COVID-19 B.1.1.7 (501Y.V1) Variant of Concern – What We Know So Far

Introduction

PHO is actively monitoring, reviewing and assessing relevant information related to Coronavirus Disease 2019 (COVID-19). “What We Know So Far” documents are intended to provide a rapid review of the evidence related to a specific aspect or emerging issue related to COVID-19.

This synthesis is an update to the version published on December 29, 2020. For simplicity, we use B.1.1.7 to refer to this variant.

For information on other variants of concern (VOCs), see also PHO’s rapid reviews for B.1.351, P. 1, and VOC-202102/02.

Key Findings

- The B.1.1.7 variant that was originally detected in the United Kingdom (UK), has now spread internationally with community transmission reported in multiple countries.
- As of February 10, 2021, 236 cases of B.1.1.7 have been confirmed in Ontario across 12 public health units, 92% of whom did not have a recent history of international travel.
- Based on the observed rapid rise in incidence and the higher secondary attack rates, reproductive number ($R_t$) and viral load, B.1.1.7 appears to have higher transmissibility than other non-VOCs. The magnitude of increase in transmissibility varies and the biological mechanism behind the increased transmissibility has not been clearly determined yet.
- There is evidence of higher risk of hospitalization and death from B.1.1.7 infection, the level of risk identified seems to depend on the modelling approach and duration of follow-up.
- Routine COVID-19 testing currently performed in Ontario is able to detect B.1.1.7 but unable to differentiate it from other circulating strains. Additional screening and sequencing is done to specifically identify B.1.1.7.
- There is no clear evidence of a higher risk of reinfection with B.1.1.7.
- Significant immune escape and impact on vaccine effectiveness seems unlikely based on phase 3 clinical trial data and laboratory data using pseudovirus-expressing B.1.1.7 mutations.
- Most of the current evidence is from the UK context; caution should be exercised when attempting to generalize the findings to other jurisdictions.
Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mutations occur regularly and most mutations (referred to as "synonymous") do not result in any change in viral proteins. Some mutations ("non-synonymous") change the amino acid sequence resulting in changes in viral proteins, including some in the receptor-binding domain (RBD) of the spike (S) protein. The spike protein, encoded by the S gene, is the key protein on the viral surface involved with binding to the angiotensin-converting enzyme 2 (ACE2) cell surface receptor and initiating cell entry during infection. It is also a major target of the immune system. As a result, spike mutations may alter virus infectivity, replication and pathogenicity, and can result in an altered host immune response.

The B.1.1.7 variant of SARS-CoV-2, also known as VOC 202012/01 or 501Y.V1, has 14 non-synonymous mutations, 6 synonymous mutations and 3 deletions. Key B.1.1.7 mutations that may change the properties of SARS-CoV-2 include:

- The N501Y mutation in the RBD, where amino acid asparagine (N) has been replaced with tyrosine (Y). This mutation may enhance the binding ability of the spike protein to human and mammalian ACE2 receptors.2
- The Δ69-70 in the S protein, where two amino acids at positions 69 and 70 have been deleted. This mutation has been suggested to be involved in potential evasion of the human immune response.3 It has also been associated with some false-negative signals by molecular tests that target the S gene (see Epidemiology below).

The B.1.1.7 variant gained attention from the public health authority in England in early December 2020 due to its rapidly increasing incidence across the South East of England.4 A risk assessment including an epidemiological modelling analysis suggested potential for increased transmissibility with potential significant public health implications leading Public Health England (PHE) to reclassify it from a Variant Under Investigation (VUI) to a Variant of Concern (VOC) on December 18, 2020.5 Since then, this variant has spread globally and generated concern over its potential to cause more severe infections, impact on diagnostic assays and lack of immunity from prior infection or vaccination. In January 2021, the European Centre for Disease Prevention and Control (ECDC) considered the risk associated with the introduction and community spread of this variant as high/very high. They urged member states to: enhance their surveillance and laboratory capacities; ensure compliance with non-pharmaceutical interventions; implement stricter control measures where high transmissibility was evident; slow down importation of new cases; prepare their health care system for surges in demand; and step up vaccination for high-risk groups.6

Since the emergence of B.1.1.7, routine sequencing has revealed that some B.1.1.7 sequences have an additional mutation of interest in the spike gene, E484K. On January 26, 2021, the E484K mutation in the spike protein was detected in 11 sequences of B.1.1.7.7 Enhanced contact tracing brought the number of B.1.1.7 cases with the E484K mutation to 21 (predominantly around the South West of England) by February 9.8 On investigating the risk based on the epidemiological, immunological or pathogenic properties, the New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) designated this as a new VOC, designated as VOC 202102/02 (B.1.1.7 cluster with E484K).9 This new variant retains the characteristics of B.1.1.7 while the additional mutation may affect neutralization by polyclonal and monoclonal antibodies.9,10
Methods

In considering feasibility, scope, and a need for responsiveness, we chose a rapid review as an appropriate approach to understanding B.1.1.7. A rapid review is a knowledge synthesis where certain steps of the systematic review process are omitted in order to be timely (e.g., quality assessment).\textsuperscript{11}

From January 17 to February 15, 2021, PHO Library Services conducted daily searches of primary and preprint literature using the MEDLINE database (search strategies available upon request). In addition, we performed grey literature searches daily using news feeds in the Shared Library Services Partnership. English-language peer-reviewed and non-peer-reviewed (preprints) records that described B.1.1.7 were included.

