PINNACLECARE

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Topic: Update on COVID-19 Variants

SARS-CoV-2 Mutations

A new variant of SARS-CoV-2 has been detected in the United Kingdom, and the mutations identified in the virus are predicted to lead to a more infectious form of the virus (PHE Press Release, 2020). There is currently no evidence that the mutations would lead to a change in other characteristics of the virus, such as the severity of disease or an increased mortality.

The new variant is referred to as B.1.1.7.

Emergence of B.1.1.7

Based on genomic studies, researchers estimate that the new variant emerged in September, 2020 and was present at low levels in the population of the United Kingdom until the middle of November, 2020. At that time, researchers noticed that the infection rates in geographical areas where B.1.1.7 was present did not decrease after implementation of mobility restrictions, suggesting a change in the transmissibility (PHE Technical Report, 2020).

> **The variant has since spread to other areas around the world, including the United States.**

The first case of B.1.1.7 in the United States was reported in Colorado. The person infected had no international travel history, suggesting that local spread of the variant is occurring (Dall, 2020). Another case was later confirmed in California (Branswell, 2020).

Genomic sequencing of virus cases has not been widely performed in the United States, and therefore it is unknown how many other people in the country may have the new variant. Researchers investigating the characteristics of SARS-CoV-2 have been using data on the genome sequence and submitting them to a national database for use by other researchers, but there is not a federal program to collect virus samples for genetic sequencing that allows for the investigation of the geographic and demographic representation of different forms of the virus (Joseph, 2020).

For perspective, there was an average of around 200,000 new cases a day in the United States during the month of December, and the genomic sequences from only 250 cases diagnosed in

December were logged into the global database of SARS-CoV-2 sequence data (called GISAID). Out of the 250 samples, there were not any instances of B.1.1.7. Trevor Bedford, a computational biologist at Fred Hutchinson Cancer Research Institute, proposes that the fact that none of the submitted sequences were B.1.1.7 suggests that it is not widely prevalent throughout the country yet (Branswell, 2020). However, the information shows how little genomic data is available for the vast number of cases in the United States.

The CDC has reported that they are scaling up their capacity in order to perform genomic sampling to 750 samples each week, and the CDC is also providing funding so that local laboratories can also increase their capacity. These increases are expected to allow for sequencing of about 3,500 samples a week in the United States.

There have also been cases of B.1.1.7 reported in 14 other countries around the world, including European countries, Canada, Japan, South Korea, Lebanon, and Australia (Schnirring, 2020).

Based on this information, there seems to be little chance that the variant can be contained from spread around the world.

Possible Increase in Transmissibility of B.1.1.7

The increased rate of infection for the new variant is so far based mainly on hypothetical estimates of the role of the affected parts of the viral proteins from previous experiments and the increased prevalence and infection rate observed in the United Kingdom. Experiments to directly measure the characteristics of the new variant are underway, but have not been completed at the time this report was prepared (Kupferschmidt, 2020).

Based on the initial calculations, the increase in transmissibility for B.1.1.7 was estimated to be around 70% (Mandavilli, 2020). However, more recent estimates with larger amounts of data estimate an increase in transmissibility of 56% compared to previous variants of SARS-CoV-2 (Davies et al., 2020).

The more recent study released on December 30, 2020 describes in more detail comparisons between the community mobility data observed in regions with the B.1.1.7 variant and the areas of the United Kingdom where there the prevalence of B.1.1.7 is still low (Davies et al. , 2020). The researchers also explored potential changes in the reproduction number in areas where B.1.1.7 is the most common type of SARS-CoV-2 infection. The **reproduction number** describes the number of people one sick individual infects.

Viruses with a higher reproduction number have characteristics that allow them to spread more quickly.

However, the reproduction number can also be affected by human behavior. Examples of this influence by human behavior include increases in the reproduction number from lack of mask use in crowded areas or decreases in the reproduction number during a community-wide lockdown.

In previous observations of transmission of SARS-CoV-2, there was a high correlation between changes in the reproduction number and community mobility data.

Based on evaluation of information from Google mobility and data from a social contact survey the researchers found no evidence of differences in the amount of social interactions between the regions in England with high and low prevalence of B.1.1.7, but there was an increase in the number of infections occurring in regions with B.1.1.7. This situation is a departure from previous observations of SARS-CoV-2. Up to now during the pandemic, increased transmission was associated with increased social interactions.

