Manuscript Doi: 10.1093/ecco-jcc/jjab046

SARS-CoV-2 vaccination in IBD: past lessons, current evidence and future challenges.

1. Judith Wellens MD, Translational Gastro-intestinal Unit, Nuffield Department of Medicine, John Radcliffe Hospital, Oxford, OX3 9DU.
Translational Research for Gastrointestinal Diseases, University hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium. judith.wellens@icloud.com

2. Jean-Frédéric Colombel, Professor of Medicine, MD, PhD, Department of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York city, New York, USA. One Gustavo L. Levy Place, Box 1069; New York, NY 10029, USA. jean-frederic.colombel@mssm.edu

3. Jack J Satsangi DPhil Lee Placito Professor of Gastroenterology, Translational Gastro-intestinal Unit, Nuffield Department of Medicine, John Radcliffe Hospital, Oxford, OX3 9DU. jack.satsangi@ndm.ox.ac.uk

4. Serre-Yu Wong, MD, PhD, The Henry D. Janowitz Division of Gastroenterology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, USA. One Gustavo L. Levy Place, Box 1069; New York, NY 10029, USA. serre-yu.wong@mountsinai.org

Article type: Review

Address for correspondence: Judith Wellens, Judith.wellens@icloud.com. +32474815145
Experimental Medicine Division, Level 5, Room 5800, John Radcliffe Hospital, Headley Way, Headington, OX3 9DU, United Kingdom

ABSTRACT

Since the beginning of the pandemic, patients with inflammatory bowel diseases (IBD) have been considered at high-risk for infection and complications of COVID-19. However, IBD patients and patients taking immunosuppressive therapy were excluded from clinical phase III vaccine trials, complicating the assessment of effectiveness of these new vaccines. From past experience we know that adapted vaccination strategies may be appropriate in some IBD patients to optimize immunogenicity. We review current evidence on SARS-CoV-2 vaccination relevant to IBD patients, including immune responses from humoral to cellular, emerging data on new variants and off-label vaccination schemes. We also identify clinical and scientific knowledge gaps that can be translated into both large-scale population-based studies and targeted vaccine studies to describe the precise immune responses induced by SARS-CoV-2 vaccines in IBD patients. We strongly endorse the recommendation of vaccinating IBD patients to ensure maximal protection from COVID-19 both for the individual and the community.

Keywords: vaccination strategies, inflammatory bowel disease, SARS-CoV-2, immunogenicity

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1. Introduction

The inflammatory bowel diseases (IBD), principally Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory conditions of the gastrointestinal tract of global importance, with prevalence rates of approximately 0.5- 1% in Western populations.[1] The clinical management of IBD during the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic has been an area of great concern to patients and physicians worldwide. While IBD patients have altered underlying immune responses which may leave them more vulnerable to infections [2], immunosuppressive treatment is widely accepted as a key determinant of risk for serious, opportunistic and vaccine preventable infections [3,4].

Of immediate concern given the recent roll-out of several vaccines to combat COVID-19 (Corona Virus Disease 2019), is the consideration that the immunological response to vaccination may be blunted in IBD patients receiving immunosuppressant treatment, increasing the need for alternative strategies.[3] IBD patients were not included in safety and efficacy phase III-trials for COVID-19 vaccines, and neither were patients managed with immunosuppressive therapies. In this review we aim to complement existing recommendations considering vaccination for SARS-CoV-2 in IBD patients by integrating knowledge of efficacy and safety of vaccines other than SARS-CoV-2 in IBD patients with the rapidly emerging data from vaccination and viral evolution in SARS-CoV-2.[5]

2. SARS-CoV-2

2.1 SARS-CoV-2 in IBD

By the time of writing in the beginning of 2021, over 111 million confirmed SARS-CoV-2 cases, including over 2.4 million deaths, have been reported to the World Health Organization (WHO). Although COVID-19 leads to few or mild symptoms in the majority of affected patients, it may cause severe and lethal disease in others, more specifically progressive pneumonia, acute respiratory distress syndrome and organ failure driven by hyperinflammation and a cytokine storm syndrome. SARS-CoV-2 uses the receptor ACE2 to enter the host cell

and can infect intestinal tissue, where ACE2 is highly expressed, notably more abundant in ileal than colonic tissue. With the demonstration that this receptor is induced in patients with active colonic IBD, and also influenced by increasing age, active smoking status and active disease[6], real concern arose that active disease could lead to increased susceptibility. The question as to whether immunosuppressant therapy increases this risk by the nature of the therapy or paradoxically decreases it by addressing intestinal or systemic inflammation, is unclear.[6–8] As a result, early in the first wave of the pandemic, guidelines from the International Organization for the study of Inflammatory Bowel Disease (IOBD) were released suggesting that after an assessment of potential risks and benefits, maintenance therapies should not be withheld.[8] Furthermore, patients on immunomodulation were asked to adapt stringent hygienic measures, 'shielding' from the community if possible or put in place extended social distancing to avoid infection.[7,9]

The initial data that emerged regarding the risk of severe COVID-19 in IBD patients in 2020 were relatively reassuring. The first observational data reporting on this risk, came from Italian centers and reported no increased negative outcomes in IBD patients, even when on anti-TNF therapy.[10] The Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) observational database of reported COVID-19 in IBD patients, a large worldwide initiative concurred with this evidence, showed that systemic corticosteroids, but not anti-TNF was associated with severe COVID-19.[11] However, more recently, the extended follow-up report from the SECURE-IBD of 1439 patients in 47 countries raised concern that thiopurine monotherapy and combination therapy of thiopurines and infliximab was associated with increased risk for severe COVID-19, compared to infliximab monotherapy.

