British Society of Gastroenterology Inflammatory Bowel Disease section and IBD Clinical Research Group position statement on SARS-CoV2 Vaccination

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Abstract

SARS-CoV2 has caused a global health crisis and mass vaccination programmes provide the best opportunity for controlling transmission and protecting populations. Despite the impressive clinical trial results of the BNT162b2 *(*Pfizer/BioNTech), ChAdOx1 nCoV-19 vaccine (Oxford/AstraZeneca) and mRNA-1273 (Moderna) vaccines, important unanswered questions remain, especially in patients with pre-existing conditions. In this position statement endorsed by the British Society of Gastroenterology Inflammatory Bowel Disease (IBD) section and IBD Clinical Research Group, we consider SARS-CoV2 vaccination strategy in patients with IBD. The risks of SARS-CoV2 vaccination are anticipated to be very low, and we strongly support SARS-CoV2 vaccination in IBD patients. Based on data from previous studies with other vaccines, there are conceptual concerns that protective immune responses to SARS-CoV2 vaccination may be diminished in some IBD patients, such as those taking anti-TNF drugs. However, the benefits of vaccination, even in anti-TNF treated patients, are likely to outweigh these theoretical concerns. Key areas for further research are discussed, including vaccine hesitancy and its effect in the IBD community, the impact of immunosuppression on vaccine efficacy and the search for predictive biomarkers of vaccine success.

Key messages:

1.	We strongly support SARS-CoV2 vaccination for patients with IBD.
2.	The risks of SARS-CoV2 vaccination in IBD patients are anticipated to be very low.
3.	In IBD patients taking immunosuppressive drugs, including biologics and small molecule inhibitors, the key concerns are related to the theoretical risk of sub-optimal vaccine responses rather than vaccine side effects.
4.	We recommend that IBD patients accept whichever approved SARS-CoV2 vaccination is offered to them, in accordance with UK Department of Health and Social Care and the Medicines and Healthcare products Regulatory Agency (MHRA) guidance.
5.	It is important that patients with IBD are offered consistent and unbiased advice. This will be disseminated through the BSG and Crohn's & Colitis UK.

Introduction

The coronavirus disease of 2019 (COVID-19) pandemic is caused by a novel RNA coronavirus termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), not previously known to infect humans[1,2]. SARS-CoV2 causes life-threatening pneumonia, acute respiratory distress syndrome and multi-organ failure[1,2], which has been responsible for a global health emergency. Effective treatment and prevention strategies are urgently needed. Vaccination is a key strategy to protect the health of the world's population from COVID-19 and is likely to be especially important in high risk individuals, such as those with pre-existing conditions[3]. Without a vaccine, the World Health Organisation estimates that 80% of the world population will eventually become infected by this virus.

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC) is a typical immune-mediated inflammatory disease, estimated to affect 620,000 people in the UK, and its incidence continues to increase globally[4,5]. As with other IMIDs patients with IBD may require immunosuppressive drugs, such as high-dose corticosteroids (≥20mg prednisolone or equivalent), immunomodulators (thiopurines, methotrexate and calcineurin inhibitors), anti-cytokine therapies (including anti-TNF and anti-IL-12p40), anti-integrin therapies (vedolizumab) and small molecule inhibitors of signalling (Tofacitinib), which may leave them vulnerable to infection[6,7]. Concerns about the health of IMID patients during the COVID-19 pandemic has led to the introduction of radical and unprecedented health policies, including mandatory prolonged physical distancing measures, such as shielding. However, the risks associated with immunosuppression are not limited to increased susceptibility to infection. Immunosuppressive drugs may reduce the effectiveness of some vaccines, which could have major implications for the safety of immunosuppressed patients in the COVID-19 era.

SARS-CoV2 vaccines are an important opportunity to suppress viral transmission and protect individual patients from COVID-19. Several SARS-CoV2 vaccines are in advanced clinical development, and currently there are three that are approved in the UK (see table 1 and figure 1). It is likely that additional vaccines will become available in the future. The BNT162b2 vaccine *(*Pfizer/BioNTech)[8], the ChAdOx1 nCoV-19 vaccine (Oxford/AstraZeneca)[9] and the mRNA-1273 (Moderna)[10] have been given authorisation for temporary supply by the UK Department of Health and Social Care and the Medicines and Healthcare products Regulatory Agency (MHRA) under Regulation 174 of the Human Medicine Regulations 2012[11-13]. A timeline of SARS-CoV2 vaccine development is shown in appendix 1.

