Australian Government
National Health and Medical Research Council

NHMRC

National COVID-19 Health and Research Advisory Committee[a]

Date of advice: 14 April 2021

SARS-CoV-2-variants: transmissibility, clinical relevance and implications

Focus:

This paper is focused on providing information about the transmissibility and clinical significance of three SARS-CoV-2 variants of current global concern: B.1.1.7, B.1.351, P.1.

Key points[b]

The following points provide a summary of the information available in pre-print and published literature, or reported in expert presentations, seminars or summaries. This advice is point in time and may need further review as more evidence is available.

This report was reviewed by Professor Michael Good AO, Professor Sharon Lewin AO and Professor Bart Currie (NCHRAC members).

1. A comparative analysis on what is known about the variants of concern is provided at Attachment A.
2. Key mutations in the spike (S) protein of variants of concern make them more transmissible than any other SARS-CoV-2 variants identified to date.
3. Variants B.1.1.7, B.1.351, P.1 share a key mutation (N501Y) on the S protein that increases binding affinity to the host's angiotensin-converting enzyme 2 (ACE2) receptor.
4. B.1.351 and P.1 share additional mutations (E484K, K417T/N) that suggest enhanced transmissibility and increased resistance to neutralisation antibodies in convalescent sera.
5. B.1.1.7 is estimated to be 1.4–1.9 times more transmissible than pre-existing variants while B.1.351 is estimated to be 1.5 times more transmissible. The transmissibility rate of P.1 has not been clearly quantified.
6. People infected with the B.1.1.7 variant have been shown to be infectious for longer and have a higher viral load in nasal swabs than the original Wuhan or D614G strains and therefore a longer period of isolation is recommended. No evidence was identified that quantified the infectious period for B.1.351 or P.1.

[a] NHMRC is providing secretariat and project support for the Committee, which was established to provide advice to the Commonwealth Chief Medical Officer on Australia's health response to the COVID-19 pandemic. The Committee is not established under the NHMRC Act and does not advise the NHMRC CEO.

[b] See Background section for definitions of key terms.

7. Monitoring of the evidence regarding the infectious period of the variants will be important to inform any changes to isolation and quarantine policies.
8. No evidence was identified in relation to the serial interval and generation time for variants B.1.1.7, B.1.351 and P.1 to indicate whether there are any changes that might support enhanced transmissibility. However, modelling from the United Kingdom (UK) for B.1.1.7 suggests that a shorter generation serial interval alone is unlikely to contribute to the rapid spread observed.
9. No evidence was identified that detailed asymptomatic/pre-symptomatic transmissibility of the variants.
10. Analyses of comparative mortality of the B.1.1.7 variant in the UK have shown increased hazards of death ranging from 35–64% compared to non B.1.1.7 strains.
11. Variant B.1.351 poses a high re-infection risk to people previously infected with another strain of SARS-CoV-2. This may also apply to variant P.1.
12. In-vitro studies have shown that the neutralising activity of anti-viral treatments such as monoclonal antibodies and convalescent plasma are impacted by some variants of concern. However, the use of monoclonal antibodies may be beneficial for pre and post-exposure prophylaxis where vaccination is not possible.
13. Reduced efficacy of pre-existing vaccines against variants of concern has been demonstrated. Booster or modified vaccines may be required, though this has not been determined. Regulatory agencies including the TGA have considered this and a regulatory approach similar to annual influenza vaccine updates may be taken.
14. The emerging variants of concern can impact the accuracy of some SARS-CoV-2 diagnostic tests. As the variants of concern have mutations in the spike protein, assays that detect the spike protein can yield false negative results. In Australia, the use of tests that do not target the spike protein reduces the likelihood of misdiagnosis.
15. Evidence from multiple countries with extensive transmission of variants of concern indicates that the implementation of public health and social measures has been effective in reducing COVID-19 case incidence and hospitalisations.