Whilst the SECURE registry addressed the incidence of severe complications, the study has not allowed assessment of susceptibility to mild or subclinical infection. In this context, observational seroprevalence data from Germany, Italy, the UK, and US (private communication) in IBD patients on either vedolizumab or infliximab did not show an elevated seroprevalence of SARS-CoV-2, suggesting continuation of infusion medications and attending infusion centers are safe practices. [10,12–15] Indeed these data leave open the possibility of a protective effect of cytokine blockers.[12] It is important to note that these are observational studies and carry the risk of confounding bias. For example, more restrictive social behaviors might explain these results.

Several large prospective studies are currently under way to assess seroprevalence longitudinally in IBD patients treated with infusion therapies (vedolizumab and infliximab), namely the global International study of

COVID-19 Antibody Response Under Sustained Immune Suppression in IBD (ICARUS)[16] and the UK Impact of Biologic and Immunomodulatory Therapy on SARS-CoV-2 Infection and Immunity in Patients with Inflammatory Bowel Disease (CLARITY-IBD) initiatives (ISRCTN45176516). These studies will yield important information on IBD patients' immunological response to natural infection with SARS-CoV-2 and the effects of immunomodulating therapeutics, which are important baseline data as we look to assess responses to SARS-CoV-2 vaccines in these patients. When available, the data can be contrasted to our current knowledge of the pathophysiology and immune response associated with natural recovery in the immunocompetent host, as is discussed in section 4.1.

2.2 SARS-CoV-2 vaccines

The pandemic has catalyzed a rapid joint response from research and industry to produce a novel vaccine. This has paved the way for the development of new vaccination strategies such as mRNA platforms and use of adenoviral vectors, of which there are now registered vaccines, while others are still in various stages of development (figure 1).[17,18] Most current vaccines target the spike protein of SARS-CoV-2, which is the protein that binds to the ACE2 receptor, since analysis of convalescent patients suggested that this is an immunodominant antigen, eliciting both antibody and T cell responses.[19]

The ChAdOx1 nCoV-19 vaccine developed by AstraZeneca in Oxford, is a replication-defective chimpanzee adenovirus-vectored vaccine that expresses the full-length SARS-CoV-2 spike glycoprotein gene. The advantage of the adenovirus vector is that viral antigens can be transferred safely to host cells without the risk of replication (of living viral vaccines) and without the need for adjuvants, but with preserved induction of strong T cell responses[20]. A simian adenovirus was used to bypass potential pre-existing immunity to the vector. This vaccine was indeed shown to induce both humoral and T cell responses in rhesus macaques and humans.[18,21]. In their phase I/II trials, Barrett and colleagues showed that the vaccine elicited a multifunctional antibody response, with the formation of Fc-mediated antibody responses (such as antibody-dependent neutrophil/monocyte phagocytosis, complement activation and natural killer cell activation), along with neutralizing antibodies to the spike protein (figure 2).[22] In the interim analysis of their phase III trial (4 RCTs in

the UK, South-Africa and Brazil), these laboratory data were backed up by an overall efficacy of 70.4% (with a effectiveness of up to 90.0% in subjects receiving a lower first dose, followed by a standard dose).[23] Local and systemic adverse events were common, but mild overall and were better tolerated in older adults.[18] These interim results were confirmed by a pooled analysis of the full primary results, reporting evidence for a 3-month interval with vaccine efficacy of 76.0% at day 22-90 after the first dose.[24]

Another vaccine now available that deploys a similar approach is the Sputnik V vaccine, also known as Gam-COVID-Vac. This Russian vaccine contrasts to the AstraZeneca one, in that it is a heterologous recombinant adenovirus-based vaccine (rAd). Although it also carries the gene for the full-length spike glycoprotein, the vector for the first shot is a rAd type 26, followed by an rAd type 5 to minimize anti-vector immunity.[25] Delivered with a 21-day interval, an interim phase III trial analysis showed an efficacy of 91.6% (COVID-19 confirmed cases) with good tolerability.[25]

In addition, there are currently two types of mRNA vaccines available: the 1273 and BNT162b2 vaccine by Moderna and Pfizer BioNtech, respectively. Both are lipid nanoparticle–encapsulated mRNA-based vaccines encoding the spike glycoprotein of SARS-CoV-2, a platform that has proven capable of forming neutralizing antibodies in a T cell-dependent manner.[17,26–28] In their phase III trials, induction of both neutralizing antibodies and T cell responses was reported, although more detailed functional studies like in the ChAdOx1 nCoV-19 are currently not available. Efficacy data for both vaccines proved to be above expectations early in the phase III trials. For the BNT162b2 vaccine, 21,720 participants received the vaccine versus 21,728 who received placebo injections, and the reported protection of against COVID-19 was 95%.[29] For the mRNA-1273 vaccine, there were 15,210 participants in each of the vaccine and placebo arms, and a 94.1% efficacy at preventing COVID-19 illness was reported.[30] The most common side-effects were short-term, mild-to-moderate injection site pain and mild systemic reactions, consistent with other approved vaccines.[29,30]

