 4.5% of all cases in Florida were caused by B.1.1.7. Extrapolating based on the known characteristics of the variant, the researchers found that it was taking 9.8 days to double the number of cases overall in the United States, 12.2 days to double the number of cases in California, and 9.1 days in Florida.

The estimates of this analysis agree with the CDC estimate that B.1.1.7 will become the dominant form of SARS-CoV-2 in the United States by March of 2021.

In an interview in *CIDRAP News*, Mark Zeller, one of the authors of the study, indicated that, as stated in the CDC report, he also thought that vaccination efforts would have very limited effectiveness in slowing the spread of B.1.1.7. He stated that “"It will still take many months before enough people are vaccinated to slowdown transmission significantly” (Van Beusekom, 2021).

The quick spread of B.1.1.7 has also been apparent in Ireland where the 14-day infection rate rose 10-fold in three weeks (Reuters, 2021). In the week of December 20, B.1.1.7 accounted for 9% of the samples being sequenced for surveillance. Two weeks later, on January 3, 25% of the samples tested were B.1.1.7, and as of January 11, 45% of the samples tested were B.1.1.7.

As of February 9, 2021, the number of reported cases of P.1 and B.1.351 were still very small in the United States with nine cases of B.1.351 in three states, and 3 cases of P.1 in two states. However, levels of sequencing the genome of new cases are still very low in this country, and the data may be incomplete.

In the article by Washington and colleagues, the authors state:

> "Given that the SARS-CoV-2 VOCs [variants of concern] B.1.1.7, B.1.351, and P.1 are still at relatively low frequency in the U.S., there is still time to implement the necessary surveillance programs and mitigation efforts in the weeks to come. Unless decisive and immediate public health action is taken, the increased transmission rate of these lineages and resultant higher effective reproduction number of SARSCoV-2 will likely have devastating consequences to COVID-19 mortality and morbidity in the U.S. in a few months, if decisive action is not immediately taken."

Possible Consequences of the Viral Mutations

Mutations in a virus can lead to a number of different outcomes. Most mutations are inconsequential, and the change in the amino acids does not affect how the virus functions. However, if the mutations are in areas of the virus that are key for important tasks in the virus lifecycle, mutations can lead to differences in the infection they cause.

The main concerns for potential changes in SARS-CoV-2 in relationship to the current world-wide outbreak include changes that affect **diagnostic tests**, **increases in transmission** of the virus, **increases in the severity** of COVID-19 or an increase in the lethality of the disease, changes that reduce **natural immunity** to the virus, and changes that affect the **efficacy of the vaccines**.

Diagnostic Tests

Mutations in some viruses have also been known to affect diagnostic tests if the mutation occurs in the region recognized by the test. Most of the PCR-based tests for COVID-19 detect multiple targets in the RNA of the virus, in most cases identifying three different proteins from SARS-CoV-2, so that mutations would have a minimal effect on the accuracy of the tests. In other words, all three targets would need to have substantial changes for the test to no longer identify an infection, which is a very unlikely occurrence.

The tests used in the United Kingdom may have been ideally situated to detect B.1.1.7 because one of the mutations present in this variant removed a section of RNA that is part of the test. However, the other two components of the test are unaffected by the mutations and continue to allow for identification of infected individuals. This coincidental occurrence allows health officials to more easily track cases of the new variant without having to perform complete genomic sequencing on each sample (Kupferschmidt, 2020).

Researchers from Johns Hopkins University recently released a statement addressing questions about how the new variants and increased vaccination might affect testing for SARS-CoV-2 (West et al., 2021).

They found that of the 246 molecular diagnostic tests with an Emergency Use Authorization (or EUA), 85.4% of the tests detect targets other than the spike protein.

Of the remaining tests, 7.3% detect the spike protein in addition to other targets in the SARS-CoV-2 genome. Based on information available for antigen-based tests with an EUA, 90.1% of rapid antigen tests detect nucleocapsid protein, which is part of the shell that surrounds the virus and does not often accumulate mutations.

Vaccination will not affect the performance of the PCR-based tests because they detect RNA from the virus genome. While some of the vaccines are mRNA-based, the vaccines do not contain enough RNA to be detected, and the mRNA from the vaccine does not multiply after inoculation.

Antibody tests will only detect antibodies from vaccination if the test is designed to identify antibodies from the same part of the spike protein. During an infection, the immune system produces antibodies to various parts of the virus, but a vaccine contains only limited parts that are included to produce the largest impact on an infection.

Based on their assessment the researchers found that "most diagnostic tests now in use will remain accurate with the variant strains, and vaccination should not interfere with diagnostic or antibody tests."

Changes to Transmission

All of the variants recently identified are thought to lead to increased transmission of the virus due to similar changes in the spike protein that allow better interactions with human cells.

The majority of the impact on transmission is thought to result from N501Y.

Researchers have observed that people with B.1.1.7 have a larger amount of virus in their upper airways than people infected with other variants. Increased levels of virus in the nose and mouth could cause an increase in the amount of virus released by an individual into their surroundings, which could account for the increased transmission. In some cases, researchers found an increase in the amount of virus of between 10 to 10,000 times that reported earlier in the pandemic (Mandavilli, 2020). The amount of virus being produced by an individual can change based on what part of the timeline of infection a person is tested, meaning that more detailed information is required to make sure that this factor is not affecting the measurements.

The changes in transmission appear to affect all individuals equally, and no groups have been found to be more affected than others.

For example, children continue to have a lower rate of infection than adults, but the overall rate for both groups has increased.

It can be difficult when a new variant is detected to determine if the increased prevalence is due to chance superspreading events or actual increases in the transmissibility. Based on the fact that the increased spread of the viruses is occurring similarly in multiple regions, researchers can infer that they are indeed more transmissible (Volz et al., 2021). Laboratory experiments are underway to determine exact values and mechanisms for increased transmission, but these results will most likely have little effect on the response to the outbreak.

While values on the increase in transmission are not yet available for B.1.351 and P.1, researchers have estimated that there is a 35% to 70% increase in the transmission rates for B.1.1.7.

There is also evidence that B.1.1.7 has a higher reproduction number than previous variants (Rambault et al., 2020). The **reproduction number** describes the number of people a sick individual infects. Viruses with a higher reproduction number have characteristics that allow them to spread more quickly.

