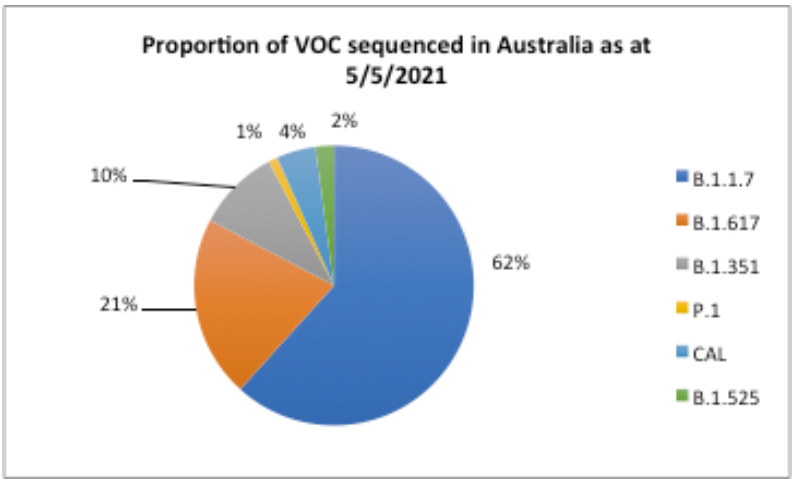
Feedback from operational stakeholders who manage or respond to outbreaks is that they are often too busy to review literature or obtain relevant background information to assist them with acute response. Unlike a traditional analytical outbreak investigation report, ***Watching Briefs*** *are intended as a rapid resource for public health or other first responders in the field on topical, serious or current outbreaks, and provide a digest of relevant information including key features of an outbreak, comparison with past outbreaks and a literature review. They can be completed by responders to an outbreak, or by anyone interested in or following an outbreak using public or open source data, including news reports.*

Watching brief

Title	COVID-19 Variants of Concern in Australia, September 2020- April 2021
Authors	Danielle Hutchinson, Hermione Williams and Haley Stone University of New South Wales, Sydney, Australia
Date of first report of the outbreak In Australia	Original (reference strain): Wuhan, Hubei Province, China Late December 2019 (1). First confirmed case in Australia 25/1/20 (2). Dates of first confirmed variants: D614G 24/03/20 (3) B.1.1.7 30/11/20 (3) B.1.351 10/12/20 (3) P.1 1/3/21 (3) CAL (B.1.427/B.1.429) 8/12/20 (3) B.1.525 6/1/21 (3) B.1.617 1/12/20 (3)

Disease or outbreak	**COVID-19 variants:** D614G Spike D614G amino acid change (from original Wuhan reference strain, dominant globally since March 2020) (4). B.1.1.7 (501Y.V1 UK/Kent Variant) – first emerged in the UK in September 2020 and has multiple mutations in spike protein: S:N501Y, SP681H: Adjacent to S1/S2 furin cleavage site, and also deletions Δ69–70, and Δ144/145 (5). B.1.351 (501Y.V2 South African Variant) – first sequenced in South Africa in October 2020, after a peak in new infections in the Nelson Mandela Bay area, after a short decline following the first wave (6). B.1.351 has multiple mutations in spike protein: S:N501Y, S:E484K, S:K417N, S:D80A, with deletions Δ242–244 (5). P.1 (501Y.V3 Brazil Variant) - first sequenced January 6 2021 in travellers entering Japan from Brazil, is believed to have emerged in 2020 in Brazil (5). P.1 has multiple mutations in spike protein: S:N501Y, S:E484K, S:K417N, S: H655Y (5). CAL (B1.427/B1.429) (20C/S:452R Californian variant) – first emerged in California, USA in October 2020 and has mutation L452R (5). B1.525 (Nigerian/Denmark variant) first emerged in Nigeria in December 2020 (6). B.1.525 has multiple mutations in spike protein: Q:F888L, S:E484K: , S:Q677H, deletions Δ69/70, Δ144 and also exhibits mutations in N-protein (5, 7). B.1.617 - Consists of 3 distinct lineages, B.1.617.1, B.1.617.2 (first detected in India in December 2020), and B.1.617.3 (first detected in India in October 2020) (5). There is little known about the variant at this time, however it shares key mutations with other VOCs (5).
Origin (*country, city, region*)	Original (reference strain): Wuhan, Hubei Province, China D614G March 2020 (4) B.1.1.7 September 2020, Kent/UK (8) B.1.351 Found in samples dating back to October 2020, South Africa (5) P.1 first detected on January 6 but had reported to have arose in 2020 (5) CAL (B.1.427/B.1.429) October 2020 California USA (9) B.1.525 (December 2020 Nigeria (10)) B.1.617 B.1.617.1, B.1.617.2 (first detected in India in December 2020), and B.1.617.3 (first detected in India in October 2020) (5).

Suspected Source (specify food source, zoonotic or human origin or other)	SARS-COV-2 is assumed to have a zoonotic origin, however the specific animal source remains elusive (1). The virus has undergone genetic mutation when replicating through continued human-to-human transmission (11). The original strain in Wuhan was replaced globally by D614G after March 2020 (4). This strain dominated through 2020, but by September 2020, new variants began emerging independently in multiple locations, with the UK, South African and Brazilian variants arising around the same time independent of each other (12). Until then it was believed that coronavirus was a more stable virus than influenza, and that mutations were less frequent (4). However, the rate of mutation observed has been similar to influenza A (13). One theory that has been proposed to explain the mechanisms of mutations of the spike protein arising simultaneously at geographically separate locations is that prolonged infection in immunocompromised hosts may drive antigenic evolution (14). During virus replication in persistent infection, the variations that occur involve recurrent deletions in the spike protein, which confer resistance to neutralising antibodies (13). Usually coronaviruses acquire genome substitutions slowly, however this pattern of acquiring deletions in the immunocompromised patient may accelerate the evolution of SARS-CoV-2 and cause emerging variants, with adaptive features of immune escape and increased infectivity (13,15). The use of convalescent plasma in immunocompromised patients is associated with emergence of viral variants, as “selective pressure” causes viruses with mutations to survive (15). Viral evolution has also been shown in asymptomatic patients and viral shedding can occur for more than 70 days after diagnosis due to impaired viral clearance (16). This may lead to increased transmission, as the current isolation recommendations are inadequate for the population group (14).
Date of outbreak beginning	October or November 2019 (original strain), with first cases detected in December 2019 (1)
Date outbreak declared over	N/A
Affected countries & regions	Global
Number of cases (specify at what date if ongoing)	The detection of variants depends on sequencing capacity, which varies widely between countries. Therefore global estimates below are a function of testing and genomic sequencing capacity, as well as incidence. Testing and sequencing rates in Australia have been high. **As at 8/5/21:** **Global** **Australia** Confirmed cases 156 921 961 29 906(17) **VOC as at 5/5/21** D614G globally dominant strain (16)

