Covid-19 vaccine-induced antibodies are attenuated and decay rapidly in infliximab treated patients

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Abstract

To inform healthcare policy for immunosuppressed patients there is a need to define SARS-CoV-2 vaccine responses. Here we report SARS-CoV-2 vaccine-induced antibody and T cell responses in patients treated with anti-tumour necrosis factor (anti-TNF), a commonly used biologic in inflammatory diseases, compared to patients treated with vedolizumab, a gut-specific antibody targeting integrin $\alpha4\beta7$ that does not impair systemic immunity. In anti-TNF recipients, the magnitude of anti-SARS-CoV2 antibodies was reduced five-fold, and rapidly decayed towards the seroconversion threshold by 14 weeks after second dose of vaccine. In contrast, anti-SARS-CoV-2 antibodies were sustained up to 16 weeks in vedolizumab-treated patients. Anti-SARS-CoV2 antibody decay was not observed in vaccinated patients previously infected with SARS-CoV-2. T cell responses were absent in one-fifth of anti-TNF and vedolizumab-treated patients after a second dose of either vaccine. Our data have important implications for anti-TNF recipients, including the need for vaccine prioritization, booster doses, and social distancing strategies.

Main

Vaccination programmes have reduced SARS-CoV-2 infections, transmission, hospitalisations and deaths. Whether the durability of vaccine responses will stem further waves of disease, including the spread of the delta variant is controversial. Public health bodies in the United Kingdom[1] and other countries have committed to a booster dose of vaccines later this year; however, in the USA and Europe, the Centre for Disease Control and prevention (CDC) and the European Medicines Agency (EMA) are waiting for data on infection breakthrough in the vaccinated population before further guidance is issued[2,3]. Specific recommendations will be needed for the large minority of the population who may for various reasons mount suboptimal immune responses.

Patients treated with immunosuppressive drugs were excluded from the registration trials of the SARS-CoV-2 vaccines and real-world effectiveness data are limited. Drugs targeting tumor necrosis

factor (TNF), such as infliximab, are the most frequently prescribed biological therapies used in the treatment of immune-mediated inflammatory disorders (IMIDs). Observational studies indicate that most patients with inflammatory bowel disease (IBD), an archetypal IMID, mount serological responses following SARS-CoV-2 vaccines; although most were underpowered to discern the impact of specific drugs, including immunomodulators (azathioprine, mercaptopurine, and methotrexate) and/or biologic therapies[4,5]. We recently reported, however, that antibody responses following SARS-CoV-2 infection or a single-dose of either the BNT162b2 or ChAdOx1 nCoV-19 SARS-CoV-2 vaccines are impaired in anti-TNF treated patients[6,7]. We hypothesised here that antibody and T cell responses following the second doses of BNT162b2 or ChAdOx1 nCoV-19 vaccines would be attenuated and less durable in infliximab-treated patients.

CLARITY IBD is a 40-week prospective observational study investigating immune responses to SARS-CoV2 infection and vaccination in IBD patients[6]. We measured anti-SARS-CoV-2 spike (S) receptor binding domain (RBD) antibodies in patients with IBD treated with either infliximab, or vedolizumab, a gut-specific antibody targeting integrin $\alpha4\beta7$, that does not impair systemic immunity. We report data from 2052 infliximab- and 925 vedolizumab-treated participants without evidence of prior SARS-CoV-2 infection, who had received uninterrupted biologic therapy since recruitment and had an antibody test performed between 14 and 70 days after a second dose of either the BNT162b2 or ChAdOx1 nCoV-19 SARS-CoV-2 vaccines. Participant characteristics are shown in Supplementary Table 2. Secondary outcome analyses are also presented for 283 infliximab- and 137 vedolizumab-treated patients who had had PCR-confirmed SARS-CoV-2 infection prior to vaccination. Seroconversion was defined as an anti-S RBD antibody concentration ≥15 U/mL, a threshold associated with viral neutralization of ≥20% with a positive predictive value of 99.10 % (95% CI: 97.74-99.64)[7]. Anti-SARS-CoV-2 antibody non-persistence was defined as the time to a four-fold decrease in anti-S RBD antibodies. Anti-S RBD antibody levels were compared with samples from 605 fully vaccinated adult participants from the Virus Watch study, a community cohort of 10,000

individuals representative of the UK population of England and Wales[8]. T cell responses to first and second doses of either vaccine are reported in 225 infliximab- and 76 vedolizumab-treated patients without prior infection. T cell responses were measured using interferon-γ ELISpot assays following stimulation of peripheral blood mononuclear cells (PBMC) with a pool of SARS-CoV-2 spike peptides.

Geometric mean [geometric SD] anti-S RBD antibody concentrations were significantly lower in patients treated with infliximab than vedolizumab, following a second dose of both the BNT162b2 (547.5 U/mL [6.3] vs 3980.4 U/mL [5.5], p <0.0001) and ChAdOx1 nCoV-19 (189.3 U/mL [5.1] vs 781.5 U/mL [3.6], p <0.0001) vaccines (Fig. 1a). Multivariable linear regression analyses in patients without prior SARS-CoV-2 infection confirmed that antibody concentrations were attenuated between four and five-fold in infliximab-, compared with vedolizumab-, treated patients in participants who received either the BNT162b2 (fold change [FC] 0.17 [95% CI 0.13, 0.22], p<0.0001) or ChAdOx1 nCoV-19 ([FC] 0.25 [95% CI 0.21, 0.30], p<0.0001) vaccines. Age ≥ 60 years, thiopurine or methotrexate use in patients who received the BNT162b2, but not the ChAdOx1 nCoV-19 vaccine, current smoking and Crohn's disease were also independently associated with lower anti-S RBD antibody concentrations. Conversely, non-white ethnicity was associated with higher antibody concentrations when data from both vaccines were taken together (Extended Data Fig. 1).

