COVID-19: Variants Update

Date: 21 May 2021

During the COVID-19 pandemic, the Ministry of Health has seen high interest in all aspects of the virus from not only the scientific and health community but the general public as well. This update is designed to provide new information on variants of the virus that are of interest or concern. The first three pages of this update are provided as a brief overview, followed by the full technical report.

Information gathered in the last week is provided in red text.

Background

SARS-CoV-2, the virus that causes COVID-19, can undergo genetic mutations. These can occur naturally over time or from selective pressures.[1] While the vast majority of mutations do not change the virus in any meaningful way, some mutations, particularly those relating to virus’s spike protein, could affect the transmissibility of the virus, disease severity, and the effectiveness of treatments or vaccines.[2] There is concern that if infection of SARS-CoV-2 persists for extended periods of time, such as within an immunocompromised person, it could serve as a way for mutations to accumulate.[3, 4]

Mutation nomenclature (i.e., how mutations are named) describes what has occurred at a specific location of the viral genome.[5] For example, the ‘E484K’ mutation means that at the position 484, the amino acid changed from glutamic acid (E) to lysine (K).[6] When a deletion occurs, the location is provided (e.g., deletion 144). Mutations constitute different lineages of the virus, commonly referred to as ‘variants’. A variant is referred to as a ‘strain’ when it becomes sufficiently different from its patent virus, either by showing distinct physical properties or behaving in a pathologically or immunologically different way.

Potentially problematic variants that may have concerning epidemiological, immunological, or pathogenic properties are raised for formal investigation by two main investigative groups - the Public Health England Variant Technical Group[7, 8] and the SARS-CoV-2 Interagency Group in collaboration with the Centers for Disease Control and Prevention (CDC) in the United States (US).[9]

New variants are discovered through whole genome sequencing – a laboratory testing process, for which most countries have had low testing capacity prior to the COVID-19 pandemic. New Zealand now sequences all viable SARS-CoV-2 samples, however, the use and application of whole genome sequencing has varied between countries, and globally genomic surveillance of SARS-CoV-2 remains limited.[10, 11] The Global Initiative on Sharing Avian Influenza Data (GISAID) is a consortium that promotes and provides open access to genomic sequence data. Despite its original purpose for sharing avian (bird) flu data, it has proved to be beneficial in the fight against SARS-CoV-2. Submission of SARS-CoV-2 sequences to this repository has been key in tracking emerging variants. The US reports weekly published sequences from the National SARS-CoV-2 Strain Surveillance (NS3) programme, CDC contracts, and other sequencing efforts here and sequencing information from the UK can be found here.

Within this document, we will provide information on how “variants under investigation” (VUI), “variants of interest” (VOI), and “variants of concern” (VOC) are identified and describe what is known about their current epidemiological spread, before reviewing the emerging evidence and research on transmissibility, disease severity, vaccine protection, treatment effectiveness, and immune escape properties.
New information in this update

- Up to 17 May 2021, whole genome sequencing in New Zealand has identified the following VOCs:
  - 173 sequences of B.1.1.7. There is no change in B.1.1.7 sequences since the previous update.
  - 28 sequences of B.1.351. There is no change in B.1.351 sequences since the previous update.
  - 5 sequences of P.1. There is no change in P.1 sequences since the previous update.
  - 12 sequences of B.1.617.2. This is an increase of two B.1.617.2 sequences since the previous update.

- Public Health England reported among contacts that had not travelled, the secondary attack rate for B.1.617.2 was 11.5% (95% CI: 9.6-13.9%), which is similar to the secondary attack rate of 10.0% (95% CI: 9.9-10.1%) for B.1.1.7.

- Based on the mutations present in B.1.617 and its increased growth rate, Public Health England reported ‘high confidence’ that B.1.617.2 is at least as transmissible as B.1.1.7. Therefore, it is estimated that B.1.617.2 has an increased transmissibility of at least 40% compared to previously circulating, non-B.1.1.7, variants.

- There was a 6.8-fold reduction in neutralisation of the VUI B.1.617.1 among convalescent sera and vaccinated individuals with the Pfizer and Moderna vaccines. It was noted that despite the reduction, B.1.617.1 was still neutralised in all vaccinated individuals meaning mRNA vaccines are likely able to still confer immunity against the variant.

- A study reported on neutralising antibodies against B.1.1.7, B.1.351, and P.1 from sera of individuals vaccinated with the Moderna (mRNA-1273) vaccine. While B.1.351 had the greatest impact on neutralisation, a 3 to 15-fold reduction, binding and functional antibodies against the three VOCs were still present after six months.

- A phase 3 trial of the Novavax (NVX-CoV2373) vaccine among 15,187 participants reported a vaccine efficacy of 86.3% (71.3-93.5%) against symptomatic B.1.1.7 with onset 7 days after the second dose.

- A follow-up to the study in Manaus, Brazil, where the P.1 variant predominates, estimated that approximately 17% of infections in the second wave (from November 2020 onwards) were reinfections, presumed to be infections of the P.1 variant. However, there are several limitations to this study: not a population-wide sample (238 blood donors), small sample (10 reinfections), whole genome sequencing was not used to determine variant type; P.1 was assumed, given the geographical location, which may include some non-P.1 cases.

