



**Anti-SARS-CoV2 antibody responses are attenuated in patients with inflammatory bowel disease treated with infliximab**

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**impacT of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY**

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| <b>Title</b>        | <b>Anti-SARS-CoV2 antibody responses are attenuated in patients with inflammatory bowel disease treated with infliximab</b>   |
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**impaCt of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY**

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| <b>Word count</b>                 | 2917 excluding abstract and summary box   |

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**impact of biologics therapy on SARS-CoV-2 Infection and immunity CLARITY****3 Abstract****4 Objective**

5 Anti-TNF drugs impair protective immunity following pneumococcal, influenza, and viral hepatitis  
6 vaccination and increase the risk of serious respiratory infections. We sought to determine whether  
7 infliximab-treated patients with inflammatory bowel disease have attenuated serological responses  
8 to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections.

**9 Design**

10 Antibody responses in participants treated with infliximab were compared to a reference cohort  
11 treated with vedolizumab, a gut-selective anti-integrin  $\alpha 4\beta 7$  monoclonal antibody that is not  
12 associated with impaired vaccine responses or increased susceptibility to systemic infections. 6935  
13 patients were recruited from 92 UK hospitals between 22nd September and 23rd December 2020.

**14 Results**

15 Rates of symptomatic and proven SARS-CoV-2 infection were similar between groups.  
16 Seroprevalence was lower in infliximab- than vedolizumab-treated patients (3.4% [161/4685], vs  
17 6.0% [134/2250],  $p < 0.0001$ ). Multivariable logistic regression analyses confirmed that infliximab (vs  
18 vedolizumab; odds ratio [OR] 0.66 [95% CI 0.51-0.87],  $p = 0.0027$ ) and immunomodulator use (OR  
19 0.70 [95% CI 0.53-0.92],  $p = 0.012$ ) were independently associated with lower seropositivity. In  
20 patients with confirmed SARS-CoV-2 infection seroconversion was observed in fewer infliximab- than  
21 vedolizumab-treated patients (48% [39/81], vs 83% [30/36],  $p = 0.00044$ ) and the magnitude of anti-  
22 SARS-CoV2 reactivity was lower (median 0.8 COI [0.2-5.6] vs 37.0 [15.2-76.1],  $p < 0.0001$ ).



**impaCt of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY**23 *Conclusions*

24 Infliximab is associated with attenuated serological responses to SARS-CoV-2 that were further  
25 blunted by immunomodulators used as concomitant therapy. Impaired serological responses to  
26 SARS-CoV-2 infection might have important implications for global public health policy and individual  
27 anti-TNF treated patients. Serological testing and virus surveillance should be considered to detect  
28 suboptimal vaccine responses, persistent infection, and viral evolution to inform public health policy.

**impact of biologics therapy on SARS-CoV-2 Infection and immunity CLARITY****Summary Box****1. What is already known about this subject?**

- Anti-tumour necrosis factor (TNF) drugs are effective treatments for immune-mediated inflammatory diseases (IMIDs), however, by suppressing immune responses, they impair vaccine effectiveness and increase susceptibility to serious infection.
- In the early phase of the COVID-19 pandemic, patients with IMIDs treated with anti-TNF drugs were subject to the most restrictive public health measures
- Registry studies have not reported an increased risk of adverse outcomes from SARS-CoV-2 in patients treated with anti-TNF therapies. However, the impact of these therapies on serological responses and subsequent immunity to SARS-CoV-2 infection remains unknown

**2. What are the new findings?**

- Rates of symptomatic and proven SARS-CoV-2 infection were similar between infliximab- and vedolizumab-treated patients with inflammatory bowel disease.
- Seroprevalence, seroconversion, and the magnitude of anti-SARS-CoV-2 antibody reactivity was significantly attenuated in infliximab- compared with vedolizumab-treated patients.
- Concomitant immunomodulator use with a thiopurine or methotrexate further blunted serological responses to SARS-CoV-2 infection in infliximab-treated patients, with only a third of patients having detectable anti-SARS-CoV-2 antibodies.

**3. How might it impact on clinical practice in the foreseeable future?**

**impact of biologic therapy on saRs-cov-2 Infection and immuniTY CLARITY**

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5 50       • For the individual anti-TNF treated patient, lower rates of seroconversion and reduced anti-  
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7 51       SARS-CoV-2 antibody reactivity levels may ultimately increase their susceptibility to  
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9 52       recurrent COVID-19  
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11 53       • Impaired serological responses might lead to chronic nasopharyngeal colonisation which  
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13 54       may act as a reservoir to drive persistent transmission and the evolution of new SARS-CoV-2  
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15 55       variants.  
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17 56       • Serological testing and virus surveillance should be considered to detect suboptimal vaccine  
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19 57       responses, persistent infection, and viral evolution to inform public health policy.  
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21 58       • If attenuated serological responses following vaccination are also observed, then modified  
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23 59       immunisation strategies will need to be designed for millions of patients worldwide.  
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**impact of biologic therapy on SARS-CoV-2 Infection and immunity CLARITY****61 Introduction**

62 Induction of protective immunity following SARS-CoV-2 (severe acute respiratory syndrome  
63 coronavirus 2) infection and/or vaccination is critical to suppress transmission. By suppressing  
64 immune responses, biologic and immunosuppression therapies may lead to chronic SARS-CoV-2  
65 infection and have recently been implicated in the evolution and emergence of novel variants.<sup>1-3</sup>

66 Immune-mediated inflammatory diseases (IMIDs) including inflammatory bowel disease (IBD), the  
67 inflammatory arthritides, and psoriasis affect about 3-7 % of Western populations.<sup>4,5</sup> Drugs targeting  
68 tumour necrosis factor (TNF) are the most frequently prescribed biologics used in the treatment of  
69 IMIDs with over 2 million patients receiving treatment worldwide.<sup>6</sup> However, anti-TNF drugs impair  
70 protective immunity following pneumococcal,<sup>7</sup> influenza,<sup>8</sup> and viral hepatitis<sup>9</sup> vaccinations and  
71 increase the risk of serious infection, most notably with respiratory pathogens.<sup>10</sup> Consequently, in  
72 the early phase of the COVID-19 pandemic, patients with IMIDs treated with anti-TNF drugs were  
73 subject to the most restrictive public health measures.<sup>11</sup> Data from disease-specific registries are  
74 reassuring, however, citing similar rates and risk factors for SARS-CoV-2 infection, hospitalisation,  
75 and outcomes to background populations.<sup>12-14</sup> Whether anti-TNF drugs impair serological responses  
76 and subsequent immunity to SARS-CoV-2 infection is unknown.

77 We hypothesised that anti-SARS-CoV2 antibody responses would be impaired following SARS-CoV-2  
78 infection in patients with IBD treated with infliximab, a commonly prescribed anti-TNF drug. To test  
79 this hypothesis, we compared antibody responses in patients with IBD treated with infliximab, to a  
80 reference cohort treated with vedolizumab. Vedolizumab is a gut-selective anti-integrin  $\alpha4\beta7$   
81 monoclonal antibody, administered in hospital with the same dosing schedule as infliximab and is  
82 not associated with increased susceptibility to systemic infection or attenuated serological  
83 responses to vaccination.<sup>15</sup>

**impact of biologic therapy on SARS-cov-2 Infection and immunity CLARITY****Objectives**

We aimed to define, in patients with IBD, whether biologic class, concomitant use of an immunomodulator, and/or social distancing measures impact:

- i) seroprevalence of SARS-CoV-2.
- ii) subsequent seroconversion in patients with infection confirmed by prior polymerase chain reaction (PCR) testing.
- iii) magnitude of anti-SARS-Cov-2 reactivity.

**impact of biologics therapy on SARS-CoV-2 Infection and immunity CLARITY****92 Methods****93 Patient and Settings**

94 CLARITY IBD is a UK wide, multicentre, prospective observational cohort study investigating the  
95 impact of infliximab and vedolizumab and/or concomitant immunomodulators (thiopurines or  
96 methotrexate) on SARS-CoV-2 acquisition, illness, and immunity in patients with IBD.

97 Consecutive patients were recruited at the time of attendance at infusion units from 92 National  
98 Health Service (NHS) hospitals across the UK (**See Supplementary Table S1**) between 22<sup>nd</sup>  
99 September 2020 and 23<sup>rd</sup> December 2020.

100 The eligibility criteria were:

- 101 i) age 5 years and over
- 102 ii) diagnosis of inflammatory bowel disease
- 103 iii) current treatment with infliximab or vedolizumab for 6 weeks or more, with a dose of drug  
104 received in the past 16 weeks

105 Patients were excluded if they had participated in a SARS-CoV-2 vaccine trial.

106 Here we report the seroprevalence of anti-SARS-CoV-2 antibodies at entry to the CLARITY IBD study.

**107 Outcome Measures**

108 The primary outcome was the proportion of participants with a positive anti-SARS-CoV-2 antibody  
109 test. Secondary outcomes were the proportion of participants with a positive anti-SARS-CoV-2  
110 antibody following a positive PCR test to SARS-CoV-2 and the magnitude of the anti-SARS-CoV-2  
111 antibody reactivity.

**impact of biologic therapy on SARS-cov-2 Infection and immunity CLARITY****112 Variables**

113 Variables recorded by participants included demographics (age, sex, ethnicity, comorbidities, height  
114 and weight, smoking status, and postcode), IBD disease activity (PRO2),<sup>16,17</sup> IBD-related quality of life  
115 (IBD Control),<sup>18</sup> mental well-being (PHQ-8<sup>19</sup> and GAD-7<sup>20</sup>), SARS-CoV-2 outcomes aligned to the  
116 COVID-19 symptoms study<sup>21</sup> (symptoms, previous testing, and hospital admissions for COVID-19)  
117 and social-distancing behaviour during the lockdown periods. During lockdown, the population of  
118 the UK were instructed to adhere to restrictions on social and professional activities with specific  
119 advice to vulnerable groups to undertake more extreme social exclusion measures referred to as  
120 shielding.<sup>11</sup>

121 Study sites completed data relating to IBD history (age at diagnosis, disease duration, and phenotype  
122 according to the Montreal classifications,<sup>22</sup> previous surgeries, and duration of current biologic and  
123 immunomodulator therapy).

124 Wherever possible, data were entered electronically into a purpose-designed REDCap database  
125 hosted at the Royal Devon and Exeter NHS Foundation Trust.<sup>23</sup> At sites without access to electronic  
126 devices or the internet, participants completed their questionnaires on paper case record forms that  
127 were subsequently entered by local research teams.

**128 Case definition**

129 Cases were defined according to the recently published World Health Organisation (WHO)  
130 framework.<sup>24</sup> In brief, this framework uses symptoms and the results of nucleic acid amplification  
131 testing to determine whether patients are suspected, probable, or confirmed cases of COVID-19.  
132 Participants who reported fever and cough, or anosmia/ageusia, or any three or more of the  
133 following symptoms: fever, cough, general weakness/fatigue, myalgia, sore throat, coryza,  
134 dyspnoea, and altered mental status were considered suspected/probable COVID-19 cases. We

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5 135 omitted the gastrointestinal symptoms because patients with active IBD may suffer anorexia,  
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7 136 nausea, vomiting, and diarrhoea. We linked our data by NHS number or Community Health Index to  
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9 137 Public Health England, Scotland, and Wales who archive dates and results of all SARS-CoV-2 PCR  
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11 138 tests undertaken in the UK. Confirmed cases were those participants with a positive PCR test to SARS  
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13  
14 139 CoV-2.

**140 Laboratory methods**

141 Laboratory analyses were performed at the Academic Department of Blood Sciences at the Royal  
142 Devon and Exeter NHS Foundation Trust. We used the Roche Elecsys Anti-SARS-CoV-2 immunoassay  
143 to detect antibodies to SARS-CoV-2 in serum samples.<sup>25</sup> This sandwich electrochemiluminescence  
144 immunoassay uses a recombinant protein of the nucleocapsid antigen for the determination of  
145 antibodies against SARS-CoV-2. The electrochemiluminescence signal from a negative and positive  
146 calibrator are assigned a value of 0.8 and 1.2, respectively, and a cut-off is set at a signal equivalent  
147 to 1. The electrochemiluminescence signal from the reaction product of the sample is compared to  
148 the cut-off signal and expressed as positive when  $\geq 1.0$  or negative when  $< 1$ , as well as quantitatively  
149 in the form of a Cut-Off Index (COI: calculated by sample signal/cut-off signal).

150 In house assay validation experiments demonstrated the intra- and inter-assay coefficient of  
151 variation were 2.2 and 7.0%, respectively. No effect was observed on recovery of anti-SARS-CoV-2  
152 antibodies following four freeze/thaw cycles. SARS-CoV-2 antibodies were stable in uncentrifuged  
153 blood and serum at ambient temperature for up to seven days permitting postal transport from  
154 research sites to the central laboratory. No analytical interference was observed for the detection of  
155 anti-SARS-CoV-2 with infliximab or vedolizumab up to 10,000 mg/L and 60,000 mg/L, respectively, or  
156 with anti-drug antibodies to infliximab or vedolizumab up to 400 AU/mL and 38 AU/mL respectively.



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### 157 **Study size**

158 Limited data are available regarding the risk of SARS-CoV-2 in patients with IBD to inform sample size  
159 calculations.

160 The following assumptions were made to determine our sample size

- 161 • Proportion of patients treated with each drug(s): vedolizumab: 30% (20% with concomitant  
162 immunomodulator), infliximab: 70% (60% with concomitant immunomodulator)
- 163 • Seroprevalence of SARS-CoV-2 in the background population: 0.05
- 164 • Odds ratio for SARS-CoV-2 seropositivity with immunomodulator use: 0.8
- 165 • Odds ratio SARS-CoV-2 seropositivity for infliximab versus vedolizumab:  $\leq 0.7$ .
- 166 • Attrition rate: 20%

167 We calculated that a sample size of 6970 patients would provide 80% power for the comparison of  
168 infliximab versus vedolizumab, controlling for immunosuppressant status in a multivariable logistic  
169 regression model at the 0.05 significance level.

### 170 **Ethical consideration and roles of funders**

171 CLARITY IBD is an investigator-led, UK National Institute for Health Research COVID-19 urgent public  
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174 (Switzerland), Biogen Inc (USA), Celltrion Healthcare (South Korea), and Galapagos NV (Belgium).

175 None of our funding bodies had any role in study design, data collection or analysis, writing or  
176 decision to submit for publication. The Surrey Borders Research Ethics committee approved the  
177 study (REC reference: REC 20/HRA/3114) in September 2020. Patients were included after providing  
178 informed, written consent. The sponsor was the Royal Devon and Exeter NHS Foundation Trust. The

**impact of biologic therapy on SARS-cov-2 Infection and immunity CLARITY**

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5 179 protocol is available online at <https://www.clarityibd.org>. The study was registered with the ISRCTN  
6  
7 180 registry, ISRCTN45176516.  
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**181 Statistics**

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11  
12 182 Statistical analyses were undertaken in R 4.0.3 (R Foundation for Statistical Computing, Vienna,  
13  
14 183 Austria). All tests were two tailed and p-values <0.05 were considered significant. We included  
15  
16 184 participants in the primary analysis if they had completed the patient questionnaire and had an anti-  
17  
18 185 SARS-CoV-2 serology result. We included patients with missing clinical data in analyses for which  
19  
20 186 they had data and have specified the denominator for each variable. Continuous data were reported  
21  
22 187 as median and interquartile range, and discrete data as numbers and percentages, unless otherwise  
23  
24 188 stated. We used patients' postcodes to assign them to one of the ten UK administrative regions and  
25  
26 189 present seroprevalence rates mapped to these regions. We also used postcodes to derive  
27  
28 190 participants' income and employment deprivation scores using combined English and Welsh data  
29  
30 191 from 2019<sup>26</sup> and Scottish data from 2020.<sup>27</sup> Univariable analyses, using Fisher's exact and Mann-  
31  
32 192 Whitney U tests were used to identify demographic, disease, and treatment related factors  
33  
34 193 associated with SARS-CoV-2 seropositivity. A priori, we included age, sex, ethnicity, region, income  
35  
36 194 deprivation score, comorbidity, body mass index, and social distancing measures that are known to  
37  
38 195 affect SARS-CoV-2 acquisition and COVID-19 outcomes<sup>28</sup> alongside IBD diagnosis, biologic  
39  
40 196 medication, immunomodulator, and 5-aminosalicylate (5-ASA) use. We used multivariable logistic  
41  
42 197 regression models to identify factors independently associated with seropositivity.  
43  
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48  
49 198 We undertook Fisher's exact and Mann-Whitney U tests to compare the rates of, and time to,  
50  
51 199 seroconversion in infliximab- and vedolizumab-treated patients with confirmed COVID-19, and to  
52  
53 200 identify factors associated with failure of seroconversion in infliximab-treated patients. We explored  
54  
55 201 the magnitude of antibody reactivity using density plots, stratified by drug exposure among  
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202 participants with a positive PCR to anti-SARS-CoV-2 at least two weeks prior to measurement of  
203 serology.