With the current information, British scientists estimate that the **reproduction number of B.1.1.7 has increased from 1.1 to 1.5**, which means that early forms of SARS-CoV-2 would lead to ten infections from one person, but B.1.1.7 would lead to 15 infections from one person (Joseph, 2020b). In a single step, this might seem like a small increase, but when each of those 15 people infect 15 more people, and so on, the rate of infection increases very quickly.

The number of cases of B.1.1.7 in Denmark in January were increasing by 70% each week even with a strict nationwide lockdown in place.

Epidemiological data from the data in Denmark indicates that the new strain is 20% to 50% more contagious, which is lower than the estimate determined in England. Denmark is uniquely situated to monitor the spread of B.1.1.7 because officials have a large viral-genome surveillance system in place (Birnbaum and Sorensen, 2021). At the end of January, the country was sequencing the genome of every positive COVID-19 test to identify the spread of the variant while the United States sequences just 0.3% of COVID-19 positive tests.

Based on the data, it is expected that B.1.1.7 will become the dominant form of COVID-19 in mid-February in Denmark, and experts predict that the number of cases of COVID-19 could quadruple by April.

Changes to the Severity of COVID-19

Initial estimates suggested that B.1.1.7 had increased transmission, but no change in the severity of disease (Horby et al., 2021).

However, it has since been determined that infection with B.1.1.7 is associated with an increased risk of death compared to previous versions of SARS-CoV-2.

In one study, it was determined that the relative hazard for death within 28 days of a positive test for B.1.1.7 **increased by 28%**. The increased risk was observed across **all age groups**. A second study found an increase in the case fatality rate between 29% and 36%, and the effect was also observed to occur across all age groups.

The most recent report, with the largest amount of data, included 47% of all SARS-CoV-2 community tests and 7% of COVID-19 deaths in England from September 1, 2020 to January 22, 2021 (Davies et al., 2021). This report confirms the earlier estimates of a 30% increase in the risk of death from B.1.1.7 compared to previous versions of SARS-CoV-2.

This change in the risk of death corresponds to a change in the overall risk of death after contracting COVID-19 for a man aged 55–69 years increasing from 0.56% to 0.73% in the 28 days after diagnosis.

An increase in the risk was observed regardless of the age, sex, ethnicity, deprivation level, care home residence, locale of residence, or date of test. The researchers were not able to determine the mechanism in viral infection that led to an increased risk of death from B.1.1.7. Table 1 shows the increased risk of death for individuals with COVID-19 in different age groups.

Table 1. Increases in the risk of death from B.1.1.7 based on age.

Age in years	Risk of death from B.1.17	Risk of death from previous SARS-CoV-2 variants
Women, 70–84	3.7%	2.9%
Women, 85 or older	16.4%	12.8%
Men, 70-84	6.1%	4.7%
Men, 85 or older	21.7%	17.1%

The researchers also found that the number of people infected with B.1.1.7 was similar between men and women, suggesting that there is not a difference in the number of people who get ill based on sex. However, there was an increase in the number of people aged one year to 34 years who contracted B.1.1.7 compared to those 85 years or older. The increased number of younger people with B.1.1.7 was initially thought to be due to a potential increased infectivity of children, but that scenario was found to be incorrect in later studies.

Based on the results of the study, the authors conclude that the absolute risk of death from COVID-19 remains low with B.1.1.7 amongst age groups less than 54 years, and the absolute risk remains higher in males compared to females.

Changes to the Immune Response from B.1.351 and P.1

The B.1.351 and P.1 variants have been shown to be more transmissible, but there is also increasing evidence that they may be able to avoid immune responses generated from previous

infection with SARS-CoV-2. Mutations in the spike protein in the two variants are located in areas where the spike protein binds to human cells, the receptor binding domain (or RBD), and the opposite side of the spike protein called the N-terminal domain (or NTD) (Callaway, 2021). These regions are also two of the main sites of antibody interaction as well.

Variants' Avoidance of Antibodies

Antibodies detect a viral protein (or antigen) by sensing the three dimensional shape, in a manner similar to puzzle pieces fitting together. If the shape of the antigen changes due to a mutation, the fit between the antibody and the antigen is not as good, and the antibody doesn't interact as well. As the interaction becomes poorer between the antibody and the antigen, the immune response will become smaller and less effective.

In order to test if antibodies from a previous infection with SARS-CoV-2 will still react to the new variants, researchers utilize antibodies in the plasma of individuals who recovered from COVID-19, commercial antibodies developed as a treatment for COVID-19, and antibodies generated by people who have been vaccinated against COVID-19.

Which parts of SARS-CoV-2 are most likely to mutate due to exposure to antibodies?

In one experiment, researchers were testing which parts of the virus were most likely to mutate to avoid a strong neutralizing response from the many different types of antibodies in convalescent plasma (Anderano et al., 2020). SARS-CoV-2 was grown in the presence of the antibodies over several generations in order to observe if any mutations became evident. After growth in the presence of antibody for 74 days, the researchers detected a virus with the E484K substitution in the RBD, which is also found in the B.1.351 and P.1.

> **The shape of the E848K mutation was modeled into the three-dimensional shape of the spike protein, and it was found that the change in the shape of the spike protein from the mutation would prevent antibodies from interacting.**

An evaluation of the antibodies in the convalescent plasma used in this study indicated that most of the antibodies interact with the RBD and NTB of the spike protein. The importance of these regions in the immune response is also evident from previous studies that indicate that a single mutation in the RBD or NTD can reduce the ability of convalescent plasma to neutralize the virus by up to 10-fold in some cases (Greaney et al., 2021).

> **The authors of the paper found that SARS-CoV-2 with the E484 K mutant was able to escape the immune response from the multiple different types of antibodies present in convalescent plasma.**

They report that these results were remarkable because, while it is typically easy for a virus to escape from the effects of a single antibody targeted to a single site on the virus (or antigen), it is usually difficult for mutations in a slowly evolving virus like SARS-CoV-2 to circumvent the effects of multiple antibodies targeted to different antigens. Additionally, changes in only three amino acids in the spike protein were sufficient to negate the neutralizing ability of **all** the antibodies in convalescent plasma in one experiment.

Are there mutations in SARS-CoV-2 that have a larger effect on antibody escape?

In another study of the effect of E484K on antibody recognition, researchers evaluated the change in the neutralization from antibodies in several different samples of convalescent plasma due to mutations in the RBD region of the spike protein (Greaney et al., 2021).

Based on their experiments, the researchers found that there are three main regions of the RBD that are important for the interaction of antibodies, and that antibodies that target the RBD contribute the most to the neutralization effect of the convalescent plasma. Some of the mutations they identified led to a reduction in the interaction between the antibodies and the RBD that in turn led to a greater than ten-fold reduction in the ability to neutralize the virus.

