Real-time estimation of immunological responses against emerging SARS-CoV-2 variants in the UK: a mathematical modelling study

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Summary

Background The emergence of SARS-CoV-2 variants and COVID-19 vaccination have resulted in complex exposure histories. Rapid assessment of the effects of these exposures on neutralising antibodies against SARS-CoV-2 infection is crucial for informing vaccine strategy and epidemic management. We aimed to investigate heterogeneity in individual-level and population-level antibody kinetics to emerging variants by previous SARS-CoV-2 exposure history, to examine implications for real-time estimation, and to examine the effects of vaccine-campaign timing.

Methods Our Bayesian hierarchical model of antibody kinetics estimated neutralising-antibody trajectories against a panel of SARS-CoV-2 variants quantified with a live virus microneutralisation assay and informed by individual-level COVID-19 vaccination and SARS-CoV-2 infection histories. Antibody titre trajectories were modelled with a piecewise linear function that depended on the key biological quantities of an initial titre value, time the peak titre is reached, set-point time, and corresponding rates of increase and decrease for gradients between two timing parameters. All process parameters were estimated at both the individual level and the population level. We analysed data from participants in the University College London Hospitals–Francis Crick Institute Legacy study cohort (NCT04750356) who underwent surveillance for SARS-CoV-2 either through asymptomatic mandatory occupational health screening once per week between April 1, 2020, and May 31, 2022, or symptom-based testing between April 1, 2020, and Feb 1, 2023. People included in the Legacy study were either Crick employees or health-care workers at three London hospitals, older than 18 years, and gave written informed consent. Legacy excluded people who were unable or unwilling to give informed consent and those not employed by a qualifying institution. We segmented data to include vaccination events occurring up to 150 days before the emergence of three variants of concern: delta, BA.2, and XBB 1.5. We split the data for each wave into two categories: real-time and retrospective. The real-time dataset contained neutralising-antibody titres collected up to the date of emergence in each wave; the retrospective dataset contained all samples until the next SARS-CoV-2 exposure of each individual, whether vaccination or infection.

Findings We included data from 335 participants in the delta wave analysis, 223 (67%) of whom were female and 112 (33%) of whom were male (median age 40 years, IQR 22–58); data from 385 participants in the BA.2 wave analysis, 271 (70%) of whom were female and 114 (30%) of whom were male (41 years, 22–60); and data from 248 participants in the XBB 1.5 wave analysis, 191 (77%) of whom were female, 56 (23%) of whom were male, and one (<1%) of whom preferred not to say (40 years, 21–59). Overall, we included 968 exposures (vaccinations) across 1895 serum samples in the model. For the delta wave, we estimated peak titre values as 490·0 IC_{50} (95% credible interval 224·3–1515·9) for people with no previous infection and as 702·4 IC_{50} (300·8–2322·7) for people with a previous infection before omicron; the delta wave did not include people with a previous omicron infection. For the BA.2 wave, we estimated peak titre values as 858·1 IC_{50} (689·8–1363·2) for people with no previous infection, 1020·7 IC_{50} (725·9–1722·6) for people with a previous infection before omicron, and 1422·0 IC_{50} (679·2–3027·3) for people with a previous omicron infection. For the XBB 1.5 wave, we estimated peak titre values as 703·2 IC_{50} (415·0–3197·8) for people with no previous infection, 1215·9 IC_{50} (511·6–7338·7) for people with a previous infection before omicron, and 1556·3 IC_{50} (757·2–7907·9) for people with a previous omicron infection.

Interpretation Our study shows the feasibility of real-time estimation of antibody kinetics before SARS-CoV-2 variant emergence. This estimation is valuable for understanding how specific combinations of SARS-CoV-2 exposures influence antibody kinetics and for examining how COVID-19 vaccination-campaign timing could affect population-level immunity to emerging variants.

Lancet Infect Dis 2024

Published **Online** September 11, 2024 https://doi.org/10.1016/S1473-3099(24)00484-5

See **Online/Comment** https://doi.org/10.1016/S1473-3099(24)00513-9

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Funding Wellcome Trust, National Institute for Health Research University College London Hospitals Biomedical Research Centre, UK Research and Innovation, UK Medical Research Council, Francis Crick Institute, and Genotype-to-Phenotype National Virology Consortium.

Introduction

Ongoing antigenic evolution of SARS-CoV-2 has led to multiple COVID-19 waves driven by novel variants. In response, countries have implemented repeated rounds of COVID-19 vaccination since original dose schedules in 2021, and have updated vaccines to include antigens more closely related to circulating variants.[1] Understanding how previous SARS-CoV-2 exposures influence subsequent immune responses to SARS-CoV-2 is therefore crucial to inform ongoing planning for future disease burden, vaccine design, and vaccine deployment.

A preprint paper[2] indicated considerable inter-individual variability in neutralising responses against SARS-CoV-2, with some individuals exhibiting broad responses against a range of variants and others exhibiting a much narrower response that was restricted to a few variants more closely related to those already encountered through vaccination or infection. During the emergence of the omicron BA.1 variant, cross-reactive neutralising responses were observed among individuals who had received three doses of mRNA vaccine containing the ancestral antigen only.[3] Similar cross-reactivity has also been observed against subsequent variants among individuals who have received updated omicron-specific vaccines.[4] Strength and persistence of this cross-reactivity are key drivers of the potential effects of vaccination campaigns that occur before or during emerging waves of SARS-CoV-2 infections.[5] One major challenge is that analysis of cross-reactive responses needs to be conducted against an increasingly complex background of accumulating and partly observed SARS-CoV-2 antigen exposures. For example, first SARS-CoV-2 exposures might lead to so-called immune imprinting,[6] which attenuates subsequent immunity against novel SARS-CoV-2 variants. Such

Research in context

Evidence before this study

We searched PubMed from database inception to Feb 2, 2024, using the keywords ("SARS-CoV-2" OR "COVID-19" OR "COVID") AND ("modeling" OR "modelling" OR "inference" OR "mathematical") AND ("antibody kinetics" OR "antibody dynamics") AND "vaccines", without language restrictions. Our search returned nine results, within which we found five studies that had done descriptive and modelling analyses of titres over time after SARS-CoV-2 vaccination, including against emerging variants, typically via serum collected at specific timepoints (eg, 7 days or 30 days). However, we did not find any detailed modelling studies that estimated underlying individual-level antibody kinetics via live neutralising-antibody data against multiple variants across multiple years for SARS-CoV-2 and we did not find any studies that examined how accurate such an analysis would have been in real time.

Added value of this study

We estimated individual-level responses after SARS-CoV-2 vaccination by combining detailed data on neutralising response from a longitudinal cohort sampled between April 1, 2020, and Feb 1, 2023, with a Bayesian hierarchical model of antibody kinetics that incorporated a biologically motivated antibody-kinetics process with timings of previous SARS-CoV-2 infection or COVID-19 vaccination. Considering individual kinetics, we were able to adjust for multiple previous SARS-CoV-2 exposures and their effect on responses across individuals, combining population-level and individual-level variation in a single model. This adjustment within our modelling framework allowed us to compare the effect of previous exposure on subsequent responses and to examine counterfactual outcomes, such as the level of neutralising responses that would have been observed had COVID-19 vaccination campaigns been earlier or later relative to the variant wave. To our knowledge, we are the first to estimate individual-level and population-level antibody kinetics after vaccination across multiple variants during multiple years. Furthermore, to our knowledge, we are the first to assess how accurate such estimates would have been in real time.

Implications of all the available evidence

Our model, informed by immunological processes observed in other studies, was able to estimate individual-level antibody kinetics against newly emerged SARS-CoV-2 variants in real time at times of uncertainty regarding estimates produced by more traditional methods, for which other data modalities (eg, vaccine efficacy) are not yet available to policy makers. We found that individuals with more previous SARS-CoV-2 infections consistently had higher peak neutralising titres and more persistent responses than individuals with fewer previous SARS-CoV-2 infections, as measured by set-point titre, particularly among those who had exposures that were antigenically more similar to the novel variant. These patterns would have been identifiable from banked samples in the earliest stages of each variant wave. Counterfactual vaccination timings constructed with our modelled individual-level estimates could be used in the future to optimise vaccine campaigns.

imprinting can be overcome with subsequent exposures to antigens that are closer to the circulating or anticipated variant.[7] However, interpretation of such data makes implicit assumptions of previous SARS-CoV-2 exposures in the population to enable comparison across exposure groups. If analysis focuses on reported symptomatic infections only, for example, it could be implicitly conditioning on an immunologically biased subset of the population.