Background

NCHRAC were requested to provide advice on variants of concern in January 2021 following the identification of SARS-CoV-2 variants associated with more rapid spread in UK, South Africa and Brazil/Japan.

Below is a summary of the main concepts/available literature that underpin the key points above.

The World Health Organization (WHO) recognise a variant of concern if, through a comparative assessment, it has been demonstrated to be associated with:

- an increase in transmissibility or detrimental change in COVID-19 epidemiology
- an increase in virulence or change in clinical disease presentation, or

- decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics.

Even though the mutation rate for SARS-CoV-2 is lower than other viruses, e.g. influenza and human immunodeficiency virus, we are seeing the emergence of variants of concerns for two reasons. First, each time a person is infected with SARS CoV-2, there is an opportunity for the virus to mutate. The millions of infections worldwide currently provides many opportunities for random mutations. Second, variants can emerge within a host, specifically in the setting of immunosuppression where there is prolonged virus excretion, a sub-optimal antibody response or there is the administration of therapeutics that can provide immune pressure for mutation, for example, convalescent plasma or monoclonal antibodies.[1,2]

There is currently no standard nomenclature used to refer to SARS-CoV-2 variants in the literature. This paper uses the lineage designation according to the Phylogenetic Assignment of Named Global Outbreak (PANGO) to refer to the variants of concern: B.1.1.7, B.1.351, P.1, and uses 'variants of concern' collectively.[3] Alternative names used to refer to these variants are provided below.

Variant (PANGO lineage)	Alternative name(s)	First identified
B.1.1.7	20I/501Y.V1 (clade) VOC 202012/01	United Kingdom September 2020
B.1.351	20H/501Y.V2 (clade) VOC 202012/02	South Africa December 2020
P.1 (or B.1.1.28.1)	20J/501Y.V3	Brazil/Japan January 2021

Other active variants of note:

The Centers for Disease Control and Prevention (CDC) declared a variant spanning B.1.427 and B.1.429 lineages (or CAL.20C/L452R) a concern (16 March 2021); it was originally identified in Southern California (US) in November 2020.[4,5] The WHO has designated this a variant of interest, not concern, at the time of writing.[6]

The Australian Government is concerned with the sustained increase in COVID-19 cases in Papua New Guinea (PNG) and is providing assistance in the public health response.[7] B.1.466.2 is the lineage variant most commonly found in returned travellers from/via PNG. It has not been officially designated a variant of concern globally however, it is of concern to our region.

Context

There have been relatively few SARS-CoV-2 cases of B.1.1.7, B.1.351 and P.1 in Australia since they were first identified in late 2020 and early 2021, compared with case numbers

observed globally. To date, all cases in Australia have been linked to overseas arrivals in mandatory hotel quarantine.

Australia currently requires negative polymerase chain reaction (PCR) tests within the 72 hours prior to departure for returning international travellers and masks are required on both domestic and international flights. All COVID-19 cases are being monitored across Australian laboratories with genome sequencing. Cases confirmed to have a variant of concern are required to isolate for a minimum of 14 days (increased from 10 days) before they are considered for potential release from isolation.[8]

Additional precautionary measures in state/territory quarantine policy are being implemented where warranted to minimise the spread of COVID-19 into the community. Australia is in a strong position to detect B.1.1.7, B.1.351 and P.1 early, and manage the risk of spread of SARS-CoV-2 variants, particularly in health care or managed quarantine settings.

Prevalence

The number of countries reporting cases of each of the three variants has continued to increase each week since their emergence:

- 130 countries have reported cases of B.1.1.7;
- 80 countries reporting cases of B.1.351 and
- 45 countries with cases of P.1[9]

B.1.1.7 is the most common variant detected in Australia (200 cases since 30 November 2020) to date. Fewer cases of B.1.351 (35 cases) and P.1 (2 cases) have been detected.[10] These numbers largely reflect travel patterns to Australia and also global frequency of the variants of concern. To date, all cases have been linked to overseas arrivals in mandatory hotel quarantine.[11,12] Table 1 provides a breakdown of cases with a variant of concern by jurisdiction as reported by the Communicable Diseases Genomics Network.

