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SARS-CoV-2 anti-spike IgG antibody responses after second dose of ChAdOx1 or BNT162b2 in the UK general population

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Abstract

We investigated anti-spike IgG antibody responses following second doses of ChAdOx1 or BNT162b2 SARS-CoV-2 vaccines in the UK general population. In 186,527 individuals, we found significant boosting of anti-spike IgG by second doses of both vaccines in all ages and using different dosing intervals, including the 3-week interval for BNT162b2. After second vaccination, BNT162b2 generated higher peak levels than ChAdOX1. Antibody levels declined faster at older ages than younger ages with BNT162b2, but were similar across ages with ChAdOX1. With both vaccines, prior infection significantly increased antibody peak level and half-life. Protection was estimated to last for 0.5-1 year after ChAdOx1 and >1 year after BNT162b2, but could be reduced against emerging variants. Reducing the dosing interval to 8 weeks for both vaccines or further to 3 weeks for BNT162b2 may help increase short-term protection against the Delta variant. A third booster dose may be needed, prioritised to more vulnerable people.

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Introduction

On 8th December 2020, the United Kingdom (UK) started its national SARS-CoV-2 vaccination programme. The Pfizer-BioNTech BNT162b2 vaccine was first approved, then the Oxford-AstraZeneca ChAdOx1 nCoV-19 and mRNA-1273 Moderna vaccines[1–3]. Vaccines were prioritised to older adults, frontline healthcare and social-care workers, and clinically vulnerable individuals, and then offered to other adults in decreasing age order[4]. To 26th July 2021, 88% and 71% of the adult population (aged ≥18y) have received one and two doses, respectively (https://coronavirus.data.gov.uk/details/vaccinations).

With wide-spread Alpha transmission, in January 2021 the UK government extended the dosing interval from 3-4 to 12 weeks for all vaccines to maximize first dose coverage, based on preliminary data showing high efficacy from single BNT162b2 (90%) and ChAdOx1 (70%) doses[5]. This approach raises several questions. Although the ChOxAd1 trial found higher vaccine efficacy with dosing intervals ≥6 weeks[6], BNT162b2 trials did not compare different dosing intervals. Subsequent UK studies showed extended BNT162b2 dosing intervals generated a higher antibody response than the 3-week interval[7–9]. However, these studies were based on relatively small sample sizes (N<600) or specific population groups such as healthcare workers, potentially reducing generalisability, and antibody levels were only measured at specific times after second doses. Protection against the Delta variant is stronger after a second than a first dose, meaning that shorter dosing intervals could provide increased protection faster if response is not compromised[10–12]. Few studies have investigated longer-term antibody changes after the second dose, which are important in assessing the duration of protection and the need for booster doses.

We used data from the UK's national COVID-19 Infection Survey (ISRCTN21086382), a large representative sample of households with longitudinal follow-up, to investigate real-world longer-term anti-trimeric spike IgG antibody responses following second ChAdOx1 or BNT162b2 vaccinations, and examined the impact of dosing interval, age, and prior infection status on antibody peak levels and declines. Since IgG antibodies are correlated with neutralising activity, which is associated with protection from infection[13–15], our results help inform regarding the degree and duration of protection against SARS-CoV-2 infection.

Results

From 8th December 2020 to 26th July 2021, 186,527 participants received two ChAdOx1 or two BNT162b2 vaccinations and had at least one antibody measurement from 91 days before the first vaccination onwards. The median (interquartile range, IQR) age was 59 (47-69) years, 102,036 (54.7%) were female, and 176,294 (94.5%) reported white ethnicity. 6,378 (3.4%) reported working in patient-facing healthcare, and 55,205 (29.6%) having a long-term health condition. 109,729 (58.8%) and 60,157 (32.3%) participants without evidence of prior infection (see Methods) received two doses of ChAdOx1 or BNT162b2, as did 11,139 (6.0%) and 5,502 (2.9%) with evidence of prior infection, respectively. These four cohorts contributed 502,369 anti-spike IgG measurements **(Figure S1)**. The median (IQR) [range] dosing interval was 76 (68-78) [17-167] and 76 (66-78) [17-154] days for those receiving ChAdOx1 without or with prior infection, respectively, and 73 (62-77) [17-194] and 70 (57-77) [17-162] days respectively for BNT162b2 **(Table S1).**

Anti-spike IgG response following first and second dose

In participants receiving two vaccinations without prior infection, generalised additive models (GAM) showed generally similar antibody trajectories for both vaccines **(Figure 1** for 60-year-olds**, Table S2a**; predicted trajectories for other age groups in **Figure S2)**. Anti-spike IgG levels increased after the first dose, peaked ~21 days later, then gradually declined until the second dose, after which they reached even higher peak levels ~21 days later, then gradually declined again. In these unadjusted analyses, there was no evidence of differences in antibody levels and declines after the second dose across 8-week to 12-week dosing intervals for both ChAdOx1 and BNT162b2 vaccines. For example, with an 8-, 10-, and 12-week dosing interval for 60-year-olds, the anti-spike IgG levels (in ng/ml, with 95% CIs in parentheses) were 279 (260-302), 300 (288-312), and 294 (280-310) for ChAdOx1, and 699 (636-769), 757 (723-792), and 754 (703-808) for BNT162b2 at 21 days after the second dose**.** However, the antibody trajectory was different for the 3-week BNT162b2 dosing interval, where antibody levels gradually increased from the start of the first dose until around 42 days after the second dose, after which antibody levels were similar to those with 8–12-week dosing intervals, although slightly lower in 80-year-olds (**Figure S2)**.

Post-first dose, peak levels were lower in older participants, but age differences were attenuated after the second dose. For example, with a 10-week BNT162b2 dosing interval, 21 days post-first dose IgG levels were 517 (426-627) for 20-year-olds, 344 (317-374) for 40-year-olds, 228 (214-244) for 60-year-olds, and 144 (128-161) for 80-year-olds, while 21 days post-second dose, they were 783 (673-911), 745 (700-793), 757 (723-792), and 786 (723-853) respectively **(Figure 2, Table S2b;** predicted trajectories for other dosing intervals in **Figure S3)**. Results were similar for ChAdOx1, but

overall antibody levels were lower. For example, in 20-, 40-, 60-, and 80-year-olds with a 10-week dosing interval, 21 days post-first dose levels were 215 (177-162), 157 (147-168), 127 (121-134), and 72 (63-83), and 309 (258-370), 270 (253-287), 300 (288-312), 299 (271-330) 21 days post-second dose, respectively.

In participants with evidence of prior infection, antibody levels started from levels above 42 ng/ml and gradually increased for both vaccines. Similarly, there was no evidence of differences in antibody levels and declines after the second dose for dosing intervals from 8 to 12 weeks **(Figure 1, Figure S4).** Antibody levels rose to lower levels in older than younger participants after the first dose, but the difference was attenuated after the second dose **(Figure 2, Figure S5)**. Compared with those without prior infection, antibody levels after the first and second dose were more similar in those with prior infection, but there was a second dose boosting effect for 80-year-olds **(Figure 3)**. Also, for ChAdOx1, participants without prior infection had lower antibody levels post-second dose than those with prior infection post-first dose; but for BNT162b2, two vaccinations without prior infection led to higher antibody levels than previously infected participants having only one dose, especially for 80-year-olds **(Figure 3**; predicted trajectories for other dosing intervals in **Figure S6).**

Determinants of anti-spike IgG peak levels and half-life after the second dose

ChAdOx1

Of the 120,868 participants (with or without prior infection) who received two ChAdOx1 doses, 71,987 participants contributed 94,599 antibody measurements ≥21 days after the second dose, median (IQR) [range] 1 (1-2) [1-4] measurements per participant. Assuming antibody levels declined exponentially, using Bayesian linear mixed models we estimated a mean peak anti-spike IgG level of 312 ng/ml (95% credibility interval, Crl 308-314), and mean half-life 82 days (80-83) **(Figure S7)**. There was no evidence of non-linearity in antibody declines on a log scale, that is no evidence that rates of antibody decline flattened off over the follow-up period (up to 87 days post second vaccination). In the multivariable Bayesian linear mixed model, all factors considered (age, sex, ethnicity, reporting a long-term health condition, healthcare work, deprivation, dosing interval and prior infection status) were independently associated with anti-spike IgG peak levels 21 days post-second dose, but most effects were small compared with the overall peak **(Figure 4, Table S3)**. The largest effects were from prior infection, peak 258 ng/ml higher (246-271) and ethnicity, peak 69 ng/ml (58-80) higher in those reporting non-white ethnicity. Peak levels were slightly lower in males, those reporting a long-term health condition, those not working in healthcare, with shorter dosing intervals, younger age, and greater deprivation. For half-life, only prior infection status had a substantive effect, with a longer half-life in those with prior infection (46 days longer, 95%Crl 33-62).