- The FDA has reviewed data evaluating the combination of casirivimab and imdevimab against B.1.1.7, B.1.351, P.1, B.1.427, B.1.429, and B.1.526 and report minimal impact (≤2 fold change) on antibody neutralisation activity.

- Up to date information on global cases can be found at:
  - B.1.1.7 (cov-lineages.org and outbreak.info)
  - B.1.351 (cov-lineages.org and outbreak.info)
  - P.1 (cov-lineages.org and outbreak.info)
  - B.1.617.2 (cov-lineages.org and outbreak.info)
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VOC Summary

Current VOCs have “evidence of an increase in transmissibility, more severe disease (increased hospitalisations or deaths), significant reduction in neutralisation by antibodies generated during previous infection or vaccination, reduced effectiveness of treatments or vaccines, or diagnostic detection failures”. [9] Table 1 collates key information on nomenclature, transmissibility, severity, immune evasion and countries in which the variants have been identified.

Table 1. Summary of characteristics for Variants of Concern as of 21 May 2021, red text denotes new information, red highlights note variables of particular concern.

<table>
<thead>
<tr>
<th>Lineage</th>
<th>B.1.1.7</th>
<th>B.1.351</th>
<th>P.1</th>
<th>B.1.617.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country first identified</td>
<td>United Kingdom ‘Kent Variant’</td>
<td>South Africa</td>
<td>Brazil</td>
<td>India</td>
</tr>
<tr>
<td>Other names</td>
<td>501Y.V1, VOC-202012/01, VOC-20DEC-01</td>
<td>501Y.V2, VOC-202012/02, VOC-20DEC-02</td>
<td>501Y.V3, B.1.1.28.1, VOC-202101/02, VOC-21JAN-02</td>
<td>VOC-21APR-02</td>
</tr>
<tr>
<td>Transmissibility</td>
<td>• “~40-80% more transmissible (R0 ~3.5-5.2)*</td>
<td>• Not well established. Preliminary estimate ~50% more transmissible</td>
<td>• Not established. Preliminary estimates 40%-160% more transmissible</td>
<td>• Not well established. However, it is believed to be at least as transmissible as B.1.1.7 (approximately 40%) with ‘high confidence’ by Public Health England in the UK</td>
</tr>
<tr>
<td>Severity</td>
<td>• Mortality: 60-70% increased mortality compared to previous variants</td>
<td>• Mortality: Not well established. One report of no increased risk of mortality</td>
<td>• Mortality: Not established. One report of no increased risk of mortality</td>
<td>• Mortality: Not well established</td>
</tr>
<tr>
<td></td>
<td>• Hospitalisation risk: 30-70% increased risk</td>
<td>• Hospitalisation: Not well established. One report of approximately 3.6 times risk of hospitalisation</td>
<td>• Hospitalisation: Not well established. One report of approximately 2.6 times risk of hospitalisation</td>
<td></td>
</tr>
<tr>
<td>Immune evasion</td>
<td>Minimal</td>
<td>Moderate-Strong</td>
<td>Moderate-Strong</td>
<td>Not well established. Some preliminary laboratory evidence of minimal to moderate reduction in neutralisation. No estimates of vaccine efficacy or effectiveness.</td>
</tr>
<tr>
<td>Countries reporting sequences</td>
<td>133</td>
<td>89</td>
<td>49</td>
<td>52</td>
</tr>
</tbody>
</table>

*Assuming R0 for original SARS-CoV-2 of approximately 2.5 to 2.9 [12, 13]
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Variants of Concern - further detail

Current VOCs designated by Public Health England are:

- **B.1.1.7**: VOC-20DEC-01 (VOC-202012/01 or 501Y.V1); emerged in Kent, UK.
- **B.1.351**: VOC-20DEC-02 (VOC-202012/02 or 501Y.V2); emerged in South Africa.
- **P.1**: VOC-21JAN-02 (VOC-202101/02 or 501Y.V3); detected in Japan, emerged in Manaus, Brazil.
- **B.1.1.7 with E484K**: VOC-21FEB-02 (VOC-202102/02); emerged in Bristol, UK.
- **B.1.617.2**: VOC-21APR-02; emerged in India.

In addition, the CDC also categorises variants B.1.427 and B.1.429 as VOCs (“California variants”).

In a Technical Briefing from Public Health England on 11 March 2021, a variant risk assessment framework was published, describing how the risk for new variants is determined using the following indicators: zoonotic emergence and transmission, transmissibility between humans, infection severity, susceptibility and immunity, vaccines, and drugs and therapeutics.[14] The latest Technical Briefing on the VOCs in England is linked here.

The CDC has introduced an additional category termed ‘Variant of High Consequence’. This will include variants that show clear evidence that prevention measures or medical countermeasures have significantly reduced effectiveness relative to previously circulating variants. As of 21 May 2021, the CDC lists no variants in this category. The link to the CDC’s website describing SARS-CoV-2 variant classifications and definitions is available here. The CDC is also tracking the proportion of variants circulating in the US for both VOC and VOI (Figure 1).[15]

**Variants under Investigation and Variants of Interest**

Variants with unconfirmed or preliminary evidence of immune evasion, increased transmissibility, or other concerning features are considered Variants of Interest. They may also be designated as a ‘Variant Under Investigation’ (VUI) by Public Health England.[16]

Variants designated as a VUI are named by a year, month, and number (e.g., VUI-21MAR-02). The CDC defines a ‘Variant of Interest’ (VOI) as a variant with ‘specific genetic markers that have been associated with changes to receptor binding, reduced neutralisation by antibodies generated against previous infection or vaccination, reduced efficacy of treatments, potential diagnostic impact, or predicted increase in transmissibility or disease severity.[9] The CDC has no naming convention for VOIs.