The effect of immunosuppression on SARS-CoV2 vaccines

Although the MHRA does not list immunosuppression as a contraindication to the BNT162b2, ChAdOx1 nCoV-19 or mRNA-1273 vaccines, it does indicate that there is a theoretical possibility that immunosuppressive drugs could reduce the effectiveness of the vaccines. This is based on evidence from studies looking at the impact of immunosuppression on the immunogenicity of vaccines used for other infectious diseases (figure 2). Infliximab monotherapy is linked to impaired induction of protective immunity following hepatitis B[14], hepatitis A[15], pneumococcal[16,17] and influenza[18-20] vaccination, which may be more pronounced when anti-TNF therapy is combined with immunomodulators including thiopurines or methotrexate[21,22]. Vedolizumab, however, which has a gut specific mechanism of action, does not hinder hepatitis B or influenza vaccination, but is associated with impaired antibody responses to cholera toxin, administered orally[23]. There is a lack of data for some of the newer drugs used in IBD, although lessons have been learned in other immune-mediated inflammatory diseases. For instance, in psoriasis, antibody responses to pneumococcal and tetanus vaccines are preserved, and possibly even enhanced in patients treated with ustekinumab, a monoclonal antibody that blocks the p40 subunit of IL12 and IL23[22]. In rheumatoid arthritis, tofacitinib results in diminished induction of protective immune responses to pneumococcal vaccination, but responses to influenza vaccination are maintained[24].

Vaccination logistics in IBD patients

The Joint Committee on Vaccination and Immunisation (JCVI) is responsible for advising which sectors of society are prioritized in national vaccination programmes. As of 30th December 2020, priority sequencing is based on providing protection to the persons most at risk of morbidity and mortality from COVID-19[25]. Since mortality from COVID-19 increases exponentially with age, the initial JCVI prioritisation is primarily age-based. The order of priority for phase 1 of the vaccination programme is listed in table 2.

In keeping with the BSG risk grid[26], it is anticipated that IBD patients who are under the age of 65 years and in the moderate BSG risk category will fall into category 6 (individuals aged 16 years to 64 years with underlying health conditions which put them at higher risk of serious disease and mortality). IBD patients in the BSG high risk category, including those with other comorbidities such as diabetes, chronic respiratory disorders, or morbid obesity, will fall into category 4 (clinically extremely vulnerable individuals). Irrespective of their position in the BSG risk grid, IBD patients who are resident in care homes (category 1), are frontline health and social care workers (category 2) or are aged 75 years or older (category 3) are further prioritized.

In Phase 3 clinical trials, efficacy data for the BNT162b2 vaccine were obtained based on two doses given 21 days apart. Corresponding data for the ChAdOx1 nCoV-19 vaccine and the mRNA-1273 vaccine were based on two doses given 28 days apart. In the context of the rapidly worsening epidemiology of COVID-19 in the UK in late 2020 and given data indicating high efficacy from the first dose of both the BNT162b2 vaccine and the ChAdOx1 nCoV-19 vaccine, the JCVI is prioritising the delivery of the first dose of vaccine to as many eligible individuals as possible**.** Consequently, in the UK the second dose of vaccine may be delivered between 3 to 12 weeks after the first dose of the BNT162b2 vaccine and between 4 to 12 weeks after the first dose of the ChAdOx1 nCoV-19 vaccine[25]. At the time of writing, updated JCVI advice is pending for the mRNA-1273 vaccine. JCVI further advises that the same vaccine should be used for both doses and that switching between vaccines or missing the second dose is not advised.