The part of the spike protein with the largest effect on binding of antibodies and neutralization of the virus was determined to be E484.

When the glutamate (E) normally observed at position 484 was changed to lysine (E484K), glutamine (E484Q), or proline (E484P), there was a **35 to 60-fold decrease** in the ability of antibodies to neutralize the virus. Other researchers have also observed a reduction in the ability of antibodies to neutralize virus with mutations at E484, highlighting the importance of this part of the RBD in mediating the immune response.

The mutation E484K is found in both the B.1.351 and P.1 variants. Both variants also have two other mutations in the spike protein at N501Y and K417N. The contribution of these mutations to avoidance of antibody recognition was much lower than that of E484K, suggesting that they provide an advantage to the virus in other ways.

There was a large amount of variation between the effects of convalescent plasma from different individuals, suggesting that the effect of the variants may vary between individuals.

For example, most of the samples showed a large reduction in neutralizing ability towards viruses that contained E484K, but there were some individuals where antibodies continued to have strong neutralizing capabilities. There was also some evidence that the effect of mutations changed over time in convalescent plasma obtained at different times after the infection.

Is there a difference in the contribution of the RBD or NTD?

In a study investigating regions of the spike protein that often contain deletion mutations, researchers found that there were four regions in the NTD that were most likely to be removed (McCarthy et al., 2021). One of these sections was the ΔH69/ΔV70 deletion that is found in B.1.1.7, and it is also present in a number of other SARS-CoV-2 genomes around the world. The part of the protein that encompasses ΔH69/ΔV70 is a section that has been found to interact with antibodies. When a version of ΔH69/ΔV70 SARS-CoV-2 was tested against a single, neutralizing antibody that binds to the NTD, the mutation was found to eliminate the neutralizing effect of the antibody. However, when convalescent plasma was used, which contains numerous different antibodies to different parts of the virus, there was not a noteworthy

change in the neutralizing ability of the convalescent plasma with the single ΔH69/ΔV70 deletion.

The results from this study suggest that while the region of the protein that contains ΔH69/ΔV70 participates in binding to antibodies, additional changes in SARS-CoV-2 would be needed to allow for it to escape from the immune response.

How do the mutations in the variants affect their binding to specific antibodies?

An investigation of the effects of mutations in B.1.1.7 and B.1.351 on the response of antibodies also highlighted the binding of the ΔH69/ΔV70 region of the NTD as well as reaffirmed the importance of the E484K mutation in the RBD of B.1.351 (Wang et al., 2021). The researchers looked at how different mutations in B.1.1.7 and B.1.351 affected the ability of different antibodies to neutralize the virus. In some cases, the mutant viruses were completely resistant to the antibodies, and there was no evidence of neutralization. Others had varying levels of reduction of neutralization, and some had no effect at all. The results of the evaluations are listed in Table 2.

The response of B.1.1.7 in this study is similar to what was observed in the above study where additional mutations will be needed for B1.1.7 to avoid the immune response while B.1.351 was highly resistant to multiple antibodies.

Table 2. Response of B.1.1.7 and B1.351 to different antibodies.

	B.1.1.7	B1.351
Single antibodies targeted to NTD	Resistant	Resistant
Single antibodies targeted to RBD	Slightly reduced neutralization	Resistant
Convalescent plasma	3 fold reduction in neutralization	11 to 33-fold reduction in neutralization
Bamlanivimab (Eli Lilly)	Normal activity	Resistant
Casirivimab (Regeneron)	Normal activity	Resistant
Imdevimab (Regeneron)	Normal activity	Normal activity

The researchers also evaluated the response to commercial antibody therapies from Regeneron, Eli Lilly, and others not available in the United States. As summarized in Table 2, they found that **bamlanivimab from Eli Lilly no longer neutralized B.1.351**, but was still effective against B.1.1.7. Addition of a second antibody, CB6 that targets the RBD, in combination with bamlanivimab did not restore the neutralizing ability against B.1.351. The Regeneron therapy is composed of two antibodies, casirivimab and imdevimab. The testing showed that the cocktail had its normal level of activity against B.1.1.7, but **casirivimab was not effective against B.1.351 while the other component, imdevimab had normal activity**. The lack of effect of bamlanivimab was due to the E484K mutation while K417N and E484K affected casirivimab. The researchers also looked at the effects of the variant mutations on

antibodies from individuals participating in vaccine trials for Moderna and Pfizer-BioNTech, and the results are described below.

How does virus from people with COVID-19 react to convalescent plasma?

Another study investigated the ability of the live B.1.351 virus to evade the antibodies in convalescent plasma from six individuals. Live virus is actual virus obtained from sick individuals, rather than a virus engineered with some of the mutations as was used in other experiments. The six people who donated convalescent plasma were confirmed to **not** have been infected with a virus containing any of the RBD or NTD mutations from the emerging variants (Cele et al., 2021).

The researchers report that the amount of antibody needed to inhibit the activity of the virus was 6 to 200-times higher than that observed with earlier versions of SARS-CoV-2.

> **In other words, the experiments indicated that the ability of antibodies from the convalescent plasma to neutralize B.1.351 was greatly reduced.**

As reported in the other studies, there was a large variation in the response between the samples from different individuals. In the most extreme case, there was a **complete elimination of activity of the antibodies**.

How do specific regions of the spike protein affect antibody binding?

Finally, a group of researchers looked at antibodies known to interact with specific parts of the viral spike protein to investigate the contribution of each region (Wibmer et al., 2021). Antibodies targeted to K417, E484, and a deletion in the NTD (Δ242-244) all were unable to interact to the spike protein of B.1.351, suggesting that there are contributions to antibody interactions from all three sites.

The researchers also evaluated the response of convalescent plasma from 44 individuals with either high or low levels of neutralizing antibodies.

> **They found that 44% of the samples had no detectable neutralization activity, and only 7% retained near normal neutralization to the B.1.351 variant.**

The samples that retained the ability to neutralize were obtained from individuals with severe disease who also had some of the highest neutralization levels against the original virus.

The amount of non-neutralizing antibodies in the convalescent plasma that could bind to the B.1.351 variant was also evaluated. These types of antibodies do not prevent the virus from infecting cells, but they can still alert the immune system to the presence of a virus, allowing for other parts of the immune system to respond to the pathogen. The results of the analysis showed that a considerable part of the non-neutralizing antibody components of convalescent plasma are still able to bind the spike protein of B.1.351. Further study will be needed to determine if the non-neutralizing antibody activity will be sufficient to provide partial protection in the form of reduced symptom severity.