There were very small reductions in half-life at older ages and with shorter dosing intervals. There was no evidence of association between half-life and sex, ethnicity, having a long-term health condition, and being a healthcare worker in participants who received ChAdOx1.

BNT162b2

In 65,677 participants (with or without prior infection) who received two BNT162b2 doses, 44,033 participants contributed 71,549 antibody measurements ≥21 days after the second dose (≥42 days for those with 3-week dosing interval, see Methods, **Figure 1**), median (IQR) [range] 2 (1-3) [1-4] per participant. The estimated mean peak level was 762 ng/ml (95%CrI 754-766), and the mean half-life was 112 days (109-114) **(Figure S7).** There was again no evidence of non-linearity in antibody declines on the log scale, i.e. no evidence that antibody declines flattened off over time through 119 days follow-up. Factors had greater effects on peak levels for BNT162b2 than ChAdOx1, and more had substantive effects on half-life. Specifically, age, sex, reporting a long-term health condition, dosing interval, and prior infection were independently associated with both peak level and half-life; and working in healthcare with peak level and ethnicity with half-life **(Figure 4, Table S3)**. Peak levels were lower and half-life shorter at older ages (9 ng/ml lower per 10-years older, 95%CrI 6-12; 11 days shorter per 10-year older, 95%CrI 9-12), in males (30 ng/ml lower, 95%CrI 21-38; 15 days shorter, 95%CrI 10-19), and those reporting long-term health conditions (25 ng/ml lower, 95%CrI 16-34; 10 days shorter, 95%CrI 5-14). Within extended dosing intervals, a longer dosing interval was associated with a lower peak level (10 ng/ml lower per 1-week longer, 95%CrI 6-15), but a longer half-life (7 days longer per 1-week longer, 95%CrI 4-9). Compared with an 8-week extended schedule, a 3-week dosing interval was associated with a shorter half-life including all participants (23 days shorter, 95%CrI 8-37). However, when restricting to participants ≤70 years, there was no evidence of differences in half-life between 3-weeks (100 days) and 8-weeks (100 days), and the 3-week trajectory was closer to the trajectory from the extended dosing intervals (**Table S3, Figure S8**). Prior infection was associated with a higher peak level (22 ng/ml higher, 95%CrI 6-39), although the impact was likely under-estimated due to the assay quantification limits, and a longer half-life (87 days longer, 95%CrI 60-121). There was no evidence that deprivation was associated with either peak level or half-life with BNT162b2.

Comparing the effects of factors between the two vaccines, and with our previous findings on natural infection[16] **(Figure 5)**, effects of some factors were relatively consistent between ChAdOx1, BNT162b2 and/or natural infection, albeit with differing effect sizes (e.g age, sex, on half-life; sex, ethnicity on peak; prior infection on peak and half-life), whilst for others effects were in opposite directions (e.g age on peak, ethnicity on half-life). As above, other than for prior infection, factors had a much greater effect for BNT162b2 than ChAdOx1, particularly on half-life.

Duration of antibody response and association with protection

The estimated time from second vaccination to antibody levels reaching the 42 ng/ml positivity threshold was around 250-300 and 400-600 days for ChAdOx1 participants without and with prior infection, respectively, with relatively little variation across age, sex, dosing interval, long-term health conditions **(Figure 6)**. For BNT162b2, the estimated durations varied substantially across these factors. In participants without prior infection, the time was 500-1000 days at younger ages, versus 300-500 days at older ages, and was substantially longer in females, those with longer dosing intervals, and without long-term health conditions. Two doses following previous infection resulted even longer durations with BNT162b2, especially for younger age groups. Among participants ≤70 years with BNT162b2, the estimated durations between 3- and 8- week dosing interval were similar.

Emerging viral variants may need higher antibody levels for the same level of neutralising activity[17]; a sensitivity analysis therefore assumed 2- to 5-fold greater levels would be required, and compared three populations in order of vulnerability: 40-year-old females without long-term health conditions, 60-year-old males without long-term health conditions, and 80-year-old males with long-term health conditions. If 5-fold higher antibody levels were required, for a 40-year-old female without long-term health conditions or prior infection, the estimated time from second dose to 42 versus 42*5=210 ng/ml reduced from 250 to 50 days with ChAdOx1 and from 600 to 300 days with BNT162b2. For an 80-year-old male with long-term health conditions, the time reduced from 220 to 50 days with ChAdOx1 and from 350 to 150 days with BNT162b2 **(Figure 7).** With increasing vulnerability, the differences between the two vaccines in the estimated duration above different thresholds were smaller.

Non-responders to vaccinations

We previously used latent class mixed models to identify 5.8% and 5.1% of a smaller population of participants receiving one ChAdOx1 or BNT162b2 dose, respectively, as non-responders[18]. Because latent class models would not fit with larger numbers, we used a heuristic rule based on these previous observations to define non-response as all antibody measurements <28 ng/ml (similar levels as with the previous non-response class) and having at least one antibody measurement 21 days after the first or second dose. To examine robustness, we also restricted to those having at least two antibody measurements, and after both doses (rather than each separately). Across different assumptions **(Table S4)**, we found that 5.9-8.7% and 5.0-7.3% of participants were classed as non-responders to the first ChAdOx1 or BNT162b2 dose, respectively, similar to previously. However, only 0.6-1.0% and 0.1-0.7% participants were non-responders to the second ChAdOx1 or BNT162b2 dose, respectively, and 0.5-0.6% and 0.1-0.3% were non-responders to both first and second doses of ChAdOx1 or BNT162b2, respectively.

Discussion

With the increasing coverage of second SARS-CoV-2 vaccinations, estimating antibody responses after second doses is important in understanding how long antibodies and associated protection might last. In this study, based on a large random sample of the UK population, we found significant boosting of anti-spike IgG induced by the second dose of both ChAdOx1 and BNT162b2 vaccines in all age groups and using different dosing intervals, including the three-week dosing interval for BNT162b2. Consistent with our previous findings[18], those receiving ChAdOx1 had lower anti-spike IgG responses than BNT162b2. For younger individuals, levels declined faster after a second ChAdOx1 dose, but with increasing age, levels declined faster after a second BNT162b2 dose – although this was offset by higher peak levels. In the most vulnerable groups, the net effect was a similar duration of time above different thresholds from the two vaccines, but with longer durations with BNT162b2 in younger groups. After the second vaccination, older age, male sex, and long-term health condition were all associated with substantially faster antibody declines in participants who received BNT162b2 but had no or little effect on declines with ChAdOx1.

Antibody trajectories after vaccination differed substantially by prior infection status. Previous studies reported that a single dose of BNT162b2 or Sputnik V, an adenovirus-based vaccine, elicited high immune responses in previously infected individuals, and their post-vaccination antibody levels were similar to, or higher than, those without prior infection who received two doses[19–22]. We found slightly lower IgG levels after a single BNT162b2 dose in previously infected participants than in those with two BNT162b2 doses without prior infection, particularly at older ages. This suggests that a second BNT162b2 dose may still be helpful for previously infected individuals where supplies are sufficient, especially for older populations. However, for ChAdOx1, the post-second dose IgG levels in those without prior infection were lower than in those previously infected with one ChAdOx1 dose, suggesting natural infection generates a stronger antibody response than ChAdOX1 vaccination.