The COVID-19 Science and Technical Advisory team is monitoring the developments of VUI/VOIs, which are summarised below in Table 2.
### Table 2. Variants Under Investigation by Public Health England and Variants of Interest by CDC as of 21 May 2021

<table>
<thead>
<tr>
<th>VUI*</th>
<th>Classified by</th>
<th>Lineage</th>
<th>Origin</th>
<th>Evidence</th>
</tr>
</thead>
</table>
• Possible reduced antibody neutralisation from studies on the spike protein mutation E484K.[17] |
| VUI-21FEB-01 (VUI-2021102/01) | Public Health England | A.23.1 with E484K | Liverpool, United Kingdom, December 2020 | • Spike protein mutations F157L, V367F, Q613H and P681R. The V367F and Q613H changes are reported to modestly increase infectivity.[18] |
• Reduced antibody neutralisation by monoclonal antibodies and post-vaccine sera.[9] |
| VUI-21FEB-04 (VUI202102/04) | Public Health England | B.1.1.318 | United Kingdom, February 2021 | • Contains spike mutations T95I, 144 deletion, E484K, P681H, D796H. Identified in England in February 2021 through routine genomic surveillance.[14] |
| VUI-21MAR-02 | Public Health England | P.3 | To be determined, likely Philippines [20, 21] | • Contains spike mutations E484K, NS01Y, P681H, 141-143del.[21, 22]  
• From parent lineage B.1.1.28 (the same as P.1 and P.2 detected in Brazil).[23] |
| Public Health England monitoring but has not classified as VUI or VOC. | CDC classified as VOC | B.1.429/B.1.427 or CAL.20C | Southern California | • Designated a VOC by the CDC but is being monitored by Public Health England as of 22 April 2021.[23]  
• Characterised by the mutations S13I, W152C, L452R, D614G,[9]  
• May have approximately a 20% increased transmission compared to previous variants. From September 2020 through January 2021, the variant increased from 0% to 50% of sequenced cases in California. The increased transmission could be attributed to a 2-fold increase in viral shedding.[24] |
| VUI-21APR-01, VUI-21APR-03 | Public Health England | B.1.617 and B.1.617.3. Note, B.1.617.2 was classified as a VOC on 6 May 2021 by Public Health England | India | • Genomic surveillance in India reported a variant containing mutations E484Q and L452R on 24 March 2021. The implications of these mutations on disease severity, transmission, and other factors is still under investigation.[25]  
• On 19 May 2021, B.1.617 accounted for 84.8% of sequences submitted to GISAID from India over the previous four weeks.[26] However, genomic surveillance in India is poor and the true prevalence is unknown. |

*Public Health England changed the nomenclature for VUI in March 2021, using 2-number year and 3-letter month. Old naming convention provided in parenthesis for cross-reference.
Additional data on notable VUIs

Several pre-prints have investigated antibody neutralisation of B.1.617 and its sub-lineages. Laboratory data suggests B.1.617 is moderately able to reduce antibody neutralisation from previous infections and from vaccination with the Pfizer vaccine and is completely resistant to monoclonal antibody medicines.[27] These findings were corroborated by two other pre-prints.[28, 29] There was a 6.8-fold reduction in neutralisation of B.1.617.1 among convalescent sera and vaccinated individuals with the Pfizer and Moderna vaccines.[28] It was noted that despite the reduction, B.1.617.1 was still neutralised in all vaccinated individuals, implying that mRNA vaccines are likely able to still confer immunity against the variant. In another pre-print, among 43 participants that received two doses of the Covishield vaccine, there was a significant two-fold reduction in neutralisation titer of B.1.617.1 compared to B.1 variant.[30]

Public Health England has released detailed reports on the B.1.617 cases in England.[31-33]

- Public Health England determined that there are 3 clades (otherwise known as lineal descendants of this variant), named B.1.617.1, B.1.617.2, and B.1.617.3. On 6 May 2021, Public Health England escalated B.1.617 to a VOC. Information on B.1.617.2 is now covered below under the evidence on specific VOCs.

New Zealand cases and global spread

Increased cases of VOC are expected in New Zealand MIF/MIQ facilities as the global presence of these variants extends geographically and new variants become predominant. Figure 1 below displays the proportion of variants circulating in the US in the two weeks ending 24 April 2021 as reported by the US CDC.[15]

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Review of evidence on specific VOCs

B.1.1.7

B.1.1.7: Genomic characteristics

The B.1.1.7 variant is characterised by notable spike protein mutations 69/70 deletion, 144 deletion, N501Y, P681H, and A570D (Figure 2).[34] There are an additional four spike protein mutations D614G, T716I, S982A, and D1118H.