Other vaccination strategies have emerged - in the recently published phase I trial of BBV152, a whole-virion inactivated vaccine that is linked to a toll-like receptor (TLR) 7/8 agonist to help stimulate cell-mediated responses, was shown to be safe and induce serological response. Such a vaccine delivers many more epitopes

to elicit both humoral and cellular immune responses, which can be an important asset when mutations arise in the spike glycoprotein.[31]

2.3 Vaccinating IBD patients: is today better than tomorrow?

A statement from the IOBD was recently released; using the Delphi method, the group's consensus clearly states that vaccination is safe and the ideal timing for vaccination is as early as possible.[32] Concurring with this, both D' Amico et al and the British Society of Gastroenterology Inflammatory Bowel Disease section and IBD Clinical Research Group position statement proclaim that the advantages to vaccination outweigh the possible disadvantages from vaccinating our patients and that unbiased and consistent advice should be provided to patients to discourage vaccine hesitancy.[5,33] Moreover, all cited sources emphasize that vaccine effectiveness rather than safety is the key concern in IBD patients, and patients should be encouraged to receive vaccination whenever possible to reach the highest possible vaccination rate.[32,33]

However, patients with an 'immunosuppressed or immunodeficient state' were excluded from COVID-19 vaccine clinical trials to-date. Thus, there are no evidence-based data on efficacy and safety for IBD patients. This lack of evidence is complicated further by the fact that the immune response in natural infection in otherwise healthy subjects is still incompletely characterized, especially regarding durability of a (protective) immune response after natural infection and after vaccination. The many uncertainties (Box1) can be addressed through large-scale, prospective clinical trials, and painstaking post-marketing surveillance, complemented by 'deep' immunological studies to fully understand the effect of both natural infection and vaccination on this special population.

3. Vaccination in IBD: lessons from the past

Although numerous groups and experts support the importance of adequate vaccination of IBD patients[34,35], the percentage of physicians that monitor and routinely recommend vaccination to IBD patients is low (approximately 50%)[2,4], resulting in a lower vaccination uptake in IBD patients compared to the general population.[4,36] Importantly, vaccination in IBD is considered to be safe and is not associated with disease onset

or exacerbation.[32,33] Studies assessing the inherent immunogenicity of vaccination strategies in IBD are scarce and mainly date back to a time when treatment options were limited (table 1). However, the therapeutic armamentarium that is available today comprises a variety of immunomodulatory drugs, which may be important determinants of altered immunogenicity to vaccination efforts (table 2-3).

Regarding influenza vaccination, several studies have suggested attenuated responses in IBD patients. A study of 132 IBD patients reported adequate immunogenicity with lower response to the inactivated quadrivalent influenza vaccine when treated with infliximab.[37] Furthermore, a prospective study in 255 IBD patients confirmed high seroprotection rates, but with lower persistence in patients with anti-TNF treatment.[38] This was confirmed again in a study with 66 IBD patients that showed inhibited response to some strains when under infliximab, immunomodulators or the combination of both.[39] Yet another study on the adjuvanted 2009 A/H1N1 pandemic vaccine showed that patients on infliximab had a worse serological response than healthy controls, and worse still when treated with a combination of infliximab and other immunosuppressive therapy.[40]

On the other hand, in a large rheumatological study, adequate serological protection was found after a single influenza vaccination, without significant effect of TNF-blockers.[41] A similar study that included IBD patients also showed that the proportion of patients attaining a protective response was not significantly altered (although a modest decrease in antibody response to A/H3N2 and B was noted), suggesting vaccination in these patients is productive.[42]

Looking at non-influenza vaccines, the hepatitis B vaccine has been extensively studied and has been found to be less immunogenic in IBD patients than in non-IBD controls, which is even more pronounced when treated with immunosuppressant medication.[4] Mechanistically, recent research in patient with ankylosing spondylitis has revealed that TNF blockade severely inhibits T cell dependent humoral responses, resulting in suppressed responses to hepatitis B vaccination. On the other hand, T cell independent response to the 23-valent

pneumococcal polysaccharide vaccine (PPSV-23) was only modestly affected.[44] Interestingly, a study of 15 CD patients showed that clinical response to infliximab was associated with an improvement of splenic function measured by a decreased proportion of pitted red cells and expansion of the IgM-memory B cell pool. This memory B cell population is important for protection against encapsulated bacteria, illustrating the complexity of vaccination responses.[44] Regarding new vaccination platforms, one study regarding adenoviral vector vaccines *in vitro* has shown that mucosal-associated invariant T (MAIT) cells contribute to maximal immunogenicity in a TNF- dependent manner in both mice and humans.[45] This raises the concern that there may be reduced protection conferred via adenoviral-based vaccines, when receiving anti-TNF based, maintenance therapy. Moreover, the functionality of MAIT cells in mounting and effective immune response in IBD patients without TNF blockers, needs to be determined. While only recently discovered in 1993, MAIT cells represent about 10% of our T cell population and are profusely found in peripheral blood, liver, gut and lungs. They perform innate-like immunity functions upon recognition of bacterial metabolites through an MHC-class I-related MR-I molecule or through T cell receptor-independent activation via inflammatory and antiviral cytokines to combat viral infection and have both (tissue specific) effector and memory functions, which are attractive for vaccine development for pathogens that propagate through mucosal entry.[46] In IBD patients, MAIT cells in the peripheral blood are found to be reduced, but exert a more activated state, while data on MAIT cells in inflamed gut tissue are conflicting.[47] What this means for vaccination response in IBD patients, is currently unknown.