When estimating antibody declines after the second dose, prior infection was associated with a higher peak level and a longer half-life for both vaccines, but the effect was greater on peak level for ChAdOx1 and on half-life for BNT162b2. The more modest increase in peak level for BNT162b2 may indicate that two BNT162b2 doses produces high and comparable IgG levels regardless of prior infection status, but could also be due to the upper limit of quantification of 800 ng/ml for the assay. The stronger post-vaccination response seen after prior infection may also reflect enhanced boosting from exposure to ongoing virus transmission.

From the unadjusted GAM models, dosing intervals between 8 and 12 weeks generated similar antibody levels and had similar trajectories post-second dose for both ChAdOx1 and BNT162b2, suggesting variations in these extended dosing intervals did not have a large influence on the post-vaccine antibody response. In these unadjusted models, the 3-week BNT162b2 interval had lower antibody levels 21 days post-second dose than extended dosing intervals, but this was because antibody levels were still rising at this time point, and antibody levels were similar from around 42 days post-second dose. In the adjusted Bayesian model, a 3-week interval had a 23-day shorter half-life than an 8-week interval in the whole population; however, when restricted to ≤70 years, both a 3-week interval and an 8-week interval had a half-life of 100 days at the reference group.

Recent studies have suggested that BNT162b2 extended dosing intervals yield much higher antibody neutralising and IgG responses than the original 3-week interval, including a UK study on 175 older adults comparing 12-week and 3-week intervals 2-3 weeks post-second dose[7], the PITCH study on 503 UK healthcare workers comparing 6–14-week and 3-4 week intervals 4 weeks post-second dose [8], and another UK study on 569 adults comparing >6-week and 3-week intervals 14-34 days post-second dose[9]. These differences are plausibly related to these studies only measuring antibody levels at specific time points after second vaccination, which may not be optimal for comparison (**Figure 1**), given the 3-week dosing interval antibody levels increasing from 3-6 weeks post-second dose.

In our GAM models, older individuals had lower antibody levels after a first dose, but age differences attenuated post-second dose; hence, although boosting of responses was seen in all individuals post-second dose, this was most marked for those who were older. Anti-spike IgG levels have previously reported to be inversely correlated with age after the first dose but age-independent after the second dose[23]. Although all age groups had high antibody responses after the second dose, from our linear mixed model, older individuals still independently had lower IgG peak levels and a shorter half-life for BNT162b2, indicating attenuated responses in older individuals. Age-related differences were smaller for ChAdOx1, older individuals having a slightly higher peak level and slightly shorter half-life.

We found that females had a higher peak IgG level for both vaccines and a longer half-life for BNT162b2, similarly to natural infection[16], and consistent widely reported enhanced immune responses in females[24–28]. Healthcare workers had higher IgG peak levels for both vaccines, potentially reflecting a “healthy worker” effect[29], ongoing occupational exposure or undetected prior infection. We also found that those reporting non-white ethnicity had higher IgG peak levels with ChAdOx1 and a longer half-life with BNT162b2. A few previous studies also reported higher antibody levels with non-white ethnicity after natural infection[16,30,31], so this could be due to genetic or

societal differences. However, another explanation may also be undetected prior infection, as many vaccinated participants did not have antibody tests before April 2021, and PCR testing was not widely available in the UK during the first wave until August 2020.

Having a long-term health condition was also associated with a lower peak level for both vaccines and a shorter half-life for BNT162b2; this may be expected due to impaired immunity, but the complete absence of effect for ChAdOx1 (given study power) likely reflects differences in the immune responses to these vaccines. Multiple other such differences in associations with the two vaccines were seen, e.g. factors associated with peak levels did not affect half-life for ChAdOx1, while for BNT162b2 factors were more consistently associated with both a lower peak level and a shorter half-life. Differences in vaccine response are expected given the differing design and mechanism of action of BNT162b2, an mRNA vaccine, and ChAdOx1, an adenovirus vector-based vaccine[32,33]. Alternative booster vaccines might reduce vaccine-specific differences, e.g. the Com-COV trial found a heterologous schedule generated a higher anti-spike IgG response for ChAdOX1/BNT162b2 than ChAdOx1/ChAdOx1, although side-effects were also more frequent[34].

Although many studies have estimated antibody half-lives after natural infection, data on antibody declines after second vaccination are limited. We estimated the half-lives of anti-spike IgG after second ChAdOx1 or BNT162b2 doses were 81 days and 115 days in those without prior infection, and 127 days and 202 days in those previously infected, indicating a relatively sustained antibody response. Assuming observed antibody declines can be extrapolated further, the predicted duration of antibody positivity (≥42ng/ml) was around 200-300 days for ChAdOx1 and 400-1000 days for BNT162b2 in those without prior infection and could be much longer for those previously infected. Due to the different factor effects, these estimated durations were similar across different population groups for ChAdOx1 but varied more for BNT162b2. Based on strong correlations between anti-spike IgG levels from our assay and neutralising activity (R^2=0.88) **(Figure S9),** which is associated with protection from re-infection[13], the protection against SARS-CoV-2 infection could last for 0.5-1 years for those receiving ChAdOx1 and over a year for BNT162b2. However, variants of concern may require a higher antibody level for the same level of protection[17]. Studies have reported a fivefold-reduced neutralizing response against Beta (B.1.351) and Delta (B.1.617.2) than Alpha (B.1.1.7) after two vaccine doses[35,36]. Given this, if a 5-fold higher threshold was needed for effective protection, the duration of protection could be reduced to less than 2 months for those receiving ChAdOx1 and 5-10 months for BNT162b2 without prior infection. However, protection against severe infection is likely to last considerably longer[13]. Further, in a recent study of vaccine effectiveness including all COVID-19 Infection Survey participants, not just those with antibody measurements, vaccine effectiveness against new infections, and infections with higher viral burden

or symptoms, remained high through 4 months, although dropped faster for BNT162b2 than ChAdOx1 (e.g. for higher viral burden infections from 92% to 79%, and for ChAdOx1 from 69% to 61% between 14 and 90 days after the second vaccination)[12]. This suggests that mechanisms other than current antibody levels such as memory-based responses, T cells or the innate immune response are involved in protection against infection[33]; further, the difference between vaccines in changes in antibody levels and protection suggests they may be having very different effects on laying down long-term memory.

Similar to our previous findings[18], around 6-9% and 5-7% of participants were non/low-responders who did not substantial increase their antibody levels after the first ChAdOx1 or BNT162b2 dose. However, non-response to a second dose was much smaller, <1%, suggesting that this can significantly boost an initial suboptimal response in most individuals, with nearly everyone seroconverting after the second ChAdOx1 or BNT162b2 dose.

Study limitations include insufficient data to include two mRNA-1273 Moderna vaccine doses in analyses. We measured anti-spike IgG antibody using a single assay, with the upper limit of quantification approached by a reasonable number of measurements (n=4189, 5.9%) in the few weeks following second BNT162b2 vaccination, potentially leading to under-estimating peak levels and over-estimating half-lives in those with the highest responses, e.g. younger age groups. As antibody responses were calibrated to a monoclonal antibody they can be compared with other studies. Neutralising antibodies and T-cell responses were not measured, but neutralisation titres were strongly correlated with anti-spike IgG titres **(Figure S9)**. We are not currently powered to assess correlates of protection, the relationship between antibody levels and vaccine effectiveness, which requires further investigation.

In summary, the second ChAdOx1 or BNT162b2 dose significantly boosts anti-spike IgG levels, and dosing interval has a limited impact on antibody response. This supports reducing the dosing interval to 8 weeks to increase protection against the widespread Delta variant; for BNT162b2, this could probably be reduced further to 3-weeks in those who have not yet received their second dose (predominantly ≤40 years). Older individuals, males, and those with long-term health conditions have substantially faster antibody declines with BNT162b2 but not ChAdOX1. Protection based on current positivity thresholds can last for at least 0.5-1 year for ChAdOx1 and over a year for BNT162b2; however, given the reduced effectiveness against variants of concern, the duration of protection may be significantly reduced. These results may inform vaccination strategies; a third boosting dose may be needed, and could be prioritised to the more vulnerable population groups.

