

Original research

Vaccine escape, increased breakthrough and reinfection in infliximab-treated patients with IBD during the Omicron wave of the SARS-CoV-2 pandemic

Nicholas A Kennedy ^{1,2} Malik Janjua ^{1,2} Neil Chanchlani ^{1,2} Simeng Lin ^{1,2} Claire Bewshea ² Rachel Nice^{2,3} Timothy J McDonald ³ Cressida Auckland⁴ Lorna W Harries ⁵ Merlin Davies⁵ Stephen Michell⁶ Klaartje B Kok ^{7,8} Christopher A Lamb ^{9,10} Philip J Smith ¹¹ Ailsa L Hart ¹² Richard CG Pollok ^{13,14} Charlie W Lees ^{15,16} Rosemary J Boyton ^{17,18} Daniel M Altmann ¹⁹ Shaji Sebastian ^{20,21} Nicholas Powell ^{22,23} James R Goodhand ^{1,2} Tariq Ahmad ^{1,2}

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/gutjnl-2022-327570>).

For numbered affiliations see end of article.

Correspondence to

Dr Tariq Ahmad, Department of Gastroenterology, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK; tariq.ahmad1@nhs.net

NAK and MJ contributed equally.
NP, JRG and TA contributed equally.

Received 8 April 2022
Accepted 16 July 2022



© Author(s) (or their employer(s)) 2022. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Kennedy NA, Janjua M, Chanchlani N, et al. *Gut* Epub ahead of print: [please include Day Month Year]. doi:10.1136/gutjnl-2022-327570

ABSTRACT

Objective Antitumour necrosis factor (TNF) drugs impair serological responses following SARS-CoV-2 vaccination. We sought to assess if a third dose of a messenger RNA (mRNA)-based vaccine substantially boosted anti-SARS-CoV-2 antibody responses and protective immunity in infliximab-treated patients with IBD.

Design Third dose vaccine induced anti-SARS-CoV-2 spike (anti-S) receptor-binding domain (RBD) antibody responses, breakthrough SARS-CoV-2 infection, reinfection and persistent oropharyngeal carriage in patients with IBD treated with infliximab were compared with a reference cohort treated with vedolizumab from the impact of biologic therapy on SARS-CoV-2 Infection and immunity (CLARITY) IBD study.

Results Geometric mean (SD) anti-S RBD antibody concentrations increased in both groups following a third dose of an mRNA-based vaccine. However, concentrations were lower in patients treated with infliximab than vedolizumab, irrespective of whether their first two primary vaccine doses were ChAdOx1 nCoV-19 (1856 U/mL (5.2) vs 10 728 U/mL (3.1), $p < 0.0001$) or BNT162b2 vaccines (2164 U/mL (4.1) vs 15 116 U/mL (3.4), $p < 0.0001$). However, no differences in anti-S RBD antibody concentrations were seen following third and fourth doses of an mRNA-based vaccine, irrespective of the combination of primary vaccinations received. Post-third dose, anti-S RBD antibody half-life estimates were shorter in infliximab-treated than vedolizumab-treated patients (37.0 days (95% CI 35.6 to 38.6) vs 52.0 days (95% CI 49.0 to 55.4), $p < 0.0001$). Compared with vedolizumab-treated, infliximab-treated patients were more likely to experience SARS-CoV-2 breakthrough infection (HR 2.23 (95% CI 1.46 to 3.38), $p = 0.00018$) and reinfection (HR 2.10 (95% CI 1.31 to 3.35), $p = 0.0019$), but this effect was uncoupled from third vaccine dose anti-S RBD antibody concentrations. Reinfection occurred predominantly during the Omicron wave and was predicted by SARS-CoV-2

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Vaccine-induced anti-SARS-CoV-2 spike (anti-S) receptor-binding domain (RBD) antibody responses are attenuated and less durable in infliximab-treated than vedolizumab-treated patients with IBD.
- ⇒ During the delta wave of the COVID-19 pandemic, breakthrough SARS-CoV-2 infection was more common in infliximab-treated than vedolizumab-treated patients, and were associated with lower anti-S RBD antibody concentrations following two doses of SARS-CoV-2 vaccines.
- ⇒ Higher, more sustained antibody concentrations are observed in patients with a history of SARS-CoV-2 infection prior to vaccination, but whether infliximab treatment is linked to increased risk of SARS-CoV-2 reinfection is unknown.

antinucleocapsid concentrations after the initial infection. We did not observe persistent oropharyngeal carriage of SARS-CoV-2. Hospitalisations and deaths were uncommon in both groups.

Conclusions Following a third dose of an mRNA-based vaccine, infliximab was associated with attenuated serological responses and more SARS-CoV-2 breakthrough infection and reinfection which were not predicted by the magnitude of anti-S RBD responses, indicative of vaccine escape by the Omicron variant.

Trial registration number ISRCTN45176516.

INTRODUCTION

The COVID-19 pandemic has been characterised by successive waves of more transmissible SARS-CoV-2 variants of concern (VOC), culminating most recently in B.1.1.529 (Omicron) and

WHAT THIS STUDY ADDS

- ⇒ A third dose of a messenger RNA (mRNA)-based vaccine substantially boosted anti-S RBD antibody responses in infliximab-treated and vedolizumab-treated patients; however, anti-S RBD antibody concentrations remained attenuated in patients treated with infliximab, irrespective of the combination of primary vaccinations received.
- ⇒ There was a diminishing return on anti-S RBD antibody responses with a fourth dose of an mRNA-based vaccine, irrespective of biological type or combination of primary vaccinations received.
- ⇒ Breakthrough infection after a third dose of an mRNA-based vaccine was more common and occurred earlier in infliximab-treated than in vedolizumab-treated patients. Breakthrough infection was not associated with the magnitude of post-third dose vaccine anti-S RBD antibody concentrations.
- ⇒ Reinfection with the B.1.1.529 (Omicron) variant was more common in patients treated with infliximab, compared with vedolizumab, and was predicted by SARS-CoV-2 antinucleocapsid concentrations after initial infection. We did not observe persistent oropharyngeal carriage.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Despite Omicron variant breakthrough infection, vaccines continue to protect against severe illness, hospitalisations and death in infliximab-treated and vedolizumab-treated patients with IBD.
- ⇒ A current correlate of protection from B.1.1.529 (Omicron) infection is unknown and at present there is no role for routine antibody concentration testing against ancestral anti-S RBD.
- ⇒ Vaccination regimens for patients treated with antitumour necrosis factor (TNF) therapy should include at least one dose of an existing mRNA vaccine and booster vaccine doses need to be administered every 4–6 months.
- ⇒ Anti-TNF-treated patients have attenuated responses to vaccination and are at increased risk of breakthrough infection. Whether, in the setting of novel variants of concern, this will translate to an increased risk of severe COVID-19 is unknown.

its subvariants BA.2–5 that are able to evade adaptive immunity following prior infection and vaccination. The B.1.1.529 (Omicron) variant of SARS-CoV-2 was designated a variant of concern by WHO on 26 November 2021,¹ and BA.4 and BA.5 are now the dominant variants in the UK and are spreading rapidly worldwide. Compared with the ancestral Wuhan strain, B.1.1.529 has >32 mutations including 15 in the spike receptor binding domain (RBD).² Current COVID-19 vaccines continue to protect against severe illness, hospitalisations and death.³ However, the B.1.1.529 variant is causing high numbers of SARS-CoV-2 breakthrough infection and reinfection because of antigenic escape.⁴

By suppressing immune responses, immunosuppressive therapies, including biologicals, increase the risk of SARS-CoV-2 infection, persistent nasopharyngeal carriage and viral evolution.^{5,6} We have recently shown that treatment with the antitumour necrosis factor (TNF) therapies, infliximab and adalimumab, impairs antibody responses following SARS-CoV-2 infection.^{7,8} Furthermore, we demonstrated vaccine-induced antibody responses are attenuated and less durable in patients

treated with infliximab, translating to a 50% increased risk of breakthrough SARS-CoV-2 infection, compared with patients treated with vedolizumab, a gut-selective anti-integrin $\alpha 4\beta 7$ monoclonal antibody.^{9–11}

For patients with IBD treated with immunosuppressive therapies, these findings, along with data from other immunosuppressed patient cohorts,^{11–13} provided evidence for the prioritisation of third primary SARS-CoV-2 vaccine doses,¹⁴ even before the emergence of the B.1.1.529 (Omicron) variant.

We sought to assess if a third dose of an mRNA-based vaccine substantially improved anti-SARS-CoV-2 antibody responses, and if infliximab-treated compared with vedolizumab-treated patients are at increased risk of SARS-CoV-2 breakthrough infection, reinfection or persistent oropharyngeal carriage.

METHODS**Study design, population and clinical setting**

CLARITY IBD is a UK-wide, multicentre, observational cohort study investigating the impact of biological and/or concomitant immunomodulators on SARS-CoV-2 acquisition, illness and immunity in patients with IBD (www.clarityibd.org).

The overarching aims, study design and sample size calculations have been described previously.^{8,9} In brief, 7224 consecutive patients were recruited at the time of attendance at infusion units between 22 September 2020 and 23 December 2020 (online supplemental table 1). Patients with a diagnosis of IBD, aged 5 years and over, treated with infliximab or vedolizumab were eligible for inclusion. Follow-up visits coincided with biological infusions and typically occurred 8 weekly.

Data were linked by National Health Service (NHS) number or Community Health Index to NHS England, Public Health England, Scotland and Wales data who hold dates of vaccine uptake and dates and results of SARS-CoV-2 PCR tests undertaken in the UK. When central data on vaccination were missing, we used patient reports. The alpha and B.1.1.529 (Omicron) variants are characterised by an S-gene deletion which leads to loss of one of the three gene targets employed in the SARS-CoV-2 Taq Path PCR assay¹⁵ used by most UK public health laboratories. Therefore, S-gene target failure can be used as a marker of infection with the alpha or the B.1.1.529 (Omicron) subvariants.

In the UK, vaccines were administered to the most clinically vulnerable, and then through progressively lower risk and younger age groups from December 2020. Citizens received either the mRNA-based vaccine, BNT162b2 or the adenovirus-vector vaccine, ChAdOx1 nCoV-19 for the first two doses. From 13 September 2021, patients deemed to be clinically extremely vulnerable, including those with IBD treated with anti-TNF therapies and vedolizumab were offered a third and fourth primary vaccine dose with an mRNA-based vaccine (either BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna)) at least 8 weeks after their second dose.¹⁴

Here, we report anti-SARS-CoV-2 antibody responses after a third primary and fourth dose with an mRNA-based vaccine, rates of SARS-CoV-2 breakthrough infection and reinfection and persistent oropharyngeal carriage.

Outcomes

Participants were eligible for our immunogenicity analysis if they had an anti-SARS-CoV-2 spike (anti-S) RBD antibody test between 14 and 70 days after a third and fourth vaccine dose with an mRNA-based vaccine.

Anti-SARS-CoV-2 antibody assays

To determine antibody responses specific to vaccination, we used the Roche Elecsys anti-S immunoassay alongside the nucleocapsid (N) immunoassay.^{16 17} This double sandwich electrochemiluminescence immunoassay uses a recombinant protein of the RBD on the spike protein as an antigen for the determination of antibodies against SARS-CoV-2. Sample electrochemiluminescence signals are compared with an internal calibration curve and quantitative values are reported as units (U)/mL, which are identical to WHO's International Standard (binding antibody units/mL).¹⁸

The Roche Elecsys anti-SARS-CoV-2 (N) immunoassay is a sandwich electrochemiluminescence immunoassay that uses a recombinant protein of the nucleocapsid antigen for determination of antibodies against SARS-CoV-2 infection. Using a cut-off index (COI) of 1, the manufacturer reports clinical sensitivity and specificity of 99.5% (95% CI 97.0 to 100) and 99.8% (95% CI 99.7 to 99.9), respectively, >14 days after PCR-confirmed COVID-19. We have previously reported that anti-N antibody responses following SARS-CoV-2 natural infection are impaired in patients treated with infliximab compared with vedolizumab.⁸ As such, a threshold of 0.12 COI was set using receiver operator characteristic curve and area under the curve analysis of anti-N antibody results from participants 2 weeks following a PCR-confirmed infection to maximise sensitivity and specificity, beyond which patients were deemed to have had prior SARS-CoV-2 infection.

Breakthrough SARS-CoV-2 infection

SARS-CoV-2 infection was defined by a positive PCR test to SARS CoV-2. Breakthrough infection was defined as a SARS CoV-2 infection, diagnosed by positive PCR test, >14 days after a third dose of a SARS-CoV-2 vaccine.

Reinfection with SARS-CoV-2 and persistent oropharyngeal carriage

We defined SARS-CoV-2 reinfection as a recurrence of symptoms compatible with COVID-19, accompanied by a positive PCR test, >90 days after the onset of the primary infection.¹⁹

Because PCR positivity may persist for prolonged periods following initial infection and asymptomatic carriage is common, it is difficult to differentiate reinfection from persistent oropharyngeal carriage. To assess the risk of persistent carriage, participants aged 18 years and over with a previous history of confirmed SARS-CoV-2 infection, but without ongoing symptoms, were invited to carry out a home buccal swab test between 20 May 2021 and 7 January 2022.

We used PCR to detect SARS-CoV-2 RNA, and in positive samples, for the presence of envelope (E) and subgenomic RNAs (sgRNA).²⁰ sgRNAs are generated after SARS-CoV-2 enters cells and are poorly incorporated into mature virions and can be used as marker for actively replicating, rather than inactivated or neutralised, virus. Methods have been reported previously.²⁰ In brief, RNA was extracted using the Chemagic Viral DNA/RNA Kit on the Chemagic 360D platform. Viral loads were measured by quantitative real-time PCR for E gene and E-gene-derived sgRNA sequences, respectively. Reactions were performed using the SuperScript One-Step RT-PCR System with Platinum Taq DNA Polymerase (Thermo Fisher, Waltham, USA). Reactions were carried out in 384 well plates on the QuantStudio 12K Flex Real-Time PCR System (Applied Biosystems, Foster City, USA). Probes and primers were obtained from Thermo Fisher

(Waltham, USA). E gene and E sgRNA viral loads were determined in relation to known quantities of synthetic standards by standard curve analysis. Synthetic standards consisted of the probe and primer binding sites in a single long oligonucleotide for each of E gene and E gene-derived sgRNA sequences and were obtained from Invitrogen (Waltham, USA).

Variables

Variables recorded by participants were demographics (age, sex, ethnicity, comorbidities, height and weight, smoking status and postcode), IBD disease activity (PRO2), SARS-CoV-2 symptoms aligned to the COVID-19 symptoms study (symptoms, previous testing and hospital admissions for COVID-19) and vaccine uptake (type and date of primary vaccination). Study sites completed data relating to IBD history (age at diagnosis, disease duration and phenotype according to the Montreal classifications), previous surgeries and duration of current biological and immunomodulator therapy, COVID-19 hospitalisations and deaths. Data were entered electronically into a purpose-designed Research Electronic Data Capture database hosted at the Royal Devon and Exeter NHS Foundation Trust.²¹ Participants without access to the internet or electronic device completed their questionnaires on paper case record forms that were subsequently entered by local research teams.

Statistical analysis

Statistical analyses were undertaken in R V.4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-tailed and p values <0.05 were considered significant. We included patients with missing clinical variables in analyses for which they had data and have specified the denominator for each variable. Continuous data are reported as median and IQR, and discrete data as numbers and percentages.

Anti-S RBD antibody concentrations are reported as geometric means and SD. T-tests of log-transformed anti-S RBD antibody concentrations were used to compare antibody responses by vaccine type, biological drug type, breakthrough infection and reinfection status. Multivariable linear regression models were used to identify factors independently associated with log anti-S RBD concentration. Based on our previous findings,^{9 10} a priori, we included age, ethnicity, biological medication and immunomodulator use. 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 of >60 years was chosen based on graphical inspection of the relationship between age and anti-S RBD antibody concentrations.

We visualised durability of antibody responses by calculating 15-day rolling geometric mean anti-S RBD antibody concentrations. Anti-S RBD antibody half-lives were estimated using an exponential model of decay. Linear mixed models were fit using the lme4 and lmerTest package, with biological treatment and vaccine type as fixed effects and each subject as a random effect. CIs were calculated using likelihood ratios. P values for comparison of half-lives were estimated from the full linear mixed effects model that incorporated vaccine, biological drug and prior SARS-CoV-2 infection status.