These studies raise the concern that patients receiving immunosuppressive therapies like anti-TNF (combination therapy) may be at risk for reduced vaccination responses. The question is: can attenuated vaccine responses be overcome in IBD patients? Strategies to address this for other vaccines have involved alternate dosing and schedules. The aforementioned study of 132 patients, showed no effect for an added booster of the quadrivalent inactivated influenza virus.[37] These results are similar to an earlier randomized study on the trivalent influenza vaccine, also reporting that a second booster did not improve the immune response in 78 IBD patients treated with immunosuppressant therapy.[48]

Alternatively, a higher dosage protocol could be considered. A randomized controlled trial in 59 IBD patients (40 on infliximab and 19 on vedolizumab) and 20 healthy controls, generated significantly higher H3N2 antibody levels when receiving the high dose vaccine compared with the standard dose.[49] In contrast, H1N1 postimmunization antibody levels were not significantly different. Interestingly, IBD patients receiving the high dose influenza vaccine and those on vedolizumab who received standard dose had equivalent antibody concentrations to healthy controls. Taken together, these data suggest that higher dose influenza vaccines could be beneficial in patients on anti-TNFs but not needed in patients receiving vedolizumab.[49] Regarding hepatitis B vaccination, a significantly higher seroconversion rate was found in 148 Crohn's disease patients (with or without immunosuppressive therapy) after adapting a double dosage and faster protocol (Engerix B double dose at 0, 1 and 2 months vs. the standard protocol (Engerix-B single dose at 0, 1 and 6 months).[50]

Of note, considering the timing of infusion relative to administration of a vaccine, a randomized controlled trial in influenza in 137 IBD patients on infliximab maintenance therapy showed no difference in serological protection whether the vaccine was administered midway or at the time of infusion.[51]

There is limited evidence on vaccination efficacy for the newer therapies such as vedolizumab, ustekinumab and tofacitinib. Nonetheless, the current evidence available for these therapies is generally encouraging.[52,53] Interestingly, IBD patients receiving ustekinumab appear to mount robust humoral and T cell responses to influenza vaccination.[54] On the other hand, there may be reduced responses to oral vaccination strategies in patients on vedolizumab, possibly due to reduced homing of T cells, assessed after administering an oral cholera vaccine.[55] As we look to other diseases for which these medications are prescribed, in rheumatoid arthritis patients, tofacitinib is associated with a reduced humoral response to the PPSV23 vaccine (pneumococcal polysaccharide vaccine).[56,57] Notably, ustekinumab is also used in psoriasis, but with a different dosing regimen than when treating colitis, thus complicating comparison.[58]

4. SARS-CoV-2 vaccination efforts in IBD: host-virus considerations and studies needed

4.1 A call to arms - immune responses to SARS-CoV-2 vaccination

As SARS-CoV-2 vaccine distribution broadens, patients and clinicians will be first and foremost eager to know clinical efficacy of vaccination in IBD patients. In addition to this, it is crucial to note that immune protection induced by vaccinations is mediated through a complex interplay amongst innate, humoral, and cell-mediated responses. Variations in both the quality and quantity of an immune response can be substantial, as illustrated by a more than 100-fold difference in antibody titers after vaccination for hepatitis B.[59] A recent review highlights vaccine-related factors, including type, product, adjuvant, dose, and administration factors (i.e. schedule, site, route, time of vaccination), and individual factors, such as immunogenetics, microbiota, anti- and probiotics, malnutrition and vitamin deficiencies, that could contribute to an individual's humoral responses.[59,60] Therefore, clinicians and scientists must take into account measurements of immune responses and individual determinants of SARS-CoV-2 immune responses. First, "correlates of protection" must be defined, for example "a specific immune response to a vaccine that is closely related to protection against infection, disease, or other defined end point".[61] This is important as some vaccines might only protect against clinical disease, but not asymptomatic infection with viral shedding. In such a case, the pathogen could still be transmissible with major complications in controlling the virus on community level.[61]

Second, antibodies are often used as a surrogate of response, but there are several important details to keep in mind. Since neutralizing antibodies to SARS-CoV-2 have been shown to protect against disease in animal models and both convalescent plasma and industrialized antibodies have been used with varying clinical success, it is generally assumed that neutralizing antibodies are necessary for immunity to SARS-CoV-2 and have been the primary endpoint in vaccination efficacy trials.[62–64] The main SARS-CoV-2 neutralizing antibodies studied recognize Spike (S) protein, which mediates receptor binding, adhesion and cellular entry. The S protein is the main target of vaccine-induced immune responses to date (with the exception of whole attenuated or inactivated virus vaccines) and can be measured by a variety of commercially available assays. Of note, other commercial assays measure antibodies to nucleocapsid (N) protein, which can be robust during

early stages of infection. These antibodies would not be generated in response to vaccination with S protein vaccines, but they are expected to appear when attenuated/inactive virus vaccines would be used or after natural infection with SARS-CoV-2.

To complicate this analysis of response further, "adequate" levels of binding antibodies do not necessarily mean they are also functional in terms of neutralization capacity for viruses.[59,61] In fact, antibody response *in vitro* does not necessarily correlate with health outcomes. It is important to note that seroconversion does not translate into disease protection, and the correlate can also be true - a lack of seroconversion is not necessarily associated with susceptibility.[59,65] In addition, antibody levels may wane with time, but seronegative individuals can still be protected through other immune mechanisms, as shown, after hepatitis B vaccination.[59] Thus, while measuring antibodies is straightforward, interpretation of results can be rather complex.