Based on their results, the authors suggest that most individuals infected with previous SARS-CoV-2 lineages will have minimal or no detectable neutralization activity against B.1.351.

Is P.1 similar to B.1.351?

The P.1 lineage also contains many of the key mutations (E484K, K417T, and changes in the same area of the NTD) as B.1.351, suggesting that it will also display a similar ability to avoid the immune response from previous cases of COVID-19. This has indeed become evident based on the detection of numerous cases of re-infection, which are described below.

They also discuss that many of the commercially available antibody treatments were designed to target residues K417 or E484 (including those from Eli Lilly and Regeneron) and therefore, may not be effective for the treatment of B.1.351 or P.1. The second generation of therapeutic antibodies are often targeted against the region of the NTD that also is mutated in both variants.

Re-Infection

There have been increasing reports of individuals who previously had COVID-19 being re-infected with the new variants, suggesting that the changes observed in the ability of antibodies to neutralize the virus do indeed affect the ability of the immune system to prevent a repeat infection.

In one report, a 45-year-old woman in Brazil was infected on May 20, 2020 and then later re-infected on October 26, 2020 (Nonaka et al., 2021). Researchers determined the genetic sequence of testing samples from both illnesses, and found that they were from different lineages. The second infection was caused from a version of SARS-CoV-2 with the E484K mutation and of the lineage where P.1 and P.2 evolved from (B.1.1.248). The second instance of COVID-19 caused more severe symptoms than the first episode, but hospitalization was not required either time (Brito, 2021).

There is also a confirmed report of re-infection with B.1.1.7 eight months after a man in the United Kingdom recovered from a first episode of COVID-19 (Harrington et al., 2021). The 78-year-old man has a history of type-2 diabetes and numerous other chronic conditions. During the first illness, he had mild illness and an uneventful recovery. He had periodic antibody tests that were required for dialysis appointments, and the level of antibodies did not decline over the period between the infections. He was diagnosed with COVID-19 a second time on December 8, 2020, and required treatment in the hospital on December 14, 2020 due to symptoms from COVID-19, including severe hypoxia.

There was no evidence of waning immunity or an immunocompromised state in the individual in this report that would indicate a susceptibility to re-infection, but there is evidence of a large variation in the immune response between individuals, suggesting that it is difficult to predict who will develop a strong response to infection that leads to long-term immunity.

The most convincing evidence of the potential for re-infection comes from the Brazilian city of Manaus (Douclef, 2021, Schnirring, 2021 and Kupferschmidt, 2021). This city of 2.2 million had previously experienced a large outbreak of COVID-19. Antibody testing (also called seroprevalence testing) of the population in the area over the summer showed that 76% of the Manaus residents had been infected in the first outbreak. This level of infection is above the level of 67% infection that has been estimated to achieve a herd immunity threshold, and many experts felt that the risk of further outbreaks in the area would be low.

However, a new outbreak started in December in Manaus, and the level of infections is as high as the previous outbreak. Hospitals in the area have run out of oxygen and space to treat patients. An infectious disease specialist in the city, Marcus Venecia Lacerda, stated in an interview with NPR that the second surge may even be worse than the first.

> **Researchers monitoring the situation sequenced the genomes from 31 samples positive for COVID-19 collected between December 15 and 23, 2020 and found that 42% were the P.1 variant.**

Additionally, 65% of the samples were part of the B.1.128 lineage that P.1 and P.2 evolved from. Samples tested in March to November, 2020 did not contain any instances of P.1.

Further studies are underway to determine if the resurgence is due to a waning immune response or avoidance of an immune response by the new variants, but whatever the cause, the large surge of re-infections in Brazil suggest that natural immunity may not be as good at prevention of new infections as hoped.

Changes to the Efficacy of Vaccines

The change in the efficacy of vaccines in response to new variants of SARS-CoV-2 differs slightly from the changes that affect an immune response to infection. During infection, the body produces numerous different antibodies to many areas of the virus. However, vaccines contain only a subset of antigens from the virus, and usually only a single antigen. In the case of the currently available vaccines, they all deliver copies of the spike protein or copies of just the RBD region of the spike protein. The immune system will produce multiple antibodies that interact in different ways to the protein, so that there will be some that can interact with areas on the antigen that have not changed in new variants, but large changes or changes in multiple key regions may lead to less effective vaccines.

Moderna and Pfizer-BioNTech Vaccines

The clinical studies of the Moderna and Pfizer-BioNTech vaccines occurred before B.1.1.7, B.1.351, and P.1 were widespread, and therefore, the results from the studies indicate the effect of the vaccines on the original form of SARS-CoV-2 only. Researchers have used blood samples from participants in the studies to investigate if antibodies produced in response to the vaccine are active against the new variants.

One of the reports from a preprint investigated the effect of Pfizer-BioNTech vaccine on a virus generated with the N501Y mutation from B.1.1.7 (Xie et al, 2021). Researchers from the University of Texas Medical Branch engineered two viruses, one with the original amino acid at site 501 in the spike protein (asparagine, or N) and one with the amino acid that was mutated (tyrosine, or Y). Blood samples that had been saved from 20 participants in one of the clinical trials for the Pfizer-BioNTech vaccine were tested against the engineered viruses.

Those participants who produced neutralizing antibodies against the initial version of the virus also had a neutralizing effect against those with N501Y.

Additionally, the amount of antibodies present in the blood serum that responded to both viruses was observed to be equivalent.

However, the version of virus used in the experiments did not contain all the mutations observed in the variants. The researchers at the University of Texas Medical Branch had already created the virus for other laboratory experiments, allowing for a quick evaluation in coordination with researchers from Pfizer. It is possible that virus with all of the mutational changes might not react as will with antibodies produced in response to the Pfizer-BioNTech vaccine.

Pfizer also reported that it has tested antibodies produced by participants in the vaccine trials against 15 other potential mutations in the spike protein without a deleterious effect, but the specific mutations were not listed (Erman, 2021).

The researchers from the University of Texas in coordination with those at Pfizer have expanded their investigation and published the results in the journal *Nature Medicine* (Xie et al., 2021b). In the expanded experiments, the researchers also included engineered viruses that contained multiple mutants in the spike protein from B.1.1.7 (Δ69/70, N501Y, and D614G) and those from B.1.351 (E484K, N501Y, and D614G), but they did not contain all the mutations in the whole virus.