The main priority with timing is administration of the vaccine at the earliest opportunity. This is especially important with healthcare systems under considerable strain during vaccine roll out and it is recommended that IBD patients accept the first available vaccine appointment offered. For the majority of patients, active IBD should not be a barrier to vaccination, although in patients with severe IBD flares or those requiring hospitalisation, it may be preferable to consider a short delay pending recovery. This is to prevent confusion arising from incorrect attribution of vaccine related adverse effects to complications of acute illness, and vice versa. Maintenance immunosuppression should not be withheld for vaccination and the timing of subcutaneous/intravenous IBD medications should not delay vaccination. There is some evidence with annual influenza vaccination that the timing of anti-TNF administration does not significantly impact on vaccination immunogenicity[27]. High dose systemic corticosteroids, particularly in combination with other immunosuppressants, may reduce vaccine immunogenicity, as has been observed with annual influenza vaccination[22]. Where possible, SARS-CoV2 vaccination should be administered whilst patients are taking the lowest dose of systemic corticosteroid. These considerations should be interpreted in the context of individual cases and discussed with patients. In patients participating in IBD clinical trials, provisions for vaccination should be included in trial protocols and discussed with the sponsor.

It is not necessary to perform serology testing before administering vaccination, even in those with suspected or proven prior infection. IBD patients should receive both doses of SARS-CoV2 vaccination, even if they have previously been infected with SARS-CoV2. This is because data on whether individuals acquire sufficient immunity following COVID-19 are lacking, as are data on the duration and strength of acquired immunity. It is advised that vaccination is performed at least four weeks after onset of COVID-19 symptoms or four weeks

from the first PCR positive specimen in asymptomatic patients[28]. IBD patients should be encouraged to have both the annual influenza and the SARS-CoV2 vaccinations, although co-administration at the same visit is not advised. Other vaccines such as the influenza and pneumococcal vaccines should be scheduled at intervals of at least seven days from SARS-CoV2 vaccination[28]. Following SARS-CoV2 vaccination, IBD patients are presently advised to continue to follow existing guidance on social distancing or shielding, determined by their position in the BSG risk grid[26].

SARS CoV-2 vaccination safety in IBD patients

Patients with IBD will have many questions regarding vaccination and specific data to inform many of these concerns are not yet available. However, there are several factors that can offer some reassurance. There is a robust and comprehensive regulatory process in place and approval is only given when there are compelling safety data. Standards for testing and monitoring of vaccines are generally higher than for most other medical interventions due to their intended use in healthy individuals, in whom the level of acceptable risk is lower. The approved SARS-CoV2 vaccines have been tested in tens of thousands of patients with safety profiles comparable to other vaccines commonly used in IBD patients, and have been appraised by multiple independent regulators, including the MHRA, the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA). The BNT162b2 vaccine, the ChAdOx1 nCoV-19 vaccine and the mRNA-1273 vaccine have received regulatory approval, which apply to patients with IBD. Moreover, for all three vaccines, immunosuppression is not a contraindication. To date there are no studies reporting the effect of any SARS-CoV2 vaccine specifically in IBD patients, as these patient groups have been excluded from the phase 3 vaccination studies. Nevertheless, insights into how different IBD therapies impact host immunity can be inferred from serological responses to other vaccination programs. Notably, other commonly used vaccines (e.g. influenza, HBV, HAV, etc) are also very low risk in IBD patients, although they were never specifically trialled in IBD patients prior to approval.

Regulatory approval is based on safety data generated from monitoring over 19,000 vaccine recipients for at least two months after their second dose (serious side effects from vaccines are very rare beyond this point). Side effect profiles from SARS-CoV2 vaccines are in line with events observed with other commonly used vaccines. Data from the BNT162b2 phase 3 trial, which enrolled >40,000 subjects, the ChAdOx1 nCoV-19 phase 3 trials, which enrolled >23,000 subjects, and the mRNA-1273 phase 3 trial, which enrolled >30,000 subjects, demonstrated that mild local injection site reactions (e.g. pain, redness and swelling) and systemic features (fatigue, headache, chills) were common, but serious adverse events were

rare[9,10,29]. For instance, there were 4 serious adverse events in BNT162b2 recipients, 79 in ChAdOx1 nCoV-19 recipients and 71 in mRNA-1273 recipients. Very rare events of neuroinflammatory disorder have been reported with the ChAdOx1 nCoV-19 vaccine, but a causative role has not been established. There were 2 deaths in BNT162b2 recipients and 4 deaths in placebo recipients, which were considered to be unrelated to the vaccine or placebo. There were four non-COVID-19 related deaths in ChAdOx1 nCoV-19 trials, three in controls and one in the vaccine recipients. All were considered unrelated to vaccination. Five deaths occurred in the mRNA-1273 trial, three in the placebo group (one from intra-abdominal perforation, one from cardiopulmonary arrest, and one from severe systemic inflammatory syndrome in a participant with chronic lymphocytic leukaemia and diffuse bullous rash) and two in the vaccine group (one from cardiopulmonary arrest and one by suicide). In the event of patients experiencing significant side effects related to vaccination, these should be reported through the Coronavirus Yellow Card reporting website[30]. If common side effects such as pain or fever are troublesome, they can be treated with analgesia and/or anti-pyretic medication such as paracetamol.

