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

**Simeng Lin** ( simeng.lin1@nhs.net )
Royal Devon and Exeter NHS Foundation Trust https://orcid.org/0000-0002-4201-4879

**Nicholas A Kennedy**
Department of Gastroenterology, Royal Devon and Exeter NHS Foundation Trust
https://orcid.org/0000-0003-4368-1961

**Aamir Saifuddin**
Department of Gastroenterology, St Marks Hospital and Academic Institute

**Diana Muñoz Sandoval**
Department of Infectious Disease, Imperial College London

**Catherine Reynolds**
Department of Infectious Disease, Imperial College London https://orcid.org/0000-0002-1371-653X

**Rocio Castro Seoane**
Department of Immunology and Inflammation, Imperial College London

**Sherine Kottoor**
Department of Metabolism, Digestion and Reproduction, Imperial College London

**Franziska Pieper**
Department of Infectious Disease, Imperial College London

**Kai-Min Lin**
Department of Infectious Disease, Imperial College London https://orcid.org/0000-0003-2109-1530

**David K Butler**
Department of Infectious Disease, Imperial College London

**Neil Chanchlani**
Department of Gastroenterology, Royal Devon and Exeter NHS Foundation Trust
https://orcid.org/0000-0003-0207-6706

**Rachel Nice**
Department of Biochemistry, Exeter Clinical Laboratory International, Royal Devon and Exeter NHS Foundation Trust

**Desmond Chee**
Department of Gastroenterology, Royal Devon and Exeter NHS Foundation Trust
https://orcid.org/0000-0003-3473-9447

**Claire Bewshea**
Exeter Inflammatory Bowel Disease and Pharmacogenetics Research Group, University of Exeter
https://orcid.org/0000-0002-0965-9587

**Malik Janjua**
Department of Gastroenterology, Royal Devon and Exeter NHS Foundation Trust
**Timothy J McDonald**
Department of Biochemistry, Exeter Clinical Laboratory International, Royal Devon and Exeter NHS Foundation Trust https://orcid.org/0000-0003-3559-6660
**Shaji Sebastian**
Department of Gastroenterology, Hull University Teaching Hospitals NHS Trust https://orcid.org/0000-0002-3670-6545
**James L Alexander**
Department of Gastroenterology, Imperial College Healthcare NHS Trust
**Laura Constable**
Department of Metabolism, Digestion and Reproduction, Imperial College London
**James C Lee**
Genetic Mechanisms of Disease Laboratory, The Francis Crick Institute
**Charles D Murray**
Department of Gastroenterology, Royal Free London NHS Foundation Trust https://orcid.org/0000-0001-6736-1546
**Ailsa L Hart**
Department of Gastroenterology, St Mark’s Hospital and Academic Institute https://orcid.org/0000-0002-7141-6076
**Peter M Irving**
Department of Gastroenterology, Guy's and St Thomas' NHS Foundation Trust https://orcid.org/0000-0003-0972-8148
**Gareth-Rhys Jones**
Department of Gastroenterology, Western General Hospital, NHS Lothian https://orcid.org/0000-0001-7355-2357
**Klaartje B Kok**
Department of Gastroenterology, Royal London Hospital, Barts Health NHS Trust
https://orcid.org/0000-0002-5942-9149
**Christopher A Lamb**
Department of Gastroenterology, Newcastle upon Tyne Hospitals NHS Foundation Trust
https://orcid.org/0000-0002-7271-4956
**Charlie W Lees**
Department of Gastroenterology, Western General Hospital, NHS Lothian https://orcid.org/0000-0002-0732-8215
**Daniel M Altmann**
Department of Immunology and Inflammation, Imperial College London https://orcid.org/0000-0002-2436-6192
**Rosemary J Boyton**

Department of Infectious Disease, Imperial College London

**James R Goodhand**

Department of Gastroenterology, Royal Devon and Exeter NHS Foundation Trust
https://orcid.org/0000-0003-3112-376X

**Nick Powell**

Department of Metabolism, Digestion and Reproduction, Imperial College London
https://orcid.org/0000-0003-3231-6950

**Tariq Ahmad**

Department of Gastroenterology, Royal Devon and Exeter NHS Foundation Trust
https://orcid.org/0000-0002-6058-5528

---

**Brief Communication**

**Keywords:** SARS-CoV-2, immune-mediated inflammatory diseases, inflammatory bowel disease, anti-TNF therapy, infliximab, vedolizumab, immunosuppressant, vaccine, ChAdOx1 nCoV-19, BNT162b2, durability, CLARITY, T-Lymphocytes

**Posted Date:** July 30th, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-755879/v1



---

**Version of Record:** A version of this preprint was published at Nature Communications on March 16th, 2022. See the published version at https://doi.org/10.1038/s41467-022-28517-z.

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

**Authors:** Simeng Lin, MBChB[1,2†], Nicholas A Kennedy, PhD[1,2†], Aamir Saifuddin, BM.BCh[3,4†] Diana Muñoz Sandoval PhD[5†], Catherine J Reynolds PhD[5], Rocio Castro Seoane, PhD[6], Sherine H Kottoor, PhD[4], Franziska P Pieper MSc[5], Kai-Min Lin PhD[5], David K. Butler MSc[5], Neil Chanchlani, MBChB[1,2], Rachel Nice, MSc[2,7], Desmond Chee, MBBS[1,2], Claire Bewshea, MSc[2], Malik Janjua, MBBS [1,2], Timothy J McDonald, PhD[7], Shaji Sebastian, MD[8,9], James L Alexander, PhD,[4,10] Laura Constable, MRes[4], James C Lee PhD[11,12,13], Charles D Murray PhD[11], Ailsa L Hart PhD[3], Peter M Irving, MD[14,15], Gareth-Rhys Jones,[16,17], Klaartje B Kok, PhD[18,19], Christopher A Lamb, PhD[20,21], Charlie W Lees, PhD[16,22], Daniel M Altmann PhD[6], Rosemary J Boyton PhD[5,23†], James R Goodhand, MBBS[1,2†], Nick Powell, PhD[4,10†] , Tariq Ahmad, DPhil[1,2*†], Contributors of the CLARITY IBD study.