Kaplan-Meier curves and Cox proportional hazard regression models were used to identify treatment and vaccine-related factors associated with time to breakthrough infection and reinfection. Multivariable logistic regression analysis was used to identify factors associated with hospitalisation among those with a positive SARS-CoV-2 PCR across the pandemic. Where

appropriate, the same analyses were used to compare antibody responses in participants with PCR evidence of SARS-CoV-2 infection at any time prior to vaccination.

Ethics and role of the funding source

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, Hull University Teaching Hospital NHS Trust, NIHR Imperial Biomedical Research Centre, Crohn's and Colitis UK (M2021/1), Guts UK and by unrestricted educational grants from F. Hoffmann-La Roche (Switzerland), Biogen (USA), Celltrion Healthcare (South Korea), Takeda (UK) and Galapagos (Belgium). This study was supported by an NCSI programme UKRI award to RB, DA, NP and TA (MR/W020610/1). None of our funding bodies had any role in study design, data collection or analysis, writing or decision to submit for publication.

The sponsor was the Royal Devon and Exeter NHS Foundation Trust. The protocol is available online at <https://www.clarityibd.org>. The study was registered with the ISRCTN registry, ISRCTN45176516.

RESULTS

Patient characteristics

Between 22 September 2020 and 23 December 2020, 7224 patients were recruited to the CLARITY study from 92 UK hospitals. In our primary immunogenicity analyses, we included 918 infliximab-treated and 442 vedolizumab-treated participants without a history of prior SARS-CoV-2 infection, who had received uninterrupted biological therapy since recruitment and had an antibody test between 14 and 70 days after a third dose with an mRNA-based SARS-CoV-2 vaccine. Participant characteristics are shown in [table 1](#). Additional analyses are presented for 512 infliximab-treated and 185 vedolizumab-treated participants with a history of SARS-CoV-2 infection before the third vaccine dose ([table 2](#)).

Anti-SARS-CoV-2 (S) antibody level following third COVID-19 vaccine

The peak geometric mean (SD) anti-S RBD antibody concentration was higher in recipients of three doses of an mRNA-based vaccine than recipients of two ChAdOx1 nCoV-19 vaccines and a third dose with an mRNA-based vaccine (4085 U/mL (5.1) vs 3275 U/mL (5.5), $p=0.016$). Geometric mean (SD) anti-S

Table 1 Baseline characteristics of participants without a history of prior SARS-CoV-2 infection, who received uninterrupted biological therapy since recruitment and had an antibody test between 14 and 70 days after a third dose with an mRNA-based SARS-CoV-2 vaccine

Variable	Level	Vedolizumab	Infliximab	Overall	P value
Vaccine	BNT162b2	41.9% (185/442)	41.5% (381/918)	41.6% (566/1360)	0.91
	ChAdOx1 nCoV-19	58.1% (257/442)	58.5% (537/918)	58.4% (794/1360)	
Age (years)		51.7 (37.9–63.4)	43.7 (32.3–55.6)	46.3 (33.6–58.3)	<0.0001
Sex	Female	50.6% (223/441)	46.4% (424/914)	47.7% (647/1355)	0.12
	Male	49.2% (217/441)	53.4% (488/914)	52.1% (706/1355)	
	Intersex	N<5	N<5	N<5	
	Prefer not to say	N<5	N<5	N<5	
Ethnicity	White	93.0% (410/441)	95.2% (870/914)	94.5% (1280/1355)	0.32
	Asian	5.0% (22/441)	2.7% (25/914)	3.5% (47/1355)	
	Mixed	1.1% (5/441)	1.1% (10/914)	1.1% (15/1355)	
	Black	N<5	0.5% (5/914)	0.5% (7/1355)	
	Other	N<5	0.4% (4/914)	0.4% (6/1355)	
Diagnosis	Crohn's disease	36.7% (162/442)	70.2% (644/918)	59.3% (806/1360)	<0.0001
	UC/IBDU	63.3% (280/442)	29.8% (274/918)	40.7% (554/1360)	
Duration of IBD (years)		10.0 (5.0–19.0)	9.0 (4.0–17.0)	9.0 (4.0–18.0)	0.0064
Age at IBD diagnosis (years)		36.0 (22.7–48.5)	29.8 (21.4–41.6)	31.2 (21.9–44.1)	<0.0001
Immunomodulators at vaccine		19.9% (88/442)	58.7% (539/918)	46.1% (627/1360)	<0.0001
5-ASA		33.9% (150/442)	21.6% (198/918)	25.6% (348/1360)	<0.0001
Steroids		5.7% (25/442)	2.4% (22/918)	3.5% (47/1360)	0.0038
BMI		25.8 (23.1–29.7)	26.1 (22.9–30.4)	25.9 (23.0–30.3)	0.88
Heart disease		7.3% (32/440)	2.9% (26/912)	4.3% (58/1352)	0.00029
Diabetes		8.2% (36/440)	4.5% (41/912)	5.7% (77/1352)	0.0082
Lung disease		16.1% (71/440)	12.0% (109/912)	13.3% (180/1352)	0.040
Kidney disease		2.3% (10/440)	1.2% (11/912)	1.6% (21/1352)	0.16
Cancer		1.1% (5/440)	N<5	0.5% (7/1352)	0.040
Smoker	Yes	6.1% (27/440)	8.4% (77/912)	7.7% (104/1352)	0.17
	Not currently	37.5% (165/440)	33.3% (304/912)	34.7% (469/1352)	
	Never	56.4% (248/440)	58.2% (531/912)	57.6% (779/1352)	
Exposure to documented cases of COVID-19		7.0% (31/440)	7.5% (68/912)	7.3% (99/1352)	0.82
Income deprivation score		0.090 (0.054–0.140)	0.087 (0.053–0.142)	0.088 (0.053–0.141)	0.83
Active disease (PRO2)		20.4% (85/416)	23.5% (203/864)	22.5% (288/1280)	0.23
Time between first two vaccine doses (weeks)		10.9 (10.0–11.1)	11.0 (10.0–11.1)	11.0 (10.0–11.1)	0.51
Time between second and third vaccine doses (weeks)		27.3 (25.6–28.9)	26.8 (24.3–28.4)	27.0 (24.7–28.7)	0.00064
Time from second dose to serum sample (weeks)		32.8 (30.4–35.4)	32.1 (29.6–35.1)	32.4 (29.9–35.1)	0.016
Time from third dose to serum sample (weeks)		5.6 (3.9–7.7)	5.7 (3.7–7.6)	5.7 (3.8–7.6)	0.93

Values presented are median (IQR) or percentage (numerator/denominator). P values represent the results of a Mann-Whitney U test, Kruskal-Wallis test or Fisher's exact test.

5-ASA, 5-aminosalicylic acid; BMI, body mass index; IBDU, IBD unclassified; mRNA, messenger RNA; PRO2, IBD disease activity.

Table 2 Baseline characteristics of participants with a history of prior SARS-CoV-2 infection, who received uninterrupted biological therapy since recruitment and had an antibody test between 14 and 70 days after a third dose with an mRNA-based SARS-CoV-2 vaccine

Variable	Level	Vedolizumab	Infliximab	P value
Vaccine	BNT162b2	36.2% (67/185)	41.2% (211/512)	0.26
	ChAdOx1 nCoV-19	63.8% (118/185)	58.8% (301/512)	
Max anti-N prefirst dose		0.3 (9.6)	0.2 (3.4)	<0.0001
Max anti-S prefirst dose		1.6 (13.0)	0.6 (3.8)	0.00022
Max anti-N presecond dose		0.7 (14.5)	0.2 (3.9)	<0.0001
Max anti-N presampling postsecond dose		4.2 (12.2)	1.0 (7.5)	<0.0001
Max anti-N pre/at sampling postsecond dose ≥ 0.12		97.3% (180/185)	95.3% (488/512)	0.29
Positive PCR or patient-reported swab presampling postsecond dose		46.5% (86/185)	53.1% (272/512)	0.12
Age (years)		45.3 (35.9–58.4)	39.9 (30.3–51.5)	<0.0001
Sex	Female	45.4% (84/185)	42.0% (214/510)	0.56
	Male	54.9% (101/185)	57.8% (295/510)	
	Intersex	N<5	N<5	
	Prefer not to say	N<5	N<5	
Ethnicity	White	92.4% (171/185)	89.8% (458/510)	0.58
	Asian	4.9% (9/185)	6.7% (34/510)	
	Mixed	N<5	1.4% (7/510)	
	Black	N<5	1.6% (8/510)	
	Other	N<5	N<5	
Diagnosis	Crohn's disease	35.1% (65/185)	64.8% (332/512)	<0.0001
	UC/IBDU	64.9% (120/185)	35.2% (180/512)	
Duration of IBD (years)		10.0 (5.0–17.0)	9.0 (3.0–16.0)	0.059
Age at IBD diagnosis (years)		33.3 (23.8–41.8)	27.2 (20.1–37.6)	0.00010
Immunomodulators at vaccine		20.0% (37/185)	59.4% (304/512)	<0.0001
5-ASA		34.6% (64/185)	21.3% (109/512)	0.00049
Steroids		5.4% (10/185)	1.2% (6/512)	0.0024
BMI		26.7 (23.9–31.9)	26.0 (23.4–29.6)	0.028
Heart disease		4.9% (9/185)	1.6% (8/509)	0.023
Diabetes		5.9% (11/185)	2.9% (15/510)	0.073
Lung disease		18.4% (34/185)	12.5% (64/510)	0.064
Kidney disease		3.8% (7/185)	N<5	0.0019
Cancer		N<5	N<5	
Smoker	Yes	6.5% (12/185)	6.5% (33/510)	0.0075
	Not currently	40.0% (74/185)	27.8% (142/510)	
	Never	53.5% (99/185)	65.7% (335/510)	
Exposure to documented cases of COVID-19		17.3% (32/185)	13.8% (70/510)	0.27
Income deprivation score		0.107 (0.061–0.164)	0.091 (0.053–0.164)	0.085
Active disease (PRO2)		17.3% (31/179)	18.2% (88/484)	0.91
Time between first two vaccine doses (weeks)		10.9 (9.7–11.1)	10.9 (9.9–11.1)	0.93
Time between second and third vaccine doses (weeks)		27.1 (25.6–29.1)	27.6 (25.7–30.0)	0.14
Time from second dose to serum sample (weeks)		33.1 (30.1–35.9)	33.4 (30.3–36.5)	0.36
Time from third dose to serum sample (weeks)		6.1 (3.7–7.6)	5.7 (3.9–7.7)	0.96

Values presented are median (IQR) or percentage (numerator/denominator). P values represent the results of a Mann-Whitney U test, Kruskal-Wallis test or Fisher's exact test. 5-ASA, 5-aminosalicylic acid; BMI, body mass index; IBDU, IBD unclassified; mRNA, messenger RNA; PRO2, IBD disease activity.

RBD antibody FC between peak antibody concentrations after second and third vaccine doses was greater in recipients of two ChAdOx1 nCoV-19 vaccines, followed by a third dose with an mRNA-based vaccine, compared with recipients of three mRNA-based vaccine doses (FC 11.1 (4.0) vs FC 3.7 (4.1)), $p < 0.0001$ (figure 1).

Anti-S RBD antibody concentrations were lower in infliximab-treated than vedolizumab-treated patients following a third dose with an mRNA-based vaccine (1978 U/mL (4.7) vs 12 384 U/mL (3.3), $p < 0.0001$), irrespective of whether they had received their first two vaccine doses with the ChAdOx1 nCoV-19 (1856 U/mL (5.2) vs 10 728 U/mL (3.1), $p < 0.0001$) or BNT162b2 vaccines (2164 U/mL (4.1) vs 15 116 U/mL (3.4), $p < 0.0001$) (figure 2).

Multivariable linear regression analyses in patients without prior SARS-CoV-2 infection confirmed that antibody concentrations were reduced 5.5-fold in infliximab-treated compared with vedolizumab-treated patients after a third dose with an mRNA-based vaccine (FC 0.18 (95% CI 0.15 to 0.21), $p < 0.0001$) (figure 3). Age ≥ 60 years and methotrexate use were also independently associated with lower anti-S RBD antibody concentrations. Receipt of three doses of an mRNA-based vaccine and a longer interval between second and third vaccine doses were associated with higher anti-S RBD antibody concentrations.

In patients without prior infection, anti-S RBD antibody half-life estimates were shorter in infliximab-treated than vedolizumab-treated patients following three doses of a

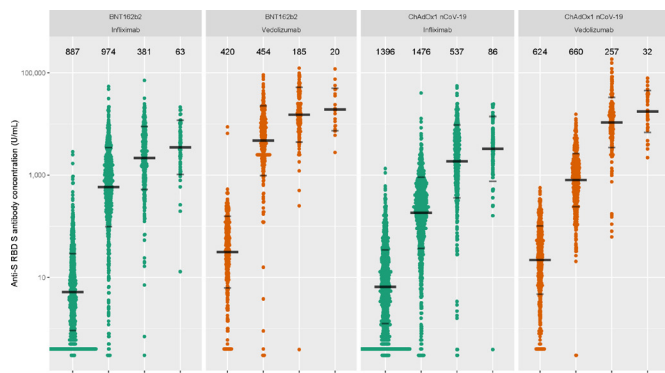


Figure 1 Anti-SARS-CoV-2 spike (anti-S) receptor-binding domain (RBD) antibody concentration stratified by biological therapy (infliximab vs vedolizumab) and type of vaccine. The wider bar represents the geometric mean, while the narrower bars are drawn one geometric SD either side of the geometric mean. The biological treatment infliximab is shown in green and vedolizumab in orange. The number of individuals tested for each group are shown in black at the top of each panel.

SARS-CoV-2 vaccine: 37.0 days (95% CI 35.6 to 38.6) vs 52.0 days (95% CI 49.0 to 55.4), respectively. Antibody concentrations following a third vaccine dose were higher in patients with a prior history of SARS-CoV-2 infection (online supplemental figure 1). Among patients with a history of SARS-CoV-2 infection at any point before third vaccination dose, geometric mean (SD) anti-S RBD antibody concentrations were lower in infliximab-treated compared with vedolizumab-treated patients after third vaccination with an mRNA-based vaccine (4059 U/mL (4.7) vs 18 788 U/mL (3.0), $p < 0.0001$).

Anti-SARS-CoV-2 (S) antibody level following fourth COVID-19 vaccine

Anti-S RBD antibody concentrations were lower in infliximab-treated than vedolizumab-treated patients following a fourth

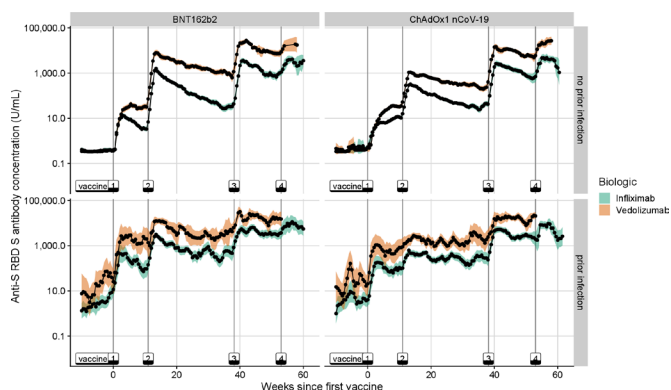


Figure 2 Rolling geometric mean anti-SARS-CoV-2 spike (anti-S) receptor-binding domain (RBD) antibody concentration over time from the date of the first dose of the SARS-CoV-2 vaccine (week 0) stratified by biological therapy (infliximab vs vedolizumab), vaccine and history of prior SARS-CoV-2 infection. Geometric means are calculated using a rolling 15-day window (ie, 7 days either side of the day indicated). The shaded areas represent the 95% CIs of the geometric means. Each dose of SARS-CoV-2 vaccine is marked out by vertical grey lines and annotated at the bottom of each panel. The biological treatment infliximab is shown in green and vedolizumab is shown in orange. The top panels represent those without prior infection and the bottom panels represent those who have had a prior infection.