204 We conducted sensitivity analyses using propensity matching to account for significant differences in  
205 baseline variables between infliximab- and vedolizumab-treated patients using the MatchIt  
206 package.<sup>29</sup> Patients were matched exactly on diagnosis, immunomodulator use, and cancer and then  
207 using optimal matching, on age, comorbidities, ethnicity, and presence of active disease.

### 208 Results

#### 209 *Patient characteristics*

210 Between September 22<sup>nd</sup> 2020 and December 23<sup>rd</sup> 2020, 7226 patients were recruited from 92 UK  
211 hospitals. Serum samples and completed questionnaires were available in 96.0% (6935/7226)  
212 patients. Of these, 67.6% (4685/6935) were treated with infliximab and 32.4% (2250/6935) were  
213 treated with vedolizumab. Participant characteristics are shown in **Table 1**.

214 Adherence to social distancing measures during the UK lockdown period between April and July  
215 2020, and exposure to COVID-19 cases was similar between infliximab and vedolizumab treated  
216 patients (**Table 1**). Fewer infliximab-treated patients were tested by PCR for SARS-CoV-2 (36.5%  
217 [1712/4685], vs 39.0% [877/2250],  $p=0.050$ ). There were no differences between the proportions of  
218 infliximab- and vedolizumab-treated patients who: reported symptoms of suspected or probable  
219 COVID-19 (8.3% [389/4685], vs 8.9% [201/2250],  $p=0.38$ ); tested positive by PCR for SARS-CoV-2  
220 (5.2% [89/1712], vs 4.3% [38/877],  $p=0.39$ ); or were hospitalised with confirmed COVID-19 (0.2%  
221 [8/4685], vs 0.2% [5/2250],  $p=0.77$ ).

**impacT of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY****222 Seroprevalence of anti-SARS-CoV-2 antibodies in anti-TNF and vedolizumab treated patients**

223 Overall, the seroprevalence of anti-SARS-CoV-2 antibodies was 4.3% (295/6935, 95% CI 3.8% - 4.8%).

224 The proportion of patients with a positive anti-SARS-CoV-2 antibody test was lower in infliximab-  
225 than vedolizumab-treated patients (3.4% [161/4685], vs 6.0% [134/2250],  $p < 0.0001$ ) (**Table 2**).

226 Seropositivity was also associated with younger age, non-white ethnicity, UK region, higher income  
227 deprivation score, having never smoked, ulcerative colitis, no concomitant immunomodulator use,  
228 recent steroid use, exposure to confirmed cases of COVID-19, reported symptoms of suspected or  
229 probable COVID-19, and social distancing measures during the UK government's lockdown period  
230 (**Table 2 and 3, See Supplementary Figure S1**).

231 Multivariable logistic regression analyses confirmed that infliximab (vs vedolizumab; odds ratio [OR]  
232 0.66 [95% CI 0.51 - 0.87],  $p = 0.0027$ ) and immunomodulator use (OR 0.70 [95% CI 0.53 - 0.92],  
233  $p = 0.012$ ) were independently associated with lower seropositivity (**Figure 1**). Conversely, non-white  
234 ethnicity, several UK regions, higher income deprivation score, and nonadherence to social  
235 distancing measures were independently associated with an increased risk of SARS-CoV-2  
236 seropositivity. There was no significant interaction between the effect of infliximab (vs vedolizumab)  
237 and immunomodulator use (OR for interaction term 1.03 [95% CI 0.57 - 1.92],  $p = 0.92$ ). In our  
238 propensity matched analysis, we confirmed lower seroprevalence in infliximab- compared to  
239 vedolizumab-treated patients 3.9% (67/1704), vs 6.2% (105/1707)  $p = 0.0037$  (**See Supplementary**  
240 **Table S2**).

**241 Seroconversion in patients with confirmed SARS-CoV-2 infection**

242 Sensitivity analyses in participants with confirmed SARS-CoV-2 infection demonstrated that fewer  
243 infliximab- than vedolizumab-treated patients had seroconverted (48% [39/81], vs 83% [30/36],  
244  $p = 0.00044$ ). The magnitude of anti-SARS-Cov2 reactivity was lower in patients with previous PCR

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5 245 confirmed SARS-CoV-2 infection treated with infliximab than with vedolizumab (median 0.8 COI [0.2  
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7 246 - 5.6] vs 37.0 [15.2 - 76.1],  $p < 0.0001$ ; **Figure 2**). This difference was also seen restricting our analyses  
8  
9 247 to participants whose antibody reactivity results were above the threshold (1 COI) for seropositivity  
10  
11 248 ( $p < 0.0001$ ; **See Supplementary Figure S2**).

12  
13  
14 249 Failure of seroconversion was associated with concomitant immunomodulator use. In patients  
15  
16 250 treated with infliximab alone, the seroconversion rate was 60% (24/40) and in patients treated with  
17  
18 251 infliximab and immunomodulator combination therapy, the rate was 37% (15/41,  $p = 0.046$ ). There  
19  
20 252 was also a significant difference in the magnitude of anti-SARS-Cov2 reactivity ( $p = 0.035$ ; **See**  
21  
22 253 **Supplementary Figure S3**). The median interval from a positive PCR test to serological testing at  
23  
24 254 recruitment in infliximab-treated patients was 32 days [IQR 20 – 54] and for vedolizumab-treated  
25  
26 255 patients was 40 days [IQR 24 - 83] ( $p = 0.082$ ). An increase in anti-SARS-Cov2 antibody reactivity was  
27  
28 256 observed four weeks after a positive PCR test in vedolizumab- (47.2 COI [IQR 24.1 - 113.0] vs 14.5 COI  
29  
30 257 [IQR 0.4 – 30.7],  $p = 0.0079$ ), but not infliximab-treated patients (0.7 COI [IQR 0.2 - 7.5] vs 1.1 COI [IQR  
31  
32 258 0.4 - 4.5],  $p = 0.70$ ) (**Figure 3**).

**Discussion**

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40 260 We have shown that infliximab-treated patients have attenuated serological responses to SARS-CoV-  
41  
42 261 2 infection with lower seroprevalence, seroconversion and antibody reactivity. Similar rates of  
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44 262 symptomatic and proven SARS-CoV-2 infection between infliximab- and vedolizumab-treated  
45  
46 263 patients suggest that our findings cannot be explained by differences in acquisition or severity of  
47  
48 264 infection alone. Rather, infliximab seems to be directly influencing the serological response to  
49  
50 265 infection. Concomitant immunomodulator use with a thiopurine or methotrexate further blunted  
51  
52 266 serological responses to both drugs with fewer than half of patients (37%) having detectable anti-  
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54 267 SARS-CoV-2 antibodies after a median of 5.4 weeks following PCR confirmed infection.  
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5 268 Infliximab may directly impede the immune mechanisms responsible for generating antibody  
6  
7 269 responses. This is biologically plausible, since the pro-inflammatory actions of TNF include  
8  
9 270 stimulation of B-cell immunoglobulin synthesis, induction of germinal centre formation, co-  
10  
11 271 stimulation of antigen-activated T-cells and maturation of antigen presenting cells.<sup>30-32</sup>  
12  
13  
14 272 Impaired serological responses to SARS-CoV-2 infection have important implications for global public  
15  
16 273 health policy and individual anti-TNF treated patients. From a public health perspective, impaired  
17  
18 274 serological responses might lead to chronic nasopharyngeal colonisation which may act as a  
19  
20  
21 275 reservoir to drive persistent transmission and the evolution of new SARS-CoV-2 variants.<sup>2</sup> Virus  
22  
23 276 surveillance will define if persistent infection and viral evolution occurs in this patient group.<sup>3</sup>  
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25  
26 277 For the individual anti-TNF treated patient, lower rates of seroconversion and reduced anti-SARS-  
27  
28 278 CoV-2 antibody reactivity levels may ultimately increase their susceptibility to recurrent COVID-19.  
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30  
31 279 Accepting that vaccination is critical to suppress transmission, serology testing should be considered  
32  
33 280 to detect suboptimal vaccine responses to inform the need for the most restrictive social distancing  
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35 281 measures to protect patients and public health. If attenuated serological responses following  
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37 282 vaccination are observed, then modified vaccination schedules given in combination, might need to  
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40 283 be considered in these patients.  
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43 284 Any negative impact on seroconversion following infection or vaccination needs to be balanced  
44  
45 285 against theoretical benefits for the individual patient of reducing the excessive cytokine production  
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47 286 that characterises severe COVID-19 disease. Indeed, this is the rationale behind the proposals for  
48  
49 287 trials of anti-TNF therapy in severe COVID-19 (ISRCTN40580903, ISRCTN33260034).<sup>33</sup>  
50  
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53 288 Our study has other important findings. We have identified associations of SARS-CoV-2 seropositivity  
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55 289 with non-white ancestry and nonadherence to social-distancing guidance. These findings are  
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58 290 consistent with observations reported in general non-immunosuppressed populations.<sup>28</sup> The

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291 mechanisms underlying these associations are complex and multi-factorial and likely include multi-  
292 generational living, at-risk employment, inability to work from home, socioeconomic deprivation,  
293 and religious congregation.

294 The region specific seroprevalence rates for vedolizumab-treated patients are consistent with those  
295 reported in the general UK population. Whilst direct comparisons to other datasets are limited,  
296 confounded in part by differences in the time of testing during the pandemic and the diagnostic  
297 accuracies of the anti-SARS-CoV-2 assays used, this adds to the evidence that patients with IBD are  
298 at a similar risk of SARS-CoV-2 infection as the general population.<sup>34</sup>

299 The main strength of this study was our recruitment of over 7,000 consecutive patients within a  
300 narrow window mitigating against the potential for time during the pandemic course to be a  
301 significant co-variate. Other strengths include comprehensive electronic collection of patient-  
302 reported outcomes, linkage with SARS-CoV-2 public health testing data, case ascertainment aligned  
303 with the WHO criteria, inclusion of social distancing behaviours, and the use of a sensitive and  
304 specific serological assay.<sup>35</sup>

**305 Limitations**

306 We acknowledge, however, the following limitations. Firstly, it is not known whether attenuated  
307 immune responses in infliximab-treated patients translates into increased risk of infection.

308 Moreover, we only assessed humoral responses to infection, and it is likely that protective immunity  
309 additionally requires induction of memory T-cell responses. Secondly, our patient reported data are  
310 subject to recall bias which may have underestimated the prevalence of possible COVID-19  
311 symptoms. Thirdly, the only anti-TNF drug investigated in this study was infliximab. However, we  
312 suspect that our key findings apply to other anti-TNF monoclonal antibodies used to treat IMIDs,  
313 including adalimumab, certolizumab, and golimumab.

**impact of biologics therapy on SARS-CoV-2 Infection and immunity CLARITY****314 Conclusions**

315 In summary, infliximab therapy is associated with attenuated serological responses to SARS-CoV-2  
316 infection. Poor antibody responses in infliximab-treated patients were observed despite similar rates  
317 of symptomatic and proven SARS-CoV-2 infection as vedolizumab-treated patients. Anti-SARS-CoV2  
318 antibody responses were further attenuated in infliximab recipients concomitantly treated with  
319 immunomodulators, including thiopurines and methotrexate.

320 Impaired serological responses to SARS-CoV-2 infection might have important implications for global  
321 public health policy and millions of anti-TNF treated patients. Serological testing and virus  
322 surveillance should be considered to detect suboptimal vaccine responses, persistent infection, and  
323 viral evolution to inform public health policy.

324



**impacT of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY****Figure Captions**

325 **Figure Captions**  
326 *Figure 1: Forest plot showing the coefficients from a multivariable logistic regression model of*  
327 *associations with a positive anti-SARS-CoV-2 antibody. Abbreviations: 5-ASA = aminosalicylates, UC =*  
328 *ulcerative colitis, IBDU = inflammatory bowel disease unclassified.*

329 *Figure 2: Density plot of the magnitude of anti-SARS-CoV-2 antibody reactivity stratified by biologic*  
330 *amongst participants who had a positive PCR to anti-SARS-CoV-2 at least two weeks prior to their*  
331 *serology sample. Abbreviations: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, PCR*  
332 *= polymerase chain reaction, COI = Cut-Off Index.*

333 *Figure 3: Boxplot of the magnitude of anti-SARS-CoV-2 antibody reactivity stratified by biologic and*  
334 *time since prior positive PCR test. Abbreviations: SARS-CoV-2 = severe acute respiratory syndrome*  
335 *coronavirus 2, PCR = polymerase chain reaction, COI = Cut-Off Index.*

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**impact of bioLogic therapy on SARS-cov-2 Infection and immunity CLARITY****338 Contributions**

339 NAK, JRG, CB, SS, NP, TA participated in the conception and design of this study. CB was the project  
340 manager and coordinated patient recruitment. RN and TJM coordinated all biochemical analyses and  
341 central laboratory aspects of the project. NAK, JRG, DC, SL, NC, JB, RC, NMC, ALH, PMI, KBK, CAL, JKL,  
342 JM, DPM, SJM, CDM, KVP, RCP, TR, RKR, CPS, PJS, JB, TJM, CWL, SS, NP, TA were involved in the  
343 acquisition, analysis, or interpretation of data. Data analysis was done by NAK. Drafting of the  
344 manuscript was done by NAK, JRG, DC, SL, NC, TR, CWL, SS, NP, TA, SS and TA obtained the funding  
345 for the study. All the authors contributed to the critical review and final approval of the manuscript.  
346 NAK and TA have verified the underlying data.

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**Patient involvement**

43 448  
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45 449 We conducted an electronic survey to gauge the opinion of patients with IBD on the patient  
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47 450 questionnaires to be delivered as part of the CLARITY IBD study. We surveyed 250 patients across 74  
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49 451 hospitals. All our proposed questions for study inclusion were rated as important or very important  
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51 452 by at least 83% of participants. The Exeter IBD Patient Panel refined the questions included in the  
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53 453 study questionnaire, reviewed the study protocol, supported the writing of the patient information  
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55 454 sheet, and participated in testing of electronic consent form and patient questionnaire. A member of  
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**impact of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY**

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5 455 the Exeter IBD Patient Panel sits on the study management committee, ensuring patient  
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7 456 involvement in all aspects of study delivery, data analysis and dissemination of findings.  
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**457 Data sharing**

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13 458 The study protocol including the statistical analysis plan is available at [www.clarityibd.org](http://www.clarityibd.org). Individual  
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15 459 participant de-identified data that underlie the results reported in this article will be available  
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17 460 immediately after publication for a period of 5 years. The data will be made available to investigators  
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19 461 whose proposed use of the data has been approved by an independent review committee. Analyses  
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22 462 will be restricted to the aims in the approved proposal. Proposals should be directed to  
23  
24 463 tariq.ahmad1@nhs.net; to gain access data requestors will need to sign a data access agreement.  
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impact of biologic therapy on SARS-cov-2 infection and immunity CLARITY