[†] Denotes equal contribution

* Corresponding author

Affiliations:

[1] Department of Gastroenterology, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK

[2] Exeter Inflammatory Bowel Disease and Pharmacogenetics Research Group, University of Exeter, UK

[3]Department of Gastroenterology, St Marks Hospital and Academic Institute, London, UK

[4]Department of Metabolism, Digestion and Reproduction, Imperial College London, London, UK

[5]Department of Infectious Disease, Imperial College London, London, UK

[6]Department of Immunology and Inflammation, Imperial College London, London, United Kingdom

[7]Department of Biochemistry, Exeter Clinical Laboratory International, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK

[8]IBD Unit, Department of Gastroenterology, Hull University Teaching Hospitals NHS Trust, Hull, UK

[9]Hull York Medical School, University of Hull, Hull, UK

[10]Department of Gastroenterology, Imperial College Healthcare NHS Trust, London, UK

[11]Department of Gastroenterology, Royal Free London NHS Foundation Trust, London, UK

[12]Genetic Mechanisms of Disease Laboratory, The Francis Crick Institute, London, UK

[13]Cambridge Institute of Therapeutic Immunology and Infectious Disease, Jeffrey Cheah Biomedical Centre, Cambridge Biomedical Campus, University of Cambridge, Cambridge, UK

[14]Department of Gastroenterology, Guy's and St Thomas' NHS Foundation Trust, London, UK

[15]School of Immunology & Microbial Sciences, King's College London, London, UK

[16]Department of Gastroenterology, Western General Hospital, NHS Lothian, Edinburgh, UK

[17]Centre for Inflammation Research, The Queen's Medical Research Institute, The University of Edinburgh, Edinburgh, UK

[18]Department of Gastroenterology, Royal London Hospital, Barts Health NHS Trust, London, UK

[19]Centre for Immunobiology, Blizard Institute, Barts and the London School of Medicine, Queen Mary University of London, London, UK

[20]Department of Gastroenterology, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

[21]Translational & Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK

[22]Institute of Genetic and Molecular Medicine, University of Edinburgh, Edinburgh, UK

[23]Lung Division, Royal Brompton Hospital and Harefield Hospitals, London, UK

**Address for correspondence:** Prof Tariq Ahmad, Exeter Inflammatory Bowel Disease and Pharmacogenetics Research Group, RILD building, Barrack Road, Exeter. EX2 5DW, UK, tariq.ahmad1@nhs.net

**Key words:** SARS-CoV-2, immune-mediated inflammatory diseases, inflammatory bowel disease, anti-TNF therapy, infliximab, vedolizumab, immunosuppressant, vaccine, ChAdOx1 nCoV-19, BNT162b2, durability, CLARITY, T-Lymphocytes

**Word count: 1683**

**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

84 factor (TNF), such as infliximab, are the most frequently prescribed biological therapies used in the
85 treatment of immune-mediated inflammatory disorders (IMIDs). Observational studies indicate that
86 most patients with inflammatory bowel disease (IBD), an archetypal IMID, mount serological
87 responses following SARS-CoV-2 vaccines; although most were underpowered to discern the impact
88 of specific drugs, including immunomodulators (azathioprine, mercaptopurine, and methotrexate)
89 and/or biologic therapies[4,5]. We recently reported, however, that antibody responses following
90 SARS-CoV-2 infection or a single-dose of either the BNT162b2 or ChAdOx1 nCoV-19 SARS-CoV-2
91 vaccines are impaired in anti-TNF treated patients[6,7]. We hypothesised here that antibody and T cell
92 responses following the second doses of BNT162b2 or ChAdOx1 nCoV-19 vaccines would be
93 attenuated and less durable in infliximab-treated patients.
94
95 CLARITY IBD is a 40-week prospective observational study investigating immune responses to SARS-
96 CoV2 infection and vaccination in IBD patients[6]. We measured anti-SARS-CoV-2 spike (S) receptor
97 binding domain (RBD) antibodies in patients with IBD treated with either infliximab, or vedolizumab,
98 a gut-specific antibody targeting integrin $\alpha 4\beta 7$, that does not impair systemic immunity. We report
99 data from 2052 infliximab- and 925 vedolizumab-treated participants without evidence of prior
100 SARS-CoV-2 infection, who had received uninterrupted biologic therapy since recruitment and had
101 an antibody test performed between 14 and 70 days after a second dose of either the BNT162b2 or
102 ChAdOx1 nCoV-19 SARS-CoV-2 vaccines. Participant characteristics are shown in Supplementary
103 Table 2. Secondary outcome analyses are also presented for 283 infliximab- and 137 vedolizumab-
104 treated patients who had had PCR-confirmed SARS-CoV-2 infection prior to vaccination.
105 Seroconversion was defined as an anti-S RBD antibody concentration ≥15 U/mL, a threshold
106 associated with viral neutralization of ≥20% with a positive predictive value of 99.10 % (95% CI:
107 97.74-99.64)[7]. Anti-SARS-CoV-2 antibody non-persistence was defined as the time to a four-fold
108 decrease in anti-S RBD antibodies. Anti-S RBD antibody levels were compared with samples from 605
109 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***

CLARITY IBD is an investigator-led, UK National Institute for Health Research COVID-19 urgent public health study, funded by the Royal Devon and Exeter NHS Foundation Trust, NIHR Imperial Biomedical Research Centre, Hull University Teaching Hospital NHS Trust, and by unrestricted educational grants from F. Hoffmann-La Roche AG (Switzerland), Biogen GmbH (Switzerland), Celltrion Healthcare (South Korea), Takeda (UK), and Galapagos NV (Belgium). None of our funding bodies had any role in study design, data collection or analysis, writing, or decision to submit for publication. Patients were included after providing informed, written consent. The sponsor was the Royal Devon and Exeter NHS Foundation Trust. The Surrey Borders Research Ethics committee approved the study (REC reference: REC 20/HRA/3114) in September 2020. The protocol is available online at https//www.clarityibd.org. The study was registered with the ISRCTN registry (ISRCTN45176516).