Moreover, serum at the individual level will be infrequently collected, further hindering the ability to infer full individual-level antibody kinetics according to previous SARS-CoV-2 exposure and rigorously compare responses across groups. For instance, in sparse sampling designs, an individual with a high peak titre that declines rapidly after vaccination will be indistinguishable from an individual with a lower titre that persists over time. This occurrence could produce incorrect conclusions about the population-level effect of the timing of vaccine campaigns, as a synchronised vaccine campaign that generates a large peak in responses around the time of variant emergence could have a different effect on epidemic dynamics to one that produces a flatter and lower average response.

In real time, there can also be data limited by time available to provide insights into the level of pre-existing immunity against emerging variants. Data on neutralising-antibody responses can typically be generated early in a new wave because testing can be conducted on any samples from vaccine studies that happened to have been collected immediately before variant emergence. Vaccine effectiveness from case–control or test-negative studies is commonly reported as a subsequent measure of vaccine-mediated immunity, but there are three main limitations.[8] First, these studies compare reported infection events in different groups, so depend on the timescale of the epidemic and will be delayed relative to neutralisation data. Second, undetected SARS-CoV-2 infections during vaccine roll-out can bias estimates towards the null because the unvaccinated or unboosted control group might have infections that are homologous to the circulating variant, whereas the vaccine typically contains heterologous antigens from earlier variants. Third, and increasingly relevant, although vaccine status is typically known in such studies, previous asymptomatic or subclinical infections will frequently be undetected in many studies,[9] particularly those focused on routine surveillance data.

As a result, there is a pressing need to understand the extent to which previous SARS-CoV-2 exposures from both vaccination and infection influence underlying antibody kinetics at the individual level, and how these responses combine to affect the overall level of immunity against emerging variants. We aimed to investigate heterogeneity in individual-level and population-level antibody kinetics to emerging variants by previous SARS-CoV-2 exposure history, to examine implications for real-time estimation, and to examine the effects of vaccine-campaign timing.

Methods

Data sources

We analysed data from participants in the University College London Hospitals (UCLH)–Francis Crick Institute (hereafter referred to as Crick) Legacy study cohort (NCT04750356) who underwent surveillance for SARS-CoV-2 either through asymptomatic mandatory occupational health screening once per week between April 1, 2020, and May 31, 2022, or symptom-based testing between April 1, 2020, and Feb 1, 2023.[9] Briefly, the Legacy study is an ongoing, prospective, cohort study established in Feb 12, 2021, to track serological responses to vaccination during the UK COVID-19 vaccination programme in a prospective cohort of healthy staff volunteers. Retrospective data were collected after the study began, namely vaccination and self-reporting of symptoms. People included in the Legacy study were either Crick employees or health-care workers at Camden and North West London NHS Foundation Trust, Ealing and Northwick Park hospitals, or University College London hospitals. Legacy was approved by London Camden and Kings Cross Health Research Authority Research and Ethics committee (reference 20/HRA/4717; Integrated Research Application System number 286469). All participants gave written informed consent on enrolment in the study.

Inclusion and exclusion criteria for Legacy were as previously reported.[3,10–13] Briefly, Legacy participants were adults older than 18 years, employed by an institution that operated the UCLH–Crick asymptomatic PCR testing pipeline from 2020 to 2022,[9] and gave written informed consent for assessment of their immune response to COVID-19 vaccination and ongoing infection surveillance. Legacy excluded people who were unable or unwilling to give informed consent and those not employed by an institution that used the UCLH–Crick PCR testing pipeline. Participants were sampled routinely every 6 months, with further samples collected before and after COVID-19 vaccine doses and after each reported infection episode, as shown in a preprint paper.[14]

Rather than binding IgG or neutralisation assays against pseudovirus, Legacy generated live virus neutralising titres against a panel of SARS-CoV-2 variants in a high-throughput microneutralisation assay, which was associated with individual-level data on previous SARS-CoV-2 exposures among the study population.[10] Participant data were collected and managed with REDCap electronic data capture tools hosted at University College London.[15,16] Pseudonymised data were exported from REDCap into R for rolling linkage with laboratory data, visualisation, and analysis.

Infection episodes were defined as a positive SARS-CoV-2 test, either through asymptomatic occupational screening or after additional symptomatic testing,

via either PCR testing or antigen-based testing. Participants underwent mandatory occupational health screening between April 1, 2020, and May 31, 2022, and we continued active voluntary surveillance after this period to capture waves of subsequent variant dominance. As in a preprint paper,[14] we used a hierarchical approach to assign the infecting variant viral sequencing (if available), PCR genotype (ie, S gene target failure), or date of infection (if no molecular testing was completed). We excluded episodes from analysis if we were unable to establish the infecting variant, which were usually infections occurring at the transition of dominant variants of concern without additional molecular testing. As the spike sequence of omicron BA.4 and BA.5 are identical, we merged episodes assigned as BA.4 (by sequencing), BA.5 (by sequencing), or BA.4/5 (by PCR genotyping or date) into a single group referred to as BA.4/5.

Delta was designated a variant of concern on May 7, 2021,[17] shortly after most individuals in the Legacy cohort had received their second COVID-19 vaccine dose. Omicron BA.2 was designated as a variant of concern on Jan 24, 2022,[17] after most individuals in the cohort had received their third COVID-19 vaccine dose. XBB 1.5 was characterised as a novel variant of concern on Jan 9, 2023,[18] shortly after most individuals in the cohort had received their fourth COVID-19 vaccine dose.

The live virus isolates used were the same as previously described,[3,11–13] and our viral culture technique was unchanged (appendix pp 7–9). Omicron sub-variants isolated at the Crick were collected from participants reporting acute symptomatic infection following previously described active surveillance protocols.[3,11–13]

See Online for appendix

High-throughput live virus microneutralisation assays were done as previously described.[3,13] Briefly, Vero E6 cells (Institut Pasteur, Paris, France) at 90–100% confluency were infected with SARS-CoV-2 variants in a 384-well format in the presence of serial dilutions of patient serum samples (appendix p 3).

Neutralisation assays implement titrations of serum samples and are, therefore, typically affected by lower and upper limits of detection (ie, the smallest and largest possible measurable titre).[3] In the Legacy study, titre values were given by IC_{50}, corresponding to the reciprocal of the dilution at which 50% of viral infection is inhibited. The reported IC_{50} was derived from a four-parameter dose-response logistic curve with duplicates of serial dilutions (ie, 1:40, 1:160, 1:640, and 1:2560) and reporting a continuous distribution between 40 and 2560. There were three circumstances in which a non-numerical titre was reported: if all dilutions inhibited viral infection to greater than 50% (hereafter referred to as complete inhibition, arbitrarily assigned 5120), if no dilutions inhibited viral infection (hereafter referred to as no inhibition, assigned 5), and if lower dilutions inhibited viral infection but the dose-response curve did not reach IC_{50} (hereafter referred to as weak inhibition, assigned 10; appendix p 4).

We segmented the data to include vaccination events occurring up to 150 days before the emergence of delta, BA.2, and XBB 1.5, defined as three designation dates: May 7, 2021, for delta; Jan 24, 2022, for BA.2; and Jan 9, 2023, for XBB 1.5. We split the data for each wave into two categories: real-time and retrospective. The real-time dataset contained neutralising-antibody titres that were collected up to the date of emergence in each wave; the retrospective dataset contained all samples until the next SARS-CoV-2 exposure of each individual, whether vaccination or infection. To assess the accuracy of real-time fits relative to retrospective fits, we calculated the absolute difference between the two at the population level. We considered responses to a total of n vaccination events among a total of N individuals, stratified by date of variant emergence, vaccine type administered, and previous infection history. We stratified by infection history by considering three categories of individuals: no previous infection, previous infection before omicron, and previous infection with omicron (appendix pp 5–6, 36–37).

Model details and statistical analysis

Our Bayesian hierarchical model of antibody kinetics was constructed to infer the quantitative kinetics of neutralising-antibody titres after antigenic SARS-CoV-2 exposure, incorporating biological knowledge of underlying antibody processes in our definition of the functional form of antibody kinetics. Previous studies have observed a biphasic plateau to a set point in neutralising responses, as has also been observed for post-infection functional immune responses against dengue[19] and influenza.[20] We therefore specified a model that included an initial rise in neutralising titre post-exposure, a decline phase, and a set-point phase. We fit the model between exposure events at the individual level, so the model time horizon was different for each individual and exposure event. We simulated population-level trajectories for 120 days.

