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AZD1222-induced neutralising antibody activity against SARS-CoV-2 Delta VOC

The SARS-CoV-2 B.1.617.2 Delta variant of concern (VOC) continues to drive a sharp increase in COVID-19 cases in the UK, with a current doubling time of 3·5–16 days,[1] consistent with previous pandemic waves during 2020–21, and a sustained increase in the reproduction number (R) to 1·2–1·4.[2] Daily hospital admissions and the number of patients requiring mechanical ventilation are now increasing in both England and Scotland, despite the ongoing roll-out of widespread vaccination in the UK.[1]

The ChAdOx1 nCoV-19 (AZD1222, Oxford–AstraZeneca) vaccine forms the core of the UK's vaccination programme and the global COVAXX programme. To determine B.1.617.2 sensitivity to AZD1222-induced neutralising antibodies (NAbs) and to compare this to our previous measurements of NAbs induced by BNT162b2 (Pfizer–BioNTech),[3] we carried out a second initial analysis of Legacy study participants vaccinated with AZD1222. Legacy was initiated in early 2021 by University College London Hospitals and the Francis Crick Institute in London, UK, to track serological responses to vaccination during the national COVID-19 vaccination programme in prospectively recruited healthy staff volunteers. A description of the methods and clinical cohort are available in the appendix. The Legacy study was approved by the London Camden and Kings Cross Health Research Authority Research and Ethics committee (IRAS number 286469) and is sponsored by University College London Hospitals.

Using a high-throughput live-virus SARS-CoV-2 neutralisation assay, we determined NAb titres (NAbTs) against five SARS-CoV-2 strains in 106 participants (median age 34 years, IQR 29–42) after either one dose of AZD1222 (n=50, median time after first dose 41 days [IQR 30–51]) or two doses of AZD1222 (n=63, median time after second dose 31 days [IQR 19·5–46·0]; appendix p 7). The median interval between doses was 63 days (IQR 62·0–69·5). Consistent with our previous findings,[3] we included a strain with the original spike sequence (Wildtype), a strain with an Asp614Gly mutation isolated during the first wave of infection in the UK, in 2020 (D614G), and VOCs B.1.1.7 (Alpha, first detected in Kent, England), B.1.351 (Beta, first detected in South Africa), and B.1.617.2 (Delta, first detected in India).

Two doses of AZD1222 generated NAb activity against the Wildtype strain bearing a spike identical to that encoded by the vaccine in all participants (median NAbT IC_{50}=419), with a 2·1–fold (95% CI 2·0–2·2) reduction in median NAbT relative to two doses of BNT162b2 (appendix p 2). Moreover, median NAbTs against all SARS-CoV-2 variants were further reduced relative to BNT162b2: 2·4-fold (95% CI 2·3–2·6) against D614G, 2·4-fold against B.1.1.7 (2·2–2·5), 2·5-fold (1·3–2·8) against B.1.351, and 2·5-fold (1·4–2·7) against B.1.617.2. Given the low responses against the latter two VOCs, we found that stratification of NAbTs into three groups (IC_{50} low [<40], medium [40–256], high [>256]) was most illustrative: whereas nearly all participants had a quantifiable NAbT against the D614G and B.1.1.7 variants (55 [87%] of 63 [95% CI 76–94%]; appendix p 2), significantly fewer participants had quantifiable NAbTs against B.1.351 and B.1.617.2 VOCs after two doses of AZD1222 (38 [60%] of 63 [95% CI 47–72%] against B.1.351; and 39 [62%] of 63 [49–74%] against B.1.617.2), relative to the former two variants (χ^2 test p<0·0011). This contrasts strongly with our previous results, which showed that more than 95% of participants had quantifiable NAbTs against B.1.351 and B.1.617.2 after two doses of BNT162b2 (189 [97%] of 195 against B.1.351; and 186 [95%] of 195 against B.1.617.2). Analysis of these data by ordered logistic regression confirmed vaccine type was associated with decreased NAbTs, independent of SARS-CoV-2 strain, in two-dose vaccine recipients (p=0·0017; appendix p 4).