Seroconversion rates after the first vaccine dose were lower in infliximab- compared to vedolizumab-treated patients. However, administration of a second dose of vaccine triggered a >100-fold increase in antibody concentrations with the BNT162b2 vaccine and >30-fold with the ChAdOx1 nCoV-19 vaccine in both treatment groups (Fig. 1a). More infliximab- than vedolizumab-treated patients failed to seroconvert after their second vaccine dose (6.1% vs 1.3%, p < 0.0001).

Following two doses of either vaccine, anti-S RBD antibodies were sustained to more than 16 weeks in patients treated with vedolizumab (Fig. 1b) and were not different to those observed in

participants in the Virus Watch community cohort (Extended Data Fig 2): however, in infliximab-treated patients geometric mean concentrations decayed towards the seroconversion threshold, defined as anti-S RBD ≥15 U/mL, by 18 and 14 weeks after a second dose of the BNT162b2 and ChAdOx1 nCoV-19 vaccines, respectively (Fig. 1b). Cox proportional regression analysis demonstrated that infliximab compared to vedolizumab treatment was independently associated with anti-SARS-CoV-2 antibody non-persistence (hazard ratio (HR) 2.95 (95% CI 2.17 to 4.02), p < 0.0001) (Extended Data Fig. 3).

Amongst patients with SARS-CoV-2 infection prior to vaccination, geometric mean [SD] anti-S RBD antibody concentrations were lower in infliximab- compared with vedolizumab-treated patients after a second dose of BNT162b2 (1811.3 U/mL [3.5] vs 10079.6 U/mL [2.2], p <0.0001) and ChAdOx1 nCoV-19 (575.1 U/mL [5.2] vs 2595.1 [3.8] p <0.0001) vaccines. In all patients, antibody concentrations following vaccination were higher than those observed in patients without prior infection (Fig. 1b). Irrespective of vaccine or biologic type, anti-S RBD antibodies were maintained to more than 14 weeks.

There were no significant differences in the magnitude of anti-spike T cell responses observed in infliximab- compared with vedolizumab-treated patients after one or two doses of either vaccine (Fig. 2a). The proportion of patients failing to mount detectable T cell responses were similar in both groups (infliximab 19.6% vs. vedolizumab 19.2%). For recipients of one and two doses of BNT162b2 vaccine there was a modest positive correlation between T cell responses and antibody concentration. This association was not observed in recipients following either dose of the ChAdOx1 nCoV-19 vaccine (Fig. 2b). When T cell responses were ranked by magnitude of antibody responses, most patients who did not mount an antibody response had a detectable T cell response (Extended Data Fig. 4). In addition to the uncoupling of the T cell and antibody responses demonstrated, this analysis emphasised that about one fifth made no T cell responses irrespective of vaccine used and a

minority of individuals carry neither detectable antibody nor T cell responses after 2 doses of vaccine (Fig. 2b, Extended Data Fig. 4).

As many countries enter the third wave of COVID-19, our data have important implications for millions of patients treated with anti-TNF drugs, who could remain susceptible to infection even after vaccination. However, the sustained antibody responses observed in vaccinated patients with prior infection indicates that a third antigen exposure significantly bolsters the serological response and supports the rationale for providing booster doses to this patient population, who otherwise may face further prolonged periods of restrictive social distancing. Early data from solid organ transplant recipients reported that seroprevalence rates improved by about a third following a third dose of the BNT162b2 vaccine after two months[9]. When starting a biologic, it would be reasonable to consider differences in SARS-CoV-2 vaccine response as one of the factors when determining which drug to use. For patients who need to start anti-TNF therapy, they and their families should receive SARS-CoV-2 vaccines without an extended delay between doses. Whether the timing of booster doses, the temporary discontinuation of immunomodulators[10], the use of adjuvants including the influenza vaccines (ComFluCOV)[11] and/or switching between vaccines with different mechanisms of action[12] is more effective in immunosuppressed patients warrants further study.

The biology underpinning loss of durable antibody responses and uncoupling of the B cell and T cell responses merit further research. TNF is a pleiotropic cytokine and its activities include maturation of antigen presenting cells, modulation of T cell responses and stimulation of immunoglobulin synthesis[13–15]. TNF neutralization, or genetic ablation, results in substantial loss of B-cells in primary follicles in germinal centres, reduced numbers of memory B-cells in the periphery but preserved numbers of T cells[13]. Uncoupling of humoral and T cell immunity to SARS-CoV-2 has been observed in healthy individuals[16], and although the relative contributions of memory B cell and T cell responses have yet to be fully defined in SARS-CoV-2 immunity, the preservation of T cell immunity

reported here should provide some reassurance for anti-TNF treated patients although it is noteworthy that one fifth made no anti-spike T cell response following two doses of either vaccine. Chronic TNF exposure, a feature of many IMIDs, can render T cells anergic and can be reversed by anti-TNF treatment[17]. This may in part explain why the magnitude of T cell responses observed in anti-TNF-treated patients in this study did not differ significantly from patients treated with vedolizumab.