Prior to posting, PHO subject-matter experts review all “What We Know So Far” documents.

As the COVID-19 outbreak continues to evolve and the scientific evidence rapidly expands, the information provided in this document is only current as of the date of respective literature searches.

Findings

We reviewed 68 reports for this update. Given the emerging nature of B.1.1.7, most of the literature reviewed are preprints (i.e., not peer-reviewed) and government reports.

Epidemiology

The prevalence of B.1.1.7 may be largely underestimated as testing capacity of COVID-19 in general, and sequencing for the variant in particular, varies significantly across countries.\textsuperscript{6,12}

About 57,400 cases of COVID-19 with B.1.1.7 have been identified globally as of February 11, 2021,\textsuperscript{13} and B.1.1.7 cases have been reported in 90 countries/territories across six continents. Most of the B.1.1.7 cases were reported in England, with 55,922 confirmed and probable cases as of February 10, 2021.\textsuperscript{14} Besides the UK, community transmission has also been reported in multiple countries including Belgium,\textsuperscript{6} Brazil,\textsuperscript{15} Canada,\textsuperscript{16,17} Denmark,\textsuperscript{6} Ireland,\textsuperscript{6} Israel,\textsuperscript{6} the Netherlands,\textsuperscript{14} Portugal,\textsuperscript{6} Slovakia\textsuperscript{14} and the United States (US).\textsuperscript{18}

Some laboratories in the UK use a three-target assay (Thermofisher TaqPath) that gives negative results for the S-gene target as a result of the Δ69-70 mutation while the N and ORF1ab genes test positive. This S-gene target failure (SGTF) has been used as a proxy for B.1.1.7 in England, based on findings that 99.6% (27,001/27,099) of Δ69-70 sequences are SGTF compared to 0.04% (10/22,846) without the Δ69-70 mutation, and >99% of Δ69-70 are B.1.1.7.\textsuperscript{14} From mid-November to late December 2020, there was a significant increase in the number of COVID-19 cases in England and that coincided with the increasing proportion of SGTF. By February 7, 2021, 95.0% of the COVID-19 cases were SGTF with distribution across all age groups.\textsuperscript{14}

In Canada, the Public Health Agency of Canada reported 135 cases of B.1.1.7 across the country as of February 2, 2021.\textsuperscript{19} Since then, the number of B.1.1.7 cases has more than tripled to 429 as of February 12,\textsuperscript{20} with cases reported in all provinces by February 14, 2021.\textsuperscript{17,21-29}
Transmissibility

Most of the 25 reports reviewed in this section came from preprints (16) and government publications (6), and most of the findings suggest a high degree of transmissibility of B.1.1.7 relative to other lineages by means of the rapid rise in incidence, higher reproductive number ($R_t$), increased affinity with ACE2 receptor which is used by SARS-CoV-2 for cell entry, higher viral load, or higher secondary attack rates. The magnitude of increase in transmissibility varies by the proxy used, the geographic region, the modelling approach, the scope and practice of pandemic control measures, and the relative transmissibility of concurrent circulating strains. Although the majority of literature reviewed presented evidence of increased transmissibility for B.1.1.7, the biological mechanism is not yet clear.

A government report and two preprints highlighted a rapid rise in COVID-19 incidence with B.1.1.7:

- An ECDC report notes that as of January 19, 2021, the proportion of COVID-19 cases with B.1.1.7 has been increasing in the UK (a 3.7-fold increase from week 49 to week 53 of 2020) and in Ireland (from <2% in early December to 46% in early January).  
- In Portugal, the proportion of COVID-19 cases with SGTF or S-gene target late amplification (cycle threshold [Ct] values for S gene at least 5 units higher than the maximum Ct value detected for the N and ORF1ab targets) increased at 70% (95% confidence interval [CI]: 63%–76%) per week, rising from 5.8% to 13.3% of all COVID-19 cases during week 49 of 2020 to week 2 of 2021. 
- At a hospital and cardiac centre in Lebanon, the number of patients with B.1.1.7 increased dramatically over a 12-day period in January, and the proportion of COVID-19 cases with SGTF also increased from 16% to ≈60%.

