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Title:
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Date:
2021-06-01

Citation:
Andersson, P., Sherry, N. L. & Howden, B. P. (2021). Surveillance for SARS-CoV-2 variants of concern in the Australian context. Medical Journal of Australia, 214 (11), pp.500-502.e1. https://doi.org/10.5694/mja2.51105.

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Surveillance for SARS-CoV-2 variants of concern in the Australian context

Genomic surveillance enhances detection and response to emerging SARS-CoV-2 variants

Genomic sequencing of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been rapidly implemented and scaled-up in Australia and globally during the first 12 months of the coronavirus disease 2019 (COVID-19) pandemic. This has allowed an unprecedented view of viral evolution in near real-time. As with all microbes, the natural evolutionary process introduces changes in the SARS-CoV-2 genome, with some changes providing new variants with improved fitness. This may manifest as changes in viral behaviour, such as transmission, disease severity, immune evasion or vaccine efficacy, and may also affect diagnostic sensitivity.[1] The COVID-19 pandemic has seen pathogen genomics integrated into day-to-day public health responses in many countries, including in Australia.[2-5] Moreover, a global collective sequencing effort has generated more than 1 000 000 publicly available sequences on the Global Initiative for Sharing Avian Influenza Data (GISAID; www.gisaid.org) platform. In Australia, SARS-CoV-2 genomic data have become a vital tool routinely used to support outbreak investigations and to trace international incursions.[2] These data are now an expected element of government briefings to mainstream media. While the mutation rate of SARS-CoV-2 is relatively low at one to two substitutions per month, the natural selective pressure occurring during sustained transmission among the high global case numbers, and long term infections in immunocompromised individuals, provides opportunities for SARS-CoV-2 to adapt. Genomic sequencing data are now vital in the global surveillance efforts of variant detection and for linking defined variants to viral behaviour of particular concern for the control and management of the pandemic.

SARS-CoV-2 variants of concern

At the time of writing (March 2021), there are three variants considered to be variants of concern (VOCs) by the international community for which there is sufficient experimental and epidemiological evidence, supporting a true change in the behaviour of the virus. These VOCs have been named VOC-20DEC-01, VOC-20DEC-02 and VOC-21JAN-02 by Public Health England.[1] A fourth VOC was announced in May 2021.[6] The VOCs are defined by a set of characteristic mutations and can be assigned to evolutionary distinct groups of the virus, such as those described by the Pango lineage scheme[7] — an adaptable hierarchical classification system that has been adopted internationally. While often used synonymously, the latter naming convention (Pango lineage) refers to evolutionary aspects of the virus, while the former (VOC-ID) also considers the epidemiological behaviour of the virus. In this article, we refer to the VOCs by their Pango lineage: B.1.1.7 (VOC-20DEC-01), B.1.351 (VOC-20DEC-02), P.1 (VOC-21JAN-02) and B.1.617 (Box). In addition to these relatively well defined VOCs, there are an increasing number of variants of interest (VOI) for which evidence of functional differences in virus behaviour is still emerging. The VOIs currently include lineages B.1.525, B.1.427/B.1.429 and P.2 (Box). Furthermore, new variants are being frequently reported in online fora and described in preprint scientific articles. A critical activity for public health laboratories responsible for sequencing and reporting SARS-CoV-2 genomic data is to ensure that they remain cognisant of all emerging evidence concerning mutations and lineages, so that their reporting ensures appropriate public health awareness and responses.

In late February 2021, the World Health Organization established the SARS-CoV-2 Virus Evolution Working Group. The Group is tasked with evaluating new variants and coordinating a harmonised global monitoring and assessment system, and have recently proposed working definitions for VOIs and VOCs.[9] Before the creation of this Group, individual governments made declarations on an ad hoc basis. To date, the most common trigger has been changes in the transmission dynamics, with rapid increases in case numbers or a marked shift in the lineage diversity in a particular geographical area. For B.1.1.7, there is established evidence for increased transmissibility.[10] However, for B.1.351, P.1 and B.1.617, it has been more difficult to identify whether the growing incidence is due to increased transmissibility or immune evasion or other epidemiological factors (Box).[6,11-13] Evidence continues to emerge on the observed effects and potential viral fitness costs of the mutations from both population studies and in vitro models. As vaccines are rolled out across the globe, there may be increased signals associated with selection for escape or breakthrough variants. Viral evolution and adaptation are inevitable, and it becomes critical to identify variants that are true causes for concern amid the noise. The rapid progress of the pandemic means that a considerable proportion of information that is useful to inform the declaration of VOIs and VOCs must be distilled from rapid and early access versions such as preprints or scientific blogs, creating additional challenges in the assessment of reliable data. In addition to international recommendations, there is an immediate need for national leadership regarding the prioritisation of public health responses around VOIs and VOCs and for the establishment of a nationally consistent surveillance system for their detection.

