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

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Introline: “Genomic surveillance enhances detection and response to emerging SARS-CoV-2 variants”

The rapid implementation and scale-up of genomics-based surveillance of SARS-CoV-2 in Australia and globally during the first 12 months of the COVID-19 pandemic has allowed an unprecedented view of viral evolution in near to real time. Genomic data was used to rapidly develop highly accurate diagnostic tests, understand transmission dynamics of the virus and underpinned the rapid development of the vaccines. Currently, genomics is revealing the emergence of new mutations and variants of the virus, and the public health community is now needing to determine the significance of these new variants, and whether they warrant intensified public health responses.

Genomic sequencing of the SARS-CoV-2 virus has been rapidly implemented and scaled-up in Australia and globally during the first 12 months of the COVID-19 pandemic, allowing an unprecedented view of viral evolution in near to 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 is one or many viral behaviours, such as transmission, disease severity, immune evasion or vaccine efficacy and may also impact diagnostic sensitivity [1]. The SARS-CoV-2 pandemic has seen pathogen genomics integrated into day-to-day public health responses in many countries, including Australia [2-5] and 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) platform. In Australia, SARS-CoV-2 genomic data has become a vital tool routinely used to support outbreak investigations and to trace international incursions [2], and is now an expected element of government briefings to mainstream media. While the mutation rate of SARS-CoV-2 is relatively low at 1-2 substitutions/month, the natural selective pressures occurring during sustained transmission amongst the high global case numbers and long-term infections in immunocompromised individuals provides opportunities for the SARS-CoV-2 virus to adapt. Genomic sequencing data is now vital in the global surveillance efforts of variant detection and linking defined variants to viral behaviours of particular concern for the control and management of the pandemic.

SARS-CoV-2 variants of concern

At the time of writing, there are three variants considered to be variants of concern (VOC) by the international community, where sufficient experimental and epidemiological evidence exists supporting a true change in the behaviour of the virus. These have been named VOC-20DEC-01, VOC-20DEC-02 and VOC-21JAN-02 by Public Health England [1]. 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 Pangolin lineage scheme [6] an adaptable hierarchical classification system that has been adopted internationally. While often used synonymously, one should remember that the latter naming convention (Pangolin lineage)

refer to evolutionary aspects of the virus, while the former (VOC-ID) also considers the epidemiological behaviour of the virus. Here we refer to the VOCs by their Pangolin lineage, B.1.1.7 (VOC-20DEC-01), B.1.351 (VOC-20DEC-02) and P.1 (VOC-21JAN-02) (Box 1). 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 1). Further, new variants are being frequently reported in online fora and described in pre-print scientific articles. A critical activity for public health laboratories (PHLs) responsible for sequencing and reporting SARS-CoV-2 genomic data is to ensure that they remain cognisant of all emerging evidence around concerning mutations and lineages, so that their reporting to public health agencies ensure appropriate public health awareness and responses.

In late February 2021, the World Health Organization (WHO) established the SARS-CoV-2 Virus Evolution Working Group, tasked with assessing new variants and coordinating a harmonized global monitoring and assessment system, and have recently proposed working definitions for VOIs and VOCs [7]. Prior to this, declarations were made on an *ad hoc* basis by individual governments. To date, the most common trigger has been changes in 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 [8], but for B.1.351 and P.1 it has been more difficult to identify whether the increased incidence is due to increased transmissibility or immune evasion [9-11] (Box 1). Evidence continues to emerge on the observed effects and potential viral fitness costs of the mutations both from population studies and in-vitro models. As vaccines are rolled out in countries across the globe, there may be increased signals associated with selection for escape or break-through 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/early access versions such as pre-prints 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 prioritisations of public health responses around VOIs and VOCs, and the establishment of a nationally consistent surveillance system for their detection.

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 Pangolin lineage scheme lists the characteristic mutations for each of the VOI and VOC lineages, and minimum number of these required to assign the lineage [6,12]. 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, PHLs 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, PHLs are monitoring and reporting on VOCs to their public health units (PHUs), while genomic sequencing capability is accessible to all jurisdictions, ongoing investment in sequencing capacity in smaller jurisdictions will further reduce turn-around-times. The strategy in Australia, where genome sequencing is attempted in the majority, if not all, COVID-19 cases, not only provides the best possible opportunity to detect VOCs, but has also resulted in one of the most complete national data sets in the world with 58% of positive cases sequenced, allowing historical observations of VOIs as they are declared. National coordination of which VOIs and VOCs to monitor and case definitions for their detection is

emerging, through coordinated efforts between PHLs and PHUs, to allow rapid, consistent, and effective data sharing and reporting with key stakeholders. All national activities are in line with the Australia's recently endorsed National Microbial Genomics Implementation Plan [13] which is operationalised through the Communicable Diseases Genomics Network (cdgn.org.au) and a genomics-enabled PHL 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, allowing for efficient information sharing and rapid identification of interjurisdictional outbreaks. The Communicable Diseases Network of Australia, have published changes to the management of VOC cases detected in Australia [14]. These currently include prolonging the period before release from isolation if asymptomatic (14 days), additional RT-PCR tests taken at 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.

Most VOCs to-date in Australia have been detected in travellers in quarantine, and with essentially no community transmission, variants are unlikely to develop domestically, meaning that Australia will likely continue to have a reactive approach to declaration of VOCs based on overseas data. Australia'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 is 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 [9-11], it is important to note that 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 WGS and strategic sequence sampling to ensure

detection of potentially important variant, and Australia's capability may play a vital role for the Pacific region.

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

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Box 1: Current SARS-CoV-2 variants of concern and evidence for public health impact. Note, this is a rapidly evolving area and data was current as of 23 March 2021. Up to date data on VOCs can be found at www.cdgn.org.au.

	Variants under surveillance (Pangolin lineage)					
	Variant of Concern			**Variants of interest**		
	B.1.1.7	**B.1.351**	**P.1**	**B.1.525**	**B.1.427/B.1.429**	**P.2**
Other names	20I/501Y.V1, VOC-202012/01	20H/501Y.V2, VOC-202012/02	20J/501Y.V3, VOC-202101/02	20A/S:484K; VUI-202102/03	20C/S:452R; CAL.20C	VUI-21JAN-01
Country, date detected	England, September 2020	South Africa, December 2020	Brazil, December 2020	Nigeria & UK (returned travellers from Nigeria), December 2020	USA (California), June 2020	Brazil, April 2020
Detection in Australia	Yes	Yes	Yes	Yes	Yes	Yes
No. countries with cases	>110	>65	>30	>35	>25	>30
Variant impacts:						
Diagnostic tests	++	-	-	-	-	
Increased transmission	+++	+	?	Under investigation. E484K mutation (potential immune and vaccine escape)	Under investigation. L452R mutation (potential immune escape)	Under investigation. E484K mutation (potential immune and vaccine escape)
Disease severity	+	-	?			
Vaccine/ immune escape	+	++	+ (reinfections reported, no current evidence			

			of vaccine escape)			

Level of evidence: +++ Strong evidence, ++ Good evidence, + Some evidence, - No evidence, ? No clear data; based on rapidly evolving evidence from multiple data sources but summarised in the World Health Organization Weekly Epidemiological Update on COVID-19 – 23 March 2021 [15].