Findings from modelling studies also estimated higher transmissibility of B.1.1.7:

- Early modelling studies in the UK estimated that transmissibility may be increased by 71% (95% CI: 67%–75%) with the potential to increase $R_t$ by 0.39–0.93. 
- In the US, a modelling analysis of 212 sequenced B.1.1.7 samples from the US and 292 B.1.1.7 from outside the US suggested that B.1.1.7 arrived in the US at the end of November, 2020. Since then, B.1.1.7 has spread to at least 30 states, making up ≈2.1% of all SARS-CoV-2 positive samples by the last week of January 2021. The proportion of B.1.1.7 among sequenced SGTF samples has increased from below 20% in late December 2020 to ≈90% by mid-January 2021 (ranging from ≈95% in California to ≈70% in Florida). Using a logistic growth model, Washington et al. estimated B.1.1.7 has a 35%–46% higher transmissibility in the US, ranging from 29%–37% in California to 38%–49% in Florida. However, in a phylogenetic analysis of SGTF across the US, Larsen et al. found that B.1.1.7 remained at 0.4% of all COVID-19 cases sequenced by Helix as of January 2, 2021, after two months of circulation. The authors speculate that intensity of local pandemic control measures and relative transmissibility of other concurrent circulating strains might contribute to the difference observed in the transmissibility of B.1.1.7 in different regions.
- In Ontario, regression analysis of SGTF (including samples with Ct values of 30 and above) from samples collected at community laboratory in the Greater Toronto Area revealed an increase of 10-fold per month (1.8-fold per week). The proportion of SGTF in COVID-19 samples rose from 2.0% on December 16, 2020 to an estimated 15.2% on February 3, 2021. In addition, the percentage of B.1.1.7 among SGTF increased from 33.3% in late December 2020 to 96% in January 2021.
REPRODUCTION NUMBER

The reproduction number ($R_t$) is the average number of secondary cases generated by an index case. The epidemic is growing when $R_t$ is greater than 1, and the epidemic is coming under control when $R_t$ is less than 1. Other than one preprint from Ontario, most of the data on $R_t$ values for B.1.1.7 were data from the UK. All six studies (five preprints and one peer-reviewed) and two government documents report a higher $R_t$ for B.1.1.7, ranging from $R_t$ values of 1.17–1.72; percentage increase in $R_t$ by 43%–75% using SGTF as a proxy or by 59%–82% based on gene sequencing; or additive increase in $R_t$ value by 0.25–0.93.

- In a regression analysis, Brown et al. analyzed daily counts of SGTF collected from community laboratories in the Greater Toronto Area in Ontario. Between December 16, 2020 and February 3, 2021, the estimated $R_t$ for SGTF cases was 1.17 (95% CI: 0.94–1.46) overall, and 1.21 (95% CI: 0.96–1.52) for non-outbreak–related SGTF cases; the $R_t$ for non-SGTF cases was 0.82 (95% CI: 0.65–1.01). 
- In a modelling study, Vöhringer et al. estimated an average $R_t$ of 1.25 for B.1.1.7, compared to 0.85 for other circulating lineages during the lockdown in England.
- Using N501Y and Δ69-70 mutations as proxies for B.1.1.7, a peer-reviewed article by Leung et al. estimated a 75% increase in $R_t$ between September 22 and December 1, 2020 in the UK.
- Using different modelling approaches, Davies et al. estimated an increase in $R_t$ by 43%–71% using SGTF as proxy, and 59%–82% using gene sequence data, compared to all other variants in England.
- In another modelling study using data from November 8 to December 12, 2020 reported to the National Health Service in England, Volz et al. estimated a median additive increase of 0.63, or 74% increase, in $R_t$ for B.1.1.7 compared to other lineages during a period of increased public health measures.
- Using daily incidence data for Scotland, Wales and England, Graham et al. estimated an additive increase of 0.28 (95% CI: 0.01–0.61), or a 28% (95% CI: 2%–61%) increase, in $R_t$ during December 2–27, 2020 (after the second lockdown was lifted).
- A risk assessment by NERVTAG concludes that this variant has higher transmissibility compared to other variants identified in the UK, but the magnitude of additional growth rate is uncertain. The advisory group reviewed three analyses which reported an $R_t$ between 1.57 and 1.72; an increase in $R_t$ by 0.39 (unweighted) to 0.93 (weighted); a faster generation time of 71%; or a 56% increase in transmissibility, compared to other circulating strains in the UK.

Additional research is required to understand the mechanism for increased transmissibility (e.g., how soon one becomes infective after an infection, viral load, ease of binding of the variant to host cells).

AFFINITY TO ANGIOTENSIN-CONVERTING ENZYME 2 RECEPTORS

B.1.1.7 carries some key mutations in the gene that encodes the spike (or S) protein. The spike protein is the key protein on the viral surface involved with binding to the ACE2 cell surface receptor and initiating entry into the cell during infection. One of the key mutations changes the asparagine (N) amino acid to a tyrosine (Y) at position 501 (designated by N501Y), which occurs at the receptor binding domain (RBD) of the spike protein. There is some evidence that N501Y mutation may increase infectivity by enhancing spike protein binding to ACE2 receptors.
• Gu et al. reported increased infectivity in mouse lung by SARS-CoV-2 that had gone through serial passaging in the respiratory tract of BALB/c mice. The N501Y mutation was detected in the adapted clinical isolate through deep sequencing.\textsuperscript{2}

• An \textit{in silico} analysis by Islam et al. examined the high resolution crystal structure of the complex formed by the spike protein RBD and the human ACE2 receptor. The authors found that, compared with the Wuhan reference strain, the N501Y mutation may enhance affinity for host cells by providing conformational stability.\textsuperscript{41}