We acknowledge some limitations in our study. Although our data show major differences in the magnitude and durability of antibody responses, we have not assessed immunoglobulin classes, the quality of antibody responses, or their effectiveness against the Wuhan and variants of concern. However, there are strong positive associations between vaccine efficacy and viral neutralization across the COVID-19 vaccine trials[18,19]. Importantly, anti-RBD antibodies, such as the ones measured in this study, strongly correlate with Wuhan Hu-1 live virus neutralization assays[20].

In conclusion, our data show that in infliximab-treated patients, anti-SARS-CoV-2 spike antibody responses are attenuated and less durable following BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccination. As early as 14 to 18 weeks after completing the vaccination course, many anti-TNF treated patients have lost antibody-mediated protection from the virus, potentially leaving them susceptible to infection. One fifth of both infliximab- and vedolizumab-treated patients did not mount a T cell response and a small subset of patients had both poor antibody and T cell responses. This could have important implications for health policy recommendations for patients taking anti-TNF drugs, including vaccine prioritization, dosing intervals, booster requirements, and social distancing strategies.

Methods

Anti-SARS-CoV2 Serology

To determine antibody responses specific to vaccination we used the Roche Elecsys Anti-SARS-CoV-2 spike (S) immunoassay[21] alongside the nucleocapsid (N) immunoassay[22]. This double sandwich electrochemiluminescence immunoassay uses a recombinant protein of the receptor binding domain on the spike protein as an antigen for the determination of antibodies against SARS-CoV-2. Sample electrochemiluminescence signals are compared to an internal calibration curve and quantitative values are reported as units (U)/mL. In-house assay validation experiments were previously reported[6,7]. Seroconversion was defined at a threshold of 15 U/mL. ElecSys Anti-SARS-CoV-2 spike (S) RBD concentrations of greater than or equal to 15 U/ml are associated with neutralization of ≥20% with a positive predictive value of 99.10 % (95% CI: 97.74-99.64)[7].

At entry to CLARITY IBD and at follow-up visits, all patients were tested for previous SARS-CoV-2 infection using the Roche Elecsys anti-SARS-CoV-2 (N) immunoassay. Because antibody responses are impaired following PCR-confirmed natural infection we set a threshold of 0.25 times the cut-off index (COI) at or above which patients were deemed to have had prior infection [6]. We defined a second threshold of 0.12 times the COI, below which patients were deemed to have no evidence of prior infection. Patients with a PCR test confirming SARS-CoV-2 infection at any time prior to vaccination were deemed to have evidence of past infection irrespective of any antibody test result.

Peripheral blood mononuclear cell isolation

Whole blood was collected in lithium heparin tubes and peripheral blood mononuclear cells (PBMCs) were isolated by density-gradient centrifugation using Lymphoprep™ (Stem Cell Technologies) layered on to SepMate™ (Stem Cell Technologies) tubes. PBMC isolation was performed within 12 hours of venepuncture. Purified PBMCs were cryopreserved in 10% DMSO/50% FBS and stored in liquid nitrogen pending batch analysis. For T cell assays blood was sampled 3-6 weeks after vaccination.

Spike-peptide specific T cell responses

IFNg T cell ELISpot assays were performed using pre-coated plates (Mabtech 3420-2APT) and using the protocol described previously[16,20]. Two-hundred thousand cells were seeded per well and cells were stimulated with a peptide pool, containing 18 peptides derived from SARS-CoV-2 spike protein[23] at a concentration of 10 µg/ml/peptide. Plates were cultured for 18-20 hours before development and data collected using an AID classic ELISpot plate reader (Autoimmun Diagnostika GMBH). Results are expressed as difference in (delta) spot forming cells (SFC) per 10^6 PBMC between peptide stimulation and a media only control. A response below 2 standard deviations of the media only control wells was deemed to be a null response. Data was excluded if response to the positive control anti-CD3 stimulation was <200 SFC per 10^6 PBMCs.

Ethical consideration and role of funders

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Statistics

The sample size for CLARITY IBD was based on the number of participants required to demonstrate a difference in the impact of infliximab and vedolizumab on seroprevalence and seroconversion

following SARS-CoV-2 infection, with an estimated background seroprevalence of 0.05. We calculated that a sample of 6970 patients would provide 80% power to detect differences in the seroprevalence of SARS-CoV-2 antibodies in infliximab- compared with vedolizumab-treated patients, whilst controlling for immunomodulator status at the 0.05 significance level.

Statistical analyses were undertaken in R 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two tailed and p-values reported without any correction for multiple testing. P-values <0.05 were considered significant. We included patients with missing clinical data in analyses for which they had data and have specified the denominator for each variable. Anti-S RBD antibody concentrations are reported as geometric means and standard deviations. Other continuous data are reported as median and interquartile range, and discrete data as numbers and percentages, unless otherwise stated.

Univariable analyses, using t-tests of log-transformed anti-S RBD antibody concentration and Spearman's rank correlation coefficients, were used to identify demographic, disease, vaccine, and treatment-related factors associated with the concentration of anti-S RBD antibodies.