577 **Table 1: Baseline characteristics stratified by biologic**

| Variable                        | Infliximab         | Vedolizumab        | Overall            | p       |                   |
|---------------------------------|--------------------|--------------------|--------------------|---------|-------------------|
| Age (years)                     | 37.1 (27.2 - 50.6) | 43.8 (31.9 - 58.6) | 39.0 (28.7 - 53.2) | <0.0001 |                   |
| Sex                             | Female             | 45.5% (2134/4685)  | 48.3% (1087/2250)  | 0.089   |                   |
|                                 | Male               | 54.3% (2546/4685)  | 51.5% (1159/2250)  |         |                   |
|                                 | Intersex           | 0.0% (1/4685)      | 0.0% (1/2250)      |         | 0.0% (2/6935)     |
|                                 | Prefer not to say  | 0.1% (4/4685)      | 0.1% (3/2250)      |         | 0.1% (7/6935)     |
| Ethnicity                       | White              | 88.5% (4143/4683)  | 88.2% (1981/2247)  | 0.20    |                   |
|                                 | Asian              | 6.6% (308/4683)    | 7.6% (171/2247)    |         | 6.9% (479/6930)   |
|                                 | Mixed              | 2.2% (104/4683)    | 2.3% (51/2247)     |         | 2.2% (155/6930)   |
|                                 | Black              | 1.8% (82/4683)     | 1.2% (27/2247)     |         | 1.6% (109/6930)   |
|                                 | Other              | 1.0% (46/4683)     | 0.8% (17/2247)     |         | 0.9% (63/6930)    |
| Diagnosis                       | Crohn's disease    | 66.6% (3121/4685)  | 36.8% (828/2250)   | 0.00050 |                   |
|                                 | Ulcerative colitis | 31.1% (1457/4685)  | 60.1% (1353/2250)  |         | 40.5% (2810/6935) |
|                                 | IBD-unclassified   | 2.3% (107/4685)    | 3.1% (69/2250)     |         | 2.5% (176/6935)   |
| Duration of IBD (years)         | 7.0 (3.0 - 15.0)   | 9.0 (4.0 - 16.0)   | 8.0 (3.0 - 15.0)   | <0.0001 |                   |
| Age at IBD diagnosis (years)    | 26.3 (18.9 - 37.5) | 30.4 (21.6 - 44.1) | 27.6 (19.8 - 39.8) | <0.0001 |                   |
| Immunomodulators at recruitment | 56.3% (2639/4685)  | 18.8% (424/2250)   | 44.2% (3063/6935)  | <0.0001 |                   |
| 5-ASA at recruitment            | 22.2% (1039/4685)  | 35.2% (791/2250)   | 26.4% (1830/6935)  | <0.0001 |                   |
| Steroids in 2020                | 14.2% (664/4685)   | 21.9% (492/2250)   | 16.7% (1156/6935)  | <0.0001 |                   |
| BMI                             | 24.4 (21.5 - 28.1) | 24.9 (22.0 - 28.4) | 24.5 (21.7 - 28.2) | 0.044   |                   |
| Heart disease                   | 2.1% (97/4685)     | 5.0% (113/2250)    | 3.0% (210/6935)    | <0.0001 |                   |
| Diabetes                        | 3.4% (158/4685)    | 6.8% (154/2250)    | 4.5% (312/6935)    | <0.0001 |                   |
| Lung disease                    | 12.6% (588/4685)   | 16.7% (375/2250)   | 13.9% (963/6935)   | <0.0001 |                   |
| Kidney disease                  | 0.9% (42/4685)     | 2.1% (47/2250)     | 1.3% (89/6935)     | <0.0001 |                   |

impact of biologic therapy on SARS-cov-2 Infection and immunity CLARITY

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| Cancer   |   | 0.2% (11/4685)    | 1.7% (39/2250)    | 0.7% (50/6935)    | <0.0001 |
| Smoker   | Yes   | 11.5% (538/4684)  | 9.2% (206/2249)   | 10.7% (744/6933)  | 0.00050 |
|  | Not currently   | 28.5% (1333/4684) | 34.4% (773/2249)  | 30.4% (2106/6933) |         |
|  | Never   | 60.1% (2813/4684) | 56.5% (1270/2249) | 58.9% (4083/6933) |         |
| Meets clinical criteria for suspected or probable COVID-19         |   | 8.3% (389/4685)   | 8.9% (201/2250)   | 8.5% (590/6935)   | 0.38    |
| Tested with PCR for SARS-CoV-2                                     |   | 36.5% (1712/4685) | 39.0% (877/2250)  | 37.3% (2589/6935) | 0.050   |
| Positive PCR for SARS-CoV-2  |   | 5.2% (89/1712)    | 4.3% (38/877)     | 4.9% (127/2589)   | 0.39    |
| Positive PCR for SARS-CoV-2 at least 2 weeks prior to serum sample |   | 5.3% (81/1537)    | 4.4% (36/809)     | 5.0% (117/2346)   | 0.43    |
| Hospitalised for confirmed COVID-19                                |   | 0.2% (8/4685)     | 0.2% (5/2250)     | 0.2% (13/6935)    | 0.77    |
| Shielding behaviour Apr-Jul  | I remained in my house or garden  | 35.2% (1647/4681) | 33.3% (749/2248)  | 34.6% (2396/6929) | 0.41    |
|  | I only left the house for exercise on my own or with members of my household                    | 38.5% (1804/4681) | 39.9% (897/2248)  | 39.0% (2701/6929) |         |
|  | I encountered people from outside of my household but <i>maintained social distancing</i>       | 24.4% (1142/4681) | 24.6% (554/2248)  | 24.5% (1696/6929) |         |
|  | I encountered people from outside of my household but <i>did not maintain social distancing</i> | 1.9% (88/4681)    | 2.1% (48/2248)    | 2.0% (136/6929)   |         |
| Exposure to documented cases of COVID-19                           |   | 11.4% (533/4683)  | 10.7% (240/2250)  | 11.1% (773/6933)  | 0.39    |
| PHQ8   |   | 4.0 (1.0 - 8.0)   | 5.0 (1.0 - 9.0)   | 4.0 (1.0 - 9.0)   | 0.018   |
| GAD7   |   | 3.0 (0.0 - 7.0)   | 3.0 (0.0 - 7.0)   | 3.0 (0.0 - 7.0)   | 0.12    |

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impact of biologics therapy on SARS-cov-2 Infection and immunity CLARITY

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| Income deprivation score | 0.099 (0.057 - 0.168) | 0.095 (0.056 - 0.160) | 0.097 (0.57 - 0.165) | 0.24    |
| Active disease (PRO2)    | 6.7% (303/4534)       | 12.6% (272/2166)      | 8.6% (575/6700)      | <0.0001 |
| IBD Control 8            | 13.0 (10.0 - 16.0)    | 13.0 (9.0 - 16.0)     | 13.0 (9.0 - 16.0)    | 0.024   |
| IBD Control VAS          | 80.0 (66.0 - 93.0)    | 79.0 (61.0 - 91.0)    | 80.0 (65.0 - 92.0)   | 0.00022 |

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579 Values shown are medians (interquartile range) and percentages (proportions) as appropriate. **Abbreviations:** IBD = inflammatory bowel disease, 5-  
580 ASA = aminosalicylates, BMI = Body Mass Index, COVID-19 = coronavirus, PCR = polymerase chain reaction, SARS-CoV-2 = severe acute respiratory  
581 syndrome coronavirus 2, PHQ8 = Patient Health Questionnaire depression scale, GAD7 = General Anxiety Disorder assessment, PRO2 = Patient Reported  
582 Outcome, VAS = Visual Analogue Scale  
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584 **impaCt of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY**

585 **Table 2: Seroprevalence to anti-SARS-CoV-2, stratified by**  
586 **baseline characteristics**

| Variable                            |                                     | Seroprevalence  | p       |
|-------------------------------------|-------------------------------------|-----------------|---------|
| Biologic treatment                  | Infliximab                          | 3.4% (161/4685) | <0.0001 |
|                                     | Vedolizumab                         | 6.0% (134/2250) |         |
| Biologic/ immunomodulator treatment | Infliximab with immunomodulator     | 3.0% (78/2639)  | 0.00050 |
|                                     | Infliximab without immunomodulator  | 4.1% (83/2046)  |         |
|                                     | Vedolizumab with immunomodulator    | 4.5% (19/424)   |         |
|                                     | Vedolizumab without immunomodulator | 6.3% (115/1826) |         |
| Sex                                 | Female                              | 4.3% (137/3221) | 1.0     |
|                                     | Male                                | 4.3% (158/3705) |         |
|                                     | Intersex                            | 0.0% (0/2)      |         |
|                                     | Prefer not to say                   | 0.0% (0/7)      |         |
| Ethnicity                           | White                               | 3.5% (217/6124) | 0.00050 |
|                                     | Asian                               | 9.2% (44/479)   |         |
|                                     | Mixed                               | 7.7% (12/155)   |         |
|                                     | Black                               | 13.8% (15/109)  |         |
|                                     | Other                               | 11.1% (7/63)    |         |
| Diagnosis                           | Crohn's disease                     | 3.2% (128/3949) | 0.00050 |
|                                     | Ulcerative colitis                  | 5.5% (155/2810) |         |
|                                     | IBD-unclassified                    | 6.8% (12/176)   |         |
| Immunomodulators at recruitment     | No                                  | 5.1% (198/3872) | <0.0001 |
|                                     | Yes                                 | 3.2% (97/3063)  |         |
| 5-ASA at recruitment                | No                                  | 3.9% (198/5105) | 0.012   |
|                                     | Yes                                 | 5.3% (97/1830)  |         |
| Steroids in 2020                    | No                                  | 4.0% (232/5779) | 0.031   |
|                                     | Yes                                 | 5.4% (63/1156)  |         |
| Heart disease                       | No                                  | 4.3% (287/6725) | 0.86    |
|                                     | Yes                                 | 3.8% (8/210)    |         |
| Diabetes                            | No                                  | 4.2% (280/6623) | 0.57    |
|                                     | Yes                                 | 4.8% (15/312)   |         |
| Lung disease                        | No                                  | 4.4% (260/5972) | 0.34    |
|                                     | Yes                                 | 3.6% (35/963)   |         |
| Kidney disease                      | No                                  | 4.3% (294/6846) | 0.19    |
|                                     | Yes                                 | 1.1% (1/89)     |         |
| Cancer                              | No                                  | 4.3% (293/6885) | 1.0     |
|                                     | Yes                                 | 4.0% (2/50)     |         |

## impacT of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY

|  |   |                 |         |
|--|---|-----------------|---------|
| Smoker   | Yes   | 2.2% (16/744)   | 0.00050 |
|  | Not currently   | 3.4% (71/2106)  |         |
|  | Never   | 5.1% (207/4083) |         |
| Meets clinical criteria for suspected or probable COVID-19         | No  | 2.5% (158/6345) | <0.0001 |
|  | Yes   | 23.2% (137/590) |         |
| Tested with PCR for SARS-CoV-2                                     | No  | 2.9% (128/4346) | <0.0001 |
|  | Yes   | 6.5% (167/2589) |         |
| Positive PCR for SARS-CoV-2  | No  | 3.8% (93/2462)  | <0.0001 |
|  | Yes   | 58.3% (74/127)  |         |
| Positive PCR for SARS-CoV-2 at least 2 weeks prior to serum sample | No  | 3.8% (85/2229)  | <0.0001 |
|  | Yes   | 59.0% (69/117)  |         |
| Hospitalised for confirmed COVID-19                                | No  | 4.1% (285/6922) | <0.0001 |
|  | Yes   | 76.9% (10/13)   |         |
| Shielding behaviour Apr-Jul  | I remained in my house or garden  | 3.8% (92/2396)  | 0.0020  |
|  | I only left the house for exercise on my own or with members of my household                    | 3.9% (104/2701) |         |
|  | I encountered people from outside of my household but <i>maintained social distancing</i>       | 4.9% (83/1696)  |         |
|  | I encountered people from outside of my household but <i>did not maintain social distancing</i> | 11.0% (15/136)  |         |
| Exposure to documented cases of COVID-19                           | No  | 3.1% (192/6160) | <0.0001 |
|  | Yes   | 13.3% (103/773) |         |
| Active disease (PRO2)  | No  | 4.3% (266/6125) | 0.67    |
|  | Yes   | 3.8% (22/575)   |         |

587

588 Values shown are percentages (proportions).

589

590 **Abbreviations:** IBD = inflammatory bowel disease, 5-ASA = aminosaliclates, COVID-19 =  
 591 coronavirus, PCR = polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome  
 592 coronavirus 2, PRO2 = Patient Reported Outcome

593

## impact of bioLogic therapy on SARS-cov-2 Infection and immunity CLARITY

594 **Table 3: Baseline characteristics, stratified by baseline anti-SARS-CoV-2**  
 595 **antibody status**  
 596

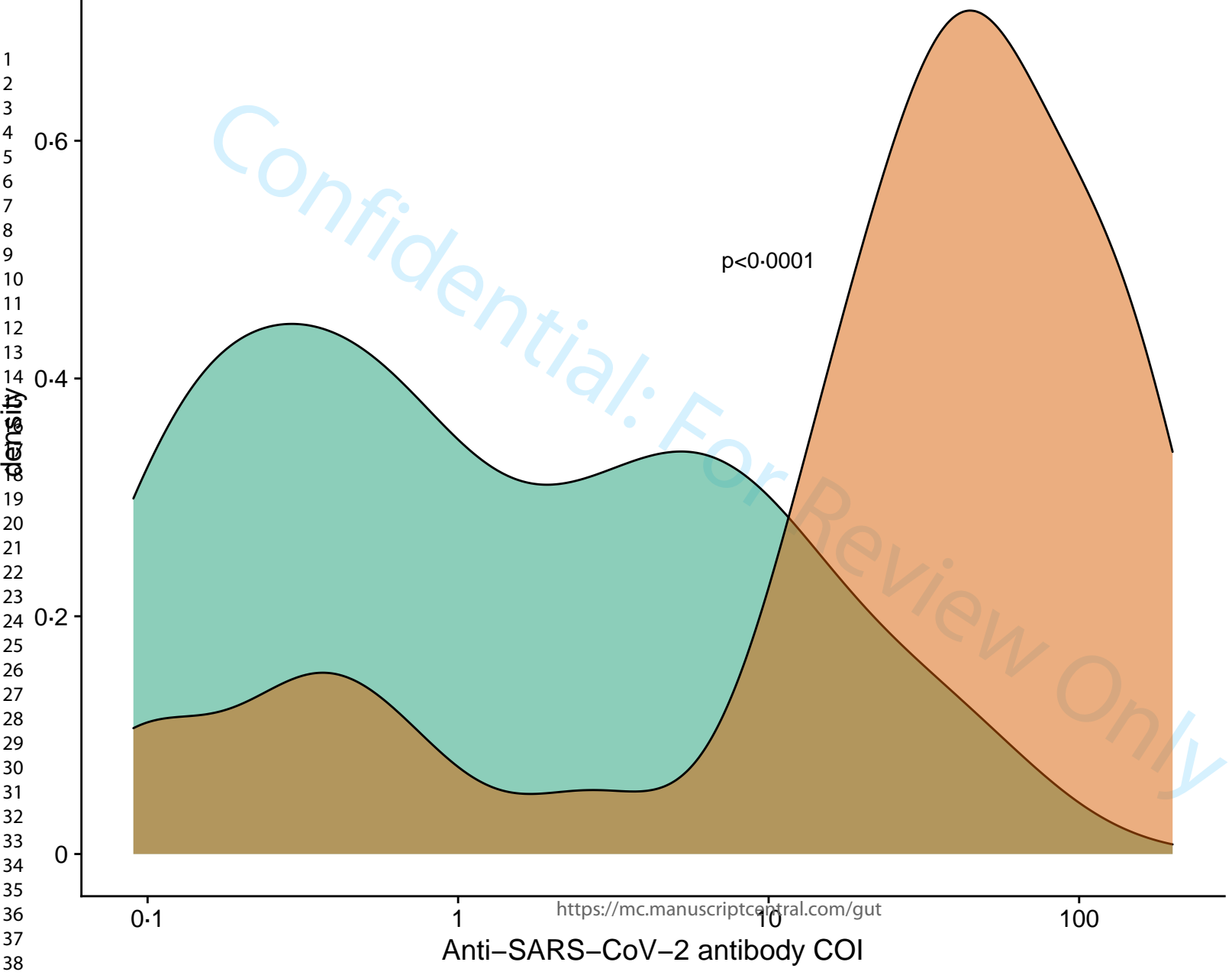
| Variable                     | Positive              | Negative              | p       |
|------------------------------|-----------------------|-----------------------|---------|
| Age (years)                  | 36.3 (26.9 - 50.6)    | 39.2 (28.7 - 53.3)    | 0.017   |
| Duration of IBD (years)      | 7.0 (3.0 - 15.0)      | 8.0 (3.0 - 15.0)      | 0.25    |
| Age at IBD diagnosis (years) | 26.4 (19.8 - 36.4)    | 27.6 (19.8 - 40.0)    | 0.12    |
| BMI                          | 24.7 (21.7 - 28.1)    | 24.5 (21.7 - 28.3)    | 0.75    |
| PHQ8                         | 4.0 (1.0 - 8.0)       | 4.0 (1.0 - 9.0)       | 0.40    |
| GAD7                         | 2.0 (0.0 - 6.0)       | 3.0 (0.0 - 7.0)       | 0.050   |
| Income deprivation score     | 0.120 (0.666 - 0.204) | 0.097 (0.056 - 0.163) | <0.0001 |
| IBD Control 8                | 13.0 (10.0 - 16.0)    | 13.0 (9.0 - 16.0)     | 0.32    |
| IBD Control VAS              | 79.0 (67.0 - 92.0)    | 80.0 (65.0 - 92.0)    | 0.61    |