Furthermore, there is good evidence to support the role of cellular immunity in combatting SARS-CoV-2.[66,67] Myriad studies have emerged showing distinct cytokine signatures and T cell specific responses independent of antibody responses and a profound T cells response in SARS-CoV-2 is believed crucial in mounting an effective antibody response, cytotoxic capacities and inducing a long term immunological memory to protect against reinfection, even with cross-reactive properties.[68] These will be important to explore in IBD patients, for which little is known regarding T cell responses to SARS-CoV-2. Evidence from cytomegalovirus (CMV) suggests passive antibodies have the ability to protect, but once latent infection has been established, T cell function is necessary to control reactivation and clinical disease.[61] In the case of influenza, antibody titers after vaccination are shown to be unreliable for predicting risk of influenza in the elderly, again necessitating a T cell response.[20] Assays that measure B and T cell activation, lymphoproliferation, and cytokine responses to SARS-CoV-2 in IBD patients are needed, as well as standards for the general population and more 'classic' virology for comparison.

As an added factor, the genetic profile may be important in the vaccinee, and several HLA haplotypes in the general population have been associated with a higher risk of vaccination failure; however, whether these genetic factors cause deficient antigen presentation or diminished recognition by immune cells and whether this will be important in SARS-CoV-2 remains unknown.[2] Large ongoing genomics research efforts will be informative, as they have been in identifying determinants of severe COVID-19.

Finally, immune development could be influenced by SARS-CoV-2 infection in the gut, which is of particular importance in IBD patients. COVID-19 appears to be associated with gut dysbiosis that can reflect disease severity and persist after viral clearance.[69] Intriguingly, memory B cells appear to undergo continued clonal turnover and somatic hypermutation six months after resolution of primary SARS-CoV-2 infection.[70] While yet to be proven as the causative persistent antigen presence driving long term enhancement of B cell responses, SARS-CoV-2 RNA was found in intestinal tissue biopsies from asymptomatic convalescent patients in whom nasopharyngeal swab PCRs were negative.[70]

Taken together, in order to improve vaccine immunogenicity and efficacy, studies quantifying immune responses and individual determinants for response to vaccination in IBD patients will be essential to pursue.[59]

4.2 SARS-CoV-2: a moving target

Recently, the topic of viral mutation was brought to the attention of both the lay press and the scientific community due to the emergence of several SARS-CoV-2 variants, broadly known as the 'UK', 'South-African' and 'Brazilian' variant.[71–73] Interestingly, these kind of mutants were long expected, and there are currently more than 35,000 genome sequences publicly available with an ever-growing number.[74] As reported by the Center for Disease Control (CDC), the 'UK' variant goes under the various names of B.1.1.7 lineage (a.k.a. 20I/501Y.V1 Variant of Concern (VOC) 202012/01) and has a mutation in the receptor binding domain of the spike protein at position 501 (N501Y), where amino acid asparagine (N) has been replaced with tyrosine (Y). Importantly, this variant also has several other mutations, including: 69/70 deletion, P681, ORF8 stop codon (Q27stop) and has been associated epidemiologically with increased transmissibility.[75] A 'South African' variant is known as the B.1.351 lineage (20H/501Y.V2) and has multiple mutations in S protein, including K417T, E484K, N501Y.[75] Lastly, the 'Brazilian' variant P.1 lineage (20J/501Y.V3) contains 17 unique amino acid changes and 3 deletions. This variant contains three mutations in the spike protein receptor binding domain: K417T, E484K, and N501Y.[75]

These variants are concerning because they have been associated both with increased transmissibility and evasion of neutralizing capacity of antibodies (in vitro).[76,77] Notably, one of the first studies addressing this question on the 'South African' variant showed that the mutant virus exhibited substantial to complete escape from neutralization by convalescent plasma.[78] Subsequent studies assessing the serum neutralizing capacity after vaccination with the mRNA-1273 and BNT162b2 vaccine by Wu et al. and Liu et al respectively, reported weaker neutralization responses to the B.1.1351-spike virus, which is of concern and warrants further study.[79,80]

Of recent special interest, is the E484K mutation, that has now not only been found in the 'South African' and 'Brazilian' variant, but has also emerged in UK samples.[81] Concern has arisen since Collier and colleagues released a preprint that assessed the immune response after BNT162b2 vaccination using a viral pseudotypes.[82] After a single vaccination, the neutralizing serum capacity was reduced by a 3.85-fold when comparing the wild-type to the B.1.1.7 containing pseudoviruses. This reduction was even more severe when an E484K mutation was introduced to the B.1.17 background.