B.1.1.7: Transmissibility

Several studies have reported increased transmissibility of B.1.1.7, with most studies estimating an increase between 40-80%. [35-42]
B.1.1.7 has gone on to replace previous variants in several countries, for example in the UK, Israel, and US.[8, 15, 41] From 16 January to 27 March, the proportion of variant B.1.1.7 sequenced increased from 3.1% to 44.1% in the US.[15] Additionally, possible reinfections were identified in 0.7% of cases (95% CI: 0.6-0.8) in a study of 36,059 participants, although the reinfection rate was not considered higher for B.1.1.7 than previous variants.[40]

One hypothesis for the increased transmissibility of B.1.1.7 relates to the N501Y mutation, which could provide a selective advantage to the virus by increasing how tightly the spike protein binds to the human host cell ACE2 receptor.[43-47] Increased transmission may also be the result of patients with B.1.1.7 variant having increased viral loads compared to those infected with non-B.1.1.7 variants.[48-51] However, others have reported no statistical difference in viral loads for B.1.1.7 and proposed that the higher viral loads are the result of ascertainment bias.[52] A further study found no difference in viral replication between B.1.1.7 and earlier variants in primary human airway epithelial cells.[53]

A modelling study on seasonal transmission of B.1.1.7 found there was an association with increased transmission of the variant in colder and hotter temperatures.[54] However, these data should be interpreted cautiously, as it was based on modelling and reported in pre-print. Other data suggests moderate temperatures, such as during spring and fall, may decrease transmission of SARS-CoV-2,[55] supporting the possibility of a slight seasonal component where more extreme temperatures of the winter and summer could have an effect on transmission in some places. This is in contrast to some communicable diseases such as influenza that have a strong seasonal component and are present predominantly in winter.

**B.1.1.7: Clinical presentation and disease severity**

**Clinical presentation**

The types of symptoms associated with B.1.1.7 are broadly similar to previous variants.[40] The UK Office for National Statistics undertakes a survey of those testing positive for COVID-19.[56] Individuals with the B.1.1.7 variant may be more likely to have a cough, sore throat, fatigue or myalgia (muscle aches) and may be less likely to report loss of smell or taste (Figure 3). A separate study reported that patients may present on hospital admission with hypoxia more often than non-B.1.1.7 cases.[57]
Figure 3. Comparison of self-reported symptoms for B.1.1.7 (light green) and non-B.1.1.7 variant (dark green) (UK Office of National Statistics)

**Duration**

Some studies have found B.1.1.7 to have an increased duration of infection. Daily longitudinal PCR tests were performed on a cohort of 65 individuals to determine if B.1.1.7 was associated with longer duration of infection.[58] Among seven participants infected with B.1.1.7, the mean overall duration of infection was 13.3 (95% CI: 10.1-16.5) days compared to 8.2 (95% CI: 6.5-9.7) days for 58 participants with non-B.1.1.7. While the duration of infection was statistically significant, the small sample size should be noted and interpreted with caution. A modelling study of publicly available sequencing data supported the hypothesis of B.1.1.7 having increased duration of infection.[35]

A further study reported a statistically significant longer duration of RNA positivity in nasopharyngeal swabs of 16 days among 136 B.1.1.7 patients versus 14 days among 965 non-B.1.1.7 patients.[50] However, a study of 36,920 users of the COVID Symptom Study app reported no differences in the duration of symptoms associated with B.1.1.7.[40]

**Hospitalisation and mortality**

Multiple large epidemiological studies have reported an increased risk of hospitalisation, intensive care admissions, and mortality for the B.1.1.7 variant compared to previous variants.

Among a cohort of 198,420 patients, the adjusted hazard ratio for critical care admission was 1.99 (95% CI: 1.59-2.49) for B.1.1.7 compared to non- B.1.1.7,[59] meaning those infected with the B.1.1.7 variant had almost double the risk of critical care admission than those infected with previous variants. A large surveillance study in seven countries of the European Union found that B.1.1.7 cases had 1.7 (95% CI: 1.0-2.9) times the risk of hospitalisation and 2.3 (95% CI: 1.4-3.5) times the risk of intensive care admission compared to non-VOC
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Data from Denmark reported that the B.1.1.7 variant patients had a 64% increased risk of hospitalisation compared to patients with previous variants.[60] Lastly, a matched cohort analysis of 2,821 B.1.1.7 cases matched to 2,821 non-B.1.1.7 cases in England from October to December 2020 reported a 34% increased risk in hospitalisation associated with the B.1.1.7 variant compared to non-B.1.1.7 cases.[62] Several analyses performed by the New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) concluded infection with B.1.1.7 is associated with an increased risk of hospitalisation.[63]

Regarding mortality, there is substantial evidence of an increased risk of death for those infected with B.1.1.7 compared to previous variants. Using a database of over two million positive SARS-CoV-2 community tests and 17,452 COVID-19 deaths in England from 1 September 2020 to 14 February 2021, researchers estimated a mortality hazard ratio of 1.6 (95% CI: 1.4-1.8), meaning a 60% increased risk of death associated with B.1.1.7 compared to previous variants.[64] A matched cohort study of 54,906 pairs estimated an increase of deaths from 2.5 per 1,000 for non-B.1.1.7 cases to 4.1 per 1,000 for B.1.1.7 cases.[65] Additionally, several analyses by NERVTAG estimated an increased risk of mortality between approximately 30-70% compared to the previous variants.[63] In an adjusted analysis accounting for demographics and comorbidities, the risk of death for B.1.1.7 in England from 16 November 2020 through 5 February 2021 was two-thirds higher (hazard ratio 1.67; 95% CI: 1.34–2.09) compared with non-VOC.[66] However, in the same matched cohort of 2,821 B.1.1.7 cases described above on risk of hospitalisation, there was no statistically significant difference in risk of death.