In regions in England where B.1.1.7 is present in high levels, the transmission of the virus has increased without an increase in social interactions, suggesting a change in the characteristics of the virus itself.

Further study of the epidemiological characteristics of B.1.1.7 indicate that the reproduction number has increased from 1.1 to 1.5 in B.1.1.7 (Rambaut et al., 2020). This increase means that earlier forms of SARS-CoV-2 allowed one person with COVID-19 to infect ten other people, but infection with the B.1.1.7 variant of SARS-CoV-2 would lead to 15 infections from one person (Joseph, 2020). In a single step, this might seem like a small increase, but when each of those 15 people infects 15 more people, and so on, the rate of infection for the community increases very quickly.

An example put forth by Adam Kucharski, a professor at the London School of Hygiene and Tropical Medicine who focuses on mathematical analyses of infectious-disease outbreaks, compares the different outcomes of a hypothetical virus variant with 50% increased lethality and one with a 50% increase in transmissibility (Tufekci, 2020).

Table 2. Comparison of hypothetical changes in lethality or transmissibility of a virus.

Virus Characteristic	Original variant of SARS-CoV-2	Virus with increased lethality	Virus with increased transmission
Reproduction rate	1.1	1.1	1.65
Infection fatality risk	0.8%	1.2%	0.8%
Number of active infections in a community at the start of the outbreak	10,000	10,000	10,000
Number of deaths in a month	**129**	**193**	**978**

By changing the number of people that are infected, a virus with an increased transmission rate will lead to a large increase in the number of people who are infected without the implementation of sufficient prevention methods. If the lethality of the virus does not change, each person who becomes infected will have the same risk of dying from the infection as has been previously reported.

However, while the same percentage of people who are sick will die, the number of people who are sick could be much larger.

Additional information is still required to determine if there has been a fundamental change that occurred in the B.1.1.7 variant of SARS-CoV-2, but the current evidence is strongly in favor of a change in the virus rather than increased infection rates due to human behavior. Earlier in the pandemic, another possible variant of SARS-CoV-2 (called B.1.177) was identified in Spain, which appeared to have a higher rate of transmission. However, it was later determined that the rapid spread of the virus was due to travelers who spent their holidays in Spain and then returned to their home countries.

Genomic Changes in B.1.1.7

Investigation of the gene sequence indicates that there are 23 total mutations in B.1.1.7 compared to previous SARS-CoV-2 variants that both change the components making up the protein and remove sections of the protein (a process called deletion). The large number of mutations that occurred in a small amount of time is remarkable for viral evolution (17 mutations at one time), and scientists who investigate viral genes stated that they have not seen such a vast change in so little time before (Kupferschmidt, 2020).

One possibility for the quickly evolving strain that has been proposed is that it occurs in immunocompromised individuals who are infected with SARS-CoV-2 for long periods (Kupferschmidt, 2020b).

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

If the virus is then transmitted to others late in the infection cycle of the immunocompromised individual, it allows for escape of a highly mutated form of the virus. Several examples of this process have been identified and reported in publications, and one individual in England who was immunocompromised due to treatment for lymphoma was found to shed infectious virus for 101 days after diagnosis. Genomic sequencing of the virus from this patient was found to contain some of the mutations detected in B.1.1.7. Further supporting this theory is the fact that the B.1.1.7 variant has returned to the more typical and slower rate of mutation now that it is widespread in people with healthy immune systems. This type of accelerated mutation rate has also been documented in influenza with mutations from immunocompromised individuals eventually spreading globally.

Some of the changes in B.1.1.7 are in key areas of the spike protein of the virus. The **spike protein** is the part of the virus that extends from the surface of the sphere (also called the **capsid**) that surrounds the genetic RNA of SARS-CoV-2. The spike protein interacts with human cells and allows the virus to invade, or infect, the cell. Differences in the **amino acid** components of the spike protein can alter how well the spike protein interacts with the human cell. Some changes enhance the interaction and others would reduce the interaction with the cell.