Mann-Whitney U test was used to compare the magnitude of T cell response (SFC/10^6 PBMCs) stratified by treatment and vaccine received, and Spearman's rank correlation coefficient was calculated to determine correlation between antibody and T cell responses. Multivariable linear regression models were used to identify factors independently associated with log anti-S RBD levels. A priori, we included age, ethnicity, biological medication and immunomodulator use. No stepwise regression was performed. Results are presented after exponentiation, so that the coefficients of the model correspond to the fold change (FC) associated with each binary covariate. For age, a cut-off was chosen based on graphical inspection of the relationship between age and anti-S RBD antibody concentrations.

We compared the durability of antibody responses by calculating 15-day rolling geometric mean anti-S RBD antibody concentrations. For this analysis we included participants who had an antibody

test carried out between 1 and 70 days after second vaccine dose. Time to a four-fold reduction in detectable anti-S RBD antibodies were visualised using Kaplan-Meier curves. Cox proportional hazard regression models were used to identify demographic, disease and treatment-related factors associated with anti-S RBD antibody non-persistence.

We conducted sensitivity analyses to compare antibody responses stratified by participants with serological or PCR evidence of SARS-CoV-2 infection at any time prior to vaccination.

Data availability

The study protocol including the statistical analysis plan is available at www.clarityibd.org. Individual participant de-identified data that underlie the results reported in this article will be available immediately after publication for a period of 5 years. The data will be made available to investigators whose proposed use of the data has been approved by an independent review committee. Analyses will be restricted to the aims in the approved proposal. Proposals should be directed to tariq.ahmad1@nhs.net. To gain access data requestors will need to sign a data access agreement.

Code availability

Code used for data analysis will be available upon request directed to nick.kennedy1@nhs.net.

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Author Contributions

NAK, JRG, CB, SS, NP, TA participated in the conception and design of this study. CB was the project manager and coordinated patient recruitment. RN and TJM coordinated all biochemical analyses and central laboratory aspects of the project. SL, NAK, AS, DMS, CJR, RCS, SHK, FPP, KML, DKB, NC, DC, CB, MJ, SS, JLA, LC, JCL, CDM, ALH, PMI, GRJ, KBK, CAL, CWL, DMA, RJB, JRG, NP, TA were involved in the acquisition, analysis, or interpretation of data. DMS, CJR, KML, DKB, and FFP performed, analysed and interpreted T cell experiments. T cell experiments were supervised, designed, analysed and interpreted by RJB and DMA. Data analysis was done by NAK, DMS and RJB. Drafting of the manuscript was done by SL, NAK, NC, SS, CWL, DMA, RJB, JRG, NP, TA. NP and TA obtained the funding for the study. All the authors contributed to the critical review and final approval of the manuscript. NAK, NP and TA have verified the underlying data.

Competing Interests

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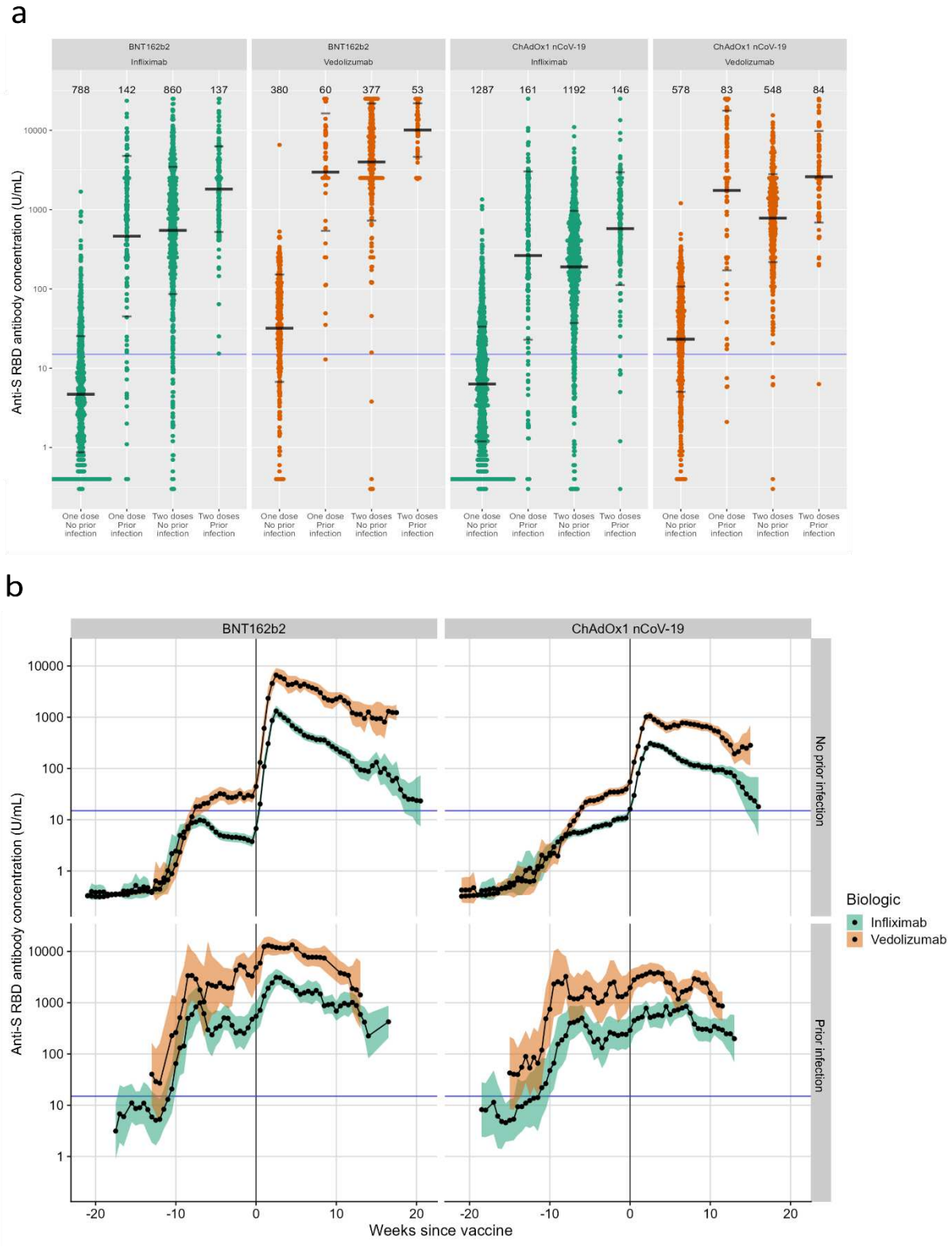


