What have we learnt from COVID: results from UK studies

Dr Nick Kennedy
Consultant Gastroenterologist
Royal Devon & Exeter NHS Foundation Trust

September 2021
UK-GAS-2100117

The slides have been reviewed for off label information by Ferring Pharmaceuticals

Exeter IBD Research Group

Disclosures

- NAK has received honoraria from AbbVie, Dr Falk, Ferring, Pharmacosmos, Tillotts, Celltrion, Galapagos and Takeda
- CLARITY IBD is an investigator-led, UK National Institute for Health Research COVID-19 urgent public health study, funded by the Royal Devon and Exeter NHS Foundation Trust, Hull University Teaching Hospital NHS Trust, and by unrestricted educational grants from F. Hoffmann-La Roche AG (Switzerland), Biogen GmbH (Switzerland), Celltrion Healthcare (South Korea), Takeda (UK) and Galapagos NV (Belgium).

Exeter IBD Research Group

Overview

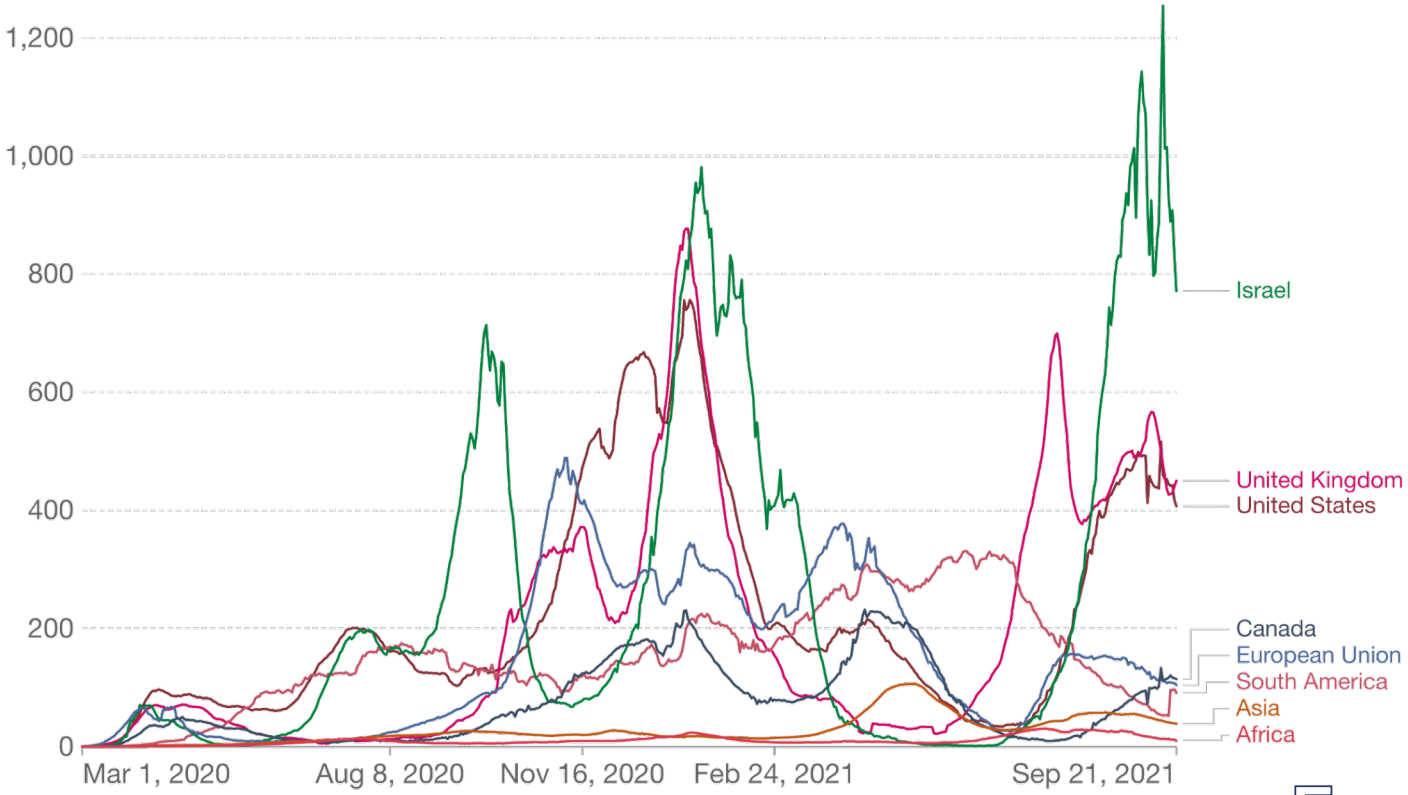
- Risk of severe COVID-19
- Adaptations of treatment
- Vaccination

Exeter IBD Research Group

Daily new confirmed COVID-19 cases per million people

Shown is the rolling 7-day average. The number of confirmed cases is lower than the number of actual cases; the main reason for that is limited testing.

Our World in Data



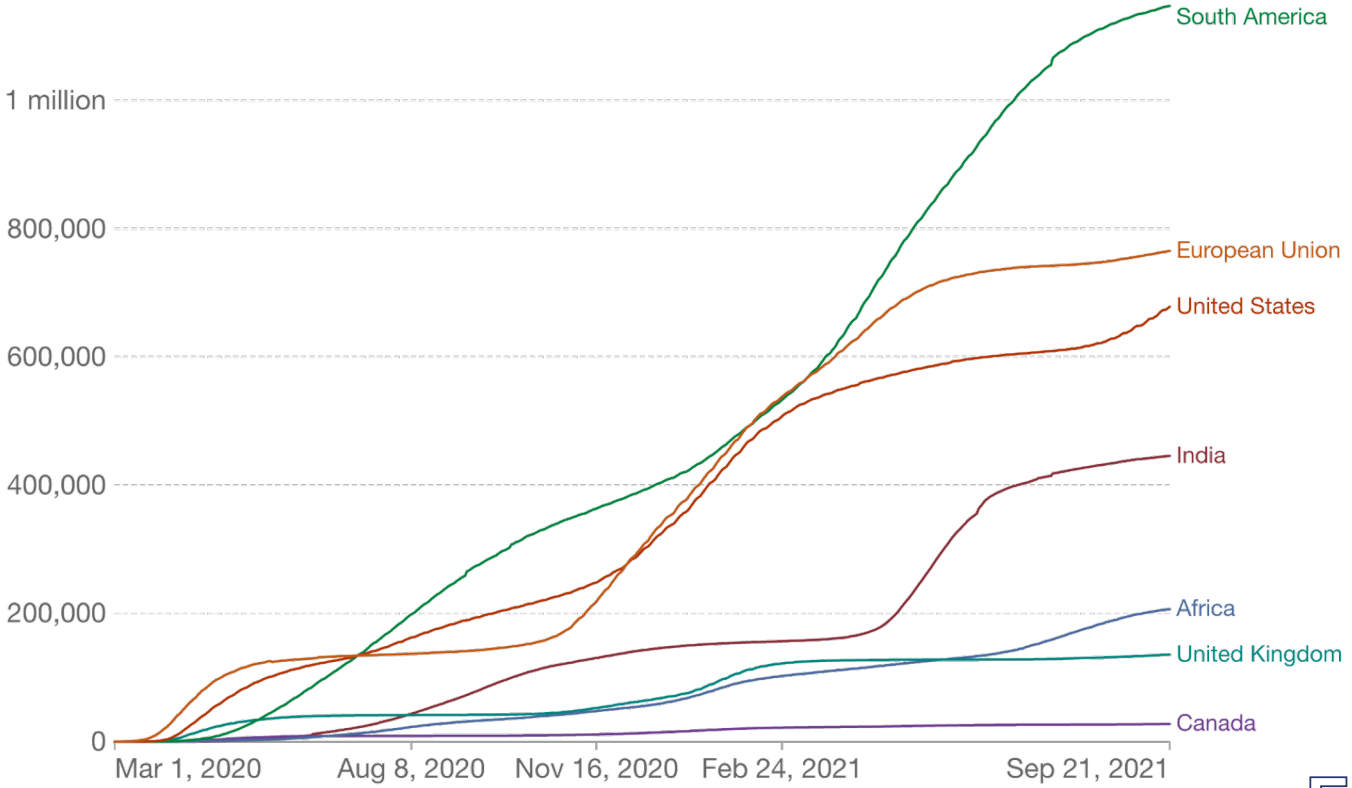
Source: Johns Hopkins University CSSE COVID-19 Data

Exeter IBD Research Group

Cumulative confirmed COVID-19 deaths

Limited testing and challenges in the attribution of the cause of death means that the number of confirmed deaths may not be an accurate count of the true number of deaths from COVID-19.