***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.

## Acknowledgements

CLARITY IBD is a UK National Institute for Health Research (NIHR) Urgent Public Health Study. The NIHR Clinical Research Network supported study set-up, site identification, and delivery of this study. This was facilitated by Professor Mark Hull, the National Speciality Lead for Gastroenterology. We acknowledge the contribution of our Patient Advisory Group who helped shape the trial design around patient priorities. Our partners, Crohn's and Colitis UK (CCUK), continue to support this group and participate in Study Management Team meetings. We thank Professor Graham Cooke and Dr Katrina Pollock for their helpful discussions and review of the

data. Laboratory tests were undertaken by the Exeter Blood Sciences Laboratory at the Royal Devon and Exeter NHS Foundation Trust. The Exeter NIHR Clinical Research Facility coordinated sample storage and management. Tariq Malik and James Thomas from Public Health England, Guy Stevens, Katie Donelon, Elen de Lacy from Public Health Wales and Johanna Bruce from Public Health Scotland supported linkage of central SARS-CoV-2 PCR test results with study data. Roche Diagnostics Limited provided the Elecsys Anti-SARS-CoV-2 immunoassay for the study. Faculty of Medicine at Imperial College London, Exeter NIHR Clinical Research Facility, Jeffrey Cheah Biomedical Centre at the University of Cambridge, Newcastle University Medical School and The Queen's Medical Research Institute at the University of Edinburgh facilitated PBMC extractions for the T cell experiments. We thank Professor Robert Aldridge for access to data from the Virus Watch Collaborative. SL is supported by a Wellcome GW4-CAT fellowship. NC acknowledges support from CCUK. JCL is a Lister Prize Fellow and acknowledges support from the Cambridge NIHR Biomedical Research Centre and the Francis Crick Institute which receives core funding from Cancer Research UK (FC001169), the UK Medical Research Council (FC001169), and the Wellcome Trust (FC001169). GRJ is supported by a Wellcome Trust Clinical Research Career Development Fellowship (220725/Z/20/Z). CAL acknowledges support from the NIHR Newcastle Biomedical Research Centre and the support of the Programmed Investigation Unit at Royal Victoria Infirmary, Newcastle upon Tyne. CWL is funded by a UKRI Future Leaders Fellowship. RJB and DMA are supported by MRC (MR/S019553/1, MR/R02622X/1 and MR/V036939/1), NIHR Imperial Biomedical Research Centre (BRC):ITMAT, Cystic Fibrosis Trust SRC (2019SRC015), and Horizon 2020 Marie Skłodowska-Curie Innovative Training Network (ITN) European Training Network (No 860325). NP is supported by the NIHR Imperial Biomedical Research Center (BRC). We acknowledge the study co-ordinators of the Exeter Inflammatory Bowel Disease Research Group: Marian Parkinson and Helen Gardner-Thorpe for their ongoing administrative support to the study. The sponsor of the study was the Royal Devon and Exeter NHS Foundation Trust.

## 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

Dr. S Lin reports non-financial support from Pfizer, non-financial support from Ferring, outside the submitted work. Dr. Kennedy reports grants from F. Hoffmann-La Roche AG, grants from Biogen Inc, grants from Celltrion Healthcare, grants from Galapagos NV, non-financial support from Immundiagnostik, during the conduct of the study; grants and non-financial support from AbbVie, grants and personal fees from Celltrion, personal fees and non-financial support from Janssen, personal fees from Takeda, personal fees and non-financial support from Dr Falk, outside the submitted work. Dr Saifuddin has received travel expense support from Dr Falk Pharma. Dr. Chee reports non-financial support from Ferring, personal fees and non-financial support from Pfizer, outside the submitted work. Prof. Sebastian reports grants from Takeda, Abbvie, AMGEN, Tillots Pharma, personal fees from Jaansen, Takeda, Galapagos, Celltrion, Falk Pharma, Tillots pharma, Cellgene, Pfizer, Pharmacocosmos, outside the submitted work. Dr Alexander reports sponsorship from Vifor Pharma for accommodation/travel to BSG 2019, outside

the submitted work. Dr Lee reports personal fees from Abbvie, personal fees from C4X Discovery, personal fees from PredictImmune and personal fees from AG pus diagnostics.