Variable	N	Fold change (95% CI)	P value
Infliximab (vs vedolizumab)	912/1352	0.18 (0.15, 0.22)	<0.0001
BNT162b2 vaccine (dose 1 and 2)	563/1352	1.16 (0.99, 1.36)	0.060
Thiopurine	569/1352	0.87 (0.73, 1.03)	0.11
Methotrexate	96/1352	0.53 (0.39, 0.72)	<0.0001
Steroids	66/1352	0.90 (0.63, 1.28)	0.54
Crohn's disease (vs UC or IBDU)	799/1352	0.87 (0.74, 1.03)	0.10
Age ≥ 60	303/1352	0.74 (0.61, 0.89)	0.0014
Non-white ethnicity	77/1352	1.28 (0.92, 1.78)	0.14
Current smoker	104/1352	0.82 (0.62, 1.09)	0.18
Interval ≥ 26 weeks	897/1352	1.33 (1.13, 1.57)	0.00054

Figure 3 Exponentiated coefficients of linear regression models of log anti-SARS-CoV-2 spike (anti-S) receptor-binding domain (RBD) antibody concentration after a third dose with a messenger RNA-based vaccine. The resultant values represent the fold change of antibody concentration associated with each variable. IBDU, IBD unclassified.

dose with an mRNA-based vaccine (3353 U/mL (3.9) vs 18 152 U/mL (2.6), $p < 0.0001$), irrespective of whether they had received two doses of ChAdOx1 nCoV-19 (3257 U/mL (4.3) vs 17 535 U/mL (2.6), $p < 0.0001$) or BNT162b2 (3489 U/mL (3.4) vs 19 183 U/mL (2.6), $p < 0.0001$) vaccines first (figure 1). There was no difference between geometric mean (SD) anti-S RBD peak antibody concentrations following third and fourth doses of an mRNA-based vaccine, irrespective of the combination of primary vaccinations received (figure 2).

Breakthrough SARS-CoV-2 infection following three doses of vaccine

Incident SARS-CoV-2 infection across the entire CLARITY IBD cohort are shown in figure 4. Overall, 15.0% (393/2619 (95% CI 13.6% to 16.4%)) patients had a breakthrough infection after the third vaccine dose. S-gene target failure, indicative of infection with the B.1.1.529 (Omicron) variant, was observed in 74.9% (128/171) of those patients with breakthrough infection for whom PCR gene detection patterns were available.

Univariable factors associated with time to breakthrough infection are shown in online supplemental table 2. Younger age, infliximab treatment, concomitant thiopurine and lack of exposure to steroids were associated with a shorter time to breakthrough infection. In a multivariable model including anti-S

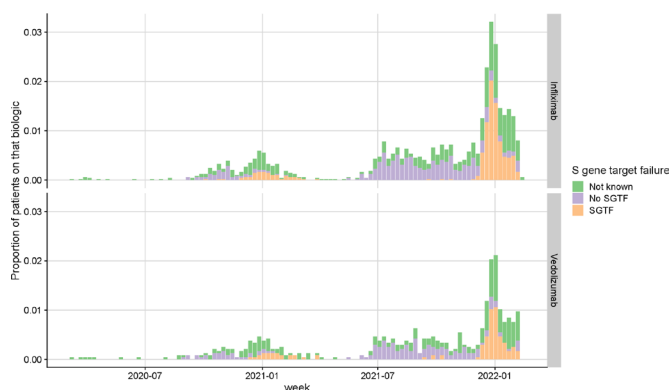


Figure 4 Proportion of patients with SARS-CoV-2 infection, stratified by biological therapy (infliximab vs vedolizumab) and S-gene target failure (SGTF) over time. Proportion of PCR-positive SGTF infection shown in orange.

Variable	N	Hazard ratio	P value
Infliximab (vs vedolizumab)	993/1453	2.23 (1.46, 3.38)	0.00018
BNT162b2 vaccine (dose 1 and 2)	595/1453	1.12 (0.85, 1.48)	0.41
Thiopurine	615/1453	0.94 (0.69, 1.27)	0.67
Methotrexate	104/1453	0.65 (0.34, 1.26)	0.21
Steroids	71/1453	0.68 (0.30, 1.54)	0.35
Age ≥ 60	322/1453	0.37 (0.23, 0.61)	<0.0001
log10(Anti-S)	1453/1453	1.21 (0.95, 1.54)	0.12

Figure 5 Coefficients of cox proportional hazards models of time to breakthrough infection after a third dose with a messenger RNA-based vaccine. The resultant values represent the hazard ratio for breakthrough infection associated with each variable.

RBD antibody concentrations, infliximab treatment, compared with vedolizumab treatment, and younger age, but not antibody responses, were significantly associated with a shorter time to breakthrough infection (figure 5).

SARS-CoV-2 reinfection and persistent carriage

In our analyses of reinfection, we included 757 infliximab-treated and 274 vedolizumab-treated participants who had at least 91 days of follow-up following a first positive PCR test while treated with their original biological. Overall, 12.5% (129/1031 (95% CI 10.5% to 14.7%)) patients had a reinfection with SARS-CoV-2. S-gene target failure was observed in 83.6% (56/67) patients for whom PCR gene detection patterns were available.

Time to reinfection was shorter in infliximab-treated than vedolizumab-treated patients (HR 2.10, 95% CI 1.31 to 3.35, $p=0.0019$). Reinfection was associated with SARS-CoV-2 anti-N antibody level 2–10 weeks after the first PCR-confirmed infection. For every 10-fold rise in anti-N RBD antibody concentration, we observed a 0.73-fold (95% CI 0.56 to 0.95, $p=0.02$) reduction in hazard of reinfection. Reinfection was not associated with SARS-CoV-2 anti-S antibody level 2–10 weeks after the third vaccine dose.

Of note, 3.1% (68/2185) participants with an initial positive SARS-CoV-2 PCR had a further positive test between 15 and 90 days later. To investigate whether participants shed replication-competent virus beyond 14 days, 207 adult patients with SARS-CoV-2 infection (positive RT-PCR from nasopharyngeal swabs) within the previous 90 days were sent kits in the post to carry out a home buccal swab test for a SARS-CoV-2 RT-PCR. One hundred sixty-eight patients returned the kits and three were positive for SARS-CoV-2, 16, 26 and 28 days after a positive PCR test. None of these samples tested positive for E gene or E gene-derived subgenomic RNA indicating non-replicating virus.

Overview of all COVID-19 infections, hospitalisations and deaths in the CLARITY cohort

In a Cox proportional hazards model of all infections across the entire CLARITY cohort, there were independent protective effects of prior infection and vaccination on the risk of SARS-CoV-2 infection. We observed a significant interaction between biological use and vaccination, whereby the protective effect of vaccination on the risk of infection was reduced in patients treated with infliximab compared with vedolizumab,

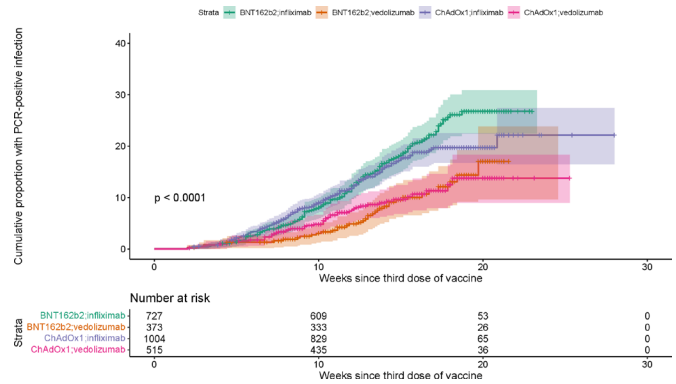


Figure 6 Kaplan-Meier graphs comparing the time to PCR-confirmed SARS-CoV-2 infection following a third dose of vaccine, stratified by biological therapy and vaccine type. Infliximab-treated patients are represented in green (those who received BNT162b2 for their first two doses) and purple (those who received ChAdOx1 nCoV-19 for their first two doses), and vedolizumab-treated patients in orange (those who received BNT162b2 for their first two doses) and pink (those who received ChAdOx1 nCoV-19 for their first two doses). The number of participants at each time point are displayed in black at the bottom of each figure. P values are calculated using log-rank test.

irrespective of vaccine type (figure 6). No interaction was seen between biological type and the protective effect of prior infection (figure 7).

Overall, 26/2186 (1.2%) patients had been hospitalised with COVID-19 after a median of 2.5 (IQR 0–8) days following a positive PCR test. Univariable analyses demonstrated that hospitalisation was associated with treatment with vedolizumab, older age, higher BMI, comorbid heart disease, diabetes, lung disease and cancer and having had fewer than two vaccine doses. Multivariable logistic regression confirmed that hospitalisation with COVID-19 was independently associated with older age (per decade: OR 1.69, 95% CI 1.28 to 2.25, $p<0.0001$) and a history of cancer (OR 113.63, 95% CI 14.12 to 1125.64, $p<0.0001$), whereas having at least two doses of SARS-CoV-2 vaccine (OR 0.24, 95% CI 0.10 to 0.56, $p=0.0011$) was protective (online supplemental figure 2).

There were 15 deaths in the CLARITY cohort, 3 were due to COVID-19. Two deaths occurred in unvaccinated participants and one in a participant who had received two vaccine

Variable	Hazard ratio	P value
Biologic		
Vedolizumab	Reference	
Infliximab	0.83 (0.66, 1.04)	0.11
Prior infection		
Unvaccinated	0.26 (0.17, 0.40)	<0.001
Vaccination		
Post first dose	1.03 (0.65, 1.63)	0.91
Post second dose	0.69 (0.52, 0.93)	0.01
Post third dose	0.51 (0.37, 0.70)	<0.001
Patient's age		
Biologic:Prior infection		
Biologic	Reference	
Infliximab	1.05 (0.65, 1.70)	0.83
Biologic:Vaccination		
Biologic		
Infliximab	1.35 (0.82, 2.22)	0.24
Infliximab	1.64 (1.25, 2.16)	<0.001
Infliximab	2.05 (1.51, 2.78)	<0.001

Figure 7 Cox proportional hazards model of factors associated with the risk of SARS-CoV-2 infection. The resultant values represent the HR of the risk of developing SARS-CoV-2 infection for each variable independently, and the interaction between biological treatment and prior infection, and biological treatment and each vaccine dose.

doses. The vaccinated patient had no comorbidities and received his last vedolizumab dose 3 weeks prior to testing positive for SARS-CoV-2.

DISCUSSION

Key results

After primary vaccination, anti-SARS-CoV-2 spike antibody concentrations were highest in the recipients of three doses of an mRNA-based vaccine. Infliximab treatment was associated with attenuated, less durable anti-SARS-CoV-2 antibody responses and a twofold increase in subsequent breakthrough SARS-CoV-2 infection. Unlike earlier in the pandemic, during the B.1.1.529 (Omicron) wave, magnitude of SARS-CoV-2 ancestral spike antibody concentrations did not predict protective immunity. Anti-SARS-CoV-2 antibody concentrations were higher and more sustained in participants with prior SARS-CoV-2 infection compared with those without prior infection. Reinfection occurred predominantly during the B.1.1.529 (Omicron) wave, was more common in infliximab-treated than vedolizumab-treated patients and were predicted by SARS-CoV-2 anti-N concentrations. We did not observe persistent oropharyngeal carriage. Hospitalisations and deaths remained uncommon.

Interpretation

In keeping with the original vaccine trials,^{22 23} after two vaccine doses, the highest anti-S RBD antibody concentrations were observed in recipients of the BNT162b2 vaccine. However, a third dose of an mRNA-based vaccine substantially improved responses in patients who had previously received the ChAdOx1 nCoV-19 vaccine, in support of previous studies demonstrating the benefit of heterologous booster vaccinations.^{24 25} Few published studies have reported the impact of biological and immunomodulator drugs on anti-SARS-CoV-2 antibody responses after three or four doses of a COVID-19 vaccine in patients with IBD.²⁶

Previous observational studies following one or two doses of a SARS-CoV-2 vaccine showed that most patients mount a serological response.^{27–32} Drawing conclusions across studies, however, is limited by differences in study sample size, control populations, the numbers and types of vaccines administered and the assays and seroconversion thresholds adopted to define response. Perhaps unsurprisingly then, results regarding the impact of specific biological and/or immunomodulator drugs are contradictory. Those studies that were adequately powered concluded that anti-TNF monotherapy attenuates serological responses, which are further impaired by combination immunomodulator use and in particular by methotrexate.^{8 9 11} Our half-life estimates suggest that further booster doses may be required for infliximab-treated patients without prior infection, after about 4 months to maintain antibody concentrations above peak prethird dose concentrations.¹⁰ Based on our postfourth dose antibody responses, however, there appears to be a ceiling effect on peak anti-S RBD antibody concentrations, irrespective of biological type or combination of primary vaccinations received.

Overall, vaccination continued to provide protective immunity during the B.1.1.529 (Omicron) wave. However, breakthrough SARS-CoV-2 infection occurred more commonly and earlier in infliximab-treated than vedolizumab-treated patients. Because infliximab does not increase the risk of SARS-CoV-2 infection prior to vaccination, the increased risk of breakthrough infection observed here is likely mediated by attenuated vaccine responses. Our findings that antinucleocapsid concentrations predict reinfection reflects the conserved nature of

the SARS-CoV-2 nucleocapsid sequence. In contrast, the spike sequence has rapidly evolved from the ancestral Wuhan Hu-1 strain sequence used in currently available vaccines. This is likely to explain why the anti-S-RBD antibody concentrations does not predict the risk of breakthrough infection with the omicron variant. In the age of VOCs, no reliable serological correlate of protection currently exists making routine anti-S RBD antibody testing to assess vaccine responses of limited utility, although it remains a useful marker demonstrating an immune response to vaccination.

As the pandemic evolved, reinfection with the new VOC has become more frequent. Similar to the situation in the general population, in this study, prior to the emergence of B.1.1.529 (Omicron), breakthrough infection and reinfection with COVID-19 were relatively uncommon in our vaccinated population. Thereafter, treatment with infliximab was associated with a twofold increased risk of reinfection compared with treatment with vedolizumab that was predicted by the immune responses at the time of the initial infection. While we observed that 3.1% of our patients tested positive for SARS-CoV-2, 15–90 days after their index diagnosis, we did not observe persistent oropharyngeal carriage of replication-competent virus in our substudy. Our findings may be limited by our sample size, however, against this, in the general population 13% of immunocompetent participants had evidence of persistent carriage of live virus.²⁰ However, and unlike Davies *et al*, we undertook this work during a low prevalence phase of the pandemic when the delta variant was dominant, and relied on cross-sectional rather than sequential testing with a longer interval between first and last PCR tests.

Despite the increased risk of breakthrough and recurrent SARS-CoV-2 infection in patients treated with infliximab, hospitalisations and deaths were reassuringly uncommon. This is likely to reflect the effectiveness of vaccination and the lower virulence of the B.1.1.529 (Omicron) variant. Moreover, anti-TNF therapy may prevent severe illness through inhibition of systemic inflammatory response associated with severe COVID-19.^{33 34} While hospitalisations were uncommon, a large number of infected patients risk a high burden of long COVID-19 in a population who already experience increased rates of fatigue, cognitive dysfunction and mood disorders than the general population.^{35 36} Several groups have suggested that anti-TNF therapy protects patients from severe COVID-19 illness.³⁷ Because long COVID-19 has been linked to more severe initial disease,³⁸ further work is needed to understand the effect of anti-TNF therapy on the prevalence and biology of long COVID-19.

Limitations and generalisability

We acknowledge the following limitations. First, our sample size although larger than similar studies, did not allow us to determine the effectiveness of vaccination against breakthrough infection with specific SARS-CoV-2 variants. Second, we have not been able to evaluate the impact of biological therapy on immunity that follows infection independent of vaccination, as only 5% of patients were unvaccinated at latest follow-up. Finally, we only assessed anti-S RBD antibody responses to infection, while a comprehensive appraisal of protective immunity would incorporate analysis of specific T cell immunity.

Anti-TNF drugs are used to treat a number of other immune-mediated inflammatory disease, which together affect about 3%–7% of Western populations including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, hidradenitis suppurativa and uveitis. Our findings are likely to be

generalisable to other anti-TNF drugs including adalimumab, certolizumab, golimumab and etanercept and across these other disease indications. Recent data from the VIP study suggests that anti-SARS-CoV-2 antibody responses following vaccination are also impaired in patients with IBD treated with other systemic immunosuppressant drugs, including tofacitinib, and allowing for sample size constraints, ustekinumab.¹¹

As a consequence of attenuated and less durable immunity, the potential benefits of vaccination against the risk of SARS-CoV-2 breakthrough infection and reinfection were reduced by infliximab treatment. The growing immunity in the population will potentially accelerate antigenic evolution, increasing the risk of reinfection and potentially for higher disease severity in reinfected patients.³⁹ Patients with attenuated responses to vaccination should be considered vulnerable to future more virulent SARS-CoV-2 variants.

