GastroHep WILEY

SARS-CoV-2 vaccination in patients with inflammatory bowel disease

Ralley E. Prentice[1] | **Clarissa Rentsch[1]** | **Aysha H. Al-Ani[1]** | **Eva Zhang[1]** |
Douglas Johnson[2,3] | **John Halliday[1]** | **Robert Bryant[4]** | **Jacob Begun[5]** |
Mark G. Ward[6,7] | **Peter J. Lewindon[8,9]** | **Susan J. Connor[10,11,12]** |
Simon Ghaly[13,14] | **Britt Christensen[1,15]**

[1]Department of Gastroenterology, The Royal Melbourne Hospital, Melbourne, VIC, Australia

[2]Departments of Infectious Diseases and General Medicine, The Royal Melbourne Hospital, Melbourne, VIC, Australia

[3]Department of Medicine, Royal Melbourne Hospital, University of Melbourne, Melbourne, VIC, Australia

[4]Department of Gastroenterology, The Queen Elizabeth Hospital, Adelaide, Australia

[5]Department of Gastroenterology, Mater Hospital, Brisbane, Australia

[6]Department of Gastroenterology, Alfred Health, Melbourne, VIC, Australia

[7]Monash University, Melbourne, VIC, Australia

[8]Department of Gastroenterology, Lady Cilento Children's Hospital, Brisbane, QLD, Australia

[9]Queensland Children's Medical Research Institute, University of Queensland, Brisbane, QLD, Australia

[10]Department of Gastroenterology & Hepatology, Liverpool Hospital, Liverpool, NSW, Australia

[11]South West Sydney Clinical School, University of New South Wales, Sydney, NSW, Australia

[12]Ingham Institute of Applied Medical Research, Sydney, NSW, Australia

[13]Department of Gastroenterology, St. Vincent's Hospital Sydney, Sydney, NSW, Australia

[14]St. Vincent's Clinical School, University of New South Wales Sydney, Sydney, NSW, Australia

[15]University of Melbourne, Melbourne, VIC, Australia

Correspondence
Britt Christensen, The Royal Melbourne Hospital , Gastroenterology Department, 300 Grattan St, Parkville, Victoria, Australia.
Email: britt.christensen@mh.org.au

Abstract

Background: The current COVID-19 pandemic, caused by Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), has drastically impacted societies worldwide. Vaccination against SARS-CoV-2 is expected to play a key role in the management of this pandemic. Inflammatory conditions such as inflammatory bowel disease (IBD) often require chronic immunosuppression, which can influence vaccination decisions.

Aim: This review article aims to describe the most commonly available SARS-CoV-2 vaccination vectors globally, assess the potential benefits and concerns of vaccination in the setting of immunosuppression and provide medical practitioners with guidance regarding SARS-CoV-2 vaccination in patients with IBD.

Methods: All published Phase 1/2 and/or Phase 3 and 4 studies of SARS-CoV-2 vaccinations were reviewed. IBD international society position papers, safety registry data and media releases from pharmaceutical companies as well as administrative and medicines regulatory bodies were included. General vaccine evidence and

recommendations in immunosuppressed patients were reviewed for context. Society position papers regarding special populations, including immunosuppressed, pregnant and breast-feeding individuals were also evaluated. Literature was critically analysed and summarised.

Results: Vaccination against SARS-CoV-2 is supported in all adult, non-pregnant individuals with IBD without contraindication. There is the potential that vaccine efficacy may be reduced in those who are immunosuppressed; however, medical therapies should not be withheld in order to undertake vaccination. SARS-CoV-2 vaccines are safe, but data specific to immunosuppressed patients remain limited.

Conclusions: SARS-CoV-2 vaccination is essential from both an individual patient and community perspective and should be encouraged in patients with IBD. Recommendations must be continually updated as real-world and trial-based evidence emerges.