• Liu et al. conducted binding assays of ACE2 with purified proteins of cells engineered with N501-RBD and Y501-RBD, and found that the mutated Y501 protein had a ≈10-fold higher binding affinity for ACE2.\textsuperscript{42}

• Molecular dynamic simulations also provide additional support for the possibility of stronger affinity of the N501Y mutation to ACE2 receptors.\textsuperscript{43-45}

**VIRAL LOAD**

Increased viral load in respiratory specimens may be associated with increased viral shedding and increased transmissibility.\textsuperscript{49} Findings on viral load associated with B.1.1.7 were inconsistent based on two preprints\textsuperscript{46,50} and one peer-reviewed report,\textsuperscript{47} and all examined data from the UK. For the studies that reported on higher viral loads for B.1.1.7, it remains to be explored if the association was causative or correlative (e.g., patient demographics and clinical status, sampling methods). These reports use real-time PCR Ct values as a surrogate to assess viral load. The Ct value is defined as the number of cycles of amplification (in real-time reverse transcription PCR tests) required for the fluorescence of a PCR product to be detected crossing a threshold, which is above the background signal. Although a lower Ct value indicates a higher viral load, Ct values in isolation provide a relative measure rather than the actual quantity of the viral load in a specimen.\textsuperscript{49}

• Kidd et al. analyzed COVID-19 test results received between October 25 and November 25, 2020 from a laboratory as part of a test and contact tracing operation. Compared to non-SGTF samples, SGTF samples had significantly lower median Ct values for the ORF gene target (22.30 vs. 18.16; P<0.0001) and N-gene target (23.16 vs. 19.39; P<0.0001). About 35\% of SGTF samples had Ct values <15, compared to 10\% of non-SGTF samples. Inferring relative viral load from Ct values, viral loads in SGTF samples can be up to 10,000-fold higher than that in non-SGTF samples.\textsuperscript{47}

• Golubchik et al. used N501Y mutation as proxy and analyzed patient samples taken between October 13 and November 13, 2020. The authors found that the B.1.1.7 samples (n=88) had 3-fold higher viral load, compared to non-B.1.1.7 samples (n=1,299) in Kent and outside Greater London. However, within Greater London, the difference was not significant.\textsuperscript{46}

• Walker et al. used SGTF as a proxy for B.1.1.7 and reported that viral loads in 3,531 B.1.1.7 samples were not substantially higher than those in 8,545 samples of non-B.1.1.7. Substantial decreases in Ct values in B.1.1.7 samples from around 30 in mid-November 2020 to a minimum of around 20 in January 2021 were noted, whereas the Ct values in non-B.1.1.7 samples remained at around 22–27 in the same period. Growth rates for B.1.1.7 and non-B.1.1.7 samples were similar; however, when restricting analyses to new infections with Ct values below 30.\textsuperscript{50}

**SECONDARY ATTACK RATES**

The secondary attack rate is the percentage of contacts who become infected; this rate is sometimes used to compare the risk of transmission of different infectious agents or across different settings.\textsuperscript{51}
Data comparing the secondary attack rates for B.1.1.7 and non-B.1.1.7 were identified from preliminary findings from a retrospective matched cohort study using the contact tracing system and genomic sequencing in England. Details on settings, index and contact demographics, and large outbreaks were not available.

- Between October 5 and December 6, 2020, the secondary attack rates were 15.1% for index cases with B.1.1.7, compared to 9.8% for index cases with non-B.1.1.7.\(^5\)
- Between November 30, 2020 and January 10, 2021, the secondary attack rates were 12.9% for index cases with B.1.1.7, compared to 9.7% for index cases with non-B.1.1.7.\(^7\)

### Disease Severity

We reviewed data from two government reports,\(^5,52\) three preprints\(^37,39,53\) and one peer-reviewed article\(^54\) that explored the relationship between B.1.1.7 and disease severity. All data were from the UK. There is evidence to suggest an increased risk of hospitalization and death associated with B.1.1.7. However, there are some contradicting studies based on modelling approaches and there are limitations to the data. Further investigations are ongoing.

