Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Anaesth Crit Care Pain Med 40 (2021) 100868

Contents lists available at ScienceDirect

Anaesthesia Critical Care & Pain Medicine

journal homepage: www.elsevier.com

Editorial

SARS-CoV-2 variants of concern: the knowns and unknowns

Keywords:
SARS-CoV-2
Mutation
Whole genome sequencing

Towards the end of 2020, a number of new severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) variants were detected through genomic surveillance programs in different regions of the world. Three in particular have subsequently been designated as key variants of concern (VOC) by the World Health Organization due to multiple mutations in the spike glycoprotein, some of which are common between the three VOCs. These are 501Y.V1 (PANGO lineage B.1.1.7) first detected in the United Kingdom [1], 501Y.V2 (B.1.351) first detected in South Africa [2], and 501Y.V3 (P.1) first detected in Japan but originating in Brazil [3]. The concern with these variants related to the potential biological significance of the constellation of mutations and the association with changing SARS-CoV-2 epidemiology. All three have spread around the world—as of the 16th of April 2021, 501Y.V1, 501Y.V2 and 501Y.V3 have been reported in 110, 70 and 36 countries respectively [4]. Since detection of these variants, the scientific community has worked at speed to understand the significance of these variants and their potential impact on the pandemic. So where do we stand with our understanding, and what are the key clinical and public health implications?

Evidence from a number of different analyses suggest an increase in transmissibility of 501Y.V1 in the UK in the region of 40–80% [5,6]. Preliminary estimates from mathematical models are consistent with similar increases in transmissibility for 501Y.V2 and 501Y.V3 [7,8]. The exact mechanism for the increased transmissibility of 501Y.V1/B.1.1.7 is not yet clear, although modelling has suggested this could be most likely attributable to an increased risk of virus transmission per contact [6]. This may be a consequence of the N501Y mutation in the spike receptor-binding domain (RBD), common to all three VOCs, which enhances the binding affinity of spike to the human angiotensin-converting enzyme 2 (hACE2) receptor [9], but could also be linked to the P681H mutation adjacent to the S1/S2 furin cleavage site [10]. Some initial data suggested that infection with 501Y.V1 may be associated with higher viral load [11,12], but this has not been a consistent finding across different analyses and early data may have been confounded by underlying epidemic dynamics [13]. It could also be that the virus can more easily establish infection upon exposure (with a lower infectious dose) but there are no empirical data at present to support that. While we await further research to identify the mechanism for the increased transmissibility, it's important to remember that the underlying physics of SARS-CoV-2 transmission remain the same, and existing transmission prevention measures remain appropriate.

The mechanism for the transmission advantage of 501Y.V2 and 501Y.V3 may be more complicated, as the evidence suggests that both have the ability to evade neutralising antibodies (NAbs) elicited by prior infection, primarily as a result of mutations in the RBD at positions E484 and K417 and, particularly in the case of 501Y.V2, mutations in the N-terminal domain of spike [14–16]. Both these variants emerged in locations that had high attack rates in the first wave of the epidemic, which may have created the conditions for the selection of these variants, and the capacity to cause re-infection then may have contributed to the transmissibility of these variants. Models have suggested that these two variants could evade 20% or more of population immunity elicited by previously circulating lineages [7,8]. However, determining the true extent of re-infections has been difficult, particularly given the pressure that public health systems have been under and the likely under-detection of asymptomatic or mild infections. There was some preliminary clinical data from South Africa, from the placebo arm of a vaccine trial, that prior infection seemed to offer no protection against re-infection (at a time when 501Y.V2 was the dominant circulating variant) [17], but updated results suggest this may not be so clear cut [18]. Better understanding of the rate of re-infection with these variants and the clinical features of re-infection cases is still required.

In terms of severity of disease, there is now consistent evidence from the United Kingdom that 501Y.V1 is associated with an increased risk of hospitalisation and death [19–22]. These studies provide similar estimates that mortality may be increased by around 60%. The evidence suggests that this increased risk is consistent across age groups, and that there is no disproportionate effect in any age group [20,21]. The evidence around severity associated with 501Y.V2 and 501Y.V3 is still emerging and is less clear cut. Understanding whether increased mortality is due to a biological effect of the variant or related to the pressures on the health system from the intensity of transmission is particularly challenging. One analysis from South Africa estimated that mortality in the second wave was around 20% higher than in the first wave, even after adjusting for the intensity of admissions and other factors, which could be consistent with an effect of

https://doi.org/10.1016/j.accpm.2021.100868

501Y.V2 [23]. Modelling from Brazil suggests a 20–90% higher risk of mortality following the emergence of P.1, but the direct effect of the variant of mortality again cannot be distinguished from a broader effect of a rapid increase in cases and health system pressure [8].