	B.1.1.7 558 583 353 (3) Detected in 108 countries (4) B.1.351 14 747 37 (3) Detected in 67 countries (4) P.1 11 092 7 (3) Detected in 31 countries B.1.525 3 333 9 (3) Detected in 11 countries CAL (3/4/21) 38 598 18 (3) Detected in 37 countries B.1.617 3 781 79 (3) Detected in 18 countries  **Figure 1.** Proportion of VOC sequenced in Australia Nov 2020 - 3/4/2021 (GISAID, 2021)
Clinical features	COVID-19 infections commonly cause fever, cough, dyspnoea, fatigue, headache and loss of taste/smell (18). **Severity** The main factors in hospitalization and death due to SARS-CoV-2 infection are comorbidities and patient age (19). Compared to the previously circulating Wuhan strain: D614G Previously considered to have no increase in disease severity (hospitalization), however it has been associated with increased mortality, and could result in increased case severity through higher viral loads (20).

	B.1.1.7 Estimated risk of mortality is increased (from 2.5 to 4.1 deaths per 1,000 cases) (21,22). Average infections last 13.3 days compared with 8.2 days for other variants (23). B.1.351 At this stage, no evidence to suggest increased severity of disease (24). Vaccine escape has been described, with reduced efficacy to several vaccines, as low as 0-10% efficacy for the ChadOx1 vaccine (25). P.1 infections have been shown to have a higher mortality, by 1.1-1.8 times, although this may be confounded by healthcare system capacity in Manaus, Brazil (26). CAL (B.1.427/B.1.429) Increased mortality has been reported, but may be due to small sample size, could also be due to hospital load (27). B.1.525 At this stage, no data to suggest increased severity of disease, but data is limited at the time of this analysis.
Mode of transmission (dominant mode and other documented modes)	Dominant mode of transmission through direct human to human airborne transmission, including at close range (28,29). Faecal aerosols and the faecal-oral route are also possible; and fomite and contact transmission are less likely but possible (30). **VOC Transmissibility** D614G Increased transmissibility compared to the original Wuhan strain due to higher viral loads in the upper respiratory tract (31). B.1.1.7 Substitution of N501Y increases the accessibility of the receptor binding domain and affinity with host cell receptors, thereby enhancing transmissibility by allowing the virus to better establish and propagate infection (32-33). It has been shown to have a higher reproduction number, with transmissibility 40-90% greater than D614G (34,35). B.1.351 This variant is associated with a higher viral load, which may cause an increase in transmissibility (24). One modelling study estimates that it is 50% more transmissible than other circulating variants (32). P.1 has been shown to be 1.7 – 2.4 times more transmissible than previously circulating strains (26). CAL (B.1.427/B.1.429) Elevated household secondary attack rate suggests increased transmissibility (27). B.1.525 S:Q677H may increase transmissibility by increasing stability of S1:S2 association, and was quickly responsible for 20% of Nigerian confirmed cases (7). B.1.617 S:P681R as B.1.1.7 – may enhance transmission by increased receptor binding (5)

Demographics of cases	No gender difference in confirmed cases in Australia, with age susceptibility for confirmed infection peaking in the 20-29 year age group (36). Susceptibility to severe disease increases with age (37). A global mathematical analysis shows that SARS-CoV-2 infection rates are positively associated with age, smoking status, travel history, presence of comorbidities and population density (but not with poverty) (38). B.1.1.7 - Analysis of the second wave compared to the first wave in London (where the first wave is assumed to have no cases of B.1.1.7), suggested potential increased severity in females, and a slight decrease in the average age of cases (from 62 to 60 years, and cases were less likely to have comorbidities (39). No information for other variants.
Case fatality rate	Global CFR as at 3/4/21 = 2.2% (17). The case fatality rate is influenced by age, sex, comorbidities, and in some cases ethnicity (40). In Australia, most deaths have been in older adults, especially in aged care (37). **CFRs in VOCs compared to Wuhan strain** While exact CFRs are unable to be calculated, the following trends have been reported: D614G: increased case fatality rate (20) B.1.1.7: increased (22) B.1.351: no change (24) P.1: increased (26) CAL (B.1.427/B.1.429): no information B.1.525: no information B.1.617: no information
Complications	Complications of SARS-CoV-2 infection includes respiratory system conditions (e.g., pneumonia), circulatory system conditions (e.g., cardiac arrest), hematologic disorders (e.g., disseminated intravascular coagulation), renal disorders (e.g., acute kidney failure) and disturbances of smell and taste (40). **Resistance** D614G has same or better neutralisation when compared to original, Wuhan reference virus (4).

	B.1.1.7 Deletion ΔH69/ΔV70 is linked to immune escape and viral infectivity (34,41). B.1.351 suite of mutations has reshaped the antigenic surfaces on the spike protein, causing almost complete resistance to neutralization by some polyclonal and monoclonal antibodies (42-44). S:E484K has been shown to be resistant to convalescent antibodies (5). P.1 Is significantly less resistant to naturally or vaccine acquired antibodies when compared to B.1.531, even though it has similar mutations (45). CAL (B.1.427/B.1.429) L453R confers resistance to antibodies (46). B.1.525 S:E484K confers resistance convalescent antibodies, and S:F888L may assist in immune escape (5). B.1.617 S:E484Q as P.1 and B.1.351 – linked to immune escape (5). **Re-infection** D614G Equivalent or better neutralization with convalescent sera (4). B.1.1.7 Susceptible to neutralizing antibodies by Spike vaccines (47,48). No evidence that reinfection is higher than other strains (24,49). B.1.351 Variant is largely resistant to neutralizing antibodies formed by being infected with previously circulating lineages and therefore poses significant re-infection risk (50,51) P.1 Lineage was found in 42% of the samples collected from positive cases between 15 to 23 December 2020 (26,50). Recent rapid increase in COVID-19 cases in locations that had high infection rates in the past may indicate an increased transmissibility or re-infection rates of the new variants (52). Additionally, people with P.1 have been found to have a double infection of two distinct strains (P.1 and others) (53). CAL (B.1.427/B.1.429) Reduced susceptibility to antibodies from prior infections (54). B.1.525 Unknown. B.1.617 S:E484Q as P.1 and B.1.351 – linked to risk of re-infection (5).
Available prevention	Behavioural measures such as social distancing and wearing masks offer best available prevention (55). A large proportion of the global population will need to be fully vaccinated to provide herd immunity, assuming high efficacy of vaccines, and a short term duration of protection (1-2 years) (56). Non-pharmaceutical interventions have been shown to have a higher impact on the epidemic curve