The antibody titre trajectories were modelled with a piecewise linear function that depended on six explicit process parameters (ie, model inputs) corresponding to the key biological quantities of an initial titre value (T_0), time the peak titre is reached (t_p), set-point time (t_s), and corresponding rates of increase (m_1) and decrease (m_2 and m_3) for gradients between the two timing parameters (appendix pp 9–18). All six of these process parameters were estimated at both the individual level and the population level. We removed any observations above a threshold rise of 1 log titre without an associated exposure because infection surveillance was never perfect, meaning individuals had noticeable titre increases without an associated vaccination or infection. We therefore assumed there had been an infection at some point.

We fitted the model using R version 4.3.2 and Stan version 2.34.1[21] six times—twice per wave, once for the real-time fits and once for the retrospective fits. For each fit, we ran four chains using the no U-turn sampling

	Delta wave			BA.2 wave			XBB wave		
	Ancestral	Alpha	Delta	Delta	BA.1	BA.2	BA.5	BQ.1.1	XBB 1.5
Exposures and bleed events									
Exposures (vaccinations)	335/968 (35%)	335/968 (35%)	335/968 (35%)	385/968 (40%)	385/968 (40%)	357/968 (37%)	248/968 (26%)	247/968* (26%)	248/968 (26%)
Bleeds	734/1895 (39%)	754/1895 (40%)	767/1895 (40%)	772/1895 (41%)	776/1895 (41%)	699/1895 (37%)	350/1895 (19%)	343/1895 (18%)	346/1895 (18%)
Bleeds censored below	10/164 (6%)	39/164 (24%)	77/164 (47%)	5/164 (3%)	11/164 (7%)	9/164 (6%)	4/164 (2%)	5/164 (3%)	4/164 (2%)
Bleeds censored above	111/635 (18%)	7/635 (1%)	8/635 (1%)	178/635 (28%)	50/635 (8%)	32/635 (5%)	170/635 (27%)	65/635 (10%)	14/635 (2%)
Vaccines†									
BNT162b	266/659 (40%)	266/659 (40%)	266/659 (40%)	338/659 (51%)	338/659 (51%)	311/659 (47%)	55/659 (8%)	55/659 (8%)	55/659 (8%)
AZD1222	65/74 (88%)	65/74 (88%)	65/74 (88%)	9/74 (12%)	9/74 (12%)	8/74 (11%)	0/74	0/74	0/74
mRNA1273	1/44 (2%)	1/44 (2%)	1/44 (2%)	36/44 (82%)	36/44 (82%)	36/44 (82%)	7/44 (16%)	7/44 (16%)	7/44 (16%)
mRNA1273.214	0/105	0/105	0/105	0/105	0/105	0/105	105/105 (100%)	105/105 (100%)	105/105 (100%)
BNT162b2 and BA1	0/79	0/79	0/79	0/79	0/79	0/79	79/79 (100%)	78/79 (99%)	79/79 (100%)
Other	1/3 (33%)	1/3 (33%)	1/3 (33%)	1/3 (33%)	1/3 (33%)	1/3 (33%)	1/3 (33%)	1/3 (33%)	1/3 (33%)
NA	2/4 (50%)	2/4 (50%)	2/4 (50%)	1/4 (25%)	1/4 (25%)	1/4 (25%)	1/4 (25%)	1/4 (25%)	1/4 (25%)
Sites									
Camden and North West London NHS Foundation Trust	25/51 (49%)	25/51 (49%)	25/51 (49%)	22/51 (43%)	22/51 (43%)	20/51 (39%)	23/51 (45%)	23/51 (45%)	23/51 (45%)
Francis Crick Institute	207/377 (55%)	207/377 (55%)	207/377 (55%)	232/377 (62%)	232/377 (62%)	216/377 (57%)	160/377 (42%)	160/377 (42%)	160/377 (42%)
Ealing and Northwick Park hospitals	22/36 (61%)	22/36 (61%)	22/36 (61%)	24/36 (67%)	24/36 (67%)	24/36 (67%)	13/36 (36%)	13/36 (36%)	13/36 (36%)
University College London hospitals	81/155 (52%)	81/155 (52%)	81/155 (52%)	107/155 (69%)	107/155 (69%)	97/155 (63%)	52/155 (34%)	51/155 (33%)	52/155 (34%)
Demographic characteristics									
Age, years	42 (30–54)	42 (30–54)	42 (30–54)	42 (30–54)	42 (30–54)	42 (30–54)	40 (29–52)	40 (29–52)	40 (29–52)
Sex									
Female	223/335 (67%)	223/335 (67%)	223/335 (67%)	271/385 (70%)	271/385 (70%)	271/385 (70%)	191/248 (77%)	191/248 (77%)	191/248 (77%)
Male	112/335 (33%)	112/335 (33%)	112/335 (33%)	114/385 (30%)	114/385 (30%)	114/385 (30%)	56/248 (23%)	56/248 (23%)	56/248 (23%)
Prefer not to say	0	0	0	0	0	0	1/248 (<1%)	1/248 (<1%)	1/248 (<1%)

Data are n/N (%) or mean (SD). NA=not available. *One individual receiving BNT162b2 and BA1 vaccines had a log titre rise >1 when their serum was neutralised against BQ.1.1, and was therefore removed from the analysis. †N is the total vaccination of the respective type across waves.

Table: **Exposure events and individuals by wave, titre type, and vaccine type, as well as demographic characteristics**

algorithm in parallel for 3000 samples each, discarding the first 1000 samples from each chain as warm-up iterations. Convergence of the chains was assessed with the R-hat statistic condition less than 1·05 for each model parameter. Inference took approximately 30 min in total on a 2021 M1 MacBook Pro for the six separate model fits.

Using the mean of the individual-level fitted trajectories simulated with 5000 posterior draws, we reconstructed population-immunity titre values against multiple variants across all individuals over calendar time considering variation in timing of individual vaccination, previous SARS-CoV-2 exposure, and antibody kinetics to examine counterfactual scenarios. We investigated the effect of the timing of vaccination on the mean population-level titre distribution at the time of emergence of each variant. We shifted the timing of vaccination for each individual backwards or forwards by up to 75 days.

The internal validity of our model was tested via convergence diagnostics, such as R-hat values, effective