There are certain groups of IBD patients in whom vaccination is not advised or should be considered on the basis of a benefit versus risk analysis. Vaccination is not currently approved in those under 16 years of age. This is because almost all children will have asymptomatic or very mild disease if affected by COVID-19[31,32] and there are currently no data on the safety and efficacy of SARS-CoV2 vaccination in children. In pregnancy, the routine use of SARS-CoV2 vaccines is not recommended due to the lack of safety data in this population[25]. There is some evidence that severe COVID-19 may be associated with premature birth, but evidence currently suggests that infection during pregnancy poses no additional risk of foetal developmental problems, nor increased risk of miscarriage[33,34]. The JCVI advises that vaccination should be considered in pregnant women in whom the risk of exposure to SARS-CoV2 is high and unavoidable, or in women with underlying health conditions that put them at very high-risk of serious complications of COVID-19. In these cases, risk and benefit should be discussed with individual patients[25,35]. The JCVI advises that breastfeeding is not a contraindication to vaccination. The clinical need for immunisation should be considered and women informed about the absence of safety data for the vaccine in the context of breastfeeding[25,34]. The BNT162b2, ChAdOx1 nCoV-19 and mRNA-1273 vaccines are contraindicated if there is a history of hypersensitivity to the active substance or any of the vaccine excipients. A history of an adverse reaction to other medications, including IBD patients who have had severe immediate-onset anaphylaxis following biologic treatment, is not a contraindication to the BNT162b2, ChAdOx1 nCoV-19 or mRNA-1273 vaccines.

Guidance on allergies for other SARS-CoV2 vaccines will be issued by the MHRA as the vaccines are approved.

IBD disease activity following SARS-CoV2 vaccination

Since SARS-CoV2 vaccines have not been tested in patients with IBD it is not possible to judge whether vaccination will have an impact on IBD disease activity. However, no serious gastrointestinal side-effects to SARS-CoV2 vaccinations have yet been reported. Furthermore, there are reassuring data from studies of IBD patients receiving other commonly employed vaccinations. In a trial of 96 IBD patients administered 23-valent polysaccharide pneumococcal vaccine there were no serious adverse events and no reported deteriorations in IBD disease activity[16]. In a study of influenza H1N1 vaccination, just 12 (11%) of 108 subjects enrolled had an increase of >2 points in either the Harvey Bradshaw Index (HBI) or Simple Colitis Clinical Activity Index (SCCAI) during six months of follow up[18]. Only three patients required consequent alteration in their IBD medication. There was no unvaccinated control group, making it difficult to determine whether these findings were truly associated with vaccination. In another study of trivalent influenza vaccination given to 255 IBD patients, no significant variations in HBI or Mayo scores were seen during two years of follow up following vaccination[36].

Research opportunities

We have identified some key research priorities with regard to SARS-CoV2 vaccination in IBD patients. In light of data showing impaired responses to pneumococcal, influenza and other vaccines in IBD patients on immunosuppression, there is a pressing need to understand whether different immunosuppressive regimens impair the development of anti-SARS-CoV2 immunity in this high-risk population. Although routine serological testing of vaccine immunogenicity may not be available in all IBD units, where available this information could help to guide future studies regarding the need to implementation of mitigation strategies, such as administration of further booster doses of vaccine. This information might also help to inform advice given about physical distancing strategies, including shielding in the event of future surges in COVID-19. The emerging field of precision vaccination seeks to define how baseline features can predict which individual patients will respond to vaccination and to what extent[37]. Baseline characteristics that have been investigated as predictors of vaccination response to other vaccines include germ line genetics, host transcriptional responses, microbiome, metabolome, and particular immune features[37-42]. Future research should employ multi-platform approaches to study biomarkers predicting vaccination outcome. Finally, the uptake of recommended vaccines amongst IBD patients has historically been suboptimal[43]. There is a necessity for qualitative research on attitudes towards SARS-CoV2 vaccination in

IBD patients. Rates of acceptance of vaccination should also be tracked and reasons for non-uptake explored.