Strategies that bypass the negative effect of the anti-TNF on vaccine-induced immune responses are now required. Further work is needed to assess whether the next generation of anti-SARS-CoV-2 vaccines, temporarily withholding immunomodulators at the time of vaccination⁴⁰ and/or timing booster doses towards the end of an anti-TNF treatment cycle when drug levels are lowest⁷ may induce greater immunogenicity. In the meantime, anti-TNF patients should be prioritised for booster vaccine doses with an mRNA-based vaccine.

CONCLUSION

Following a third dose of anti-SARS-CoV-2 mRNA-based vaccine, infliximab treatment was associated with attenuated serological responses, and breakthrough SARS-CoV-2 infection and reinfection. Breakthrough infection was not predicted by the magnitude of anti-S RBD responses, indicative of vaccine escape by the B.1.1.529 (Omicron) variant.

Author affiliations

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

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

³Department of Biochemistry, Exeter Clinical Laboratory International, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK

⁴Department of Microbiology, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK

⁵Institute of Biomedical and Clinical Sciences, University of Exeter, Exeter, UK

⁶College of Life and Environmental Sciences, University of Exeter, Exeter, UK

⁷Centre for Immunobiology, Blizard Institute, Barts and the London School of Medicine, Queen Mary University of London, London, UK

⁸Department of Gastroenterology, Royal London Hospital, Barts Health NHS Trust, The Royal London Hospital, London, UK

⁹Department of Gastroenterology, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

¹⁰Translational & Clinical Research Institute, Newcastle University Faculty of Medical Sciences, Newcastle upon Tyne, UK

¹¹Department of Gastroenterology, Royal Liverpool Hospital, Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK

¹²Department of Gastroenterology, St Mark's Hospital and Academic Institute, London, UK

¹³Department of Gastroenterology, St George's University Hospitals NHS Foundation Trust, London, UK

¹⁴Institute for Infection & Immunity, St George's University of London, London, UK

¹⁵Department of Gastroenterology, Western General Hospital, Edinburgh, UK

¹⁶Institute of Genetic and Molecular Medicine, University of Edinburgh Western General Hospital, Edinburgh, UK

¹⁷Department of Infectious Disease, Imperial College London, London, UK

¹⁸Lung Division, Royal Brompton and Harefield Hospitals, Guy's and St Thomas' NHS Foundation Trust, London, UK

¹⁹Department of Immunology and Inflammation, Imperial College London, London, UK

²⁰IBD Unit, Department of Gastroenterology, Hull University Teaching Hospitals NHS Trust, Hull, UK

²¹Hull York Medical School, University of Hull, Hull, UK

²²Department of Metabolism, Digestion and Reproduction, Imperial College London, London, UK

²³Department of Gastroenterology, Imperial College Healthcare NHS Trust, London, UK

Correction notice This article has been corrected since it published Online First. Grammatical errors have been amended in the abstract, key messages and discussion.

Twitter Nicholas A Kennedy @DrNickKennedy, Neil Chanchlani @nchanchlani1, Simeng Lin @SimengLin, Claire Bewshea @PANTSresearch, Timothy J McDonald @T_J_McDonald, Cressida Auckland @miRNAgirl, Merlin Davies @Merlin_Davies, Klaartje B Kok @klaartjekok, Christopher A Lamb @DrChrisLamb, Ailsa L Hart @drailsahart, Richard CG Pollok @NA, Charlie W Lees @charlie_lees, Rosemary J Boyton @BoytonRosemary, Daniel M Altmann @Daltmann10, Shaji Sebastian @ibdsb, Nicholas Powell @NickPowellLab, James R Goodhand @JamesGoodhand1 and Tariq Ahmad @tariqahmadIBD

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, Johanna Bruce and Eva Lahnsteiner from Public Health Scotland and the team from NHS Digital Access Request Service 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. The Department of Microbiology at the Royal Devon and Exeter NHS Trust performed SARS-CoV-2 PCR and antibody tests, and subgenomic experiments were performed by the RNA-mediated disease mechanism group at the University of Exeter.

Collaborators Contributors to the CLARITY IBD study—please see supplemental file for all names.

Contributors NAK, JRG, CB, SS, NP and 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. NAK, MJ, NC, SL, CB, LWH, MD, KBK, CAL, PJS, AH, RCP, CWL, RB, DA, SS, NP, JRG and TA were involved in the acquisition, analysis or interpretation of data. CA and SM performed SARS-CoV-2 variants characterisation analysis and interpretation. LWH and MD performed and interpreted RNA and subgenomic analyses. Data analysis was done by NAK. Drafting of the manuscript was done by NAK, MJ, NC, SL, JRG and TA. TA and RB obtained the funding for the study. All the authors contributed to the critical review and final approval of the manuscript. NAK, NP, JRG and TA have verified the underlying data. TA is the guarantor of the article.

Funding SL is supported by a Wellcome GW4-CAT fellowship (222850/Z/21/Z). NC acknowledges support from CCUK. 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. RB and DA are supported by MRC (MR/W020610/1, MR/S019553/1, MR/R02622X/1 and MR/V036939/1), NCSI4P, NIHR EME NIHR134607 and NIHR COV-LT2-0027, Innovate UK SBRI894, NIHR Imperial BRC Institute for Translational Medicine and Therapeutic, 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. This research used data assets made available by National Safe Haven as part of the Data and Connectivity National Core Study, led by Health Data Research UK in partnership with the Office for National Statistics and funded by UK Research and Innovation (research which commenced between 1 October 2020 and 31 March 2021 grant ref MC_PC_20029; 1 April 2021 and 30 September 2022 grant ref MC_PC_20058). This study was supported by an NCSI programme UKRI award to RB, DA, NP and TA (MR/W020610/1). The sponsor of the study was the Royal Devon and Exeter NHS Foundation Trust.

Competing interests NAK reports grants from F. Hoffmann-La Roche, grants from Biogen, grants from Celltrion Healthcare, grants from Galapagos, 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 Pharma, outside the submitted work. SL reports non-financial support from Pfizer, non-financial support from Ferring, outside the submitted work. LWH declares an interest in SENISCA as founder and Chief Scientific Officer. KBK reports personal fees from Janssen, personal fees from Takeda, personal fees from PredictImmune, personal fees from Amgen, outside the submitted work. CAL 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. PJS reports speaker fees and advisory board sponsorship from Janssen, Celltrion, AbbVie, Tillotts Pharma, Galapagos, Amgen, Dr Falk Pharma and Takeda outside the submitted work. AH reports personal fees from AbbVie, personal fees from Allergan, personal fees from BMS, personal fees from Celltrion, personal fees from Dr Falk Pharma, personal fees from GSK, personal fees from Takeda, personal fees from Pfizer, personal fees from Janssen, personal fees from Galapagos, personal fees from AstraZeneca, outside the submitted work. RCP reports acting as consultant, advisory board member, speaker or recipient of educational grant from Dr Falk Pharma, Ferring, Janssen, Pharmacosmos and Takeda, outside the submitted work. CWL 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 Celltrion, personal fees from Ferring, personal fees from BMS, during the conduct of the study. RB and DA are members of the Global T cell Expert Consortium and have consulted for Oxford Immunotec outside the submitted work. SS reports grants from Takeda, AbbVie, Amgen, Tillotts Pharma, personal fees from Janssen, Takeda, Galapagos, Celltrion, Dr Falk Pharma, Tillotts Pharma, Cellgene, Pfizer, Pharmacosmos, outside the submitted work. NP reports personal fees from Takeda, personal fees from Janssen, personal fees from Pfizer, personal fees from Bristol-Myers Squibb, personal fees from AbbVie, personal fees from Roche, personal fees from Lilly, personal fees from Allergan, personal fees from Celgene, outside the submitted work; and NP has served as a speaker/advisory board member for AbbVie, Allergan, Bristol-Myers Squibb, Celgene, Dr Falk Pharma, Ferring, Janssen, Pfizer, Tillotts Pharma, Takeda and Vifor Pharma. JRG reports grants from F. Hoffmann-La Roche, grants from Biogen, grants from Celltrion Healthcare, grants from Galapagos, non-financial support from Immundiagnostik, during the conduct of the study. TA reports grants and non-financial support from F. Hoffmann-La Roche, grants from Biogen, grants from Celltrion Healthcare, grants from Galapagos, non-financial support from Immundiagnostik, during the conduct of the study; personal fees from Biogen, grants and personal fees from Celltrion Healthcare, personal fees and non-financial support from Immundiagnostik, personal fees from Takeda, personal fees from ARENA, personal fees from Gilead, personal fees from Adcock Ingram Healthcare, personal fees from Pfizer, personal fees from Genentech, non-financial support from Tillotts Pharma, outside the submitted work.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the 'Methods' section for further details.

Patient consent for publication Not applicable.

Ethics approval The Surrey Borders Research Ethics committee approved the study (REC reference: REC 20/HRA/3114) in September 2020. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. 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.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

This article is made freely available for personal use in accordance with BMJ's website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may download and print the article for any lawful,

non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

ORCID iDs

Nicholas A Kennedy <http://orcid.org/0000-0003-4368-1961>
 Malik Janjua <http://orcid.org/0000-0002-3999-8555>
 Neil Chanchlani <http://orcid.org/0000-0003-0207-6706>
 Simeng Lin <http://orcid.org/0000-0002-4201-4879>
 Claire Bewshea <http://orcid.org/0000-0002-0965-9587>
 Timothy J McDonald <http://orcid.org/0000-0003-3559-6660>
 Lorna W Harries <http://orcid.org/0000-0001-7791-8061>
 Klaartje B Kok <http://orcid.org/0000-0002-5942-9149>
 Christopher A Lamb <http://orcid.org/0000-0002-7271-4956>
 Philip J Smith <http://orcid.org/0000-0003-1568-3978>
 Ailsa L Hart <http://orcid.org/0000-0002-7141-6076>
 Richard CG Pollok <http://orcid.org/0000-0001-6452-6763>
 Charlie W Lees <http://orcid.org/0000-0002-0732-8215>
 Rosemary J Boyton <http://orcid.org/0000-0002-5608-0797>
 Daniel M Altmann <http://orcid.org/0000-0002-2436-6192>
 Shaji Sebastian <http://orcid.org/0000-0002-3670-6545>
 Nicholas Powell <http://orcid.org/0000-0003-3231-6950>
 James R Goodhand <http://orcid.org/0000-0003-3112-376X>
 Tariq Ahmad <http://orcid.org/0000-0002-6058-5528>

REFERENCES

- World Health Organization. Classification of omicron (B.1.1.529): SARS-CoV-2 variant of concern, 2021. Available: [https://www.who.int/news/item/26-11-2021-classification-of-omicron-\(b.1.1.529\)-sars-cov-2-variant-of-concern](https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern)
- Hoffmann M, Krüger N, Schulz S, et al. The omicron variant is highly resistant against antibody-mediated neutralization: implications for control of the COVID-19 pandemic. *Cell* 2022;185:447–56.
- Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. *BMJ* 2021;n1088.
- Andrews N, Stowe J, Kirsebom F, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) variant. *N Engl J Med Overseas Ed* 2022;386:1532–46.
- Choi B, Choudhary MC, Regan J, et al. Persistence and evolution of SARS-CoV-2 in an immunocompromised host. *N Engl J Med Overseas Ed* 2020;383:2291–3.
- Avanzato VA, Matson MJ, Seifert SN, et al. Case study: prolonged infectious SARS-CoV-2 shedding from an asymptomatic immunocompromised individual with cancer. *Cell* 2020;183:1901–12.
- Chanchlani N, Lin S, Chee D, et al. Adalimumab and infliximab impair SARS-CoV-2 antibody responses: results from a therapeutic drug monitoring study in 11 422 Biologic-Treated patients. *J Crohns Colitis* 2022;16:389–97.
- Kennedy NA, Goodhand JR, Bewshea C, et al. Anti-SARS-CoV-2 antibody responses are attenuated in patients with IBD treated with infliximab. *Gut* 2021;70:865–75.
- Kennedy NA, Lin S, Goodhand JR, et al. Infliximab is associated with attenuated immunogenicity to BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines in patients with IBD. *Gut* 2021;70:1884–93.
- Lin S, Kennedy NA, Saifuddin A, et al. Antibody decay, T cell immunity and breakthrough infections following two SARS-CoV-2 vaccine doses in inflammatory bowel disease patients treated with infliximab and vedolizumab. *Nat Commun* 2022;13:1379.
- Alexander JL, Kennedy NA, Ibraheem H, et al. COVID-19 vaccine-induced antibody responses in immunosuppressed patients with inflammatory bowel disease (VIP): a multicentre, prospective, case-control study. *The Lancet Gastroenterology & Hepatology* 2022;7:342–52.
- Predecki M, Clarke C, Edwards H, et al. Humoral and T-cell responses to SARS-CoV-2 vaccination in patients receiving immunosuppression. *Ann Rheum Dis* 2021;80:1322–9.
- Mahil SK, Bechman K, Raharja A, et al. The effect of methotrexate and targeted immunosuppression on humoral and cellular immune responses to the COVID-19 vaccine BNT162b2: a cohort study. *Lancet Rheumatol* 2021;3:e627–37.
- Joint Committee on Vaccination and Immunisation. Joint Committee on vaccination and immunisation (JCVI) advice on third primary dose vaccination, 2021. Available: <https://www.gov.uk/government/publications/third-primary-covid-19-vaccine-dose-for-people-who-are-immunosuppressed-jcvi-advice/joint-committee-on-vaccination-and-immunisation-jcvi-advice-on-third-primary-dose-vaccination> [Accessed 6 Sep 2021].
- European Centre for Disease Prevention and Control/World Health Organization Regional Office for Europe. *Methods for the detection and characterisation of SARS-CoV-2 variants*, 2021.
- Roche Diagnostics GmbH. Elecsys® Anti-SARS-CoV-2 S assay method sheet, 2020. Available: <https://diagnostics.roche.com/gb/en/products/params/elecsys-anti-sars-cov-2-s.html> [Accessed 24 Mar 2021].

- 17 Muench P, Jochum S, Wenderoth V, *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* 2020;58:1694–714.
- Taffertshofer KWalter MMackeben P. Design and Performance Characteristics of the Elecsys Anti-SARS-CoV-2 S assay. medRxiv 2022:2022.10.1101/2022.07.04.22277103
- 19 Yahav D, Yelin D, Eckerle I, *et al.* Definitions for coronavirus disease 2019 reinfection, relapse and PCR re-positivity. *Clin Microbiol Infect* 2021;27:315–8.
- 20 Davies M, Bramwell LR, Jeffery N, *et al.* Persistence of clinically relevant levels of SARS-CoV2 envelope gene subgenomic RNAs in non-immunocompromised individuals. *Int J Infect Dis* 2022;116:418–25.
- 21 Harris PA, Taylor R, Minor BL, *et al.* The REDCap Consortium: building an international community of software platform partners. *J Biomed Inform* 2019;95:103208.
- 22 Voysey M, Clemens SAC, Madhi SA, *et al.* Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021;397:99–111.
- 23 Walsh EE, Frenck RW, Falsey AR, *et al.* Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. *N Engl J Med* 2020;383:2439–50.
- 24 Costa Clemens SA, Weckx L, Clemens R, *et al.* Heterologous versus homologous COVID-19 booster vaccination in previous recipients of two doses of CoronaVac COVID-19 vaccine in Brazil (RHH-001): a phase 4, non-inferiority, single blind, randomised study. *The Lancet* 2022;399:521–9.
- 25 Atmar RL, Lyke KE, Deming ME, *et al.* Homologous and heterologous Covid-19 booster vaccinations. *N Engl J Med* 2022;386:1046–57.
- 26 Schell TL, Knutson KL, Saha S, *et al.* Humoral immunogenicity of 3 COVID-19 messenger RNA vaccine doses in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2022;izac082.
- 27 Wong S-Y, Dixon R, Martinez Pazos V, *et al.* Serologic response to messenger RNA coronavirus disease 2019 vaccines in inflammatory bowel disease patients receiving biologic therapies. *Gastroenterology* 2021;161:715–8.
- 28 Classen JM, Muzalyova A, Nagl S, *et al.* Antibody response to SARS-CoV-2 vaccination in patients with inflammatory bowel disease - results of a single-center cohort study in a tertiary hospital in Germany. *Dig Dis* 2021. doi:10.1159/000521343. [Epub ahead of print: 10 Dec 2021].
- 29 Cerna K, Duricova D, Lukas M, *et al.* Anti-SARS-CoV-2 vaccination and antibody response in patients with inflammatory bowel disease on Immune-modifying therapy: prospective Single-Tertiary study. *Inflamm Bowel Dis*;70.
- 30 Edelman-Klapper H, Zittan E, Bar-Gil Shitrit A, *et al.* Lower serologic response to COVID-19 mRNA vaccine in patients with inflammatory bowel diseases treated with Anti-TNFα. *Gastroenterology* 2022;162:454–67.
- 31 Jena A, Mishra S, Deepak P, *et al.* Response to SARS-CoV-2 vaccination in immune mediated inflammatory diseases: systematic review and meta-analysis. *Autoimmun Rev* 2022;21:102927.
- 32 Kappelman MD, Weaver KN, Boccheri M, *et al.* Humoral immune response to messenger RNA COVID-19 vaccines among patients with inflammatory bowel disease. *Gastroenterology* 2021;161:1340–3.
- 33 Soy M, Keser G, Atagündüz P, *et al.* Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. *Clin Rheumatol* 2020;39:2085–94.
- 34 Akiyama S, Hamdeh S, Micic D, *et al.* Prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases: a systematic review and meta-analysis. *Ann Rheum Dis* 2021;80:384–91.
- 35 Tadin Hadjina I, Zivkovic PM, Matetic A, *et al.* Impaired neurocognitive and psychomotor performance in patients with inflammatory bowel disease. *Sci Rep* 2019;9:1–13.
- 36 Goodhand JR, Wahed M, Mawdsley JE, *et al.* Mood disorders in inflammatory bowel disease: relation to diagnosis, disease activity, perceived stress, and other factors. *Inflamm Bowel Dis* 2012;18:2301–9.
- 37 Gianfrancesco M, Hyrich KL, Al-Adely S, *et al.* Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 global rheumatology alliance physician-reported registry. *Ann Rheum Dis* 2020;79:859–66.
- 38 Crook H, Raza S, Nowell J, *et al.* Long covid-mechanisms, risk factors, and management. *BMJ* 2021;374:n1648.
- 39 Markov PV, Katzourakis A, Stilianakis NI. Antigenic evolution will lead to new SARS-CoV-2 variants with unpredictable severity. *Nat Rev Microbiol* 2022;20:251–2.
- 40 Park JK, Lee MA, Lee EY, *et al.* Effect of methotrexate discontinuation on efficacy of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomised clinical trial. *Ann Rheum Dis* 2017;76:1559–65.