	than vaccination alone, so behavioural measures should be kept in place during vaccine rollout to reduce deaths and decrease health system costs (57). **Vaccine effectiveness in VOCs** <u>Vaccine target</u> The aggregates of the Spike protein are important in the receptor binding of SARS-CoV-2 to human cells, and the receptor binding domain is the main target for neutralising antibodies following SARS-CoV-2 infection (58). Therefore the S-protein is a target for vaccines to activate an immune response, however if major antigenic variations occur in the S-protein, current vaccines may not be effective (59). The D614G substitution on the S-protein does not affect the vaccine induced neutralising antibodies, and therefore should not decrease vaccine efficacy (60). Two studies have shown that the N501Y mutation seen in the B.1.1.7 variant does not lead to antibody evasion, and therefore should not impact vaccine induced neutralisation (61,62). There is some debate if there is a minor drop in real-world efficacy, however this may have been due to the small sample size in the trial (63). Substitution of E484K is related to a high rate of immune escape, so variants with this spike mutation will theoretically have lower levels of immunity following vaccination or infection (64,65). This implicates B1.351, which has shown to have lower rates of vaccine efficacy for Pfizer (66), Moderna (67) and AstraZeneca (68). However, the lowest efficacy is for Astrazeneca (0-10% (25)). The mRNA vaccines and Novavax have reduced immunogenicity but produce neutralising antibody titres within the expected protective range (47). P.1 and B.1.525 also demonstrate this mutation, however there is no data to date regarding vaccine efficacy for these variants (58). The L245R mutation characteristic of the CAL variant confers resistance to antibodies (46), however it has been shown that T-cell reactivity is maintained following infection or vaccination, therefore while infection or re-infection is not prevented, disease severity may be lessened (69). Vaccine elicited neutralising antibodies from Moderna and Novavax are likely to be effective against the CAL variant (47). **Current vaccine technologies (using recombinant spike glycoprotein)** 1) Nucleic acid – mRNA based vaccines The mRNA is transported by lipid microvesicles, and once it enters the human cell, the vaccine induces the cell to produce an antigen coded by the mRNA (70). The target antigen is the spike protein or its variants. (71). Current vaccines which have been approved are Pfizer and Moderna (72). 2) Non-replicating viral vector-based vaccines The DNA of the Spike protein is carried by an adenovirus, exploiting the capacity of the virus to infect human cells and therefore deliver the mRNA into the cells, creating an immune response (69). Currently AstraZeneca (using a chimpanzee adenovirus) and Johnson & Johnson (using a human adenovirus) have been approved for emergency or full use in some countries (71).

	3) Protein-based vaccines Sub-unit vaccine, using an immunogenic segment from the pathogen to produce an immune response (71). Novavax (9NVX-CoV2373) uses spike nanoparticles and matrix adjuvant (71). Interim results have shown that the vaccine is safe and has greater than 90% efficacy (72), however it has not yet been approved for use (71). **Vaccine efficacy against Variants of Concern** *Pfizer after second dose:* D614G 94.6% (95% CI, 89.9 to 97.3) against symptomatic infection (73). B.1.1.7 reduced levels of neutralization by vaccinated sera (11). B.1.351 reduced levels of neutralization by vaccinated sera (11) .Sensitivity to sera from individuals vaccinated with Pfizer has been shown to have decreased neutralisation titers against B1.351, compared to B.117 and D614G (74). February 2021: Pfizer and BioNTech announced they had begun an evaluation into the safety and immunogenicity of a potential third dose of the vaccine to determine whether it would increase immunity to the COVID-19 variants (73). P.1 T-Cell reactivity is maintained – theoretically this would not prevent infection but may decrease disease severity (71). CAL (B.1.427/B.1.429) T-Cell reactivity is maintained (71). B.1.525 no data re vaccine efficacy (58). *Moderna after second dose:* D614G 94.1% (95% CI, 89.3 to 96.8) against symptomatic infection (75). B.1.1.7 Largely unaffected (76). B.1.351 decreased efficacy (neutralisation reduced by 2/3) (67). February 2021: Moderna announced it had sent a booster vaccine candidate based on the B.1.351 variant to NIAID for a phase 1 trial (77). P.1 T-Cell reactivity is maintained (71) CAL (B.1.427/B.1.429) T-Cell reactivity is maintained (71). Vaccine elicited neutralising antibodies from Moderna are likely to be effective against the CAL variant (47). B.1.525 no data re vaccine efficacy (58). *AstraZeneca-Oxford after second dose:* D614G 62.01% (95% CI, 41.0 to 75.7)% against symptomatic infection (63).

	B.1.1.7 70.4% (95% CI, 43.6-84.5) against symptomatic infection (63). B.1.351 10.4% (95 CI, -76.8 to 54.8) (25). P.1 no data re vaccine efficacy (58). CAL (B.1.427/B.1.429) no data re vaccine efficacy (58). B.1.525 no data re vaccine efficacy (58). *Johnson and Johnson* D614G 66.90% (95% CI, 59.0 to 73.4) (78). B.1.1.7 not specified (78). B.1.351 efficacy or mild-to moderate disease was lower (52%) in South Africa, where the B.1.351 accounted for more than 90% of sequences in the trial participants (78). P.1 efficacy or mild-to moderate disease was lower (65%) in Brazil, where the P.1. accounted for more than 60% of sequences in the trial participants (78). CAL (B.1.427/B.1.429) no data re vaccine efficacy (58). B.1.525 no data re vaccine efficacy (58). *Novavax* D614G 96.4% (95% CI, 73.8 to 99.5) (79). B.1.1.7 86.3% (95%CI, 71.3 to 95.5) (79). B.1.351 48.6% (95% CI, 28.4 to 63.1) (79). P.1 no data re vaccine efficacy (58). CAL (B.1.427/B.1.429) Vaccine elicited neutralising antibodies from Novavax are likely to be effective against the CAL variant (47). B.1.525 no data re vaccine efficacy (58).
Available treatment	There is no specific antiviral treatment available at this point, only supportive care (39). **Supportive management** Dexamethasone has been shown to decrease mortality rates in individuals requiring mechanical ventilation (80). Remdesivir has been shown to improve time to recovery (81).