There are three mutations in B.1.1.7 that have been identified that have the potential to enhance the interaction between the spike protein and human cells.

The main focus of the researchers' investigation has been a change in the amino acid component that occurred at position 501 in the protein.

Proteins are made up of a chain of amino acids, similar to beads on a string, which then compact (or fold) into a more complex three-dimensional structure that allows the protein to perform its function. The 501st amino acid in the string that forms the spike protein in previous variants of SARS-CoV-2 is the amino acid called asparagine (abbreviated N), and the amino acid at this position in the B.1.1.7 variant is tyrosine (abbreviated Y). Thus, the mutation is referred to as N501Y. The chemical structures of asparagine and tyrosine are very different and would greatly alter what the surface of the spike protein looks like and how it would interact with the surface proteins of a human cell.

Based on previous investigations of the spike protein of coronaviruses, researchers from the United Kingdom who have been studying B.1.1.7 state that it is possible that the change at position 501 would be sufficient to be responsible for the observed transmission increase by itself without the other 22 mutations (PHE Technical Report, 2020).

A second mutation that may have a large impact on the variant is called P681H, and this change occurs at the site where human proteins (called furin) cut the spike protein, allowing to change its shape and infect the cell. The amino acid change in this spot is expected to make the furin protein more efficient at cutting the spike protein, allowing for an increase in transmission.

The combination of N501Y mutation and P681H in B.1.1.7 is expected to change the virus in a way that allows for increased viral production and intensified spread through increased binding of the virus to the cell (Joseph, 2020). Epidemiologists in the United Kingdom have found that more of the infections observed in children are from the new variant as well, suggesting that children's natural resistance to SARS-CoV-2, possibility due to a lower amount of the cellular protein (ACE2) that interacts with the spike protein, may be overcome by an increased interaction between the spike protein and cells.

Possible Effects of the Viral Mutations

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 (Joseph, 2020).

Increased levels of virus in the nose and mouth could cause an increase in the amount of virus released by an individual to their environment, which could account for the increased transmission.

In some cases, researchers report 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 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.

Importantly, a study of epidemiological data from the United Kingdom indicates that there have been no differences in hospitalizations, case fatality rates over the last 28 days, or people being reinfected with SARS-CoV-2 due to the new variant (Schnirring, 2020).

This information reaffirms the initial interpretations by scientist that the genetic differences have not affected the severity of COVID-19 resulting from B.1.1.7.

Vaccines

The COVID-19 vaccines that are in use and being developed target the spike protein of the virus because antibodies targeted to the spike protein neutralize the virus and make it unable to infect new cells. Mutations in the spike protein could theoretically lead to a reduction in the efficacy of a vaccine targeted against the spike protein, but researchers have not found that there is a change in the interaction of antibodies with the spike protein from B.1.1.7 (PHE Technical Report, 2020).

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 use multiple targets, in most cases three different proteins, so that mutations will 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 this new variant because one of the mutations present in B.1.1.7 deletes a section of the spike protein that is required for detection by the test. However, the other two components of the test are unaffected by the mutations and continue to allow for detection of infected individuals. This coincidental occurrence allows health officials to more easily track cases on the new variant without having to perform genomic sequencing on each sample (Kupferschmidt, 2020).

Other Potential SARS-CoV-2 Variants

Another possible new variant of SARS-CoV-2 has also been identified in South Africa, which also contains the N501Y mutation (Kupferschmidt, 2020).

This variant is referred to as 501Y.V2.

The 501Y.V2 variant has been found to be widespread in certain areas in South Africa, and seems to also have a more rapid rate of transmission than previous variants of the virus. There has been a large increase in the number of COVID-19 cases in South Africa that corresponds to the emergence of the new variant, and country-wide restrictions on gatherings, a new curfew, and a ban of alcohol sales have been implemented (Schnirring, 2020). Scientists in South Africa are performing additional laboratory studies to better define the properties of 501Y.V2.

This variant has also been detected in other countries outside of South Africa, but so far it is not as widespread as B.1.1.7.

A third variant is also being investigated in Nigeria as reported by the Africa Centers for Disease Control and Prevention, but few details are currently available (Schnirring, 2020).