Supplementary Information for ‘Vaccine escape, increased breakthrough and reinfections in infliximab-treated patients with IBD during the Omicron wave of the SARS-CoV-2 pandemic.’

Table of Contents

Supplementary Table 1: Contributors to the CLARITY IBD study	2
Supplementary Table 2: Univariable factors associated with time to breakthrough infection.....	25
Supplementary Figure 1: Antibody concentrations following a third vaccine dose in patients with a prior history of SARS-CoV-2 infection.....	26
Supplementary Figure 2: Multivariable factors associated with hospitalisation with COVID-19	27

Supplementary Table 1: Contributors to the CLARITY IBD study

Affiliation	First name	Surname
Barts Health NHS Trust	Klaartje	Kok
	Nick	Croft
	Bessie	Cipriano
	Caroline	Francia
	Nosheen	Khalid
	Ashley	Kingston
	Irish	Lee
	Anouk	Lehmann
	Kinnari	Naik
	Kevin	Samuels
	Nicolene	Plaatjies
	Hafiza	Khatun
	Farjana	Bokth
	Elise	Pabriaga
	Madiha	Islam
Basingstoke and North Hampshire Hospital	Rebecca	Saich
	Hayley	Cousins
	Wendy	Fraser
	Rachel	Thomas
	Matthew	Brown
	Benjamin	White
Basingstoke and North Hampshire Hospital (Hampshire Hospitals NHS Foundation Trust)	Nikolaos	Kirkineziadis
	Bernadette	Tilley
	Pennie	Porter
	Rachel	Bryant
	Natalia	Robaczewska
Birmingham Women's and Children's NHS Foundation Trust	Rafeeq	Muhammed
	Rehana	Bi

	Catherine	Cotter
	Jayne	Grove
	Kate	Hong
	Ruth	Howman
	Monica	Mitchell
	Sophie	Clayton
	Louise	Rogers
	Sugrah	Sultan
	Melanie	Rooney
	Charlotte	Cottrill
Bolton NHS Foundation Trust	Salil	Singh
	Chris	Dawe
	Robert	Hull
	Natalie	Silva
	Julie	Chadwick
	Laura	Robertson
Borders General Hospital	Jonathan	Manning
	Lauren	Finlayson
	Allison	Roebuck
	Joy	Dawson
Calderdale and Huddersfield NHS Foundation Trust	Sunil	Sonwalkar
	Naomi	Chambers
	Matthew	Robinson
	Andrew	Haigh
	Lear	Matapure
Cambridge University Hospitals NHS Foundation Trust	Tim	Raine
	Varun	George
	Christina	Kapizioni
	Konstantina	Strongili
	Tina	Thompson

	Mohamed	Ahmed
	Christos	Kontos
	Claire	Dawson
Cambridge Institute of Therapeutic Immunology and Infectious Disease, Jeffrey Cheah Biomedical Centre, University of Cambridge	Christophe	Bourges
	Isabella	Barbutti
	Megan E	Gozzard
Chelsea and Westminster Hospital NHS Foundation Trust	Philip	Hendy
	Rhian	Bull
	Patricia	Costa
	Lisa	Davey
	Hayley	Hannington
	Kribashnie	Nundlall
	Catarina	Martins
	Laura	Avanzi
	Jaime	Carungcong
	Sabrina	Barr
	Richard	Appleby
	Emma	Johnson
	Eathar	Shakweh
Chesterfield Royal Hospital	Kath	Phillis
	Rachel	Gascoyne
	Amanda	Crowder
	Amanda	Whileman
Countess Of Chester Hospital NHS Foundation Trust	Ian	London
	Jenny	Grounds
	Emmeline	Martin
	Susie	Pajak
	Jude	Price
	Kathryn	Cawley
	Sandra	Powell

	Nichola	Kearsley
Darlington Memorial Hospital	Anjan	Dhar
	Ellen	Brown
	Amanda	Cowton
	Kimberley	Stamp
Dartford and Gravesham NHS Trust	Ben	Warner
	Carmel	Stuart
	Louise	Lacey
The Dudley Group NHS Foundation Trust	Shanika	de Silva
	Clare	Allcock
	Philip	Harvey
	Lesley	Jones
	Elise	Cooke
	Jayne	Slater
	Dominic	King
East and North Hertfordshire NHS Trust	Johanne	Brooks
	Pearl	Baker
	Hannah	Beadle
	Carina	Cruz
	Debbie	Potter
East Lancashire Hospitals NHS Trust	Joe	Collum
	Farzana	Masters
Glangwili Hospital	Aashish	Kumar
Hywel Dda University Health Board	Samantha	Coetzee
	Mihaela	Peiu
	Becky	Icke
	Jill	Williams
	Meena	Raj
Great Ormond Street Hospital	Edward	Gaynor
	Sibongile	Chadokufa

	Bonita	Huggett
	Hamza	Meghari
	Sara	El-Khouly
	Fevronia	Kiparissi
	Waffa	Girshab
	Lynda	Russell-Walker
	Christopher	Jackson
	Sara	Sidler
Great Western Hospitals NHS Foundation Trust	Andrew	Claridge
	Emily	Fowler
	Laura	McCafferty
	Lesley	Haxton
Guy's and St Thomas' NHS Foundation Trust	Peter	Irving
	Karolina	Christodoulides
	Angela	Clifford
	Patrick	Dawson
	Sailish	Honap
	Samuel	Lim
	Raphael	Luber
	Karina	Mahiouz
	Susanna	Meade
	Parizade	Raymode
	Rebecca	Reynolds
	Anna	Stanton
	Sherill	Tripoli
	Naomi	Hare
	Sopuluchukwu	Odukwe
	Senthuran	Balachandran
	Emma	North

	Jessica	North
	Bria	Browne
	Jessica	Cordle
	Ella	Jameson
The Hillingdon Hospitals NHS Foundation Trust	Yih Harn	Siaw
	Lane	Manzano
	Jonathan	Segal
	Ibrahim	Al-Bakir
	Imran	Khakoo
	Sofiya	Portukhay
Homerton University Hospital Foundation Trust	Nora	Thoua
	Katherine	Davidson
	Jagrul	Miah
	Lisa	Canclini
	Alex	Hall
	Hassina	Furreed
	Christine	Mitchell-Inwang
Hull University Teaching Hospitals NHS Trust	Shaji	Sebastian
	Melony	Hayes
	Sally	Myers
	Alison	Talbot
	Jack	Turnbull
	Emma	Whitehead
	Katie	Stamp
	Alison	Pattinson
	Verghese	Mathew
	Leanne	Sherris
	Julie	Wilcox
	Sankaranarayanan	Ramachandran
	Hayley	Robertson

	Angela	Harvey
Imperial College Healthcare NHS Trust	Lucy	Hicks
	Tara-Marie	Byrne
	Leilani	Cabreros
	Hannah	Downing-Wood
	Sophie	Hunter
	Mohammad Aamir	Saifuddin
	Hemanth	Prabhudev
	Sharmili	Balarajah
	Jan	Krucznski
	Kalliopi	Driva
	Andrea	D'Mello
	Parith	Shah
Faculty of Medicine, Imperial College London	Hajir	Ibraheim
	Melissa	Torkizadeh
	Jonathan W	Lo
	Zhigang	Liu
James Paget University Hospitals NHS Foundation Trust	Helen	Sutherland
	Elva	Wilhelmsen
	Katherine	Mackintosh
Kettering General Hospital	Ajay M	Verma
	Juliemol	Sebastian
	Mohammad Farhad	Peerally
	Parizade	Raymode
	Anne-marie	Guerdette
	Susan	Coburn
	Ching Yee	Novem lam
	Donna	Durrant
	Belinda	Schaefer
	Solange	Serna

	Muhammad	Shahzad
King's College Hospital NHS Foundation Trust	Alexandra	Kent
	Lee Meng	Choong
	Benedetta	Pantaloni
	Pantelis	Ravdas
King's College Hospital NHS Foundation Trust (paediatric)	Babu	Vadamalayan
King's Mill Hospital	Stephen	Foley
	Becky	Arnold
	Cheryl	Heeley
	Wayne	Lovegrove
	Donna	Sowton
	Lynne	Allsop
	Heidi	Gregory
	Mandy	Gill
	Megan	Holmes
	Valeria	Balan
	Susan	Smith
	Sarah	Turner
Liverpool University Hospitals NHS Foundation Trust	Philip J	Smith
	Alan	Steel
	Giovanna	Bretland
	Sarah	King
	Martina	Lofthouse
	Lindsey	Rigby
	Sreedhar	Subramanian
	David	Tyrer
	Kate	Martin
London North West University	Christopher	Probert
	Nikolaos	Kamperidis

Healthcare NHS Trust	Temí	Adedoyin
	Manisha	Baden
	Jeannette	Brown
	Feba	Chacko
	Lisa	Young
	Michela	Cicchetti
	Mohammad	Saifuddin
	Priya	Yesupatham
Maidstone and Tunbridge Wells NHS Trust	Rohit	Gowda
	Maureen	Williams
Manchester University NHS Foundation Trust	Karen	Kemp
	Rima	Akhand
	Glaxy	Gray
	Anu	John
	Maya	John
	Tasnim	Mohammed
	Diamond	Sathe
	Natasha	Jones
	Jennifer	Soren
The Mid Yorkshire Hospitals NHS Trust	Michael	Sprakes
	Julie	Burton
	Patricia	Kane
	Stephanie	Lupton
	Jacqueline	Bartholomew
	Elizabeth	Denis
	Alison	Daniels
Milton Keynes University Hospital	George	MacFaul
	Diane	Scaletta
	Loria	Siamia
	Felicity	Williams

	Chloe	Green
	Zeljka	Ver
Newcastle Hospitals NHS Foundation Trust	Chris	Lamb
	Mary	Doona
	Ashleigh	Hogg
	Lesley	Jeffrey
	Andrew	King
	R Alexander	Speight
	Jennifer	Doyle
	Ruth	Owen
	Jenny	Haworth
	Linda	Patterson
	Vithusa	Varnaulasingam
Ninewells Hospital & Medical School	Craig	Mowat
	Debbie	Rice
	Susan	MacFarlane
	Anne	MacLeod
	Samera	Mohammed
Ninewells Hospital & Medical	Shona	Murray
	Anne	Elliott
Norfolk and Norwich University Hospitals NHS Foundation Trust	Mary	Anne Morris
	Louise	Coke
	Grace	Hindle
	Eirini	Kolokouri
	Catherine	Wright
	Claire	Lee
	Nicola	Ward
	Adele	Dann
North Bristol NHS Trust	Melanie	Lockett
	Charlotte	Cranfield

	Louise	Jennings
	Ankur	Srivastava
	Lana	Ward
	Nouf	Jeynes
	Poonam	Ranga
North Tyneside General Hospital	Praveen	Rajasekhar
	Lisa	Gallagher
	Linda	Patterson
	Jill	Ward
	Rae	Basnett
	Judy	Murphy
	Lauren	Parking
	Emma	Lawson
	Stacey	Short
Nottingham University Hospitals NHS Trust	David	Devadason
	Gordon	Moran
	Neelam	Khan
	Lauren	Tarr
	Charmaine	Olivia
	Samantha	Warbarton
	Sian	Kelly
The Pennine Acute Hospitals NHS Trust	Jimmy	Limdi
	Kay	Goulden
	Asad	Javed
	Lauren	McKenzie
	Julie	Melville
	Eleanor	Liu
	Joseph	Sabine
	Patricia	Jacob
	Denise	McSorland

	Nick	Schofield
	Lisa	Cornwall
	James	Quirke
	Emma	Crook
	Anne	Turner
Portsmouth Hospitals NHS Trust	Pradeep	Bhandari
	Michelle	Baker-Moffatt
	Joanne	Dash
	Alison	Le Poidevin
	Hayley	Downe
	Lucille	Bombero
	Helen	Blackman
	Rebecca	Smith
The Queen Elizabeth Hospital Kings Lynn NHS Trust	Alan	Wiles
	Hannah	Bloxham
	Jose	Dias
	Evelyn	Nadar
	Hollie	Curgenven
	Ellie	Gilham
Queen Elizabeth University Hospital, Glasgow	Jonathan	Macdonald
	Shona	Finan
	Faye	McMeeken
	Misbah	Mahmood
	Stephanie	Shields
	John Paul	Seenan
Royal Berkshire NHS Foundation Trust	Des	DeSilva
	Susanna	Malkakorpi
	Rachel	Carson
	Holly	Lawrence
	Ofori	Boateng

	Felix	Kpodo
University Hospitals Dorset NHS Foundation Trust	Simon	Whiteoak
	Kelli	Edger-Earley
	Luke	Vamplew
	Joanna	Samways
	Sue	Roffe
Royal Cornwall Hospitals NHS Trust	Sarah	Ingram
	Joel	James
	Sharon	Botfield
	Fiona	Hammonds
	Clare	James
	Zoe	Berry
Royal Devon and Exeter NHS Foundation Trust	Tariq	Ahmad
	Gemma	Aspinall
	Sarah	Hawkins
	Marian	Parkinson
	Helen	Gardner-Thorpe
	Suzie	Marriott
	Clare	Redstone
	Halina	Windak
	Ana-Marie	Adam
	Hannah	Mabb
	Emma	Stevenson
	Jessica	Record
Royal Free London NHS Foundation Trust	Charles	Murray
	Cynthia	Diaba
	Fexy	Joseph
	Glykeria	Pakou
	Yvonne	Gleeson
	Annalyn	Nunag

Royal Glamorgan Hospital	James	Berrill
	Natalie	Stroud
	Carla	Pothecary
	Lisa	Roche
	Keri	Turner
	Lisa	Deering
	Lynda	Israel
Royal Gwent Hospital	Evelyn	Baker
	Maxine	Nash
Royal Hampshire County Hospital (Hampshire Hospitals NHS Foundation Trust)	John	Gordon
	Emma	Levell
	Silvia	Zagalo
	Wendy	Fraser
	Ina	Hoad
	Nikolaos	Kirkineziadis
	Bernadette	Tilley
	Natalia	Robaczewska
	Bindu	Anil
Royal Hospital for Sick Children, Edinburgh	Richard	Russell
	Paul	Henderson
	Margaret	Millar
Royal Manchester Children's Hospital	Andrew	Fagbemi
	Felicia	Jennings
	Imelda	Mayor
	Jill	Wilson
	Alice	Wheeler
	Nicola	Phillips
Royal Surrey County Hospital	Christopher	Alexakis
	Natalia	Michalak
	Cheryl	Marriott