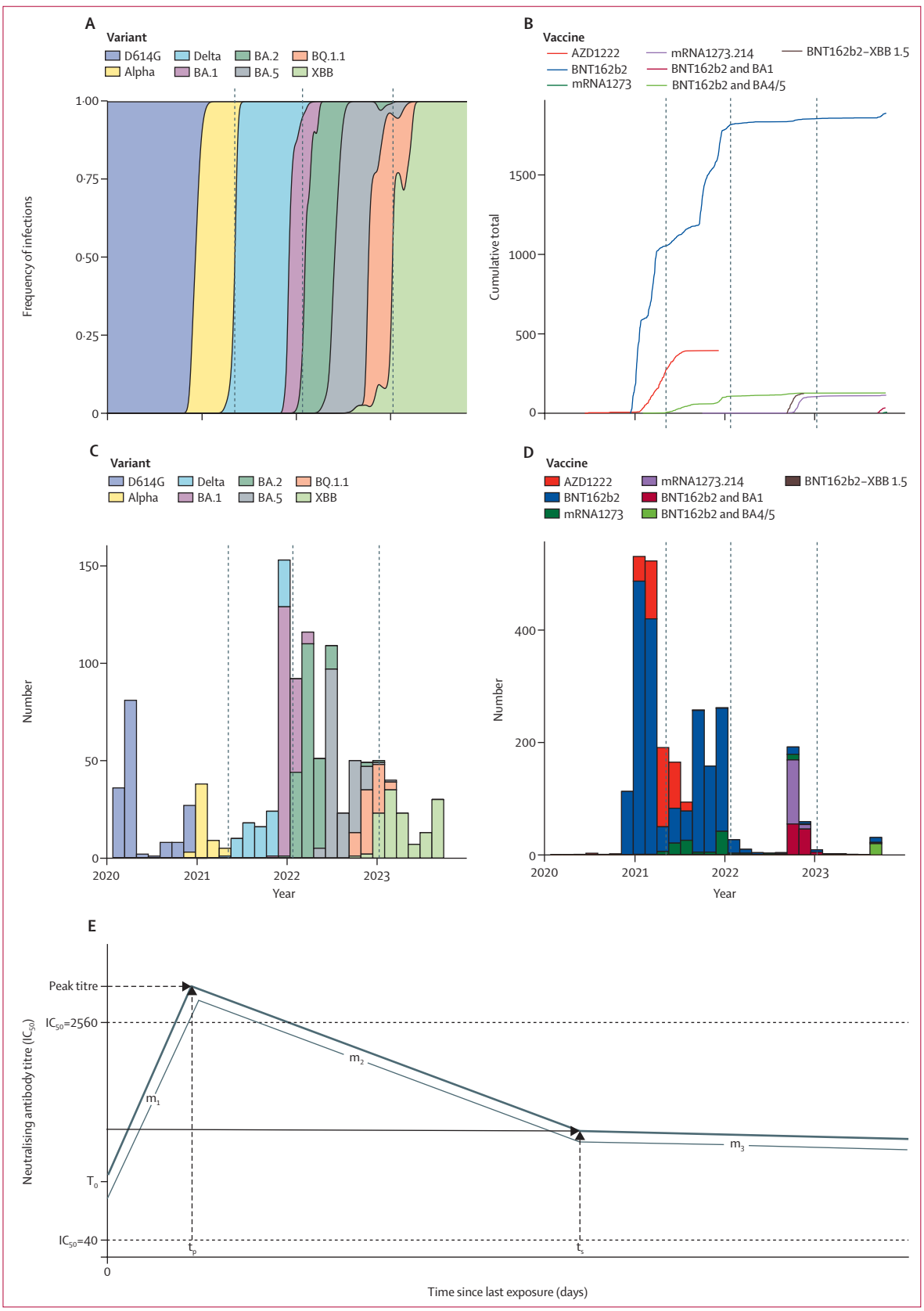


Figure 1: **Exposure events and model schematic**
(A) Estimated relative frequencies of detected infections within the cohort over time, stratified by infecting variant. (B) Estimated cumulative number of vaccinations within the cohort over time, stratified by type of vaccine. Dates of emergence of delta, omicron BA.2, and XBB 1.5 are indicated by dashed vertical lines. (C) Absolute number of detected infections over time. (D) Absolute number of vaccinations over time. Dates of emergence of delta, omicron BA.2, and XBB 1.5 are indicated by dashed vertical lines. (E) Schematic of the antibody kinetics model with three distinct phases (ie, initial boost, faster wane, and slower wane) reaching a set point corresponding to a persistent level of neutralisation. LOESS splines are fit through data to show accumulation and decline of antibodies in the cohort over time. LOESS=locally estimated scatterplot smoothing. m_1=gradient of kinetics during initial boost after exposure, until the peak. m_2=gradient of kinetics during initial wane, after the peak and before the set point. m_3=gradient of kinetics during second slower wane, after set point. t_p=time the peak titre is reached. t_s=set-point time. T_0=initial titre value.

sample size, and posterior predictive checks, ensuring a good fit to observed data. The external validity of our estimates was tested by comparing the effect size of covariates estimated elsewhere (eg, Pfizer *vs* AstraZeneca vaccines or monovalent *vs* bivalent vaccines).

Model specification was measured by visually inspecting each individual-level fit compared with the data combined with calculating the number of divergent transitions. Zero divergent transitions implied that the model was specified well enough for the no U-turn sampler algorithm to sample effectively from the posterior distribution. We also conducted a leave-one-out comparison between the model with and without the second slower wane, to justify its inclusion.

Missing data did not need to be handled explicitly in our analysis. Individuals with a single titre per model fit had their fits informed by this single data point and by the hierarchical nature of the population-level parameters. No individuals with zero data points were included.

Within-group uncertainty was modelled by fitting a standard deviation parameter within the distribution describing each of the six process parameters. Heterogeneity between individuals was modelled by fitting individual-level variation parameters for each of the six process parameters within the model.

We ran two sensitivity analyses to test the sensitivity of our results to the choice of priors: with a significantly higher prior on the amount of individual-level variation (appendix p 29), whereby we multiplied the individual-level variation priors by 10; and with significantly less informative population-level priors, whereby we multiplied the SD values by 10 (appendix p 30). We show the range of neutralising-antibody kinetics permitted by our choice of population-level priors by conducting a prior-predictive check (appendix 35).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

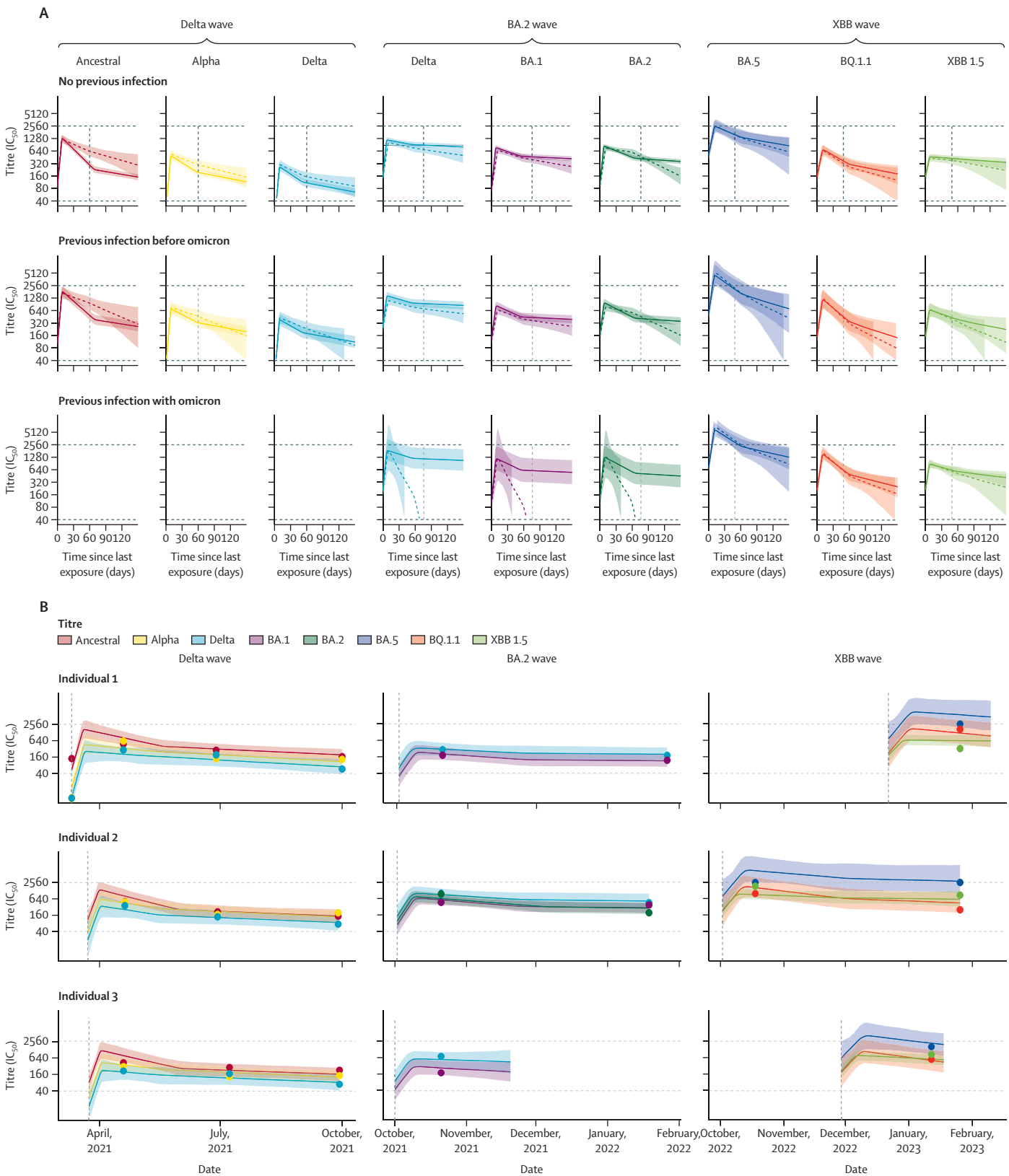
We included data from 335 participants in the delta wave analysis, 223 (67%) of whom were female and 112 (33%) of whom were male (median age 40 years, IQR 22–58); data from 385 participants in the BA.2 wave analysis, 271 (70%) of whom were female and 114 (30%) of whom were male (41 years, 22–60); and data from 248 participants in the XBB 1.5 wave analysis, 191 (77%) of whom were female, 56 (23%) of whom were male, and one (<1%) of whom preferred not to say (40 years, 21–59; table). BNT162b2 was given as a primary vaccination in the delta wave in 266 (40%) of 659 vaccines of the same type across all three waves, AZD1222 in 65 (88%) of 74 vaccines of the same type across all three waves, and mRNA1272 in one (2%) of 44 vaccines of the same type across all three waves in the delta wave analysis (table; figure 1). Overall, we included 968 exposures (vaccinations) across 1895 serum samples in the model (table). Of the 335 participants included in the delta wave analysis, 182 (54%) were also included the BA.2 wave analysis, 102 (30%) were also included in the XBB 1.5 wave analysis, and 71 (21%) were included in all three waves. 136 participants were included in the analysis for the BA.2 and XBB 1.5 waves, without inclusion in the delta wave.