A study of only hospitalised patients in the UK reported no association of severe disease and death between B.1.1.7 and non-B.1.1.7.[51] It is important to note that this study evaluates mortality given the patient is already hospitalised and is therefore an evaluation of a cohort of patients with severe COVID-19. This suggests that once a patient is admitted to hospital, with regard to mortality at least, the variant is not relevant.

B.1.1.7: Immunity, vaccines, and therapeutics

Laboratory data

Neutralising antibodies remain effective against the B.1.1.7 variant in preventing viral entry into host cells.[67-70]

Laboratory studies with the Pfizer vaccine have shown a nearly identical antibody response and neutralising titres against the B.1.1.7 lineage, supporting protection of the vaccine against B.1.1.7.[67, 71-76] Similar findings were reported for the Moderna (mRNA-1273) vaccine, reporting high levels of antibodies recognising and neutralising B.1.1.7 up to 6 months post-vaccination.[77]

In a clinical trial of the AstraZeneca vaccine, laboratory virus neutralisation activity by vaccine-induced antibodies was lower against the B.1.1.7 variant than against non-B.1.1.7 among 311 participants.[78]

Clinical data

Novavax[79] and Moderna[80, 81] reported good vaccine efficacy of their vaccines against the B.1.1.7 variant. Johnson & Johnson/ Janssen did not report on vaccine efficacy with the B.1.1.7 variant specifically.[82]

A study assessing the real-world effectiveness of the Pfizer and AstraZeneca vaccines in the UK (where there is widespread circulation of B.1.1.7) reported a single dose of either vaccine resulted in an 80% reduction of hospitalisation.[83] A UK study of staff working in public hospitals found the Pfizer vaccine effectively prevented both symptomatic and asymptomatic infection despite B.1.1.7 being prevalent.[84] A pre-print of a phase 3 trial
of the Novavax (NVX-CoV2373) vaccine among 15,187 participants reported a vaccine efficacy of 86.3% (71.3-93.5%) against symptomatic B.1.1.7 with onset 7 days after the second dose.[85]

There is no evidence that suggests B.1.1.7 can evade immunity and cause breakthrough infections among those fully vaccinated at a rate higher than previous variants.[78, 84, 86] Even with a very high estimated prevalence of 94.5% of B.1.1.7 in Israel, an analysis of national surveillance data reported high efficacy of the Pfizer vaccine against infection, asymptomatic infection, and COVID-19 related hospitalisation and death.[87] In a real-world analysis of the Pfizer vaccine in Qatar, vaccine efficacy was estimated to be 89.5% (95% CI: 85.9-92.3%) at 14 or more days after the second dose.[88]

**Therapeutics**

B.1.1.7 can be efficiently neutralised by the monoclonal antibody treatment Bamlanivimab.[89] The FDA has reviewed data evaluating the combination of casirivimab and imdevimab against B.1.1.7, B.1.351, P.1, B.1.427, B.1.429, and B.1.526 and report minimal impact (≤2 fold change) on antibody neutralisation activity.[90]

**B.1.1.7 with E484K mutation**

**B.1.1.7 with E484K mutation: Transmissibility**

As above with B.1.1.7 but contains the E484K mutation. The E484K mutation itself may,[67] or may not impact affinity.[44]

**B.1.1.7 with E484K mutation: Clinical presentation and disease severity**

As above with B.1.1.7.

**B.1.1.7 with E484K mutation: Immunity, vaccines, and therapeutics**

Multiple studies have reported a decrease in neutralisation activity against variants with E484K mutation.[17, 72, 81, 91, 92] This is important because VOC B.1.351 and P.1 also carry the E484K mutation.

The monoclonal antibody treatment Bamlanivimab may not provide protection against B.1.1.7 with E484K mutation.[89]

**B.1.351**

**B.1.351: Genomic characteristics**

The B.1.351 is characterised by 17 mutations, with eight spike protein mutations D80A, D215G, 241/243 deletion, K417N, E484K, N501Y, D614G, and A701V (Figure 4).[93, 94]
B.1.351: Transmissibility

Several of the mutations in B.1.351, specifically K417N, E484K, and N501Y, may affect the affinity for the spike protein to bind to human host cells.

As noted under transmissibility of B.1.1.7, several studies have reported N501Y may increase affinity,[43-47] and when combined with K417N and E484K, studies have estimated between a 3-fold and 19-fold increase in affinity of the B.1.351 variant to bind to human host cells compared to other variants.[44, 45, 92]

It is estimated that B.1.351 may be 1.5 (95% CI: 1.2-2.1) times as transmissible as previous variants.[95] B.1.351 was prevalent in a prospective surveillance study in Zimbabwe, accounting for 95% of sequences tested in January 2021.[96]

Case reports suggest that reinfection with B.1.351 after prior infection is possible.[97]

B.1.351: Clinical presentation and disease severity

There is limited evidence for severity of disease for B.1.351.