597  
 598 Values shown are medians (interquartile range).  
 599

600 **Abbreviations:** IBD = inflammatory bowel disease, BMI = body mass index, PHQ8 = Patient Health  
 601 Questionnaire depression scale, GAD7 = General Anxiety Disorder assessment, VAS = Visual  
 602 Analogue Scale  
 603



| Variable                                | Gut N                         | Odds ratio | OR (95% CI)        | p       |
|---|-------------------------------|------------|--------------------|---------|
| <b>Biologic</b>                         |                               |            |                    |         |
|   | Vedolizumab                   | 2245       | Reference          |         |
|   | Infliximab                    | 4675       | 0.66 (0.51, 0.87)  | 0.0027  |
| <b>Immunomodulator</b>                  | 3059                          |            | 0.70 (0.53, 0.92)  | 0.012   |
| <b>5-ASA</b>                            | 1825                          |            | 0.99 (0.74, 1.32)  | 0.94    |
| <b>Steroid use at any point in 2020</b> | 1154                          |            | 1.27 (0.93, 1.70)  | 0.12    |
| <b>Age &gt; 70</b>                      | 387                           |            | 0.56 (0.27, 1.06)  | 0.097   |
| <b>Region</b>                           |                               |            |                    |         |
|   | South West                    | 958        | Reference          |         |
|   | East Midlands                 | 467        | 2.12 (1.01, 4.42)  | 0.044   |
|   | East of England               | 644        | 2.04 (1.03, 4.12)  | 0.043   |
|   | London                        | 1188       | 3.35 (1.93, 6.20)  | <0.0001 |
|   | North East                    | 284        | 2.37 (1.06, 5.18)  | 0.031   |
|   | North West                    | 630        | 3.92 (2.18, 7.44)  | <0.0001 |
|   | Scotland                      | 423        | 1.29 (0.54, 2.94)  | 0.55    |
|   | South East                    | 654        | 2.52 (1.30, 5.03)  | 0.0069  |
|   | Wales                         | 451        | 1.22 (0.51, 2.79)  | 0.64    |
|   | West Midlands                 | 527        | 3.06 (1.63, 5.98)  | 0.00067 |
|   | Yorkshire and the Humber      | 694        | 3.10 (1.69, 5.94)  | 0.00038 |
| <b>Ethnicity</b>                        |                               |            |                    |         |
|   | White                         | 6116       | Reference          |         |
|   | Asian                         | 479        | 1.97 (1.35, 2.81)  | 0.00031 |
|   | Mixed                         | 154        | 1.86 (0.95, 3.36)  | 0.052   |
|   | Black                         | 108        | 3.32 (1.75, 5.94)  | 0.00011 |
|   | Other                         | 63         | 2.47 (0.98, 5.33)  | 0.034   |
| <b>Shielding Apr–Jul</b>                |                               |            |                    |         |
|   | Remained at home              | 2391       | Reference          |         |
|   | Exercise w/ own household     | 2699       | 1.09 (0.81, 1.47)  | 0.57    |
|   | Met others, social distancing | 1694       | 1.33 (0.97, 1.83)  | 0.072   |
|   | No social distancing          | 136        | 2.83 (1.51, 5.01)  | 0.00062 |
| <b>Diagnosis</b>                        |                               |            |                    |         |
|   | Crohn's disease               | 3941       | Reference          |         |
|   | UC/IBDU                       | 2979       | 1.44 (1.09, 1.90)  | 0.011   |
| <b>Heart disease</b>                    | 210                           |            | 0.98 (0.43, 1.97)  | 0.96    |
| <b>Diabetes</b>                         | 311                           |            | 1.03 (0.57, 1.73)  | 0.93    |
| <b>Lung disease</b>                     | 963                           |            | 0.83 (0.56, 1.18)  | 0.32    |
| <b>Cancer</b>                           | 50                            |            | 0.70 (0.11, 2.36)  | 0.63    |
| <b>Income deprivation score</b>         | 6920                          |            | 5.36 (1.42, 19.55) | 0.012   |

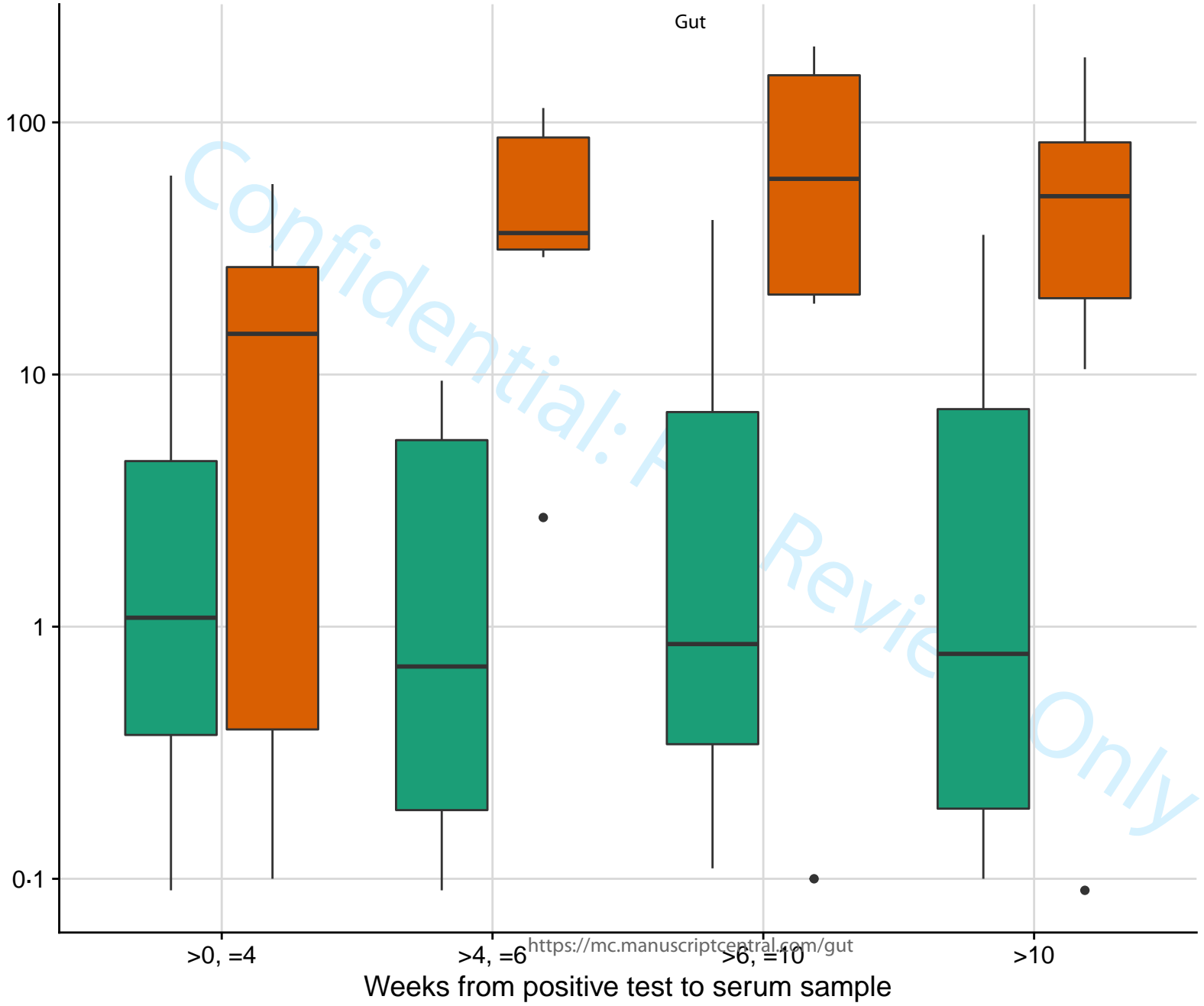


**Biologic**  
■ Infliximab  
■ Vedolizumab

Gut

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Biologic  
Infiximab  
Vedolizumab

Weeks from positive test to serum sample

<https://mc.manuscriptcentral.com/gut>

# Supplementary Appendix for ‘Anti-SARS-CoV2 antibody responses are impaired in patients with inflammatory bowel disease treated with infliximab’

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Supplementary Appendix for 'Anti-SARS-CoV2 antibody responses are impaired in patients with inflammatory bowel disease treated with infliximab'

Supplementary Table S1: Contributors to the CLARITY IBD study

| Affiliation   | First name  | Surname    |
|---|-------------|------------|
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|   | Rachel      | Thomas     |
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|   | Catherine   | Cotter     |
|   | Jayne       | Grove      |
|   | Kate        | Hong       |
|   | Ruth        | Howman     |
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|   | Rachel      | Gascoyne   |
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|   | Emmeline    | Martin     |
|   | Susie       | Pajak      |
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|   | Lucy        | Pritchard  |
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Supplementary Appendix for 'Anti-SARS-CoV2 antibody responses are impaired in patients with inflammatory bowel disease treated with infliximab'

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|   | Alex            | Hall            |
| Huddersfield Royal Infirmary                          | Sunil           | Sonwalkar       |
|   | Naomi           | Chambers        |
|   | Andrew          | Haigh           |
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Supplementary Appendix for 'Anti-SARS-CoV2 antibody responses are impaired in patients with inflammatory bowel disease treated with infliximab'

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|   | Glaxy       | Gray          |
|   | Anu         | John          |
|   | Maya        | John          |
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Supplementary Appendix for 'Anti-SARS-CoV2 antibody responses are impaired in patients with inflammatory bowel disease treated with infliximab'

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|   | Farzana     | Masters        |
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|   | Cynthia     | Diaba          |
|   | Fexy        | Joseph         |
|   | Glykeria    | Pakou          |
|   | Mark        | Furman         |
|   | Dan         | Crespi         |
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|   | Natalie     | Stroud         |
|   | Carla       | Pothecary      |
|   | Lisa        | Roche          |
|   | Keri        | Turner         |
|   | Lisa        | Deering        |
|   | Lynda       | Israel         |
| Royal Gwent Hospital                        | Evelyn      | Baker          |
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|   | Rina        | Mardania Evans |
|   | Maxine      | Nash           |
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|   | Emma        | Levell         |
|   | Silvia      | Zagalo         |
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|   | Kevin       | Samuels        |
|   | Nicolene    | Plaatjies      |
|   | Hafiza      | Khatun         |
|   | Farjana     | Bokth          |
|   | Elise       | Pabriaga       |
|   | Caroline    | Fracia         |
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|   | Felicia     | Jennings       |
|   | Imelda      | Mayor          |
|   | Jill        | Wilson         |
| Royal Shrewsbury Hospital                   | Jeff        | Butterworth    |
|   | Colene      | Adams          |
|   | Elizabeth   | Buckingham     |
|   | Danielle    | Childs         |
|   | Alison      | Stephens       |
|   | Jo          | Stickley       |
| Royal Surrey Hospital                       | Christopher | Alexakis       |
|   | Natalia     | Michalak       |
| Royal United Hospital, Bath                 | John        | Saunders       |
|   | Helen       | Burton         |
|   | Vanessa     | Cambridge      |
|   | Tonia       | Clark          |
|   | Charlotte   | Ekblad         |



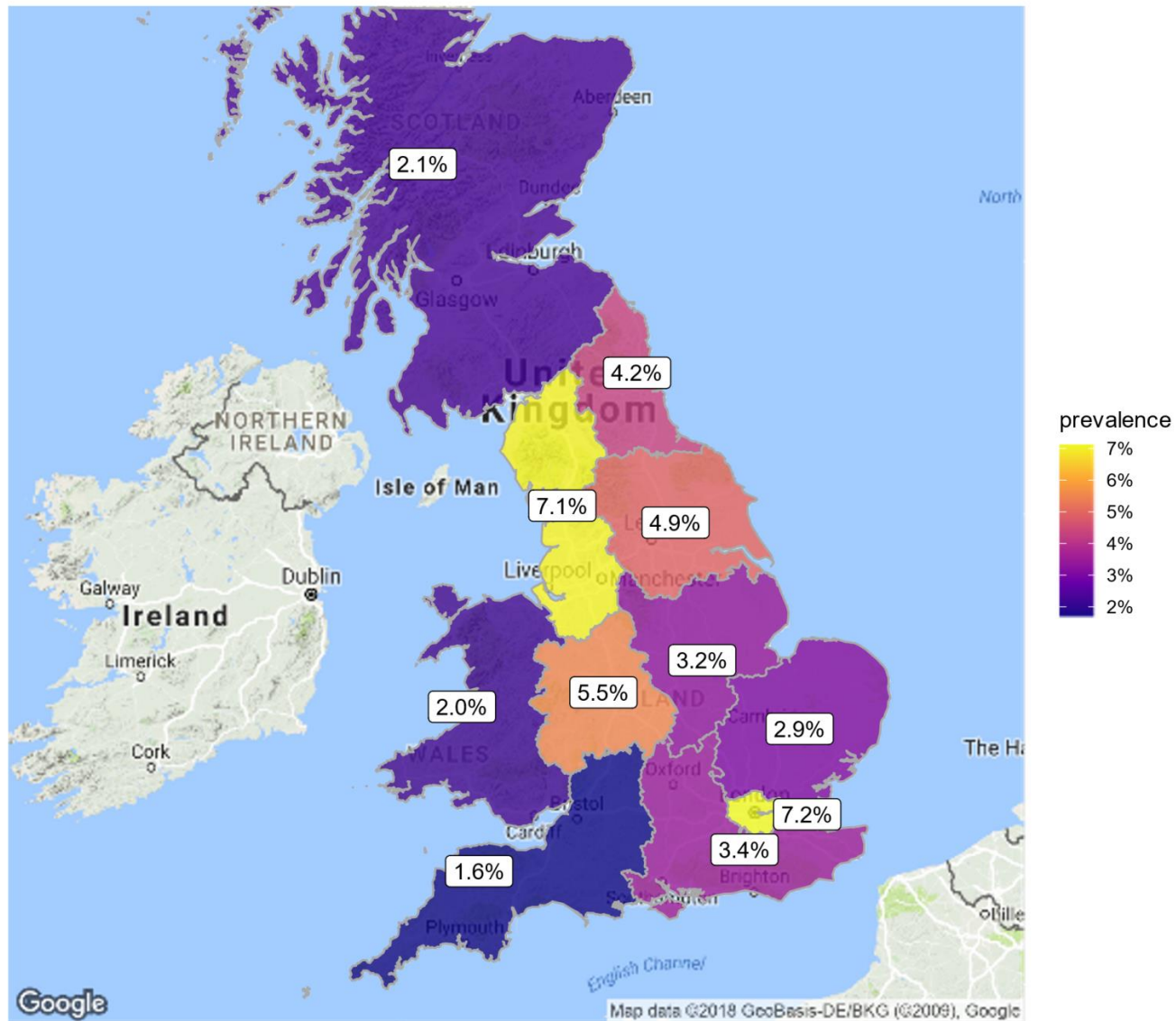
Supplementary Appendix for 'Anti-SARS-CoV2 antibody responses are impaired in patients with inflammatory bowel disease treated with infliximab'

|   |             |             |
|---|-------------|-------------|
|   | Sarah       | Hierons     |
|   | Joyce       | Katebe      |
|   | Emma        | Saunbury    |
|   | Rachel      | Perry       |
| Royal Victoria Infirmary                          | Chris       | Lamb        |
|   | Mary        | Doona       |
|   | Ashleigh    | Hogg        |
|   | Lesley      | Jeffrey     |
|   | Andrew      | King        |
|   | R Alexander | Speight     |
| Royal Wolverhampton NHS Trust                     | Matthew     | Brookes     |
|   | Kathryn     | Davies      |
|   | Marie       | Green       |
|   | Ann         | Plumbe      |
| Russells Hall Hospital (Dudley Group)             | Shanika     | de Silva    |
|   | Clare       | Allcock     |
|   | Philip      | Harvey      |
| Salford Royal NHS Foundation Trust                | Clare       | Ormerod     |
|   | Helen       | Christensen |
|   | Anne        | Keen        |
|   | Jonathan    | Ogor        |
| Salisbury District Hospital                       | Alpha       | Anthony     |
|   | Emily       | Newitt      |
| Sandwell and West Birmingham NHS Trust            | Edward      | Fogden      |
|   | Kalisha     | Russell     |
| Scarborough Hospital                              | Ajay        | Muddu       |
|   | Laura       | Barman      |
|   | Janine      | Mallinson   |
| Sheffield Teaching Hospitals NHS Foundation Trust | Anne        | Phillips    |
|   | Muaad       | Abdulla     |
| Singleton Hospital                                | Caradog     | Thomas      |
|   | Elaine      | Brinkworth  |
|   | Lynda       | Connor      |
|   | Amanda      | Cook        |
|   | Tabitha     | Rees        |
| Southampton General Hospital                      | Fraser      | Cummings    |
|   | Clare       | Harris      |
|   | Amy         | Jones       |
|   | Liga        | Krauze      |
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|   | Audrey      | Torokwa     |
| Southend Hospital                                 | Ioannis     | Koumoutsos  |
|   | Viji        | George      |
|   | Swapna      | Kunhunny    |
|   | Sophie      | Laverick    |
| Southmead Hospital                                | Melanie     | Lockett     |
|   | Charlotte   | Cranfield   |
|   | Louise      | Jennings    |
|   | Ankur       | Srivastava  |
|   | Lana        | Ward        |
|   | Nouf        | Jeynes      |
| St George's Hospital                              | Kamal       | Patel       |
|   | Mariam      | Ali         |
|   | Hilda       | Mhandu      |
|   | Aleem       | Rana        |
|   | Katherine   | Spears      |
|   | Joana       | Teixeira    |
|   | Richard     | Pollok      |
|   | Nicholas    | Reps        |
|   | Mark        | Mencias     |
|   | Abigail     | Seaward     |
| St George's Hospital (children)                   | Nicholas    | Reps        |
|   | Nicholas    | Reps        |
| St James's University Hospital                    | Christian   | Selinger    |
|   | Jenelyn     | Carbonell   |
|   | Felicia     | Onovira     |
|   | Doris       | Quartey     |
| Stepping Hill Hospital                            | Zahid       | Mahmood     |
|   | Racheal     | Campbell    |
|   | Liane       | Marsh       |
| Surrey and Sussex Healthcare NHS Trust            | Monira      | Rahman      |
|   | Sarah       | Davies      |
|   | Ruth        | Habibi      |