Across all variants and SARS-CoV-2 exposure histories, we estimated that titres peaked around 9·3 days (95% credible interval [CrI] 2·06–13·2) after vaccination. The titres then transiently declined before transitioning to a more stable titre level around 60·8 days (50·6–71·7) after vaccination, after which the decline was more gradual.

We compared estimates of neutralising-antibody responses against emerging variants based only on serological data available in real time with estimates based on all subsequently available samples, stratified by infection history against the emerging variant (figure 2). As more serological samples became available after variant emergence, we could estimate the tail of the antibody kinetics with more confidence and refine our estimates of the overall trajectory (figure 3). When we sampled the differences of the real-time posterior fit and the retrospective fits across all timepoints, up to the mean of time emergence after exposure within each wave, we estimated a difference of 0·05 log titres (95% CrI –0·93 to 4·08). Furthermore, at the peak of the trajectories, real-time fits were within 0·05 $\log_2[IC_{50}]$ (–1·27 to 0·94) units across all titre types and SARS-CoV-2 exposure histories (figure 3B). Real-time estimates remained consistent, with retrospective fits up to the time of emergence of the novel variant across all waves and infection histories—except for people with a previous omicron infection in the BA.2 wave (figure 3B), for whom the mean time of emergence occurred 60 days after exposure for the delta wave, 76 days after exposure for the BA.2 wave, and 49 days after exposure for the XBB 1.5 wave. As the real-time

Figure 2: **Estimated antibody kinetics after vaccination by invading variant and infection history**

(A) Population-level kinetics against the two currently circulating variants and the emerging variant in each wave. Darker model fits with solid lines were fit with data only from exposures that occurred before dashed lines, representing real-time fits. Lighter fits with dashed lines were fit with data from all exposures. Inclusion in real-time fits was calculated at the individual level. For all model fits, lines indicate median estimates and shaded regions indicate 95% credible intervals. Model fits were generated by simulating the model with population-level parameter estimates, stratified by infection history and variant tested against. Vertical dashed lines indicate mean time between the last exposure of each individual and the designation date of the variant for each wave (eg, some vaccinations were 50 days before the fixed date for a wave, but others were 60 days). (B) Individual-level model fits for three individuals with exposures in each of the three waves considered, stratified by titre type.

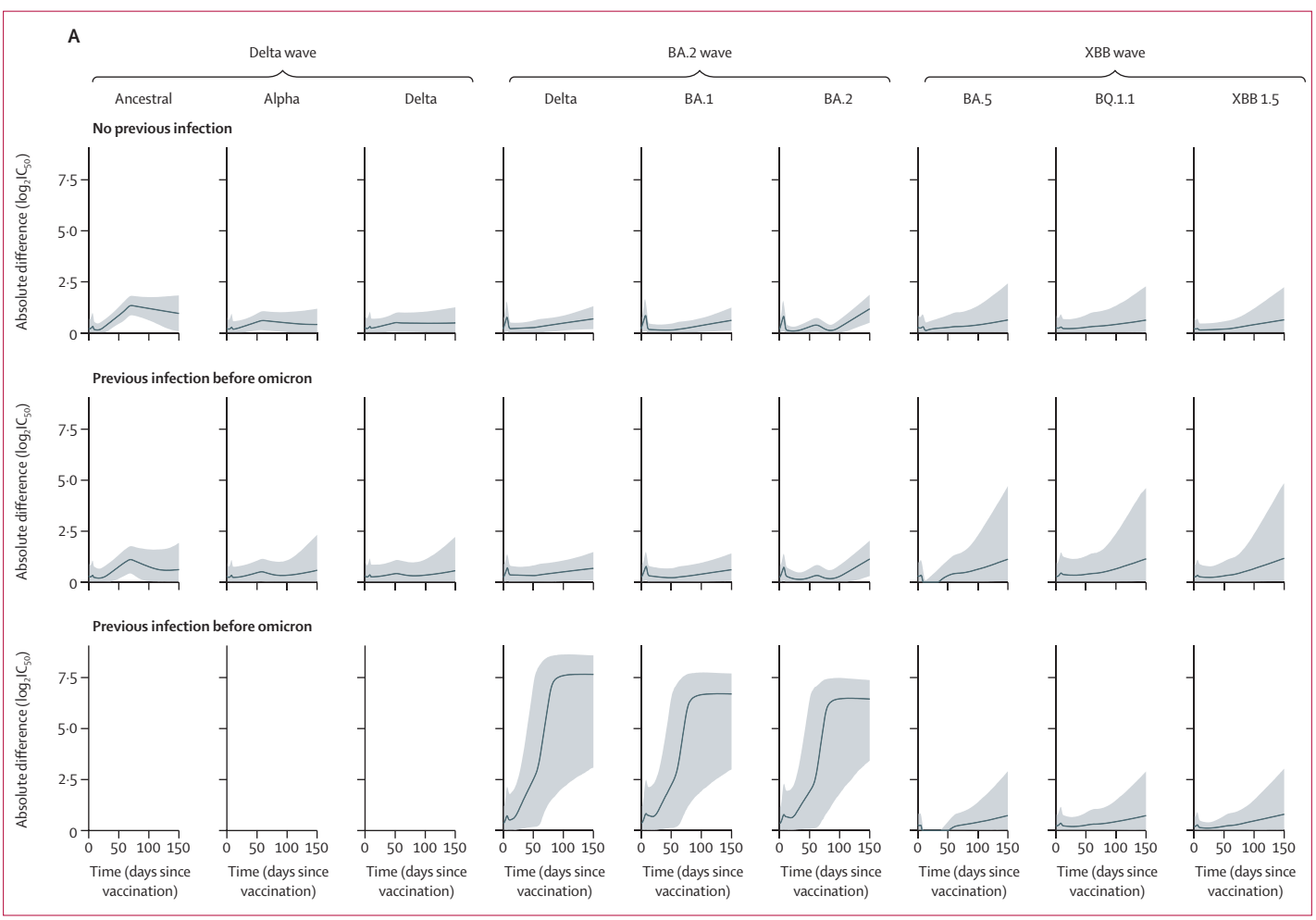

A
Delta wave
BA.2 wave
XBB wave
Ancestral
Alpha
Delta
Delta
BA.1
BA.2
BA.5
BQ.1.1
XBB 1.5
No previous infection
Previous infection before omicron
Previous infection with omicron
Titre (IC50)
5120
2560
1280
640
320
160
80
40
0 30 60 90120
Time since last exposure (days)
B
Titre
Ancestral
Alpha
Delta
BA.1
BA.2
BA.5
BQ.1.1
XBB 1.5
Delta wave
BA.2 wave
XBB wave
Individual 1
Individual 2
Individual 3
Titre (IC50)
2560
640
160
40
April, 2021
July, 2021
October, 2021
October, 2021
November, 2021
December, 2021
January, 2022
February, 2022
October, 2022
November, 2022
December, 2022
January, 2023
February, 2023
Date

datasets were truncated at the date of emergence of each novel SARS-CoV-2 variant, the model with real-time data predicted into a time period without any data. Therefore, uncertainty of the resulting estimates increased (figure 3A; appendix pp 19–22).

For the delta wave, we estimated peak titre values as 490·0 IC_{50} (95% CrI 224·3–1515·9) for people with no previous infection and as 702·4 IC_{50} (300·8–2322·7) for people with a previous infection before omicron; the delta wave did not include people with a previous omicron infection. For the BA.2 wave, we estimated peak titre values as 858·1 IC_{50} (689·8–1363·2) for people with no previous infection, 1020·7 IC_{50} (725·9–1722·6) for people with a previous infection before omicron, and 1422·0 IC_{50} (679·2–3027·3) for people with a previous omicron infection. For the XBB 1.5 wave, we estimated peak titre values as 703·2 IC_{50} (415·0–3197·8) for people with no previous infection, 1215·9 IC_{50} (511·6–7338·7) for people with a previous infection before omicron, and 1556·3 IC_{50} (757·2–7907·8) for people with a previous omicron infection (figure 4).