A large surveillance study of 23,343 samples across seven countries in the European Union found 436 B.1.351 cases. In this study, B.1.351 cases had 3.6 (95% CI: 2.1-6.2) times the odds of hospitalisation and 3.3 (95% CI: 1.9-5.7) times odds of intensive care admission compared to non-VOC cases. There was no evidence of association of B.1.351 with risk of death after adjusting for age, sex, and week of reporting, where the adjusted odds ratio was 1.1 (95% CI: 0.4-3.4).[60] However, the estimates of ICU admission were small (<20).

B.1.351: Immunity, vaccines, and therapeutics

Laboratory data

There is substantial evidence that B.1.351 is inhibited less efficiently by convalescent plasma and more resistant to neutralising antibodies.[17, 67, 70, 91, 92, 98-101]

A study examining antibody responses in patients infected with B.1.351 had broad neutralising antibody responses to both the original variant and P.1, indicating vaccines designed against mutations in the spike protein of B.1.351 may elicit cross-reactive responses against other variants.[102] Multiple studies on the Pfizer vaccine have shown that antibody neutralisation of the B.1.351 variant in vaccine sera was substantially reduced.[100, 103-106] In a study on both Pfizer and AstraZeneca vaccines, the B.1.351 neutralisation titre was reduced 8- to 9-fold in vaccinees and the researchers concluded the mutations E484K, K417N, and N501Y were the likely cause.[92]

Conversely, some studies have reported that T-cell responses to vaccination or previous infection do not target mutations in B.1351, suggesting T-cell responses are unlikely to be affected.[107-109] A laboratory study tested two antibodies that target the receptor-binding domain of the spike protein, 1-57 and 2-7, and found them to be unaffected by B.1.351.[110]
A study measuring neutralisation activity in 24 serum samples from clinical trials of two vaccine candidates in China reported a slightly reduced activity against the B.1.351 variant but this was not statistically significant.[111] The authors note that while their findings suggest B.1.351 does not escape immunity, the reduced antibody neutralisation may impact overall clinical vaccine efficacy.

Among individuals vaccinated with the Moderna (mRNA-1273) vaccine, there was a 3 to 15-fold reduction in antibody neutralisation.[77] With regard to duration of immunity, after a six month follow-up, 54%, 58%, and 79% of individuals had detectable antibodies against pseudovirus, live virus, and ACE2 blocking, respectively. Moderna is developing a vaccine targeted towards the B.1.351 variant called mRNA-1273.351. In a clinical study of the mRNA-1273.351 vaccine, individuals were vaccinated with a third dose of either the original vaccine (mRNA-1273) or the variant targeted vaccine (mRNA-1273.351), six months after their second dose. The results found increased neutralisation in those given mRNA-1273.351, the targeted vaccine, compared to those given the original vaccine. This is encouraging evidence that suggests vaccines can be altered to target multiple variants, however, trials will continue, and real-world efficacy is still unavailable.[112]

**Clinical data**

Results from Novavax[79], Johnson & Johnson/Janssen[82] and Moderna[80, 81] provide strong evidence that B.1.351 has the ability to evade vaccine-generated immunity to a significant degree.

Johnson & Johnson/Janssen presented data to the FDA on 26 February showing 94.5% of sequenced cases from participants in South Africa were B.1.351, and vaccine efficacy for moderate to severe disease in South African participants was 64.0% (95% CI 41.2-78.7%).[113] Data on the Novavax vaccine from a phase 2a/b, randomised placebo-controlled trial in South Africa found that post-hoc vaccine efficacy in preventing mild to moderate disease caused by B.1.351 was 51.0% (95% CI: -0.6-76.2%).[114]

The AstraZeneca vaccine had a vaccine efficacy of 10.4% (95% CI: -76.8-54.8%) against mild-to-moderate illness associated with B.1.351 with onset >14 days after second injection.[115] In this same study, vaccine efficacy against mild-to-moderate illness associated non-B.1.351 variants with onset >14 days after one dose was 75.4% (95% CI: 8.9-95.5%). Sample sizes resulted in substantially large confidence intervals. The South African government halted its rollout of the AstraZeneca vaccine following an analysis that it did not protect against mild or moderate disease caused by the B.1.351 variant.[116] The World Health Organization has authorised the AstraZeneca vaccine for emergency use through COVAX.[117]

A study from Israel noted breakthrough infections (i.e., being infected by SARS-CoV-2 after receiving a vaccine) by variant B.1.351 among those vaccinated with the Pfizer vaccine.[86] However, this study is a pre-print and there were only a total of nine B.1.351 cases in the study. Pfizer has begun evaluating a third dose that is formulated based on the B.1.351 variant mutations.[118] In a real-world analysis of the Pfizer vaccine in Qatar, vaccine efficacy was estimated to be 75% (95% CI: 70.5-78.9%) against B.1.351 at 14 or more days after the second dose.[88]

Moderna has completed manufacturing of clinical trial material for its B.1.351 variant-specific vaccine candidate, mRNA-1273.351. It has shipped doses to the National Institutes of Health (NIH) for a Phase 1 clinical trial that will be led and funded by the NIH’s National Institute of Allergy and Infectious Diseases.[119]
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**Therapeutics**

Monoclonal antibody treatments, including Bamlanivimab and Casirivimab, have been shown to be ineffective against B.1.351. Studies have reported either partial neutralisation or no neutralisation.[70, 89, 92, 120-122] The consensus is that escape from monoclonal antibody treatments is due to the E484K, K417N and N501Y mutations.