	Sarah	Stone
	Veronika	Pristopan
Royal United Hospitals Bath	John	Saunders
	Helen	Burton
	Vanessa	Cambridge
	Tonia	Clark
	Charlotte	Ekblad
	Sarah	Hierons
	Joyce	Katebe
	Emma	Saunbury
	Rachel	Perry
The Royal Wolverhampton NHS Trust	Matthew	Brookes
	Kathryn	Davies
	Marie	Green
	Ann	Plumbe
Salford Royal NHS Foundation Trust	Clare	Ormerod
	Helen	Christensen
	Hannah	Howlett
	Anne	Keen
	Jonathan	Ogor
	Marie	Greenhaigh
	Karen	Knowles
	Shanzi	Yin
	Maria	Poulaka
Salisbury District Hospital	Alpha	Anthony
	Emily	Newitt
	Fiona	Trim
	Ruth	Casey
	Katherine	Seymour
	Catherine	Reed

	Lijo	Joy
Sandwell and West Birmingham NHS Trust	Edward	Fogden
	Kalisha	Russell
	Samia	Hussain
Sheffield Teaching Hospitals NHS Foundation Trust	Anne	Phillips
	Muaad	Abdulla
Shrewsbury and Telford Hospital NHS Trust	Jeff	Butterworth
	Colene	Adams
	Mandy	Carnahan
	Elizabeth	Buckingham
	Danielle	Childs
	Alison	Magness
	Jo	Stickley
	Nichola	Motherwell
	Louise	Tonks
	Hannah	Gibson
	Susie	Pajak
	Kate	Wistance
Singleton Hospital Swansea Bay University Health Board	Caradog	Thomas
	Elaine	Brinkworth
	Lynda	Connor
	Amanda	Cook
	Tabitha	Rees
	Rachel	Harford
	Sean	Farley
	Marie	Jones
Somerset NHS Foundation Trust	Emma	Wesley
	Alison	Moss
	Jacob	Lucas
	Claire	Lorimer

	Maria	Oleary
	Maxine	Dixon
	Fiona	Goodchild
	Rebecca	Twenlow
	Corinne	Pawley
South Tees Hospitals NHS Foundation Trust	Arvind	Ramadas
	Julie	Tregonning
	Olaku	Okeke
	Wendy	Jackson
Southend University Hospital NHS Foundation Trust	Ioannis	Koumoutsos
	Viji	George
	Swapna	Kunhunni
	Sophie	Laverick
	Isla	Anderson
	Sophie	Smith
	Joan	Joyce
	Sarala	Janarthan
St George's University Hospitals NHS Foundation Trust	Kamal	Patel
	Mariam	Ali
	Hilda	Mhandu
	Aleem	Rana
	Katherine	Spears
	Joana	Teixeira
	Richard	Pollok
	Mark	Mencias
	Abigail	Seaward
	Jessica	Sousa
	Nooria	Said
	Mark	Soomaroo
	Valentina	Raspa

	Asha	Tacouri
St George's University Hospitals NHS Foundation Trust (paediatric)	Nicholas	Reps
	Rebecca	Martin
	Tinashe	Samakomva
St James's University Hospital (The Leeds Teaching Hospital NHS Trust)	Christian	Selinger
	Jenelyn	Carbonell
	Felicia	Onovira
	Doris	Quartey
	Alice	L'Anson
	Andrew	Ashworth
	Jessica	Bailey
	Angie	Dunn
	Gjuzel	Bespaloï
	Harold	Rasalan
Stockport NHS Foundation Trust	Zahid	Mahmood
	Racheal	Campbell
	Liane	Marsh
	Tricia	Coughlan
	Wisam	Jafar
	Janet	Marrs
	Christopher	McPheat
Surrey and Sussex Healthcare NHS Trust	Monira	Rahman
	Sarah	Davies
	Ruth	Habibi
	Ellen	Jessup-Dunton
	Teishel	Joefield
	Reina	Layug
Tameside and Glossop Integrated Care NHS Foundation Trust	Vinod	Patel
	Joanne	Vere
	Victoria	Turner

	Susan	Kilroy
	Martina	Coulding
	Martyn	Clark
	Jacqueline	McCormick
	Attiya	Nisar
Torbay and South Devon NHS Foundation Trust	Gareth	Walker
	Stacey	Atkins
	Jasmine	Growdon
	Becky	George
	Charlotte	McNeill
	Bryony	Reed
	Angela	Foulds
	Catherine	Marshall
	Michele	Allison
	Briony	Dillon
University Hospitals Birmingham NHS Foundation Trust	Rachel	Cooney
	Lillie	Bennett
	Louise	Bowlas
	Sharafaath	Shariff
University Hospitals Bristol NHS Foundation Trust	Aileen	Fraser
	Dwayne	Punnette
	Rebecca	Lambert
	Charlotte	Bishop-Hurman
	Elizabeth	Undrell
	Katherine	Belfield
University Hospitals of Derby and Burton NHS Foundation Trust	Said	Din
	Catherine	Addleton
	Marie	Appleby
	Johanna	Brown
	Kathleen	Holding

	Catherine	Fraser
	Janice	Birkenshaw
	Jodie	Williams
	Kamille	Maulion
	Meg	Lane
	Arita	Kravale
	Claud	Smith
University Hospitals of Leicester NHS Trust	Patricia	Hooper
	John	deCaestecker
	Olivia	Watchorn
	Ellie	Clarke
University Hospitals Plymouth NHS Trust	Chris	Hayward
	Susan	Inniss
	Lucy	Pritchard
	Karen	Rudge
	Amanda	Carney
	Sarah	Griffie
United Lincolnshire Hospitals NHS Trust	Jervoise	Andreyev
	Sathish	Babu
	Caroline	Hayhurst
	Carol	Lockwood
	Lynn	Osborne
	Amanda	Roper
	Karen	Warner
	Julia	Hindle
	Tara	Lawrence
	Kimberley	Netherton
	Caroline	Watt
	Kinga	Szymiczek
University College London Hospitals	Shameer	Mehta

NHS Foundation Trust	James	Bell
	William	Blad
	Lisa	Whitley
	Roman	Jastrub
University Hospital Llandough	Dhamaraj	Durai
	Mark	Baker
	Elizabeth	John Sivamurugan
	Mim	Evans
University Hospital Southampton NHS Foundation Trust	Fraser	Cummings
	Clare	Harris
	Amy	Jones
	Liga	Krauze
	Sohail	Rahmany
	Michelle	Earl
	Jenny	Vowles
	Audrey	Torokwa
	Mirela	Petrova
	Andrew	Procter
	Jo	Stanley
	Claudia	Silvamoniz
	Marion	Betty
University Hospital of Wales (paediatric)	Amar	Wahid
	Zoe	Morrison
	Rhian	Thomas-Turner
	Louise	Yendle
	Jennifer	Muller
Exeter NIHR Clinical Research Facility, University of Exeter	Marcus	Mitchell
	John	Kirkwood
	Anna	Barnes
West Hertfordshire Hospitals NHS	Rakesh	Chaudhary

Trust	Melanie	Claridge
	Chiara	Ellis
	Cheryl	Kemp
	Ogwa	Tobi
	Jentus	Milton
West Middlesex University Hospital (Chelsea and Westminster NHS Hospital Foundation Trust)	Emma	Johnston
	Metod	Oblak
	Richard	Appleby
	Carmen	Winpenny
	Marie-Louise	Svensson
West Suffolk NHS Foundation Trust	Jo	Godden
	Marium	Ashhar
Western General Hospital	Charlie	Lees
	Debbie	Alexander
	Kate	Covil
	Lauranne	Derikx
	Sryros	Siakavellas
	Helen	Baxter
	Scott	Robertson
	Linda	Smith
	Beena	Poulose
	Anne	Colemam
	Margareta	Balint
	Gareth	Rhys-Jones
	Helen	Watters
	Susan	Begg
	Beatriz	Grosalcalde
	Judy	Coyle
Withybush General Hospital	Kerrie	Johns
	Rachel	Hughes

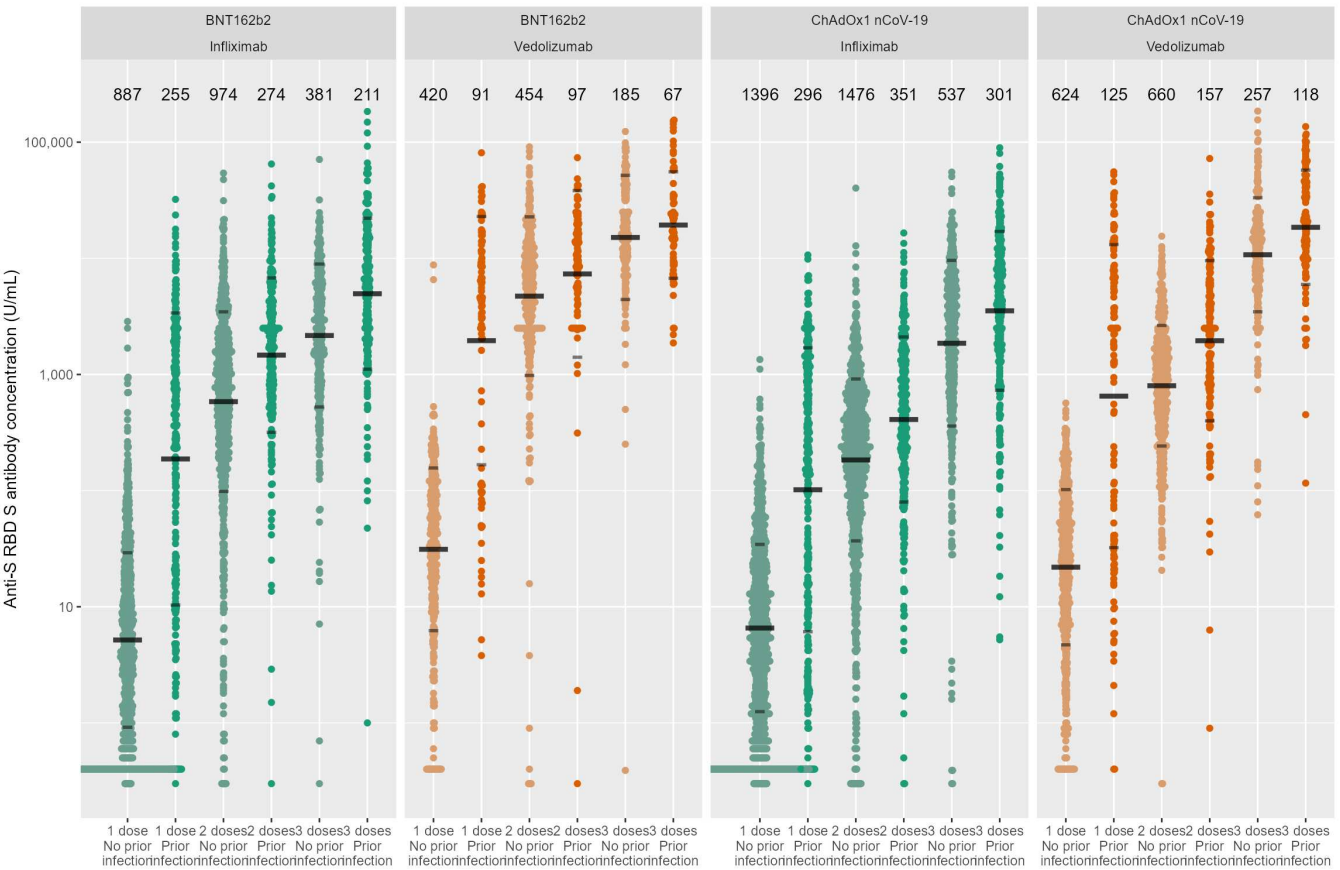
	Janet	Phipps
	Abigail	Taylor
	Catherine	MacPhee
	Suzanne	Brooks
	Jolene	John
	Michelle	Edwards
Yeovil District Hospital NHS Foundation Trust	Katie	Smith
	Linda	Howard
	Dianne	Wood
York Teaching Hospital NHS Foundation Trust	Ajay	Muddu
	Laura	Barman
	Janine	Mallinson
	Tania	Neale
	Diana	Ionita
	Kerry	Elliot
	Alison	Turnball
Ysbyty Gwynedd	Iola	Thomas
	Alice	Thomas
	Kelly	Andrews
	Jonathon	Sutton
	Caroline	Mulvaney Jones
	Julia	Roberts
	Jeannie	Bishop

Supplementary Table 2: Univariable factors associated with time to breakthrough infection

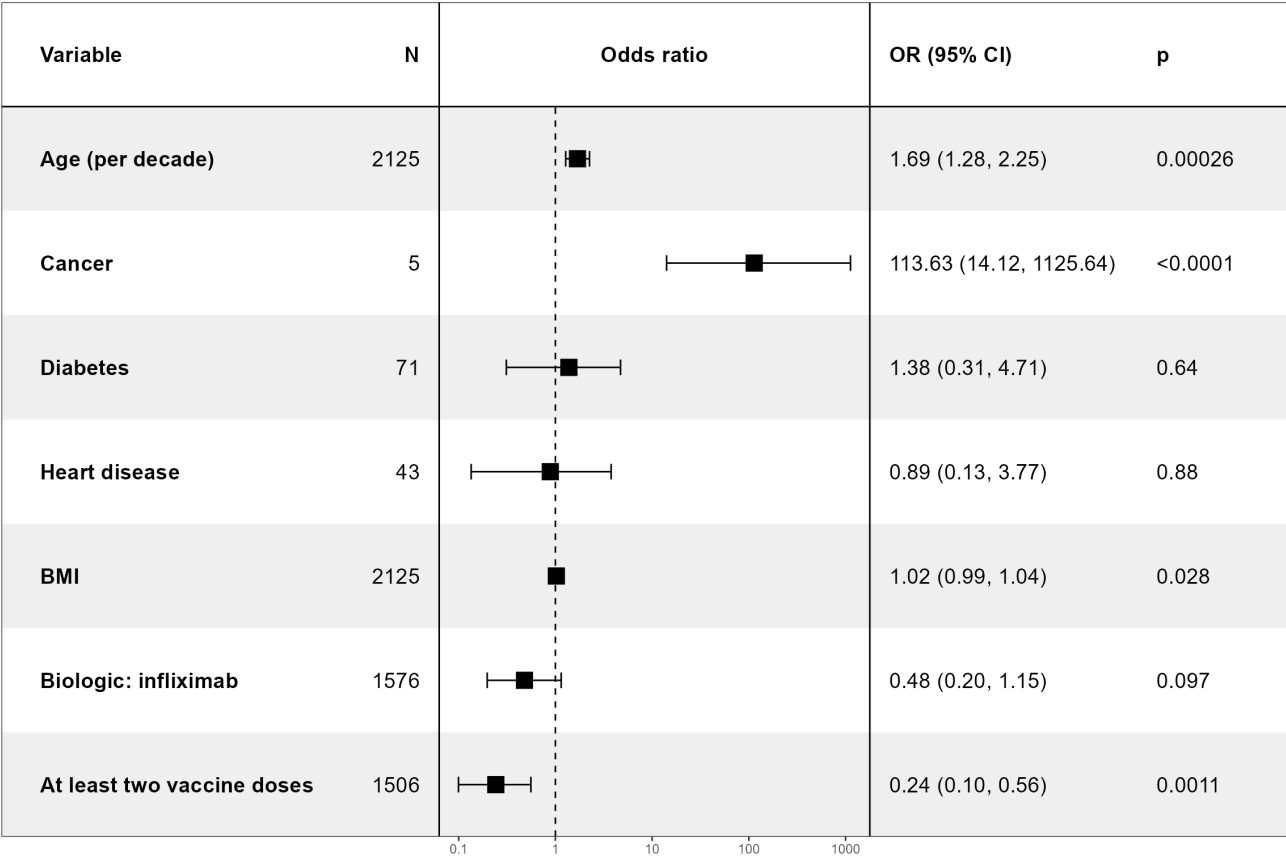
Variable	Level	Hazard ratio (95% CI)	p
Infliximab (vs vedolizumab)	TRUE	1.83 (1.44 - 2.33)	<0.0001
Thiopurine	TRUE	1.52 (1.24 - 1.85)	<0.0001
Methotrexate	TRUE	0.77 (0.50 - 1.20)	0.25
Vaccine	BNT162b2	Reference	
	ChAdOx1 nCoV-19	0.89 (0.73 - 1.09)	0.26
Steroids	TRUE	0.52 (0.30 - 0.90)	0.021
Age >= 60	TRUE	0.26 (0.18 - 0.38)	<0.0001
Crohn's disease (vs UC or IBDU)	TRUE	0.98 (0.81 - 1.22)	0.96
Non-white ethnicity	TRUE	1.19 (0.83 - 1.69)	0.34
Current smoker	TRUE	0.90 (0.62 - 1.29)	0.55
Anti-spike (S) receptor binding domain antibody concentrations (overall)		0.98 (0.82 - 1.18)	0.85

Abbreviations: UC = ulcerative colitis, IBDU = IBD unclassified

Supplementary Figure 1: Antibody concentrations following a third vaccine dose in patients with a prior history of SARS-CoV-2 infection.