Our World in Data



Source: Johns Hopkins University CSSE COVID-19 Data

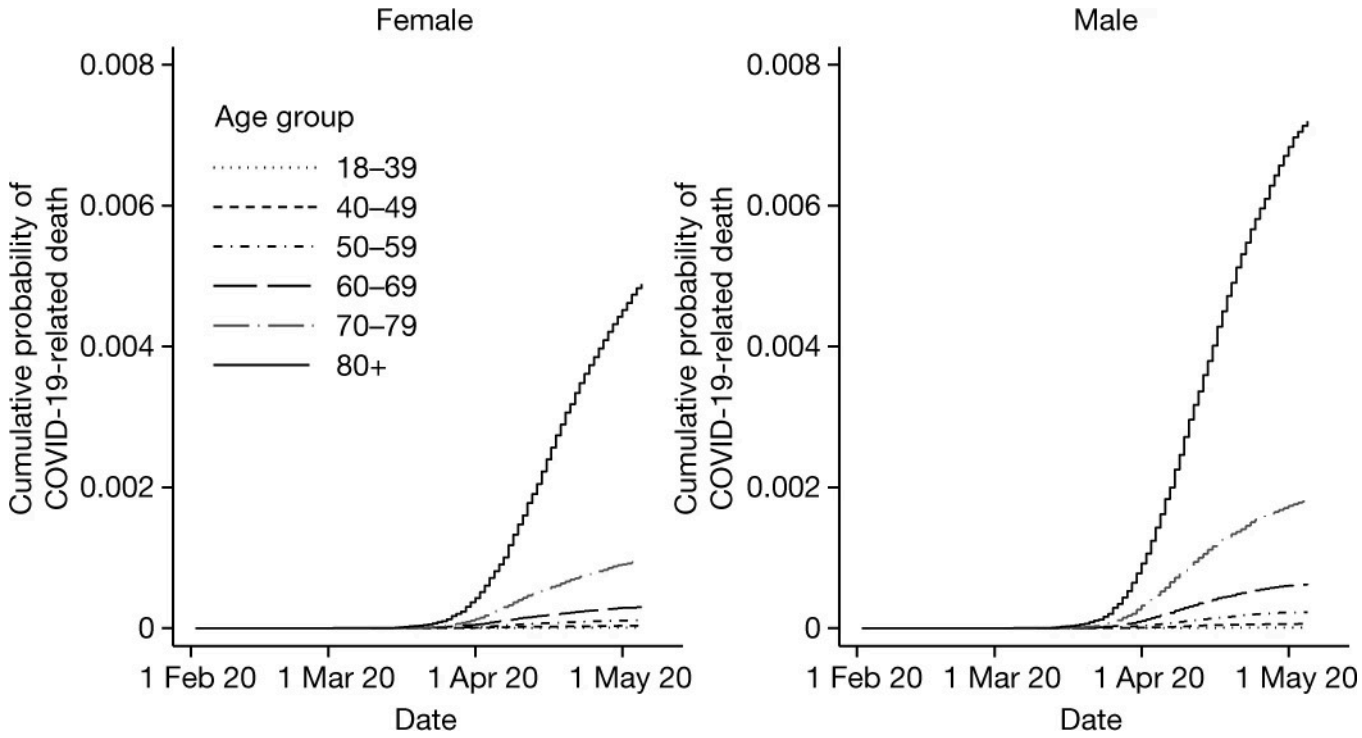
Exeter IBD Research Group

RISK OF SEVERE COVID-19

Exeter IBD Research Group

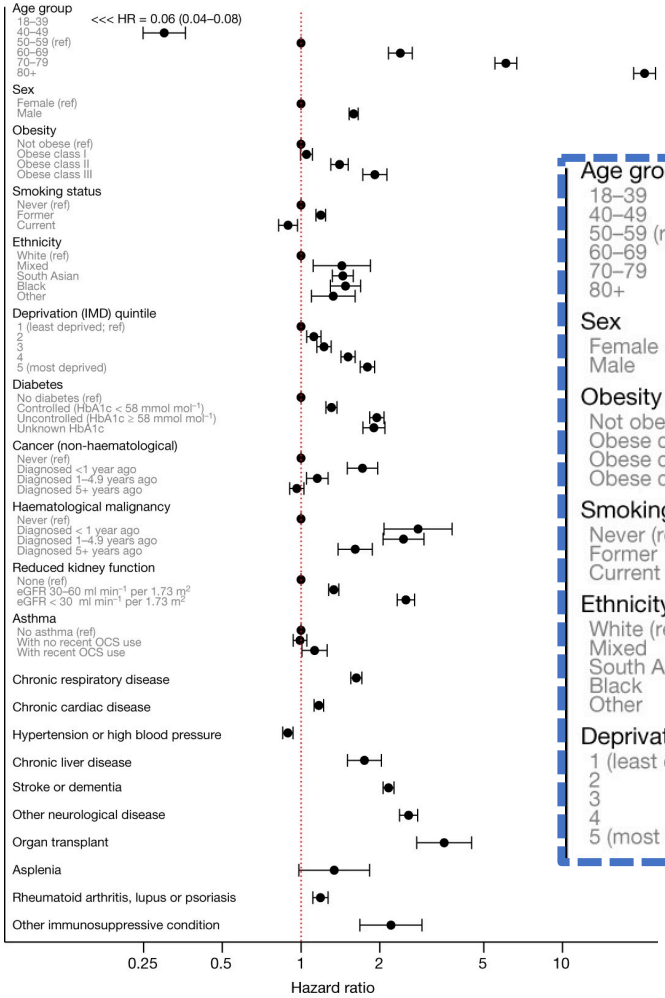
Article

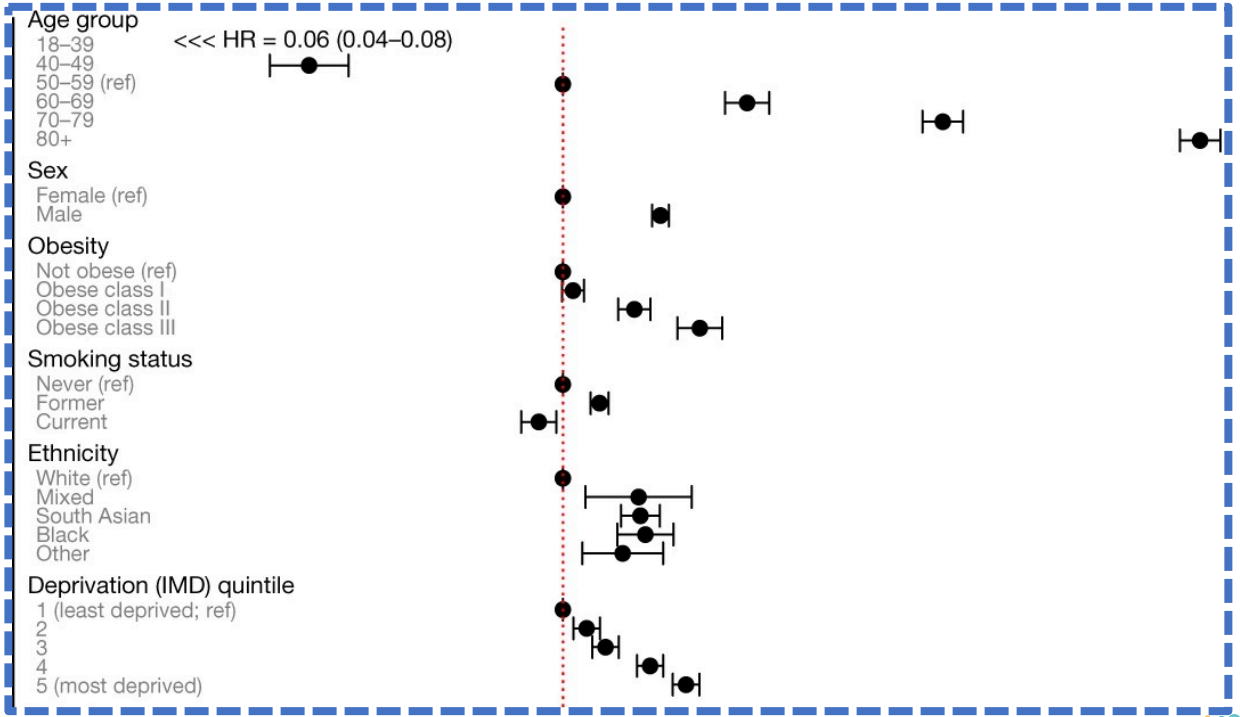
Factors associated with COVID-19-related death using OpenSAFELY