Summary of Information Currently Known about B.1.1.7

- The new variant, B.1.1.7, appears to have an increased transmissibility that cannot be accounted for by an increase in the amount of social interactions in the community.
- The observed increases in transmission are estimated to be around 56%.
- Measurement of the actual transmission rate in laboratory experiments is ongoing, but results are not yet available.
- Increased transmission rates of 50% could greatly increase the number of people who become infected with COVID-19.
- The percentage of people with COVID-19 who die does not seem to be affected by the mutations, but a large increase of the number of infected individuals would likewise lead to an increase in the number of deaths.
- B.1.1.7 has already been identified in countries around the world so that containment to the United Kingdom is unlikely, and community spread of the variant has been observed in the United States.
- Use of the non-pharmaceutical interventions (e.g. mask use, social distancing, and avoidance of gatherings with people outside your household) are expected to still be effective in the prevention of transmission of B.1.1.7 until vaccines are widely available.
- More stringent use of non-pharmaceutical interventions may be required to prevent transmission of B.1.1.7 compared to the level of use that was previously sufficient to prevent infection of SARS-CoV-2.

References

Branswell H. With limited surveillance of Covid-19 variant, it's déjà vu all over again. *STAT News.* Published December 30, 2020. Accessed January 4, 2021 at https://www.statnews.com/2020/12/31/with-limited-surveillance-of-covid-19-variant-its-deja-vu-all-over-again/

The European Centre for Disease Prevention. Rapid increase of a SARS-CoV-2 variant with multiple spike protein mutations observed in the United Kingdom. Published December 20, 2020. Accessed on December 28, 2020 at https://www.ecdc.europa.eu/sites/default/files/documents/SARS-CoV-2-variant-multiple-spike-protein-mutations-United-Kingdom.pdf

Dall C. Biden criticizes slow vaccine rollout, Colorado confirms nation's first UK variant case. *CIDRAP*. Published December 29, 2020. Accessed January 4, 2021 at https://www.cidrap.umn.edu/news-perspective/2020/12/biden-criticizes-slow-vaccine-rollout-colorado-confirms-nations-first-uk

Joseph A. The looming questions scientists need to answer about the new variant of the coronavirus. *STAT News*. Published December 21, 2020. Accessed on December 28, 2020 at https://www.statnews.com/2020/12/21/looming-questions-new-variant-coronavirus/

Kupferschmidt K. Mutant coronavirus in the United Kingdom sets off alarms, but its importance remains unclear. *Science*. Published December 20, 2020. Accessed on December 28, 2020 at https://www.sciencemag.org/news/2020/12/mutant-coronavirus-united-kingdom-sets-alarms-its-importance-remains-unclear

Kupferschmidt K. U.K. variant puts spotlight on immunocompromised patients' role in theCOVID-19 pandemic. *Science*. Published December 23, 2020. Accessed on January 4, 2021 at https://www.sciencemag.org/news/2020/12/uk-variant-puts-spotlight-immunocompromised-patients-role-covid-19-pandemic

Mandavilli A. How Does the Coronavirus Variant Spread? Here's What Scientists Know. *The New York Times.* Published on December 31, 2020. Accessed on January 4, 2021 at https://www.nytimes.com/2020/12/31/health/coronavirus-variant-transmission.html

Public Health England. Investigation of novel SARS-COV-2 variant: Variant of Concern 202012/01. Published December 21, 2020. Accessed on December 28, 2020 at https://www.gov.uk/government/publications/investigation-of-novel-sars-cov-2-variant-variant-of-concern-20201201

Public Health England. COVID-19 (SARS-CoV-2): information about the new virus variant. Published December 20, 2020. Accessed on December 28, 2020 at https://www.gov.uk/government/news/covid-19-sars-cov-2-information-about-the-new-virus-variant

Rambault A et al., Preliminary genomic characterisation of an emergent SARS-CoV-2lineage in the UK defined by a novel set of spike mutations. *Virological.org* Published December 18, 2020. Accessed on December 28, 2020 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

Schnirring L. Multiple countries report UK SARS-CoV-2 variant cases. *CIDRAP*. Published December 28, 2020. Accessed on January 4, 2021 at https://www.cidrap.umn.edu/news-perspective/2020/12/multiple-countries-report-uk-sars-cov-2-variant-cases