Comparison with past outbreaks	The COVID-19 global pandemic is ongoing, and therefore is useful to analyse the evolution of the genomic variation of the virus and compare with the epidemic curve when considering variants of concern. It has been shown that disease transmission and epidemic severity are directly related to variant emergence (82). This showed that genomic diversity is predictive of high transmission rates and that that mutations are associated with an increase in cases. Therefore, when exposure occurs during large gatherings, an outbreak occurs (82).
Unusual features	Compared to original (Wuhan) strain: D614G strain demonstrates increased transmissibility and viral loads (20,30). B.1.1.7 is associated with increased transmissibility, mortality and duration of infection, and a higher viral load (21,13,84-85). B.1.351 is associated with increased viral load, increased transmissibility, vaccine escape and increased reinfection risk (24,44,42-44). P.1 demonstrates increased mortality, increased transmissibility, and increased reinfection rates (26). CAL (B.1.427/B.1.429) is associated with increased mortality, increased transmissibility and increased resistance to neutralising antibodies (27,46). B.1.525 demonstrates increased transmissibility and immune escape (5,7).
Critical analysis	Variants of concern have been sequenced in Australia after introduction from returned travellers. Tracking the VOC sequences in Australia can contribute actionable decision-making information. Below is a graphical representation of the sequences reported to GISAID between the dates of November 2020 (when the first sequence was recorded in Australia) to 5th May 2021 (3). B.1.1.7 is the most frequently reported (353 sequences) with the number of confirmed cases increasing (3). B. 1.351 n= 37 sequences, P.1 n=7, CAL n=18, B.1.525 n=9, B.1.617 n = 79 (5). **Emerging VOC - B.1.617** There is little known about the variant at this time, however it shares key mutations with other VOCs: S:P681R which may enhance transmission by increased receptor binding (5, 86) S:E484Q which is linked to immune escape and risk of re-infection. This mutation is not present in B.1.617.2 (5, 86). S:L452R which is linked to increased transmissibility (5, 86).

On the 7th May 2021, Public Health England classified B.1.617.2 as a Variant of Concern, based on evidence that suggests that it is equally as transmissible as B.1.1.7, with rising cases and community transmission occurring in England (86). There is no evidence of more severe disease or decreased vaccine effectiveness at this stage (86). Several countries, including Australia, have imposed bans on travel from India due to escalating case numbers emergence of the new COVID-19 variant B.1.617 (87).

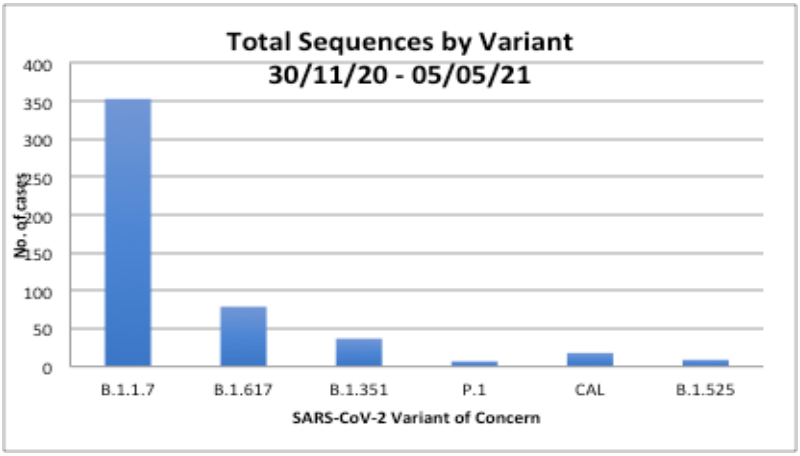


Figure 2. Total Sequences by Variant of Concern in Australia (GISAID, 2021)

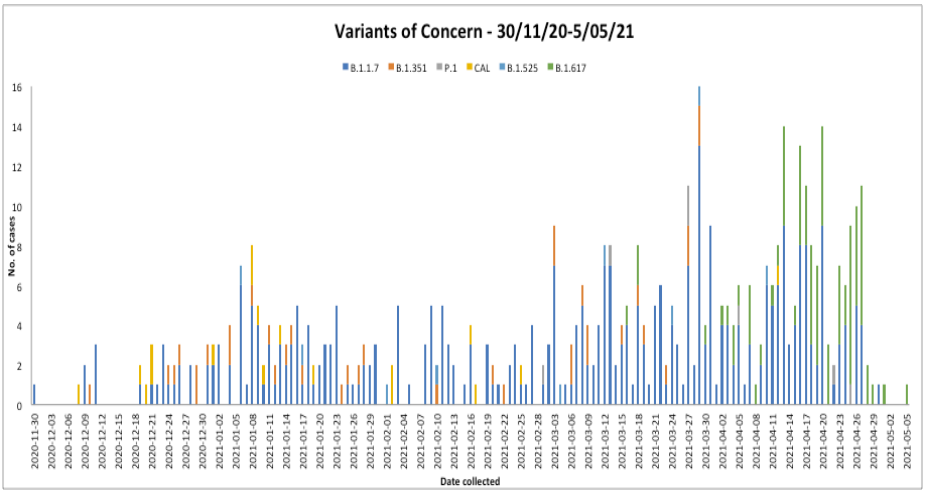


Figure 3. No. Cases of Variants of Concern in Australia by date collected (GISAID, 2021)