Supplementary Figure 2: Multivariable factors associated with hospitalisation with COVID-19



Abbreviations: BMI = body mass index, CI = confidence interval

Supplementary Information for ‘Vaccine escape, increased breakthrough and reinfections in infliximab-treated patients with IBD during the Omicron wave of the SARS-CoV-2 pandemic.’

Table of Contents

Supplementary Table 1: Contributors to the CLARITY IBD study	2
Supplementary Table 2: Univariable factors associated with time to breakthrough infection.....	25
Supplementary Figure 1: Antibody concentrations following a third vaccine dose in patients with a prior history of SARS-CoV-2 infection.....	26
Supplementary Figure 2: Multivariable factors associated with hospitalisation with COVID-19	27

Supplementary Table 1: Contributors to the CLARITY IBD study

Affiliation	First name	Surname
Barts Health NHS Trust	Klaartje	Kok
	Nick	Croft
	Bessie	Cipriano
	Caroline	Francia
	Nosheen	Khalid
	Ashley	Kingston
	Irish	Lee
	Anouk	Lehmann
	Kinnari	Naik
	Kevin	Samuels
	Nicolene	Plaatjies
	Hafiza	Khatun
	Farjana	Bokth
	Elise	Pabriaga
	Madiha	Islam
Basingstoke and North Hampshire Hospital	Rebecca	Saich
	Hayley	Cousins
	Wendy	Fraser
	Rachel	Thomas
	Matthew	Brown
	Benjamin	White
Basingstoke and North Hampshire Hospital (Hampshire Hospitals NHS Foundation Trust)	Nikolaos	Kirkineziadis
	Bernadette	Tilley
	Pennie	Porter
	Rachel	Bryant
	Natalia	Robaczewska
Birmingham Women's and Children's NHS Foundation Trust	Rafeeq	Muhammed
	Rehana	Bi

	Catherine	Cotter
	Jayne	Grove
	Kate	Hong
	Ruth	Howman
	Monica	Mitchell
	Sophie	Clayton
	Louise	Rogers
	Sugrah	Sultan
	Melanie	Rooney
	Charlotte	Cottrill
Bolton NHS Foundation Trust	Salil	Singh
	Chris	Dawe
	Robert	Hull
	Natalie	Silva
	Julie	Chadwick
	Laura	Robertson
Borders General Hospital	Jonathan	Manning
	Lauren	Finlayson
	Allison	Roebuck
	Joy	Dawson
Calderdale and Huddersfield NHS Foundation Trust	Sunil	Sonwalkar
	Naomi	Chambers
	Matthew	Robinson
	Andrew	Haigh
	Lear	Matapure
Cambridge University Hospitals NHS Foundation Trust	Tim	Raine
	Varun	George
	Christina	Kapizioni
	Konstantina	Strongili
	Tina	Thompson

	Mohamed	Ahmed
	Christos	Kontos
	Claire	Dawson
Cambridge Institute of Therapeutic Immunology and Infectious Disease, Jeffrey Cheah Biomedical Centre, University of Cambridge	Christophe	Bourges
	Isabella	Barbutti
	Megan E	Gozzard
Chelsea and Westminster Hospital NHS Foundation Trust	Philip	Hendy
	Rhian	Bull
	Patricia	Costa
	Lisa	Davey
	Hayley	Hannington
	Kribashnie	Nundlall
	Catarina	Martins
	Laura	Avanzi
	Jaime	Carungcong
	Sabrina	Barr
	Richard	Appleby
	Emma	Johnson
	Eathar	Shakweh
Chesterfield Royal Hospital	Kath	Phillis
	Rachel	Gascoyne
	Amanda	Crowder
	Amanda	Whileman
Countess Of Chester Hospital NHS Foundation Trust	Ian	London
	Jenny	Grounds
	Emmeline	Martin
	Susie	Pajak
	Jude	Price
	Kathryn	Cawley
	Sandra	Powell

	Nichola	Kearsley
Darlington Memorial Hospital	Anjan	Dhar
	Ellen	Brown
	Amanda	Cowton
	Kimberley	Stamp
Dartford and Gravesham NHS Trust	Ben	Warner
	Carmel	Stuart
	Louise	Lacey
The Dudley Group NHS Foundation Trust	Shanika	de Silva
	Clare	Allcock
	Philip	Harvey
	Lesley	Jones
	Elise	Cooke
	Jayne	Slater
	Dominic	King
East and North Hertfordshire NHS Trust	Johanne	Brooks
	Pearl	Baker
	Hannah	Beadle
	Carina	Cruz
	Debbie	Potter
East Lancashire Hospitals NHS Trust	Joe	Collum
	Farzana	Masters
Glangwili Hospital	Aashish	Kumar
Hywel Dda University Health Board	Samantha	Coetzee
	Mihaela	Peiu
	Becky	Icke
	Jill	Williams
	Meena	Raj
Great Ormond Street Hospital	Edward	Gaynor
	Sibongile	Chadokufa

	Bonita	Huggett
	Hamza	Meghari
	Sara	El-Khouly
	Fevronia	Kiparissi
	Waffa	Girshab
	Lynda	Russell-Walker
	Christopher	Jackson
	Sara	Sidler
Great Western Hospitals NHS Foundation Trust	Andrew	Claridge
	Emily	Fowler
	Laura	McCafferty
	Lesley	Haxton
Guy's and St Thomas' NHS Foundation Trust	Peter	Irving
	Karolina	Christodoulides
	Angela	Clifford
	Patrick	Dawson
	Sailish	Honap
	Samuel	Lim
	Raphael	Luber
	Karina	Mahiouz
	Susanna	Meade
	Parizade	Raymode
	Rebecca	Reynolds
	Anna	Stanton
	Sherill	Tripoli
	Naomi	Hare
	Sopuluchukwu	Odukwe
	Senthuran	Balachandran
	Emma	North

	Jessica	North
	Bria	Browne
	Jessica	Cordle
	Ella	Jameson
The Hillingdon Hospitals NHS Foundation Trust	Yih Harn	Siaw
	Lane	Manzano
	Jonathan	Segal
	Ibrahim	Al-Bakir
	Imran	Khakoo
	Sofiya	Portukhay
Homerton University Hospital Foundation Trust	Nora	Thoua
	Katherine	Davidson
	Jagrul	Miah
	Lisa	Canclini
	Alex	Hall
	Hassina	Furreed
	Christine	Mitchell-Inwang
Hull University Teaching Hospitals NHS Trust	Shaji	Sebastian
	Melony	Hayes
	Sally	Myers
	Alison	Talbot
	Jack	Turnbull
	Emma	Whitehead
	Katie	Stamp
	Alison	Pattinson
	Verghese	Mathew
	Leanne	Sherris
	Julie	Wilcox
	Sankaranarayanan	Ramachandran
	Hayley	Robertson

	Angela	Harvey
Imperial College Healthcare NHS Trust	Lucy	Hicks
	Tara-Marie	Byrne
	Leilani	Cabreros
	Hannah	Downing-Wood
	Sophie	Hunter
	Mohammad Aamir	Saifuddin
	Hemanth	Prabhudev
	Sharmili	Balarajah
	Jan	Krucznski
	Kalliopi	Driva
	Andrea	D'Mello
	Parith	Shah
Faculty of Medicine, Imperial College London	Hajir	Ibraheim
	Melissa	Torkizadeh
	Jonathan W	Lo
	Zhigang	Liu
James Paget University Hospitals NHS Foundation Trust	Helen	Sutherland
	Elva	Wilhelmsen
	Katherine	Mackintosh
Kettering General Hospital	Ajay M	Verma
	Juliemol	Sebastian
	Mohammad Farhad	Peerally
	Parizade	Raymode
	Anne-marie	Guerdette
	Susan	Coburn
	Ching Yee	Novem lam
	Donna	Durrant
	Belinda	Schaefer
	Solange	Serna

	Muhammad	Shahzad
King's College Hospital NHS Foundation Trust	Alexandra	Kent
	Lee Meng	Choong
	Benedetta	Pantaloni
	Pantelis	Ravdas
King's College Hospital NHS Foundation Trust (paediatric)	Babu	Vadamalayan
King's Mill Hospital	Stephen	Foley
	Becky	Arnold
	Cheryl	Heeley
	Wayne	Lovegrove
	Donna	Sowton
	Lynne	Allsop
	Heidi	Gregory
	Mandy	Gill
	Megan	Holmes
	Valeria	Balan
	Susan	Smith
	Sarah	Turner
Liverpool University Hospitals NHS Foundation Trust	Philip J	Smith
	Alan	Steel
	Giovanna	Bretland
	Sarah	King
	Martina	Lofthouse
	Lindsey	Rigby
	Sreedhar	Subramanian
	David	Tyrer
	Kate	Martin
London North West University	Christopher	Probert
	Nikolaos	Kamperidis

Healthcare NHS Trust	Temí	Adedoyin
	Manisha	Baden
	Jeannette	Brown
	Feba	Chacko
	Lisa	Young
	Michela	Cicchetti
	Mohammad	Saifuddin
	Priya	Yesupatham
Maidstone and Tunbridge Wells NHS Trust	Rohit	Gowda
	Maureen	Williams
Manchester University NHS Foundation Trust	Karen	Kemp
	Rima	Akhand
	Glaxy	Gray
	Anu	John
	Maya	John
	Tasnim	Mohammed
	Diamond	Sathe
	Natasha	Jones
	Jennifer	Soren
The Mid Yorkshire Hospitals NHS Trust	Michael	Sprakes
	Julie	Burton
	Patricia	Kane
	Stephanie	Lupton
	Jacqueline	Bartholomew
	Elizabeth	Denis
	Alison	Daniels
Milton Keynes University Hospital	George	MacFaul
	Diane	Scaletta
	Loria	Siamia
	Felicity	Williams

	Chloe	Green
	Zeljka	Ver
Newcastle Hospitals NHS Foundation Trust	Chris	Lamb
	Mary	Doona
	Ashleigh	Hogg
	Lesley	Jeffrey
	Andrew	King
	R Alexander	Speight
	Jennifer	Doyle
	Ruth	Owen
	Jenny	Haworth
	Linda	Patterson
	Vithusa	Varnaulasingam
Ninewells Hospital & Medical School	Craig	Mowat
	Debbie	Rice
	Susan	MacFarlane
	Anne	MacLeod
	Samera	Mohammed
Ninewells Hospital & Medical	Shona	Murray
	Anne	Elliott
Norfolk and Norwich University Hospitals NHS Foundation Trust	Mary	Anne Morris
	Louise	Coke
	Grace	Hindle
	Eirini	Kolokouri
	Catherine	Wright
	Claire	Lee
	Nicola	Ward
	Adele	Dann
North Bristol NHS Trust	Melanie	Lockett
	Charlotte	Cranfield

	Louise	Jennings
	Ankur	Srivastava
	Lana	Ward
	Nouf	Jeynes
	Poonam	Ranga
North Tyneside General Hospital	Praveen	Rajasekhar
	Lisa	Gallagher
	Linda	Patterson
	Jill	Ward
	Rae	Basnett
	Judy	Murphy
	Lauren	Parking
	Emma	Lawson
	Stacey	Short
Nottingham University Hospitals NHS Trust	David	Devadason
	Gordon	Moran
	Neelam	Khan
	Lauren	Tarr
	Charmaine	Olivia
	Samantha	Warbarton
	Sian	Kelly
The Pennine Acute Hospitals NHS Trust	Jimmy	Limdi
	Kay	Goulden
	Asad	Javed
	Lauren	McKenzie
	Julie	Melville
	Eleanor	Liu
	Joseph	Sabine
	Patricia	Jacob
	Denise	McSorland

	Nick	Schofield
	Lisa	Cornwall
	James	Quirke
	Emma	Crook
	Anne	Turner
Portsmouth Hospitals NHS Trust	Pradeep	Bhandari
	Michelle	Baker-Moffatt
	Joanne	Dash
	Alison	Le Poidevin
	Hayley	Downe
	Lucille	Bombero
	Helen	Blackman
	Rebecca	Smith
The Queen Elizabeth Hospital Kings Lynn NHS Trust	Alan	Wiles
	Hannah	Bloxham
	Jose	Dias
	Evelyn	Nadar
	Hollie	Curgenven
	Ellie	Gilham
Queen Elizabeth University Hospital, Glasgow	Jonathan	Macdonald
	Shona	Finan
	Faye	McMeeken
	Misbah	Mahmood
	Stephanie	Shields
	John Paul	Seenan
Royal Berkshire NHS Foundation Trust	Des	DeSilva
	Susanna	Malkakorpi
	Rachel	Carson
	Holly	Lawrence
	Ofori	Boateng

	Felix	Kpodo
University Hospitals Dorset NHS Foundation Trust	Simon	Whiteoak
	Kelli	Edger-Earley
	Luke	Vamplew
	Joanna	Samways
	Sue	Roffe
Royal Cornwall Hospitals NHS Trust	Sarah	Ingram
	Joel	James
	Sharon	Botfield
	Fiona	Hammonds
	Clare	James
	Zoe	Berry
Royal Devon and Exeter NHS Foundation Trust	Tariq	Ahmad
	Gemma	Aspinall
	Sarah	Hawkins
	Marian	Parkinson
	Helen	Gardner-Thorpe
	Suzie	Marriott
	Clare	Redstone
	Halina	Windak
	Ana-Marie	Adam
	Hannah	Mabb
	Emma	Stevenson
	Jessica	Record
Royal Free London NHS Foundation Trust	Charles	Murray
	Cynthia	Diaba
	Fexy	Joseph
	Glykeria	Pakou
	Yvonne	Gleeson
	Annalyn	Nunag

Royal Glamorgan Hospital	James	Berrill
	Natalie	Stroud
	Carla	Pothecary
	Lisa	Roche
	Keri	Turner
	Lisa	Deering
	Lynda	Israel
Royal Gwent Hospital	Evelyn	Baker
	Maxine	Nash
Royal Hampshire County Hospital (Hampshire Hospitals NHS Foundation Trust)	John	Gordon
	Emma	Levell
	Silvia	Zagalo
	Wendy	Fraser
	Ina	Hoad
	Nikolaos	Kirkineziadis
	Bernadette	Tilley
	Natalia	Robaczewska
	Bindu	Anil
Royal Hospital for Sick Children, Edinburgh	Richard	Russell
	Paul	Henderson
	Margaret	Millar
Royal Manchester Children's Hospital	Andrew	Fagbemi
	Felicia	Jennings
	Imelda	Mayor
	Jill	Wilson
	Alice	Wheeler
	Nicola	Phillips
Royal Surrey County Hospital	Christopher	Alexakis
	Natalia	Michalak
	Cheryl	Marriott

	Sarah	Stone
	Veronika	Pristopan
Royal United Hospitals Bath	John	Saunders
	Helen	Burton
	Vanessa	Cambridge
	Tonia	Clark
	Charlotte	Ekblad
	Sarah	Hierons
	Joyce	Katebe
	Emma	Saunbury
	Rachel	Perry
The Royal Wolverhampton NHS Trust	Matthew	Brookes
	Kathryn	Davies
	Marie	Green
	Ann	Plumbe
Salford Royal NHS Foundation Trust	Clare	Ormerod
	Helen	Christensen
	Hannah	Howlett
	Anne	Keen
	Jonathan	Ogor
	Marie	Greenhaigh
	Karen	Knowles
	Shanzi	Yin
	Maria	Poulaka
Salisbury District Hospital	Alpha	Anthony
	Emily	Newitt
	Fiona	Trim
	Ruth	Casey
	Katherine	Seymour
	Catherine	Reed