We estimated that the timing of both the peak and the set point of population-level kinetics occurred earlier as exposures accumulated. For example, peak time shifted from 9·23 days (95% CrI 6·38 to 12·03) after vaccination in the delta wave to 8·85 days (5·99 to 11·71) after vaccination in the BA.2 wave to 7·96 days (4·83 to 10·92) after vaccination in the XBB 1.5 wave. Moving from delta to BA.2 to XBB 1.5 in chronological order, peak timings occurred 0·431 days (–0·753 to 1·301) and 0·933 days (–1·341 to 3·190) sooner than in the previous wave. Similarly, set-point time shifted from 68·4 days (61·3 to 75·6) after vaccination in the delta wave to 65·1 days (57·8 to 72·4) after vaccination in the BA.2 wave to 58·7 days (50·7 to 66·5) after vaccination in the XBB 1.5 wave. Moving from delta to BA.2 to XBB 1.5 in chronological order, set-point timings occurred 7·423 days (0·529 to 14·612) and 6·463 days (1·872 to 14·714) sooner than in the previous wave.

The neutralising-antibody response was higher in individuals administered with the BNT162b2 (Pfizer, New York, NY, USA) vaccine than with the AZD1222



(Figure 3 continues on next page)

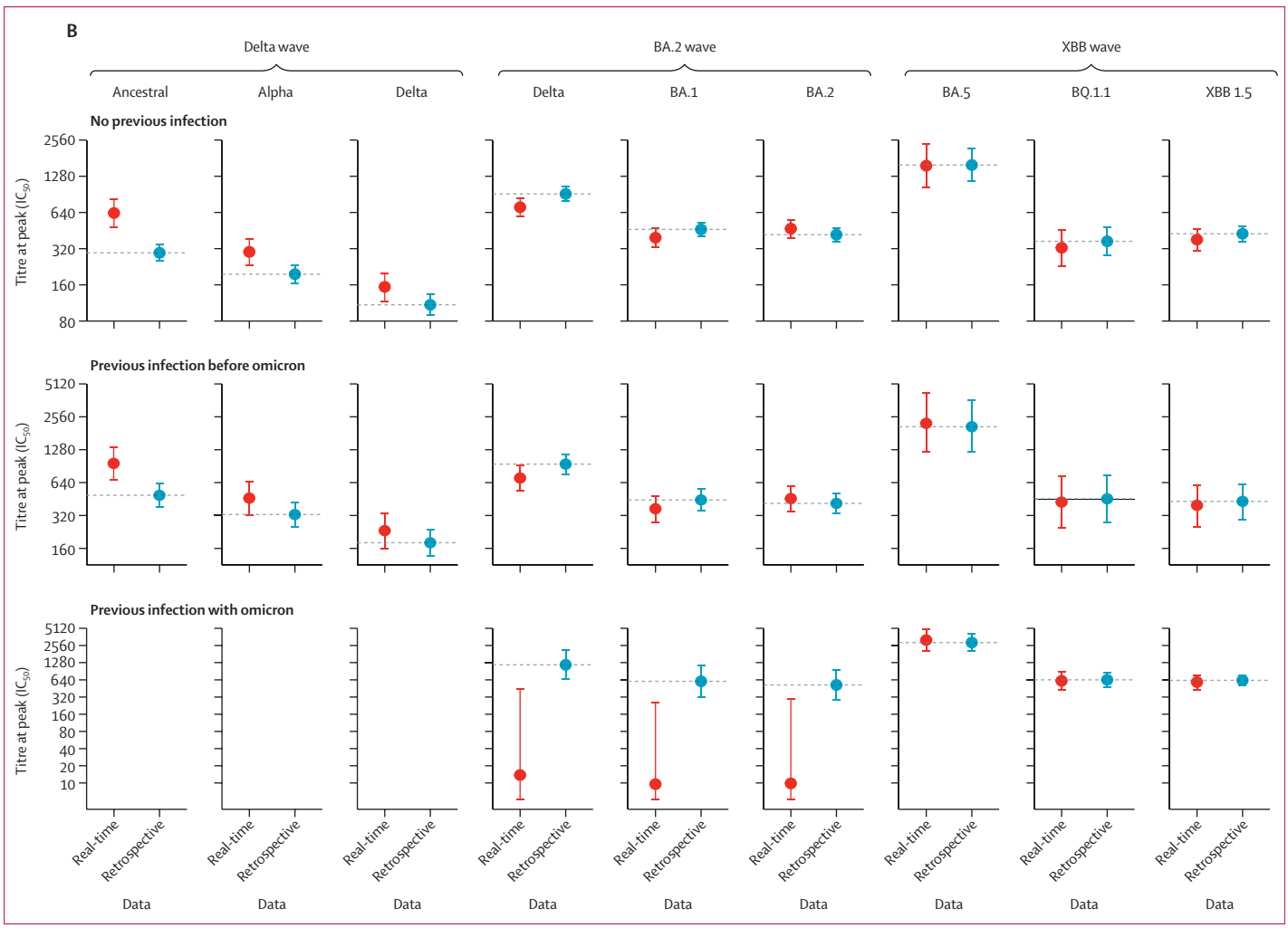


Figure 3: **Accuracy of real-time estimates relative to retrospective estimates**
(A) Absolute difference between population-level, real-time estimates and retrospective estimates. (B) Estimated peak titre value for real-time and retrospective model fits at time of novel emergence of the variant of concern. Horizontal dashed lines indicate peak titre value, estimated with a retrospective Bayesian model fit for comparison. Error bars show 95% credible intervals.

(AstraZeneca, Cambridge, UK) vaccine (appendix pp 25–26) during the delta wave. Furthermore, fitting our model to data from the XBB 1.5 wave and stratifying by monovalent vaccines (ie, BNT162b2 and mRNA1273) versus bivalent BA.1-containing vaccines (ie, BNT162b2 and BA1 and mRNA1273.214), we found a higher neutralising-antibody response for vaccines that contained BA.1 (appendix pp 27–28).

Combining the overall shapes of underlying antibody kinetics and the distribution of vaccination timings, we found that a vaccine campaign 15–60 days ahead of the designation of delta as a variant of concern could have increased expected population-antibody levels, with the peak cross-reactive titre occuring slightly ahead of the variant-of-concern designation date (figure 5). By contrast, we estimated an earlier or later campaign during the BA.2 and XBB 1.5 waves would have had little effect due to combined magnitude and durability of individual-level, cross-reactive responses after vaccination among a population with increasing numbers of previous omicron exposures (figure 5). Specifically, we estimated that the wave of BA.1 before BA.2 and waves of BA.2 and BA.4/5 before XBB 1.5 reduced the relative contribution of vaccine timing to mean population-level titre values at the start of subsequent variant waves (figure 5).

Discussion

Using data from a longitudinal dataset of neutralising-antibody titre values and previous SARS-CoV-2 exposure histories in a Bayesian hierarchical model of antibody kinetics, we estimated individual-level and population-level responses during three major SARS-CoV-2 variant waves. Previous SARS-CoV-2 infections, particularly from antigenically similar viruses, were estimated to increase expected peak titre values, reduce the