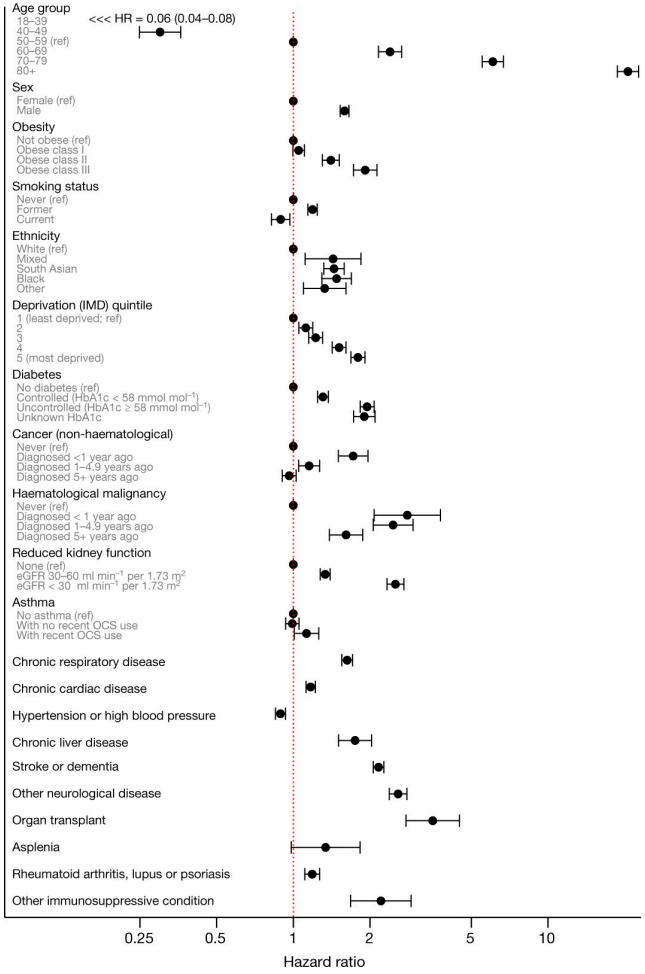
Article

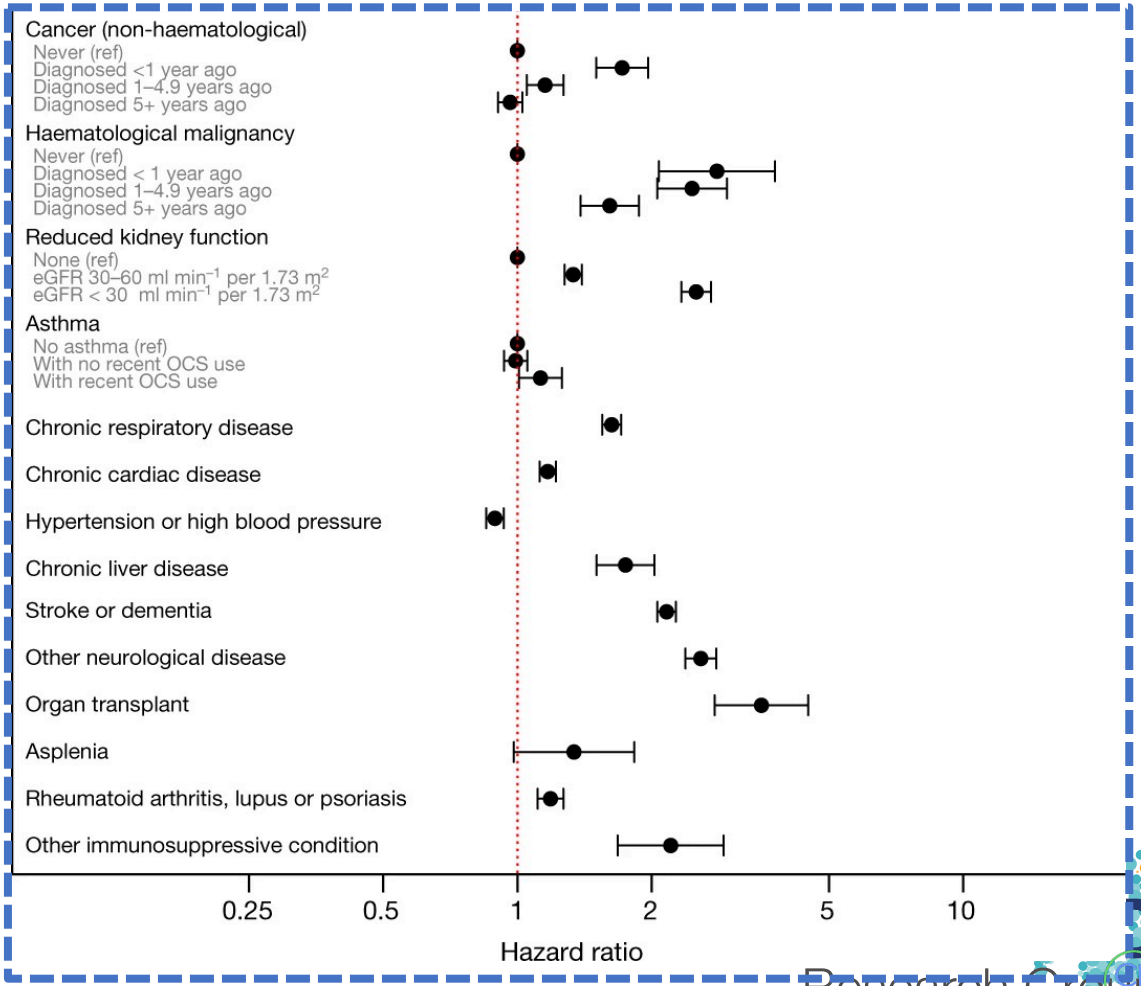
Factors associated with COVID-19-related death using OpenSAFELY





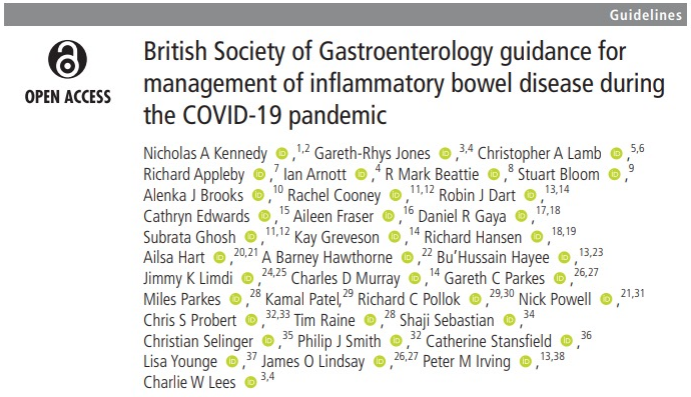
Exeter IBD Research Group





Risks of IBD therapies and severe COVID-19

- Early in pandemic, much uncertainty
- Initial guidance based on experience from China and Italy, other viruses
- Risk grid developed for shielding program



Guidelines

OPEN ACCESS

British Society of Gastroenterology guidance for management of inflammatory bowel disease during the COVID-19 pandemic

Nicholas A Kennedy [1,2] Gareth-Rhys Jones [3,4] Christopher A Lamb [5,6] Richard Appleby [7] Ian Arnott [4] R Mark Beattie [8] Stuart Bloom [9] Alenka J Brooks [10] Rachel Cooney [11,12] Robin J Dart [13,14] Cathryn Edwards [15] Aileen Fraser [16] Daniel R Gaya [17,18] Subrata Ghosh [11,12] Kay Greveson [14] Richard Hansen [18,19] Ailsa Hart [20,21] A Barney Hawthorne [22] Bu'Hussain Hayee [13,23] Jimmy K Limdi [24,25] Charles D Murray [14] Gareth C Parkes [26,27] Miles Parkes [28] Kamal Patel [29] Richard C Pollok [29,30] Nick Powell [21,31] Chris S Probert [32,33] Tim Raine [28] Shaji Sebastian [34] Christian Selinger [35] Philip J Smith [32] Catherine Stansfield [36] Lisa Younge [37] James O Lindsay [26,27] Peter M Irving [13,38] Charlie W Lees [3,4]

PREPARE IBD

- Cohort study of patients with IBD who flared and/or had COVID-19
- Sub-study of 211 patients with COVID-19

Lamb CA et al. Aliment Pharmacol Ther. 2021 Jun 1;53(11):1236–40 doi:10.1111/APT.16349.

Exeter IBD Research Group

PREPARE IBD

Multivariable logistic regression of non-medication factors and severe COVID-19 outcomes

Variable	OR (95% CI)	*P* value
Age (for each year)	1.03 (1.00-1.05)	0.035
Comorbidities (per comorbidity)	1.68 (1.23-2.35)	0.0014
Non-white ethnicity	1.98 (0.92-4.28)	0.078
Active IBD	0.58 (0.26-1.26)	0.17

Multivariable logistic regression of medications and severe COVID-19 outcomes

(Each medication was added individually to the model including the non-medication covariates above)

Variable	OR (95% CI)	*P* value
Mesalazine	2.03 (1.01-4.12)	0.048
Prednisolone	2.42 (0.47-11.28)	0.27
Thiopurine (azathioprine/mercaptopurine)	0.47 (0.12-1.48)	0.23
Vedolizumab	0.23 (0.03-1.13)	0.10
Anti-TNF (infliximab and adalimumab)	1.06 (0.28-3.41)	0.92
All biologics	0.62 (0.22-1.63)	0.35

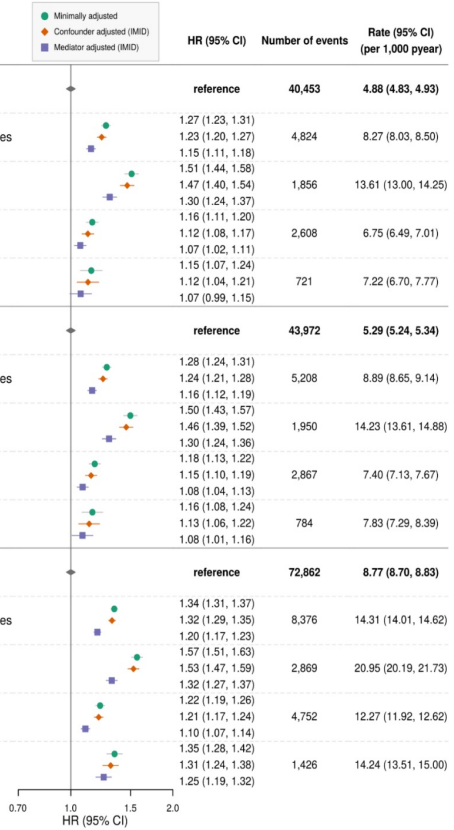
Lamb CA et al. Aliment Pharmacol Ther. 2021 Jun 1;53(11):1236–40 doi:10.1111/APT.16349.

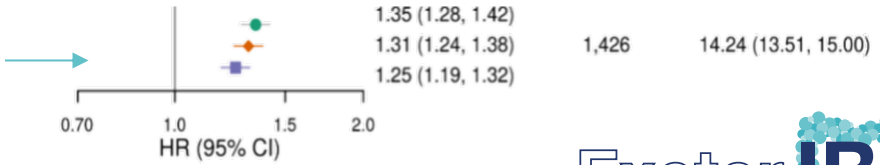
Exeter IBD Research Group

OpenSafely cross-IMID study

Figure 2. Forest plot of hazard ratios (HRs) for COVID-19-related death, critical care admission/death and hospitalisation for IMID vs general population

Outcome	Exposure	HR (95% CI)	Number of events	Rate (95% CI) (per 1,000 pyear)
COVID-19 death	General population	reference	40,453	4.88 (4.83, 4.93)
	All immune-mediated inflammatory diseases	1.27 (1.23, 1.31) 1.23 (1.20, 1.27) 1.15 (1.11, 1.18)	4,824	8.27 (8.03, 8.50)
	Inflammatory joint disease	1.51 (1.44, 1.58) 1.47 (1.40, 1.54) 1.30 (1.24, 1.37)	1,856	13.61 (13.00, 14.25)
	Inflammatory skin disease	1.16 (1.11, 1.20) 1.12 (1.08, 1.17) 1.07 (1.02, 1.11)	2,608	6.75 (6.49, 7.01)
	Inflammatory bowel disease	1.15 (1.07, 1.24) 1.12 (1.04, 1.21) 1.07 (0.99, 1.15)	721	7.22 (6.70, 7.77)
COVID-19 ICU/death	General population	reference	43,972	5.29 (5.24, 5.34)
	All immune-mediated inflammatory diseases	1.28 (1.24, 1.31) 1.24 (1.21, 1.28) 1.16 (1.12, 1.19)	5,208	8.89 (8.65, 9.14)
	Inflammatory joint disease	1.50 (1.43, 1.57) 1.46 (1.39, 1.52) 1.30 (1.24, 1.36)	1,950	14.23 (13.61, 14.88)
	Inflammatory skin disease	1.18 (1.13, 1.22) 1.15 (1.10, 1.19) 1.08 (1.04, 1.13)	2,867	7.40 (7.13, 7.67)
	Inflammatory bowel disease	1.16 (1.08, 1.24) 1.13 (1.06, 1.22) 1.08 (1.01, 1.16)	784	7.83 (7.29, 8.39)
COVID-19 hospitalisation	General population	reference	72,862	8.77 (8.70, 8.83)
	All immune-mediated inflammatory diseases	1.34 (1.31, 1.37) 1.32 (1.29, 1.35) 1.20 (1.17, 1.23)	8,376	14.31 (14.01, 14.62)
	Inflammatory joint disease	1.57 (1.51, 1.63) 1.53 (1.47, 1.59) 1.32 (1.27, 1.37)	2,869	20.95 (20.19, 21.73)
	Inflammatory skin disease	1.22 (1.19, 1.26) 1.21 (1.17, 1.24) 1.10 (1.07, 1.14)	4,752	12.27 (11.92, 12.62)
	Inflammatory bowel disease	1.35 (1.28, 1.42) 1.31 (1.24, 1.38) 1.25 (1.19, 1.32)	1,426	14.24 (13.51, 15.00)