Table 1: State and territories aggregated case data by variant of concern (as at 31 March 2021)

State/Territory	B.1.1.7	B.1.351	P.1
ACT	0	5	0
NSW	53	6	2
NT	4	0	0
QLD	38	11	0
SA	17	1	0
TAS	0	0	0
VIC	63	3	0
WA	25	9	0
Totals:	200	35	2 cases

Source: 10 Communicable Diseases Genomics Network – current variants of concern[13]

Summary of available literature

Below is a summary of available information that underpin the key points above.

Transmissibility

Key mutations

The SARS-CoV-2 S glycoprotein plays a major role in infectivity. All three variants involve amino acid mutations on the S protein which is instrumental in allowing the virus to invade human cells. The increased binding affinity of the variants results in lower the threshold for infection and creates a greater challenge for antibodies (ie. immune response).

B.1.1.7 is known to have a single mutation in the receptor-binding domain (RBD) at position 501 (N501Y), although a mutation at position 484 (E484K) has also been detected in some sequences in the UK.[14] B.1.351 and P.1 share three mutations in the RBD at positions 501 (N501Y), E484K and 417 (K417T/N).[15,16] Key mutations/deletions of known biological importance have been characterised:

- 501 mutation: undergoes conformational (shape) change that enables the RBD to rotate and fit more deeply into the ACE2 receptor of the human cell and increase its binding affinity.[15,16,17]
    - The 501 mutation also allows for infection of other species, including mice and rats and therefore can expand the animal reservoir of SARS-CoV-2.[18]
- 484 mutation: this mutation leads to a change in shape and electrostatic charge (from negative to positive) and creates a strong bond between the virus and ACE2 receptor.
    - Normally, 484 is negatively charged like the ACE2 so they would repel each other[16]; as seen in D614 variant.
    - E484K allows escape from some antibodies in convalescent sera.[19,20,21,22]
- 417 mutation: this mutation alone has been shown to have a substantial decrease in antibody binding to the RBD; in combination with N501Y it has been shown to fully stop the antibody effect.[15,21,23]

The three variants of concern also share the D614G mutation that was seen in dominant variants earlier in the pandemic. There is evidence that variants with this mutation spread more quickly than viruses without this mutation though its role and significance relative to the transmissibility of the variants of concern is not clear.[24,25,26,27]

Transmission rates

B.1.1.7

Based on statistical and dynamic modelling in the UK where no change in serial interval was assumed, the reproduction number of B.1.1.7 is currently estimated to be 1.4–1.9 times more transmissible than pre-existing variants. Similar increases in transmission (1.6–1.7 times) have been reported in other countries (Denmark, Switzerland, US)[28]. B.1.1.7 is

currently reported to be doubling in frequency approximately every week and a half in the United States.[29]

B.1.351

B.1.351 has been estimated to be 1.5 times (95% CI: 1.20-2.13) more transmissible than previously circulating variants.[30,31,28]

P.1

There is no clear evidence on the transmissibility of P.1 in available literature. Estimates from (pre-print) dynamic modelling integrating genomic and mortality data suggest P.1 may be 1.4–2.2 times more transmissible than non P.1. lineages.[32] As it shares several acquired mutations with B.1.1.7 and B.1.351, which have shown increased transmissibility, it will be important to understand the relative transmissibility of P.1.[23,32]

Serial interval and generation time

Estimates of serial interval and generation time are dependent on specific factors at the time data are collected have been discussed in previous NCHRAC advice (*NCHRAC Advice 11: Incubation period, serial interval and transmissibility*). These include the profile of infectiousness over time, incubation period and changes in contact patterns and use of public health measures within a population, and therefore estimates may not be relevant to all populations.[33]

