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Neutralising antibody activity against SARS-CoV-2 VOCs B.1.617.2 and B.1.351 by BNT162b2 vaccination

The SARS-CoV-2 B.1.617.2 Variant of Concern (VOC), first detected in India, is now dominant in the UK, having rapidly[1] displaced the B.1.1.7 strain[2] that emerged in the UK with the second COVID-19 wave in late 2020. The efficacy of currently licensed COVID-19 vaccines against B.1.617.2 is unknown; although it possesses 12 mutations in its spike protein relative to the wildtype SARS-CoV-2 first detected in Wuhan, China, in December, 2019, B.1.617.2 lacks mutations at amino acid positions 501 or 484 in its ACE2 receptor-binding domain, commonly associated with VOCs (appendix p 2) or escape from neutralising antibodies (NAbs).

To determine vaccine-induced NAb escape by B.1.617.2 and compare activity to previous strains with existing estimates for population-based vaccine efficacy, we carried out an initial analysis of the Legacy study, established in January, 2021, by University College London Hospital and the Francis Crick Institute in London, UK, to track serological responses to vaccination in prospectively recruited staff volunteers (appendix p 6). A detailed description of the methods, including the clinical cohort, virus culture conditions, genetic sequencing, and neutralisation assays, and the statistical analysis are available in the appendix (p 8). The Legacy study was approved by London Camden and Kings Cross Health Research Authority Research and Ethics committee (IRAS number 286469) and sponsored by University College London.

Using a high-throughput live-virus SARS-CoV-2 neutralisation assay (performance data are shown in the appendix p 3), we determined NAb titres (NAbTs) in 250 participants (median age 42 years [IQR 33–52]) after either one dose (n=149; median time after first dose=30 days [IQR 23–38]) or two doses (n=159; median time after second dose=28 days [IQR 21–37]) of BNT162b2 (Pfizer–BioNTech) against five SARS-CoV-2 strains: a strain with the original spike sequence (Wild-type); a strain with an Asp614Gly mutation isolated during the first wave of infection in the UK, in 2020 (D614G); and VOCs B.1.617.2, B.1.351 (first detected in South Africa in late 2020), and B.1.1.7.

Two doses of BNT162b2 elicited ELISA-detected anti-Wild-type spike antibodies in all participants, and NAb activity against all strains, including the three VOCs tested, in all except six (3%) and nine (5%) of 159 participants who lacked NAb activity against B.1.617.2 and B.1.351, respectively (appendix p 2). NAbTs of sera correlated well between Wild-type and variants (appendix p 2; R_S>0·82, p<2×10^{-16}), as well as between VOCs (B.1.617.2 *vs* B.1.351: R_S=0·85, p<2×10^{-16}). However, NAbTs were 5·8-fold reduced against B.1.617.2 relative to Wild-type (95% CI 5·0–6·9), significantly more reduced than against B.1.1.7 (2·6-fold *vs* Wild-type, 95% CI 2·2–3·1), and on a similar order to the reduction observed against B.1.351 (4·9-fold *vs* Wild-type, 95% CI 4·2–5·7).

Notably, across all variants, increased age significantly correlated with reduced NAbT (appendix p 2; –0·33<R_S<–0·27; $2\cdot2\times10^{-5}$<p<$5\cdot6\times10^{-4}$), whereas no correlation was observed for sex or body-mass index (appendix p 4). NAbTs reduced over time after administration of the second dose of BNT162b2: participants (n=14) who attended an additional study visit 8–16 weeks after their second BNT162b2 dose showed significantly reduced NAbTs against all variants (appendix p 2; 0·0002<p<0·0134). While the final NAbTs against Wild-type, D614G, and B.1.1.7 remained within the quantitative range of our assay (IC_{50}>40), two participants' NAbTs against VOCs B.1.617.2 and B.1.351 dropped below 40 on their later study visit about 3 months after their second BNT162b2 dose.