	Lijo	Joy
Sandwell and West Birmingham NHS Trust	Edward	Fogden
	Kalisha	Russell
	Samia	Hussain
Sheffield Teaching Hospitals NHS Foundation Trust	Anne	Phillips
	Muaad	Abdulla
Shrewsbury and Telford Hospital NHS Trust	Jeff	Butterworth
	Colene	Adams
	Mandy	Carnahan
	Elizabeth	Buckingham
	Danielle	Childs
	Alison	Magness
	Jo	Stickley
	Nichola	Motherwell
	Louise	Tonks
	Hannah	Gibson
	Susie	Pajak
	Kate	Wistance
Singleton Hospital Swansea Bay University Health Board	Caradog	Thomas
	Elaine	Brinkworth
	Lynda	Connor
	Amanda	Cook
	Tabitha	Rees
	Rachel	Harford
	Sean	Farley
	Marie	Jones
Somerset NHS Foundation Trust	Emma	Wesley
	Alison	Moss
	Jacob	Lucas
	Claire	Lorimer

	Maria	Oleary
	Maxine	Dixon
	Fiona	Goodchild
	Rebecca	Twenlow
	Corinne	Pawley
South Tees Hospitals NHS Foundation Trust	Arvind	Ramadas
	Julie	Tregonning
	Olaku	Okeke
	Wendy	Jackson
Southend University Hospital NHS Foundation Trust	Ioannis	Koumoutsos
	Viji	George
	Swapna	Kunhunny
	Sophie	Laverick
	Isla	Anderson
	Sophie	Smith
	Joan	Joyce
	Sarala	Janarthan
St George's University Hospitals NHS Foundation Trust	Kamal	Patel
	Mariam	Ali
	Hilda	Mhandu
	Aleem	Rana
	Katherine	Spears
	Joana	Teixeira
	Richard	Pollok
	Mark	Mencias
	Abigail	Seaward
	Jessica	Sousa
	Nooria	Said
	Mark	Soomaroo
	Valentina	Raspa

	Asha	Tacouri
St George's University Hospitals NHS Foundation Trust (paediatric)	Nicholas	Reps
	Rebecca	Martin
	Tinashe	Samakomva
St James's University Hospital (The Leeds Teaching Hospital NHS Trust)	Christian	Selinger
	Jenelyn	Carbonell
	Felicia	Onovira
	Doris	Quartey
	Alice	L'Anson
	Andrew	Ashworth
	Jessica	Bailey
	Angie	Dunn
	Gjuzel	Bespalo
	Harold	Rasalan
Stockport NHS Foundation Trust	Zahid	Mahmood
	Racheal	Campbell
	Liane	Marsh
	Tricia	Coughlan
	Wisam	Jafar
	Janet	Marrs
	Christopher	McPheat
Surrey and Sussex Healthcare NHS Trust	Monira	Rahman
	Sarah	Davies
	Ruth	Habibi
	Ellen	Jessup-Dunton
	Teishel	Joefield
	Reina	Layug
Tameside and Glossop Integrated Care NHS Foundation Trust	Vinod	Patel
	Joanne	Vere
	Victoria	Turner

	Susan	Kilroy
	Martina	Coulding
	Martyn	Clark
	Jacqueline	McCormick
	Attiya	Nisar
Torbay and South Devon NHS Foundation Trust	Gareth	Walker
	Stacey	Atkins
	Jasmine	Growdon
	Becky	George
	Charlotte	McNeill
	Bryony	Reed
	Angela	Foulds
	Catherine	Marshall
	Michele	Allison
	Briony	Dillon
University Hospitals Birmingham NHS Foundation Trust	Rachel	Cooney
	Lillie	Bennett
	Louise	Bowlas
	Sharafaath	Shariff
University Hospitals Bristol NHS Foundation Trust	Aileen	Fraser
	Dwayne	Punnette
	Rebecca	Lambert
	Charlotte	Bishop-Hurman
	Elizabeth	Undrell
	Katherine	Belfield
University Hospitals of Derby and Burton NHS Foundation Trust	Said	Din
	Catherine	Addleton
	Marie	Appleby
	Johanna	Brown
	Kathleen	Holding

	Catherine	Fraser
	Janice	Birkenshaw
	Jodie	Williams
	Kamille	Maulion
	Meg	Lane
	Arita	Kravale
	Claud	Smith
University Hospitals of Leicester NHS Trust	Patricia	Hooper
	John	deCaestecker
	Olivia	Watchorn
	Ellie	Clarke
University Hospitals Plymouth NHS Trust	Chris	Hayward
	Susan	Inniss
	Lucy	Pritchard
	Karen	Rudge
	Amanda	Carney
	Sarah	Griffie
United Lincolnshire Hospitals NHS Trust	Jervoise	Andreyev
	Sathish	Babu
	Caroline	Hayhurst
	Carol	Lockwood
	Lynn	Osborne
	Amanda	Roper
	Karen	Warner
	Julia	Hindle
	Tara	Lawrence
	Kimberley	Netherton
	Caroline	Watt
	Kinga	Szymiczek
University College London Hospitals	Shameer	Mehta

NHS Foundation Trust	James	Bell
	William	Blad
	Lisa	Whitley
	Roman	Jastrub
University Hospital Llandough	Dhamaraj	Durai
	Mark	Baker
	Elizabeth	John Sivamurugan
	Mim	Evans
University Hospital Southampton NHS Foundation Trust	Fraser	Cummings
	Clare	Harris
	Amy	Jones
	Liga	Krauze
	Sohail	Rahmany
	Michelle	Earl
	Jenny	Vowles
	Audrey	Torokwa
	Mirela	Petrova
	Andrew	Procter
	Jo	Stanley
	Claudia	Silvamoniz
	Marion	Betty
University Hospital of Wales (paediatric)	Amar	Wahid
	Zoe	Morrison
	Rhian	Thomas-Turner
	Louise	Yendle
	Jennifer	Muller
Exeter NIHR Clinical Research Facility, University of Exeter	Marcus	Mitchell
	John	Kirkwood
	Anna	Barnes
West Hertfordshire Hospitals NHS	Rakesh	Chaudhary

Trust	Melanie	Claridge
	Chiara	Ellis
	Cheryl	Kemp
	Ogwa	Tobi
	Jentus	Milton
West Middlesex University Hospital (Chelsea and Westminster NHS Hospital Foundation Trust)	Emma	Johnston
	Metod	Oblak
	Richard	Appleby
	Carmen	Winpenny
	Marie-Louise	Svensson
West Suffolk NHS Foundation Trust	Jo	Godden
	Marium	Ashhar
Western General Hospital	Charlie	Lees
	Debbie	Alexander
	Kate	Covil
	Lauranne	Derikx
	Sryros	Siakavellas
	Helen	Baxter
	Scott	Robertson
	Linda	Smith
	Beena	Poulose
	Anne	Colemam
	Margareta	Balint
	Gareth	Rhys-Jones
	Helen	Watters
	Susan	Begg
	Beatriz	Grosalcalde
	Judy	Coyle
Withybush General Hospital	Kerrie	Johns
	Rachel	Hughes

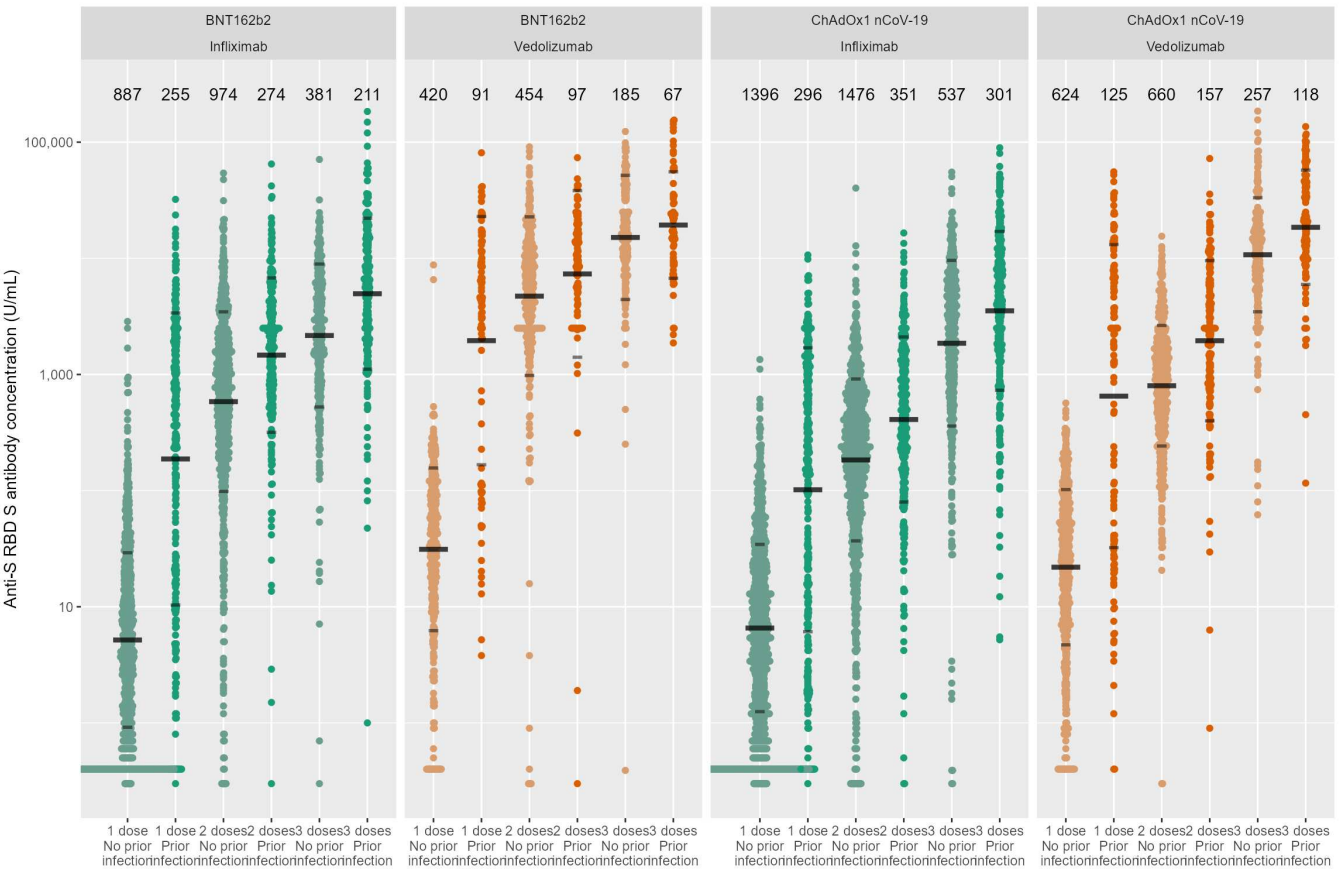
	Janet	Phipps
	Abigail	Taylor
	Catherine	MacPhee
	Suzanne	Brooks
	Jolene	John
	Michelle	Edwards
Yeovil District Hospital NHS Foundation Trust	Katie	Smith
	Linda	Howard
	Dianne	Wood
York Teaching Hospital NHS Foundation Trust	Ajay	Muddu
	Laura	Barman
	Janine	Mallinson
	Tania	Neale
	Diana	Ionita
	Kerry	Elliot
	Alison	Turnball
Ysbyty Gwynedd	Iola	Thomas
	Alice	Thomas
	Kelly	Andrews
	Jonathon	Sutton
	Caroline	Mulvaney Jones
	Julia	Roberts
	Jeannie	Bishop

Supplementary Table 2: Univariable factors associated with time to breakthrough infection

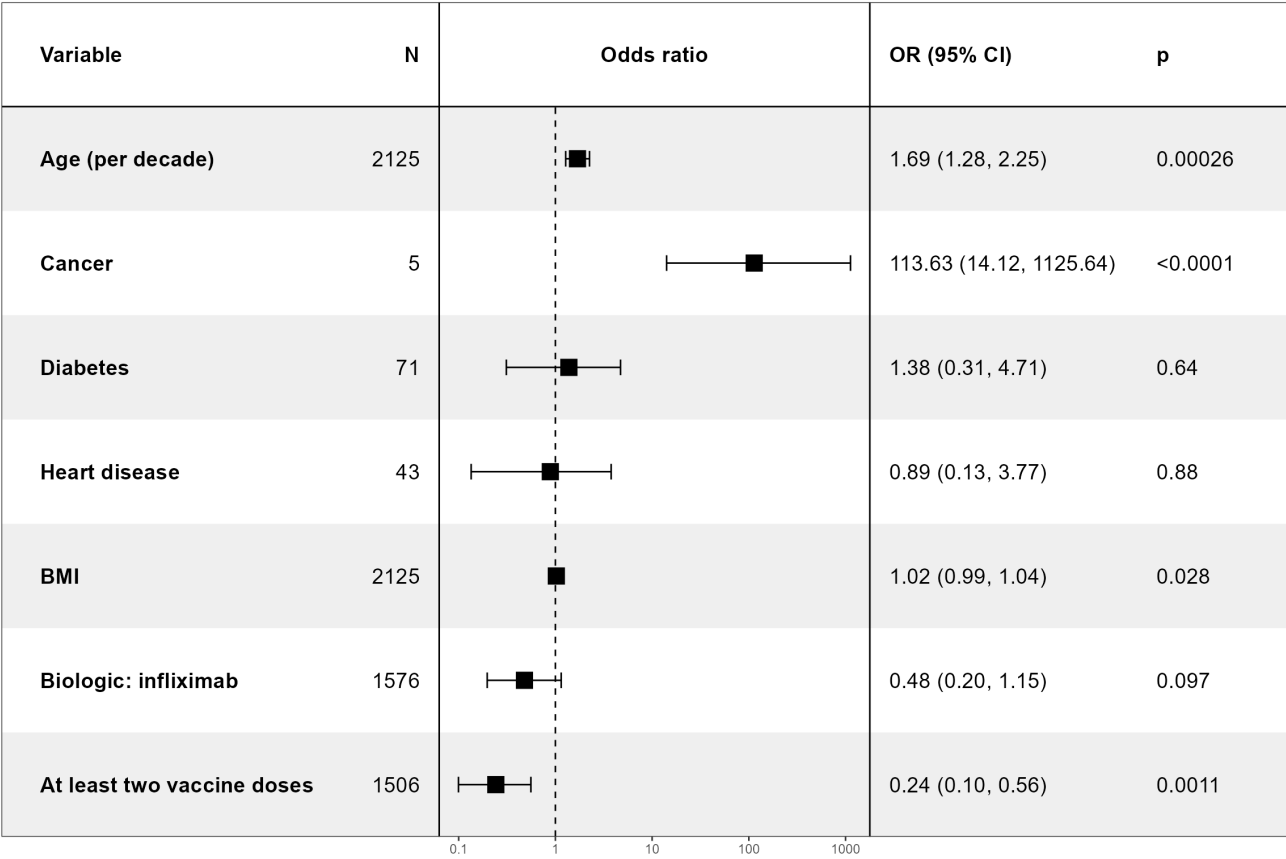
Variable	Level	Hazard ratio (95% CI)	p
Infliximab (vs vedolizumab)	TRUE	1.83 (1.44 - 2.33)	<0.0001
Thiopurine	TRUE	1.52 (1.24 - 1.85)	<0.0001
Methotrexate	TRUE	0.77 (0.50 - 1.20)	0.25
Vaccine	BNT162b2	Reference	
	ChAdOx1 nCoV-19	0.89 (0.73 - 1.09)	0.26
Steroids	TRUE	0.52 (0.30 - 0.90)	0.021
Age >= 60	TRUE	0.26 (0.18 - 0.38)	<0.0001
Crohn's disease (vs UC or IBDU)	TRUE	0.98 (0.81 - 1.22)	0.96
Non-white ethnicity	TRUE	1.19 (0.83 - 1.69)	0.34
Current smoker	TRUE	0.90 (0.62 - 1.29)	0.55
Anti-spike (S) receptor binding domain antibody concentrations (overall)		0.98 (0.82 - 1.18)	0.85

Abbreviations: UC = ulcerative colitis, IBDU = IBD unclassified

Supplementary Figure 1: Antibody concentrations following a third vaccine dose in patients with a prior history of SARS-CoV-2 infection.



Supplementary Figure 2: Multivariable factors associated with hospitalisation with COVID-19



Abbreviations: BMI = body mass index, CI = confidence interval