Dr Hart reports personal fees from Abbvie, personal fees from Allergan, personal fees from BMS, personal fees from Celltrion, personal fees from Falk, personal fees from GSK, personal fees from Takeda, personal fees from Pfizer, personal fees from Janssen, personal fees from Galapogos, personal fees from Astra Zeneca, outside the submitted work. Dr Irving reports grants and personal fees from Takeda, grants from MSD, grants and personal fees from Pfizer, personal fees from Galapagos, personal fees from Gilead, personal fees from Abbvie, personal fees from Janssen, personal fees from Boehringer Ingelheim, personal fees from Topivert, personal fees from VH2, personal fees from Celgene, personal fees from Arena, personal fees from Samsung Bioepis, personal fees from Sandoz, personal fees from Procise, personal fees from Prometheus, outside the submitted work. Dr Jones has received speaker fees from Takeda, Ferring and Janssen. Dr. Kok reports personal fees from Janssen, personal fees from Takeda, personal fees from PredictImmune, personal fees from Amgen, outside the submitted work. Dr. Lamb reports grants from Genentech, grants and personal fees from Janssen, grants and personal fees from Takeda, grants from AbbVie, personal fees from Ferring, grants from Eli Lilly, grants from Pfizer, grants from Roche, grants from UCB Biopharma, grants from Sanofi Aventis, grants from Biogen IDEC, grants from Orion OYJ, personal fees from Dr Falk Pharma, grants from AstraZeneca, outside the submitted work. Prof. Lees reports personal fees from Abbvie, personal fees from Janssen, personal fees from Pfizer, personal fees from Takeda, grants from Gilead, personal fees from Gilead, personal fees from Galapagos, personal fees from Iterative Scopes, personal fees from Trellus Health, personal fees from Celltion, personal fees from Ferring, personal fees from BMS, during the conduct of the study. Prof Boyton and Prof Altmann are members of the Global T cell Expert Consortium and have consulted for Oxford Immunotec outside the submitted work. Dr. Goodhand reports grants from F. Hoffmann-La Roche AG, grants from Biogen Inc, grants from Celltrion Healthcare, grants from Galapagos NV, non-financial support from Immundiagnostik, during the conduct of the study. Dr. Powell reports

388 personal fees from Takeda, personal fees from Janssen, personal fees from Pfizer, personal fees
389 from Bristol-Myers Squibb, personal fees from Abbvie, personal fees from Roche, personal fees from
390 Lilly, personal fees from Allergan, personal fees from Celgene, outside the submitted work;
391 and Dr. Powell has served as a speaker/advisory board member for Abbvie, Allergan, Bristol Myers
392 Squibb, Celgene, Falk, Ferring, Janssen, Pfizer, Tillotts, Takeda and Vifor Pharma. Prof. Ahmad
393 reports grants and non-financial support from F. Hoffmann-La Roche AG, grants from Biogen Inc,
394 grants from Celltrion Healthcare, grants from Galapagos NV, non-financial support
395 from Immundiagnostik, during the conduct of the study; personal fees from Biogen inc, grants and
396 personal fees from Celltrion Healthcare, personal fees and non-financial support
397 from Immundiagnostik, personal fees from Takeda, personal fees from ARENA, personal fees from
398 Gilead, personal fees from Adcock Ingram Healthcare, personal fees from Pfizer, personal fees from
399 Genentech, non-financial support from Tillotts, outside the submitted work. The following authors
400 have nothing to declare: Diana Muñoz Sandoval, Catherine Reynolds, Rocio Castro Seoane, Sherine H
401 Kottoor, Franziska Pieper, Kai-Min Lin, David Butler, Neil Chanchlani, Claire Bewshea, Rachel
402 Nice, Laura Constable, Charles D Murray, Timothy J McDonald.

## References


1. Joint Committee on Vaccination and Immunisation. JCVI interim advice: potential COVID-19 booster vaccine programme winter 2021 to 2022. https://www.gov.uk/government/publications/jcvi-interim-advice-on-a-potential-coronavirus-covid-19-booster-vaccine-programme-for-winter-2021-to-2022/jcvi-interim-advice-potential-covid-19-booster-vaccine-programme-winter-2021-to-2022 (2021).

2. US Food and Drug Administration. Joint CDC and FDA Statement on Vaccine Boosters. https://www.fda.gov/news-events/press-announcements/joint-cdc-and-fda-statement-vaccine-boosters (2021).

3. European Medicines Agency. EMA and ECDC update on COVID-19 | European Medicines Agency. https://www.ema.europa.eu/en/news/ema-ecdc-update-covid-19 (2021).

4. Wong, S.-Y. *et al.* Serologic Response to Messenger RNA Coronavirus Disease 2019 Vaccines in Inflammatory Bowel Disease Patients Receiving Biologic Therapies. *Gastroenterology* (2021) doi:10.1053/j.gastro.2021.04.025.

5. Kappelman, M. D. *et al.* Humoral Immune Response to mRNA COVID019 Vaccines among Patients with IBD. *Gastroenterology* **0**, (2021).

6. Kennedy, N. A. *et al.* Inflammatory bowel disease Anti-SARS-CoV-2 antibody responses are attenuated in patients with IBD treated with infliximab. *Gut* **0**, 1–11 (2021).

7. Kennedy, N. A. *et al.* Infliximab is associated with attenuated immunogenicity to BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines in patients with IBD. *Gut* **0**, gutjnl-2021-324789 (2021).

8. Shrotri, M. *et al.* Spike-antibody waning after second dose of BNT162b2 or ChAdOx1. *Lancet* **0**, (2021).

9. Kamar, N. *et al.* Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients. *N. Engl. J. Med.* (2021) doi:10.1056/NEJMc2108861.

10. Park, J. K. *et al.* Effect of methotrexate discontinuation on efficacy of seasonal influenza vaccination in patients with rheumatoid arthritis: A randomised clinical trial. *Ann. Rheum. Dis.* **76**, 1559–1565 (2017).

11. ISRCTN. ISRCTN14391248: Combining influenza and COVID-19 vaccination (ComFluCOV)

study. https://www.isrctn.com/ISRCTN14391248 (2021).

12. Barros-Martins, J. *et al.* Immune responses against SARS-CoV-2 variants after heterologous and homologous ChAdOx1 nCoV-19/BNT162b2 vaccination. *Nat. Med. 2021* 1–5 (2021) doi:10.1038/s41591-021-01449-9.