Figure 1: Anti-SARS-CoV-2 spike (S) receptor binding domain (RBD) antibody response and durability

a. Anti-SARS-CoV-2 spike RBD (anti-S RBD) antibody concentration stratified by biologic therapy (infliximab vs vedolizumab), type of vaccine, vaccine dose and prior infection. The wider bar represents the geometric mean, while the narrower bars are drawn one geometric standard

deviation either side of the geometric mean. Based on neutralization assays a threshold shown of 15 U/mL was used to determine seroconversion[7]. **b.** Rolling geometric mean antibody concentration over time stratified by biologic therapy (infliximab vs vedolizumab), vaccine, and prior infection. Geometric means are calculated using a rolling 15-day window (i.e. 7 days either side of the day indicated). The shaded areas represent the 95% confidence intervals of the geometric means. The blue line represents the seroconversion threshold (15 U/mL). Overall, data from 4470 participants with no prior infection (3029 on infliximab and 1441 on vedolizumab) and 683 participants with prior infection (459 on infliximab and 224 on vedolizumab) were included in this graph between 22 weeks prior and 18 weeks post second dose vaccination.

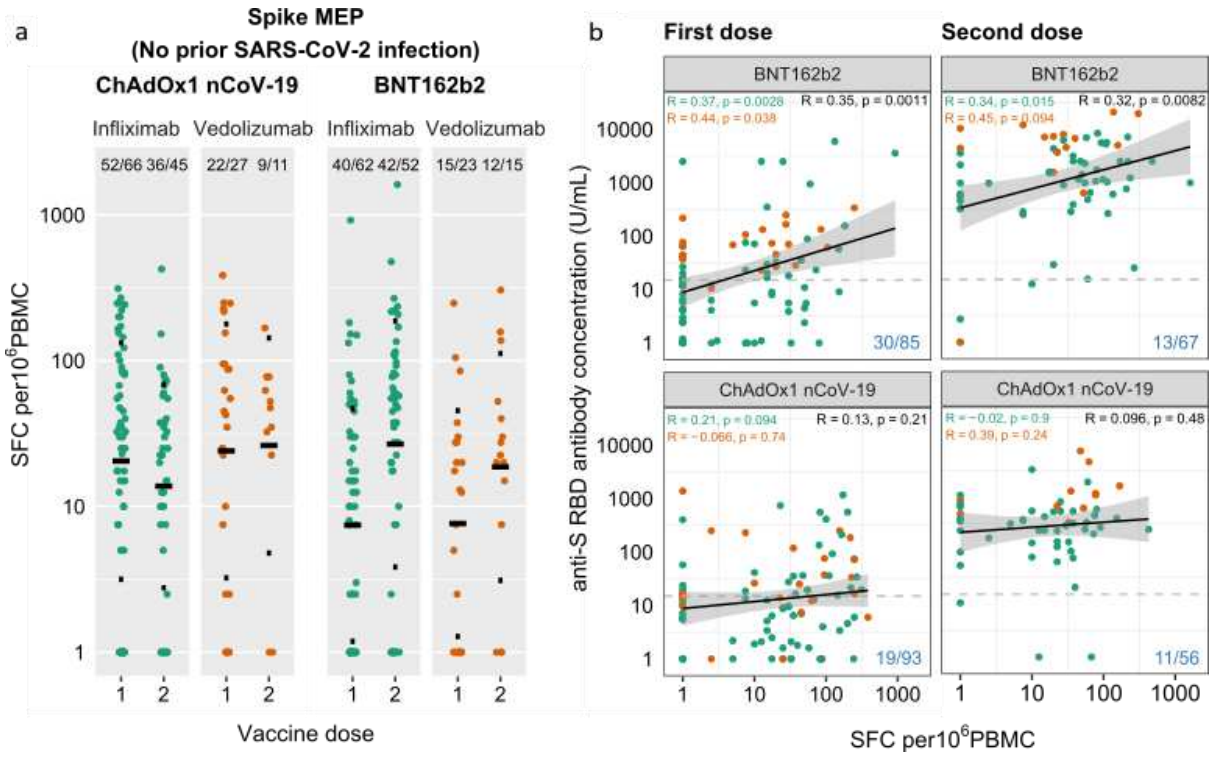
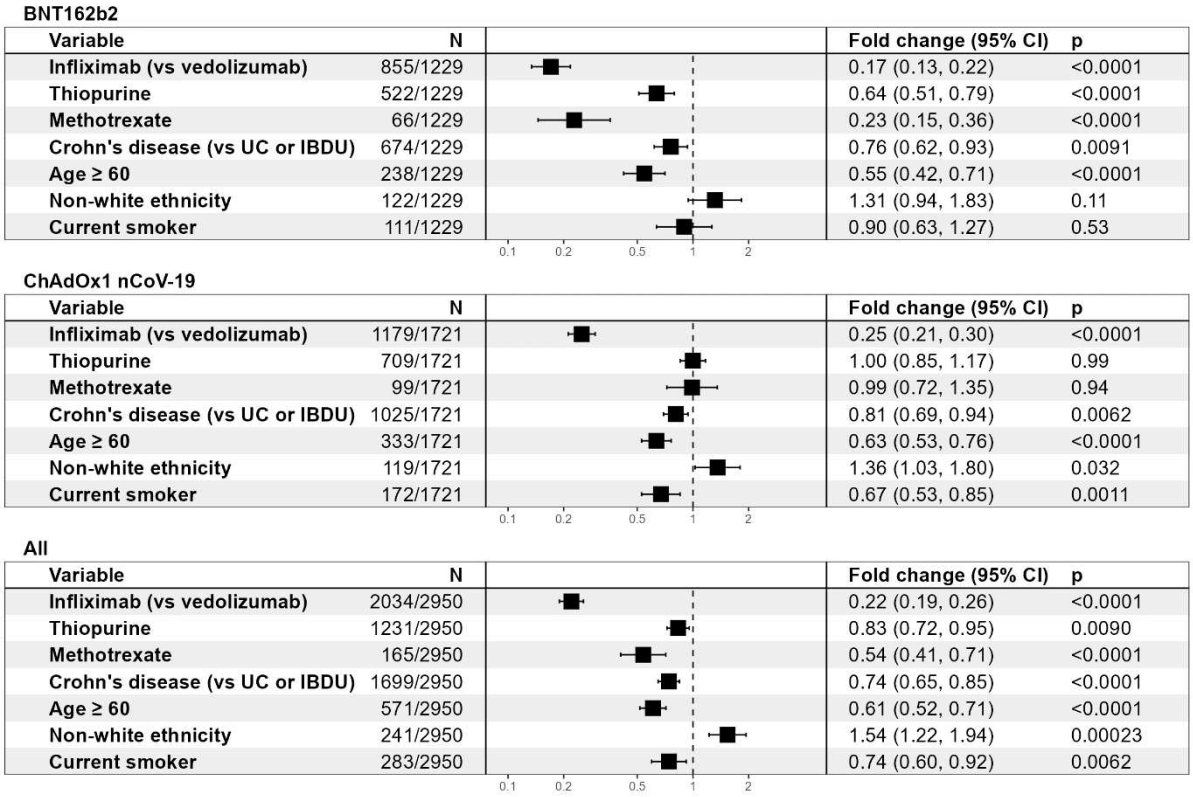


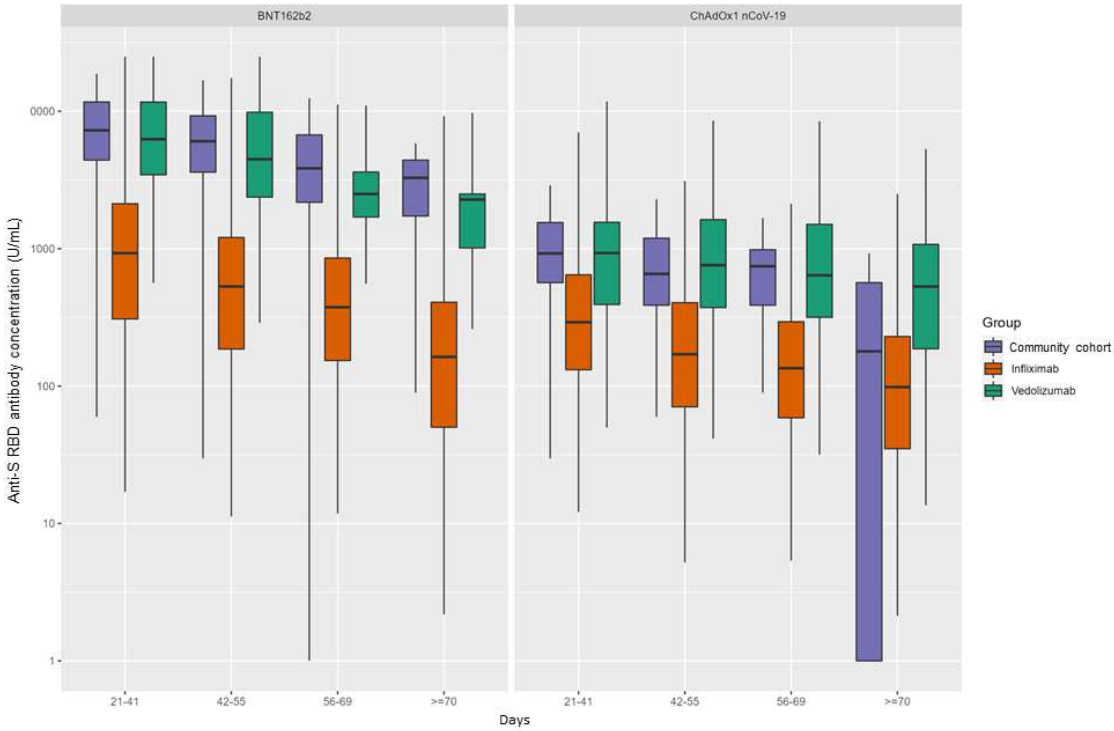
Figure 2. Anti-SARS-CoV-2 spike T cell responses stratified by biologic therapy (infliximab vs vedolizumab), vaccine type (BNT162b2 vs ChAdOx1 nCoV-19) and vaccine dose (one vs two).