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doi: 10.5694/mja2.51105

Current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern* and evidence for public health impact

	Variants of concern				Variants of interest†		
	B.1.1.7†	B.1.351†	P.1†	B.1.617	B.1.525	B.1.427/B.1.429	P.2
Other names	• 20I/501Y.V1 • VOC-20DEC-01	• 20H/501Y.V2 • VOC-20DEC-02	• 20J/501Y.V3 • VOC-21JAN-02	• B.1.617.2 • 20A/S:478K • VOC-21APR-02	• 20A/S:484K • VUI-21FEB-03	• 20C/S:452R • CAL.20C	VUI-21JAN-01
Country (date detected)	England (Sept 2020)	South Africa (Dec 2020)	Brazil (Dec 2020)	India (Oct 2020)	Nigeria and United Kingdom‡ (Dec 2020)	United States§ (June 2020)	Brazil (Apr 2020)
Detection in Australia	Yes	Yes	Yes	Yes	Yes	Yes	Yes
No. of countries with cases	> 110	> 65	> 30	> 40	> 35	> 25	> 30
Variant impacts¶							
Reduced diagnostic test sensitivity	Good evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence
Increased transmission risk	Strong evidence	Some evidence	No clear data	Some evidence	Under investigation	Under investigation	Under investigation
Increased disease severity	Some evidence	No evidence	No clear data	No clear data	No evidence	No evidence	No evidence
Risk of vaccine/immune escape	Some evidence	Good evidence	Some evidence**	Some evidence	No evidence	No evidence	No evidence

* Variants under surveillance (Pango lineage). † Data as of 23 March 2021; up-to-date data on VOCs are available at www.cdgn.org.au. ‡ Returned travellers from Nigeria. § California. ¶ Based on rapidly evolving evidence from multiple data sources but summarised in the World Health Organization Weekly Epidemiological Update on coronavirus disease 2019 (COVID-19).[8] ** Reinfections reported; no current evidence of vaccine escape. ◆

Detection of variants of concern

Variants are defined by a unique set of mutations, and lineages can currently be considered good proxies for VOCs, meaning that the detection of VOCs is reliant on genome sequencing. The Pango lineage scheme lists the characteristic mutations for each of the VOI and VOC lineages and the minimum number of these required to assign the lineage.[7,14] When a genome sequence is incomplete, it may be possible to assign a lineage but not definitively rule a VOC in or out because parts of the genome with key mutations may not be covered. While a lineage can be assigned in the absence of some of the characteristic mutations, it may not be certain that this virus exhibits the observed behaviour associated with the complete constellation of mutations. Conversely, as a case infected with a VOC has implications for public health responses, public health laboratories tend to err on the side of caution and report a sample as a VOC if characteristic mutations are present, even if the phylogenetic position is unclear because other parts of the genome were not covered.

Australia's public health response to variants of concern

Uniformly across Australia, public health laboratories are monitoring and reporting on VOCs to their public health units. While genomic sequencing capability is accessible to all jurisdictions, ongoing investment in sequencing capacity in smaller jurisdictions will further reduce turnaround times. The strategy in Australia, where genome sequencing is attempted in the majority, if not all, of COVID-19 cases, not only provides the best possible opportunity to detect VOCs but has also resulted in one of the most complete national datasets in the world with 58% of positive cases sequenced, allowing historical observations of VOIs as they are declared. Through coordinated efforts between public health laboratories and units, national coordination of which VOIs and VOCs to monitor and case definitions for their detection are emerging to allow rapid, consistent and effective data sharing and reporting with key stakeholders. In Australia, all national activities are in line with the recently endorsed implementation plan for the National Microbial Genomics Framework,[15] which is operationalised through the Communicable Diseases Genomics Network (www.cdgn.org.au) and a genomics-enabled public health laboratories network. A key feature of the national genomics surveillance for SARS-CoV-2 in Australia is AusTrakka — a national platform for near real-time comparative genomic analysis of SARS-CoV-2 genomes — which allows for efficient information sharing and rapid identification of interjurisdictional outbreaks. The Communicable Diseases Network of Australia has published guidelines for the management of VOC cases detected in the country.[16] These currently

include prolonging the period before release from isolation if asymptomatic (14 days), additional reverse transcriptase polymerase chain reaction (RT-PCR) tests taken 12–13 days from symptom onset, and requiring clinical resolution of symptoms for the previous 72 hours. As more evidence becomes available on the implications of emerging VOCs, these national public health guidelines will likely be updated further.

In Australia, most VOCs to date have been detected in travellers in quarantine. With essentially no community transmission, variants are unlikely to develop domestically, meaning that Australia will probably continue to have a reactive approach to declaration of VOCs based on overseas data. The country's well established public health genomics efforts have supported a swift national response to the emerging threat of SARS-CoV-2 VOCs and will remain critical during the pandemic, especially as vaccine roll-out broadens. International data on immune and vaccine escape are now emerging and will likely lead to an increased focus on lineages and mutations associated with such events. While some specific mutations are thought to have functional effects, such as reduced antibody neutralisation associated with E484K,[11-13] the observed data on vaccine effectiveness based on current and recently circulating lineages and the effects of mutations of concern emerging in other lineage backgrounds remain to be determined. Analogous to equitable vaccines access, it is important to consider global access to whole-genome sequencing and strategic sequence sampling to ensure detection of potentially important variants, and Australia's capability may play a vital role for the Pacific region.

In Australia, low case numbers and the universal hotel quarantine program, coupled with a well established genome sequencing capability, afford the ability to carefully assess the available evidence around VOIs and VOCs and provide well considered reporting that informs proportionate public health responses. National cooperation, data sharing and consistency in approach between genomics public health laboratories provide confidence in the detection and reporting of these variants, optimally informing public health responses.

Acknowledgements: The Microbiological Diagnostic Unit Public Health Laboratory is funded by the Victorian Government. This work was supported by a National Health and Medical Research Council Investigator Grant to Benjamin Howden (GNT1196103) and a Medical Research Future Fund COVID-19 Genomics Grant (MRF9200006). We acknowledge all Communicable Diseases Genomics Network members who have contributed to genomics-informed public health responses to the COVID-19 pandemic in Australia and in efforts to detect and report SARS-CoV-2 variants of concern.

Competing interests: No relevant disclosures.

Provenance: Not commissioned; externally peer reviewed. ■

The unedited version of this article was published as a preprint on mja.com.au on 7 May 2021.

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