13. Pasparakis, M., Alexopoulou, L., Episkopou, V. & Kollias, G. Immune and inflammatory responses in TNFα-deficient mice: A critical requirement for TNFα in the formation of primary B cell follicles, follicular dendritic cell networks and germinal centers, and in the maturation of the humoral immune response. *J. Exp. Med.* **184**, 1397–1411 (1996).

14. Ritter, U., Meissner, A., Ott, J. & Körner, H. Analysis of the maturation process of dendritic cells deficient for TNF and lymphotoxin-α reveals an essential role for TNF. *J. Leukoc. Biol.* **74**, 216–222 (2003).

15. Salinas, G. F. *et al.* Anti-TNF treatment blocks the induction of T cell-dependent humoral responses. *Ann. Rheum. Dis.* **72**, 1037–1043 (2013).

16. Reynolds, C. J. *et al.* Discordant neutralizing antibody and T cell responses in asymptomatic and mild SARS-CoV-2 infection. *Sci. Immunol.* **5**, (2020).

17. Cope, A. P. *et al.* Chronic exposure to tumor necrosis factor (TNF) in vitro impairs the activation of T cells through the T cell receptor/CD3 complex; reversal in vivo by anti-TNF antibodies in patients with rheumatoid arthritis. *J. Clin. Invest.* **94**, 749–760 (1994).

18. Khoury, D. S. *et al.* Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat. Med.* 1–7 (2021) doi:10.1038/s41591-021-01377-8.

19. Earle, K. A. *et al.* Evidence for antibody as a protective correlate for COVID-19 vaccines. *Vaccine* (2021) doi:10.1016/j.vaccine.2021.05.063.

20. Reynolds, C. J. *et al.* Prior SARS-CoV-2 infection rescues B and T cell responses to variants after first vaccine dose. *Science* **372**, 1418–1423 (2021).

21. Roche Diagnostics GmbH. Elecsys® Anti-SARS-CoV-2 S assay method sheet. https://diagnostics.roche.com/gb/en/products/params/elecsys-anti-sars-cov-2-s.html (2020).

22. Muench, P. *et al.* Development and validation of the elecsys anti-SARS-CoV-2 immunoassay as a highly specific tool for determining past exposure to SARS-CoV-2. *J. Clin. Microbiol.* **58**,

1694–1714 (2020).

23. Peng, Y. *et al.* Broad and strong memory CD4+ and CD8+ T cells induced by SARS-CoV-2 in UK convalescent individuals following COVID-19. *Nat. Immunol.* **21**, 1336 (2020).