Methods

Population and setting

The UK's Office for National Statistics (ONS) COVID-19 Infection Survey (CIS) (ISRCTN21086382) randomly selects private households on a continuous basis from address lists and previous surveys to provide a representative sample across its four countries (England, Wales, Northern Ireland, Scotland). After obtaining verbal agreement to participate, a study worker visited each household to take written informed consent from individuals ≥2 years. At the first visit, participants were asked for consent for optional follow-up visits every week for the next month, then monthly for 12 months or to April 2022. This consent was obtained from parents/carers for those 2-15 years, while those 10-15 years also provided written assent. Children aged <2 years were not eligible for the study. For the current analysis, we only included participants aged ≥16 years who were eligible for vaccination.

Individuals were surveyed on their socio-demographic characteristics, behaviours, and vaccination status. Combined nose and throat swabs were taken from all consenting household members for SARS-CoV-2 PCR testing. For a random 10-20% of households, individuals ≥16 years were invited to provide blood samples monthly for serological testing. Household members of participants who tested positive were also invited to provide blood monthly for follow-up visits. Details on the sampling design are provided elsewhere36. From April 2021, additional participants were invited to provide blood samples monthly to assess vaccine responses, based on a combination of random selection and prioritisation of those in the study for the longest period (independent of test results). The study protocol is available at https://www.ndm.ox.ac.uk/covid-19/covid-19-infection-survey/protocol-and-information-sheets. The study received ethical approval from the South Central Berkshire B Research Ethics Committee (20/SC/0195).

Vaccination data

Vaccination information was obtained from participants at visits by self-report, including vaccination type, number of doses, and vaccination dates. Participants from England were also linked to the National Immunisation Management Service (NIMS), which contains all individuals' vaccination data in the English National Health Service COVID-19 vaccination programme. There was good agreement between self-reported and administrative vaccination data (98% on type and 95% on date37). We used vaccination data from NIMS where available for participants from England, and otherwise data from the survey.

Participants aged ≥16 years who received two doses of ChAdOx1 or BNT162b2 from 8th December 2020 onwards with antibody measurements from 91 days before the first vaccination date up until

26th July 2021 were included in the main analysis. Only 1,612 participants received two doses of mRNA-1273 thus were not included **(Figure S1).**

Laboratory testing

SARS-CoV-2 antibody levels were measured on venous or capillary blood samples using an ELISA detecting anti-trimeric spike IgG developed by the University of Oxford36,38. Normalised results are reported in ng/ml of mAb45 monoclonal antibody equivalents. Before 26 February 2021, the assay used fluorescence detection as previously described, with a positivity threshold of 8 million units validated on banks of known SARS-CoV-2 positive and negative samples38. After this, it used a commercialised CE-marked version of the assay, the Thermo Fisher OmniPATH 384 Combi SARS-CoV-2 IgG ELISA (Thermo Fisher Scientific), with the same antigen and colorimetric detection. mAb45 is the manufacturer-provided monoclonal antibody calibrant for this quantitative assay. To allow conversion of fluorometrically determined values in arbitrary units, we compared 3,840 samples which were run in parallel on both systems. A piece-wise linear regression was used to generate the following conversion formula:

log10(mAb45 units) = 0.221738 + 1.751889e-07*fluorescence_units +

5.416675e-07*(fluorescence_units>9190310)*(fluorescence_units-9190310)

We used ≥42 ng/ml as the threshold for determining IgG positivity (corresponding to the 8 million units with fluorescence detection). Given the lower and upper limits of the assay, measurements <2 ng/ml (2,752 observations, 0.5%) and >800 ng/ml (13,952 observations, 2.5%) were truncated at 2 and 800 ng/ml, respectively.

Combined nose and throat swabs were tested by PCR assays using the Thermo Fisher TaqPath SARS-CoV-2 assay at high-throughput national 'Lighthouse' laboratories in Glasgow and Milton Keynes (up until 8 February 2021). PCR outputs were analysed using UgenTec FastFinder 3.300.5, with an assay-specific algorithm and decision mechanism that allows conversion of amplification assay raw data into test results with minimal manual intervention. Positive samples are defined as having at least a single N-gene and/or ORF1ab detected (although S-gene cycle threshold (Ct) values are determined, S-gene detection alone is not considered sufficient to call a sample positive36) and PCR traces exhibiting an appropriate morphology.

Statistical analysis

This analysis included participants aged ≥16 years who received two doses of ChAdOx1 or BNT162b2 vaccines with or without prior SARS-CoV-2 infection. Age was truncated at 85 years in all analyses to reduce the influence of outliers. Prior infection was defined as having a PCR-positive swab test

recorded in the survey or the English national testing programme (data were not available for Scotland, Wales, and Northern Ireland), or a prior positive anti-spike IgG result (≥42 ng/ml) any time before the first vaccination. The dosing interval was calculated from the first and second vaccination dates. For the main analysis, we excluded a small number of participants who were considered as non-responders after the first or second dose in those without prior infection, which was defined as all antibody measurements being <28 ng/ml and having at least one antibody measurement 21 days after the first or second dose (N=4,940 excluded for ChAdOx1, N=1,624 excluded for BNT162b2) **(Figure S1)**. We also excluded participants with dosing interval <49 days or >91 days for ChAdOX1 (N=3,896 excluded), and 29-48 days or >91 days for BNT162b2 (N=4,958 excluded). 17-28 days were classified as a 3-week interval for BNT162b2.

We used linear generalized additive models (GAMs) to model anti-spike IgG antibody measurements after the first and second dose. We built separate models by vaccine type and prior infection status given the hypothesis that antibody response would vary by these two factors. Each model was adjusted for age and dosing interval using a tensor product of B-splines to allow for non-linearity and interaction among age, dosing interval, and time since vaccination, setting the date of the second vaccination as t=0. The smoothing penalty was selected using fast restricted maximum likelihood as implemented in the mcgv R package. The 95% CIs were calculated using the following formula: prediction ± 1.96 × standard error of prediction. We only included antibody measurements from 14 days before the first dose (setting the most recent measurement prior to 14 days before the first dose as 14 days) for those with no evidence of prior infection, and excluded measurements taken after the 95th percentile of the observed t>0 time points to avoid the outlier influence.

We used Bayesian linear mixed interval-censored models to estimate changes in antibody levels after the second ChAdOx1 or BNT162b2 dose. We included measurements from 21 days post-second dose reflecting the peak level (except for 3-week BNT162b2, see below). Measurements taken after the 95th percentile of the observed time points from 21 days post-second dose were excluded to avoid outlier influence. We assumed an exponential fall in antibody levels over time, i.e., a linear decline on a log2 scale. To examine non-linearity in antibody declines, especially the assumption that the rate of antibody decline would flatten, we additionally fitted a model using 3-knot splines for time (knots placed at 10th, 50th, and 90th of observed time points) and compared the model fit with the log-linear model using the leave-one-out cross-validation information criterion (LOOIC). We found that the spline model had a higher LOOIC (indicating a worse model fit) than the log-linear model for ChAdOx1 (189523 vs 180735), but a slightly lower LOOIC (indicating a better model fit) for BNT162b2 (126756 vs 128882). However, for both vaccines, the estimated trajectories were similar

and there was no evidence of flattening (**Figure S10**), so we used the log-linear model for the rest of the analysis.

Population-level fixed effects, and individual-level random effects for intercept and slope were included in both models. Correlation between random effects was included in the BNT162b2 model but not the ChAdOx1 model based on preliminary analysis on a smaller random sample (N=20,000) where this correlation parameter was estimated as 0.03 (95% CrI -0.06-0.13). The outcome was right-censored at 800 ng/ml reflecting truncation of IgG values at the upper limit of quantification. We built a multivariable model to examine the association between peak levels and antibody half-lives with continuous age (16-85 years), sex, ethnicity, report having a long-term health condition, report working in patient-facing healthcare, deprivation percentile, continuous dosing interval (7-13 weeks), and prior infection status for both vaccines. For BNT162b2, we additionally examined the impact of a 3-week dosing interval (17-28 days) by creating a binary variable and excluding antibody measurements ≤42 days post-second dose for the 3-week group (identified from the GAM as they peaked at around 42 days post-second dose). A sensitivity analysis restricting the BNT162b2 model to participants ≤70 years was performed to assess the impact of a 3-week dosing interval in a younger population.