The FDA has reviewed data evaluating the combination of casirivimab and imdevimab against B.1.1.7, B.1.351, P.1, B.1.427, B.1.429, and B.1.526 and report minimal impact (≤2 fold change) on antibody neutralisation activity.[90]

**P.1**

**P.1: Genomic characteristics**

The P.1 lineage is characterised by 22 mutations, with 12 spike protein mutations L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, and V1176F (Figure 5).[123] It is important to note that E484K and N501Y spike mutations are present in both P.1 and B.1.351. Additionally, the B.1.351 variant contains a K417N mutation, while P.1 is a K417T mutation, meaning an amino acid change occurred at the same location in both variants, but the amino acid is different. The implications of the different amino acid between the two variants is unclear, but likely to be similar.

![Figure 5. Mutations of variant P.1 (outbreak.info)](image)

**P.1: Transmissibility**

Some studies have found P.1 to be more transmissible.

A modelling study fitting data from the Brazilian national health surveillance of hospitalised individuals in Manaus from December 2020 to February 2021, estimated the P.1 variant to be 2.6 (95% CI: 2.4–2.8) times more transmissible than previous variants.[124]

Another modelling study estimates that P.1 is 1.7 to 2.4 times more transmissible than earlier variants.[125] The P.1 variant was found to have approximately a 10-fold higher viral load in upper respiratory tracts than non-P.1 infections, suggesting the P.1 variant is more transmissible.[126]

However, given the scarcity of data and the number of assumptions that are required for modelling studies and limitations of real-world estimates, increased transmissibility for this variant is suspected but not well established.

**P.1: Clinical presentation and disease severity**

There is limited evidence for severity of disease for P.1.

A large surveillance study of 23,343 samples, of which 352 were P.1 variant, across seven countries in the European Union found 2.6 (95% CI: 1.4–4.8) times the risk of hospitalisation and 2.2 (95% CI: 1.8–2.9) times the
risk of intensive care admission compared to non-VOC. There was no association found between P.1 and risk of death, with an adjusted odds ratio of 0.6 (95% CI: 0.3-1.0).[60] However, estimates for ICU admission were small (<20).

**P.1: Immunity, vaccines, and therapeutics**

**Laboratory data**

Given that P.1 shares two mutations, E484K and N501Y, with the B.1.351 variant, P.1 has similar viral attributes of B.1.351. There is substantial evidence that the mutations E484K, N501Y, and K417N and the P.1 variant reduce neutralisation and escape immune response.[17, 67, 70, 91, 92, 98-130] However, the P.1 mutation K417T is a different amino acid change from K417N.[131] Data on immune escape after vaccination and antibody neutralisation is limited. Neutralising antibodies from sera of Pfizer vaccinees was found to neutralise P.1 [103] and similarly among individuals vaccinated with the Moderna (mRNA-1273) vaccine.[77]

The P.1 variant emerged in Manaus, in the Amazonas region of Brazil, where it was believed that population immunity had been achieved in the first wave of SARS-CoV-2 after a study showing 76% of blood donors in a convenience sample had detectable antibodies by October 2020.[132] It was hypothesised that the substantial increase in COVID-19 hospital admissions in Manaus in January 2021 was due to reinfections with P.1.[133] Alternative possibilities given for the resurgence were that the first wave was overestimated, that immunity began to wane, or that the new P.1 variant evades immunity generated by previous infection. There have been several case reports of individuals infected with P.1 after a previous COVID-19 infection.[134-136] A follow-up study in Manaus, Brazil, estimated that approximately 17% of infections in the second wave (from November 2020 onwards) were reinfections, presumed to be infections of the P.1 variant. However, there are several limitations to this study: not a population-wide sample (238 blood donors), small sample (10 reinfections), whole genome sequencing was not used to determine variant type (P.1 was assumed to be responsible for the reinfection, given the geographical location, which may include some non-P.1 cases).[137]

**Clinical data**

Developments will continue to be monitored and updated when information becomes available.

**Therapeutics**

Monoclonal antibody treatments such as Bamlanivimab and Casirivimab have been shown to be ineffective against P.1. Studies have reported either partial neutralisation or no neutralisation by monoclonal antibody treatments against the P.1 variant.[70, 89, 92, 120-122]

The FDA has reviewed data evaluating the combination of casirivimab and imdevimab against B.1.1.7, B.1.351, P.1, B.1.427, B.1.429, and B.1.526 and report minimal impact (≤2 fold change) on antibody neutralisation activity.[90]
B.1.617.2

B.1.617.2: Genomic characteristics

The B.1.617.2 lineage is characterised by spike protein changes T19R, 156-158 deletion, L452R, T478K, D614G, P681R, and D950N (Figure 6).[31] The L452R has been associated with increased transmissibility and a reduction in neutralisation by convalescent plasma and some monoclonal antibody medicines [24]. The P681R mutation could potentially have an effect on cell entry and infectivity, although this has not been demonstrated in practice.[36]

Figure 6. Mutations of variant B.1.617.2 (outbreak.info)