- Preliminary analysis from a retrospective matched cohort study in the UK comparing cases with B.1.1.7 to non-B.1.1.7 did not find a significant difference between hospitalization and 28-day case fatality.\(^5\)
- Graham et al. found no difference in reported symptoms, disease severity and disease duration associated with B.1.1.7 based on self-reported data on symptoms and course of infection.\(^39\)
- Modelling based on epidemiological data up to December 24, 2020 by Davies et al. also found no clear evidence of difference in disease severity associated with B.1.1.7 with similar risks of hospitalization (odds ratio [OR]: 1.14 [95% credible interval [CrI]: 0.76–1.73]); critical illness (OR: 1.15 [95% CrI: 0.62–2.14]); relative risk of death (OR: 1.09 [95% CrI: 0.87–1.37]). However, the authors noted that their findings were compatible with a spectrum of possibilities from a small reduction to a moderate increase in severity associated with this variant.\(^37\)
- Brookman compared data of patients 18 years of age or younger admitted to a hospital in south London, during the first wave (from March 1 to May 31, 2020; n=20) when B.1.1.7 was not circulating and the second wave (from November 1, 2020 to January 19, 2021; n=60) when B.1.1.7 was circulating. There were no significant differences in age, proportion of patients with comorbidities, ethnic background or deprivation score. However, the proportions of patients requiring oxygen therapy (35% vs. 8%), non-invasive ventilation (15% vs. 3%), or invasive ventilation support (20% vs. 2%) were higher in the first wave than in the second wave.\(^54\)
- NERVTAG analyzed updated and additional unpublished data from the UK and found that it is likely that B.1.1.7 is associated with a higher risk of hospitalization and death compared to non-B.1.1.7 COVID-19 cases. However, the authors noted that reliable inferences on risk of death were limited as less than 10% of all COVID-19 deaths were included in some datasets, and differentiation of nursing home cases in hospital databases might be limited by inadequate recording. In addition, adjustment by nursing home status, comorbidities and secular trends may be insufficient.\(^52\) Note also that analyses included in the NERVTAG report were unpublished communications that have not been peer-reviewed and were not publicly available for independent review.\(^52\)
  - A modelling study compared deaths from 1,722 SGTF cases vs. 1,660 non-SGTF cases. The study adjusted for misclassification of SGTF and missing data, and controlled for age, sex,
index of multiple deprivation, ethnicity, residence type, specimen date and geographic region (London School of Hygiene and Tropical Medicine):

- Relative hazard of death within 28 days of diagnosis: 1.71 (95% CI: 1.48–1.97); relative increase in case-fatality ratio (CFR) consistent across age groups.
- Hazard ratio for care home residents: 2.43 (95% CI: 1.72–3.35).
- Hazard ratio for general population: 1.53 (95% CI: 1.35–1.74); absolute risk of CFR not substantially increased for those 55 years of age or younger.

- An analysis of all cases of with SGTF vs. non-SGTF, corrected for non-B.1.1.7 SGTF (Imperial College London):
  - Mean ratio of CFR: 1.36 (95% CI: 1.18–1.56) (case-control weighting).
  - Mean ratio of CFR: 1.29 (95% CI: 1.07–1.54) (standardized CFR method).
  - Relative increases in CFR consistent across age groups; absolute risk of CFR not substantially increased for those 55 years of age or younger.

- A matched 1:1 case-control of 109,546 persons infected with B.1.1.7 vs. non-B.1.1.7 since October 1, 2020, using commercial laboratory data (University of Exeter):
  - Mortality hazard ratio: 1.7 (95% CI: 1.3–2.2) (171 deaths in SGTF cases vs. 101 deaths in non-SGTF cases).
  - Elderly patients were under-represented (0.5% of the cohort were over 80 years old).

- A retrospective matched cohort of SGTF (104 deaths, 0.2%) vs. non-SGTF (65 deaths, 0.1%) (PHE):
  - Death risk ratio within 28 days of diagnosis: 1.65 (95% CI: 1.21–2.25).

- A modelling study of SGTF (cases) vs. S-gene positive (controls) using commercial laboratory data (Public Health Scotland, Rapid Epidemiological Analysis of Comorbidities and Treatment as risk factors for COVID-19 in Scotland [REACT-SCOT] study):
  - Rate ratio of death within 28 days of diagnosis: 1.08 (95% CI: 0.78–1.49) (74/292 deaths were SGTF cases).
  - Rate ratio of death or hospital admission within 28 days of diagnosis: 1.40 (95% CI: 1.28–1.53) (1,220/3,765 events were SGTF cases).

  - Risk ratio of hospital admission: 1.63 (95% CI: 1.48–1.80).
  - Relative risk of death within 28 days of diagnosis: 1.37 (95% CI: 1.02–1.84).

- A modelling study of inpatient cohort of sequenced B.1.1.7 vs. non-B.1.1.7 from nine sites (Hospital Onset COVID Infection study):
  - Hazard ratio of in-hospital mortality: 1.09 (95% CI: 0.86–1.36; P=0.48); increased mortality only in women over 65 years of age.
  - Hazard ratio of intensive therapy unit admission: 1.15 (95% CI: 0.86–1.53; P=0.35); no evidence of increased risk with age.