For each Bayesian linear mixed interval-censored model, weakly informative priors were used **(Table S5).** Four chains were run per model with 4,000 iterations and a warm-up period of 2,000 iterations to ensure convergence, which was confirmed visually and by ensuring the Gelman-Rubin statistic was <1.05 **(Table S6).** 95% credibility intervals were calculated using highest posterior density intervals.

All analyses were performed in R 3.6 using the following packages: tidyverse (version 1.3.0), mgcv (version 1.8-31), brms (version 2.14.0), rstanarm (version 2.21.1), splines (version 3.6.1), ggeffects (version 0.14.3), arsenal (version 3.4.0), cowplot (version 1.1.0), bayesplot (version 1.7.2).

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Competing Interests statement

DWE declares lecture fees from Gilead, outside the submitted work. No other author has a conflict of interest to declare.

Data availability

Data are still being collected for the COVID-19 Infection Survey. De-identified study data are available for access by accredited researchers in the ONS Secure Research Service (SRS) for accredited research purposes under part 5, chapter 5 of the Digital Economy Act 2017. For further information about accreditation, contact Research.Support@ons.gov.uk or visit the SRS website.

Code availability

A copy of the analysis code is available at https://github.com/jiaweioxford/COVID19_vaccine_antibody_responsehttps://github.com/jiaweioxford/COVID19_second_vaccine_antibody_response.

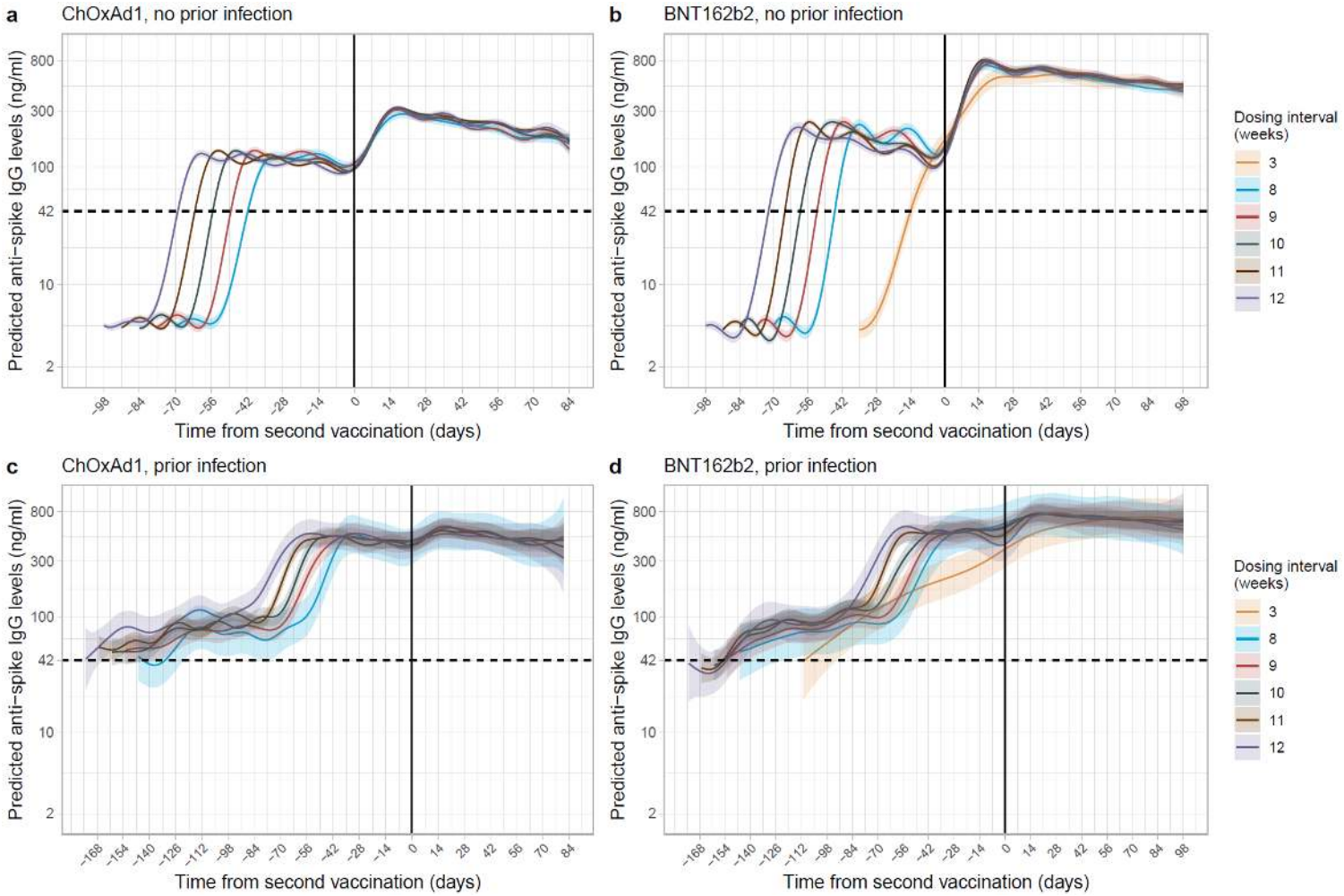

Figure 1. Predicted anti-spike IgG levels in 60-year-olds by time from second vaccination according to dosing interval, vaccine type and prior infection status. a, Participants who received two doses of ChAdOx1 without prior infection. **b**, Participants who received two doses of BNT162b2 without prior infection. **c**, Participants who received two doses of ChAdOx1 with prior infection. **d**, Participants who received two doses of BNT162b2 with prior infection. Different *x* axis scales reflect different durations of follow-up post-vaccination in the different cohorts. Predicted levels are plotted on a log scale. Black dotted line indicates the threshold of IgG positivity (42 ng/ml). Black solid line indicates the second vaccination date. Line colour indicates response predicted for 3 weeks, 8-12 weeks dosing interval. See **Figure S2, S4** for other age groups. The 95% CIs are calculated by prediction ± 1.96 × standard error of the prediction.