The effect of the mutations was again tested with blood samples from 20 participants from the Pfizer-BioNTech vaccine trial that were obtained at two weeks and four weeks after the second dose of the vaccine.

The reduction in neutralization activity was four-fold or less for all of the samples against the mutant viruses, which the researchers report as a clinically equivalent neutralization activity.

However, the level of neutralization activity against the mutants from the B.1.351 was lower than the activity observed for the virus with the mutations from B.1.1.7. They suggest that the magnitude of the difference is small. They compare the changes to the four-fold reduction in neutralizing activity used as a threshold for changing the strain included in influenza vaccines. They also discuss that the correlation between antibody neutralization in laboratory tests and protection from an immune system response is not understood for SARS-CoV-2.

Moderna released information on testing of antibodies from participants in their clinical trials on engineered virus containing the mutants from B.1.1.7 and B.1.351 in a press release and a

preprint (Moderna, 2021 and Wu et al., 2021). They report that antibodies in the blood samples from trial participants retained neutralizing ability to B.1.1.7 and B.1.351.

There was no statistically significant difference in the response to B.1.1.7, but there was a six-fold reduction in neutralizing activity towards B.1.351.

Even with the reduction, representatives from the company suggest that the neutralizing activity remains "above levels that are expected to be protective."

In the study discussed above by Wang and colleagues, the researchers investigated the effect of specific antibodies on the activity of viruses with mutations from B.1.1.7 and B.1.351, and they also obtained blood samples from participants in the clinical trial for the Moderna and Pfizer-BioNTech COVID-19 vaccines for comparison (Wang et al., 2021b).

Only a small number of individuals had more than a two-fold reduction in neutralization for either vaccine against B.1.1.7.

The average reduction in neutralizing activity against B.1.1.7 was 1.8-fold for the Moderna vaccine and 2.0 fold for the Pfizer-BioNtech vaccine.

However, the samples from every individual lost some activity against B.1.351, with some of the participants having a substantial loss of neutralizing ability.

The average loss of neutralizing activity against B.1.351 was 8.6-fold for the Moderna vaccine and 6.5-fold for the Pfizer-BioNTech vaccine, which is larger than the reduction reported by researchers from the companies. As with other measured parameters, the loss of neutralizing activity was found to be associated mainly with E484K.

Reports of Re-Infection after Vaccination with Pfizer-BioNTech Vaccine

Officials in Osnabruck, Germany have reported an outbreak of B.1.1.7 in residents of a nursing home after vaccination at the facility with the Pfizer-BioNTech vaccine (DW, 2021). The report was published on February 8, 2021, and the residents had received their second dose of the vaccine on January 25, 2021. Fourteen residents had tested positive by February 5, and, at the time, none were experiencing severe symptoms.

Clinical Trials of Vaccines when B.1.1.7, B.1.351, and P1 were circulating

Because the clinical trials of the AstraZeneca-Oxford vaccine, the Novavax vaccine, and the Johnson & Johnson vaccines occurred more recently, the new variants had begun circulating. Therefore, these vaccines have direct information on how well they perform against the new variants rather than estimations based on laboratory experiments.

Generally, the vaccines were less effective at preventing cases of COVID-19 from B.1.351 and P.1, but retained similar levels of protection from B.1.1.7. While the protection from infection

was reduced, individuals who were vaccinated still had protection from developing severe symptoms from COVID-19.

AstraZeneca-Oxford Vaccines

A preprint of results of the clinical trial for the vaccine from AstraZeneca-Oxford was released and included information on the efficacy of the vaccine over the period from October 1, 2020 to January 14, 2021 (Emary et al., 2021). In the study, positive COVID-19 samples from 1524 participants were collected and evaluated, and the viral genome of 323 samples was determined.

Based on the results, it was determined that individuals who had been vaccinated, but tested positive for COVID-19, had lower amounts of virus in their respiratory samples and tested positive for a shorter length of time. Antibodies from blood samples of vaccinated individuals showed a 9-fold reduction in neutralization activity against B.1.1.7 compared to previous versions of SARS-CoV-2.

Vaccine efficacy for the prevention of symptomatic SARS-CoV-2 infection was similar in participants infected with B.1.1.7 (74.6%) or non-B.1.1.7 lineages (84%).

Based on the results from this study, the researchers concluded that the "efficacy of the vaccine against the B.1.1.7 variant of SARS-CoV-2 is similar to the efficacy of the vaccine against other lineages. Furthermore, vaccination with the AstraZeneca-Oxford vaccine results in a reduction in the duration of shedding and viral load, which may translate into a material impact on transmission of disease."

A second analysis of the AstraZeneca-Oxford vaccine indicates that the efficacy against the B.1.351 variant is greatly reduced (Madhi et al., 2021). This trial included 2,026 individuals who were enrolled between June 24 and November 9, 2020. At the time of the analysis, 1010 participants had received one dose of the placebo, and 1011 of the participants had received one dose of the vaccine.

It was determined that 3.2% of those receiving the placebo and 2.5% of the group who were vaccinated developed mild to moderate COVID-19, which corresponds to an efficacy of 21.9%.

Genomic sequencing of the samples positive for COVID-19 indicated that 92% of the cases were of the B.1.351 variant.

When only the cases from B.1.351 were included in the analysis, it was found that the vaccine efficacy was 10.4%.

The efficacy of the vaccine was so low that officials in South Africa have suspended distribution of the vaccine (Herper, 2021).

While the results from this analysis indicate the vaccine "provides minimal protection," the study results were obtained from a very small number of participants, 25. Additionally, the researchers

were only able to assess the prevention of mild cases of COVID-19 because no severe cases were observed. While the vaccine may be ineffective at stopping infection, it may be able to blunt the severity of symptoms enough to prevent surges at hospitals of individuals needing intensive care.

Novavax

The Phase 3 trial of the Novavax vaccine took place in the United Kingdom, where there was a high prevalence of the SARS-CoV-2 B.1.1.7 variant. During the trial, over 50% of the confirmed cases in participants were from B.1.1.7 (Novamax, 2021).

> **When the results were analyzed based on the variant-type, the Novavax vaccine was found to be 95.6% effective against the original COVID-19 strain and 85.6% against B.1.1.7.**

There were a total of 62 confirmed cases of COVID-19 in the trial with 56 in the placebo group. Out of the 62 cases, all involved mild symptoms except one case with severe symptoms in the placebo group.