- A modelling study of persons infected with VOC vs. non-VOC, using commercial laboratory data between November 1, 2020 and January 27, 2021 (Intensive Care National Audit & Research Centre [ICNARC] and QResearch):
  - Hazard ratio of ICU admission (at least 12 days of follow up from diagnosis): 1.44 (95% CI: 1.25–1.67) (428/1,171 patients admitted to ICU were infected with the VOC).
  - Hazard ratio of ICU mortality (at least 28 days ICU stay): 0.94 (95% CI: 0.82–1.09).
• A regression analysis linking diagnoses since November 15, 2020 and deaths up to January 17, 2021 for randomly selected cases compatible with B.1.1.7 (Office for National Statistics Coronavirus Infection Survey):
  • Hazard ratio suggests higher risk for all-cause mortality; sample too small for reliable inference.
• Analysis of hospitalized patients infected with sequenced B.1.1.7 (n=32) vs. non-B.1.1.7 (n=184) from 1 hospital (COVID-19 Clinical Information Network [CO-CIN]):
  • Odds ratio of case fatality rate: 0.63 (95% CI: 0.20–1.69) (multinomial model).
• An analysis of the database of hospitalized patients infected with sequenced B.1.1.7 (n=202) vs. non-B.1.1.7 from 91 hospitals using different modelling approaches (COVID-19 Clinical Information Network [CO-CIN]):
  • Odds ratio of 28-day case fatality rate: 0.67 (95% CI: 0.32–1.40) (202 cases with sequenced B.1.1.7 matched 1:1 to non-B.1.1.7 by age, sex, admission date).
  • Hazard ratio of death: 0.81 (95% CI: 0.50–1.32) (103 cases of sequenced B.1.1.7 matched 1:3 to non-B.1.1.7 by age, sex, admission date).
• A population-level analysis of persons infected with VOC vs. non-VOC from PHE laboratories, hospital and commercial laboratory data—interpret with caution due to likely confounders (London School of Hygiene and Tropical Medicine):
  • Estimated higher number of hospitalizations per case by 1.4 times (95% CI: 1.3–1.5).
  • Estimated higher number of fatalities per hospitalisation by 1.4 times (95% CI: 1.2–1.5).
• Davies et al. estimated a 35% increase in hazard of death within 28 days of diagnosis with B.1.1.7 after correcting for misclassification of SGTF and adjusting for age, sex, ethnicity, deprivation level, care home residence, region and diagnosis date. The authors analyzed COVID-19 deaths linked to community-level testing results and included 858,181 persons infected with COVID-19, representing approximately 47% of all COVID-19 diagnoses between September 1, 2020 and January 22, 2021; 48% of the sample population had SGTF.

Impact on Testing
• Health Canada has requested manufacturers of all COVID-19 tests authorized for use in Canada to analyze if there may be an expected impact on performance due to SARS-CoV-2 variants, including B.1.1.7. The analyses indicate that all authorized tests are expected to continue to perform and will show positive results for persons infected with known VOCs. The Δ69-70 mutation has led to negative results in PCR assays that target the S gene (SGTF). The impact on the performance of molecular diagnostic tests overall is minimal as many assays use multiple gene targets. In fact, the SGTF and positive N- and ORF1ab-gene results have been used as proxy for B.1.1.7 where the proportion of SGTF being B.1.1.7 is high.
• Current diagnostic molecular assays used in Ontario are able to detect B.1.1.7 but cannot distinguish B.1.1.7 from other SARS-CoV-2 lineages. A VOC assay that can detect the N501Y mutation is used to screen for variants. Gene sequencing or whole genome sequencing (WGS) is required to classify the variant.
• The rapid antigen tests currently licensed by Health Canada and in use in Ontario detect the SARS-CoV-2 nucleocapsid (N) protein; therefore, they are likely to be unaffected. Preliminary laboratory analysis indicates that rapid antigen tests that target the N protein are able to detect B.1.1.7.
• A number of commercial serological assays that are used to detect COVID-19 antibodies use the S protein or a part of it as a target. Data are not yet available to determine whether antibodies against B.1.1.7 may be missed by these antibody assays.56

Immunity and Reinfection

The B.1.1.7 variant does not harbour the E484K spike gene mutation that has been associated with immune escape. Currently, there is no clear evidence of a significantly higher risk of reinfection with B.1.1.7. Although in vitro neutralization experiments have noted a small degree of resistance to neutralization by convalescent sera,58-60 there has only been one confirmed case of reinfection.61

CASE REPORT AND EPIDEMIOLOGICAL REVIEWS

• Harrington et al. reported a case of reinfection in the UK with B.1.1.7 confirmed by WGS. The reinfection happened 8 months after the first episode and caused critical illness in a 78-year-old patient on hemodialysis.61
• PHE reported that the risks of reinfection are not different between B.1.1.7 and non-B.1.1.7 (1.13 per 1,000 cases vs. 1.70 per 1,000 cases; P=1.00).5
• According to a PHE report, there is consistent evidence that convalescent sera from patients infected with B.1.1.7 show neutralising activity against other variants, and the converse is also true.62
• Graham et al. estimated a 0.7% (95% CI: 0.6%–0.8%) risk of COVID-19 reinfection, based on surveillance data from the COVID-19 UK Genetics Consortium and self-reported COVID-19 test data of 249 potential reinfections from 36,920 individuals in the UK between September 28 and December 27, 2020. Potential reinfection was defined as the occurrence of two episodes of laboratory-confirmed COVID-19 at least 90 days apart, with an asymptomatic period lasting at least seven days before the second positive test. Except for Scotland, reinfection occurrences in all regions were more positively correlated with regional increases in overall COVID-19 incidence than the B.1.1.7 percentage (Spearman rho 0.55–0.69; P<0.05). No consistent variation in reinfection rate was observed across regions or time despite an increasing percentage of cases being B.1.1.7 during the same period. The authors concluded that the risk of reinfection by B.1.1.7 may not be higher than that by other circulating lineages.39

IN VITRO NEUTRALIZATION ASSAYS

We reviewed four preprints58-60,63 and one peer-reviewed report64 of in vitro studies on the neutralizing ability of convalescent sera against pseudovirus engineered to express B.1.1.7 spike protein mutations. These studies suggest that B.1.1.7 is not resistant to neutralization by convalescent sera; however, it is important to note that in vitro data using pseudoviruses, which do not include the full set of mutations found in B.1.1.7, may not reflect the actual impact of B.1.1.7.