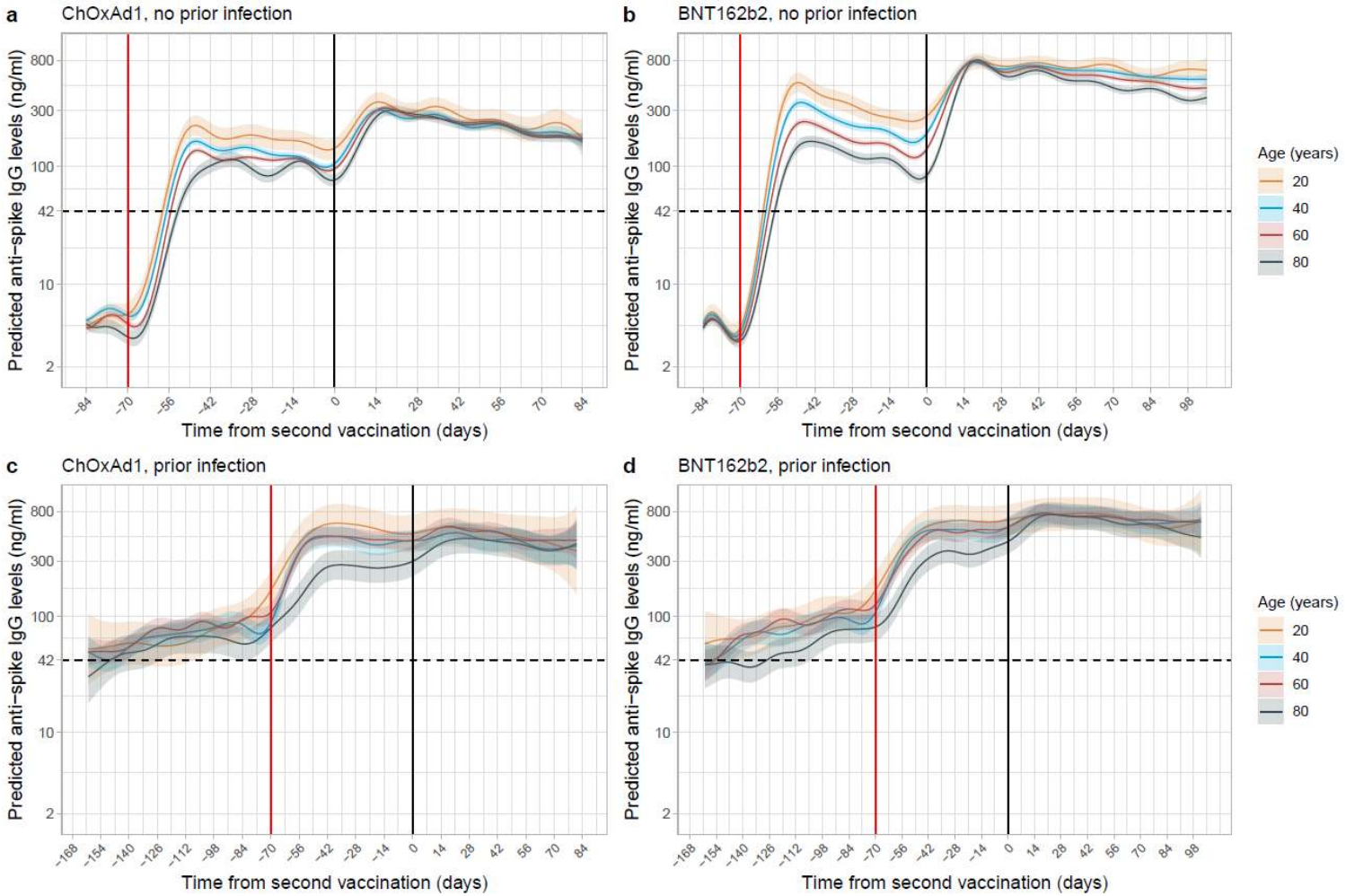

Figure 2. Predicted anti-spike IgG levels in participants with 10-week dosing interval by time from second vaccination according to age, vaccine type and prior infection status. a, Participants who received two doses of ChAdOx1 without prior infection. **b**, Participants who received two doses of BNT162b2 without prior infection. **c**, Participants who received two doses of ChAdOx1 with prior infection. **d**, Participants who received two doses of BNT162b2 with prior infection. Different *x* axis scales reflect different durations of follow-up post-vaccination in the different cohorts. Predicted levels are plotted on a log scale. Black dotted line indicates the threshold of IgG positivity (42 ng/ml). Red solid line indicates the first vaccination and black solid line indicates the second vaccination. Line colour indicates response predicted for age 20, 40, 60, and 80 years. See **Figure S3, S5** for other dosing interval groups; see **Figure 3** for comparison of vaccine type by age. The 95% CIs are calculated by prediction ± 1.96 × standard error of the prediction.

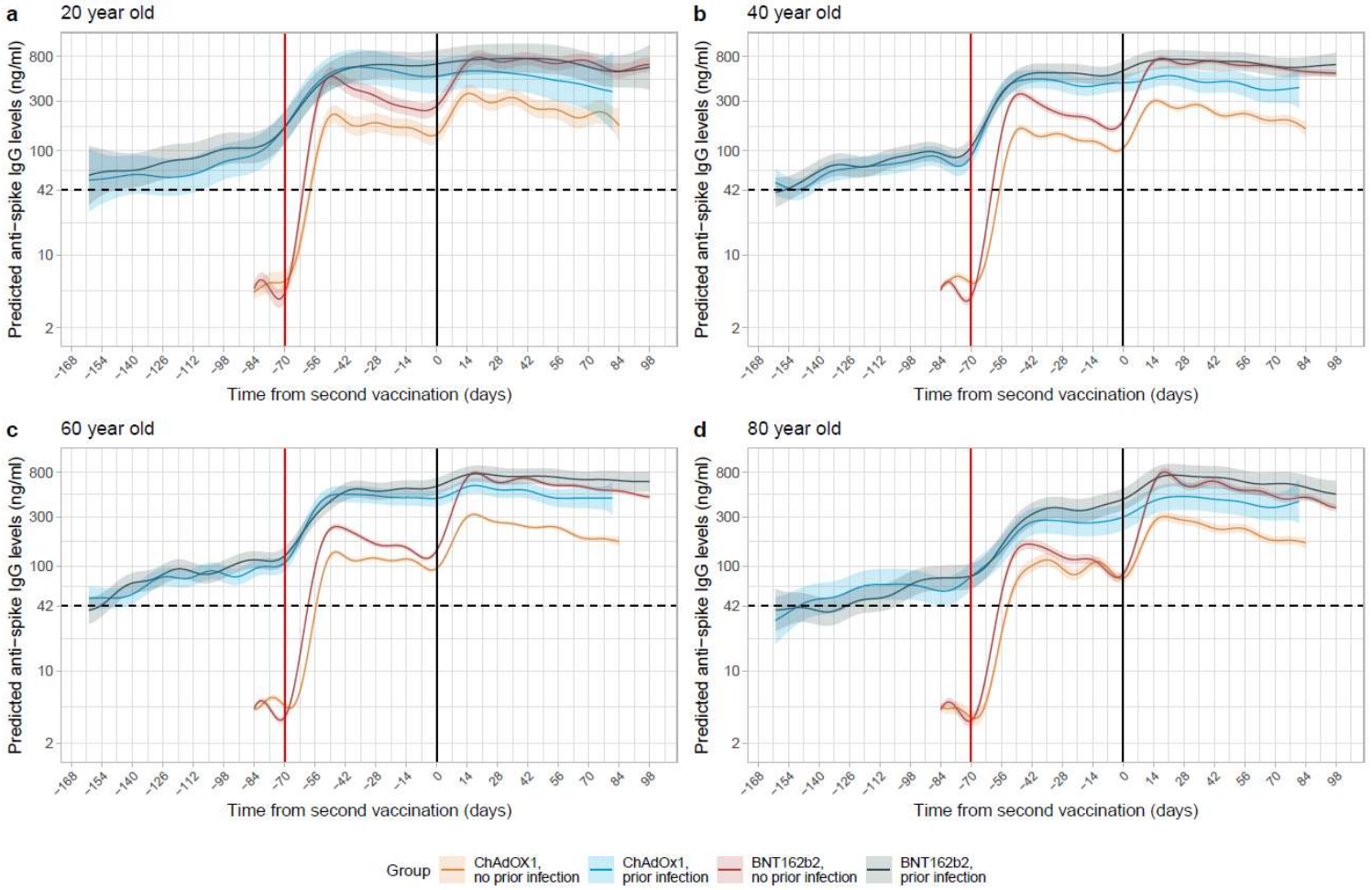

Figure 3. Predicted anti-spike IgG levels in participants with 10-week dosing interval by time from second vaccination according to vaccine type, age and prior infection status. a, 20-year-old. **b**, 40-year-old. **c**, 60-year-old. **d**, 80-year-old. Predicted levels are plotted on a log scale. Black dotted line indicates the threshold of IgG positivity (42 ng/ml). Red solid line indicates the first vaccination and black solid line indicates the second vaccination. Line colour indicates response predicted for ChAdOx1 and BNT162b2, with or without prior infection. See **Figure S6** for other dosing interval groups, see Figure 2 for comparison of age by vaccine type. The 95% CIs are calculated by prediction ± 1.96 × standard error of the prediction.