Supplementary Appendix for 'Anti-SARS-CoV2 antibody responses are impaired in patients with inflammatory bowel disease treated with infliximab'

|  |           |                |
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|  | Ellen     | Jessup-Dunton  |
|  | Teishel   | Joefield       |
|  | Reina     | Layug          |
| Tameside Hospital                          | Vinod     | Patel          |
|  | Joanne    | Vere           |
| The Pennine Acute Hospitals NHS Trust      | Jimmy     | Limdi          |
|  | Kay       | Goulden        |
|  | Asad      | Javed          |
|  | Lauren    | McKenzie       |
| The Queen Elizabeth Hospital, King's Lynn  | Alan      | Wiles          |
|  | Hannah    | Bloxham        |
|  | Jose      | Dias           |
| Torbay Hospital                            | Gareth    | Walker         |
|  | Stacey    | Atkins         |
|  | Jasmine   | Growdon        |
|  | Charlotte | McNeill        |
| University College London Hospital         | Shameer   | Mehta          |
|  | James     | Bell           |
|  | William   | Blad           |
|  | Lisa      | Whitley        |
| University Hospital Llandough, Cardiff     | Durai     | Dhamaraj       |
|  | Mark      | Baker          |
| University of Wales, Cardiff (paediatrics) | Amar      | Wahid          |
|  | Zoe       | Morrison       |
| West Hertfordshire Hospitals NHS Trust     | Rakesh    | Chaudhary      |
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|  | Chiara    | Ellis          |
|  | Cheryl    | Kemp           |
|  | Ogwa      | Tobi           |
| West Middlesex University Hospital         | Emma      | Johnston       |
|  | Metod     | Oblak          |
|  | Richard   | Appleby        |
| West Suffolk Hospital                      | Marium    | Asghar         |
| Western General Hospital, Edinburgh        | Charlie   | Lees           |
|  | Debbie    | Alexander      |
|  | Margareta | Balint         |
|  | Anna      | Coleman        |
|  | Kate      | Covil          |
|  | Lauranne  | Derikx         |
|  | Joanne    | Dobson         |
|  | Audrey    | Kuchnowski     |
|  | Beena     | Poulose        |
|  | Sryros    | Siakavellas    |
|  | Linda     | Smith          |
|  | Joyce     | Wilson         |
| Withybush General Hospital                 | Kerrie    | Johns          |
|  | Rachel    | Hughes         |
|  | Janet     | Phipps         |
|  | Abigail   | Taylor         |
| Yeovil Hospital                            | Katie     | Smith          |
|  | Linda     | Howard         |
|  | Dianne    | Wood           |
| Ysbyty Gwynedd                             | Iona      | Thomas         |
|  | Kelly     | Andrews        |
|  | Caroline  | Mulvaney Jones |
|  | Julia     | Roberts        |

Supplementary Figure S1: Regional seroprevalence of SARS-CoV-2 by NUTS1 region



**Abbreviations:** SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, NUTS = Nomenclature of territorial units for statistic

Supplementary Table S2: Baseline characteristics stratified by baseline characteristics after propensity matching by inflammatory bowel disease (IBD) subtype, immunomodulator use, cancer, age, active IBD and comorbidities

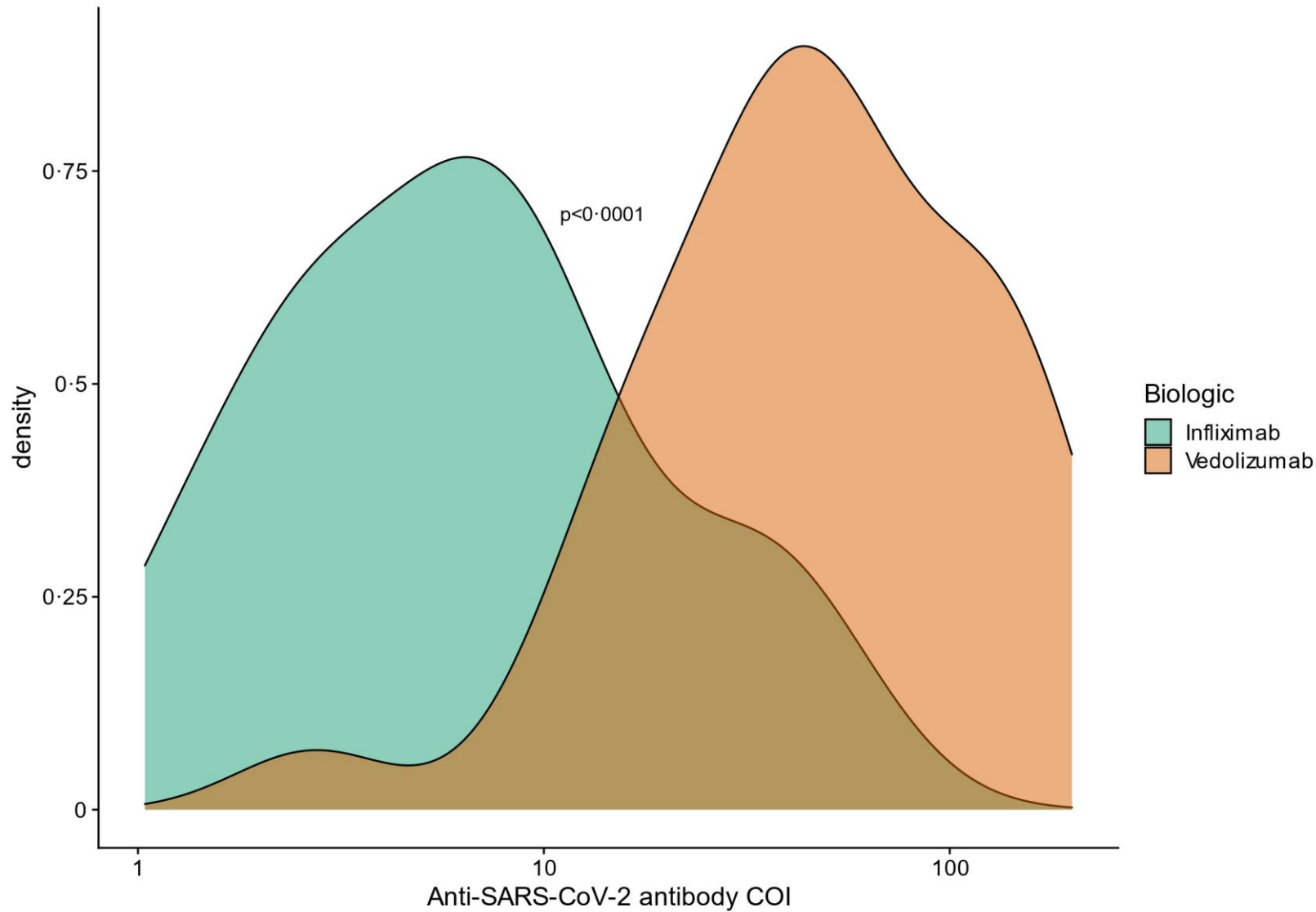
| Variable   |   | Positive           | Negative           | p      |
|--|---|--------------------|--------------------|--------|
| Positive serology to SARS-CoV-2                                    | Positive  | 3.9% (67/1704)     | 6.2% (105/1707)    | 0.0037 |
|  | Negative  | 96.1% (1637/1704)  | 93.8% (1602/1707)  |        |
| Age (years)  |   | 41.7 (31.1 - 55.6) | 41.4 (31.1 - 56.1) | 0.91   |
| Sex  | Female  | 46.4% (791/1704)   | 50.2% (857/1707)   | 0.023  |
|  | Male  | 53.6% (913/1704)   | 49.7% (848/1707)   |        |
|  | Intersex  | 0.0% (0/1704)      | 0.1% (1/1707)      |        |
|  | Prefer not to say   | 0.0% (0/1704)      | 0.1% (1/1707)      |        |
| Ethnicity  | White   | 88.6% (1510/1704)  | 88.1% (1504/1707)  | 0.99   |
|  | Asian   | 7.1% (121/1704)    | 7.4% (127/1707)    |        |
|  | Mixed   | 2.3% (40/1704)     | 2.3% (39/1707)     |        |
|  | Black   | 1.2% (21/1704)     | 1.3% (23/1707)     |        |
|  | Other   | 0.7% (12/1704)     | 0.8% (14/1707)     |        |
| Diagnosis  | Crohn's disease   | 43.4% (739/1704)   | 43.4% (740/1707)   | 1.0    |
|  | Ulcerative colitis  | 53.2% (907/1704)   | 53.3% (909/1707)   |        |
|  | IBD-unclassified  | 3.4% (58/1704)     | 3.4% (58/1707)     |        |
| Duration of IBD (years)  |   | 8.0 (3.0 - 15.0)   | 9.0 (4.0 - 16.0)   | 0.0010 |
| Age at IBD diagnosis (years)                                       |   | 29.8 (21.5 - 42.8) | 29.0 (20.8 - 41.8) | 0.29   |
| Immunomodulators at recruitment                                    |   | 23.4% (399/1704)   | 23.5% (401/1707)   | 0.97   |
| 5-ASA at recruitment   |   | 32.4% (552/1704)   | 33.4% (570/1707)   | 0.54   |
| Steroids in 2020   |   | 19.5% (333/1704)   | 21.7% (370/1707)   | 0.13   |
| BMI  |   | 25.2 (22.1 - 28.6) | 24.8 (21.9 - 28.4) | 0.52   |
| Heart disease  |   | 3.6% (61/1704)     | 3.3% (57/1707)     | 0.71   |
| Diabetes   |   | 5.3% (91/1704)     | 5.7% (97/1707)     | 0.71   |
| Lung disease   |   | 16.0% (272/1704)   | 16.0% (273/1707)   | 1.0    |
| Kidney disease   |   | 1.2% (20/1704)     | 1.8% (30/1707)     | 0.20   |
| Cancer   |   | 0.5% (8/1704)      | 0.5% (8/1707)      | 1.0    |
| Smoker   | Yes   | 11.5% (196/1704)   | 10.3% (175/1707)   | 0.48   |
|  | Not currently   | 32.2% (549/1704)   | 32.3% (551/1707)   |        |
|  | Never   | 56.3% (959/1704)   | 57.5% (981/1707)   |        |
| Meets clinical criteria for suspected or probable COVID-19         |   | 9.4% (161/1704)    | 9.0% (154/1707)    | 0.68   |
| Tested with PCR for SARS-CoV-2                                     |   | 37.9% (645/1704)   | 38.4% (656/1707)   | 0.75   |
| Positive PCR for SARS-CoV-2  |   | 5.6% (37/645)      | 4.8% (31/656)      | 0.46   |
| Positive PCR for SARS-CoV-2 at least 2 weeks prior to serum sample |   | 5.6% (33/586)      | 4.8% (29/610)      | 0.52   |
| Hospitalised for confirmed COVID-19                                |   | 0.4% (6/1704)      | 0.2% (4/1707)      | 0.55   |
| Shielding behaviour Apr-Jul  | I remained in my house or garden  | 32.3% (550/1704)   | 34.2% (583/1706)   | 0.20   |
|  | I only left the house for exercise on my own or with members of my household                    | 38.8% (661/1704)   | 40.2% (686/1706)   |        |
|  | I encountered people from outside of my household but <i>maintained social distancing</i>       | 26.6% (454/1704)   | 23.6% (403/1706)   |        |
|  | I encountered people from outside of my household but <i>did not maintain social distancing</i> | 2.3% (39/1704)     | 2.0% (34/1706)     |        |
| Exposure to documented cases of COVID-19                           |   | 11.5% (196/1703)   | 11.0% (188/1707)   | 0.66   |
| PHQ8   |   | 4.0 (1.0 - 9.0)    | 5.0 (1.0 - 9.0)    | 0.035  |
| GAD7   |   | 3.0 (0.0 - 7.0)    | 3.0 (0.0 - 7.0)    | 0.17   |
| Income deprivation score   |   | 0.1 (0.1 - 0.2)    | 0.1 (0.1 - 0.2)    | 0.049  |
| Active disease (PRO2)  |   | 10.9% (185/1704)   | 10.4% (178/1707)   | 0.70   |
| IBD Control 8  |   | 13.0 (9.0 - 16.0)  | 13.0 (9.0 - 16.0)  | 0.40   |
| IBD Control VAS  |   | 79.0 (63.8 - 92.0) | 79.0 (62.0 - 92.0) | 0.21   |

Values shown are medians (interquartile range) and percentages (proportions) as appropriate.

**Abbreviations:** IBD = inflammatory bowel disease, 5-ASA = aminosalicylates, BMI = Body Mass Index, COVID-19 = coronavirus, PCR = polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, PHQ8 = Patient Health Questionnaire depression scale, GAD7 = General Anxiety Disorder assessment, PRO2 = Patient Reported Outcome, VAS = Visual Analogue Scale

Supplementary Appendix for 'Anti-SARS-CoV2 antibody responses are impaired in patients with inflammatory bowel disease treated with infliximab'

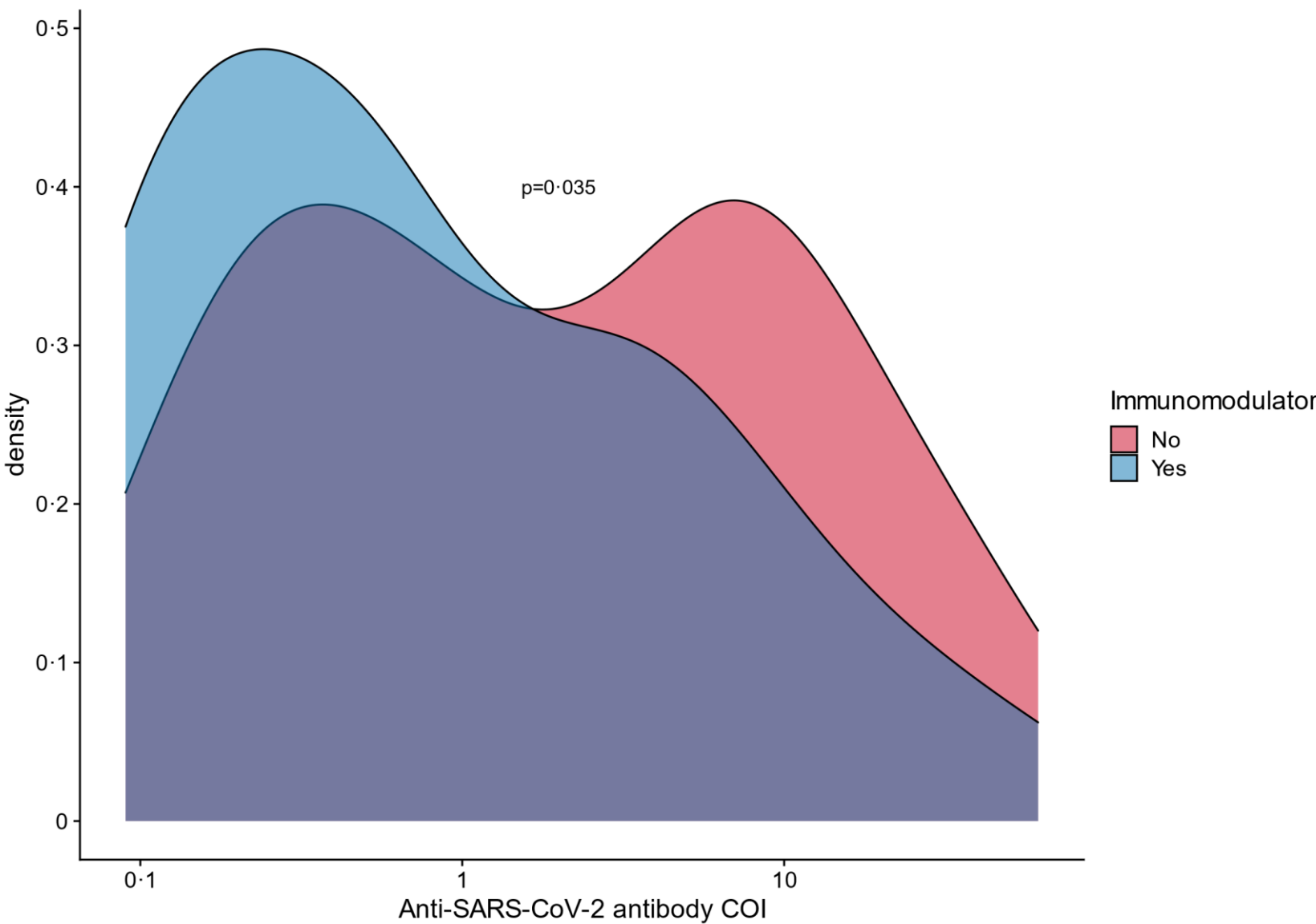
Supplementary Figure S2: Magnitude of antibody reactivity to SARS-CoV-2 in participants who had a positive PCR to SARS-CoV-2 at least two weeks earlier and positive anti-SARS-CoV-2 serology ( $\geq 1$  COI), stratified by choice of biologic



