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.

Three-dose vaccination elicits neutralising antibodies against omicron

Omicron, the SARS-CoV-2 B.1.1.529 variant of concern (VOC), was first detected in southern Africa in November, 2021, and its BA.1 sub-lineage is now dominant in the UK. Omicron BA.1 contains 32 coding changes in its spike protein (appendix p 2), and it is unclear to what extent its spread is driven by an intrinsic increase in transmissibility or escape from previous infection-induced and vaccine-induced immunity.

In the UK, the BNT162b2 (Pfizer–BioNTech) and AZD1222 (ChAdOx1 nCoV-19, Oxford–AstraZeneca) COVID-19 vaccines were administered as part of a primary two-dose course. A subsequent third dose of either BNT162b2 or mRNA1273 (Moderna) vaccine has been administered since September, 2021. To determine the ability of vaccine-induced antibodies to neutralise omicron, and to compare this to our previous measurements of VOC neutralisation by BNT162b2 and AZD1222,[1,2] we carried out a third analysis of the Legacy study cohort (NCT04750356). The Legacy study was established in January, 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 healthy staff volunteers recruited prospectively, or following a positive COVID-19 test, after vaccination. Details of the methods and clinical cohort are available in the appendix. The Legacy study was approved by 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 SARS-CoV-2 neutralisation assay, we determined neutralising antibody (NAb) titres (NAbTs) against omicron in 620 serum samples from 364 unique participants (appendix p 3) and compared these to NAbTs against alpha and delta VOCs, for which there is significant vaccine efficacy data correlated with NAbTs.[3]

In participants sampled 2–6 weeks after two-dose vaccination with BNT162b2, most (166 [83%] of 199) had a quantifiable NAbT against omicron (median 50% inhibitory concentration [IC_{50}] 122 [IQR 46–173]), which was seven fold lower [95% CI 6·3–7·4] than NAbTs against alpha (median IC_{50} 600 [IQR 384–1141]) and three fold [95% CI 2·8–3·3] lower than NAbTs against delta (median IC_{50} 301 [IQR 171–572]; appendix p 2). However, when sampled 12–16 weeks after two-dose vaccination with BNT162b2, only around half of participants (69 [51%] of 136) had a quantifiable NAbT against omicron, whereas nearly all still had a quantifiable NAbT against alpha (131 [96%] of 136) and delta (132 [97%] of 136). The drop in omicron NAbT in the 10 weeks after the second dose was significant (χ^2 p<0·0001).

The same analysis of participants following two-dose vaccination with AZD1222 showed that less than half had a quantifiable NAbT against omicron 2–6 weeks after second dose (25 [37%] of 68), dropping further (five [19%] of 26) 12–16 weeks after second dose, whereas most participants had a quantifiable NAbT against alpha (59 [87%] of 68) and delta (52 [76%] of 68) 2–6 weeks after second dose of AZD1222 (appendix p 2). Notably, NAbTs after AZD1222 vaccination differed significantly according to whether participants reported experiencing COVID-19 symptoms (χ^2 p<0·0001): those who had received two doses of AZD1222 and had not experienced COVID-19 symptoms before their second vaccine dose largely had no detectable NAb response against omicron (29 [73%] of 40; appendix pp 2, 4). In contrast, only a minority of those who had received two doses of BNT162b2 and had not experienced COVID-19 symptoms had no detectable NAb response against omicron (24 [16%] of 147), although the median NAbT against omicron in this group was significantly lower than those recipients of BNT162b2 who had not experienced COVID-19 symptoms before vaccination (median IC_{50} 92 [IQR 42–158] *vs* 165 [122–387]; p<0·0001), which is consistent with previous results of NAbTs against delta.[2]

After two doses of vaccine, 26 participants experienced subsequent breakthrough SARS-CoV-2 infection between April and November, 2021; 24 (92%) of these were probably delta infections (appendix) and presented for a study visit 1–7 weeks after a positive COVID-19 test (appendix p 2). All participants, irrespective of vaccine type, were able to subsequently neutralise omicron (median IC_{50} 573 [IQR 310–655]).

In September, 2021, the UK initiated a targeted third-dose booster campaign for those in Joint Committee on Vaccination and Immunisation Priority Groups 1–9 who had received their second dose more than 6 months earlier. These groups included health-care workers, individuals older than 50 years, and clinically vulnerable people. Participants were invited for a study visit at the time of their third dose (n=80; median days since second dose 192 [IQR 188–202]) and after their third dose (n=85; median days since third dose 20 [IQR 18–22]; median age 53 years [IQR 45–59]). All participants received BNT162b2 for all three doses (appendix p 2). Before receiving their third dose, 34 (42%) of 80 participants had detectable NAbTs against omicron, whereas nearly all participants (82 [96%] of 85) neutralised omicron after a third dose, with a median IC_{50} of 332 [IQR 193–596]. After a third

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dose of BNT162b2, NAbTs against omicron at roughly 3 weeks post-vaccination were only four fold lower (95% CI 3·3–4·5) than against alpha and only two fold lower (95% CI 1·7–2·0) than against delta.