This could foreshadow important reinfection capacity and possible ineffectiveness of the currently available vaccines (as evidenced by lower effectiveness of the Novavax and Johnson & Johnson vaccines in South-Africa vs. UK and US sites)[83,84], though it is possible that non-neutralizing antibody functions or cellular immunity respond differently to these mutated variants and that the herd immunity after natural infection or vaccination is not affected in a dramatic way. Additionaly, increasing data show that the B.1.1.7 lineage might be associated with an increased risk of hospitalization and death as communicated by the New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG).[85]

Viral surveillance is and will remain of utmost importance to diagnose potentially important mutations associated with increased infectivity or a more severe course of disease. Large-scale post-marketing (epidemiological) studies, integrated with these point-mutations and crystal structures will be key to understanding the true clinical meaning of this viral evolution.[86]

As vaccines are rolled out all over the world and the demand is high, policy makers are faced with decisions regarding prioritizing of certain groups and vaccine delivery. A strategy was adopted by the UK which involves delaying the second dose of the Pfizer/BioNtech vaccine until 12 weeks after the first dose, instead of the recommended interval of 21 days. The rationale of the Joint Committee on Vaccination and Immunization (JCVI) was that 50-60% efficacy with one dose is preferable over 95% efficacy for half the number of individuals in trying to get maximal coverage of the population as quickly as possible and thus safe more lives.[87] Unfortunately, this hypothesis was not based on evidence, and the WHO, Federal Drug Administration (FDA), European Medicines Agency (EMA) and CDC in the US all recommended against delaying this second dose. Nonetheless, Denmark also adapted the same strategy in delaying second doses up to 6 weeks. Interestingly, a preprint from a study in Scotland has been released showing an encouraging reduction of COVID-19 related hospitalization of 85% (for the BNT162b2 vaccine, 95% CI 76-91%) and 94% (for the ChAdOX1 vaccine, 95% CI 73-99%) in a prospective cohort study of 5.4 million people 28-34 days after a single dose.[88]

Moreover, in Israel, one of the leading countries regarding vaccine coverage, reported that in 200 000 patients (of age 60 or older), their chances of testing positive for the virus were reduced by 33%, 2 weeks after their first dose of the Pfizer/BioNtech vaccine.[89] Similarly, early reductions in SARS-CoV-2 infection and COVID-19 rates were seen in Israeli health-care workers after receiving the first dose of the BNT-162b2.[90]

Some concerns remain on the longevity of response continue – notably the report in the *New England Journal of Medicine* that neutralizing antibodies fell dramatically in 34 healthy participants by the time of the second dose of the Moderna vaccine.[91] This is worrisome since, similar to the Pfizer/BioNtech vaccine, the Moderna vaccine is an mRNA vaccine; in fact, the Moderna vaccine uses a higher dose (100 micrograms) than the Pfizer vaccine (30 micrograms).[92]

Although overall the real-life evidence is increasingly encouraging, longer-term follow-up will be crucial in determining how these data translate to clinical outcomes. To date, alterations in immunity after 34 days after a first dose has not been reported formally and these findings might still alter these preliminary results.[93]

To complicate this risk-benefit analysis, safety concerns have arisen from Norway regarding the vaccine itself in especially frail vulnerable individuals, by definition at increased risk from Covid-19. Although investigations are still ongoing, fatal outcomes were reported in 33 patients over 75 years of age who received the Pfizer/BioNtech vaccine in care homes.[94] In light of these current trends, it will be of utmost important to follow vaccine responses carefully in IBD patients particularly as their responses to SARS-CoV-2 vaccination whether to standard or delayed dosing are unknown.[92]

5. Concluding remarks and future directions

The mechanisms involved in the altered response to vaccines in IBD patients remain largely unknown. Since both the relative contributions of different immune cell deficiencies in IBD and the induced deficiencies by immunomodulatory drugs remain elusive, adequately predicting the immunogenicity of any given vaccine remains challenging. More basic and clinical research is necessary to understand both the immunological landscape of IBD patients and their drugs to adequately protect this patient group from vaccination preventable diseases.

In light of the current SARS-CoV-2 pandemic, we wholeheartedly agree vaccination against SARS-CoV-2 is a valuable asset against the worldwide fight against COVID-19. Although there are still many unanswered questions (such as longevity of protection, special populations including IBD and the immunocompromised, impact of new variants on protection after vaccination and natural infection and so on), vaccination provides vital protection for both the individual and the community and should be encouraged in all patients. At the same time, continued clinical vigilance and intensive research studies both on the clinical level and in the laboratory are needed to shed light on this evolving virus and what it means for our patients.

Acknowledgements

We would like to acknowledge the support from the Leona M. and Harry B. Helmsley Charitable Trust and Siemens to make the ICARUS study possible.

Author's contributions

All authors listed have made a substantial, direct and intellectual contribution to the paper and approved it for publication.

Funding

In preparation of this manuscript, no external funding was received.

Data availability statement

No new data were generated or analyzed in support of this research.

Declaration of interests

J.W. and S.Y.W have no conflicts of interest to declare. J.S. has received lecture fees from Falk Foundation, Takeda. Research support from The Helmsley Trust, ECCO Pioneer Award, EC Horizon 2020 program. J.F.C reported receiving research grants from AbbVie, Janssen Pharmaceuticals and Takeda; receiving payment for lectures from AbbVie, Amgen, Allergan, Bristol-Myers Squibb Company, Ferring Pharmaceuticals, Shire, Takeda and Tillots; has received consulting fees from AbbVie, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb Company, Celgene Corporation, Celltrion, Eli Lilly, Enterome, Ferring Pharmaceuticals, Genentech, Gilead, Iterative Scopes, Ipsen, Immunic, lmtbio, Inotrem, Janssen Pharmaceuticals, Landos, LimmaTech Biologics AG, Medimmune, Merck, Novartis, O Mass, Otsuka, Pfizer, Shire, Takeda, Tigenix, Viela bio; and holding stock options in Intestinal Biotech Development.