**Abbreviations:** PCR = polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, COI = Cut-Off Index

Supplementary Appendix for 'Anti-SARS-CoV2 antibody responses are impaired in patients with inflammatory bowel disease treated with infliximab'

Supplementary Figure S3: Magnitude of antibody reactivity to SARS-CoV-2 in participants treated with infliximab who had a positive PCR to SARS-CoV-2 at least two weeks earlier, stratified by immunomodulator use



Abbreviations: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, COI = Cut-Off Index; PCR = polymerase chain reaction

<https://mc.manuscriptcentral.com/gut>

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**impacT of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY**

|                     |  |
|---------------------|--|
| <b>Title</b>        | <b>Anti-SARS-CoV2 antibody responses are attenuated in patients with inflammatory bowel disease treated with infliximab</b>  |
| <b>Authors</b>      | Kennedy NA, PhD <sup>1,2*</sup> , Goodhand JR, MBBS <sup>1,2*</sup> , Bewshea C, MSc <sup>2</sup> , Nice R, MSc <sup>2,3</sup> , Chee D, MBBS <sup>1,2</sup> , Lin S, MBChB <sup>1,2</sup> , Chanchlani N, MBChB <sup>1,2</sup> , Butterworth J, MBCh <sup>4</sup> , Cooney R, DPhil <sup>5</sup> , Croft NM, PhD <sup>6,7</sup> , Hart AL, PhD <sup>8</sup> , Irving PM, MD <sup>9,10</sup> , Kok KB, PhD <sup>7,11</sup> , Lamb CA, PhD <sup>12,13</sup> , Limdi JK, MBBS <sup>14,15</sup> , Macdonald J, BM <sup>16</sup> , McGovern DPB, DPhil <sup>17</sup> , Mehta SJ, MD <sup>18</sup> , Murray CD, PhD <sup>19</sup> , Patel KV, MBBS <sup>20</sup> , Pollok RCG, PhD <sup>20,21</sup> , Raine T, PhD <sup>22</sup> , Russell RK, PhD <sup>23</sup> , Selinger CP, MD <sup>24</sup> , Smith PJ, MBBS <sup>25</sup> , Bowden J, PhD <sup>26</sup> , McDonald TJ, PhD <sup>2,3</sup> , Lees CW, PhD <sup>27,28</sup> , Sebastian S, MD <sup>29</sup> , Powell N, PhD <sup>30,31*</sup> , Ahmad T, DPhil <sup>1,2*</sup><br><br>*denotes equal contribution |
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**impacT of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY**

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impact of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY

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**impaCt of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY**

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| <b>Key words</b>                  | <p>SARS-CoV-2, immune-mediated inflammatory diseases, inflammatory bowel disease, anti-TNF therapy, vedolizumab, immunosuppressant, CLARITY</p>   |
| <b>Running title</b>              | Infliximab impairs anti-SARS-CoV-2 antibody responses   |
| <b>Word count</b>                 | <u>2917847</u> excluding abstract and summary box   |

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# impact of biologics therapy on SARS-CoV-2 Infection and Immunity CLARITY

## 3 Abstract

### 4 Objective

5 Anti-TNF drugs impair protective immunity following pneumococcal, influenza, and viral hepatitis  
6 vaccination and increase the risk of serious respiratory infections. We sought to determine whether  
7 infliximab-treated patients with inflammatory bowel disease have attenuated serological responses  
8 to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections.

### 9 Design

10 Antibody responses in participants treated with infliximab were compared to a reference cohort  
11 treated with vedolizumab, a gut-selective anti-integrin  $\alpha 4\beta 7$  monoclonal antibody that is not  
12 associated with impaired vaccine responses or increased susceptibility to systemic infections. [6935](#)  
13 [Patients](#) were recruited from 92 UK hospitals between 22nd September and 23rd December  
14 2020.

### 15 Results

16 Rates of symptomatic and proven SARS-CoV-2 infection were similar between groups.  
17 Seroprevalence was lower in infliximab- than vedolizumab-treated patients (3.4% [161/4685], vs  
18 6.0% [134/2250],  $p < 0.0001$ ). Multivariable logistic regression analyses confirmed that infliximab (vs  
19 vedolizumab; odds ratio [OR] 0.66 [95% CI 0.51-0.87],  $p = 0.0027$ ) and immunomodulator use (OR  
20 0.70 [95% CI 0.53-0.92],  $p = 0.012$ ) were independently associated with lower seropositivity. In  
21 patients with confirmed SARS-CoV-2 infection seroconversion was observed in fewer infliximab- than  
22 vedolizumab-treated patients (48% [39/81], vs 83% [30/36],  $p = 0.00044$ ) and the magnitude of anti-  
23 SARS-CoV2 reactivity was lower (median 0.8 COI [0.2-5.6] vs 37.0 [15.2-76.1],  $p < 0.0001$ ).

**impact of biologic therapy on SARS-CoV-2 Infection and immunity CLARITY**24 *Conclusions*

25 Infliximab is associated with attenuated serological responses to SARS-CoV-2 that were further  
26 blunted by concomitant immunomodulators used as concomitant therapy. Impaired serological  
27 responses to SARS-CoV-2 infection have ~~may~~ might have important implications for global public  
28 health policy and individual anti-TNF treated patients. Serological testing and virus surveillance  
29 should be considered to detect suboptimal vaccine responses, persistent infection, and viral  
30 evolution to inform public health policy.

**impact of biologics therapy on SARS-CoV-2 Infection and Immunity CLARITY**

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**Summary Box**

1. What is already known about this subject?

- Anti-tumour necrosis factor (TNF) drugs are effective treatments for immune-mediated inflammatory diseases (IMIDs), however, by suppressing immune responses, they impair vaccine effectiveness and increase susceptibility to serious infection.

- In the early phase of the COVID-19 pandemic, patients with IMIDs treated with anti-TNF drugs were subject to the most restrictive public health measures

- Registry studies have not reported an increased risk of adverse outcomes from SARS-CoV-2 in patients treated with anti-TNF therapies. However, the impact of these therapies on serological responses and subsequent immunity to SARS-CoV-2 infection remains unknown

2. What are the new findings?

- Rates of symptomatic and proven SARS-CoV-2 infection were similar between infliximab- and vedolizumab-treated patients with inflammatory bowel disease.

- Seroprevalence, seroconversion, and the magnitude of anti-SARS-CoV-2 antibody reactivity was significantly attenuated in infliximab- compared with vedolizumab-treated patients.

- Concomitant immunomodulator use with a thiopurine or methotrexate further blunted serological responses to SARS-CoV-2 infection in infliximab-treated patients, with only a third of patients having detectable anti-SARS-CoV-2 antibodies.

3. How might it impact on clinical practice in the foreseeable future?

**impact of bioLogic therapy on SARS-cov-2 Infection and immunity CLARITY**

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5 52       • For the individual anti-TNF treated patient, lower rates of seroconversion and reduced anti-  
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7 53       SARS-CoV-2 antibody reactivity levels may ultimately increase their susceptibility to  
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9 54       recurrent COVID-19  
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11 55       • Impaired serological responses might lead to chronic nasopharyngeal colonisation which  
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13 56       may act as a reservoir to drive persistent transmission and the evolution of new SARS-CoV-2  
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15 57       variants.  
16  
17 58       • Serological testing and virus surveillance should be considered to detect suboptimal vaccine  
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19 59       responses, persistent infection, and viral evolution to inform public health policy.  
20  
21 60       • If attenuated serological responses following vaccination are also observed, then modified  
22  
23 61       immunisation strategies will need to be designed for millions of patients worldwide.  
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## impact of biologic therapy on SARS-CoV-2 Infection and immunity CLARITY

### 63 Introduction

64 Induction of protective immunity following SARS-CoV-2 (severe acute respiratory syndrome  
65 coronavirus 2) infection and/or vaccination is critical to suppress transmission. By suppressing  
66 immune responses, biologic and immunosuppression therapies may lead to chronic SARS-CoV-2  
67 infection and have recently been implicated in the evolution and emergence of novel variants.<sup>1-3</sup>

68 Immune-mediated inflammatory diseases (IMIDs) including inflammatory bowel disease (IBD), the  
69 inflammatory arthritides, and psoriasis affect about 3-7 % of Western populations.<sup>4,5</sup> Drugs targeting  
70 tumour necrosis factor (TNF) are the most frequently prescribed biologics used in the treatment of  
71 IMIDs with over 2 million patients receiving treatment worldwide.<sup>6</sup> However, anti-TNF drugs impair  
72 protective immunity following pneumococcal,<sup>7</sup> influenza,<sup>8</sup> and viral hepatitis<sup>9</sup> vaccinations and  
73 increase the risk of serious infection, most notably with respiratory pathogens.<sup>10</sup> Consequently, in  
74 the early phase of the COVID-19 pandemic, patients with IMIDs treated with anti-TNF drugs were  
75 subject to the most restrictive public health measures.<sup>11</sup> Data from disease-specific registries are  
76 reassuring, however, citing similar rates and risk factors for SARS-CoV-2 infection, hospitalisation,  
77 and outcomes to background populations.<sup>12-14</sup> Whether anti-TNF drugs impair serological responses  
78 and subsequent immunity to SARS-CoV-2 infection is unknown.

79 We hypothesised that anti-SARS-CoV2 antibody responses would be impaired following SARS-CoV-2  
80 infection in patients with IBD treated with infliximab, a commonly prescribed anti-TNF drug. To test  
81 this hypothesis, we compared antibody responses in patients with IBD treated with infliximab, to a  
82 reference cohort treated with vedolizumab. Vedolizumab is a gut-selective anti-integrin  $\alpha4\beta7$   
83 monoclonal antibody, administered in hospital with the same dosing schedule as infliximab and is  
84 not associated with increased susceptibility to systemic infection or attenuated serological  
85 responses to vaccination.<sup>15</sup>

**impaCt of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY****Objectives**

We aimed to define, in patients with IBD, whether biologic class, concomitant use of an immunomodulator, and/or social distancing measures impact:

- i) seroprevalence of SARS-CoV-2.
- ii) subsequent seroconversion in patients with infection confirmed by prior polymerase chain reaction (PCR) testing.
- iii) magnitude of anti-SARS-Cov-2 reactivity.



## impact of biologics therapy on SARS-CoV-2 Infection and Immunity CLARITY

### 94 **Methods**

#### 95 **Patient and Settings**

96 CLARITY IBD is a UK wide, multicentre, prospective observational cohort study investigating the  
97 impact of infliximab and vedolizumab and/or concomitant immunomodulators (thiopurines or  
98 methotrexate) on SARS-CoV-2 acquisition, illness, and immunity in patients with IBD.

99 Consecutive patients were recruited at the time of attendance at infusion units from 92 National  
100 Health Service (NHS) hospitals across the UK ([See Supplementary Table S1pp 2-7](#)) between 22<sup>nd</sup>  
101 September 2020 and 23<sup>rd</sup> December 2020.

102 The eligibility criteria were:

- 103 i) age 5 years and over
- 104 ii) diagnosis of inflammatory bowel disease
- 105 iii) current treatment with infliximab or vedolizumab for 6 weeks or more, with a dose of drug  
106 received in the past 16 weeks

107 Patients were excluded if they had participated in a SARS-CoV-2 vaccine trial.

108 [Here we report the seroprevalence of anti-SARS-CoV-2 antibodies at entry to the CLARITY IBD study.](#)

#### 109 **Outcome Measures**

110 The primary outcome was the proportion of participants with a positive anti-SARS-CoV-2 antibody  
111 test. Secondary outcomes were the proportion of participants with a positive anti-SARS-CoV-2  
112 antibody following a positive PCR test to SARS-CoV-2 and the magnitude of the anti-SARS-CoV-2  
113 antibody reactivity.

**impacT of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY****114 Variables**

115 Variables recorded by participants included demographics (age, sex, ethnicity, comorbidities, height  
116 and weight, smoking status, and postcode), IBD disease activity (PRO2),<sup>16,17</sup> IBD-related quality of life  
117 (IBD Control),<sup>18</sup> mental well-being (PHQ-8<sup>19</sup> and GAD-7<sup>20</sup>), SARS-CoV-2 outcomes aligned to the  
118 COVID-19 symptoms study<sup>21</sup> (symptoms, previous testing, and hospital admissions for COVID-19)  
119 and social-distancing behaviour during the lockdown periods. During lockdown, the population of  
120 the UK were instructed to adhere to restrictions on social and professional activities with specific  
121 advice to vulnerable groups to undertake more extreme social exclusion measures referred to as  
122 shielding.<sup>11</sup>

123 Study sites completed data relating to IBD history (age at diagnosis, disease duration, and phenotype  
124 according to the Montreal classifications,<sup>22</sup> previous surgeries, and duration of current biologic and  
125 immunomodulator therapy).

126 Wherever possible, data were entered electronically into a purpose-designed REDCap database  
127 hosted at the Royal Devon and Exeter NHS Foundation Trust.<sup>23</sup> At sites without access to electronic  
128 devices or the internet, participants completed their questionnaires on paper case record forms that  
129 were subsequently entered by local research teams.

**130 Case definition**

131 Cases were defined according to the recently published World Health Organisation (WHO)  
132 framework.<sup>24</sup> In brief, this framework uses symptoms and the results of nucleic acid amplification  
133 testing to determine whether patients are suspected, probable, or confirmed cases of COVID-19.  
134 Participants who reported fever and cough, or anosmia/ageusia, or any three or more of the  
135 following symptoms: fever, cough, general weakness/fatigue, myalgia, sore throat, coryza,  
136 dyspnoea, and altered mental status were considered suspected/probable COVID-19 cases. We

**impact of bioLogic therapy on SARS-CoV-2 Infection and immunity CLARITY**

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5 137 omitted the gastrointestinal symptoms because patients with active IBD may suffer anorexia,  
6  
7 138 nausea, vomiting, and diarrhoea. We linked our data by NHS number or Community Health Index to  
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9 139 Public Health England, Scotland, and Wales who archive dates and results of all SARS-CoV-2 PCR  
10  
11 140 tests undertaken in the UK. Confirmed cases were those participants with a positive PCR test to SARS  
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13  
14 141 CoV-2.

**142 Laboratory methods**

143 Laboratory analyses were performed at the Academic Department of Blood Sciences at the Royal  
144 Devon and Exeter NHS Foundation Trust. We used the Roche Elecsys Anti-SARS-CoV-2 immunoassay  
145 to detect antibodies to SARS-CoV-2 in serum samples.<sup>25</sup> This sandwich electrochemiluminescence  
146 immunoassay uses a recombinant protein of the nucleocapsid antigen for the determination of  
147 antibodies against SARS-CoV-2. The electrochemiluminescence signal from a negative and positive  
148 calibrator are assigned a value of 0.8 and 1.2, respectively, and a cut-off is set at a signal equivalent  
149 to 1. The electrochemiluminescence signal from the reaction product of the sample is compared to  
150 the cut-off signal and expressed as positive when  $\geq 1.0$  or negative when  $< 1$ , as well as quantitatively  
151 in the form of a Cut-Off Index (COI: calculated by sample signal/cut-off signal).

152 In house assay validation experiments demonstrated the intra- and inter-assay coefficient of  
153 variation were 2.2 and 7.0%, respectively. No effect was observed on recovery of anti-SARS-CoV-2  
154 antibodies following four freeze/thaw cycles. SARS-CoV-2 antibodies were stable in uncentrifuged  
155 blood and serum at ambient temperature for up to seven days permitting postal transport from  
156 research sites to the central laboratory. No analytical interference was observed for the detection of  
157 anti-SARS-CoV-2 with infliximab or vedolizumab up to 10,000 mg/L and 60,000 mg/L, respectively, or  
158 with anti-drug antibodies to infliximab or vedolizumab up to 400 AU/mL and 38 AU/mL respectively.

