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Neutralising immunity to omicron sublineages BQ.1.1, XBB, and XBB.1.5 in healthy adults is boosted by bivalent BA.1-containing mRNA vaccination and previous Omicron infection

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The global COVID-19 landscape is increasingly complex; emerging new variants rapidly cause waves of infection in people with variably induced immunity. Most individuals now have so-called hybrid immunity from both infection and vaccination. However, sequential infecting variants, induction of immunity, and subsequent waning are interlinked, and immune protection against new variants is unclear.

In the UK, the Living with COVID-19 strategy is based on the assumption that high population hybrid immunity will continue to blunt the severity and duration of COVID-19 waves. What happened in Singapore in late 2022 suggests that this might be a fragile assumption. Omicron subvariant XBB caused more than 45 000 cases, including more than 36 000 primary infections, despite vaccination rates of more than 90%; admissions and deaths rose marginally.[1,2] One study on reinfection cases in Singapore in *The Lancet Infectious Diseases* reported that hybrid immunity from vaccination and infection with pre-omicron variants did not confer protection against XBB reinfection.[1] Although it is tempting to assign causation to immune memory,[3] this observation is underpinned by marked population heterogeneity including: differing early infection exposure, waning, or antigenic distance between inducing and re-challenge variants.

During the autumn of 2022, both the US Centers for Disease Control and Prevention and the UK's Joint Committee on Vaccination and Immunisation recommended the targeted deployment of bivalent mRNA vaccines containing BA.1 as fourth doses from August 2022.[4] After our earlier reports on enhanced neutralising immunity against omicron BA.1 after a third dose of monovalent vaccine,[5] we hypothesised that a low-level, pre-existing neutralising capacity to omicron subvariants BQ.1.1, XBB, and XBB.1.5 would be enhanced by encounters with the omicron subvariant Spike through bivalent vaccination or infection, or both. We used our live-virus assay to measure neutralising antibody titres before and after fourth doses of bivalent vaccines containing both ancestral and BA.1 subvariants (Pfizer and BioNTech BNT original and and omicron BA.1) in 85 individuals, and mRNA1273.214 (Moderna)[4] in 107 individuals (table), enrolled in the University College London Hospital and Francis Crick Institute Legacy study (NCT04750356). The Legacy study was approved by London Camden and Kings Cross Health Research Authority Research and Ethics committee (20/HRA/4717).

Firstly, we assessed neutralising antibody titres before and 3 weeks after bivalent vaccine dose against variants including BQ.1.1, XBB, and XBB.1.5 (figure A; table). We found that for ancestral and delta variants, as well as omicron BA.1, BA.2, and BA.5, median post-dose neutralising antibody titres were above the quantitative range (2560-fold diluted serum inhibited more than 50% of the viral infection in vitro, McNemar χ^2 $p=1{\cdot}25\times10^{-8}$ for ancestral, $1{\cdot}45\times10^{-10}$ for delta, $2{\cdot}00\times10^{-13}$ for BA.1, $5{\cdot}92\times10^{-10}$ for BA.2, and $8{\cdot}11\times10^{-10}$ for BA.5). Median BQ.1.1, XBB, and XBB.1.5 neutralising antibody titres were increased after bivalent fourth doses (median fold-change 3·6 [95% CI 2·8–5·1] for BQ.1.1, 3·9 [3·2–4·6] for XBB, and 3·0 [2·3–3·5] for XBB.1.5). Unlike other reports,[6] we found a post-dose difference between median neutralising antibody titres against XBB and XBB.1.5 (figure A), with XBB.1.5 neutralised less effectively than XBB (median fold-reduction 1·69 [1·5–1·85], Wilcoxon signed rank $p<2{\cdot}2\times10^{-16}$). Peak post-fourth dose titres were highest in participants with previous infection exposure (anti-nucleocapsid IgG+ group; figure B; appendix p 1). Before the fourth doses, we found that eight (7%) of

See Online for appendix

	BNT162b2 and BA1 (N=85)	mRNA1273.214 (N=107)	p value
Sex			
Female	64 (75%)	75 (70%)	0·48
Male	21 (25%)	31 (29%)	..
Unknown	0	1 (1%)	..
Age, years	51 (43–56)	53 (42–58)	0·23
Unknown	0	1 (1%)	..
Anti-N IgG at latest visit			
Negative	9 (11%)	17 (16%)	0·97
Positive	41 (48%)	79 (74%)	..
Unknown	35 (41%)	11 (10%)	..
Time of serum sample, number of days before dose 4	5 (2–14)	4 (1–13)	0·79
Time of serum sample, number of days after dose 4	24 (19–59)	19 (15–25)	0·0004

Data shown as n (%) or median (IQR). The p values were calculated using a Pearson's χ^2 test, a Wilcoxon rank sum test, or Fisher's exact test.