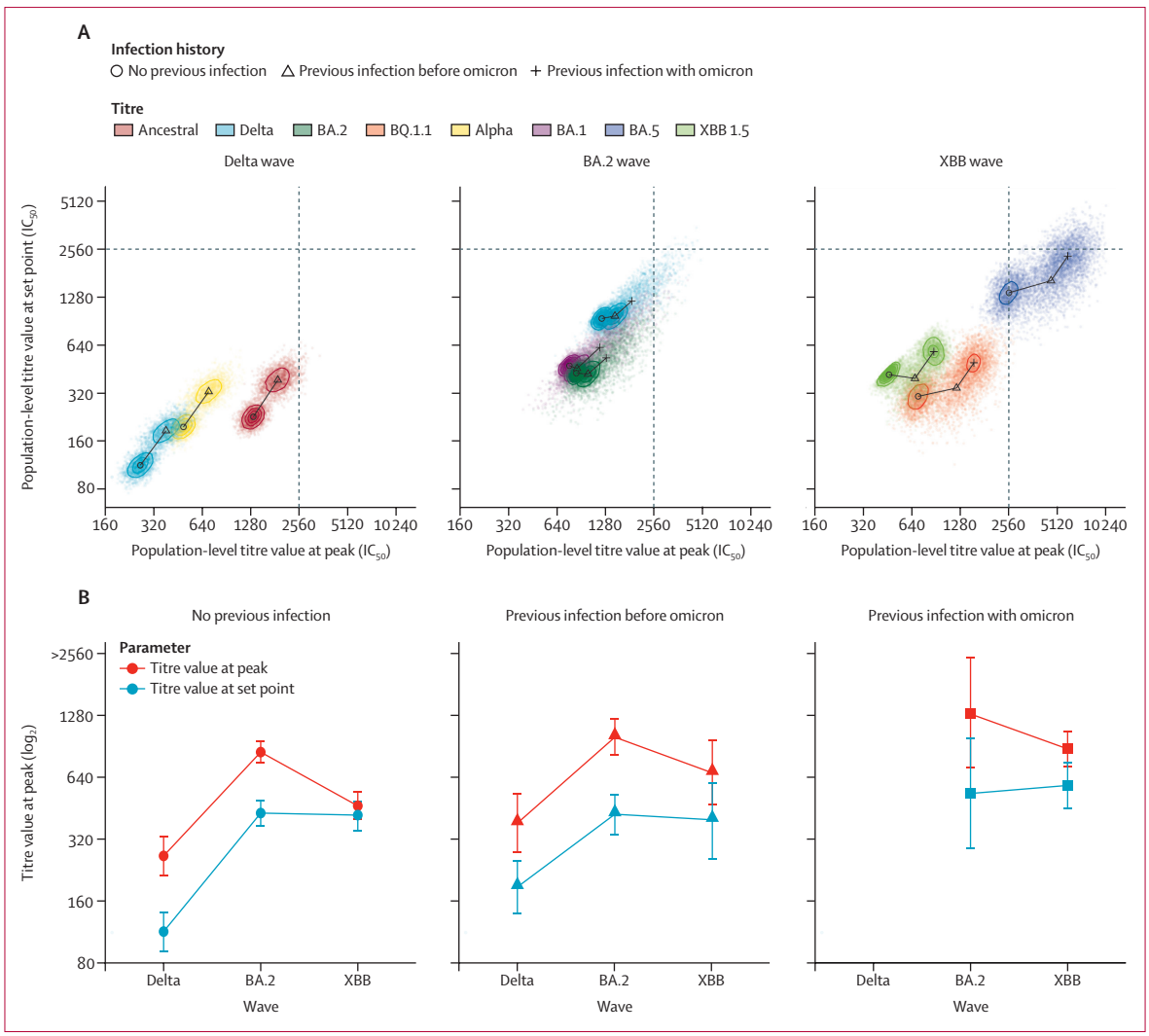


Figure 4: **Estimates of peak titre value and titre value at later set point according to variant wave and history of previous infection**
(A) Each individual-level fit during each emerging variant wave and for each variant tested the peak titre and set-point titre values. (B) Peak titre values against the emerging variant of concern. Lines joining shapes indicate variation in the pattern of response to the same variant between individuals with different infection histories.

subsequent rate of waning, and result in a more durable set-point titre against the novel variant over time. We also estimated that the higher the total number of exposures per individual, the faster after vaccination trajectories peaked.

Our finding that neutralising-antibody trajectories after repeated previous SARS-CoV-2 exposures tend to peak earlier and be more durable than each previous exposure could potentially be explained by early cross-reactive memory responses from previous infections being replaced by higher affinity, more specific responses. This process has been observed for other antigenically variable infections, such as influenza.[22] In a secondary response (ie, a repeat exposure), there is a rapid anamnestic production of antibodies from memory B cells that are ready to respond to re-encounter with an identical or similar antigen (eg, ancestral vaccine boosters or encountering delta spike after two ancestral vaccines). Subsequently, these memory B cells and newly recruited, naive B cells migrate to germinal centres and undergo rounds of somatic hypermutation and affinity maturation.[23] Antibodies derived from this phase of the response have higher affinity than the initial, rapidly produced antibody. Repeated re-exposures with the same spike (eg, serial ancestral vaccinations) therefore increase antibody affinity towards that spike, but not necessarily to spikes from other variants. The extended, slower rate of waning after repeated exposures is probably due to the increased number of long-lived plasma cells seeded to bone marrow after a successful germinal-centre response.[24] We focused on population-level summaries, but public antibody clonotypes (eg, public antibodies

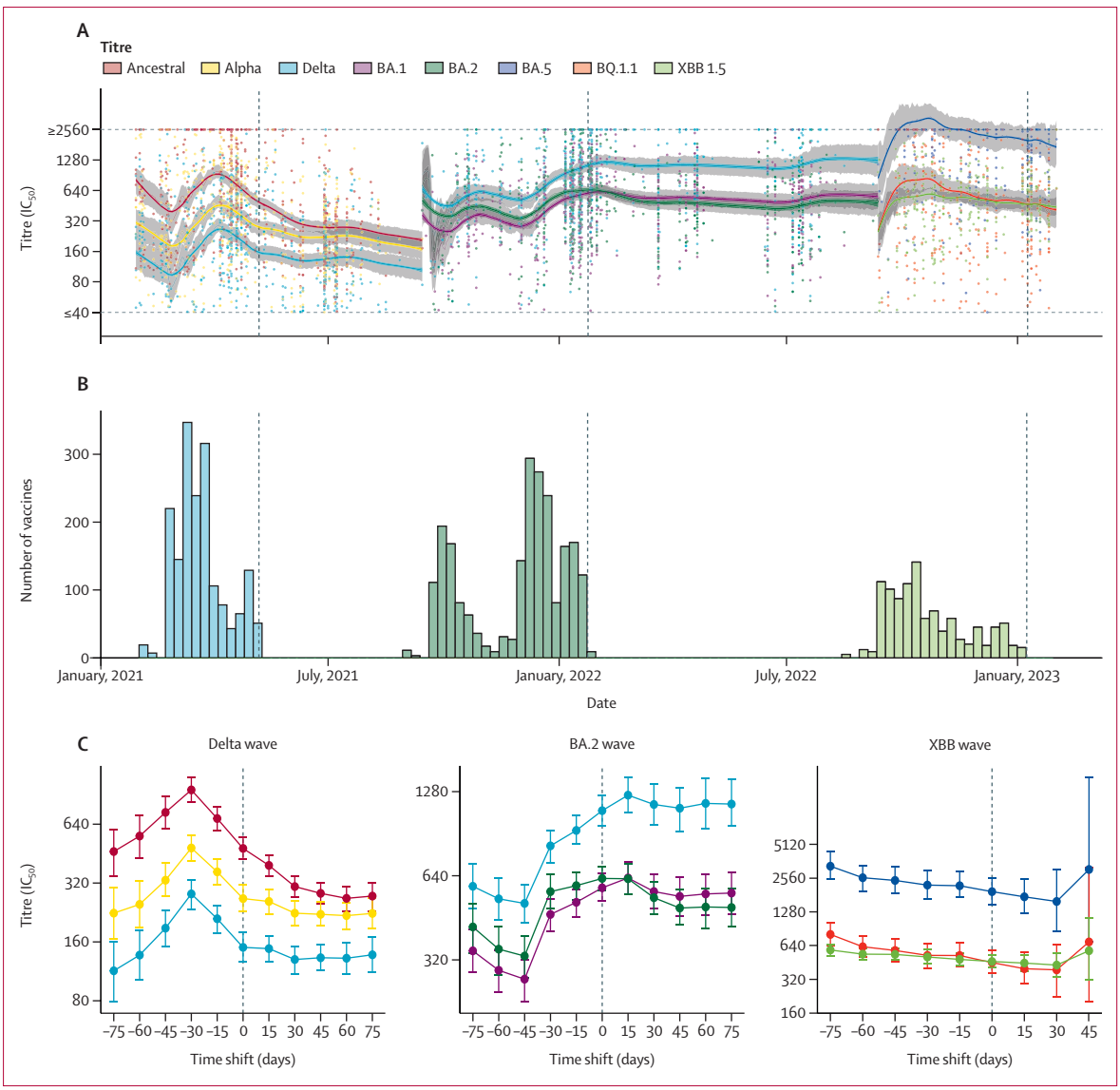


Figure 5: **Estimated neutralising antibodies in the UK population against SARS-CoV-2 against the emerging variant of concern**
(A) Population-level antibody dynamics against emerging variants, shown as LOESS spline fitted to distribution of raw measured titres. (B) Density plots of observed vaccine timings by wave. Horizontal dashed lines show dates that focal variants emerged. (C) Counterfactual scenario, whereby timing of vaccinations was shifted backwards and forwards by up to 75 days to investigate the effect on population-level titre values. LOESS=locally estimated scatterplot smoothing.

binding to a receptor-binding domain that shares *IGHV3–53* and *IGHV3–66*)[25] might be preferentially shared between individuals within similar trajectories and breadth of neutralising responses.