• Tada et al. reported that original SARS-CoV-2 (with D614G mutation) was neutralized slightly better by convalescent sera than pseudovirus with three B.1.1.7 spike gene mutations (Δ69-70/N501Y/P681H). The sera were taken from 10 convalescent individuals whose infection occurred in April 2020 (i.e., prior to the emergence of B.1.1.7).58
• Collier et al. reported >2-fold reduction in neutralizing activity in 20/60 samples of monoclonal antibodies from 15 convalescent patients against pseudovirus with eight B.1.1.7 mutations
(Δ69/V70, Δ144, N501Y and A570D in the S1 subunit; P681H, T716I, S982A and D1118H in the S2 subunit). The median age of the recovered patients was >80 years.60

- Shen et al. reported a median 1.5-fold (interquartile range [IQR] = 1.3–1.8) reduction in susceptibility of pseudovirus B.1.1.7 to neutralization (ID80) by convalescent sera (n=15), compared to that for the D614G prototype (original) (P<0.001). The authors concluded that the variant does not likely exhibit immune escape or carry a higher risk of reinfection.59

- Wang, Nair et al. reported no loss of neutralization activity by 20 convalescent sera using pseudovirus with eight B.1.1.7 mutations (Δ69-70, Δ144, N501Y, A570D, P681H, T716I, S982A, D1118H), compared to the original SARS-CoV-2 (D614G variant).63

- Li et al. reported efficient neutralization of a pseudovirus engineered to express the B.1.1.7 spike protein by convalescent sera (n=49) collected from COVID-19 patients before April 15, 2020.64

**Vaccine Effectiveness**

One vaccine efficacy trial and nine preprints of *in vitro* neutralization assays testing three vaccines (Novavax NVX-CoV2373, Moderna mRNA-1273, Pfizer-BioNTech BNT162b2 mRNA) were reviewed. These reports did not find evidence that vaccine efficacy would be significantly impacted by B.1.1.7. As the *in vitro* studies included here use pseudoviruses, which do not include the full set of spike mutations, the data may not reflect the actual impact of B.1.1.7 on vaccine efficacy.

**VACCINE TRIALS**

Preliminary data from the phase 3 trial of the Novavax NVX-CoV2373 COVID-19 vaccine in the UK with more than 15,000 participants aged 18–84 years of age, demonstrated an efficacy of 89.3% (95% CI: 75.2%–95.4%) in preventing symptomatic COVID-19 (confirmed by PCR). Out of the 62 COVID-19 cases detected, 32 were due to B.1.1.7, 24 were due to non-B.1.1.7, 6 were unknown. This yields a vaccine efficacy of 85.6% against B.1.1.7, compared to 95.6% against non-B.1.1.7.65

**IN VITRO NEUTRALIZATION ASSAYS**

Seven preprints and two peer-reviewed studies compared the neutralizing ability of COVID-19 vaccine-elicited antibodies against wild-type SARS-CoV-2 virus with that of B.1.1.7 mutations (using pseudovirus expressing B.1.1.7 spike gene mutations).

**MODERNA mRNA-1273 COVID-19 VACCINE**

- Wu et al. reported no significant impact on neutralization by sera (n=8) from individuals who received two 100 μg doses of vaccine, using pseudovirus with up to nine B.1.1.7 mutations (ΔH69ΔV70, ΔY144, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H).66

- Wang, Nair et al. reported no loss of neutralization activity (IC50) by sera (n=12) from individuals who received two 100 μg-doses of vaccine, using pseudovirus with eight B.1.1.7 mutations (Δ69-70, Δ144, N501Y, A570D, P681H, T716I, S982A, D1118H), compared to the original (D614G) variant.63

- Wang, Schmidt et al. reported a small but significant reduction in neutralization titres (IC50) by sera (n=14) elicited by two doses of the Moderna vaccine. Reduction of 1- to 3-fold (P=0.0002) in neutralizing activity was observed against pseudovirus with the N501Y mutation compared to
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the wild-type pseudovirus. The median age of the vaccinees was 43 years (range = 29–69 years).67

- Shen et al. reported a median reduction of 2.1 fold (IQR = 1.6–2.9) in neutralization efficiency (ID_{50}) by sera (n=40) elicited by two doses of vaccine against B.1.1.7, compared to the D614G prototype. The drop in neutralization efficiency was more pronounced with only one dose of the vaccine: 3.5-fold reduction (n=11) at 29 days after the first dose vs. 2.0-fold reduction (n=29) at 28 days after the second dose (P<0.01). The authors suggest that neutralization resistance by B.1.1.7 may be alleviated by antibody maturation and stressed the importance of timely inoculation of the second dose where the variant circulates.59