No evidence was identified in relation to changes in the incubation period, serial interval or generation time for variants B.1.1.7, B.1.351 and P.1. However modelling of the impact of B.1.1.7 indicated that a shorter generation interval alone was not likely to explain the increased spread of B.1.1.7 in the UK.[28]

Viral load and infectious period

Viral load may depend on which part of the respiratory tract the virus has infected (e.g. lungs or upper respiratory tract). The dose of virus needed to initiate infection in humans by all possible exposure routes may differ between SARS-CoV-2 variants, though this is not yet known.[34] It is also not known if the exposure dose determines disease severity.[34,35]

Preliminary analyses have indicated that B.1.1.7 and B.1.351 have been associated with higher viral loads compared with existing variants which can result in lower cycle threshold (Ct) values for genetic testing undertaken by polymerase chain reaction (PCR).[36,37,38,39,22] Assessments to determine if P.1 is associated with increased viral loads or a longer infection have been inconclusive.[32]

Calistri et al investigated reverse transcriptase-polymerase chain reaction (RT-PCR) results on nasopharyngeal swabs in one region of Italy (Abruzzo) and observed significantly higher viral (RNA) loads in people infected with B.1.1.7 (n=313) than other variants. Significantly lower Ct values were observed and associated with the detection of the nucelocapsid (N) protein encoding gene (a multifunctional RNA-binding protein necessary for viral RNA transcription and replication).[40] SARS-CoV-2 also persisted in the respiratory tract for longer than other variants (median 16 days vs 14 days).[39]

Kissler et al explored whether a higher or more persistent virus in the nasopharynx could contribute to increased transmissibility of B.1.1.7. They found B.1.1.7 may cause longer infections overall (mean 13.3 days; 10.1, 16.5) with similar peak viral concentration compared to non-B.1.1.7 virus (mean 8.2 days). The mean duration of the proliferation and viral clearance phases were longer for B.1.1.7 (proliferation phase 5.3 days, clearance phase of 8.0 days) than non-B.1.1.7 (proliferation phase 2.0 days, clearance phase of 6.2 days.[38]

Communicable Diseases Network Australia's (CDNA) current guidance for the release of cases with a variant of concern from isolation is different than for other variants. It specifies that at least 14 days have passed since the onset of symptoms or positive PCR if asymptomatic; and that there has been clinical resolution of fever and respiratory symptoms of the acute illness for the previous 72 hours. This includes PCR testing of cases at days 12-13; if the results show PCR has a high Ct and spike or neutralising antibodies are present, the case would be considered non-infectious and can be released from isolation.[8]

The European Center for Disease Prevention and Control (ECDC) have examined risk of SARS-CoV-2 transmission from newly infected individuals with documented previous infection or vaccination and did not find evidence to indicate that viral load or duration of shedding are reduced when individuals become re-infected with SARS-CoV-2.[41]

No clear evidence has been identified to comment on how the current variants of concern affect asymptomatic or pre-symptomatic transmissibility.

Clinical significance

Severity

Studies in the UK suggest that the B.1.1.7 variant is associated with increased mortality.[42,43] A paper by the New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) reported increased disease severity for the B.1.1.7 variant.[44] Results from community testing in the UK have identified positive B.1.1.7 variant SARS-CoV-2 cases (due to S gene target failure tests), which has given researchers the opportunity to investigate the comparative mortality of this variant of concern. Once adjusted for variables such as age, gender, location, analyses by the Imperial College of London and London School of Hygiene & Tropical Medicine showed the relative hazard of death for individuals infected with the B.1.1.7 strain to be 36% and 35% higher respectively.[42,43] Another UK matched cohort study found the hazard ratio for B.1.1.7 to be even higher (64% increased risk of death) compared with circulating SARS-CoV-2 variants.[45]

A comparable large scale analysis into the mortality rate of individuals infected with B.1.351 is not currently feasible. However, an investigation comparing the characteristics of hospitalised COVID-19 cases in waves 1 and 2 in South Africa (before and after the emergence of B.1.351 strain) showed a 20% increased risk of in-hospital mortality during the B.1.351 wave.[46]

Increased mortality has been reported for P.1 with acknowledgement that the data may be reflective of increased strain on the healthcare system in Manus where the study was conducted.[32] Further clinical investigation of the severity and mortality of the P.1 strain is required.