a. Spike MEP T cell responses SFC per 10^6 PBMC stratified by biologic therapy (infliximab vs vedolizumab), type of vaccine and vaccine dose. The horizontal bar represents the geometric mean, while the narrower bars represent one geometric standard deviation either side of the geometric mean. The number of T cell responders / total number of individuals tested are shown in black at the top of each panel. **b.** Scatterplot demonstrating the correlation between T cell responses against spike (SFC per 10^6 PBMC) and anti-SARS-CoV-2 spike antibody concentration after the first (LHS) and second (RHS) dose of BNT162B2 (top) and ChAdOx1 nCoV-19 (bottom). The number of non-T cell responders / total number of individuals tested is shown in blue on the bottom RHS of each panel. The horizontal dotted line in **b**. represents a threshold of 15 U/mL of anti-S1 SARS-CoV-2 antibody. The biologic infliximab is show in green and vedolizumab is shown in orange. R, Spearman's rank correlation. SFC, spot forming cells. MEP, mapped epitope peptide.

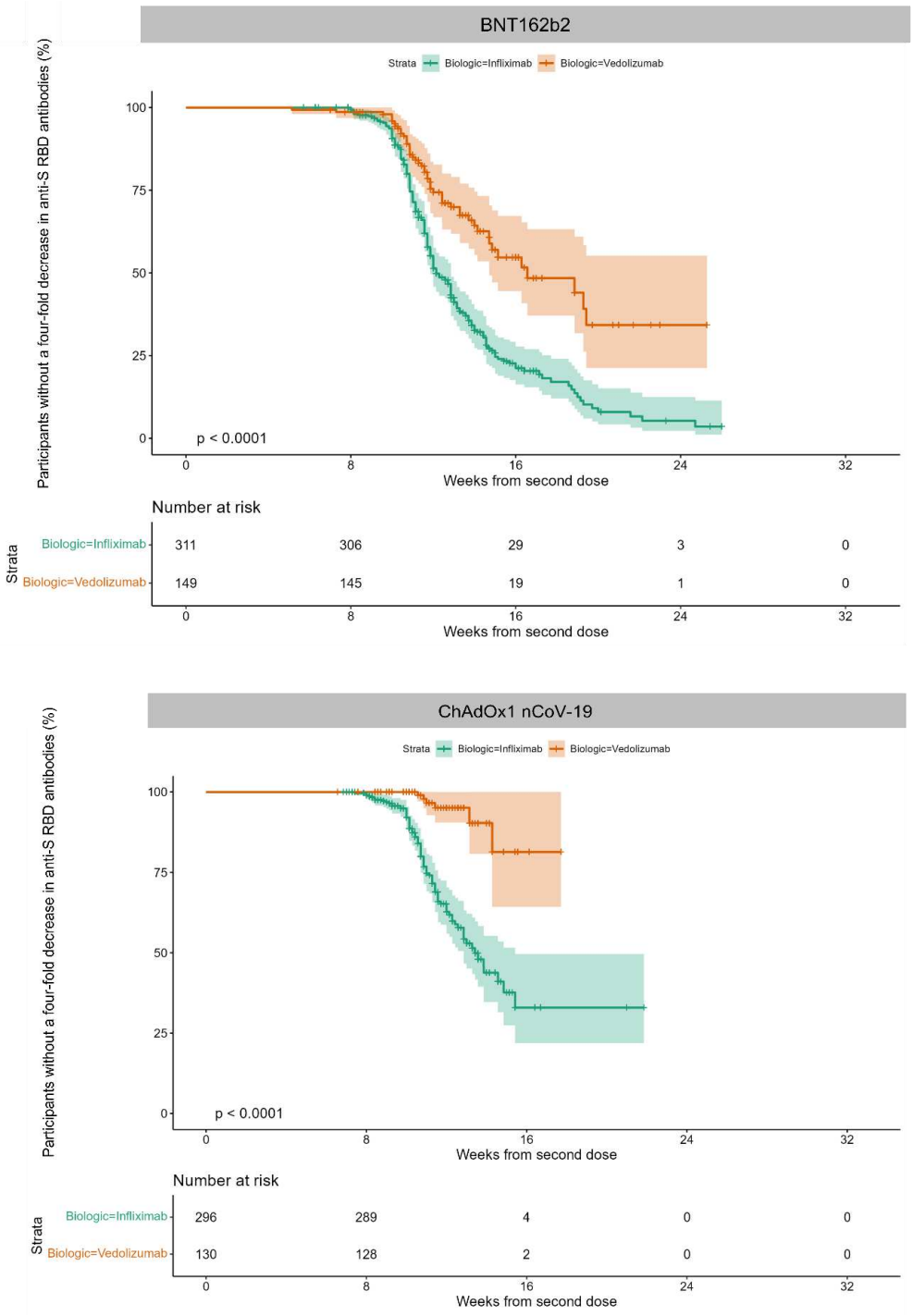


Extended Data Figure 1: Exponentiated coefficients of linear regression models of log(anti-S RBD antibody concentration)