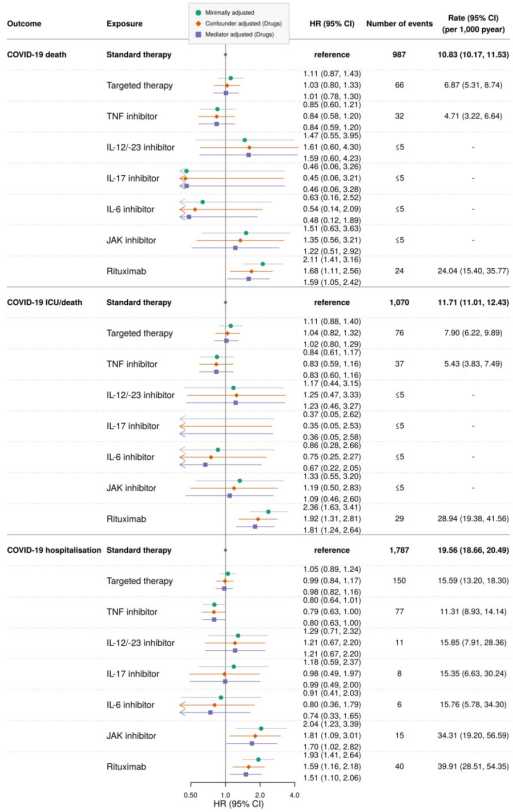
Planned comparisons were made between people with IMIDs, and IMID types (joint, bowel, skin), using the general population as the reference group.
Minimally adjusted: age and sex
Confounder adjusted (IMID): age, sex, deprivation, smoking status

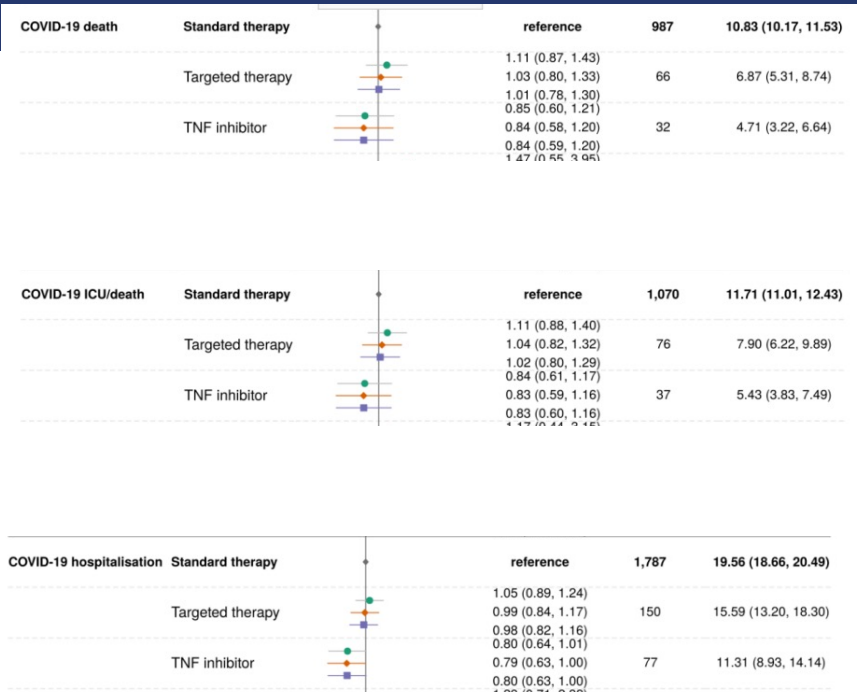
MacKenna B, Kennedy NA et al., preprint on medRXiv. doi:10.1101/2021.09.03.21262888

Exeter IBD Research Group

OpenSafely cross-IMID study

Figure 3. Forest plot of hazard ratios (HRs) for COVID-19 death, critical care admission/death and hospitalisation for standard systemic vs targeted immunosuppression

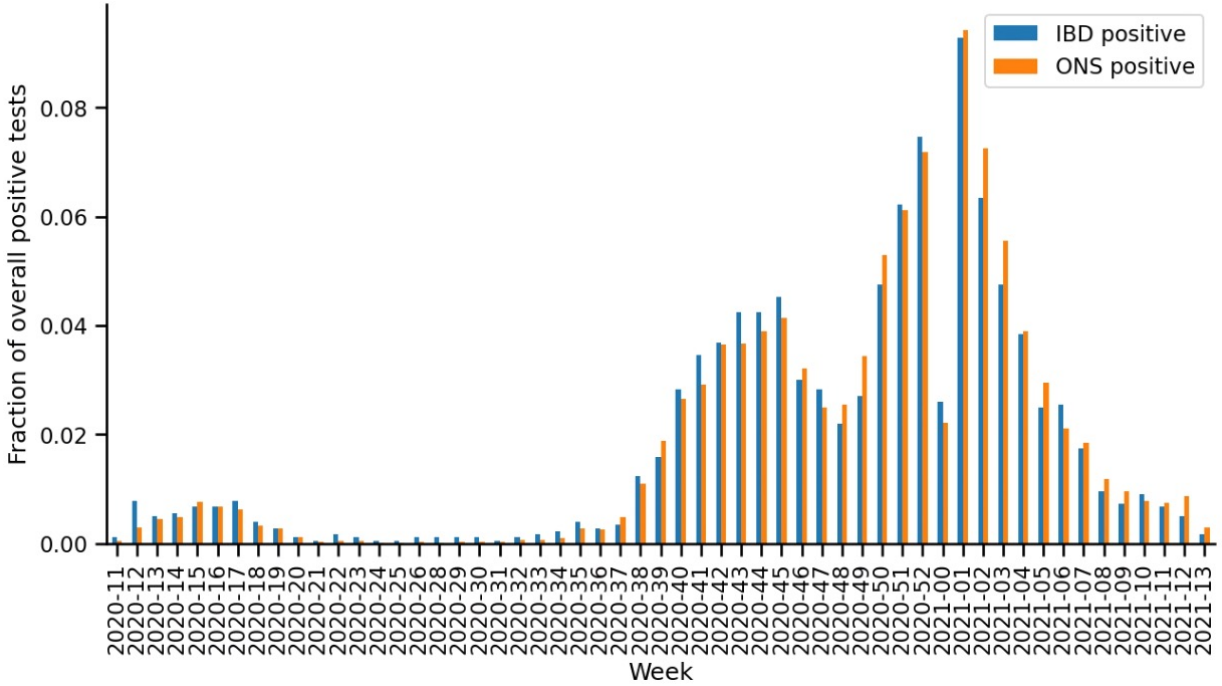




Planned comparisons were made between people with IMIDs on any targeted immune modifying therapy (and for each group on specific targeted therapies) compared to people with IMIDs on standard systemic therapy as the reference group.
Cells with counts less than 5 are redacted to protect anonymity.
Minimally adjusted: age and sex
Confounder adjusted: age, sex, deprivation, smoking status, BMI, specific IMID (inflammatory joint, bowel and skin disease), cardiovascular disease, cancer (excluding non-melanoma skin cancer), stroke, end stage renal failure, chronic liver disease, chronic respiratory disease and diabetes mellitus

MacKenna B, Kennedy NA et al., preprint on medRXiv. doi:10.1101/2021.09.03.21262888

Exeter IBD Research Group



- 1,656 COVID+ (~5%) in 31,000 BioResource participants vs ~6% in the UK.
- Testing positive for COVID-19 does not appear to be strongly associated with any particular IBD drug. (Very) maybe, mesalazine has a marginal effect (OR=1.24 [1.09-1.42], p=0.001)
- Death rate after a positive COVID test: ~1.8% (29)

Unpublished data

Exeter IBD Research Group

Meta-analysis of COVID-19 outcomes in IBD

- Systematic review and meta-analysis of 24 studies
- No increased risk over general population
- Lower risk of severe disease with biologics, higher with steroids and mesalazine

Singh et al., UEG Journal, doi:10.1177/2050640620972602

Exeter IBD Research Group

SECURE IBD

- International registry of COVID-19 in patients with IBD
- 1439 cases in Gut publication
- Thiopurines (mono/combo), corticosteroids associated with increased risk
- No association with biologics
- Mesalazine risk initially reported; subsequently refuted in re-analysis presented at ECCO 2021

doi:10.1136/gutjnl-2020-322539
doi:10.1053/j.gastro.2020.05.032

Exeter IBD Research Group

Risks of IBD therapies and severe COVID-19

- Overall, most important risk factors are not related to IBD:
  - Age
  - Comorbidities
  - Ethnicity

Exeter IBD Research Group

Patient engagement: risk assessment with the IBD Registry COVID-19 risk tool

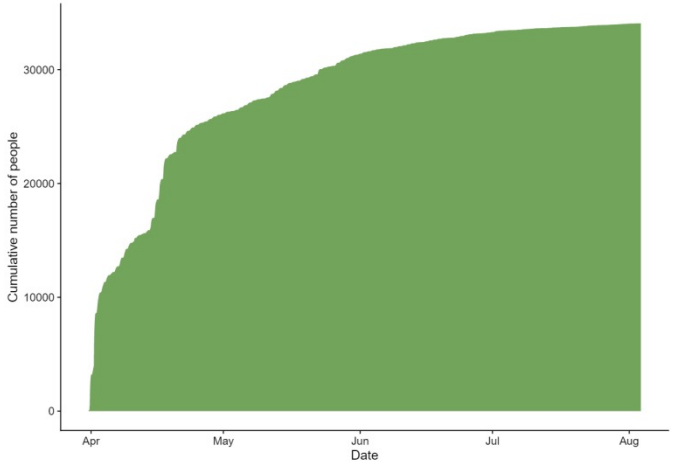
- Rapid development of BSG Guidance on management of IBD in the COVID-19 era in March 2020
- Difficulty integrating medication data (often split between primary and secondary care), comorbidities and disease activity
- Opportunity for patients to engage with their own risk assessment

Kennedy NA et al. Gut. 2020 Apr 17 [cited 2020 Apr 27]; doi:10.1136/gutjnl-2020-321244.