Table: **Demographic summary of participants in the Legacy study included the analysis of fourth dose BA.1-containing bivalent vaccine responses**

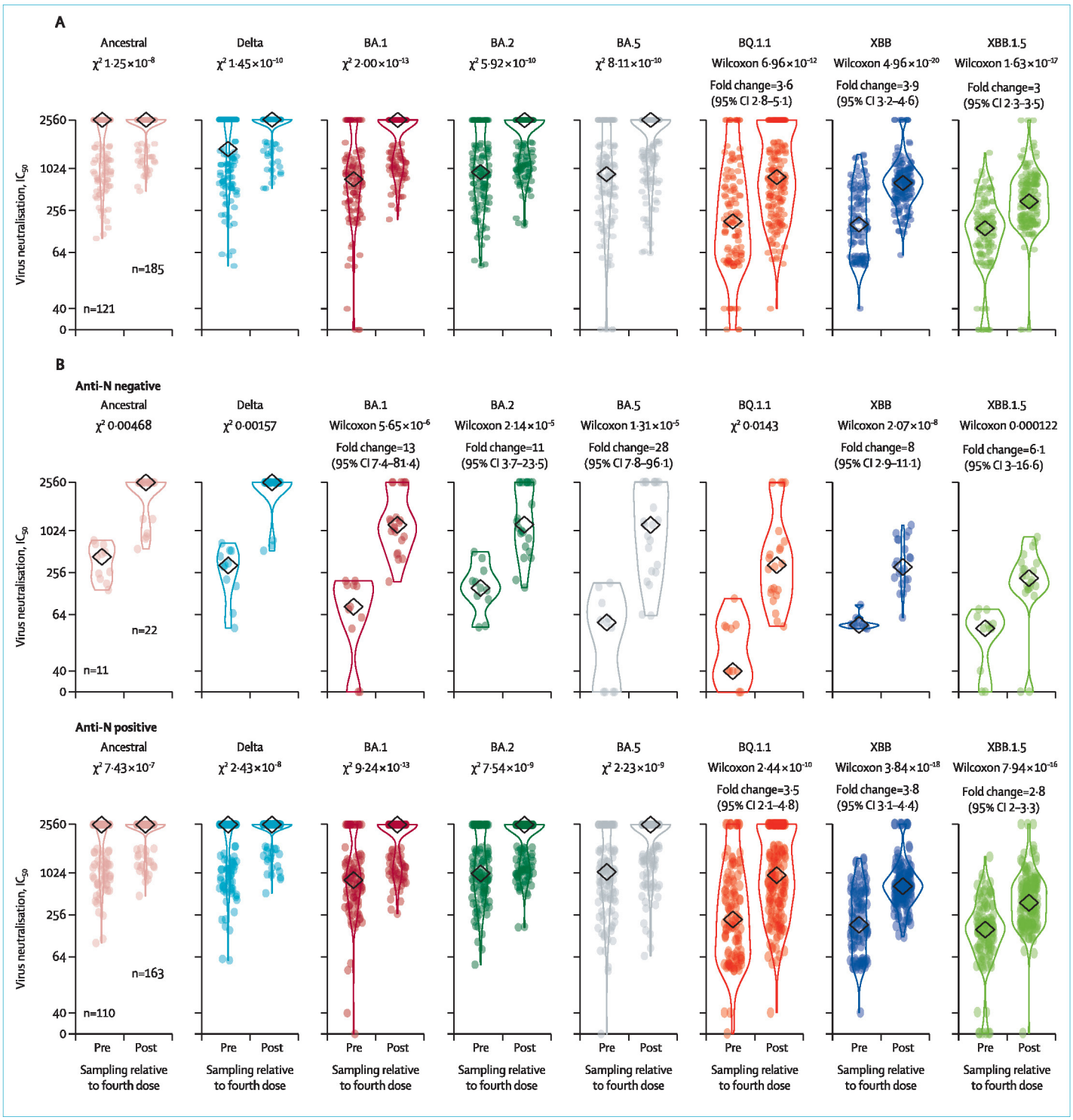

Figure: **Bivalent vaccination induces neutralising antibodies against omicron lineage variants in healthy adults**
(A) Distribution of live-virus microneutralisation titres against SARS-CoV-2 ancestral, delta, or omicron subvariants across the cohort are shown as the $\log^2$ of the IC_{50} for serum samples drawn before or after bivalent mRNA vaccination. (B) Live-virus microneutralisation titres against SARS-CoV-2 ancestral, delta, or omicron subvariants for serum samples drawn before or after bivalent mRNA vaccination, stratified by previous seroconversion to SARS-CoV-2 nucleoprotein (sero-negative or positive indicated by anti-N negative and anti-N positive, respectively). The numbers of serum samples included in each group are indicated on the ancestral plot. p values shown are from unpaired, two-tailed Wilcoxon tests, or McNemar's χ^2 tests if the median of one group was more or less than the quantitative range of the assay (40–2560). The fold-change induction of neutralising antibody titres and 95% CIs are shown where both group medians are within the quantitative range. IC_{50}=50% inhibitory concentration.

110 individuals in the anti-nucleocapsid IgG positive group had pre-fourth dose titres against XBB.1.5 of less than 40, compared with three (27%) of 11 of IgG negative individuals (Fisher's test p=0·06). We then defined a sub-cohort of participants whose only Spike exposure was through vaccination, and compared them with vaccinated participants whose first infection was an omicron subvariant after three vaccinations. We found fourth antigenic encounters resulted in broadly similar peak neutralising antibody titres against all variants of concern tested (appendix p 2). Finally, we examined whether either bivalent vaccine formulation affected post-fourth dose titres. In anti-N negative individuals, we found similar titres between BNT162b2 and BA.1 combined, and mRNA1273.214 (Wilcoxon all variants tested p>0·05; appendix p 3).

Substantial concern was generated by early data in vitro that suggested immune evasion by omicron subvariants XBB, XBB.1.5, and BQ.1.1 (appendix pp 17–21).[7] However, these data are not easily generalised: firstly, they universally use pseudovirus constructs, with variable replication of virion size or spike density, or both; secondly, many use cell lines overexpressing *ACE2* that risk underestimating neutralisation;[8] and thirdly, the serum samples used reflect local protocols and exposure that might not be widely applicable.[6] This variability has led to calls for WHO-level assay standardisation.[9]