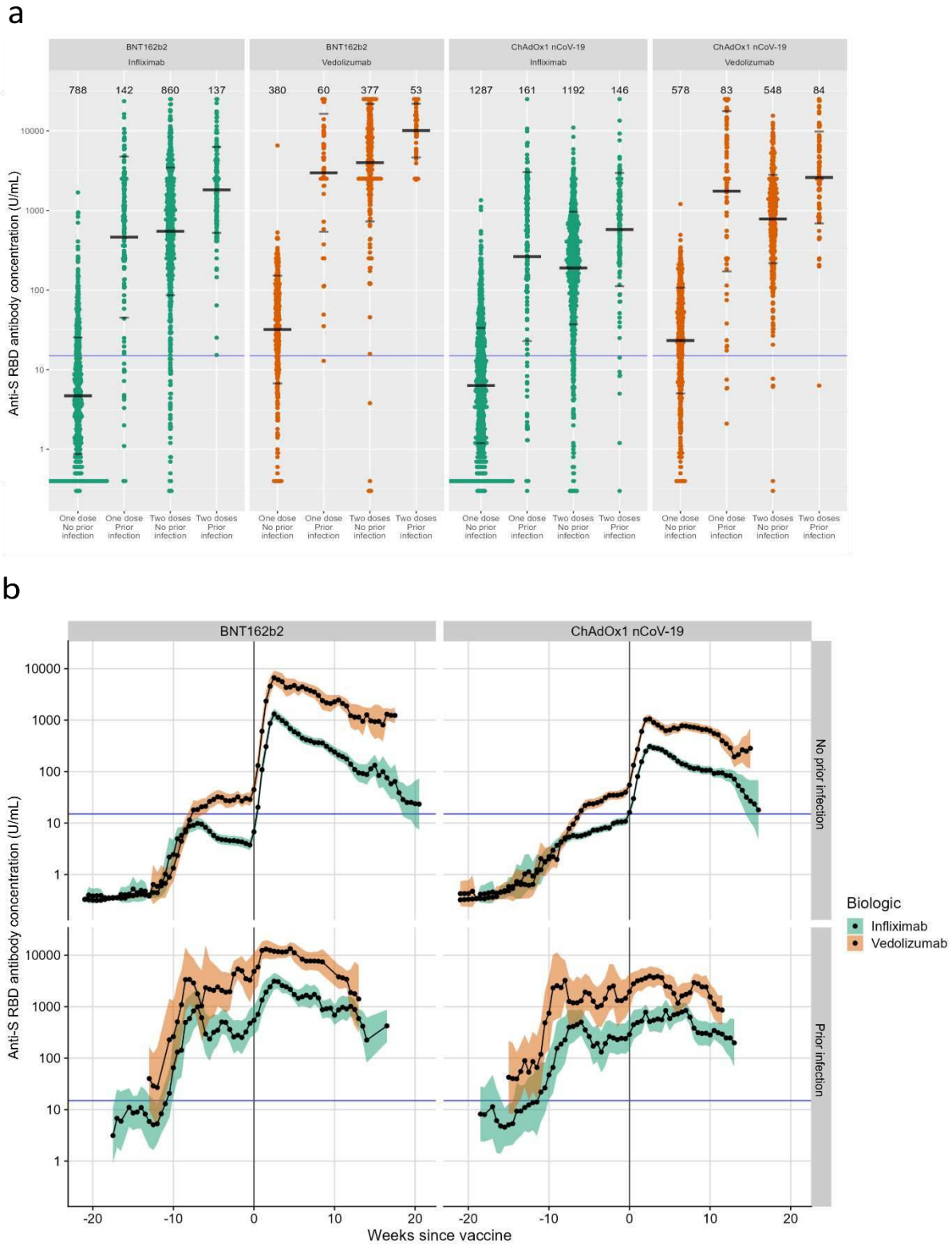



**Figure 1: Anti-SARS-CoV-2 spike (S) receptor binding domain (RBD) antibody response and durability**

**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.

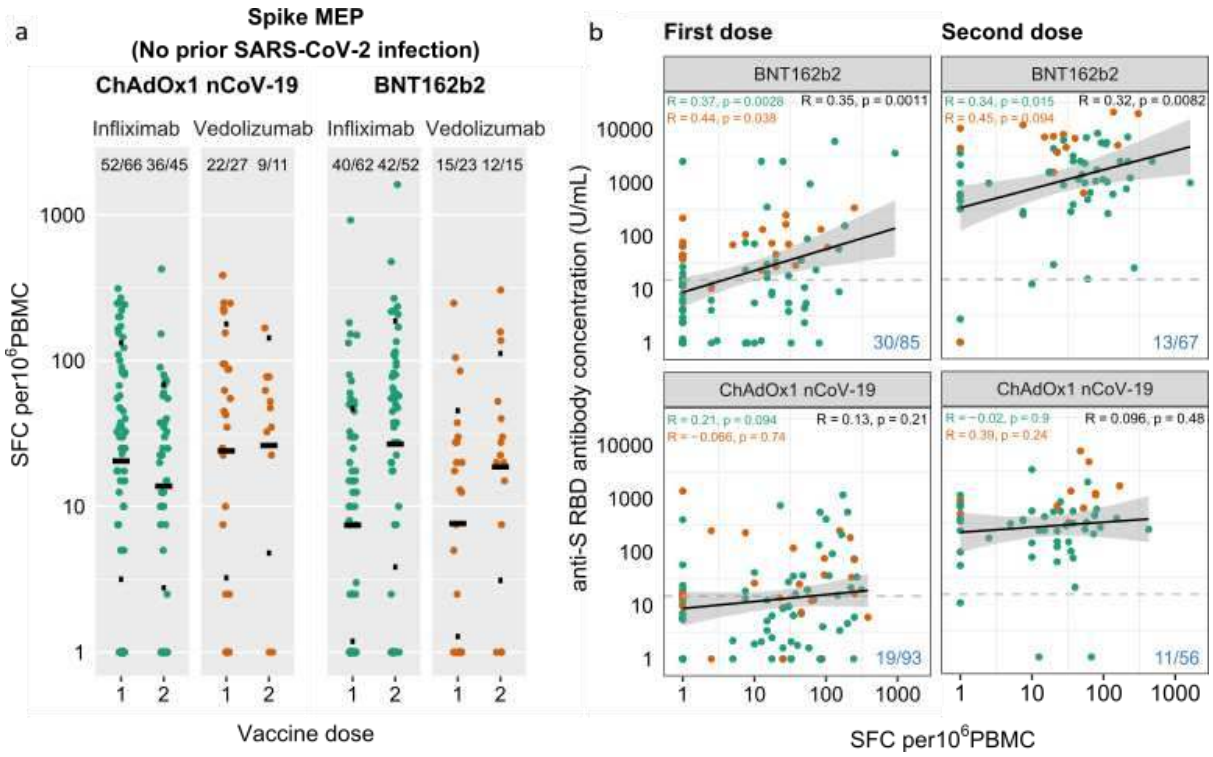
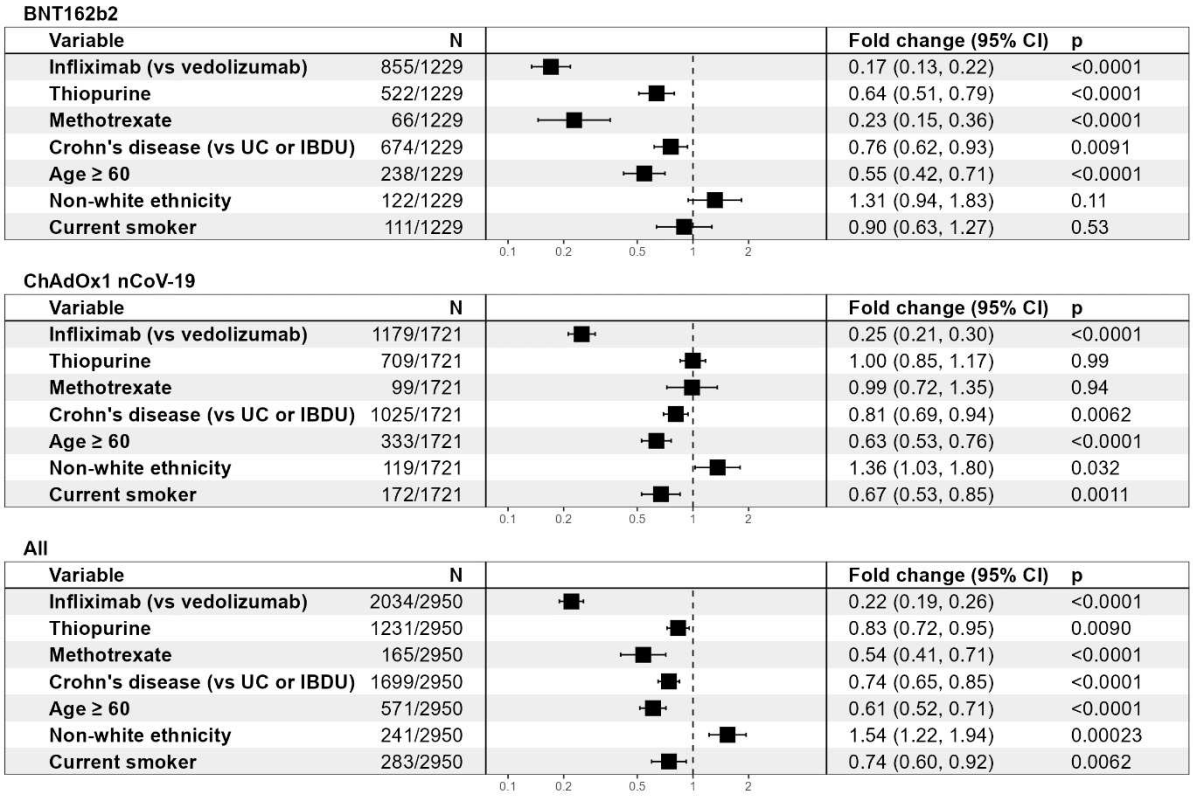