A single dose of AZD1222 generated a broad range of NAb activity against Wildtype SARS-CoV-2 (appendix p 2). Given reports of enhanced NAb responses to VOCs B.1.1.7 and B.1.351 after a single dose of mRNA vaccines in individuals with previous SARS-CoV-2 infection,[4,5] in the absence of concrete evidence of previous infection, we stratified NAbT by whether participants reported prior COVID-19 symptoms and found markedly different responses. After a single AZD1222 dose, participants with prior COVID-19 symptoms (16 [32%] of 50) had significantly higher NAbTs against all strains than those without prior COVID symptoms ($5{\cdot}1\times10^{-5}\leq p\leq 3{\cdot}1\times10^{-4}$). Since many responses fell outside of the quantitative limit of detection, stratification of NAbTs was again informative. Whereas participants without prior COVID-19 symptoms mostly had quantifiable NAbTs against Wildtype (31 [91%] of 34 [95% CI 75–98%]), significantly more NAb responses against VOCs were below the limit of detection: 22 [65%] of 34 [95% CI 46–80%]) against B.1.1.7; 30 [88%] of 34 [72–96%]) against B.1.351; and 29 [85%] of 34 [68–94%]) against B.1.617.2 ($2{\cdot}8\times10^{-10}\leq p\leq 6{\cdot}0\times10^{-6}$; appendix p 2). Analysis by ordered logistic regression confirmed that a previous history of COVID-19 symptoms was associated with increased NAbTs, independent of SARS-CoV-2 strain, in single-dose AZD1222 recipients (p=0.0016; appendix p 4).

These data, together with our previous findings,[3] reveal that AZD1222 recipients have lower NAbTs than BNT162b2 recipients against SARS-CoV-2 variants, including B.1.617.2 (appendix p 3). This finding is in line with the vaccine-induced

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NAbTs observed during clinical trials of AZD1222[4] and BNT162b2.[7] Notably, our data are consistent with preliminary observational estimates based on rates of *S* gene target failure during PCR testing in England[8] and more recent data from Scotland,[9] which reports 19% reduced AZD1222 efficacy following two doses (60%) relative to two doses of BNT162b2 (79%) against the B.1.617.2 variant and similar to reduced efficacy against the B.1.1.7 variant following two doses (73% for AZD1222 *vs* 92% for BNT162b2). The combination of these observational data with our laboratory data suggests that the correlation between NAbTs and vaccine efficacy in recent models[10] continues to perform well across different vaccine types and SARS-CoV-2 variants (appendix p 5). It further highlights that the lower starting NAbTs of AZD1222 recipients will now render vaccine efficacy more susceptible to any possible individual-level variation (eg, prior infection, age, immune status, antibody durability, comorbidities). Prevention of infection, however, appears to require substantially higher NAbTs than prevention of the most severe COVID-19 disease and death. Therefore, although reduced in-vitro neutralisation of VOCs predicts reduced AZD1222 vaccine efficacy against symptomatic infection with the same VOCs, close monitoring of the unfolding pandemic will reveal the extent to which the link with severe or fatal COVID-19 has been broken by all current vaccines.

Given our previous observation of decreased NAbTs in older BNT162b2 recipients,[3] we note that our observation here of lower median NAbTs of about 2·5-fold in two-dose AZD1222 recipients relative to two-dose BNT162b2 recipients is confounded by the fact that the AZD1222 cohort is significantly younger than the BNT162b2 cohort (median age 33 years [IQR 28–41] *vs* 42 years [33–52], $p=2{\cdot}3\times10^{-8}$); comparison of two-dose AZD1222 recipients to a more similar subset of the two-dose BNT162b2 cohort (n=58, single study site, age <50 years, dosing interval >40 days; appendix p 4), shows a more pronounced reduction in median NAbTs against B.1.617.2 between two-dose AZD1222 and two-dose BNT162b2 recipients (appendix p 5). Along with increased standardisation across serological laboratories, further serological examination of AZD1222 recipients will be needed as the UK vaccination programme continues, to assess the extent to which variables such as age affect NAbTs (especially beyond the median 31 days post-second dose examined here) and vaccine efficacy, and to establish and refine correlates of protection against all SARS-CoV-2 variants.

Our data reinforce the need to recognise the increased protection offered by a second vaccine dose as COVID-19 cases associated with the B.1.617.2 variant increase. They also suggest that further booster immunisations might be needed, especially for more susceptible groups that have received vaccines that induce lower than average NAbTs. As with mRNA vaccines, it might be feasible to prioritise the use of the AZD1222 vaccine, in light of severely restricted supply, for people with a confirmed history of COVID-19. Overall, our findings highlight the urgent need for expanded serological monitoring of NAbTs within sub-populations. This will enable a better understanding of the evolution of vaccine efficacy and facilitate the production of updated vaccines, thereby ensuring maximum protection against SARS-CoV-2 variants.

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For **data and R code on GitHub** see https://github.com/davidlvb/Crick-UCLH-Legacy-AZ-VOCs-2021-06

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