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## Paucity and discordance of neutralising antibody responses to SARS-CoV-2 VOCs in vaccinated immunodeficient patients and health-care workers in the UK



As of June, 2021, the UK population is only partly vaccinated against COVID-19, with many people having received just one vaccination dose (either BNT162b2 [Pfizer-BioNTech]) or ChAdOx1 nCoV-19 [AZD1222; Oxford-AstraZeneca]). Tracking the spread of SARS-CoV-2 Variants of Concern (VOCs) remains important for understanding the levels of vaccine-induced immunity and for identifying the emergence of vaccine escape variants. The immune correlates of protection to SARS-CoV-2 and COVID-19 established in phase 3 clinical trials following two doses of vaccine was the titre of neutralising antibodies (NAbs) to SARS-CoV-2 in study groups, before the VOCs emerged.<sup>1</sup> Vaccination programmes are leading to promising reductions in disease severity and mortality in vaccinated populations. However, the combined situation of ongoing transmission within communities, including in some vaccine recipients, alongside newly arising VOCs, continues to pose a serious threat to public health and the efficacy of these vaccines. As of Jan 11, 2021, in the UK, the interval between the first and second dose of vaccination was extended to 12 weeks. This extension achieved the aim of maximising population coverage by immunising the greatest possible number of individuals to prevent disease and hospital admissions. Encouragingly, a growing number of studies have reported a marked reduction in the number of individuals with moderate-to-severe clinical symptoms and a substantial decline in the number of hospitalised patients with COVID-19 in the UK, underscoring the success of this strategy.<sup>2,3</sup>

Many countries, both in the early and advanced stages of their vaccination campaigns, are facing new cases of infection with VOCs that have acquired mutations facilitating increased transmission and evasion of pre-existing immunity. These VOCs might cause increased morbidity and mortality.<sup>4,6</sup> The B.1.1.7 (also known as Alpha) VOC has been reported in more than 114 countries, the B.1.351 (also known as Beta) VOC in more than 68 countries, and the P.1 (also known as Gamma) VOC in more than 37 countries, and new cases continue to be reported worldwide. Additional VOCs, such as B.1.617.2,

are likely to continue to emerge and threaten our ongoing COVID-19 vaccination programmes.

Early reports in 2021, suggest that both single-dose and two-dose vaccination regimens are showing gaps in protection.<sup>7,8</sup> In South Africa, a two-dose regimen of the ChAdOx1 nCoV-19 vaccine did not show protection against mild-to-moderate COVID-19 after infection with the B.1.351 variant.<sup>9</sup> Additionally, a report of individuals immunised with BNT162b2 in Qatar found that vaccine effectiveness was 14.9% lower against the B.1.351 VOC than the B.1.1.7 VOC, and indicated a notable number of breakthrough infections.<sup>10</sup> Similar concerns were also noted in a case-cohort study in Israel, which found disproportionately high infection rates with B.1.351 in fully vaccinated compared with unvaccinated individuals.<sup>11</sup> These findings suggest that, despite aggressive immunisation programmes, the presence of circulating VOCs represent a serious concern for the emergence of vaccine escape variants that are either more transmissible or virulent, or both, than the vaccine strain or are able to escape vaccine-induced neutralising antibodies.

Understanding the threshold levels of protective immunity against VOCs in specific risk groups and in the general population during ongoing transmission is important for informing and refocusing immunisation strategies. Providing data on the immune correlates of protection in clinically vulnerable groups is needed to inform the development of effective next-generation, variant-resistant vaccines. The UK has more than 3.5 million people on the Shielded Patient List, which comprises those who are clinically extremely vulnerable and often prone to persistent infections, including patients with cancer and transplant recipients. Shielding patients have a greater risk of morbidity and mortality than the general population, and those with the inability to clear infections, such as immunodeficient patients, might themselves amplify new viral variants.<sup>12</sup>

We did a single-centre, cross-sectional study of immunodeficient outpatients and health-care workers employed at the same tertiary critical care National Health Service (NHS) Trust to understand the spectrum

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of immunity to the B.1 vaccine strain compared with three major VOCs after vaccination with one dose of either BNT162b2 or ChAdOx1 nCoV-19. To establish the current level of immunity to VOCs in a healthy population, we compared NABs induced by either BNT162b2 or ChAdOx1 nCoV-19 in 142 vaccinated health-care workers. In addition, we screened 107 outpatients with a range of immunodeficiencies for the presence of SARS-CoV-2 binding antibodies. This group included patients with both primary and secondary immunodeficiencies, such as common variable immunodeficiency syndrome and specific polysaccharide antibody deficiency syndrome. We assessed the ability of serum antibodies from vaccinated health-care workers and immunodeficient outpatients to neutralise the B.1 vaccine strain, as well as the three VOCs, B.1.1.7, B.1.351, and P.1. We used a validated SARS-CoV-2 pseudovirus neutralisation assay standardised against WHO reference standards (the National Institute for Biological Standards and Control) to calculate NAb titres.<sup>13</sup>