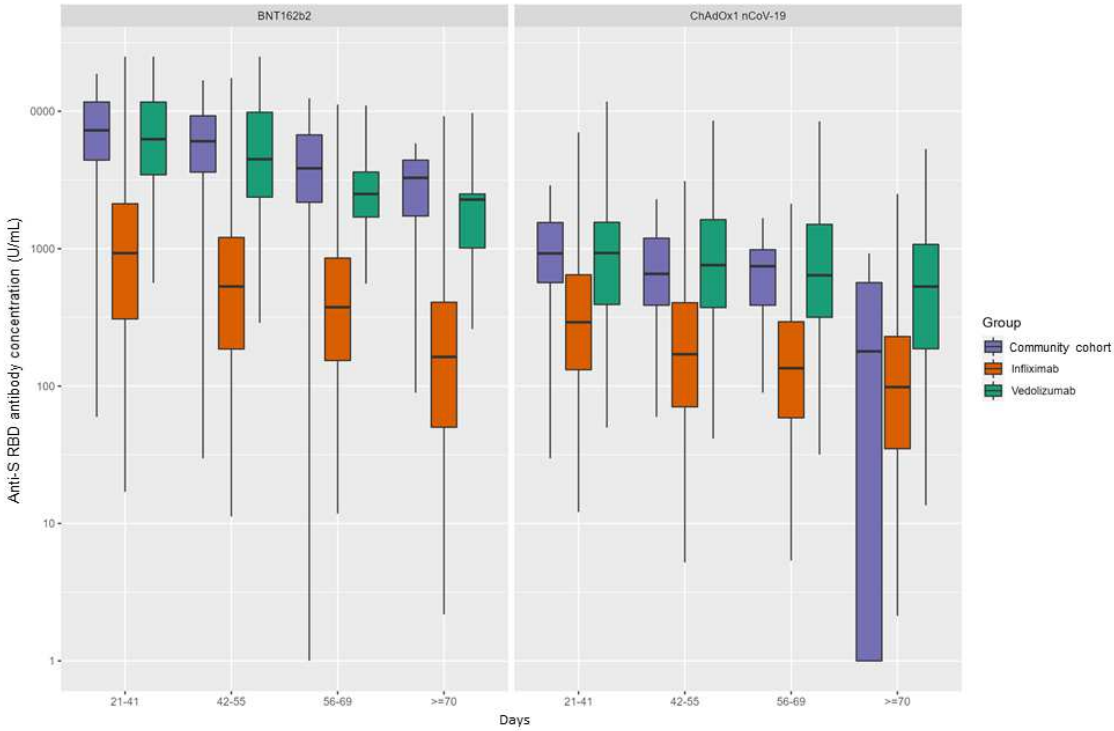

**Figure 2. Anti-SARS-CoV-2 spike T cell responses stratified by biologic therapy (infliximab vs vedolizumab), vaccine type (BNT162b2 vs ChAdOx1 nCoV-19) and vaccine dose (one vs two).**