B.1.617.2: Transmissibility

Public Health England preliminary assessment of B.1.617.2, rated as high confidence, is that it is at least as transmissible as B.1.1.7. based on the mutations present and secondary attack rates.[138] Therefore, it is estimated that B.1.617.2 has an increased transmissibility of at least 40% compared to previously non-B.1.1.7 circulating variants. However, it was highlighted that further analyses are needed to confirm. Growth rates as analysed by the WHO were similarly substantially higher for B.1.617.2, corroborating the findings by Public Health England.[139] Analyses from the European CDC warns that increased detection of B.1.617.2 in the UK may be related to increased travel to and from India for religious or other large gatherings, and that the expansion within India is within the context of a relaxation of non-pharmaceutical measures and low vaccination coverage.[140] Based on contact tracing data in the UK, the estimated secondary attack rate for B.1.617.2 among contacts who had recently travelled was 3.3% (95% CI: 2.8-3.9%), which is higher than B.1.1.7 at 1.7% (95% CI: 1.6% - 1.8%).[33] Among contacts that had not travelled, the secondary attack rate was higher at 11.5% (95% CI: 9.6-13.9%), and similar to secondary attack rates of 10.0% (95% CI: 9.9-10.1%) for B.1.1.7.

B.1.617.2: Clinical presentation and disease severity

There are insufficient data currently to assess the potential for a change in disease severity.

Public Health England’s assessment highlights that the identified B.1.617.2 cases were still too recent to allow enough time to assess its impact on disease severity in comparison to other co-circulating variants.[31]

B.1.617.2: Immunity, vaccines, and therapeutics

There are insufficient data currently to assess the potential for immune escape.

Available evidence exists only for B.1.617.1, where serum from previously infected and vaccinated individuals has been shown to neutralise B.1.617.1 equally, or more effectively than other currently circulating VOCs.[140]
## Glossary of Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
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<tbody>
<tr>
<td>The AstraZeneca vaccine</td>
<td>AZD1222 or ChAdOx1</td>
</tr>
<tr>
<td>The Pfizer/BioNTech vaccine</td>
<td>Comirnaty/BNT162b2</td>
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<tr>
<td>Immune evasion</td>
<td>The ability of the virus to evade our body’s immune response. See also immune response.</td>
</tr>
<tr>
<td>Immune response</td>
<td>The response of our immune system to an infection. It includes development of specific antibodies to the virus and also cell-mediated responses (triggered by T cells).</td>
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<tr>
<td>Monoclonal antibody</td>
<td>An antibody produced by a single cell line and consisting of identical antibody molecules. See also immune response.</td>
</tr>
<tr>
<td>Monoclonal antibody medicine</td>
<td>A type of drug that uses monoclonal antibody treatments to bind to certain cells or proteins to stimulate the body’s immune system to attack those cells/proteins. E.g., Bamlanivimab.</td>
</tr>
<tr>
<td>Mutation</td>
<td>Small change made to the pattern of nucleotides that make up the virus. These occur as the virus spreads and replicates. Most do not confer a benefit to the virus.</td>
</tr>
<tr>
<td>Naming mutations</td>
<td>Mutation nomenclature (i.e., how they are named), describes what occurred at a specific location of the genome. For example, the ‘E484K’ mutation means that at the position 484, the amino acid changed from glutamic acid (E) to lysine (K). When a deletion occurs, the location is provided (e.g., deletion 144).</td>
</tr>
<tr>
<td>N-terminal domain</td>
<td>Part of the spike protein of the SARS-CoV-2 virus.</td>
</tr>
<tr>
<td>Reproductive number</td>
<td>The reproductive number, $R_0$ (R-naught), indicates how contagious a disease is in a vulnerable population; it is the average number of people who will catch a disease from one person with the disease.</td>
</tr>
<tr>
<td>Serum (plural Sera)</td>
<td>A ‘watery’ colourless component of blood in which red blood cells (erythrocytes), white blood cells (leucocytes) and platelets are suspended.</td>
</tr>
<tr>
<td>Seropositive</td>
<td>Having detectable antibodies against the virus as measured by a blood (serological) test.</td>
</tr>
<tr>
<td>Variant</td>
<td>Viruses with mutations are referred to as variants of the original virus. New variants of SARS-CoV-2 have been emerging as the virus has spread and evolved.</td>
</tr>
<tr>
<td>Variant of Concern (VOC)</td>
<td>SARS-CoV-2 variants that are considered to have concerning epidemiological, immunological or pathogenic properties are raised for formal investigation by the New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) in the UK. At this point the variants are designated Variant Under Investigation (VUI) with a year, month, and number (since March 2021 2-number year &amp; 3-letter month). Following risk assessment with the relevant expert committee, they may be designated Variant of Concern (VOC).</td>
</tr>
<tr>
<td>Variant under Investigation (VUI)</td>
<td>See Variant of Concern</td>
</tr>
<tr>
<td>Zoonosis (plural zoonoses)</td>
<td>A disease of infection that can be transmitted from animals to humans. There are over 200 known zoonoses.</td>
</tr>
</tbody>
</table>
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**Abbreviations**

**CDC**: Centers for Disease Control and Prevention

**GSAID**: Global Initiative on Sharing Avian Influenza Data

**NERVTAG**: New and Emerging Respiratory Virus Threats Advisory Group

**RBD**: Receptor binding domain (of the virus spike protein)

**R0**: R-naught, reproductive number
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References


90. Food and Drug Administration (FDA), Fact sheet for health care providers emergency use authorization (EUA) of REGEN-COVTM (casirivimab with imdevimab) in Fact Sheet for Health Care Providers. 2021, Food and Drug Administration: FDA.