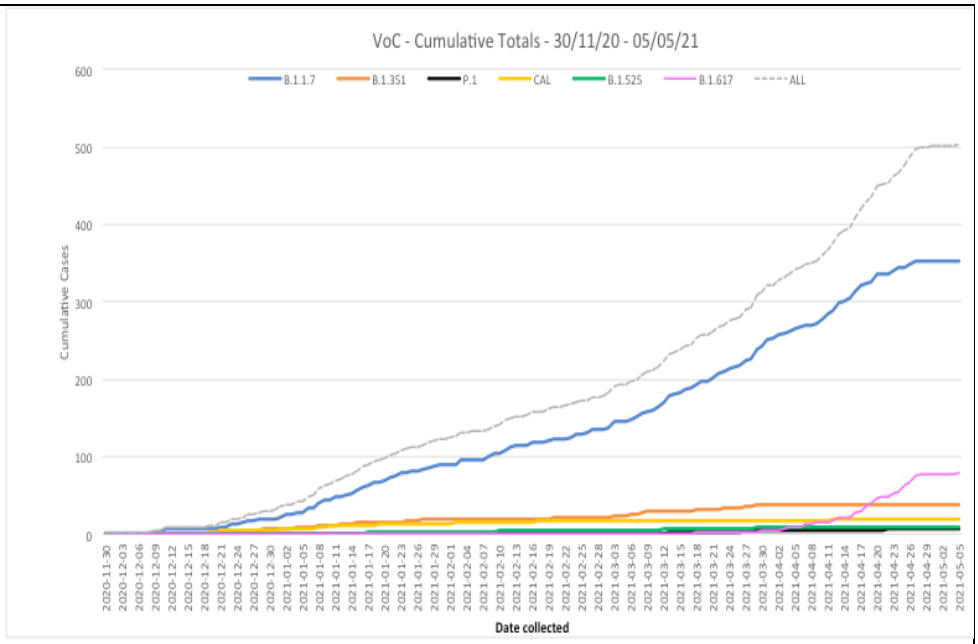


Figure 4. Cumulative total Variants of Concern in Australia (GISAID, 2021)

Vaccines in Australia

Currently there are two vaccines with provisional approval for use in Australia, Pfizer and AstraZeneca-Oxford (88,89). Current clinical guidance on the use of COVID-19 vaccines in Australia has been issued by the Australian Technical Advisory Group on Immunisation (ATAGI) (90). It states that the goal of the program is “to protect all people in Australia from the harm caused by the novel coronavirus SARS-CoV-2, through preventing serious illness and death, and, as much as possible, disease transmission” (88). It notes that initial supply will be limited, and that priority will be given to those who are at increased risk of exposure and hence of being infected with and transmitting SARS-CoV-2, and those in a setting with high transmission potential (91).

This has recently been updated to advise that the Pfizer vaccine Comirnaty is preferable to the AstraZeneca vaccine for people under 50 years of age, due to the risk of thrombosis with thrombocytopenia syndrome (TTS), a rare condition that can occur after AstraZeneca vaccine (92).

Key questions	With consideration to the above information regarding vaccine effectiveness in VOC, and the information presented regarding increasing VOC sequences in Australia, addressing the following questions is important to inform public health policy to control the spread of COVID-19 in Australia: Is the current vaccination strategy addressing the need to protect front line workers and those who will be exposed to SARS-CoV-2 returned travellers, and limiting disease transmission? The second most common VOC detected in Australia is B1351, which shows substantial vaccine escape and no efficacy against the AstraZeneca vaccine. Workers at the border and in areas at most risk of outbreaks (hotel quarantine, healthcare, aged care) may be better receiving the Pfizer vaccine while these are the only two available vaccines. What response strategies can be implemented in the short and medium term? For example, development of vaccines specifically against variants, multi-valent vaccines and increasing the immunogenicity of current vaccines by using booster doses (58). What is the risk of outbreaks in Australia caused by VOCs? Will VOCs become dominant in 2021? Are there opportunities for agreements with companies in end-stage development for supply of vaccines (including boosters matched to VOCs) with proven efficacy against VOCs? What adaptations may be required of Border and Quarantine policies? What adaptations may be required of Public Health Policies for prevention of transmission?
References	1. Pekar J, Worobey M, Moshiri N, Scheffler K, Wertheim J. Timing the SARS-CoV-2 index case in Hubei province. Science. 2021;372(6540):412-417. 2. First confirmed case of novel coronavirus in Australia [Internet]. health.gov.au. 2020 [cited 25 April 2021]. Available from: https://www.health.gov.au/ministers/the-hon-greg-hunt-mp/media/first-confirmed-case-of-novel-coronavirus-in-australia 3. GISAID - hCov19 Mutation Dashboard [Internet]. Gisaid.org. 2021 [cited 3 April 2021]. Available from: https://www.gisaid.org/spike/ 4. Korber B, Fischer W, Gnanakaran S, Yoon H, Theiler J, Abfalterer W et al. Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus. Cell. 2020;182(4):812-827.e19. 5. CoVariants: SARS-CoV-2 Mutations and Variants of Interest [Internet]. https://covariants.org/. 2021 [cited 3 April 2021]. Available from: https://covariants.org/ 6. Tegally H, Wilkinson E, Giovanetti M, Iranzadeh A, Fonseca V, Giandhari J et al. Emergence and rapid spread of a new severe acute respiratory syndrome-

related coronavirus 2 (SARS-CoV-2) lineage with multiple spike mutations in South Africa. 2020;.

7. Haseltine W. A New Covid-19 Variant From Nigeria Raises Increased Concerns For Containment And Vaccination [Internet]. Forbes. 2021 [cited 3 April 2021]. Available from: https://www.forbes.com/sites/williamhaseltine/2021/02/24/new-nigerian-variant-continues-the-trend-of-dangerous-strains-threatening-covid-19-progress/

8. Investigation of novel SARS-COV-2 variant Variant of Concern 202012/01: Technical briefing 1 [Internet]. assets.publishing.service.gov.uk. 2021 [cited 3 April 2021]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/959438/Technical_Briefing_VOC_SH_ NJL2_SH2.pdf

9. Zhang W, Davis B, Chen S, Sincuir Martinez J, Plummer J, Vail E. Emergence of a Novel SARS-CoV-2 Variant in Southern California. JAMA. 2021;.