Our results revealed either undetectable antibodies or low NAb titres in immunodeficient outpatients, with only four (5%) of 80 showing detectable neutralisation of B.1.1.7 and two (3%) showing detectable neutralisation of B.1.351 (appendix). Although several vaccinated health-care workers without previous SARS-CoV-2 exposure showed a range of NAb titres, these titres were markedly lower than in health-care workers with previous SARS-CoV-2 exposure (appendix). Of the health-care workers without previous SARS-CoV-2 exposure, 41 (45%) of 94 had detectable NABs to B.1, 35 (37%) of 96 to B.1.1.7, nine (9%) of 94 to B.1.351, and nine (10%) of 96 to P.1. By contrast, with the exception of four individuals with no detectable neutralising antibodies, vaccinated health-care workers with previous SARS-CoV-2 exposure had marked NAB responses against B.1, with an IQR of 1200–3700 international units per mL, or 1900–5900 concentration needed to achieve 50% inhibition (IC<sub>50</sub>). Notably, health-care workers with previous SARS-CoV-2 exposure showed a significant increase in NAB titres to all four strains, including the three VOCs, post-vaccination compared with pre-vaccination (all  $p < 0.0001$ ; appendix). This observation underscores the importance of vaccination, even in populations previously exposed to SARS-CoV-2. Additionally, this result supports that a second dose of vaccination, in individuals without previous exposure to SARS-CoV-2, could similarly boost immunity to greater

protective levels, such as after both natural infection and vaccination.

Furthermore, NAb titres to B.1 were highest in vaccinated health-care workers with a history of previous SARS-CoV-2 infection, with no significant difference between the responses induced by BNT162b2 or ChAdOx1 nCoV-19 vaccines ( $p = 0.82$ ; appendix). Notably, neutralisation of VOCs harbouring the E484K mutation (B.1.351 and P.1) was consistently lower than the B.1 vaccine strain in health-care workers with no evidence of previous SARS-CoV-2 infection ( $p < 0.0001$  for both strains; appendix). The key finding was the large spectrum of NAB titres, and the overall low titres of NABs, especially to B.1.351 and P.1, in health-care workers vaccinated with a single-dose, and particularly in those without previous SARS-CoV-2 exposure. Furthermore, with the exception of one immunodeficient patient with a history of SARS-CoV-2 infection, average NAb titres were five-fold lower in immunodeficient outpatients than in health-care workers (appendix), and far lower than the NAb titres associated with protection against viruses circulating early in the pandemic in phase 3 clinical trials.

These data not only underscore the risk of clinically vulnerable patients to infection with SARS-CoV-2, but also the risk of onward transmission of VOCs by individual health-care workers with no or low NABs. Our results emphasise the importance of extended surveillance of the NAb threshold titres associated with protection from infection with circulating VOCs or severe disease caused by VOCs. Larger population studies will be needed to determine the protective NAb threshold titres across representative cohorts of the UK population. These analyses will help to identify risk groups for follow-up immunisations with current vaccines or variant-specific successors. Virus NAb threshold studies will inform targeted vaccination in communities with outbreaks, and the strategic or targeted use of variant-specific vaccines in populations with the highest risk. We suggest that these studies also include health-care workers with low NAB titres and clinically vulnerable immunodeficient outpatients. Understanding the existing levels of immunity to the VOCs in the overall population will inform containment strategies in communities at risk of local VOC outbreaks. Additionally, understanding the levels of immunity in both the immunocompromised and general populations will facilitate the development of public health strategies to contain and prevent novel

See Online for appendix

variants of interest or the emergence of vaccine-resistant variants that could threaten COVID-19 immunisation programmes.

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Angalee Nadesalingam, Diego Cantoni, David A Wells, Ernest T Aguinam, Matteo Ferrari, Peter Smith, Andrew Chan, George Carnell, Luis Ohlendorf, Sebastian Einhauser, Charlotte George, Ralf Wagner, Nigel Temperton, Javier Castillo-Olivares, Helen Baxendale, \*Jonathan L Heeney, on behalf of the HICC consortium  
jlh66@cam.ac.uk

Laboratory of Viral Zoonotics, University of Cambridge, Cambridge CB3 0ES, UK (AN, DAW, ETA, MF, PS, AC, GC, LO, CG, JC-O, JLH); Viral Pseudotype Unit, Medway School of Pharmacy, University of Kent, Medway, UK (DC, NT); Institute of Clinical Microbiology and Hygiene (RW) and Institute of Medical Microbiology and Hygiene, University of Regensburg, Regensburg, Germany (SE, RW); Clinical Immunology Department, Royal Papworth NHS Foundation Trust, Cambridge, UK (HB).

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