**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.

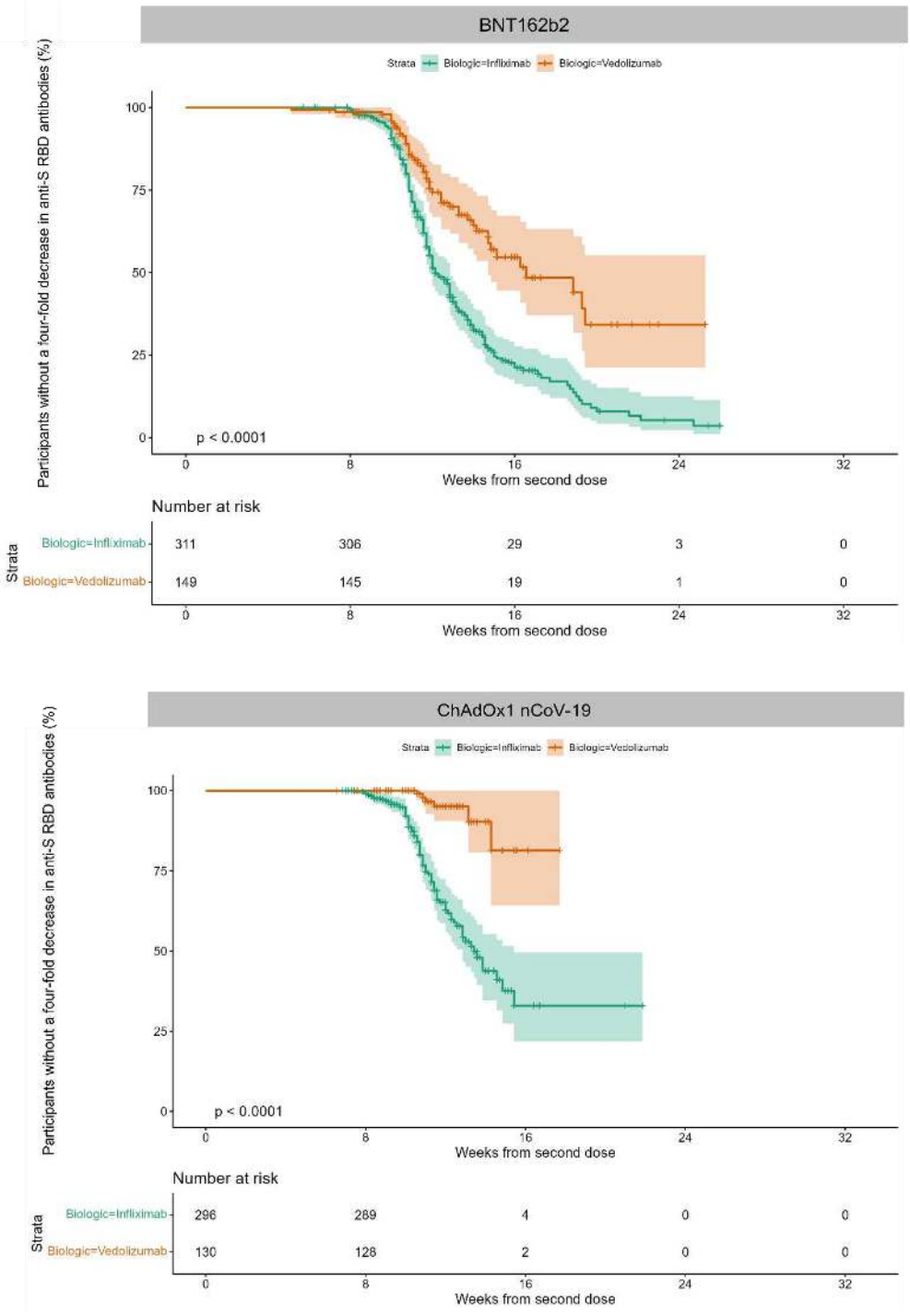



**Extended Data Figure 1: Exponentiated coefficients of linear regression models of log(anti-S RBD antibody concentration)**

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

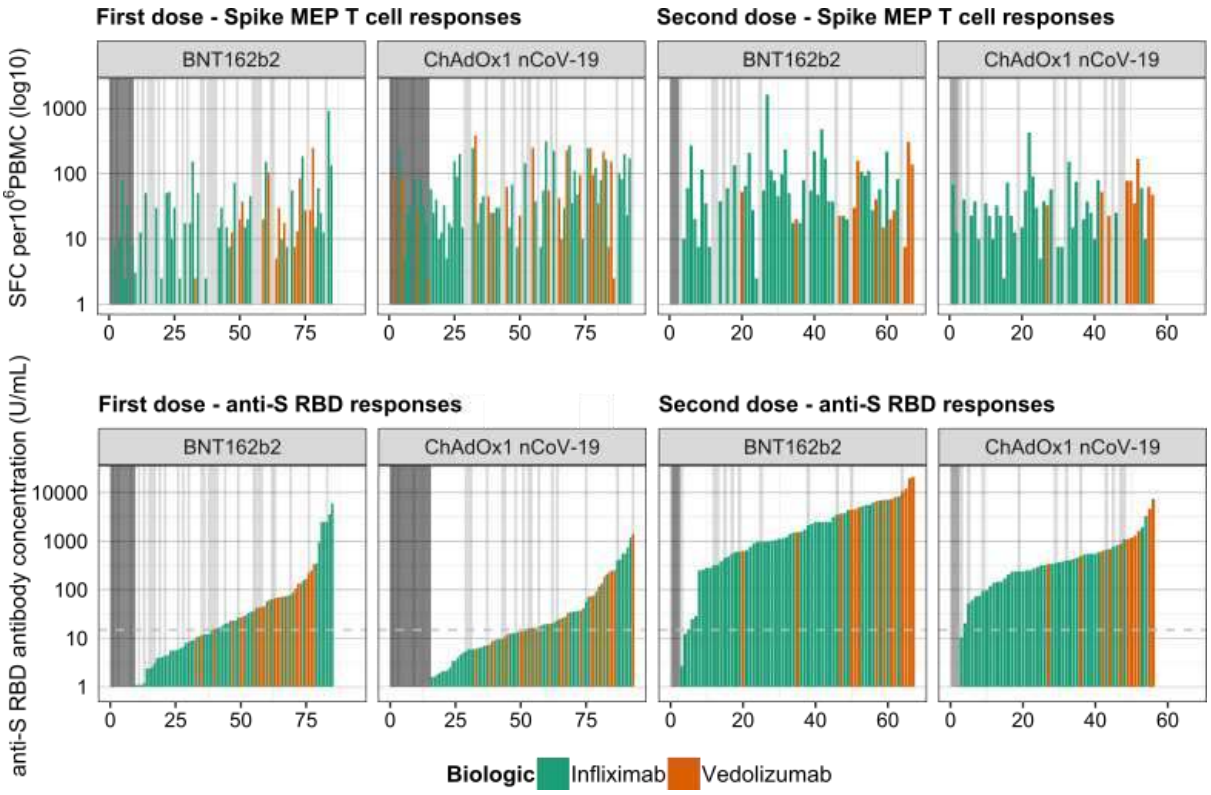



**Extended Data Figure 2: Anti-S RBD antibody levels at defined time points (days) after a second dose of vaccine in patients stratified by type of vaccine and biologic therapy (infliximab, vedolizumab) compared with individuals in the Virus Watch community cohort.**




**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

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryInformationCLARITY.pdf