What impact do these variants have on diagnostics, therapeutics and vaccines? In terms of diagnostics, all of the three VOCs are still detectable by polymerase chain reaction (PCR) assays and rapid antigen tests. 501Y.V1 does cause S-gene target failure, which affects one target of some PCR assays, but as all assays detect multiple gene targets, this does not affect the performance of the assay. The main impact on therapeutics is likely to be for monoclonal antibodies (mAbs) and other immune-based therapies such as convalescent plasma. 501Y.V2 and 501Y.V3 demonstrate significant resistance to single antibodies such as casirivimab (REGN10933) and bamlanivimab (LY-CoV555), although may still be susceptible to mAb cocktails such as REGN-CoV2 [24]. Understanding the effect on vaccines has been complicated by different trial designs, study populations, efficacy endpoints, and timing in relation to the emergence of VOCs. There is evidence to suggest that 501Y.V2 does affect the efficacy of certain vaccines [17,25], although most of the evidence is around mild to moderate symptomatic disease. There is reason to believe that protection against severe diseases may be less attenuated, and preliminary data from some vaccine trials to support this [18,26], but this remains a key question for ongoing clinical trials and for effectiveness analyses embedded in national roll-out programs.

As we surpass 3 million global deaths from COVID-19, the emergence and spread of variants associated with increased transmissibility, increased severity of disease and capacity for immune evasion has provided additional challenges for the global public health response. High levels of transmission in many parts of the world and inequitable vaccine distribution will unfortunately heighten the risk of further virus evolution with unknown consequences. The fundamentals of the public health response have not changed—but we must act with increasing urgency and global solidarity for that response to be effective.

Competing interests

The author has no competing interests to declare

References

[1] Rambaut A, Loman N, Pybus O, Barclay W, Barrett J, Carabelli A, et al. Preliminary genomic characterisation of an emergent SARS-CoV-2 lineage in the UK defined by a novel set of spike mutations;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; 2020, Published. Accessed.

[2] 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. medRxiv 2020. 2020.2012.2021.20248640.

[3] Faria NR, Claro IM, Candido D, Moyses Franco LA, Andrade PS, Coletti TM, et al. Genomic characterisation of an emergent SARS-CoV-2 lineage in Manaus: preliminary findings;https://virological.org/t/genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-manaus-preliminary-findings/586; 2021, Published. Accessed.

[4] Rambaut A, Holmes EC, O'Toole A, Hill V, McCrone JT, Ruis C, et al. A dynamic nomenclature proposal for SARS-CoV-2 lineages to assist genomic epidemiology. Nat Microbiol 2020;5(11):1403–7.

[5] Volz E, Mishra S, Chand M, Barrett JC, Johnson R, Geidelberg L. Transmission of SARS-CoV-2 lineage B.1.1.7 in England: insights from linking epidemiological and genetic data. medRxiv 2021. 2020.2012.2030.20249034.

[6] Davies N, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, et al. Estimated transmissibility and severity of novel SARS-CoV-2 variant of concern 202012/01 in England. CMMID Preprint 2021.

[7] Pearson CAB, Russell TW, Davies N, Kucharski AJ, CMMID COVID-19 working group, Edmunds WJ, et al. Estimates of severity and transmissibility of novel South Africa SARS-CoV-2 variant 501Y.V2;https://cmmid.github.io/topics/covid19/sa-novel-variant.html2021.

[8] Faria NR, Mellan TA, Whittaker C, Claro IM, Candido DdS, Mishra S, et al. Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil. Science 2021. eabh2644.

[9] Starr TN, Greaney AJ, Hilton SK, Crawford KHD, Navarro MJ, Bowen JE, et al. Deep mutational scanning of SARS-CoV-2 receptor binding domain reveals constraints on folding and ACE2 binding. Cell 2020;182(5):1295–310. e1220.

[10] Brown JC, Goldhill DH, Zhou J, Peacock TP, Frise R, Goonawardane N, et al. Increased transmission of SARS-CoV-2 lineage B.1.1.7 (VOC 2020212/01) is not accounted for by a replicative advantage in primary airway cells or antibody escape. bioRxiv 2021. 2021.2002.2024.432576.