10. O'Toole T, Scher E, Underwood A, Jackson B, Hill V, McCrone J et al. PANGO lineages [Internet]. Cov-lineages.org. 2021 [cited 3 April 2021]. Available from: https://cov-lineages.org/global_report.html

11. Bates T, Leier H, Lyski Z, McBride S, Coulter F, Weinstein J et al. Neutralization of SARS-CoV-2 variants by convalescent and vaccinated serum. medRxiv. 2021;.

12. Coronavirus Disease 2019 (COVID-19) [Internet]. Centers for Disease Control and Prevention. 2021 [cited 28 April 2021]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/scientific-brief-emerging-variants.html

13. McCarthy K, Rennick L, Nambulli S, Robinson-McCarthy L, Bain W, Haidar G et al. Recurrent deletions in the SARS-CoV-2 spike glycoprotein drive antibody escape. Science. 2021;371(6534):1139-1142.

14. Choi B, Choudhary M, Regan J, Sparks J, Padera R, Qiu X et al. Persistence and Evolution of SARS-CoV-2 in an Immunocompromised Host. New England Journal of Medicine. 2020;383(23):2291-2293.

15. Kemp S, Collier D, Datir R, Ferreira I, Gayed S, Jahun A et al. SARS-CoV-2 evolution during treatment of chronic infection. Nature. 2021;592(7853):277-282.

16. Avanzato V, Matson M, Seifert S, Pryce R, Williamson B, Anzick S et al. Case Study: Prolonged Infectious SARS-CoV-2 Shedding from an Asymptomatic Immunocompromised Individual with Cancer. Cell. 2020;183(7):1901-1912.e9.

17. Home - Johns Hopkins Coronavirus Resource Center [Internet]. Johns Hopkins Coronavirus Resource Center. 2021 [cited 3 April 2021]. Available from: https://coronavirus.jhu.edu/

18. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J et al. Clinical Characteristics of Coronavirus Disease 2019 in China. New England Journal of Medicine. 2020;382(18):1708-1720.

19. Nakamichi K, Shen J, Lee C, Lee A, Roberts E, Simonson P et al. Hospitalization and mortality associated with SARS-CoV-2 viral clades in COVID-19. Scientific Reports. 2021;11(1).

20. Goyal M, De Bruyne K, van Belkum A, West B. Different SARS-CoV-2 haplotypes associate with geographic origin and case fatality rates of COVID-19 patients. Infection, Genetics and Evolution. 2021;90:104730.

21. Challen R, Brooks-Pollock E, Read J, Dyson L, Tsaneva-Atanasova K, Danon L. Risk of mortality in patients infected with SARS-CoV-2 variant of concern 202012/1: matched cohort study. BMJ. 2021;:n579.

22. Grint D, Wing K, Williamson E, McDonald H, Bhaskaran K, Evans D et al. Case fatality risk of the SARS-CoV-2 variant of concern B.1.1.7 in England, 16 November to 5 February. Eurosurveillance. 2021;26(11).

23. Horby P, Huntley C, Davies N, Edmunds J, Ferguson N, Medley G et al. NERVTAG note on B. 1.1. 7 severity [Internet]. Assets.publishing.service.gov.uk. 2021 [cited 3 April 2021]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/961037/NERVTAG_note_on_B.1.1.7_severity_for_SAGE_77__1_.pdf

24. SARS-CoV-2 Variants [Internet]. World Health Organization. 2021 [cited 3 April 2021]. Available from: https://www.who.int/csr/don/31-december-2020-sars-cov2-variants/en/

25. Madhi S, Baillie V, Cutland C, Voysey M, Koen A, Fairlie L et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. New England Journal of Medicine. 2021;.

26. Faria N, Mellan T, Whittaker C, Claro I, Candido D, Mishra S et al. Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil. Science. 2021;:eabh2644.

27. Wadman M. California coronavirus strain may be more infectious—and lethal. Science. 2021;.

28. Tang S, Mao Y, Jones R, Tan Q, Ji J, Li N et al. Aerosol transmission of SARS-CoV-2? Evidence, prevention and control. Environment International. 2020;144:106039.

29. Greenhalgh T, Jimenez JL, Prather KA, Tufekci Z, Fisman D, Schooley R. Ten scientific reasons in support of airborne transmission of SARS-CoV-2. Lancet. 2021 Apr 15:S0140-6736(21)00869-2. doi: 10.1016/S0140-6736(21)00869-2. Epub ahead of print.

30. Holshue M, DeBolt C, Lindquist S, Lofy K, Wiesman J, Bruce H et al. First Case of 2019 Novel Coronavirus in the United States. New England Journal of Medicine. 2020;382(10):929-936.

31. Plante J, Liu Y, Liu J, Xia H, Johnson B, Lokugamage K et al. Spike mutation D614G alters SARS-CoV-2 fitness. Nature. 2020;592(7852):116-121.

32. van Oosterhout C, Hall N, Ly H, Tyler K. COVID-19 evolution during the pandemic – Implications of new SARS-CoV-2 variants on disease control and public health policies. Virulence. 2021;12(1):507-508.

33. Rambaut A, Loman N, Pybus O. Preliminary genomic characterisation of an emergent SARS-CoV-2 lineage in the UK defined by a novel set of spike mutations [Internet]. Virological.org. 2021 [cited 3 April 2021]. Available from: https://virological.org/t/preliminary-genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-the-uk-defined-by-a-novel-set-of-spike-mutations/563

34. Davies N, Jarvis C, Edmunds W, Jewell N, Diaz-Ordaz K, Keogh R. Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7. Nature. 2021;.

35. Updated rapid risk assessment from ECDC on the risk related to the spread of new SARS-CoV-2 variants of concern in the EU/EEA – first update. Eurosurveillance. 2021;26(3).

36. covid-19-cases-by-age-group-and-sex [Internet]. www.health.gov.au. 2021 [cited 3 April 2021]. Available from: https://www.health.gov.au/resources/covid-19-cases-by-age-group-and-sex

37. Channappanavar R, Perlman S. Age-related susceptibility to coronavirus infections: role of impaired and dysregulated host immunity. Journal of Clinical Investigation. 2020;130(12):6204-6213.

38. Khan W, Hussain A, Khan S, Al-Jumailey M, Nawaz R, Liatsis P. Analysing the impact of global demographic characteristics over the COVID-19 spread using class rule mining and pattern matching. Royal Society Open Science. 2021;8(1):201823.