Immune escape

SARS-CoV-2 reinfection was discussed in detail in NCHRAC's advice paper: *Reinfection: what do we know and what are the implications for vaccines?* (18 December 2020). Since that time, a population level observational study conducted in Denmark suggested protection against repeat infection is as high as 80.5% (95% CI 75.4–84.5) for the general population but reduced to 47.1% (95% CI 24.7–62.8) for people aged 65 and over.[47] At the time of this study, variants of concern had not been identified in Denmark and so molecular surveillance analysis for longitudinal cohort studies will be required to calculate rates of protection of re-infection against variants. Individuals who have been infected by previously dominant SARS-CoV-2 strains such as D614G carry neutralising antibodies, which protect against re-infection could potentially offer some immunity to new variants.[48,49]

Previous SARS-CoV-2 infection does appear to offer a level of protection against the B.1.1.7 strain. Reinfection has been reported, however neutralisation assays of sera from convalescent individuals suggest that this strain does not pose a major risk of reinfection in the community.[50,51] Analysis of COVID-19 convalescent plasma donors in South Africa revealed that variant B.1.351 showed significant escape from the neutralising antibodies from plasma from individuals who had been previous infected with SARS-CoV-2. Mutations at E484K and K417N have been implicated in the viral escape, which suggests that the P.1 variant which has changes at these positions may also escape neutralisation.[52,53] Based on these results, B.1.351 and P.1 variants pose a significant reinfection risk.[52]

Whilst neutralising antibody responses may be compromised due to current (and future) variants of concerns, T cell response could remain active and offer some protection against re-infection of the SARS-CoV-2 virus. Early research which evaluated T cells responses to determine if they could recognise the B.1.1.7, B.1.351, and B.1.1.248 variants. Results showed that T cells sourced from COVID-19 convalescent donors were able to maintain recognition of almost all mutations in the variants studied.[54]

Impact on diagnostic tests

A potentially serious impact of SARS-CoV-2 variants is the possibility of the new strains escaping detection of the currently used diagnostic tests. False negative results of new variants are possible if a mutation occurs at a positon that is targeted by a specific test and could allow SARS-CoV-2 to spread in the community. Diagnostic PCR assays with an S gene target are impacted by the B.1.1.7 variant due to 69/70 deletion.[55] Analysis of the S gene target failure has provided opportunity to approximate the prevalence of the B.1.1.7 variant.[42,43] Fortunately, most commonly used PCR tests used internationally, and in Australia do not include primers that target the S gene, which reduces the likelihood of misdiagnosing variant strains.[56,57,58]

The Therapeutic Goods Administration (TGA) are conducting a post-market review of all Point of Care and Laboratory diagnostic tests authorised for use in Australia to ensure that SARS-CoV-2 genetic variants are diagnosed correctly. The current recommendation is that a repeat test be performed (with different genetic targets) if SARS-CoV-2 infection is still suspected after a negative PCR result.[58,59]

The low number of cases in Australia has allowed for rapid genomic sequencing of all new SARS-CoV-2 cases to identify variants of concern, although not all specimens are adequate for whole genome sequencing.[8] Accordingly, diagnostic tests that are specifically designed to detect variants will be very important, for early detection and management. Rapid diagnostic screening using PCR assays that identify variants of concern (such as B.1.1.7, B.1.351 and P.1) in a few hours are in development.[60,61] Genomic analysis should be used to routinely validate and check variant of concern screen assays to ensure accuracy.