[11] Golubchik T, Lythgoe KA, Hall M, Ferretti L, Fryer HR, MacIntyre-Cockett G, et al. Early analysis of a potential link between viral load and the N501Y mutation in the SARS-COV-2 spike protein. medRxiv 2021. 2021.2001.2012.20249080.

[12] Kidd M, Richter A, Best A, Cumley N, Mirza J, Percival B, et al. S-variant SARS-CoV-2 is associated with significantly higher viral loads in samples tested by ThermoFisher TaqPath RT-QPCR. medRxiv 2020. 2020.2012.2024.20248834.

[13] Walker AS, Vihta K-D, Gethings O, Pritchard E, Jones J, House T, et al. Increased infections, but not viral burden, with a new SARS-CoV-2 variant. medRxiv 2021. 2021.2001.2013.21249721.

[14] Cele S, Gazy I, Jackson L, Hwa S-H, Tegally H, Lustig G, et al. Escape of SARS-CoV-2 501Y.V2 from neutralization by convalescent plasma. Nature 2021. http://dx.doi.org/10.1038/s41586-021-03471-w.

[15] Wibmer CK, Ayres F, Hermanus T, Madzivhandila M, Kgagudi P, Lambson BE, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. Nat Med 2021;27:622–5.

[16] Dejnirattisai W, Zhou D, Supasa P, Liu C, Mentzer AJ, Ginn HM, et al. Antibody evasion by the P.1 strain of SARS-CoV-2. Cell)2021;(Mar 30). http://dx.doi.org/10.1016/j.cell.2021.03.055. S0092-8674(21)00428-1.

[17] Shinde V, Bhikha S, Hoosain Z, Archary M, Bhorat Q, Fairlie L, et al. Preliminary efficacy of the NVX-CoV2373 Covid-19 vaccine against the B.1.351 variant. medRxiv 2021. 2021.2002.2025.21252477.

[18] Novavax I. Novavax confirms high levels of efficacy against original and variant COVID-19 strains in United Kingdom and South Africa trials;https://ir.novavaxI.com/news-releases/news-release-details/novavax-confirms-high-levels-efficacy-against-original-and-0; 2021, Published. Accessed 12 April 2021.

[19] Challen R, Brooks-Pollock E, Read JM, 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;372:n579.

[20] Davies NG, Jarvis CI, Group CC-W, Edmunds WJ, Jewell NP, Diaz-Ordaz K, et al. Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7. Nature 2021. http://dx.doi.org/10.1038/s41586-021-03426-1.

[21] Grint DJ, Wing K, Williamson E, McDonald HI, 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. Euro Surveill 2021;26(11):2100256.

[22] Patone M, Thomas K, Hatch R, Tan PS, Coupland C, Liao W, et al. Analysis of severe outcomes associated with the SARS-CoV-2 Variant of Concern 202012/01 in England using ICNARC Case Mix Programme and QResearch databases. medRxiv 2021. 2021.2003.2011.21253364.

[23] Jassat W, Mudara C, Ozougwu L, Tempia S, Blumberg L, Davies M-A, et al. Increased mortality among individuals hospitalised with COVID-19 during the second wave in South Africa. medRxiv 2021. 2021.2003.2009.21253184.

[24] Hoffmann M, Arora P, Groß R, Seidel A, Hörnich BF, Hahn AS, et al. SARS-CoV-2 variants B.1.351 and P.1 escape from neutralizing antibodies. Cell)2021;(Mar 20). http://dx.doi.org/10.1016/j.cell.2021.03.036.

[25] Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 vaccine against the B.1.351 variant. N Engl J Med)2021;(Mar 16). http://dx.doi.org/10.1056/NEJMoa2102214.

[26] Food and Drug Administration. FDA briefing document: janssen Ad26.COV2.S vaccine for the prevention of COVID-19;https://www.fda.gov/media/146217/download; 2021, Published. Accessed 12 April 2021.

Richard J. Lessells[a,b,*]

[a]*KwaZulu-Natal Research Innovation and Sequencing Platform, School of Laboratory Medicine & Medical Sciences, University of KwaZulu-Natal, Durban, South Africa*

[b]*Centre for the AIDS Programme of Research in South Africa (CAPRISA), Durban, South Africa*

[*]Corresponding author at: KwaZulu-Natal Research Innovation & Sequencing Platform, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, 719 Umbilo Road, Durban, 4001 South Africa

E-mail address: LessellsR@ukzn.ac.za

Available online 22 April 2021