The resultant values represent the fold change of antibody concentration associated with each variable. Each vaccine was modelled separately, and then a further model was created using all of the available data. Abbreviations: UC = ulcerative colitis, IBDU = IBD unclassified

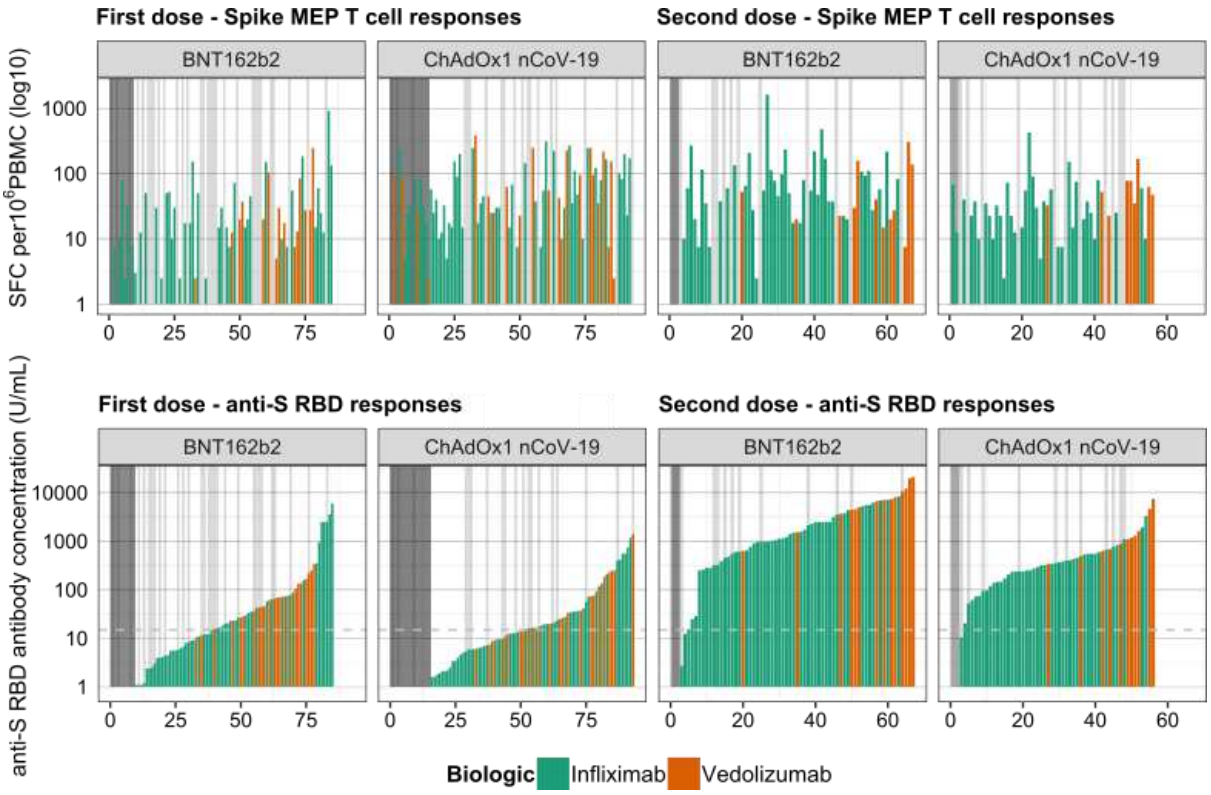


Extended Data Figure 2: Anti-S RBD antibody levels at defined time points (days) after a second dose of vaccine in patients stratified by type of vaccine and biologic therapy (infliximab, vedolizumab) compared with individuals in the Virus Watch community cohort.



Extended Data Figure 3: Kaplan-Meier graphs showing the time to a four-fold drop in anti-S RBD antibody following the second dose of vaccination stratified by type of vaccine

Patients who had more than one anti-S RBD antibody measurement at least 2 weeks after a second dose of either vaccine were included in this analysis. Overall, data from 886 patients (311 infliximab- and 139 vedolizumab-treated patients who received the BNT162b2 vaccine and 296 infliximab- and 130 vedolizumab-treated patients who received the ChAdOx1 nCoV-19 vaccine) were included in this analysis. P-value was defined using a log-rank test.



Extended Data Figure 4: Anti-spike T cell responses ordered by cumulative magnitude of anti-S RBD following two doses of the BNT162b2 or ChAdOx1 nCoV-19 vaccine shows uncoupling of the T cell and antibody responses

Top panel shows T cell responses to spike, and bottom panel shows anti-S RBD responses plotted for individual study participants ordered by increasing magnitude of anti-S RBD antibody concentration (U/mL). The vertical grey bars indicate individuals with no T cell response against spike. The horizontal dotted line represents a threshold shown of 15 U/mL of anti-S RBD.

Supplementary Files

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