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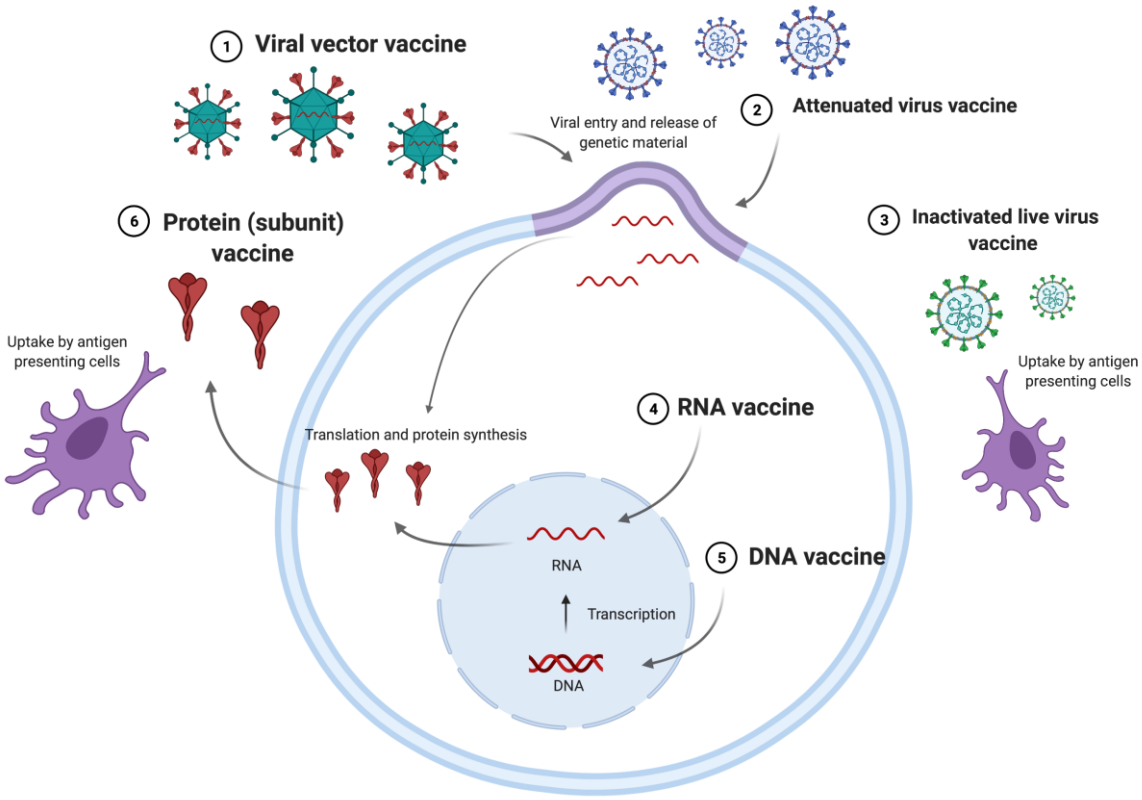

Figure 1: Mode of action of different vaccine platforms with regard to the viral replication cycle. Viral vector vaccines: AstraZeneca/Oxford, Johnson&Johnson, Sputnik V. Live attenuated vaccine. Inactivated vaccine: Sinovac, Sinopharm. RNA vaccine: Pfizer BioNtech, Moderna. DNA vaccine. Protein (subunit) vaccine: Novavax. Made with Biorender.com.