In the same press release, Novavax described the results from their Phase 2b clinical trial of the vaccine that is being conducted in South Africa. This study has enrolled over 4,400 participants, beginning in August of 2020. There have been 44 cases of COVID-19 reported in participants in the trial, and 92.6% of the cases with genome sequencing data available were found to be the B.1.135 variant. There were 29 COVID-19 cases in the placebo group and 15 cases in the vaccinated group with one case of severe symptoms in the placebo group, and all other cases were of mild to moderate severity.

> **These preliminary results suggest that the vaccine is 60% effective against the B.1.351 variant.**

The representatives from the company stressed that, in this study, around 33% of the participants had evidence of previous SARS-CoV-2 infection based on the presence of antibodies. Because of the timing of the trial, the previous infections would have been with the initial variant of the virus. The B.1.351 variant is associated with a higher rate of reinfection compared to other versions of SARS-CoV-2, making it important to determine if a vaccine is able to provide protection from reinfection.

> **The company states that the data described in the press release "suggest that prior infection with COVID-19 may not completely protect against subsequent infection by the South Africa escape variant, however, vaccination with the Novavax vaccine provided [statistically] significant protection."**

Novavax began development of new vaccine constructs against the emerging strains in early January, 2021, and identification of a booster or combination vaccine for the variants is expected within a week. Clinical testing of the updated vaccines is expected to begin in the second quarter of the year.

Johnson & Johnson COVID-19 Vaccine

The single dose Johnson & Johnson vaccine also was tested after the emergence of the variant forms of SARS-CoV-2 (Johnson & Johnson, 2021). Based on the interim results of the Phase 3 trial, the overall efficacy rate is lower than that reported for the Pfizer-BioNTech and Moderna vaccines, but the study was conducted in the United States, South America/Latin America, and South Africa, and the presence of B.1.351 and P.1 is thought to have changed the efficacy. This effect is noticeable when comparing the efficacy in different geographic regions.

When the efficacy for preventing moderate to severe disease was evaluated for participants living the United States, where the variant was not yet widespread, the Johnson & Johnson vaccine was 72% effective in the prevention of moderate to severe COVID-19.

The efficacy in prevention of moderate to severe COVID-19 was reduced in some regions where there the new variants have become widespread.

Table 3. Efficacy by region.

Region	Efficacy Rate
Entire Trial Population	66%
South and Latin America	66%
South Africa	57%
United States	72%

It was determined that 95% of cases of COVID-19 that occurred in participants in the section of the trial performed in South Africa had the B.1.135 form of COVID-19.

Importantly, the vaccine was found to be 85% effective at preventing severe symptoms from COVID-19 in ALL of the regions included in the study, including those where new variants are widespread.

The efficacy in preventing severe disease increased over time, and there were no cases of severe disease reported in any of the vaccinated participants after 49 days from the time of their vaccination.

There were also no cases that resulted in death or need for medical intervention (defined as hospitalization, ICU admission, mechanical ventilation, extracorporeal membrane oxygenation, or ECMO) in vaccinated participants after 28 days from the date of vaccination.

The onset of protection from COVID-19 was observed as early as day 14. There were no reports of any significant safety concerns relating to the vaccine, and a single dose was generally well tolerated.

References

Andreano E, Piccini G, Licastro D, Casalino L, Johnson NV, Paciello I, Monego SD, Pantano E, Manganaro N, Manenti A, Manna R, Casa E, Hyseni I, Benincasa L, Montomoli E, Amaro RE, McLellan JS, Rappuoli R. SARS-CoV-2 escape in vitro from a highly neutralizing COVID-19 convalescent plasma. *bioRxiv* [Preprint]. 2020 Dec 28:2020.12.28.424451. doi: 10.1101/2020.12.28.424451. PMID: 33398278; PMCID: PMC7781313.

Birnbaum M, Sorensen MS. Denmark is sequencing all coronavirus samples and has an alarming view of the U.K. variant. *The Washington Post*. Published January 22, 2021. Accessed January 25, 2021 at https://www.washingtonpost.com/world/europe/uk-variant-covid-denmark/2021/01/22/ddfaf420-5453-11eb-acc5-92d2819a1ccb_story.html

Brito R. South African coronavirus variant detected in reinfection casein Brazil. *Reuters*. Published January 8, 2021. Accessed January 12, 2021 at https://www.reuters.com/article/us-health-coronavirus-brazil-reinfection/south-african-coronavirus-variant-detected-in-reinfection-case-in-brazil-idUSKBN29D33S

Callaway E. 'A bloody mess': Confusion reigns over naming of new COVID variants. *Nature*. Published January 15, 2021. Accessed January 20, 2021 at https://www.nature.com/articles/d41586-021-00097-w

Callaway E. Could new COVID variants undermine vaccines? Labs scramble to find out. *Nature*. 2021 Jan;589(7841):177-178. doi: 10.1038/d41586-021-00031-0. PMID: 33432212.

CDC. US COVID-19 Cases Caused by Variants. Updated February 9, 2021. Accessed on February 10, 2021 at https://www.cdc.gov/coronavirus/2019-ncov/transmission/variant-cases.html

Cele S et al. Escape of SARS-CoV-2 501Y.V2 variants from neutralization by convalescent plasma. *medRxiv*. Published January 26, 2021. Accessed February 10, 2021 at https://www.medrxiv.org/content/10.1101/2021.01.26.21250224v1

CoVariants. Variant: S:N501. version 0.1.0 (commit: 2e90198, build: 294, branch: release) Accessed on February 10, 2021 at https://covariants.org/variants/S.N501

DW. Coronavirus digest: German nursing home sees outbreak after vaccines. *DW*. Published on February 8, 2021. Accessed on February 10, 2021 at https://www.dw.com/en/coronavirus-digest-german-nursing-home-sees-outbreak-after-vaccines/a-56491823

Davies NG et al. Increased hazard of death in community-tested cases of SARS-CoV-2 Variant of Concern 202012/01. *medRxiv*. Published February 3, 2021. Accessed on February 8, 2021 at https://www.medrxiv.org/content/10.1101/2021.02.01.21250959v2

Doucleff M. Scientists Worry About Coronavirus Variant Spreading In Brazil. *NPR*. Published January 19, 2021. Accessed on January 20, 2021 at https://www.npr.org/2021/01/19/958472446/scientists-worry-about-coronavirus-variant-spreading-in-brazil

Emary KRW et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 VOC 202012/01 (B.1.1.7). *SSRN*. Published February 4, 2021. Accessed on February 12, 2021 at https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3779160