Exeter IBD Research Group

COVID-19 risk tool

- Rapid development using REDCap platform and using expertise in IBD Registry



https://ibdregistry.org.uk/covid-19/

Comparison of risk tool data with secondary care data

- Data from the risk tool was compared with secondary care data for 2862 patients across ten hospitals
- Overall, 51% (493/966) patients identified by the risk tool as ‘high risk’ were missed by initial secondary care searches

Kennedy et al., manuscript submitted

Exeter IBD Research Group

Management of IBD

- In general, principles of management should remain the same as pre-pandemic
- Choice of therapies should be determined by disease and patient characteristics
- Control of disease activity and minimising long-term use of corticosteroids remain important goals

Exeter IBD Research Group

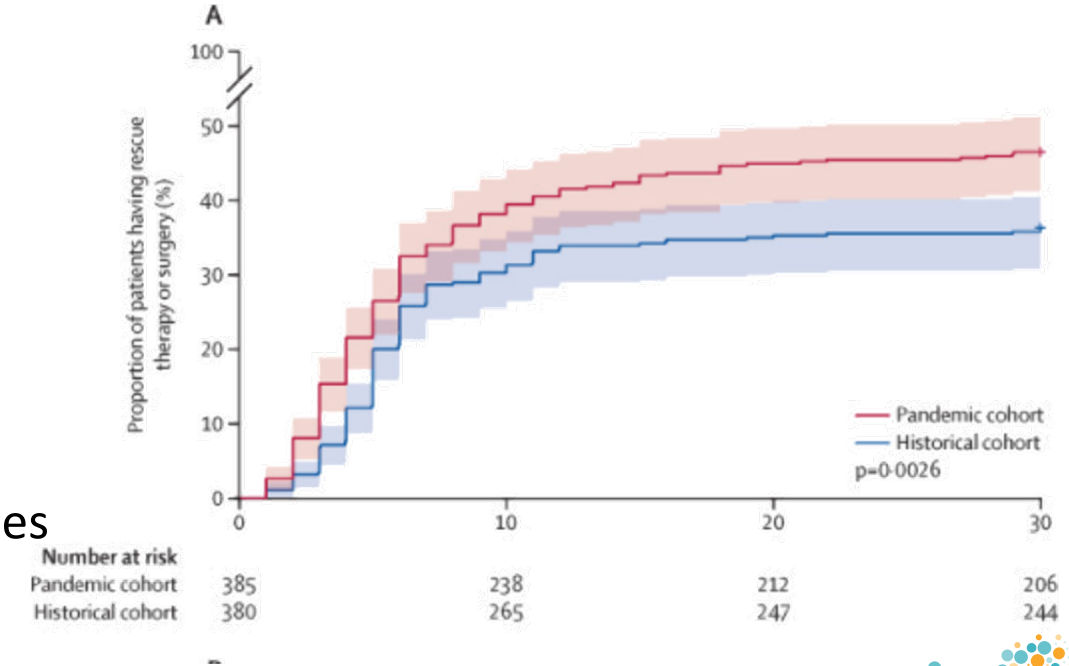
Adaptations during the pandemic: lessons from PREPARE IBD

- Study of 5,220 patients with flares of IBD (split between pandemic period and matched historic controls)
- Propensity matching done based on disease severity and age
- Increased use of poorly bioavailable steroids and newer biologics
- No difference in outcomes after three months' follow-up

Exeter IBD Research Group

Acute severe ulcerative colitis

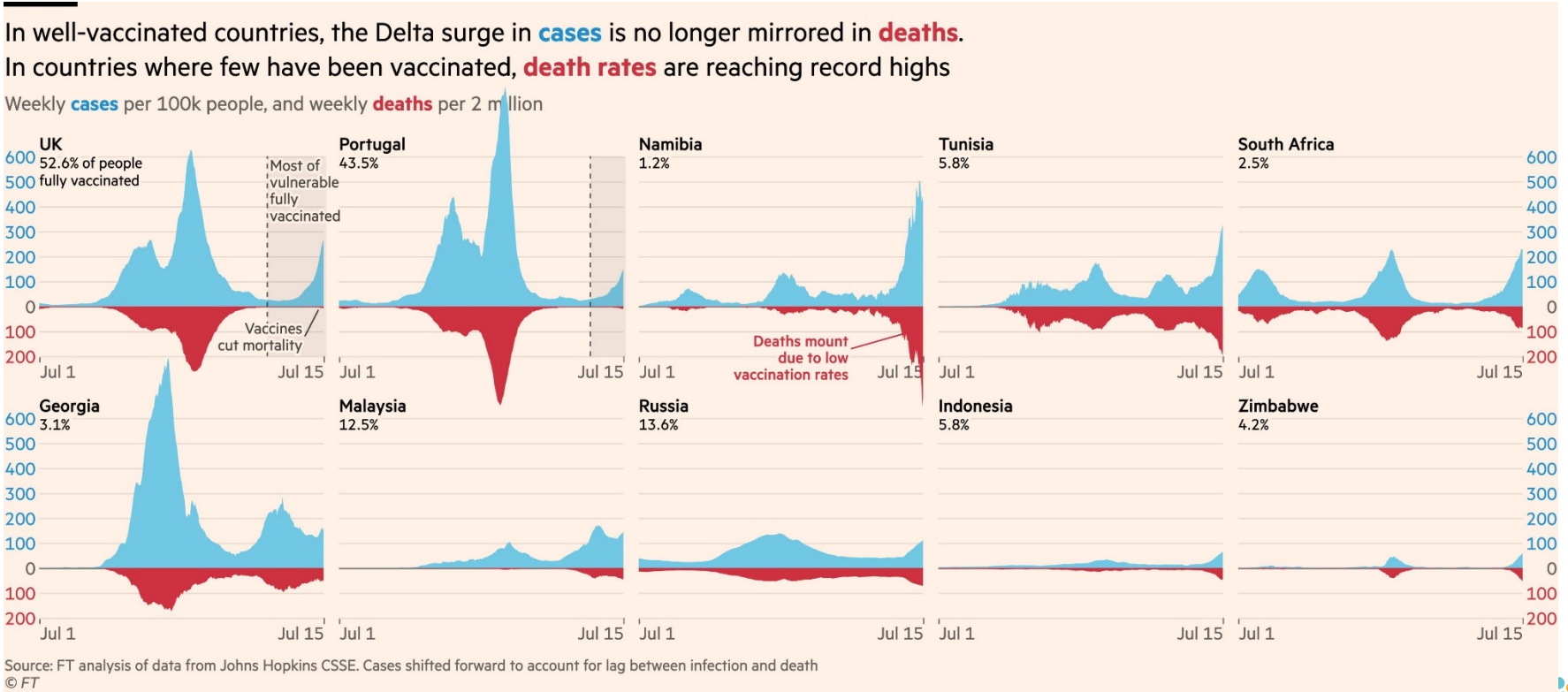
- Insights into changes in management from PROTECT ASUC study (doi:10.1016/S2468-1253(21)00016-9)
  - Increased use of ambulatory steroids
  - Reduced use of thiopurines
  - Earlier use of rescue therapy



Exeter IBD Research Group

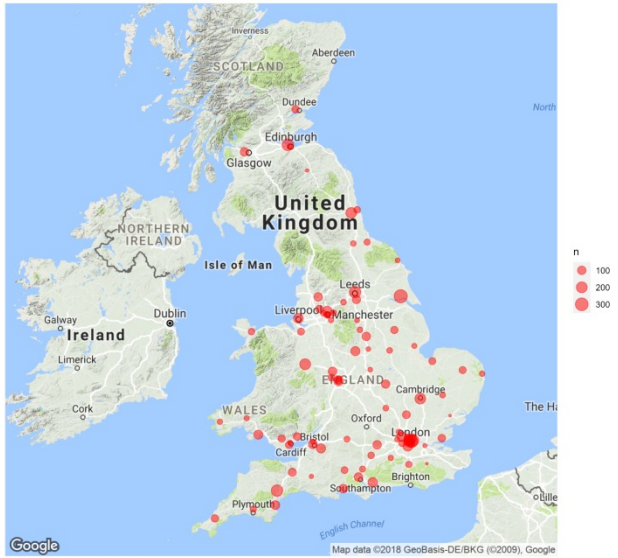
VACCINATION

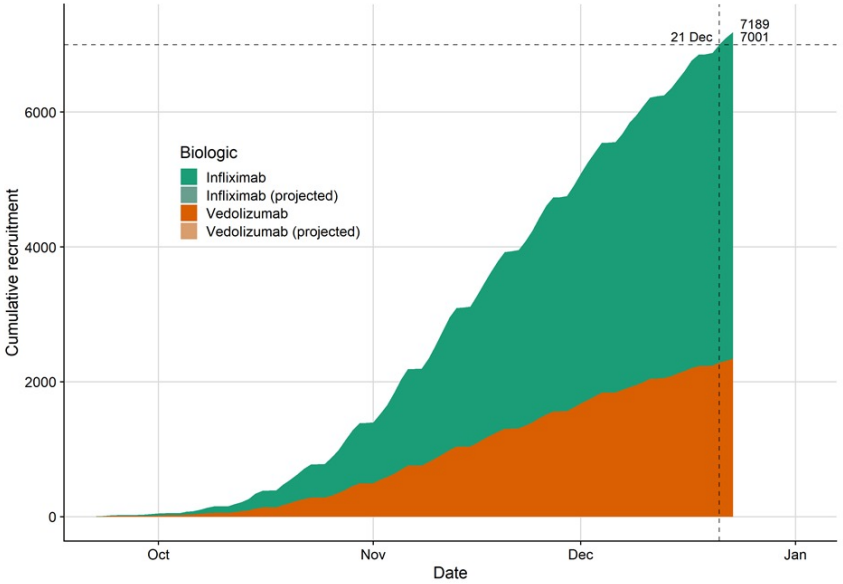
Exeter IBD Research Group



CLARITY IBD

CLARITY IBD





7229 patients recruited across 92 sites over three months

Kennedy NA et al. Gut. 2021;70(5):865–75 doi:10.1136/gutjnl-2021-324388.