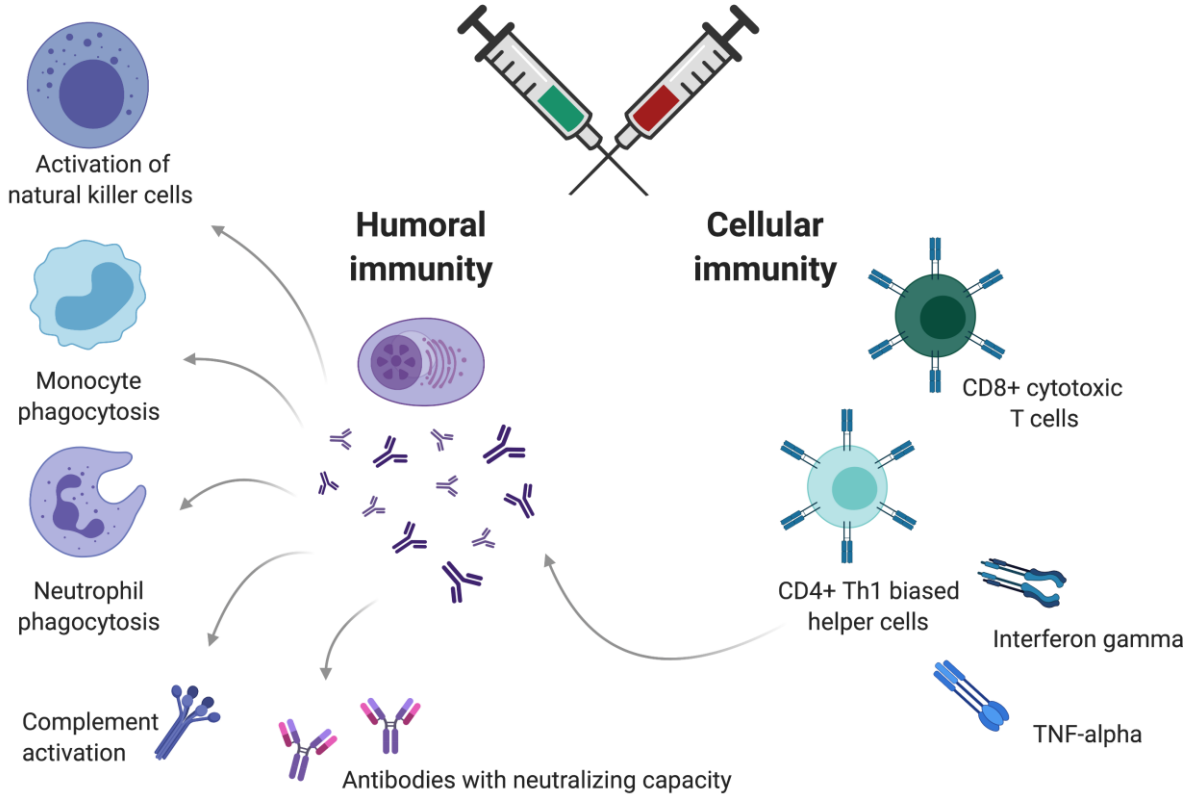

Figure 2: Activation of the immune system after vaccination with the AstraZeneca/Oxford, Pfizer/BioNtech and Moderna vaccine. Note: engagement of complement, natural killer cells and monocyte/neutrophilic phagocytosis only studied for the AstraZeneca/Oxford vaccine. Made with Biorender.com.

Manuscript Doi: 10.1093/ecco-jcc/jjab046

Box 1: COVID-19 vaccines in IBD: unanswered questions (and research strategies to answer them)

1. Vaccination for SARS-CoV-2

1. Will mutant viruses render the current vaccines ineffective?

2. Do we need heterologous vaccination strategies to face mutant virus?

3. Do we need newly developed vaccines (eg. not targeting the spike protein)?

4. Are the humoral and cellular immune responses durable after vaccination?

5. Are neutralizing antibodies the most accurate correlate of protection and is there a threshold titer to be met?

6. Can a genetic blueprint predict vaccine effectiveness?

7. Is vaccinating patients with previous natural infection rational?

Post-marketing surveillance with swift dissemination of results, together with clinical research (such as GWAS in the UK, sequencing of new strains and comparison with epidemiological data) will be necessary.

2. Vaccination for SARS-CoV-2 in IBD

1. Is vaccination safe in IBD?

2. Is vaccination effective in IBD?

3. Which treatments (if any) are associated with a decreased immunogenicity to SARS-CoV-2 vaccination?

4. Are altered vaccination scheduled necessary in IBD (such as increased dosing, relation to infusion therapy, extra dosing?)

5. Are humoral and cellular immune responses in IBD of equal quality and duration as in the general population?

6. Is one vaccination platform preferable to another in IBD patients?

The OCTAVES trial is currently rolled out in the UK to answer these questions in several chronic diseases including IBD, cirrhosis, liver transplant patients, rheumatological patients and patients on hemodialysis. In the USA, a study in California is currently recruiting to better understand the immune response in 1000 adult patients, not excluding chronic disease (clinicaltrials.gov NCT04664309).

Table 1. Evidence on mechanisms associated with a reduced vaccine response in IBD (not therapy-related)

Vaccine	Proposed mechanism of reduced response	Reference
Pneumococcus (PPSV23)	Impaired formation of memory B cells	Di Sabatino et al.[9544] Fallahi et al.[96]
Tetanus toxin	Impaired generation of IgG secreting plasma cells	Stevens et al.[97]
HBV	Not described	Altunöz et al.[98] Belle et al.[99]
Mumps	Partial impairment in T cell response	Tönnesmann et al.[100]

PPSV23: Pneumococcal polysaccharide vaccine

Table 2. Evidence of therapies associated with a reduced vaccine response in IBD.

Vaccine	Therapy regimens associated with reduced response	Reference
Influenza	Anti-TNF, thiopurines, combination therapy anti-TNF and thiopurines. 'Immunosuppression' defined as systemic corticosteroid or biologic therapy or thiopurines or combination therapy	DeBruyn et al.[101] Lu et al.[102] Doornekamp et al.[54] [103] Mamula et al.[103] Andrisani et al. [40] Hagihara et al. [39] Gelinck et al.[42] Shirai et al. [37] Launay et al. [38]
HBV	Anti-TNF, thiopurines, combination therapy anti-TNF and thiopurines, 'Immunosuppression' defined as systemic corticosteroid or biologic therapy or thiopurines or combination therapy	Gisbert et al.[104] Chaparro et al. [105] Loras et al.[106] Altunöz et al.[98] Cunha et al.[107] Andrade et al. [108] Harrington et al. [109]
Pneumococcus (PPSV 23)	Anti-TNF, combination therapy anti-TNF and thiopurines.	Melmed et al.[110] Fiorino et al. [111]
HAV	Anti-TNF therapy	Park et al. [112]
Oral cholera vaccine	Vedolizumab	Wyant et al. [55]

PPSV23: Pneumococcal polysaccharide vaccine, HAV: hepatitis A vaccine

Table 3. Evidence of therapies with intact vaccine response in IBD.

Therapy	Vaccine	Reference
Thiopurines	Pneumococcus (PPSV23), Haemophilus influenzae type B, Tetanus	Dotan et al. [113]
Vedolizumab	Influenza, Pneumococcus (PCV13, PPSV23), Hepatitis B	Harrington et al. [109] Wyant et al. [55]
Ustekinumab	Influenza	Doornekamp et al. [54]

PPSV23: Pneumococcal polysaccharide vaccine, PCV: Pneumococcal conjugate vaccine