Impact on current treatments

Monoclonal antibodies and convalescent plasma are promising anti-viral therapeutic agents for COVID-19. These antiviral treatments are appropriate in the early stages of the disease (incubation and viremic periods) rather than the later inflammatory phases.[62] Monoclonal antibodies can also be used prophylactically for populations who may not respond well to vaccines and are at high risk of developing severe disease such as the elderly or immunocompromised.[63] Unfortunately, the emergence of antibody-resistant SARS-CoV-2 variants may limit the use of some of these therapies in the clinic.[64] Wang et al[65] conducted several in-vitro experiments to investigate the neutralising activities of current therapeutics used against the B.1.1.7 and B.1.351 variants and found that:

- the neutralising activity of some monoclonal antibodies was reduced against both B.1.1.7 and B.1.351
- convalescent plasma maintained activity against B.1.1.7 but was more than 2.5 fold less effective against B.1.351.

Whilst the utility of some approved therapeutics may be reduced against variants of concern, antibodies that target a part of the spike protein that is highly conserved offers promise. There are a number of trials underway:

- A Phase II trial of a monoclonal antibody (VIR-7831) for adults with mild/moderate SARS-CoV-2 disease with high risk of progression to severe disease has shown promising results.[66]
- Interim results of a Phase III trial have suggested treatment with VIR-7831 (compared to placebo) has resulted in an 85% (p=0.002) reduction in hospitalisation. An Emergency Use Authorization submission has been made to the FDA for the use of VIR-7831 for early treatment of COVID-19.[66]
- In vitro and in vivo data in hamsters has demonstrated that antibodies VIR-7831 and VIR-7832 retain their activity against the B.1.1.7, B.1.351 and P.1 strains.[67] If these effects are seen in the clinic, these therapies could offer treatment options for early stage SARS-CoV-2 variants.

To address the emerging variants of concern, combination therapy that includes several monoclonal antibodies to target different parts of the virus may be necessary to ensure its continued viability as a treatment for SARS-CoV-2 variants.[68,64] Trials are currently underway for the use of monoclonal antibodies in this manner for assisted living residents and staff as well as close contacts of positive SARS-CoV-2 cases.[69,70,71] The use of monoclonal antibodies

may be of high relevance for both pre and post-exposure prophylaxis where vaccination is not possible or ineffective due to emerging variants.[68]

For later stage treatment, corticosteroids have been used for severe SARS-CoV-2 infection. A recent meta-analysis into their use showed this treatment to be associated with lower 28-day mortality.[72] Data is not yet available on whether the effectiveness of this treatment is impacted by the SARS-CoV-2 variants of concern; however, treatments for critically ill patients will continue to be of high importance given the association of the B.1.1.7 variant with increased mortality.[43,45,42]

Impact on vaccine efficacy

There are several ways to determine whether vaccine efficacy is impacted by the variants of concern. Clinical outcome data is best, but is currently not available for all vaccines. Efficacy can also be assessed using plasma from vaccinees to test the level of antibody required to neutralise a specific variant of concern in a laboratory-based assay. There are multiple different ways this assay can be performed, which can make cross laboratory comparisons of neutralising titres complex. Finally, the absolute level of total or neutralising antibodies is often compared between vaccines.

Although the level of neutralising antibody is often evaluated in vaccine trials, it is not yet validated as a surrogate for vaccine efficacy, for either protection from infection or protection from severe COVID-19, hospitalisation or death. It is highly likely that protection from severe disease is dependent on other factors in addition to antibodies, such as a T-cell response. T-cells respond to all parts of the virus and therefore changes in the spike protein may have less impact on the efficacy of the overall T-cell response.