39 Snell L, Wang W, Alcolea-Medina A, Charalampous T, Nebbia G, Batra R et al. First and second SARS-CoV-2 waves in inner London: A comparison of admission characteristics and the impact of the B.1.1.7 variant. 2021;.

40. Wiersinga W, Rhodes A, Cheng A, Peacock S, Prescott H. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19). JAMA. 2020;324(8):782.

41. Kemp S, Meng B, Ferriera I, Datir R, Harvey W, Papa G et al. Recurrent emergence and transmission of a SARS-CoV-2 spike deletion H69/V70. 2020;.

42. Cai Y, Zhang J, Xiao T, Lavine C, Rawson S, Peng H et al. Structural basis for enhanced infectivity and immune evasion of SARS-CoV-2 variants. 2021;.

43. Greaney A, Starr T, Gilchuk P, Zost S, Binshtein E, Loes A et al. Complete mapping of mutations to the SARS-CoV-2 spike receptor-binding domain that escape antibody recognition. 2020;.

44. Liu Z, VanBlargan L, Bloyet L, Rothlauf P, Chen R, Stumpf S et al. Landscape analysis of escape variants identifies SARS-CoV-2 spike mutations that attenuate monoclonal and serum antibody neutralization. 2020;.

45. Dejnirattisai W, Zhou D, Supasa P, Liu C, Mentzer A, Ginn H et al. Antibody evasion by the P.1 strain of SARS-CoV-2. Cell. 2021;.

46. Deng X, Garcia-Knight M, Khalid M, Servellita V, Wang C, Morris M et al. Transmission, infectivity, and antibody neutralization of an emerging SARS-CoV-2 variant in California carrying a L452R spike protein mutation. 2021;.

47. Shen X, Tang H, McDanal C, Wagh K, Fischer W, Theiler J et al. SARS-CoV-2 variant B.1.1.7 is susceptible to neutralizing antibodies elicited by ancestral Spike vaccines. 2021;.

48. Edara V, Floyd K, Lai L, Gardner M, Hudson W, Piantadosi A et al. Infection and mRNA-1273 vaccine antibodies neutralize SARS-CoV-2 UK variant. 2021;.

49. Graham M, Sudre C, May A, Antonelli M, Murray B, Varsavsky T et al. Changes in symptomatology, re-infection and transmissibility associated with SARS-CoV-2 variant B.1.1.7: an ecological study. 2021;.

50. Evidence Check: SARS-CoV-2 Variants [Internet]. aci.health.nsw.gov.au. 2021 [cited 3 April 2021]. Available from: https://aci.health.nsw.gov.au/__data/assets/pdf_file/0010/627409/20210125-Evidence-Check-SARS-CoV-2-Variants.pdf

51. Wibmer C, Ayres F, Hermanus T, Madzivhandila M, Kgagudi P, Oosthuysen B et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. Nature Medicine. 2021;.

52. Sabino E, Buss L, Carvalho M, Prete C, Crispim M, Fraiji N et al. Resurgence of COVID-19 in Manaus, Brazil, despite high seroprevalence. The Lancet. 2021;397(10273):452-455.

53. da Silva Francisco R, Benites L, Lamarca A, de Almeida L, Hansen A, Gularte J et al. Pervasive transmission of E484K and emergence of VUI-NP13L with evidence of SARS-CoV-2 co-infection events by two different lineages in Rio Grande do Sul, Brazil. 2021;.

54. Tchesnokova V, Kulakesara H, Larson L, Bowers V, Rechkina E, Kisiela D et al. Acquisition of the L452R mutation in the ACE2-binding interface of Spike protein triggers recent massive expansion of SARS-Cov-2 variants. 2021;.

55. Margraf J, Brailovskaia J, Schneider S. Adherence to behavioral Covid-19 mitigation measures strongly predicts mortality. PLOS ONE. 2021;16(3):e0249392.

56. Anderson R, Vegvari C, Truscott J, Collyer B. Challenges in creating herd immunity to SARS-CoV-2 infection by mass vaccination. The Lancet. 2020;396(10263):1614-1616.

57. Giordano G, Colaneri M, Di Filippo A, Blanchini F, Bolzern P, De Nicolao G et al. Modeling vaccination rollouts, SARS-CoV-2 variants and the requirement for non-pharmaceutical interventions in Italy. Nature Medicine. 2021;.

58. Bian L, Gao F, Zhang J, He Q, Mao Q, Xu M et al. Effects of SARS-CoV-2 variants on vaccine efficacy and response strategies. Expert Review of Vaccines. 2021;:1-9.

59. Abdel-Moneim A, Abdelwhab E, Memish Z. Insights into SARS-CoV-2 evolution, potential antivirals, and vaccines. Virology. 2021;558:1-12.

60. Weissman D, Alameh M, de Silva T, Collini P, Hornsby H, Brown R et al. D614G Spike Mutation Increases SARS CoV-2 Susceptibility to Neutralization. Cell Host & Microbe. 2021;29(1):23-31.e4.

61. Rathnasinghe R, Jangra S, Cupic A, Martínez-Romero C, Mulder L, Kehrer T et al. The N501Y mutation in SARS-CoV-2 spike leads to morbidity in obese and aged mice and is neutralized by convalescent and post-vaccination human sera. 2021;.

62. Xie X, Liu Y, Liu J, Zhang X, Zou J, Fontes-Garfias C et al. Neutralization of SARS-CoV-2 spike 69/70 deletion, E484K and N501Y variants by BNT162b2 vaccine-elicited sera. Nature Medicine. 2021;27(4):620-621

63. Emary K, Golubchik T, Aley P, Ariani C, Angus B, Bibi S et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) Vaccine Against SARS-CoV-2 VOC 202012/01 (B.1.1.7). 2021.

64. Nelson G, Buzko O, Spilman P, Niazi K, Rabizadeh S, Soon-Shiong P. Molecular dynamic simulation reveals E484K mutation enhances spike RBD-ACE2 affinity and the combination of E484K, K417N and N501Y mutations (501Y.V2 variant) induces conformational change greater than N501Y mutant alone, potentially resulting in an escape mutant. 2021;.