Exeter IBD Research Group

Apr 2020: Initial discussions among Exeter group

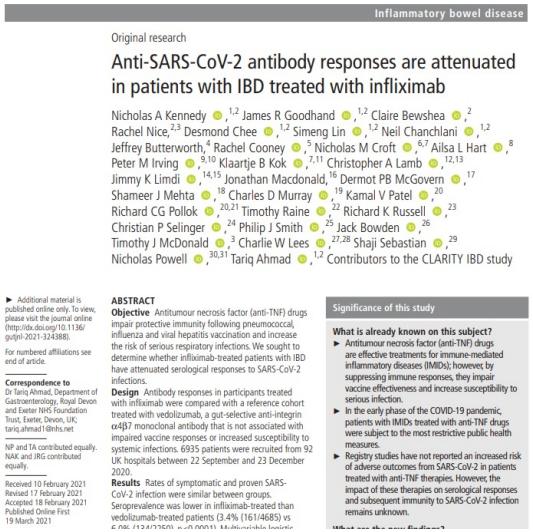
May 2020: Patient engagement exercise; initial protocol written

Sep 2020: NIHR granted urgent public health study badging
First patient recruited in Exeter

Dec 2020: 7000th patient recruited

Feb/Mar 2021: First paper on baseline data submitted and published

Mar/Apr 2021: Paper on serological response to vaccines submitted and published



Inflammatory bowel disease

Original research

Anti-SARS-CoV-2 antibody responses are attenuated in patients with IBD treated with infliximab

Nicholas A Kennedy ,[1,2] James R Goodhand ,[1,2] Claire Bewshea ,[2] Rachel Nice,[2,3] Desmond Chee ,[1,2] Simeng Lin ,[1,2] Neil Chanchlani ,[1,2] Jeffrey Butterworth,[4] Rachel Cooney ,[5] Nicholas M Croft ,[6,7] Ailsa L Hart ,[8] Peter M Irving ,[9,10] Klaartje B Kok ,[7,11] Christopher A Lamb ,[12,13] Jimmy K Limdi ,[14,15] Jonathan Macdonald,[16] Dermot PB McGovern ,[17] Shameer J Mehta ,[18] Charles D Murray ,[19] Kamal V Patel ,[20] Richard CG Pollok ,[20,21] Timothy Raine ,[22] Richard K Russell ,[23] Christian P Selinger ,[24] Philip J Smith ,[25] Jack Bowden ,[26] Timothy J McDonald ,[3] Charlie W Lees ,[27,28] Shaji Sebastian ,[29] Nicholas Powell ,[30,31] Tariq Ahmad ,[1,2] Contributors to the CLARITY IBD study

► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2021-324388).

For numbered affiliations see end of article.

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

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

Received 10 February 2021
Revised 17 February 2021
Accepted 18 February 2021
Published Online First 19 March 2021

ABSTRACT

Objective Antitumour necrosis factor (anti-TNF) drugs impair protective immunity following pneumococcal, influenza and viral hepatitis vaccination and increase the risk of serious respiratory infections. We sought to determine whether infliximab-treated patients with IBD have attenuated serological responses to SARS-CoV-2 infections.

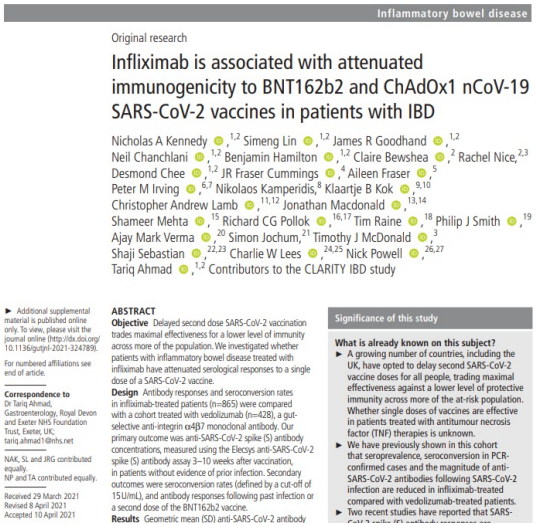
Design Antibody responses in participants treated with infliximab were compared with a reference cohort treated with vedolizumab, a gut-selective anti-integrin α4β7 monoclonal antibody that is not associated with impaired vaccine responses or increased susceptibility to systemic infections. 6935 patients were recruited from 92 UK hospitals between 22 September and 23 December 2020.

Results Rates of symptomatic and proven SARS-CoV-2 infection were similar between groups. Seroprevalence was lower in infliximab-treated than vedolizumab-treated patients (3.4% (161/4685) vs

Significance of this study

What is already known on this subject?

- Antitumour necrosis factor (anti-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.



Inflammatory bowel disease

Original research

Infliximab is associated with attenuated immunogenicity to BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines in patients with IBD

Nicholas A Kennedy ,[1,2] Simeng Lin ,[1,2] James R Goodhand ,[1,2] Neil Chanchlani ,[1,2] Benjamin Hamilton ,[1,2] Claire Bewshea ,[2] Rachel Nice,[2,3] Desmond Chee ,[1,2] JR Fraser Cummings ,[4] Aileen Fraser ,[5] Peter M Irving ,[6,7] Nikolaos Kamperidis,[8] Klaartje B Kok ,[9,10] Christopher Andrew Lamb ,[11,12] Jonathan Macdonald ,[13,14] Shameer Mehta ,[15] Richard CG Pollok ,[16,17] Tim Raine ,[18] Philip J Smith ,[19] Ajay Mark Verma ,[20] Simon Jochum,[21] Timothy J McDonald ,[3] Shaji Sebastian ,[22,23] Charlie W Lees ,[24,25] Nick Powell ,[26,27] Tariq Ahmad ,[1,2] Contributors to the CLARITY IBD study

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2021-324789).

For numbered affiliations see end of article.

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

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

Received 29 March 2021
Revised 8 April 2021
Accepted 10 April 2021

ABSTRACT

Objective Delayed second dose SARS-CoV-2 vaccination trades maximal effectiveness for a lower level of immunity across more of the population. We investigated whether patients with inflammatory bowel disease treated with infliximab have attenuated serological responses to a single dose of a SARS-CoV-2 vaccine.

Design Antibody responses and seroconversion rates in infliximab-treated patients (n=865) were compared with a cohort treated with vedolizumab (n=428), a gut-selective anti-integrin α4β7 monoclonal antibody. Our primary outcome was anti-SARS-CoV-2 spike (S) antibody concentrations, measured using the Elecsys anti-SARS-CoV-2 spike (S) antibody assay 3–10 weeks after vaccination, in patients without evidence of prior infection. Secondary outcomes were seroconversion rates (defined by a cut-off of 15 U/mL), and antibody responses following past infection or a second dose of the BNT162b2 vaccine.

Results Geometric mean (SD) anti-SARS-CoV-2 antibody

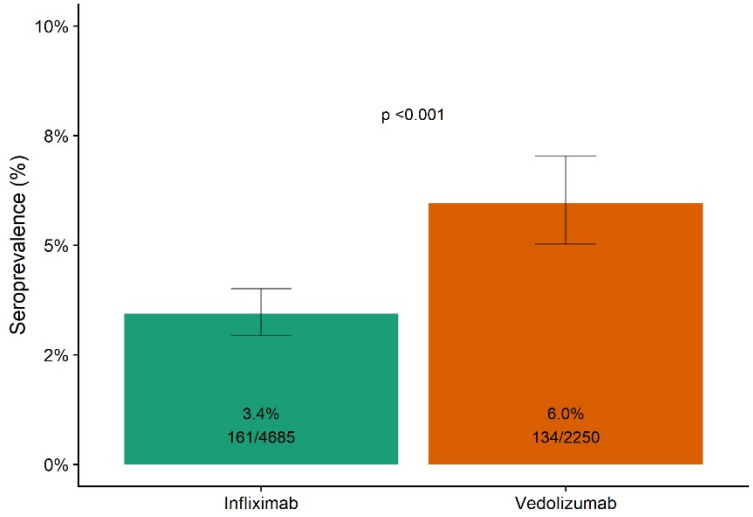
Significance of this study

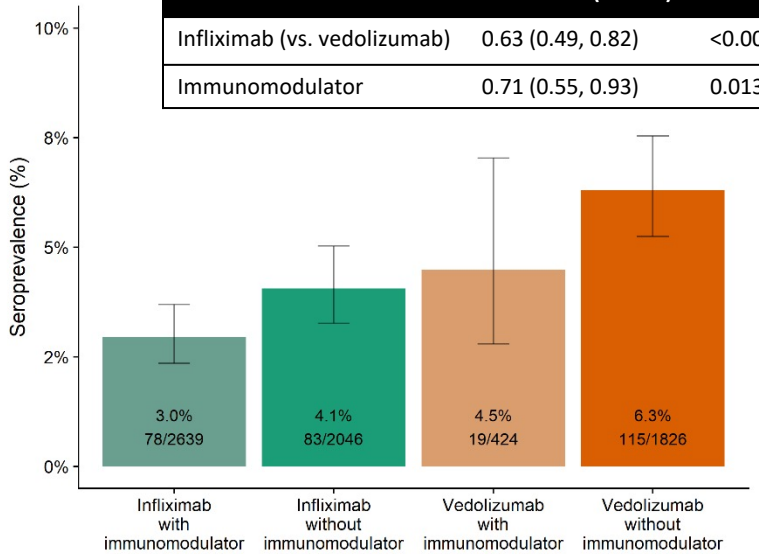
What is already known on this subject?