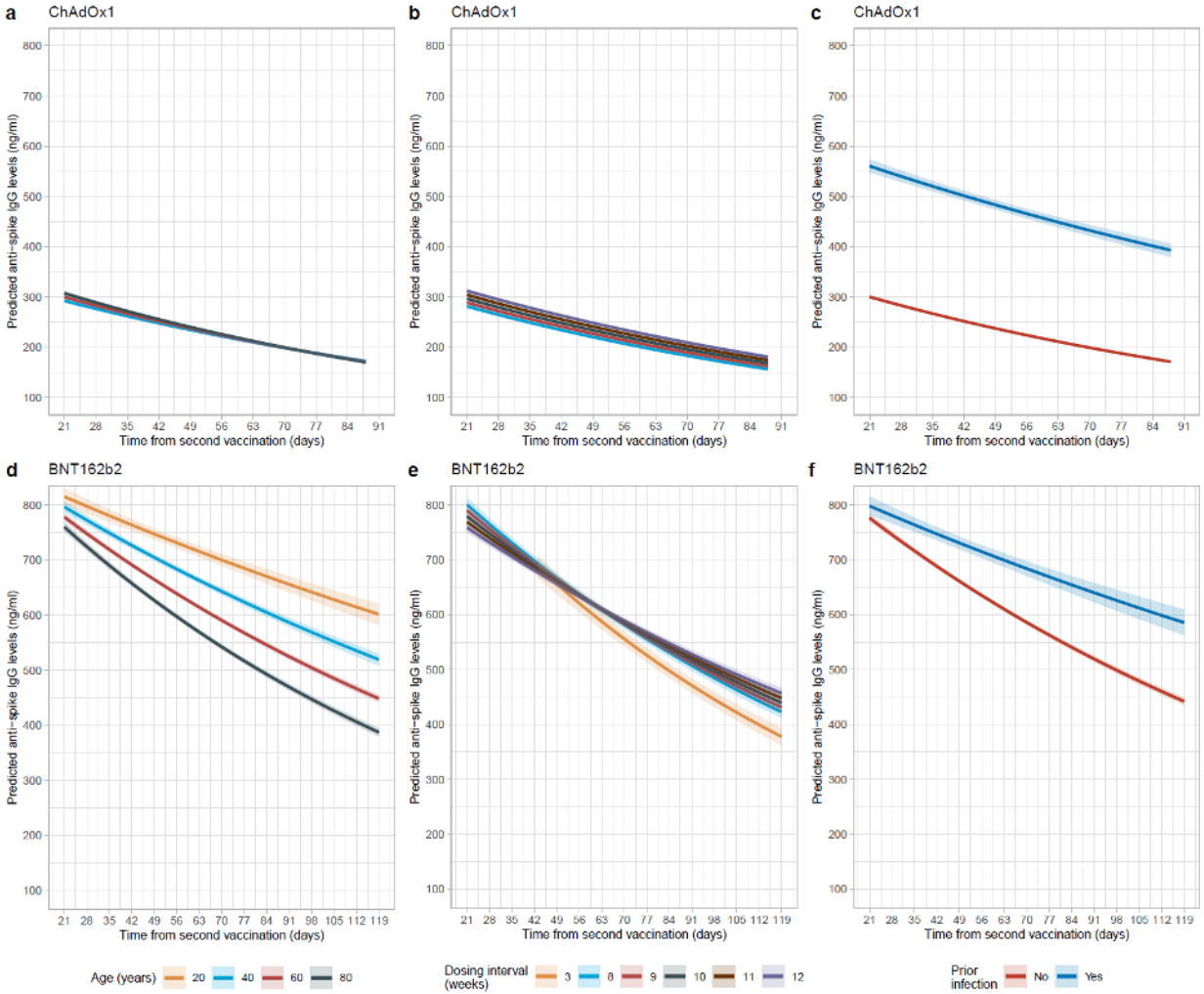

Figure 4. Posterior predicted trajectories of anti-spike IgG levels from 21 days post-second dose by age (panel a, d), dosing interval (panel b, e), and prior infection status (panel c, f). Panel a,b,c show participants who received two doses of ChAdOx1. **Panel d,e,f** show participants who received two doses of BNT162b2. Plotted at reference categories: 65 years, female, white ethnicity, not reporting a long-term health condition, not a healthcare worker, deprivation percentile=60, 10-week dosing interval, and no prior infection. In **panel a**, 20-year-old group is not plotted because the vast majority of those receiving ChAdOx1 were ≥40 years.

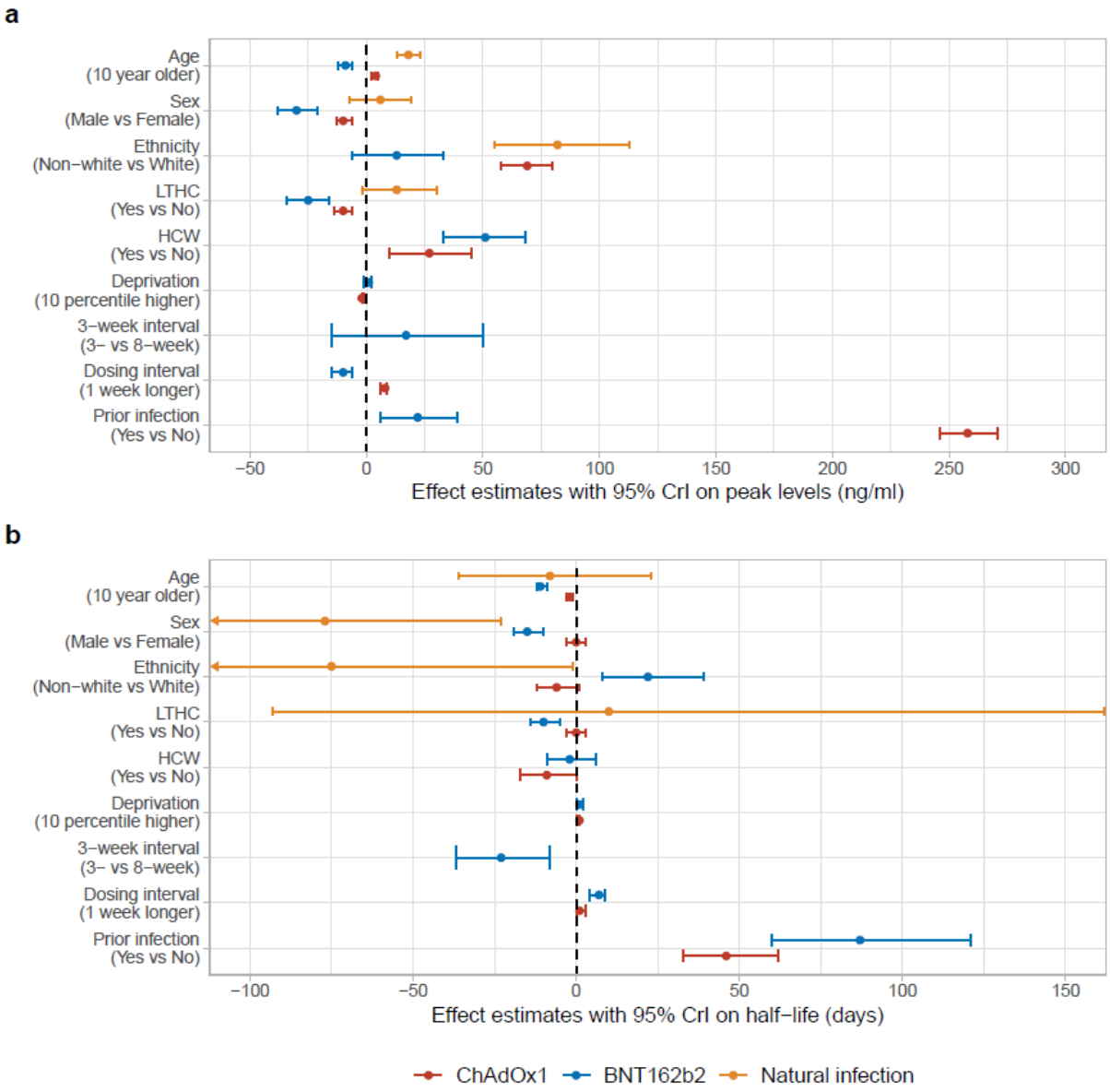

Figure 5. Comparison of effect of factors in participants who received two doses of ChAdOx1 or BNT162b2 or had natural SARS-CoV-2 infection. **a,** Effect on anti-spike IgG peak levels. **b,** Effect on anti-spike IgG half-lives. Mean estimates with 95% credibility intervals are presented. In panel b, 95% credibility intervals are truncated at -100 and 150 days for visualisation.