The Australian National Centre for Immunisation Research and Surveillance (NCIRS) are reviewing the emerging evidence on the impact on the variants of concern on vaccine efficacy internationally. A detailed review and summary of the impact of each SARS-Cov-2 variant on the major vaccines is out of scope of the paper; however, the key points about what is currently known are summarised below:

<u>Clinical trial data</u>

- Phase II/III vaccine study for the AstraZeneca(AZ) ChAdOx1 vaccine showed that vaccine efficacy in preventing asymptomatic and symptomatic COVID-19 for the B.1.1.7 strain to be 74.6% compared to 84% for non-B.1.1.7 SARS-CoV-2.[73] There was no difference in prevention of severe COVID-19 (Veysey Lancet 2021)
- A double blind RCT investigating the efficacy of AZ vaccine against B.1.351 in a small trial of 2130 participants concluded that the vaccine did not offer protection against mild to moderate disease from this variant (efficacy of 10.4%).[74] The effects of the AZ vaccine against severe disease with B1.351 is unknown.
- An observational study of clinical data in Israel where the B.1.1.7 variant was established (up to 80% of SARS-CoV-2 isolates at the time of the study) showed the Pfizer vaccine to be effective for preventing symptomatic SARS-CoV-2 as well as more serious disease.[75]

- The Novavax vaccine has demonstrated 89.3% (95% CI: 75.2 – 95.4) efficacy in a Phase III UK trial where over 50% of cases were attributed to B.1.1.7 variant. A phase IIb trial in South Africa (where the B.1.351 variant made up 90% of cases) showed lower but still clinically significant efficacy of 60% (95% CI: 19.9 – 80.1) for prevention of mild, moderate and severe SARS-CoV-2 disease.[76]
- For moderate to severe/critical disease, a Phase III trial of the Janssen vaccine showed efficacy of 72.0% (95% CI: 58.2–81.7) in the US with 96% D614G variant, 68.1% (95% CI: 48.8–80.7) in Brazil with 69% P.2 variant and 64.0% (95%CI: 41.2–78.7) with 95% B.1.351 variant.[77]

In vitro data

- An analysis of sera from recipients of the Moderna and Pfizer vaccines showed there was some loss of neutralising activity against the B.1.1.7 strain (Moderna 1.8 fold, Pfizer 2.0 fold) but a more significant reduction against the B.1.351 strain (Moderna 8.6 fold, Pfizer 6.5 fold).[78]
- A live virus neutralisation assay utilising serum samples from a Phase II/III vaccine study for the AZ (ChAdOx1) vaccine showed a 9 fold reduction in neutralisation activity against the B.1.1.7 strain.

The absolute level of neutralising antibodies may give some indication of clinical efficacy against variants of concern, but this has not yet been proven. It is acknowledged that immunosenescence is associated with reduced antibody titres and decreased vaccine responses in older adults.[79,80] Antibody levels in the elderly have been quantified following both the Pfizer and AZ vaccines. Both show a small reduction in antibody levels in people >65 years compared to <65 years.[81] A recent study of solid organ transplant recipients who were vaccinated with the Pfizer vaccine, showed far lower levels of antibody and frequency failure to generate antibodies.[82] As such, older adults who have been vaccinated may remain vulnerable to new SARS-CoV-2 variants if the vaccine efficacy is significantly reduced.

The TGA, as a member of the Access Consortium, have communicated that updates made to authorised COVID-19 vaccines due to mutations will not be treated as entirely novel products. Should it be necessary, a regulatory approach similar to the influenza virus seasonal updates could be taken for vaccine updates and boosters targeting variants of concern.[83]

The impact of the variants of concern on the effectiveness of vaccines protecting against severe disease is yet to be determined.

Approach

Several searches of Pubmed were undertaken as advice was developed to identify the most relevant and current literature. Publications and pre-print articles that met the following criteria were considered:

1. Published after October 2020

2. Related to relevant aspects of SARS-CoV-2 variants such as:
    a. rate of transmission
    b. mechanisms/characteristics underlying transmission
    c. infectious period, serial interval
    d. severity
    e. immunity/immune response including past infection
    f. response/efficacy to available vaccines or treatment/therapies of reinfection for vaccines.
3. Written in English.