- A growing number of countries, including the UK, have opted to delay second SARS-CoV-2 vaccine doses for all people, trading maximal effectiveness against a lower level of protective immunity across more of the at-risk population. Whether single doses of vaccines are effective in patients treated with antitumour necrosis factor (TNF) therapies is unknown.
- We have previously shown in this cohort that seroprevalence, seroconversion in PCR-confirmed cases and the magnitude of anti-SARS-CoV-2 antibodies following SARS-CoV-2 infection are reduced in infliximab-treated compared with vedolizumab-treated patients.
- Two recent studies have reported that SARS-

Exeter IBD Research Group

Baseline seroprevalence to anti-SARS-CoV-2 stratified by IBD treatment





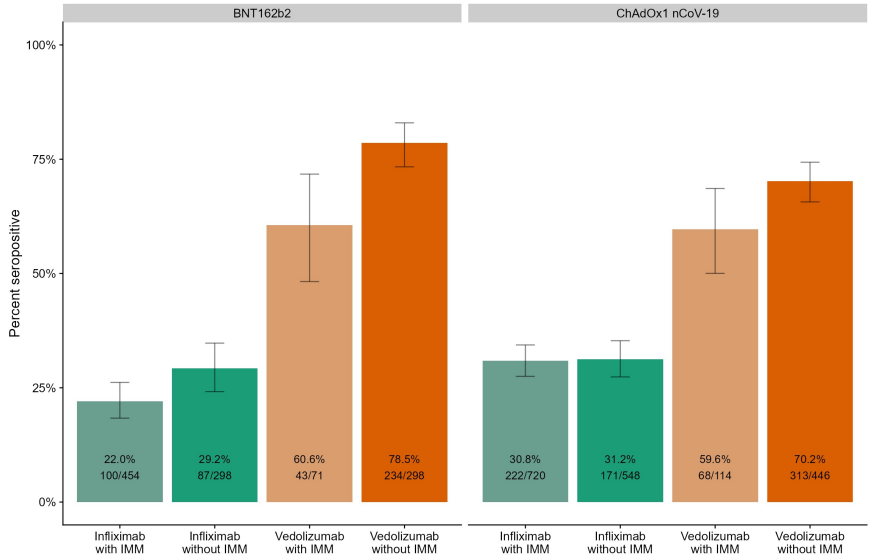
Variable	Odds ratio (95% CI)	P
Infliximab (vs. vedolizumab)	0.63 (0.49, 0.82)	<0.0001
Immunomodulator	0.71 (0.55, 0.93)	0.013

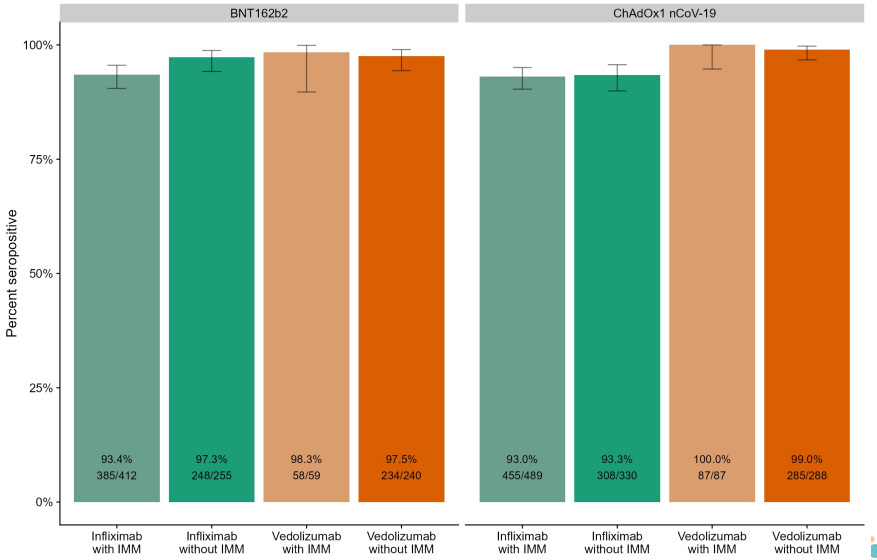
Kennedy NA et al. Gut. 2021;70(5):865–75 doi:10.1136/gutjnl-2021-324388.

Exeter IBD Research Group

More than 93% seroconvert following 2 vaccine doses

defined by an anti-SARS-CoV-2 spike antibody concentration ≥15 U/mL

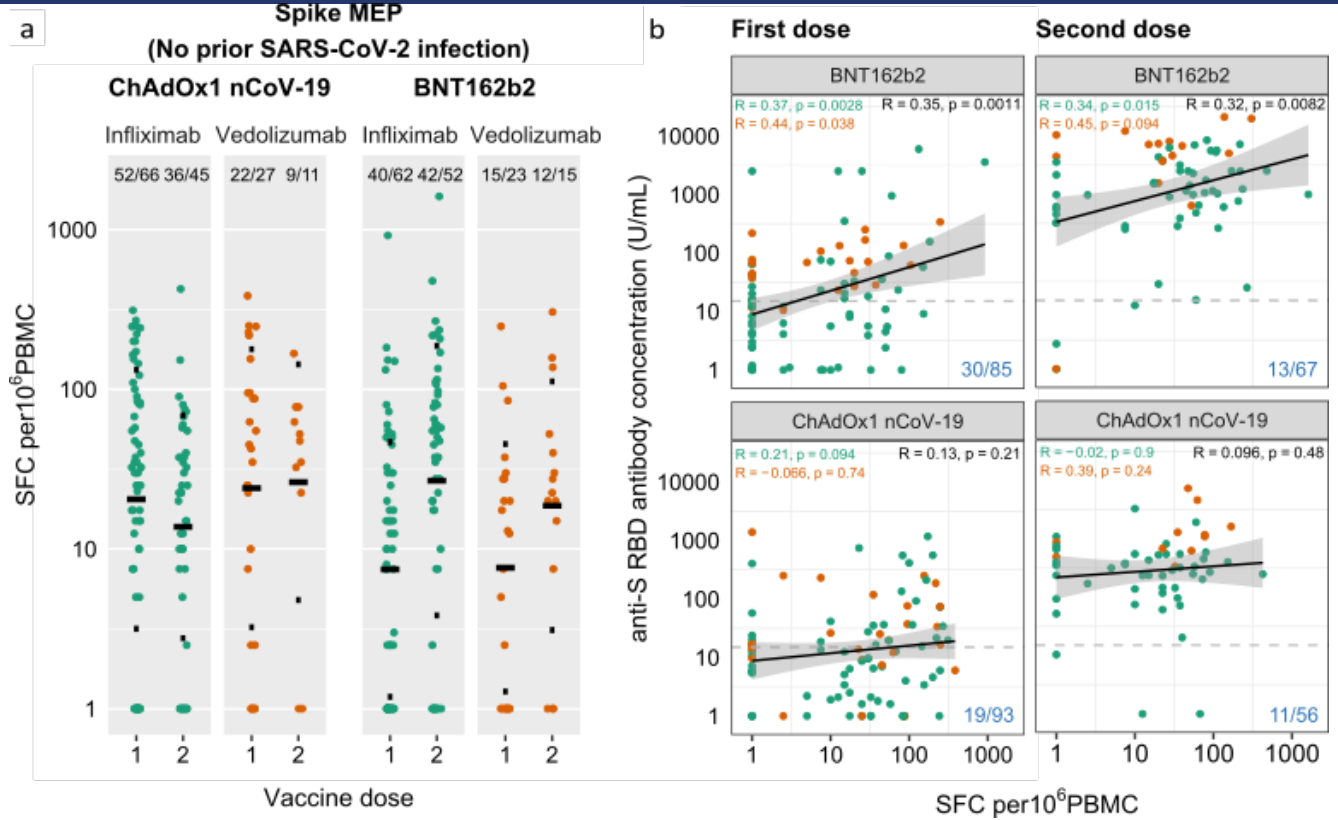




Unpublished data; earlier version of this in Lin S et al. Res Sq. 2021 Jul 30; doi:10.21203/RS.3.RS-755879/V1.