Erman M. Pfizer/BioNTech vaccine appears effective against mutation in new coronavirus variants –study. *Reuters*. Published January 7, 2021. Accessed on January 11, 2021 at https://www.reuters.com/article/health-coronavirus-pfizer-vaccine/pfizer-biontech-vaccine-appears-effective-against-mutation-in-new-coronavirus-variants-study-idUSL1N2JI2LZ

EurekaAlert. Study highlights risk of new SARS-CoV-2mutations emerging during chronic infection. Published February 5, 2021. Accessed on February 9, 2021 at https://www.eurekalert.org/pub_releases/2021-02/uoc-shr020521.php

Faria NR et al. Genomic characterisation of an emergent SARS-CoV-2 lineage in Manaus: preliminary findings. *Virological.org*. Published on January 12, 2021. Accessed on February 10, 2021 at https://virological.org/t/genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-manaus-preliminary-findings/586

Galloway SE, Paul P, MacCannell DR, Johansson MA, Brooks JT, MacNeil A, Slayton RB, Tong S, Silk BJ, Armstrong GL, Biggerstaff M, Dugan VG. Emergence of SARS-CoV-2 B.1.1.7 Lineage - United States, December 29, 2020-January 12, 2021. *MMWR Morb Mortal Wkly Rep.* 2021 Jan 22;70(3):95-99. doi: 10.15585/mmwr.mm7003e2. PMID: 33476315; PMCID: PMC7821772.

Greaney AJ et al. Comprehensive mapping of mutations to the SARS-CoV-2 receptor-binding domain that affect recognition by polyclonal human serum antibodies. *bioRxiv*. Published January 4, 2021. Accessed January 11, 2021 at https://www.biorxiv.org/content/10.1101/2020.12.31.425021v1

Harrington D, Kele B, Pereira S, Couto-Parada X, Riddell A, Forbes S, Dobbie H, Cutino-Moguel T. Confirmed Reinfection with SARS-CoV-2 Variant VOC-202012/01. *Clin Infect Dis.* 2021 Jan 9:ciab014. doi: 10.1093/cid/ciab014. Epub ahead of print. PMID: 33421056.

Herper M. South Africa halts rollout of AstraZeneca's Covid-19 vaccine aftershot falters against variant. *STAT News*. Published February 7, 2021. Accessed on February 8, 2021 at https://www.statnews.com/2021/02/07/south-africa-halts-rollout-of-astrazenecas-covid-19-vaccine-after-shot-falters-against-variant/

Hornby P et al. NERVTAG note on B.1.1.7 severity. Published January 21, 2021. Accessed on January 25, 2021 at https://www.gov.uk/government/publications/nervtag-note-on-b117-severity-20-january-2021

Johnson & Johnson. Johnson & Johnson Announces Single-Shot Janssen COVID-19 Vaccine Candidate Met Primary Endpoints in Interim Analysis of its Phase 3 ENSEMBLE Trial. Published January 29, 2021. Accessed on February 1, 2021 at https://www.jnj.com/johnson-johnson-announces-single-shot-janssen-covid-19-vaccine-candidate-met-primary-endpoints-in-interim-analysis-of-its-phase-3-ensemble-trial

Joseph A. Moderna says its Covid-19 vaccine is less effective against one coronavirus variant. *STAT News*. Published January 25, 2021. Accessed January 25, 2021 at https://www.statnews.com/2021/01/25/moderna-vaccine-less-effective-variant/

Joseph A. What we now know — and don't know — about the coronavirusvariants. *STAT News*. Published January 19, 2021. Accessed on January 21, 2021 at https://www.statnews.com/2021/01/19/coronavirus-variants-transmissibility-disease-reinfection/

Joseph A. 'What other variants might be out there?' An expert on viralevolution on what's happening with coronavirus mutations. *STAT News*. February 8, 2021. Accessed February 8, 2021 at https://www.statnews.com/2021/02/08/variants-expert-in-viral-evolution/

Kemp SA, Collier DA, Datir RP, Ferreira IATM, Gayed S, Jahun A, Hosmillo M, Rees-Spear C, Mlcochova P, Lumb IU, Roberts DJ, Chandra A, Temperton N; CITIID-NIHR BioResource COVID-19 Collaboration; COVID-19 Genomics UK (COG-UK) Consortium, Sharrocks K, Blane E, Modis Y, Leigh K, Briggs J, van Gils M, Smith KGC, Bradley JR, Smith C, Doffinger R, Ceron-Gutierrez L, Barcenas-Morales G, Pollock DD, Goldstein RA, Smielewska A, Skittrall JP, Gouliouris T, Goodfellow IG, Gkrania-Klotsas E, Illingworth CJR, McCoy LE, Gupta RK. SARS-CoV-2 evolution during treatment of chronic infection. *Nature*. 2021 Feb 5. doi: 10.1038/s41586-021-03291-y. Epub ahead of print. PMID: 33545711.

Mahase E. Covid-19: What new variants are emerging and how are they being investigated? *BMJ*. 2021 Jan 18;372:n158. doi: 10.1136/bmj.n158. PMID: 33462092.

Kupferschmidt K. New coronavirus variants could cause more reinfections, require updated vaccines. *Science*. Published January 15, 2021. Accessed January 19, 2021 at https://www.sciencemag.org/news/2021/01/new-coronavirus-variants-could-cause-more-reinfections-require-updated-vaccines

Kupferschmidt K. U.K. variant puts spotlight on immunocompromised patients' role in the COVID-19 pandemic. *Science*. Published December 23, 2020. Accessed January 20, 2021 at https://www.sciencemag.org/news/2020/12/uk-variant-puts-spotlight-immunocompromised-patients-role-covid-19-pandemic

Madhi SA et al., Safety and efficacy of the ChAdOx1 nCoV-19 (AZD1222) Covid-19 vaccine against the B.1.351 variant in South Africa. *medRvix*. Published February 12, 2021. Accessed on February 12, 2021 at https://www.medrxiv.org/content/10.1101/2021.02.10.21251247v1

Mandavilli A. How Does the Coronavirus Variant Spread? Here's What Scientists Know. *The New York Times.* Published December 31, 2020. Accessed January 5, 2021 at https://www.nytimes.com/2020/12/31/health/coronavirus-variant-transmission.html

McCarthy KR, Rennick LJ, Nambulli S, Robinson-McCarthy LR, Bain WG, Haidar G, Duprex WP. Recurrent deletions in the SARS-CoV-2 spike glycoprotein drive antibody escape. *Science*. 2021 Feb 3:eabf6950. doi: 10.1126/science.abf6950. Epub ahead of print. PMID: 33536258.