Titres declining suggested that a set-point dynamic, rather than an ongoing rapid decline, was common among neutralising responses to emerging SARS-CoV-2 variants. Furthermore, real-time estimates were consistent with retrospective estimates, which suggests that real-time estimation of an expected short-term pattern of neutralising-antibody titres is feasible up to the time of a novel variant across multiple waves given rapid generation of neutralisation data from biobanked serum samples.

Understanding the control of relative contributions of memory and naive B cells to secondary responses is an important objective for vaccinology and quantifying the role of previous SARS-CoV-2 exposure on subsequent neutralising responses, as we have done, can support generation and testing of key hypotheses. Most antigens, including spike, have many different epitopes available for antibody binding. However, not all epitopes in spike are targeted equally by germinal-centre reactions, perhaps because some fragments of the spike protein might be better recognised by existing B cells,[26] better retained on follicular dendritic cells in germinal centres,[27] or more successfully presented in the context of human

leukocyte antigens for T-cell help than other spike fragments.[28] Germinal-centre reactions are inhibited by pre-existing antibodies.[29] Repeated exposures, and the resulting increase in pre-existing antibody and its affinity, could therefore mask particular epitopes, such that previously relatively overlooked epitopes attract stronger serological responses with each subsequent exposure. This epitope masking allows epitope spreading with the potential to improve cross-neutralisation against novel variants. Although so-called original antigenic sin[30] is thought to reduce the number of viruses that are effectively recognised after repeated ancestral vaccination, epitope masking potentially confers the opposite effect to widen the pool of viruses that are recognised after repeated ancestral vaccination. As SARS-CoV-2 variant emergence continues to outpace vaccine updates, sustainable vaccination strategies should target broad and sustained responses during peak response to a specific variant, supported by up-to-date evidence on how previous SARS-CoV-2 exposures influence subsequent responses, as we have shown is possible in real time.

Our study has limitations. First, we fit to exposure events, rather than the full antibody kinetics of each individual during the study period, as individuals were likely to have had undetected SARS-CoV-2 infections during the study period. We fit only to SARS-CoV-2 vaccinations and not infections, for the same reason. However, we included infection history as a covariate and removed any observations above a threshold rise of 1 log titre without an associated exposure. Second, vaccine types varied within and between waves. However, we implicitly adjusted for this as the model was fit to individual exposure events and, therefore, variation was captured in the population-level estimates. Third, the upper limit of 2560 IC_{50} was a limitation of the data. However, our model included an adjustment within the likelihood function to estimate how far above this limit the fitted kinetics were most likely to go, which is the reason why some kinetics were estimated to be more than 2560 IC_{50} (appendix pp 9–11). Fourth, our underlying model of antibody kinetics aimed to capture the key features in a simple way. As such, model misspecification could be possible, particularly on short timescales. However, changing the underlying antibody kinetics model while maintaining the hierarchical Bayesian statistical structure was relatively straightforward. Therefore, future studies could explore the effects of alternative model structures if additional detailed data were available. Fifth, the accuracy of real-time fits was reliant on data availability. As such, estimates in groups with low numbers of exposures or observations had high uncertainty. Furthermore, the accuracy decreased relative to the retrospective fits after the truncation (ie, the variant emergence date) as the model was fitted to no data past that point. Therefore, there was a clear timeframe when one should expect real-time estimates to be potentially accurate and when not to. Finally, baseline insights from our cohort could not be fully extrapolated to the UK or other populations as it comprised health-care workers and Crick employees. However, the modelling framework and its codebase were flexible. As such, alternative exposure histories, different sampling procedures, and even neutralising-antibody data for different diseases could be explored by others in the future.

Understanding how SARS-CoV-2 immunity varies in response to novel variants considering increasingly complex previous exposures will be crucial to inform ongoing epidemic planning and vaccine campaigns. Considering individual-level antibody kinetics can provide real-time insights into immune responses against emerging SARS-CoV-2 variants, as well as enable robust comparisons across variants and exposure groups and testing of key hypotheses about how immunity accumulates across multiple exposures. Such a study is only possible when detailed, high-quality data are routinely collected during successive years and are combined with a sufficiently complex model. Such combined methods have the potential to provide early insights into the immunological effects of antigenic evolution in the near future.

Contributors

RH, NSL, BW, CSw, MYW, DLVB, ECW, and AJK conceptualised the study. TWR, RH, SW, KA, AS, SK, SGan, DLVB, ECW, and AJK conceptualised the methodology. SGam, SGan, BW, and CSw acquired funding. RH, VL, NSL, RB, MYW, and SGam acquired resources. HT, JG, MS-T, EH, NO'R, VL, NSL, BW, CSw, SGan, SGam, and RB were project administrators. SW, KA, AS, and SK created the software. HT, JG, MS-T, DG, AH, GD, RP, TS, PS-L, JB, RH, ASF, MMia, MMir, CSm, PB, HVM, LA, NO'R, PP, TC, RG, MYW, and ECW collected data. TWR, HT, JG, MS-T, DG, AH, GD, RP, TS, PS-L, JB, RH, ASF, MMia, MMir, CSm, PB, HVM, LA, NO'R, PP, TC, RG, EJC, and ECW curated the data. TWR, JH, DH, SW, AS, SK, GKa, and DLVB conducted the formal analysis. TWR, JH, DH, and DLVB visualised the data. GKe validated the data. DG, MYW, and TWR accessed and verified the data. TWR, DLVB, EJC, ECW, and AJK wrote the original draft of the manuscript. TWR, JH, DG, RH, PP, TC, RG, VL, GKa, RB, NSL, BW, CSm, CSw, SGan, SGam, MYW, DLVB, EJC, ECW, and AJK reviewed and edited the manuscript. KA, CSw, SGan, and SGam were supervisors. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

CSw receives grants from Bristol Myers Squibb, Ono Pharmaceuticals, Boehringer Ingelheim, Roche-Ventana, Pfizer, and Archer Dx; receives personal fees from Genentech, the Sarah Canon Research Institute, Medicxi, Bicycle Therapeutics, GRAIL, Amgen, AstraZeneca, Bristol Myers Squibb, Illumina, GlaxoSmithKline, MSD, and Roche-Ventana; holds stock options in Apogen Biotech, Epic Biosciences, GRAIL, and Achilles Therapeutics; is a member of a scientific advisory board for Bicycle Therapeutics, GRAIL, Relay Therapeutics, SAGA Diagnostics, and Achilles Therapeutics; is a co-founder of Achilles Therapeutics; receives consulting fees from Genentech, Medicxi, MetaboMed, Novartis, the China Innovation Centre of Roche, and the Sarah Cannon Research Institute; and receives honoraria from Amgen, AstraZeneca, Bristol Myers Squibb, Illumina, and Incyte. DLVB receives grants, paid to their institution, from AstraZeneca. EJC is an unpaid member of the Infection, Prevention and Control Committee of the UK Kidney Association. RB and DLVB are members of the Genotype-to-Phenotype 2 Consortium. AJK received the Sir Henry Dale Fellowship, jointly funded by the Wellcome Trust and the Royal Society (grant number 206250/Z/17/Z). AJK and DH were supported by the National Institutes

of Health (1R01AI141534–01A1). All other authors declare no competing interests.

Data sharing

The de-identified dataset and code to run all analyses are available at https://github.com/thimotei/legacy_nAb_kinetics/.

Acknowledgments

This study was funded by the Wellcome Trust (West Africa, West Indies, West London: Mechanisms driving heterogeneity in immunity to SARS-CoV-2 variants Consortium 226142/Z/22/Z, CC2166, CC1283, CC1114, CC2230, CC2060, and CC2041); the National Institute for Health Research University College London Hospitals Biomedical Research Centre; UK Research and Innovation; the UK Medical Research Council (MR/W005611/1, MR/Y004205/1, MR/X006751/1 paid to EJC, CC2166, CC1283, CC1114, CC2230, CC2060, and CC2041); the Francis Crick Institute, which receives its funding from Cancer Research UK (CC2166, CC1283, CC1114, CC2230, CC2060, and CC2041); and the Genotype-to-Phenotype National Virology Consortium. We thank all study participants; staff of the National Institute for Health Research Clinical Research Facility, including Miguel Alvarez and Marivic Ricamara; staff of the scientific technology platforms and COVID-19 testing pipeline at the Francis Crick Institute; and Alex Sigal, Khadija Khan, Tulio de Oliveira, and Gavin Screaton for providing source material.

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