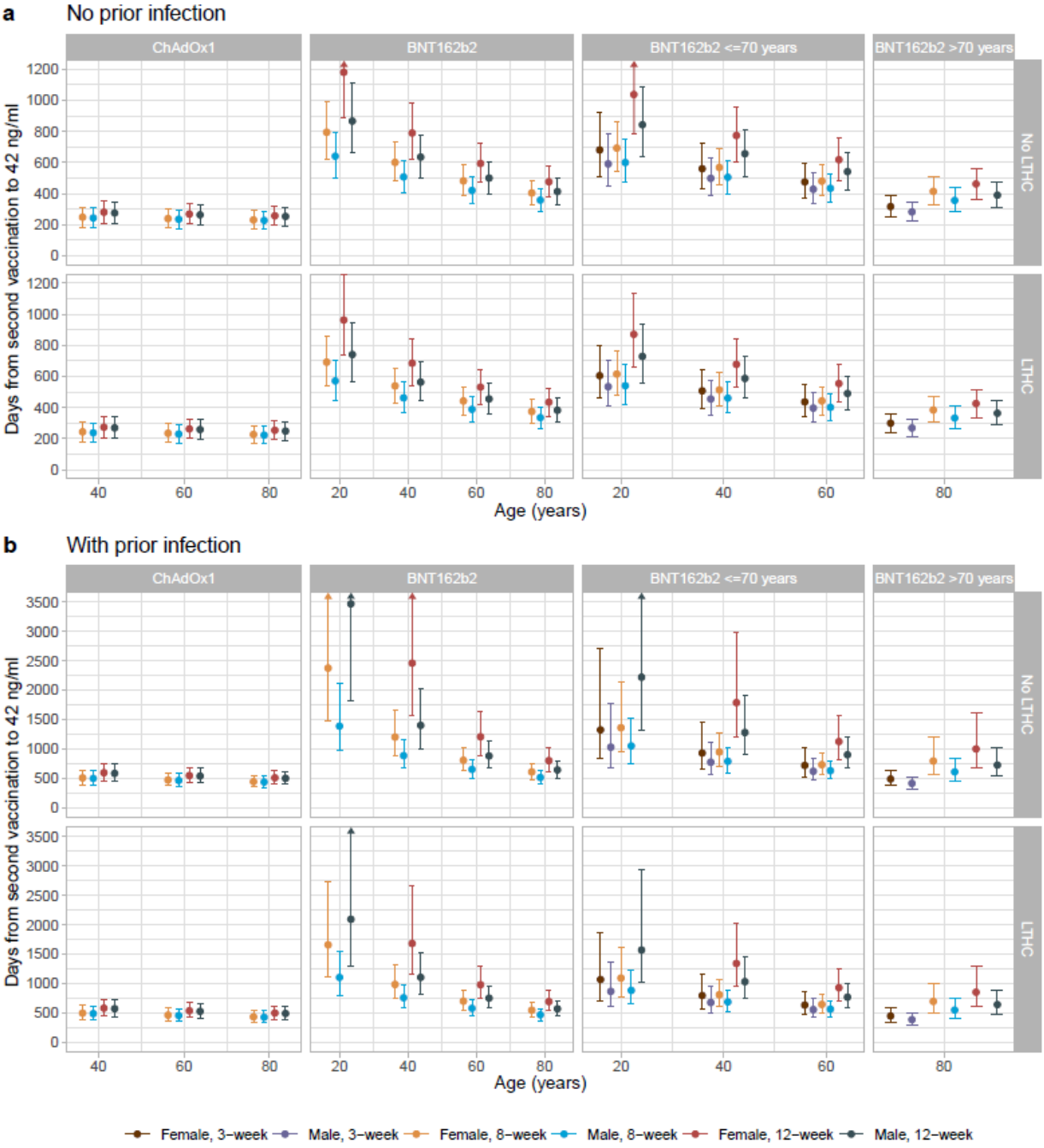

Figure 6. Posterior predicted days (95% credibility interval) from the second vaccination to the positivity threshold of 42 ng/ml in those without evidence of prior infection (panel a) and with evidence of prior infection (panel b), by age, sex, dosing interval, long-term health condition (LTHC), and vaccine type. y-axis is truncated at 1200 days (panel a) and 3500 days (panel b) for visualisation. For ChAdOx1, 20-year-old group is not plotted because the vast majority of those receiving ChAdOx1 were ≥40 years. In panel b, '20-year-old, female, 12-week' group is not plotted because their antibody levels were not estimated to decline.

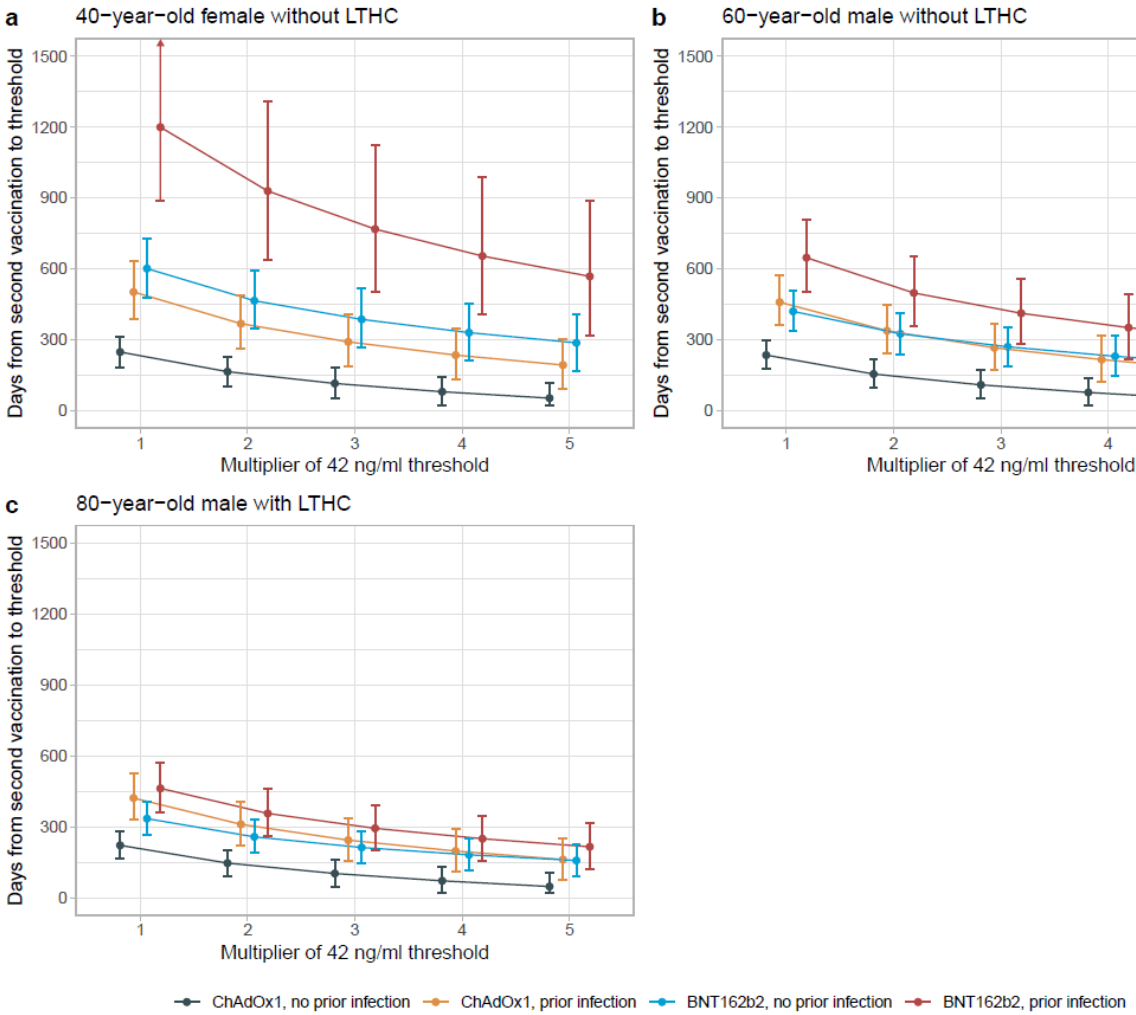

Figure 7. Posterior predicted days from the second vaccination to the positivity threshold 42 ng/ml multiplied by 1-5, according to prior infection status and vaccine type. a, in a 40-year-old female without long-term health conditions. **b**, in a 60-year-old male without long-term health conditions. **c,** in an 80-year-old male with long-term health conditions. All three panels were plotted at an 8-week dosing interval. LTHC: long-term health condition. Multipliers reflect the fact that higher antibody level may be required for protection against variants of concern.