Exeter IBD Research Group

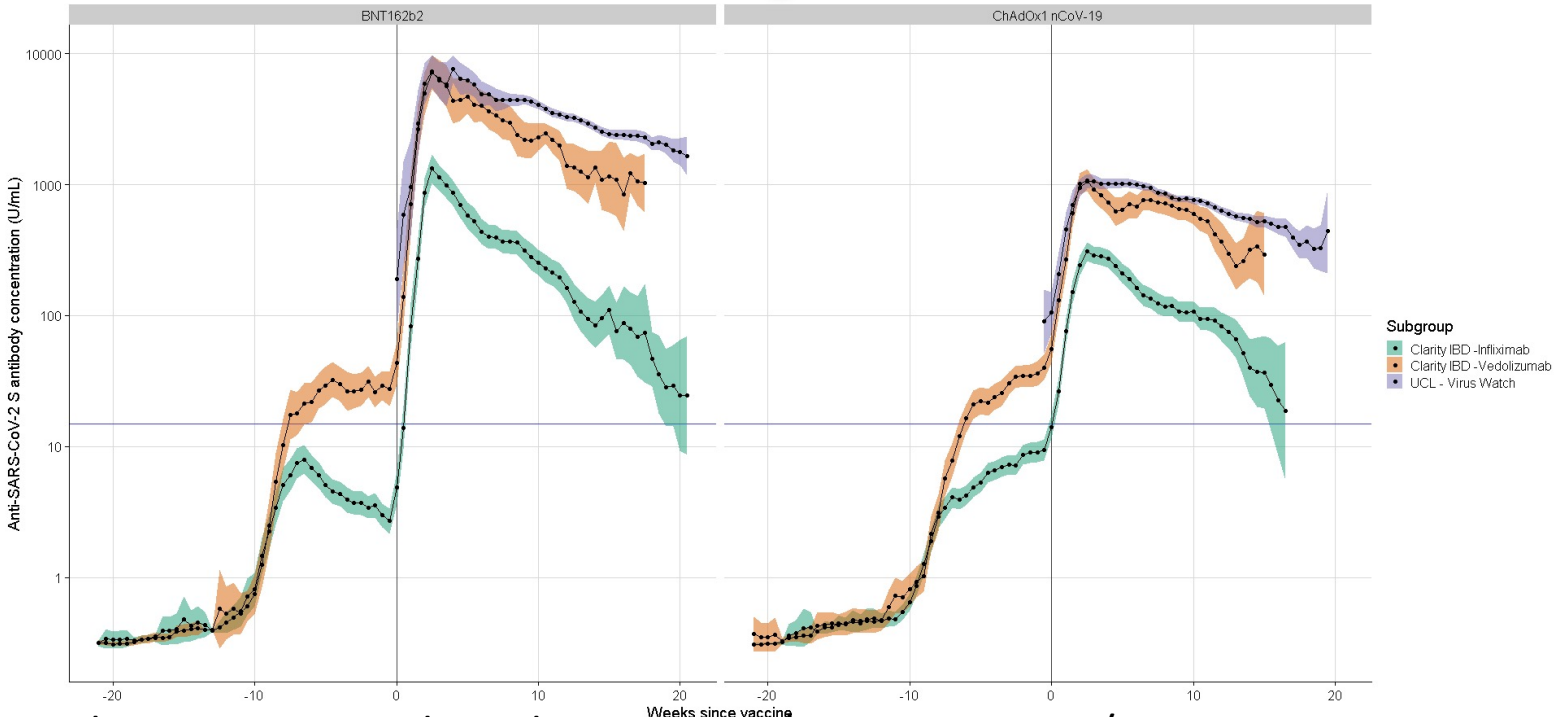
How do anti-spike T cell responses correlate with anti-spike RBD antibody responses after vaccination?



Exeter IBD Research Group

Infliximab impacts durability of antibody responses to SARS-CoV-2 vaccination

Rolling 15-day geometric mean antibody concentration in participants with no prior infec



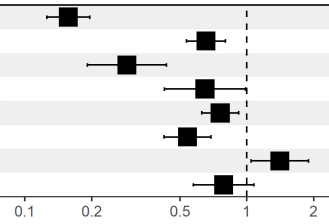
Lin S et al. Res Sq. 2021 Jul 30; doi:10.21203/RS.3.RS-755879/V1.

IBD Research Group

Factors associated with anti-SARS-CoV-2 'S' following two doses of vaccine

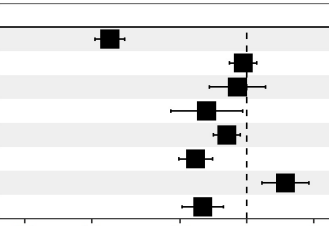
BNT162b2

Variable	N	Fold change (95% CI)	p
Infliximab (vs vedolizumab)	981/1426	0.16 (0.13, 0.20)	<0.0001
Thiopurine	599/1426	0.65 (0.53, 0.80)	<0.0001
Methotrexate	78/1426	0.29 (0.19, 0.43)	<0.0001
Steroids	70/1426	0.65 (0.42, 0.99)	0.044
Crohn's disease (vs UC or IBDU)	771/1426	0.76 (0.63, 0.92)	0.0044
Age ≥ 60	259/1426	0.54 (0.42, 0.69)	<0.0001
Non-white ethnicity	148/1426	1.41 (1.04, 1.90)	0.025
Current smoker	131/1426	0.79 (0.57, 1.08)	0.13



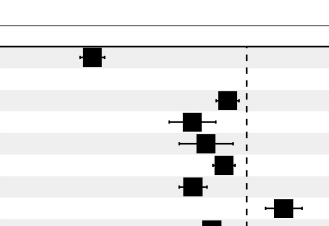
ChAdOx1 nCoV-19

Variable	N	Fold change (95% CI)	p
Infliximab (vs vedolizumab)	1457/2105	0.24 (0.21, 0.28)	<0.0001
Thiopurine	845/2105	0.96 (0.83, 1.11)	0.60
Methotrexate	116/2105	0.91 (0.68, 1.21)	0.51
Steroids	66/2105	0.66 (0.45, 0.96)	0.028
Crohn's disease (vs UC or IBDU)	1255/2105	0.81 (0.71, 0.93)	0.0035
Age ≥ 60	372/2105	0.59 (0.49, 0.70)	<0.0001
Non-white ethnicity	165/2105	1.49 (1.17, 1.90)	0.0012
Current smoker	222/2105	0.63 (0.51, 0.78)	<0.0001



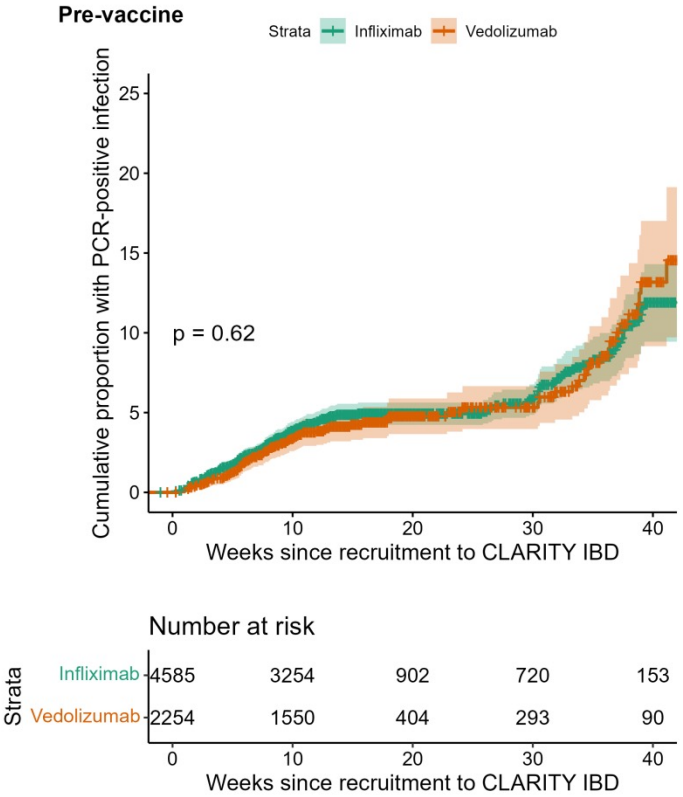
All

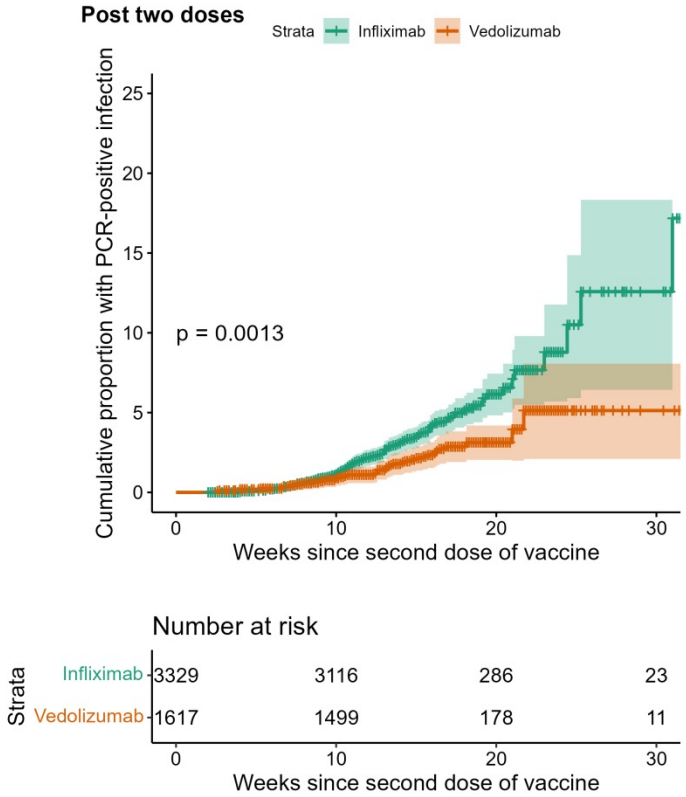
Variable	N	Fold change (95% CI)	p
Infliximab (vs vedolizumab)	2438/3531	0.20 (0.18, 0.23)	<0.0001
BNT162b2 vaccine	1426/3531	3.67 (3.29, 4.10)	<0.0001
Thiopurine	1444/3531	0.82 (0.73, 0.92)	0.00095
Methotrexate	194/3531	0.57 (0.45, 0.72)	<0.0001
Steroids	136/3531	0.65 (0.50, 0.87)	0.0030
Crohn's disease (vs UC or IBDU)	2026/3531	0.79 (0.70, 0.88)	<0.0001
Age ≥ 60	631/3531	0.57 (0.50, 0.66)	<0.0001
Non-white ethnicity	313/3531	1.47 (1.21, 1.77)	<0.0001
Current smoker	353/3531	0.69 (0.58, 0.83)	<0.0001



Unpublished data; earlier version of this in Lin S et al. Res Sq. 2021 Jul 30; doi:10.21203/RS.3.RS-755879/V1.

Breakthrough infections pre/post vaccination





Unpublished data; earlier version of this in Lin S et al. Res Sq. 2021 Jul 30; doi:10.21203/RS.3.RS-755879/V1.

Keeter IBD Research Group

Innovations in CLARITY

- ~90% e-consent
- >6 million data points from 7000 participants, mostly recorded directly using surveys
- Return of serology results direct to participants
- Responsive to changes in pandemic
  - Vaccination
  - Long COVID
  - Persistent viral carriage

Exeter IBD Research Group

Conclusions

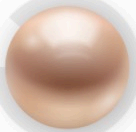
- Most risk of severe COVID-19 is from age and comorbidities, not IBD or IBD therapies

Exeter IBD Research Group

National IBD Doctors Annual Meeting 2021

CLINICAL CHALLENGES & PEARLS

IN CONTEMPORARY IBD CARE



FERRING
PHARMACEUTICALS