Reassuringly, using a high-throughput live virus assay, we found that bivalent mRNA BA.1-containing vaccines substantially increased cross-reactive neutralising immunity against then yet-to-emerge omicron subvariants, including XBB.1.5, at titres that are compatible with a low risk of systemic illness.[10] Cross-reactivity was similarly increased by fourth exposures as either infection or vaccination. Our data thus provide a partial explanation for the substantial difference between what happened subsequently in Singapore and the UK with regards to XBB infections, including a substantially smaller-than-expected peak of severe COVID-19 across the UK in the winter of 2022–23. The joint policy of targeted bivalent vaccination and early access to antivirals for at-risk individuals provided complementary protection to the widespread hybrid population immunity after earlier BA.1, BA.2, and BA.5 waves, and underpinned the living with COVID-19 strategy.

All authors declare they have no competing interests. All data (anonymised) and full R code to produce all figures and statistical analysis presented in this Correspondence are available online on Github: https://github.com/davidlvb/Crick-UCLH-Legacy-XBB-2023-03. This study was sponsored by University College London Hospitals. This study was undertaken at University College London Hospitals and University College London, which received a proportion of funding from the National Institute for Health Research University College London Hospitals Biomedical Research Centre and Clinical Research Facility. ECW, VL, and BW are supported by the Biomedical Research Centre funding scheme. This study was supported jointly by the Biomedical Research Centre and core funding from the Francis Crick Institute, which receives its funding from Cancer Research UK, the UK Medical Research Council, and the Wellcome Trust. DLVB and RB are additionally supported by the Genotype-to-Phenotype (G2P) National Virology Consortium via UK Research and Innovation and the UK Medical Research Council. The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data and the final responsibility to submit for publication.

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