Finally, we considered whether two synthetic monoclonal antibody treatments available in the UK were able to neutralise omicron. Xevudy (sotrovimab; Vir/GSK) was able to neutralise omicron (geometric mean IC_{50} 385 ng/mL [95% CI 354–419]), whereas combined casirivimab and imdevimab (Ronapreve; Regeneron) did not, even at concentrations up to 300 000 ng/mL (appendix p 2). Whereas sotrovimab was six to eight fold less effective at neutralising omicron than delta or alpha, the mean serum concentration of sotrovimab 29 days after a 500 mg infusion (24·5 µg/mL)[4] is 64 fold higher than the in vitro IC_{50} measured here.

In summary, our results show that two vaccine doses, of AZD1222 in particular, are insufficient to generate a strong NAb response against omicron. Participants who experienced a COVID-19 infection before or after two-dose vaccination generated higher NAbTs than those who did not experience a COVID-19 infection, as did those who received a third dose of BNT162b2, who produced consistently high NAbTs against omicron (and alpha and delta).

These findings have two important implications. First, they suggest that available vaccines encoding the ancestral spike protein first detected in Wuhan, China, still induce a NAb response against omicron that is equivalent to that induced by infection with other recent VOCs. This is supported by considerations of the antigenic distance between ancestral and VOC spikes.[5,6] Second, whereas each spike variant appears to induce the highest NAbT to itself with defined hierarchy of cross-reactivity,[7,8] we observe that the differential in the cross-recognition of heterologous spikes is substantially reduced after booster vaccination, in line with recent reports.[5] It will be important to dissect the features that drive this broad response across varied cohorts (vaccine type, previous infection, age, comorbidities) as future booster vaccination strategies are considered.

We also found that the monoclonal antibody sotrovimab (but not combined casirivimab and imdevimab) neutralised omicron in vitro, albeit at reduced capacity relative to alpha and delta. This finding is in line with other preliminary reports[9] and is supportive of plans to prioritise the use of sotrovimab in clinically vulnerable adults following approval by the Medicines and Healthcare products Regulatory Agency in December, 2021. Although sotrovimab probably retains activity against omicron, our results suggest it would be prudent to evaluate any changes in its efficacy across multiple settings and dosing regimens, in support of the decision to study sotrovimab in the RECOVERY and PANORAMIC trials in 2022. In the meantime, however, our results also suggest that given the lack of any other available monoclonal antibody treatment for those with omicron infections, it would be prudent to urgently consider extending the use of sotrovimab beyond those not requiring supplemental oxygen—ie, for those who are more severely ill and would have been given combined casirivimab and imdevimab previously but who might not be approved to receive sotrovimab at present.

Overall, our results suggest that NAbTs against omicron after a third vaccine dose of BNT162b2 are on a similar order to NAbTs against delta after a second dose of BNT162b2. Whereas changes in intrinsic viral characteristics such as tissue tropism or transmissibility might alter the precise level of NAbs that correlates with protection from illness, NAbTs measured in the laboratory remain the strongest correlate of protection against symptomatic and severe illness across multiple variants.[3,10] Indeed, the NAbTs we observe are broadly consistent with preliminary epidemiological data of vaccine efficacy against symptomatic disease.[11]

It is worth highlighting that comparisons between cohorts presented here are confounded by age: participants who were sampled after two doses of AZD1222 are significantly younger than participants who were sampled following two doses of BNT162b2 (median age 35 years *vs* 45 years; p<0.0001; appendix p 3), whereas the converse is true for participants who were sampled after three doses of BNT162b2 (median age 55 years). Comparison of this latter group to an older subset of the two-dose BNT162b2 cohort (n=88; age ≥45 years; appendix p 5), however, shows similar results (appendix p 5). Should the correlation between younger age and higher NAbTs we previously observed after two-dose vaccination[1] continue to hold true, our results would imply that absolute NAbTs after three-dose BNT162b2 vaccination measured here are an underestimate of those in younger cohorts. Ultimately, our observational study is constrained by the roll-out of the national COVID-19 vaccination programme: further assessment of NAbTs in younger individuals, waning of NAbTs over time, and the effect of third-dose vaccination in participants who previously received two doses of AZD1222 (which has formed the backbone of the global vaccination programme) will be necessary.

To conclude, the results from our cohort of healthy, working-age adults support a three-dose vaccination strategy against COVID-19 for the general population, and the broad neutralising response observed suggests urgent global action to deliver three-dose vaccination might increase population immunity against current VOCs (including omicron) and help prevent the emergence of new variants. Studies from diverse populations, including older and clinically extremely vulnerable people, such as those

on haemodialysis[12] or undergoing treatment for cancer[13] remain critical to understanding immunity in groups that are most at risk and require a larger share of health-care resources should they fall ill. Overall, it remains critical to monitor NAbTs over time in diverse cohorts. Many aspects of cellular immunity are at play, yet both preliminary reports of mortality reduction in antibody-negative adults infected with the alpha VOC and treated with combined casirivimab and imdevimab),[14] and recent reports of concomitant NAb waning and increasing risk of hospitalisation or death[15] across multiple populations suggest ongoing assessment of NAb against SARS-CoV-2 variants will continue to be part of an effective strategy against COVID-19 as the pandemic continues to evolve.

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For **data and R code on GitHub** see https://github.com/davidlvb/Crick-UCLH-Legacy-Omicron-2021-12]