To maximise population coverage, the UK extended the interval between the two BNT162b2 doses. Although this might have had a limited impact of protection against parental SARS-CoV-2 strains or the B.1.1.7 variant, the potential impact on protection from other VOCs is poorly understood. We found that neutralisation of VOCs was markedly different after only one dose of BNT162b2 (appendix p 2): although 177 (95%) of 186 participants tested positive for anti-spike antibodies by ELISA and mounted a detectable NAb response against Wild-type (median IC_{50}=68 [IQR 42–140]) and D614G (median IC_{50}=71 [IQR 46–111]), median NAbTs against all VOCs were below the quantitative limit of detection. Stratification of NAbTs into three groups (IC_{50} low [<40], medium [40–256], high [>256]) and assessment of the significance of the shift in their distribution relative to Wild-type by ordered logistical regression was more informative (appendix p 2). Whereas only 39 (21%) of 186 samples had low NAbTs against Wild-type, this proportion rose to 50% against B.1.1.7 (p=$1\cdot7\times10^{-6}$) and further to 75% against B.1.351 (p<3×10^{-16}) and 68% against B.1.617.2 (p<5×10^{-16}). Notably, the downwards shift in titres was also significant when compared to B.1.1.7 for B.1.351 (p=$3\cdot7\times10^{-4}$) and B.1.617.2 (p=$1\cdot2\times10^{-5}$), confirming reduced NAb activity against B.1.617.2 relative to the present B.1.1.7 strain after one vaccine dose. Notably, participants with low NAbTs tend to be older than those who produced medium or high responses (appendix p 2), and logistical regression analysis suggests age is a significant factor in reduced NAbTs, independent of strain in our samples (appendix p 7; p=0·006), following a single dose of BNT162b2.

These data, together with epidemiological data of B.1.617.2 growth, raise the possibility that

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See **Online** for appendix

this VOC presents a dual challenge of reduced vaccine efficacy akin to the B.1.351 VOC, and increased transmissibility beyond the B.1.1.7 VOC. The impact of such a change is challenging to predict: it remains difficult to assess precisely to what extent the reduction in NAbTs we observe will impact vaccine efficacy and increase disease severity in a vaccinated population, especially given the multiple factors that contribute to this process, such as long-lived humoral immunity.[3]

Nevertheless, a recent analysis of available NAb and vaccine efficacy data[4] has attempted to establish correlates of protection against earlier strains of SARS-CoV-2 and, in the context of this model, our data suggest that most participants that received two doses of BNT162b2 would be protected against B.1.617.2 infection and associated disease—consistent with preliminary data[5] inferring vaccine efficacy against B.1.617.2 in the UK based on rates of S-gene target failure during quantitative RT-PCR testing. With increasing case numbers and the proportion of sequencing-confirmed B.1.617.2 cases, coupled with wider availability of WHO International Standards and Reference Panels to standardise NAbTs across laboratories, we expect that improved vaccine efficacy estimates will allow more precise modelling of correlates of protection in the coming months.

However, it is worth highlighting that in the case of two BNT162b2 doses, our cohort of generally healthy, relatively young, recently vaccinated, and mostly single-ethnicity individuals presents a reasonable best-case scenario for NAb activity against SARS-CoV-2 variants. Indeed, regardless of the absolute vaccine efficacy requirements, peak NAbTs are significantly reduced against VOCs B.1.617.2 and B.1.351 compared with NAbTs against earlier variants, and consequently, vaccine efficacy on an individual or sub-population level will become more sensitive to reductions in NAbTs occurring as a result of factors aside from virus strain (appendix p 5), providing a basis to understand observed vaccine efficacy failure in other combinations of vaccine and target population.[6]

In the case of single-dose recipients, our data show that NAbTs are significantly lower against B.1.617.2 and B.1.351 VOCs relative to B.1.1.7, implying that although a single dose might still afford considerably more protection than no vaccination, single-dose recipients are likely to be less protected against these SARS-CoV-2 variants. These data, therefore, suggest that the benefits of delaying the second dose, in terms of wider population coverage and increased individual NAbTs after the second dose,[7] must now be weighed against decreased efficacy in the short-term, in the context of the spread of B.1.617.2. Worldwide, our data highlight the ongoing need to increase vaccine supply to allow all countries to extend second-dose protection as quickly as possible.

In the longer term, we note that both increased age and time since the second dose of BNT162b2 significantly correlate with decreased NAb activity against B.1.617.2 and B.1.351—both of which are also characteristic of the population in the UK at highest risk of severe COVID-19 (ie, older and vaccinated earlier), independent of other existing factors such as compromised immune status or comorbidity, or geographic-specific responses to vaccination.