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Table 1: Overview of published phase 3 SARS-CoV2 vaccination studies

	Pfizer/BioNTech	**Moderna**	**Oxford/AstraZeneca**
Name	*BNT162b2*	*mRNA-1273*	*ChAdOx1 nCoV-19*
Dosing schedule	2 doses, 21 days apart*	2 doses, 28 days apart*	2 doses, 28 days apart*
Mechanism	mRNA encoding a genetically modified SARS-CoV2 spike protein	mRNA encoding a genetically modified SARS-CoV2 spike protein	Non-replicating adenovirus vector, containing SARS-CoV-2 spike protein
Storage (long term)	-80°C to -60°C	-20°C	+2°C to +8°C
Reported efficacy	95%	94.5%	70%†
Safety	No serious concerns. Two anaphylactoid reactions since MHRA approval and roll-out.	No serious concerns	No serious concerns
MHRA approval	Emergency approval granted 02/12/2020	Emergency approval granted 08/01/2021	Emergency approval granted 30/12/2020

*In the UK, the JCVI has advised that the second dose of BNT162b2 can be given between 3 weeks and 12 weeks after the first dose and the second dose of both mRNA-1273 and ChAdOx1 nCoV-19 can be given between 4 weeks and 12 weeks after the first dose.

† pooled data from two trials - 62% efficacy in one study and 90% in another study in which first vaccination was given at half dose.

Table 2: The Joint Committee on Vaccination and Immunisation (JCVI) phase 1 priority groups[25]

1.	Residents in a care home for older adults and their carers
2.	All those 80 years of age and over and frontline health and social care workers
3.	All those 75 years of age and over
4.	All those 70 years of age and over, and clinically extremely vulnerable individuals
5.	All those 65 years of age and over.
6.	All individuals aged 16 years to 64 years with underlying health conditions which put them at higher risk of serious disease and mortality*
7.	All those 60 years of age and over
8.	All those 55 years of age and over
9.	All those 50 years of age and over

* The ChAdOx1 nCov-19 (Oxford/AstraZeneca) vaccine is only authorised for use in those aged 18 years of age and over, however, JCVI is of the view that this vaccine may be used in those 16-17 years of age where there is no access or availability to an alternative approved COVID-19 vaccine.

Figure 1: The coronavirus SARS-CoV2 and currently approved vaccine mechanisms. Adenovirus vector vaccines are replication-incompetent viruses that have been engineered to express the SARS-CoV2 spike protein to which the recipient immune system responds. Examples include ChAdOx1 nCov-19, JNJ-78436735 and Sputnik-V. mRNA vaccines are delivered in a lipid nanoparticle that is taken up by cells, which translate the mRNA to generate spike protein. Examples include BNT162b2, mRNA-1273 and COVAC1.

Figure 2: Summary of studies of immunogenicity of vaccines in patients taking immunosuppressive therapies. a: Pneumococcal vaccine response rate (response measured as a two-fold increase in anti-pneumococcal antibody titre) is reduced in patients administered anti-TNF monotherapy (58%) and immunomodulator (IM) & anti-TNF combination therapy (63%) relative to mesalamine treated controls (89%)[16]. b: 2009 H1N1 influenza vaccination response rate (response measured as a ≥40% heamagluttinin inhibition (HI) titre) is attenuated in patients on IM & anti-TNF combination therapy (36%) relative to non-immunosuppressed controls (64%)[18]. c: Heatmap adapted from studies of responses to vaccination in patients on IM or anti-TNF therapy showing percentage reduction in seroprotection to pneumococcal[16,44], Hepatitis B (HBV)[14], Hepatitis A (HAV)[15], influenza H1N1, H3N2 and B[45,46].

Contributors:

JLA, GM, DRG, IA and NP researched and wrote the original draft of the article. All authors reviewed, edited, and approved the Article.

Declaration of interests

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