**impacT of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY****159 Study size**

160 Limited data are available regarding the risk of SARS-CoV-2 in patients with IBD to inform sample size  
161 calculations.

162 The following assumptions were made to determine our sample size

- 163 • Proportion of patients treated with each drug(s): vedolizumab: 30% (20% with concomitant  
164 immunomodulator), infliximab: 70% (60% with concomitant immunomodulator)
- 165 • Seroprevalence of SARS-CoV-2 in the background population: 0.05
- 166 • Odds ratio for SARS-CoV-2 seropositivity with immunomodulator use: 0.8
- 167 • Odds ratio SARS-CoV-2 seropositivity for infliximab versus vedolizumab:  $\leq 0.7$ .
- 168 • Attrition rate: 20%

169 We calculated that a sample size of 6970 patients would provide 80% power for the comparison of  
170 infliximab versus vedolizumab, controlling for immunosuppressant status in a multivariable logistic  
171 regression model at the 0.05 significance level.

**172 Ethical consideration and roles of funders**

173 CLARITY IBD is an investigator-led, UK National Institute for Health Research COVID-19 urgent public  
174 health study, funded by the Royal Devon and Exeter NHS Foundation Trust, Hull University Teaching  
175 Hospital NHS Trust, and by unrestricted educational grants from F. Hoffmann-La Roche AG  
176 (Switzerland), Biogen Inc (USA), Celltrion Healthcare (South Korea), and Galapagos NV (Belgium).

177 None of our funding bodies had any role in study design, data collection or analysis, writing or  
178 decision to submit for publication. The Surrey Borders Research Ethics committee approved the  
179 study (REC reference: REC 20/HRA/3114) in September 2020. Patients were included after providing  
180 informed, written consent. The sponsor was the Royal Devon and Exeter NHS Foundation Trust. The

**impacT of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY**

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5 181 protocol is available online at <https://www.clarityibd.org>. The study was registered with the ISRCTN  
6  
7 182 registry, ISRCTN45176516.  
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**10 183 Statistics**

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12 184 Statistical analyses were undertaken in R 4.0.3 (R Foundation for Statistical Computing, Vienna,  
13  
14 185 Austria). All tests were two tailed and p-values <0.05 were considered significant. We included  
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16 186 participants in the primary analysis if they had completed the patient questionnaire and had an anti-  
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18 187 SARS-CoV-2 serology result. We included patients with missing clinical data in analyses for which  
19  
20 188 they had data and have specified the denominator for each variable. Continuous data were reported  
21  
22 189 as median and interquartile range, and discrete data as numbers and percentages, unless otherwise  
23  
24 190 stated. We used patients' postcodes to assign them to one of the ten UK administrative regions and  
25  
26 191 present seroprevalence rates mapped to these regions. We also used postcodes to derive  
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28 192 participants' income and employment deprivation scores using combined English and Welsh data  
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30 193 from 2019<sup>26</sup> and Scottish data from 2020.<sup>27</sup> Univariable analyses, using Fisher's exact and Mann-  
31  
32 194 Whitney U tests were used to identify demographic, disease, and treatment related factors  
33  
34 195 associated with SARS-CoV-2 seropositivity. A priori, we included age, sex, ethnicity, region, income  
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36 196 deprivation score, comorbidity, body mass index, and social distancing measures that are known to  
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38 197 affect SARS-CoV-2 acquisition and COVID-19 outcomes<sup>28</sup> alongside IBD diagnosis, biologic  
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40 198 medication, immunomodulator, and 5-aminosalicylate (5-ASA) use. We used multivariable logistic  
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42 199 regression models to identify factors independently associated with seropositivity.  
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49 200 We undertook Fisher's exact and Mann-Whitney U tests to compare the rates of, and time to,  
50  
51 201 seroconversion in infliximab- and vedolizumab-treated patients with confirmed COVID-19, and to  
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53 202 identify factors associated with failure of seroconversion in infliximab-treated patients. We explored  
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55 203 the magnitude of antibody reactivity using density plots, stratified by drug exposure among  
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## impacT of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY

204 participants with a positive PCR to anti-SARS-CoV-2 at least two weeks prior to measurement of  
205 serology.

206 We conducted sensitivity analyses using propensity matching to account for significant differences in  
207 baseline variables between infliximab- and vedolizumab-treated patients using the MatchIt  
208 package.<sup>29</sup> Patients were matched exactly on diagnosis, immunomodulator use, and cancer and then  
209 using optimal matching, on age, comorbidities, ethnicity, and presence of active disease.

### 210 Results

#### 211 *Patient characteristics*

212 Between September 22<sup>nd</sup> 2020 and December 23<sup>rd</sup> 2020, 7226 patients were recruited from 92 UK  
213 hospitals. Serum samples and completed questionnaires were available in 96.0% (6935/7226)  
214 patients. Of these, 67.6% (4685/6935) were treated with infliximab and 32.4% (2250/6935) were  
215 treated with vedolizumab. Participant characteristics are shown in **Table 1**.

216 Adherence to social distancing measures during the UK lockdown period between April and July  
217 2020, and exposure to COVID-19 cases was similar between infliximab and vedolizumab treated  
218 patients (**Table 1**). Fewer infliximab-treated patients were tested by PCR for SARS-CoV-2 (36.5%  
219 [1712/4685], vs 39.0% [877/2250],  $p=0.050$ ). There were no differences between the proportions of  
220 infliximab- and vedolizumab-treated patients who: reported symptoms of suspected or probable  
221 COVID-19 (8.3% [389/4685], vs 8.9% [201/2250],  $p=0.38$ ); tested positive by PCR for SARS-CoV-2  
222 (5.2% [89/1712], vs 4.3% [38/877],  $p=0.39$ ); or were hospitalised with confirmed COVID-19 (0.2%  
223 [8/4685], vs 0.2% [5/2250],  $p=0.77$ ).

**impacT of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY****224 Seroprevalence of anti-SARS-CoV-2 antibodies in anti-TNF and vedolizumab treated patients**

225 Overall, the seroprevalence of anti-SARS-CoV-2 antibodies was 4.3% (295/6935, 95% CI 3.8% - 4.8%).

226 The proportion of patients with a positive anti-SARS-CoV-2 antibody test was lower in infliximab-

227 than vedolizumab-treated patients (3.4% [161/4685], vs 6.0% [134/2250],  $p < 0.0001$ ) (**Table 2**).

228 Seropositivity was also associated with younger age, non-white ethnicity, UK region, higher income

229 deprivation score, having never smoked, ulcerative colitis, no concomitant immunomodulator use,

230 recent steroid use, exposure to confirmed cases of COVID-19, reported symptoms of suspected or

231 probable COVID-19, and social distancing measures during the UK government's lockdown period

232 (**Table 2 and 3, See Supplementary Figure S1pp-9**).

233 Multivariable logistic regression analyses confirmed that infliximab (vs vedolizumab; odds ratio [OR]

234 0.66 [95% CI 0.51 - 0.87],  $p = 0.0027$ ) and immunomodulator use (OR 0.70 [95% CI 0.53 - 0.92],

235  $p = 0.012$ ) were independently associated with lower seropositivity (**Figure 1**). Conversely, non-white

236 ethnicity, several UK regions, higher income deprivation score, and nonadherence to social

237 distancing measures were independently associated with an increased risk of SARS-CoV-2

238 seropositivity. There was no significant interaction between the effect of infliximab (vs vedolizumab)

239 and immunomodulator use (OR for interaction term 1.03 [95% CI 0.57 - 1.92],  $p = 0.92$ ). In our

240 propensity matched analysis, we confirmed lower seroprevalence in infliximab- compared to

241 vedolizumab-treated patients 3.9% (67/1704), vs 6.2% (105/1707)  $p = 0.0037$  (**See Supplementary**

242 **Table S2pp-8**).

**243 Seroconversion in patients with confirmed SARS-CoV-2 infection**

244 Sensitivity analyses in participants with confirmed SARS-CoV-2 infection demonstrated that fewer

245 infliximab- than vedolizumab-treated patients had seroconverted (48% [39/81], vs 83% [30/36],

246  $p = 0.00044$ ). The magnitude of anti-SARS-Cov2 reactivity was lower in patients with previous PCR

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5 247 confirmed SARS-CoV-2 infection treated with infliximab than with vedolizumab (median 0.8 COI [0.2  
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7 248 - 5.6] vs 37.0 [15.2 - 76.1],  $p < 0.0001$ ; **Figure 2**). This difference was also seen restricting our analyses  
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9 249 to participants whose antibody reactivity results were above the threshold (1 COI) for seropositivity  
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11 250 ( $p < 0.0001$ ; [See Supplementary Figure S2pp-10](#)).

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14 251 Failure of seroconversion was associated with concomitant immunomodulator use. In patients  
15  
16 252 treated with infliximab alone, the seroconversion rate was 60% (24/40) and in patients treated with  
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18 253 infliximab and immunomodulator combination therapy, the rate was 37% (15/41,  $p = 0.046$ ). There  
19  
20 254 was also a significant difference in the magnitude of anti-SARS-Cov2 reactivity ( $p = 0.035$ ; [See](#)  
21  
22 255 [Supplementary Figure S3pp-11](#)). The median interval from a positive PCR test to serological testing  
23  
24 256 at recruitment in infliximab-treated patients was 32 days [IQR 20 – 54] and for vedolizumab-treated  
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26 257 patients was 40 days [IQR 24 - 83] ( $p = 0.082$ ). An increase in anti-SARS-Cov2 antibody reactivity was  
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28 258 observed four weeks after a ~~first~~ positive PCR test, ~~compared to within four weeks~~, in vedolizumab-  
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30 259 ~~treated patients~~ (47.2 COI [IQR 24.1 - 113.0] vs 14.5 COI [IQR 0.4 – 30.7],  $p = 0.0079$ ), ~~which; this was~~  
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32 260 ~~but~~ not ~~seen in~~ infliximab-treated patients (0.7 COI [IQR 0.2 - 7.5] vs 1.1 COI [IQR 0.4 - 4.5],  $p = 0.70$ )  
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34 261 (**Figure 3**).

**Discussion**

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42 263 We have shown that infliximab-treated patients have attenuated serological responses to SARS-CoV-  
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44 264 2 infection with lower seroprevalence, seroconversion and antibody reactivity. Despite similar rates  
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46 265 of symptomatic and proven SARS-CoV-2 infection, the seroprevalence, seroconversion, and the  
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48 266 magnitude of anti-SARS-CoV-2 antibody reactivity were impaired in infliximab-compared with  
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50 267 vedolizumab-treated patients. Similar rates of symptomatic and proven SARS-CoV-2 infection  
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52 268 between infliximab- and vedolizumab-treated patients suggest that our findings cannot be  
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54 269 explained by differences in acquisition or severity of infection alone. Rather, infliximab seems to be  
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**impacT of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY**

270 directly influencing the serological response to infection. Concomitant immunomodulator use with a  
271 thiopurine or methotrexate further blunted serological responses to both drugs with fewer than half  
272 of patients (37%) having detectable anti-SARS-CoV-2 antibodies after a median of 5.4 weeks  
273 following PCR confirmed infection.

274 Infliximab may directly impede the immune mechanisms responsible for generating antibody  
275 responses. This is biologically plausible, since the pro-inflammatory actions of TNF include  
276 stimulation of B-cell immunoglobulin synthesis, induction of germinal centre formation, co-  
277 stimulation of antigen-activated T-cells and maturation of antigen presenting cells.<sup>30-32</sup>

278 Impaired serological responses to SARS-CoV-2 infection have important implications for global public  
279 health policy and individual anti-TNF treated patients. From a public health perspective, impaired  
280 serological responses might lead to chronic nasopharyngeal colonisation which may act as a  
281 reservoir to drive persistent transmission and the evolution of new SARS-CoV-2 variants.<sup>2</sup> Virus  
282 surveillance will define if persistent infection and viral evolution occurs in this patient group.<sup>3</sup>

283 For the individual anti-TNF treated patient, lower rates of seroconversion and reduced anti-SARS-  
284 CoV-2 antibody reactivity levels may ultimately increase their susceptibility to recurrent COVID-19.

285 Accepting that vaccination is critical to suppress transmission, serology testing should be considered  
286 to detect suboptimal vaccine responses to inform the need for the most restrictive social distancing  
287 measures to protect patients and public health. If attenuated serological responses following  
288 vaccination are observed, then modified vaccination schedules given in combination, might need to  
289 be considered in these patients.

290 Any negative impact on seroconversion following infection or vaccination needs to be balanced  
291 against theoretical benefits for the individual patient of reducing the excessive cytokine production

**impact of biologics therapy on SARS-CoV-2 Infection and Immunity CLARITY**

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5 292 that characterises severe COVID-19 disease. Indeed, this is the rationale behind the proposals for  
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7 293 trials of anti-TNF therapy in severe COVID-19 (ISRCTN40580903, ISRCTN33260034).<sup>33</sup>  
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10 294 Our study has other important findings. We have identified associations of SARS-CoV-2 seropositivity  
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12 295 with non-white ancestry and nonadherence to social-distancing guidance. These findings are  
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14 296 consistent with observations reported in general non-immunosuppressed populations.<sup>28</sup> The  
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16 297 mechanisms underlying these associations are complex and multi-factorial and likely include multi-  
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18 298 generational living, at-risk employment, inability to work from home, socioeconomic deprivation,  
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20 299 and religious congregation.  
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24 300 The region specific seroprevalence rates for vedolizumab-treated patients are consistent with those  
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26 301 reported in the general UK population. Whilst direct comparisons to other datasets are limited,  
27  
28 302 confounded in part by differences in the time of testing during the pandemic and the diagnostic  
29  
30 303 accuracies of the anti-SARS-CoV-2 assays used, this adds to the evidence that patients with IBD are  
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32 304 at a similar risk of SARS-CoV-2 infection as the general population.<sup>34</sup>  
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36 305 The main strength of this study was our recruitment of over 7,000 consecutive patients within a  
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38 306 narrow window mitigating against the potential for time during the pandemic course to be a  
39  
40 307 significant co-variate. Other strengths include comprehensive electronic collection of patient-  
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42 308 reported outcomes, linkage with SARS-CoV-2 public health testing data, case ascertainment aligned  
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44 309 with the WHO criteria, inclusion of social distancing behaviours, and the use of a sensitive and  
45  
46 310 specific serological assay.<sup>35</sup>  
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**311 Limitations**

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53 312 We acknowledge, however, the following limitations. Firstly, it is not known whether attenuated  
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55 313 immune responses in infliximab-treated patients translates into increased risk of infection.  
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57 314 Moreover, we only assessed humoral responses to infection, and it is likely that protective immunity  
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5 315 additionally requires induction of memory T-cell responses. Secondly, our patient reported data are  
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7 316 subject to recall bias which may have underestimated the prevalence of possible COVID-19  
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9 317 symptoms. Thirdly, the only anti-TNF drug investigated in this study was infliximab. However, we  
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11 318 suspect that our key findings apply to other anti-TNF monoclonal antibodies used to treat IMiDs,  
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13 319 including adalimumab, certolizumab, and golimumab.  
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**320 Conclusions**

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20 321 In summary, infliximab therapy ~~results in substantial attenuation of~~ is associated with attenuated  
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22 322 serological responses to SARS-CoV-2 infection. Poor antibody responses in infliximab-treated  
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24 323 patients were observed despite similar rates of symptomatic and proven SARS-CoV-2 infection as  
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26 324 vedolizumab-treated patients. Anti-SARS-CoV2 antibody responses were further attenuated in  
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28 325 infliximab recipients concomitantly treated with immunomodulators, including thiopurines and  
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30 326 methotrexate.  
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34 327 Impaired serological responses to SARS-CoV-2 infection ~~have~~ might ~~have~~ important implications  
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36 328 for global public health policy and millions of anti-TNF treated patients. Serological testing and virus  
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38 329 surveillance should be considered to detect suboptimal vaccine responses, persistent infection, and  
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40 330 viral evolution to inform public health policy.  
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**impacT of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY****Figure Captions**

332 **Figure Captions**  
333 *Figure 1: Forest plot showing the coefficients from a multivariable logistic regression model of*  
334 *associations with a positive anti-SARS-CoV-2 antibody. Abbreviations: 5-ASA = aminosalicylates, UC =*  
335 *ulcerative colitis, IBDU = inflammatory bowel disease unclassified.*

336 *Figure 2: Density plot of the magnitude of anti-SARS-CoV-2 antibody reactivity stratified by biologic*  
337 *amongst participants who had a positive PCR to anti-SARS-CoV-2 at least two weeks prior to their*  
338 *serology sample. Abbreviations: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, PCR*  
339 *= polymerase chain reaction, COI = Cut-Off Index.*

340 *Figure 3: Boxplot of the magnitude of anti-SARS-CoV-2 antibody reactivity stratified by biologic and*  
341 *time since prior positive PCR test. Abbreviations: SARS-CoV-2 = severe acute respiratory syndrome*  
342 *coronavirus 2, PCR = polymerase chain reaction, COI = Cut-Off Index.*

343

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**impacT of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY****345 Contributions**

346 NAK, JRG, CB, SS, NP, TA participated in the conception and design of this study. CB was the project  
347 manager and coordinated patient recruitment. RN and TJM coordinated all biochemical analyses and  
348 central laboratory aspects of the project. NAK, JRG, DC, SL, NC, JB, RC, NMC, ALH, PMI, KBK, CAL, JKL,  
349 JM, DPM, SJM, CDM, KVP, RCP, TR, RKR, CPS, PJS, JB, TJM, CWL, SS, NP, TA were involved in the  
350 acquisition, analysis, or interpretation of data. Data analysis was done by NAK. Drafting of the  
351 manuscript was done by NAK, JRG, DC, SL, NC, TR, CWL, SS, NP, TA, SS and TA obtained the funding  
352 for the study. All the authors contributed to the critical review and final approval of the manuscript.  
353 NAK and TA have verified the underlying data.