Consequently, further booster immunisations of Joint Committee on Vaccination and Immunisation Priority Groups in the UK and similar groups in other counties, as well as others with lower vaccine-induced NAbTs than the cohort of BNT162b2 recipients studied here (ideally with modified vaccines that induce NAbs that broadly neutralise emerging VOCs) are more likely to be required to maintain the highest levels of NAbs in regions where B.1.617.2 or other equally NAb-resistant strains become prevalent.

For **data and R code on GitHub** see https://github.com/davidlvb/Crick-UCLH-Legacy-VOCs-2021-05

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Divergent vaccination policies could fuel mistrust and hesitancy

With reports of a possible risk of rare blood clots in people receiving AstraZeneca's COVID-19 vaccine (Vaxzevria),[1] concerns have risen about its use in younger adults. As of May 26, 2021, country stances on the use of this vaccine generally fall into one of five response types. Why countries continue to respond so differently in response to adverse events with this vaccine is unclear, but we are concerned that divergent vaccination policies could fuel mistrust and hesitancy around immunisation.

One response is to warn of potential risks, but otherwise no set restrictions on use of Vaxzevria. The European Medicines Agency[2] and WHO[3] have issued warnings about the rare possibility of blood clots within 2 weeks of vaccination. While more data are being collected, the agencies encourage the continuation of the vaccine in all adults since current evidence suggests the benefits outweigh the risks. Many countries, including Poland, Mexico, and Brazil are following this guidance.

A second response is to not permit use. Denmark has decided to remove Vaxzevria from its vaccination programmes, whereas in Norway, further administration of the vaccine has been paused.

A third response is to advise that only older adults receive Vaxzevria; however, the age cutoff varies. In the Netherlands, Portugal, Singapore, and Spain, the vaccine is given to adults aged 60 years and older, whereas in Belgium it is given to adults aged 55 years and older, and in Australia to those aged 50 years and older.

A fourth response is to encourage younger adults to accept a different type of COVID-19 vaccine if possible. Greece is encouraging adults younger than 30 years to take alternative vaccines to Vaxzevria. Similar recommendations exist in the UK and Pakistan for those younger than 40 years (in the UK, this age cutoff was recently increased from 30 years).[2]

A fifth response is to use a mix-and-match approach for younger adults who have already received one dose of Vaxzevria. France and Germany have limited use of Vaxzevria to older adults and announced that those younger than 55 years (in France) and 60 years (in Germany) who received one dose of Vaxzevria should be given the vaccine produced by Pfizer–BioNTech or Moderna for their second dose.

The divergent responses might reflect risk tolerance, the availability of alternative vaccinations, and whether safety calculations consider the risk of the vaccine and of the virus in conjunction. Although some variation could be justified by the underlying risk–benefit calculations because of a country's age profile and its COVID-19 infection rates, we are concerned that public trust in vaccines will wane and exacerbate existing hesitancy because of these divergences. In Europe, willingness to take the vaccine has already decreased after the temporary suspensions of Vaxzevria: between February and March, 2021, one survey found that respondents who believed the vaccine was unsafe increased by 18 percentage points in France (from 43% to 61%) and by 15 percentage points in Germany (from 40% to 55%).[3,4]

Coordinated and strengthened risk communication efforts between regulatory agencies and policy makers could help improve the situation. Governments should stress the safety and importance of vaccines and agree on common lines to explain adverse events that have occurred with the Vaxzevria vaccine and similar problems that are emerging with other non-replicating viral vector COVID-19 vaccines. Communication from experts to the public should be transparent, simple, and consistent. Statements about the risks associated with the vaccines should offer perspective, acknowledging the risks associated with COVID-19 and other common medications and substances, demonstrating how extremely rare these risks are, and referring to current evidence that the authorised vaccines are safe, effective, and key to ending the pandemic.

We declare no competing interests.

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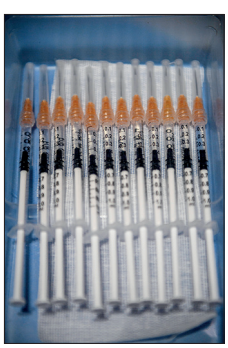

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