65. Wise J. Covid-19: The E484K mutation and the risks it poses. BMJ. 2021;:n359.

66. Supasa P, Zhou D, Dejnirattisai W, Liu C, Mentzer A, Ginn H et al. Reduced neutralization of SARS-CoV-2 B.1.1.7 variant by convalescent and vaccine sera. Cell. 2021;184(8):2201-2211.e7.

67. Wu K, Werner A, Moliva J, Koch M, Choi A, Stewart-Jones G et al. mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants. 2021;.

68. Zhou D, Dejnirattisai W, Supasa P, Liu C, Mentzer A, Ginn H et al. Evidence of escape of SARS-CoV-2 variant B.1.351 from natural and vaccine-induced sera. Cell. 2021;.

69. Tarke A, Sidney J, Methot N, Zhang Y, Dan J, Goodwin B et al. Negligible impact of SARS-CoV-2 variants on CD4+ and CD8+ T cell reactivity in COVID-19 exposed donors and vaccinees. 2021;.

70. Forni G, Mantovani A. COVID-19 vaccines: where we stand and challenges ahead. Cell Death & Differentiation. 2021;28(2):626-639.

71. Kumar A, Dowling W, Román R, Chaudhari A, Gurry C, Le T et al. Status Report on COVID-19 Vaccines Development. Current Infectious Disease Reports. 2021;23(6).

72. Mahase E. Covid-19: Novavax vaccine efficacy is 86% against UK variant and 60% against South African variant. BMJ. 2021;:n296.

73. Pfizer and BioNTech Initiate a Study as Part of Broad Development Plan to Evaluate COVID-19 Booster and New Vaccine Variants | pfpfizeruscom [Internet]. Pfizer.com. 2021 [cited 3 April 2021]. Available from: https://www.pfizer.com/news/pres74release/press-release-detail/pfizer-and-biontech-initiate-study-part-broad-development

74. Planas D, Bruel T, Grzelak L, Guivel-Benhassine F, Staropoli I, Porrot F et al. Sensitivity of infectious SARS-CoV-2 B.1.1.7 and B.1.351 variants to neutralizing antibodies. Nature Medicine. 2021;.

75. Moderna Announces it has Shipped Variant-Specific Vaccine Candidate, mRNA-1273.351, to NIH for Clinical Study | Moderna, Inc. [Internet]. Moderna, Inc. 2021 [cited 3 April 2021]. Available from:

https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-it-has-shipped-variant-specific-vaccine

76. Wang Z, Schmidt F, Weisblum Y, Muecksch F, Barnes C, Finkin S et al. mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. Nature. 2021;.

77. Tanne J. Covid-19: Moderna plans booster doses to counter variants. BMJ. 2021;:n232.

74. Voysey M, Clemens S, Madhi S, Weckx L, Folegatti P, Aley P et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. The Lancet. 2021;397(10269):99-111.

78. Janssen Ad26.COV2.S (COVID-19) Vaccine VRBPAC Briefing Document [Internet]. Fda.gov. 2021 [cited 25 April 2021]. Available from: https://www.fda.gov/media/146217/download

79. Novavax COVID-19 Vaccine Demonstrates 89.3% Efficacy in UK Phase 3 Trial [Internet]. Novavax.com. 2021 [cited 3 April 2021]. Available from: https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates-893-efficacy-uk-phase-3

80. Sterne J, Murthy S, Diaz J, Slutsky A, Villar J, Angus D et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19. JAMA. 2020;324(13):1330.

81. Beigel J, Tomashek K, Dodd L, Mehta A, Zingman B, Kalil A et al. Remdesivir for the Treatment of Covid-19 — Final Report. New England Journal of Medicine. 2020;383(19):1813-1826.

82. Bandoy D, Weimer B. Analysis of SARS-CoV-2 genomic epidemiology reveals disease transmission coupled to variant emergence and allelic variation. Scientific Reports. 2021;11(1).

83. Kissler S, Fauver J, Mack C, Tai C, Breban M, Watkins A et al. Densely sampled viral trajectories suggest longer duration of acute infection with B.1.1.7 variant relative to non-B.1.1.7 SARS-CoV-2. 2021;.

84. Kidd M, Richter A, Best A, Cumley N, Mirza J, Percival B et al. S-variant SARS-CoV-2 lineage B1.1.7 is associated with significantly higher viral loads in samples tested by ThermoFisher TaqPath RT-qPCR. The Journal of Infectious Diseases. 2021;.

85. Davies N, Abbott S, Barnard R, Jarvis C, Kucharski A, Munday J et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science. 2021;:eabg3055.

86. Confirmed cases of COVID-19 variants identified in UK [Internet]. GOV.UK. 2021 [cited 8 May 2021]. Available from: https://www.gov.uk/government/news/confirmed-cases-of-covid-19-variants-identified-in-uk

87. India COVID crisis: 15 countries that have imposed travel bans, supsensions. Khaleej Times 2021.

88. TGA provisionally approves Pfizer COVID-19 vaccine [Internet]. Therapeutic Goods Administration (TGA). 2021 [cited 25 April 2021]. Available from: https://www.tga.gov.au/media-release/tga-provisionally-approves-pfizer-covid-19-vaccine

89. TGA provisionally approves AstraZeneca's COVID-19 vaccine [Internet]. Therapeutic Goods Administration (TGA). 2021 [cited 25 April 2021]. Available from: https://www.tga.gov.au/media-release/tga-provisionally-approves-astrazenecas-covid-19-vaccine

90. Australian Technical Advisory Group on Immunisation (ATAGI). Clinical guidance on use of COVID-19 vaccine in Australia in 2021 Version 2.0. February 2021. Available at: https://www.health.gov.au/resources/publications/covid-19-vaccination-atagi-clinical-guidance-on-covid-19-vaccine-in-australia-in-2021

91. Australian Technical Advisory Group on Immunisation (ATAGI). Preliminary advice on general principles to guide the prioritisation of target populations in a COVID-19 vaccination program in Australia. November 2020. Available at: https://www.health.gov.au/resources/publications/atagi-preliminary-advice-on-general-principles-to-guide-the-prioritisation-of-target-populations-in-a-covid-19-vaccination-program-in-australia.

91. AstraZeneca ChAdOx1-S COVID-19 vaccine [Internet]. Therapeutic Goods Administration (TGA). 2021 [cited 25 April 2021]. Available from: https://www.tga.gov.au/alert/astrazeneca-chadox1-s-covid-19-vaccine-3