**354 Declarations of interest**

355 Dr. Kennedy reports grants from F. Hoffmann-La Roche AG, grants from Biogen Inc, grants from  
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456 We conducted an electronic survey to gauge the opinion of patients with IBD on the patient  
457 questionnaires to be delivered as part of the CLARITY IBD study. We surveyed 250 patients across 74  
458 hospitals. All our proposed questions for study inclusion were rated as important or very important  
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460 study questionnaire, reviewed the study protocol, supported the writing of the patient information  
461 sheet, and participated in testing of electronic consent form and patient questionnaire. A member of

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5 462 the Exeter IBD Patient Panel sits on the study management committee, ensuring patient  
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7 463 involvement in all aspects of study delivery, data analysis and dissemination of findings.  
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**464 Data sharing**

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13 465 The study protocol including the statistical analysis plan is available at [www.clarityibd.org](http://www.clarityibd.org). Individual  
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15 466 participant de-identified data that underlie the results reported in this article will be available  
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17 467 immediately after publication for a period of 5 years. The data will be made available to investigators  
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19 468 whose proposed use of the data has been approved by an independent review committee. Analyses  
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21  
22 469 will be restricted to the aims in the approved proposal. Proposals should be directed to  
23  
24 470 tariq.ahmad1@nhs.net; to gain access data requestors will need to sign a data access agreement.  
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6 **Table 1: Baseline characteristics stratified by biologic**

| Variable                        | Infliximab         | Vedolizumab        | Overall            | p       |                 |
|---------------------------------|--------------------|--------------------|--------------------|---------|-----------------|
| Age (years)                     | 37.1 (27.2 - 50.6) | 43.8 (31.9 - 58.6) | 39.0 (28.7 - 53.2) | <0.0001 |                 |
| Sex                             | Female             | 45.5% (2134/4685)  | 46.4% (3221/6935)  | 0.089   |                 |
|                                 | Male               | 54.3% (2546/4685)  | 53.4% (3705/6935)  |         |                 |
|                                 | Intersex           | 0.0% (1/4685)      | 0.0% (1/2250)      |         | 0.0% (2/6935)   |
|                                 | Prefer not to say  | 0.1% (4/4685)      | 0.1% (3/2250)      |         | 0.1% (7/6935)   |
| Ethnicity                       | White              | 88.5% (4143/4683)  | 88.4% (6124/6930)  | 0.20    |                 |
|                                 | Asian              | 6.6% (308/4683)    | 7.6% (171/2247)    |         | 6.9% (479/6930) |
|                                 | Mixed              | 2.2% (104/4683)    | 2.3% (51/2247)     |         | 2.2% (155/6930) |
|                                 | Black              | 1.8% (82/4683)     | 1.2% (27/2247)     |         | 1.6% (109/6930) |
|                                 | Other              | 1.0% (46/4683)     | 0.8% (17/2247)     |         | 0.9% (63/6930)  |
| Diagnosis                       | Crohn's disease    | 66.6% (3121/4685)  | 56.9% (3949/6935)  | 0.00050 |                 |
|                                 | Ulcerative colitis | 31.1% (1457/4685)  | 40.5% (2810/6935)  |         |                 |
|                                 | IBD-unclassified   | 2.3% (107/4685)    | 3.1% (69/2250)     |         | 2.5% (176/6935) |
| Duration of IBD (years)         | 7.0 (3.0 - 15.0)   | 9.0 (4.0 - 16.0)   | 8.0 (3.0 - 15.0)   | <0.0001 |                 |
| Age at IBD diagnosis (years)    | 26.3 (18.9 - 37.5) | 30.4 (21.6 - 44.1) | 27.6 (19.8 - 39.8) | <0.0001 |                 |
| Immunomodulators at recruitment | 56.3% (2639/4685)  | 18.8% (424/2250)   | 44.2% (3063/6935)  | <0.0001 |                 |
| 5-ASA at recruitment            | 22.2% (1039/4685)  | 35.2% (791/2250)   | 26.4% (1830/6935)  | <0.0001 |                 |
| Steroids in 2020                | 14.2% (664/4685)   | 21.9% (492/2250)   | 16.7% (1156/6935)  | <0.0001 |                 |
| BMI                             | 24.4 (21.5 - 28.1) | 24.9 (22.0 - 28.4) | 24.5 (21.7 - 28.2) | 0.044   |                 |
| Heart disease                   | 2.1% (97/4685)     | 5.0% (113/2250)    | 3.0% (210/6935)    | <0.0001 |                 |
| Diabetes                        | 3.4% (158/4685)    | 6.8% (154/2250)    | 4.5% (312/6935)    | <0.0001 |                 |
| Lung disease                    | 12.6% (588/4685)   | 16.7% (375/2250)   | 13.9% (963/6935)   | <0.0001 |                 |
| Kidney disease                  | 0.9% (42/4685)     | 2.1% (47/2250)     | 1.3% (89/6935)     | <0.0001 |                 |

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impaCt of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY

|  |   |                   |                   |                   |         |
|--|---|-------------------|-------------------|-------------------|---------|
| Cancer   |   | 0.2% (11/4685)    | 1.7% (39/2250)    | 0.7% (50/6935)    | <0.0001 |
| Smoker   | Yes   | 11.5% (538/4684)  | 9.2% (206/2249)   | 10.7% (744/6933)  | 0.00050 |
|  | Not currently   | 28.5% (1333/4684) | 34.4% (773/2249)  | 30.4% (2106/6933) |         |
|  | Never   | 60.1% (2813/4684) | 56.5% (1270/2249) | 58.9% (4083/6933) |         |
| Meets clinical criteria for suspected or probable COVID-19         |   | 8.3% (389/4685)   | 8.9% (201/2250)   | 8.5% (590/6935)   | 0.38    |
| Tested with PCR for SARS-CoV-2                                     |   | 36.5% (1712/4685) | 39.0% (877/2250)  | 37.3% (2589/6935) | 0.050   |
| Positive PCR for SARS-CoV-2  |   | 5.2% (89/1712)    | 4.3% (38/877)     | 4.9% (127/2589)   | 0.39    |
| Positive PCR for SARS-CoV-2 at least 2 weeks prior to serum sample |   | 5.3% (81/1537)    | 4.4% (36/809)     | 5.0% (117/2346)   | 0.43    |
| Hospitalised for confirmed COVID-19                                |   | 0.2% (8/4685)     | 0.2% (5/2250)     | 0.2% (13/6935)    | 0.77    |
| Shielding behaviour Apr-Jul  | I remained in my house or garden  | 35.2% (1647/4681) | 33.3% (749/2248)  | 34.6% (2396/6929) | 0.41    |
|  | I only left the house for exercise on my own or with members of my household                    | 38.5% (1804/4681) | 39.9% (897/2248)  | 39.0% (2701/6929) |         |
|  | I encountered people from outside of my household but <i>maintained social distancing</i>       | 24.4% (1142/4681) | 24.6% (554/2248)  | 24.5% (1696/6929) |         |
|  | I encountered people from outside of my household but <i>did not maintain social distancing</i> | 1.9% (88/4681)    | 2.1% (48/2248)    | 2.0% (136/6929)   |         |
| Exposure to documented cases of COVID-19                           |   | 11.4% (533/4683)  | 10.7% (240/2250)  | 11.1% (773/6933)  | 0.39    |
| PHQ8   |   | 4.0 (1.0 - 8.0)   | 5.0 (1.0 - 9.0)   | 4.0 (1.0 - 9.0)   | 0.018   |
| GAD7   |   | 3.0 (0.0 - 7.0)   | 3.0 (0.0 - 7.0)   | 3.0 (0.0 - 7.0)   | 0.12    |

impact of biologics therapy on SARS-cov-2 infection and immunity CLARITY

|                          |                       |                       |                      |         |
|--------------------------|-----------------------|-----------------------|----------------------|---------|
| Income deprivation score | 0.099 (0.057 - 0.168) | 0.095 (0.056 - 0.160) | 0.097 (0.57 - 0.165) | 0.24    |
| Active disease (PRO2)    | 6.7% (303/4534)       | 12.6% (272/2166)      | 8.6% (575/6700)      | <0.0001 |
| IBD Control 8            | 13.0 (10.0 - 16.0)    | 13.0 (9.0 - 16.0)     | 13.0 (9.0 - 16.0)    | 0.024   |
| IBD Control VAS          | 80.0 (66.0 - 93.0)    | 79.0 (61.0 - 91.0)    | 80.0 (65.0 - 92.0)   | 0.00022 |

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586 Values shown are medians (interquartile range) and percentages (proportions) as appropriate. **Abbreviations:** IBD = inflammatory bowel disease, 5-  
587 ASA = aminosalicylates, BMI = Body Mass Index, COVID-19 = coronavirus, PCR = polymerase chain reaction, SARS-CoV-2 = severe acute respiratory  
588 syndrome coronavirus 2, PHQ8 = Patient Health Questionnaire depression scale, GAD7 = General Anxiety Disorder assessment, PRO2 = Patient Reported  
589 Outcome, VAS = Visual Analogue Scale

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591 **Table 2: Seroprevalence to anti-SARS-CoV-2, stratified by**  
592 **baseline characteristics**  
593

| Variable                            |                                     | Seroprevalence  | p       |
|-------------------------------------|-------------------------------------|-----------------|---------|
| Biologic treatment                  | Infliximab                          | 3.4% (161/4685) | <0.0001 |
|                                     | Vedolizumab                         | 6.0% (134/2250) |         |
| Biologic/ immunomodulator treatment | Infliximab with immunomodulator     | 3.0% (78/2639)  | 0.00050 |
|                                     | Infliximab without immunomodulator  | 4.1% (83/2046)  |         |
|                                     | Vedolizumab with immunomodulator    | 4.5% (19/424)   |         |
|                                     | Vedolizumab without immunomodulator | 6.3% (115/1826) |         |
| Sex                                 | Female                              | 4.3% (137/3221) | 1.0     |
|                                     | Male                                | 4.3% (158/3705) |         |
|                                     | Intersex                            | 0.0% (0/2)      |         |
|                                     | Prefer not to say                   | 0.0% (0/7)      |         |
| Ethnicity                           | White                               | 3.5% (217/6124) | 0.00050 |
|                                     | Asian                               | 9.2% (44/479)   |         |
|                                     | Mixed                               | 7.7% (12/155)   |         |
|                                     | Black                               | 13.8% (15/109)  |         |
|                                     | Other                               | 11.1% (7/63)    |         |
| Diagnosis                           | Crohn's disease                     | 3.2% (128/3949) | 0.00050 |
|                                     | Ulcerative colitis                  | 5.5% (155/2810) |         |
|                                     | IBD-unclassified                    | 6.8% (12/176)   |         |
| Immunomodulators at recruitment     | No                                  | 5.1% (198/3872) | <0.0001 |
|                                     | Yes                                 | 3.2% (97/3063)  |         |
| 5-ASA at recruitment                | No                                  | 3.9% (198/5105) | 0.012   |
|                                     | Yes                                 | 5.3% (97/1830)  |         |
| Steroids in 2020                    | No                                  | 4.0% (232/5779) | 0.031   |
|                                     | Yes                                 | 5.4% (63/1156)  |         |
| Heart disease                       | No                                  | 4.3% (287/6725) | 0.86    |
|                                     | Yes                                 | 3.8% (8/210)    |         |
| Diabetes                            | No                                  | 4.2% (280/6623) | 0.57    |
|                                     | Yes                                 | 4.8% (15/312)   |         |
| Lung disease                        | No                                  | 4.4% (260/5972) | 0.34    |
|                                     | Yes                                 | 3.6% (35/963)   |         |
| Kidney disease                      | No                                  | 4.3% (294/6846) | 0.19    |
|                                     | Yes                                 | 1.1% (1/89)     |         |
| Cancer                              | No                                  | 4.3% (293/6885) | 1.0     |
|                                     | Yes                                 | 4.0% (2/50)     |         |

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## impacT of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY

|  |   |                 |         |
|--|---|-----------------|---------|
| Smoker   | Yes   | 2.2% (16/744)   | 0.00050 |
|  | Not currently   | 3.4% (71/2106)  |         |
|  | Never   | 5.1% (207/4083) |         |
| Meets clinical criteria for suspected or probable COVID-19         | No  | 2.5% (158/6345) | <0.0001 |
|  | Yes   | 23.2% (137/590) |         |
| Tested with PCR for SARS-CoV-2                                     | No  | 2.9% (128/4346) | <0.0001 |
|  | Yes   | 6.5% (167/2589) |         |
| Positive PCR for SARS-CoV-2  | No  | 3.8% (93/2462)  | <0.0001 |
|  | Yes   | 58.3% (74/127)  |         |
| Positive PCR for SARS-CoV-2 at least 2 weeks prior to serum sample | No  | 3.8% (85/2229)  | <0.0001 |
|  | Yes   | 59.0% (69/117)  |         |
| Hospitalised for confirmed COVID-19                                | No  | 4.1% (285/6922) | <0.0001 |
|  | Yes   | 76.9% (10/13)   |         |
| Shielding behaviour Apr-Jul  | I remained in my house or garden  | 3.8% (92/2396)  | 0.0020  |
|  | I only left the house for exercise on my own or with members of my household                    | 3.9% (104/2701) |         |
|  | I encountered people from outside of my household but <i>maintained social distancing</i>       | 4.9% (83/1696)  |         |
|  | I encountered people from outside of my household but <i>did not maintain social distancing</i> | 11.0% (15/136)  |         |
| Exposure to documented cases of COVID-19                           | No  | 3.1% (192/6160) | <0.0001 |
|  | Yes   | 13.3% (103/773) |         |
| Active disease (PRO2)  | No  | 4.3% (266/6125) | 0.67    |
|  | Yes   | 3.8% (22/575)   |         |

594

595 Values shown are percentages (proportions).

596

597 **Abbreviations:** IBD = inflammatory bowel disease, 5-ASA = aminosaliclates, COVID-19 =  
 598 coronavirus, PCR = polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome  
 599 coronavirus 2, PRO2 = Patient Reported Outcome

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impact of biologics therapy on SARS-CoV-2 Infection and immunity CLARITY

601 **Table 3: Baseline characteristics, stratified by baseline anti-SARS-CoV-2**  
602 **antibody status**  
603

| Variable                     | Positive              | Negative              | p       |
|------------------------------|-----------------------|-----------------------|---------|
| Age (years)                  | 36.3 (26.9 - 50.6)    | 39.2 (28.7 - 53.3)    | 0.017   |
| Duration of IBD (years)      | 7.0 (3.0 - 15.0)      | 8.0 (3.0 - 15.0)      | 0.25    |
| Age at IBD diagnosis (years) | 26.4 (19.8 - 36.4)    | 27.6 (19.8 - 40.0)    | 0.12    |
| BMI                          | 24.7 (21.7 - 28.1)    | 24.5 (21.7 - 28.3)    | 0.75    |
| PHQ8                         | 4.0 (1.0 - 8.0)       | 4.0 (1.0 - 9.0)       | 0.40    |
| GAD7                         | 2.0 (0.0 - 6.0)       | 3.0 (0.0 - 7.0)       | 0.050   |
| Income deprivation score     | 0.120 (0.666 - 0.204) | 0.097 (0.056 - 0.163) | <0.0001 |
| IBD Control 8                | 13.0 (10.0 - 16.0)    | 13.0 (9.0 - 16.0)     | 0.32    |
| IBD Control VAS              | 79.0 (67.0 - 92.0)    | 80.0 (65.0 - 92.0)    | 0.61    |

604  
605 Values shown are medians (interquartile range).  
606

607 **Abbreviations:** IBD = inflammatory bowel disease, BMI = body mass index, PHQ8 = Patient Health  
608 Questionnaire depression scale, GAD7 = General Anxiety Disorder assessment, VAS = Visual  
609 Analogue Scale  
610