Grey literature was identified via newsletters, internet searches and email alerts and led to the identification of additional references that were included in the evidence tables below. Some literature was provided directly by NCHRAC members or identified in expert presentations about the variants of concern.

Attachments

Attachment A: Comparaitve analysis of the variants of concern

References

Note: Research papers shared before peer review are identified as pre-prints and are marked with a § in the reference list. Accordingly, they should be interpreted with caution.

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Attachment A: Comparative analysis on what is known about the variants of concern

	B.1.1.7	**B.1.351**	**P.1**
Country first identified	United Kingdom	South Africa	Brazil/Japan
Alternative names(s)	20I/501Y.V1 (clade) VOC 202012/01	20H/501Y.V2 (clade) VOC 202012/02	20J/501Y.V3
Australian cases*	200	35	2
Key spike mutations	N501Y, H69/V70 deletion, P681H, Y144/145 deletion, E484K**	N501Y, E484K, K417N	N501Y, E484K, K417T
Function/behaviour	*N501Y:* located in receptor binding domain (RBD); increases binding affinity to ACE-2 receptor		
	E484K: located in RBD in a loop region outside the direct hACE2 interface; change in electrostatic charge, from negative to positive. Changes binding to monoclonal antibodies now approved by the FDA as well as vaccine induced neutralising antibodies		
	H69/V70 deletion Alter the shape of the spike. Enhances viral infectivity in-vitro, is linked to failure of diagnostic test to detect S gene. Also linked to immune escape in immunocompromised patients. *P681H* Located adjacent to furin cleavage site in spike, a known region of importance for infection and transmission. *Y144/145 deletion* Alter the shape of the spike	*K417N* Located in RBD Increase binding to cells Allows escape from some antibodies particularly when in combination with mutation N501Y	*K417T* Located in RBD Increase binding to cells
Total mutations	23	48	~35

	B.1.1.7	B.1.351	P.1
Diagnostic interference	Some diagnostic PCR assays with an S gene target are impacted by the B.1.1.7 variant due to 69/70 deletion. This effect is mitigated by the use of tests that do not include primers that target the S gene.	No evidence of significant impact. TGA conducting post-market review of all approved diagnostic tests to ensure detection of variants, in diagnostic assays for COVID-19.	
Transmissibility	Estimated to be 1.4–1.9 times more transmissible	Estimated to be 1.5 times more transmissible	Unclear, may be 1.4–2.2 times more transmissible
Serial interval and generation time	No evidence identified. However, generation time alone considered unlikely to contribute to rapid spread.	Not known	Not known
Asymptomatic/ presymptomatic	Not known	Not known	Not known
Duration of infectiousness	Estimated to be infectious for longer than other variants ~13–16 days.	Not known	Not known
Mortality	Hazard of death increases of 35–64% have been reported.	Increased risk of in-hospital mortality of 20% reported.	Under investigation
Vaccine interference	***Clinical data***		
	No evidence of substantially reduced efficacy in preventing symptomatic COVID or severe disease for AZ or Pfizer	Reduced efficacy in preventing symptomatic COVID demonstrated for Novovax and J&J. No significant reduction in prevention of severe disease. Significantly reduced efficacy in preventing mild symptomatic COVID for AZ. Effect on severe disease unknown. No available data for Pfizer or Moderna.	No data available

	B.1.1.7	B.1.351	P.1
	In-vitro data		
	Modest increase in titre needed to neutralise in vitro – sera from recipients of an mRNA vaccine ~2 fold	Substantial increase in titre needed to neutralise in vitro – sera from recipients of an mRNA vaccine ~8-10 fold	No data available
Monoclonal antibody interference	In-vitro data suggests reduced neutralising activity of some therapies.	In-vitro data suggests substantial reduction in neutralising activity of some therapies.	Not known

* Communicable Diseases Genomics Network, accessed 6 April

** identified in some B.1.1.7 sequences.