PFIZER-BIONTECH BNT162B2 mRNA COVID-19 VACCINE

- Muik et al. reported in a peer-reviewed study similar neutralizing titers by sera (n=16) elicited by two 30 µg-doses of vaccine. The ratio of the median neutralization geometric mean titer of the sera against the pseudovirus with B.1.1.7 spike protein and pseudovirus with the Wuhan reference strain spike protein was 0.79. The authors concluded escape of vaccine protection by B.1.1.7 was unlikely. Age of the vaccinees ranged from 18 to 85 years.68
- Tada et al. reported similar neutralizing titres by sera (n=5) elicited by two doses of vaccine, using pseudovirus with three B.1.1.7 mutations (Δ69-70/N501Y/P681H).58
- Xie et al. reported in a peer-reviewed study small effects on neutralization by sera (n=20) elicited by two 30 µg-doses of vaccine. The neutralization geometric mean ratio of PRNT_{50} were 1.41 proxy variant with three mutations (Δ69/70, N501Y, D614G) and 0.81 against proxy variant with different three mutations (E484K, N501Y, D614G), compared to 1.46 for the wild-type USA-WA1/2020 strain.69
- Wang, Nair et al. reported no loss in neutralization activity (IC_{50}) by sera (n=10) elicited by two 30 µg-doses of vaccine, using proxy B.1.1.7 with eight mutations (Δ69-70, Δ144, N501Y, A570D, P681H, T716I, S982A, D1118H), compared to D614G variant.63
- Wang, Schmidt et al. reported a small but significant reduction in neutralization titres (IC_{50}) by sera (n=6) elicited by two doses of the Pfizer-BioNTech vaccine. Reduction of 1- to 3-fold (P<0.0002) in neutralizing activity was observed against pseudovirus with the N501Y mutation compared to the wild-type pseudovirus. The median age of vaccinees was 43 years (range = 29–69 years).67
- Collier et al. reported modest reduction in neutralizing titres in 20/29 vaccinees elicited by one dose of vaccine (mean reduction = 3.2 fold, standard deviation = 5.7 fold) and by two doses of vaccine (mean reduction = 1.9 fold, standard deviation = 0.9 fold). Neutralization assays used a proxy variant with eight mutations (Δ69/V70, Δ144, N501Y and A570D, P681H, T716I, S982A and D1118H as proxy for B.1.1.7). The median age of the vaccinees was 63.5 years of age (IQR: 47–84).60

NOVAVAX NVX-COV2373 COVID-19 VACCINE

- Shen et al. reported a median of 2.1-fold (IQR = 1.5–3.0) reduction in neutralization efficiency (ID_{50}) by sera (n=28) elicited by two doses of vaccine against B.1.1.7, compared to the D614G prototype.59

Ontario Context as of February 10, 2021

Public Health Ontario conducted a point-prevalence study on an estimated 3,003 samples from January 20, 2021 that tested positive for SARS-CoV-2 in Ontario. Of these, 2756 were received by PHO
Laboratory and screening was completed for 2570 samples as of February 12, 2021. Of these, 113 (4.4%) samples had the N501Y mutation detected, out of which 87 were confirmed B.1.1.7 by WGS and one was confirmed as the B.1.351 variant. About 97% (110/113) of the samples were from individuals who did not have a recent history of international travel. Outbreak-associated B.1.1.7 was known for three public health units (Peel Public Health Unit, Simcoe Muskoka District Health Unit, Toronto Public Health). Note that outbreak samples may be underestimated due to missing data that hindered case-matching. For non-outbreak samples, prevalence was similar for males and females and across age groups.

A study examining the rate of SGTF as a proxy for B.1.1.7 surveillance in Ontario found that out of 11,485 positive COVID-19 tests results compiled between December 16, 2020 and February 3, 2021 at a community laboratory in the Greater Toronto Area, 448 (3.9%) were SGTF. With a 1.8-fold weekly increase observed in the 3-week period since January 13, 2021, the prevalence of SGTF in the Greater Toronto Area was modelled to be at 15.2% on February 3, 2021. As the data came from a region with high rates of COVID-19 and outbreak-related cases were included, the estimates do not apply to the whole province. However, the exponential increase in SGTF is a cause for concern.

On February 3, 2021, Ontario began screening of all positive COVID-19 samples for known VOCs. As of February 10, 2021, 236 cases of B.1.1.7 have been confirmed by WGS in 12 public health units. Over half of the cases (53% [125/236]) were between 20 and 59 years of age. About 92% (217/236) of the cases did not have a recent history of travel; about 81% (190/236) of the cases were a contact of a confirmed case or associated with an outbreak of COVID-19. These findings indicate community transmission of B.1.1.7. The Ontario Science Table reported on February 11, 2021 that between 5%–10% of COVID-19 cases could be B.1.1.7, and while public health measures appear to be effective against all variants, $R_t$ would need to be further reduced to below 0.7 in order to prevent a rise in total cases due to the increased transmissibility of B.1.1.7.
References


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