Moderna. Moderna COVID-19 Vaccine Retains Neutralizing Activity Against Emerging Variants First Identified in the U.K. and the Republic of South Africa. Published January 25, 2021. Accessed on January 12, 2021 at https://investors.modernatx.com/news-releases/news-release-details/moderna-covid-19-vaccine-retains-neutralizing-activity-against

Nonaka CKV et al. Genomic evidence of a SARS-CoV-2 reinfection case with E484K spike mutation in Brazil. *Preprints*. Published January 6, 2021. Accessed on February 12, 2021 at https://www.preprints.org/manuscript/202101.0132/v1

Novamax. Novavax COVID-19 Vaccine Demonstrates 89.3% Efficacy in UK Phase 3 Trial. Published January 28, 2021. Accessed February 2, 2021 at https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates-893-efficacy-uk-phase-3

Pater AA et al. Emergence and Evolution of a Prevalent New SARS-CoV-2 Variant in the United States. *bioRxiv*. Published January 13, 2021. Accessed on January 21, 2021 at https://www.biorxiv.org/content/10.1101/2021.01.11.426287v2

Rambault et al. Preliminary genomic characterisation of an emergent SARS-CoV-2 lineage in the UK defined by a novel set of spike mutations. *Virological.org*. Published December 20, 2020. Accessed on January 15, 2021 at https://virological.org/t/preliminary-genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-the-uk-defined-by-a-novel-set-of-spike-mutations/563

Reuters. Incidence of faster-spreading COVID-19 has risen more in Ireland. *Reuters*. Published January 11, 2021. Accessed January 14, 2021 at https://www.reuters.com/article/us-health-coronavirus-ireland/incidence-of-faster-spreading-covid-19-has-risen-more-in-ireland-pm-idUSKBN29G13Q

Schnirring L. Variant COVID among triggers for grim surge in Manaus, Brazil. *CIDRAP News*. Published January 28, 2021. Accessed on February 3, 2021 at https://www.cidrap.umn.edu/news-perspective/2021/01/variant-covid-among-triggers-grim-surge-manaus-brazil

Tegally H et al. Emergence and rapid spread of a new severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) lineage with multiple spike mutations in South Africa. *medRxiv*. Published December 22, 2021. Accessed on January 12, 2021 at https://www.medrxiv.org/content/10.1101/2020.12.21.20248640v1

Tu H et al. Distinct Patterns of Emergence of SARS-CoV-2 Spike Variants including N501Y in Clinical Samples in Columbus Ohio. *bioRxiv*. Published January 19, 2021. Accessed on January 20, 2021 at https://www.biorxiv.org/content/10.1101/2021.01.12.426407v3

Van Beusekom M. Scientists to US: Act now to leash virulent COVID variant. *CIDRAP News*. Published February 8, 2021. Accessed on February 9, 2021 at https://www.cidrap.umn.edu/news-perspective/2021/02/scientists-us-act-now-leash-virulent-covid-variant

Voloch CM et al. Genomic characterization of a novel SARS-CoV-2 lineage from Rio de Janeiro, Brazil. *medRxiv*. Published December 26, 2021. Accessed on February 11, 2021 at https://www.medrxiv.org/content/10.1101/2020.12.23.20248598v1

Volz E et al. Transmission of SARS-CoV-2 Lineage B.1.1.7 in England: Insights from linking epidemiological and genetic data. *medRxiv*. Published January 4, 2021. Accessed on February 10, 2021 at https://www.medrxiv.org/content/10.1101/2020.12.30.20249034v2

Wang P et al. Increased Resistance of SARS-CoV-2 Variants B.1.351 and B.1.1.7 to Antibody Neutralization. *bioRxiv*. Published January 26, 2021. Accessed February 10, 2021 at https://www.biorxiv.org/content/10.1101/2021.01.25.428137v3

Washington NL et al. Genomic epidemiology identifies emergence and rapid transmission of SARS-CoV-2 B.1.1.7 in the United States. *medRxiv*. Published February 7, 2021. Accessed on February 11, 2021 at https://www.medrxiv.org/content/10.1101/2021.02.06.21251159v1

West R et al. Variants, Vaccines and What They Mean ForCOVID-19 Testing. *JHU*. Published February 2, 2021. Accessed on February 8, 2021 at https://www.jhsph.edu/covid-19/articles/variants-vaccines-and-what-they-mean-for-covid19-testing.html

Wibmer CK et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. *bioRxiv*. Published January 19, 2021. Accessed on February 10, 2021 at https://www.biorxiv.org/content/10.1101/2021.01.18.427166v1

Wise J. Covid-19: The E484K mutation and the risks it poses. *BMJ*. 2021 Feb 5;372:n359. doi: 10.1136/bmj.n359. PMID: 33547053.

Wu K et al. mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global
SARS-CoV-2 variants. *bioRxiv*. Published January 25, 2021. Accessed on February 12, 2021 at https://www.biorxiv.org/content/10.1101/2021.01.25.427948v1

Xie X et al. Neutralization of N501Y mutant SARS-CoV-2 by BNT162b2 vaccine-elicited sera. *BioRxiv*. Published January 7, 2021. Accessed January 8, 2021 at https://www.biorxiv.org/content/10.1101/2021.01.07.425740v1

Xie X, Liu Y, Liu J, Zhang X, Zou J, Fontes-Garfias CR, Xia H, Swanson KA, Cutler M, Cooper D, Menachery VD, Weaver SC, Dormitzer PR, Shi PY. Neutralization of SARS-CoV-2 spike 69/70 deletion, E484K and N501Y variants by BNT162b2 vaccine-elicited sera. *Nat Med*. 2021 Feb 8. doi: 10.1038/s41591-021-01270-4. Epub ahead of print. PMID: 33558724.

Zhang W et al. Emergence of a novel SARS-CoV-2 strain in Southern California, USA. *medRxiv*. Published January 20, 2021. Accessed on January 21, 2021 at https://www.medrxiv.org/content/10.1101/2021.01.18.21249786v1

Zhang S. A Troubling New Pattern Among the Coronavirus Variants. *The Atlantic*. Published January 18, 2021. Accessed January 19, 2021 at

https://www.theatlantic.com/health/archive/2021/01/coronavirus-evolving-same-mutations-around-world/617721/