1 | INTRODUCTION

The COVID-19 pandemic is one of the most devastating global events in modern history and one for which the full toll on humanity remains to be seen. At first recognition of SARS-CoV-2 human transmission, the emergent need for a preventative vaccine became apparent. This was the catalyst for the expedient and rigorous manufacturing of a successful vaccine, an astounding feat unparalleled in history. SARS-CoV-2 vaccination provides our global community with hope for stabilisation and eventual recovery, with healthcare workers playing an essential role in safe vaccine delivery. The rapidity of vaccine development, together with the urgent need for their safe deployment, also presents significant challenges, given the paucity of experience. This is particularly the case for groups excluded from vaccine trial populations, such as immunosuppressed individuals, in whom it is prudent to balance the need for protective vaccination against safety concerns.

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is characterised by dysregulated inflammation in the gastrointestinal tract. The primary goal of IBD management is controlling this inflammation, with a significant number of patients requiring immune-based therapies.[1] These therapies include immunomodulators, tumour necrosis factors (TNF) - antagonists, non-TNF targeted biologics and targeted small molecule therapies.[2]

Active IBD and the immunosuppressive therapies integral to its management may weaken the immune system, thereby placing patients with IBD at increased risk of infections.[3] Although current data suggest that IBD alone does not increase the risk of acquisition or severity of symptomatic SARS-CoV-2 infection, thiopurines and baseline corticosteroid use may increase the risk of developing severe COVID-19.[4-6] Furthermore, SARS-CoV-2 can directly infect gastrointestinal tract cells, via the membrane-bound angiotensin-converting enzyme (ACE) 2 receptor, precipitating colonic inflammation[7] with gastrointestinal symptoms occurring in up to 17.6% of IBD patients with COVID-19.[8] The role of SARS CoV-2 in precipitating and/or aggravating an IBD flare is ill-defined, but it may precipitate or perpetuate disease activity.[9]

Effective vaccination is therefore vital, given the potential risk of adverse COVID-19 outcomes in select IBD patients. Non-live vaccinations can be administered in IBD irrespective of medical therapy.[10,11] Importantly with respect to the SARS-CoV-2 vaccinations, IBD patients on immunosuppression were excluded from clinical trials hence evidence to direct clinical decisions is sparse, but emerging. Practicable guidance to support individuals both delivering and receiving SARS-CoV-2 vaccinations in this population is therefore paramount.

The aim of this review is to summarise the commonly available SARS-CoV-2 vaccination vectors currently available globally, assess the potential benefits and concerns of vaccination in the setting of IBD and immunosuppression, and provide clinicians with advice regarding SARS-CoV-2 vaccination in patients with IBD.

2 | METHODS

The need for this review was recognised following the international implementation of vaccination programmes. A review utilising EMBASE, MEDLINE and PubMed was conducted. Existing literature and international guidelines pertaining to general vaccinations in the IBD population, including their efficacy and safety, were reviewed for the frame of reference. Evidence regarding the use of the SARS-CoV-2 vaccines, including their efficacy, safety and mechanisms of action, was also reviewed to provide context. This included reference to published position statements from the British Society of Gastroenterology[12] and the International Organisation for the Study of Inflammatory Bowel Disease (IOBD)[13] regarding SARS-CoV-2

vaccination in patients with IBD. The focus was on vaccinations likely to become available in the short- to medium-term globally with at least phase 2 data published at the time of writing.

Articles specific to the use of the COVID-19 vaccinations in patients with IBD, pregnant, breastfeeding and immunosuppressed patients consist mainly of expert opinion, regulatory agency, safety reporting registry data and society position statements, thus are based on low levels of evidence. As such, recommendations must be interpreted with caution and will be subject to reassessment and revision.

3 | RESULTS

3.1 | IBD and COVID-19 risk

Due to the frequent need for immunosuppressive therapies, there has been concern that IBD patients are at increased risk of contracting SARS-CoV-2 and developing COVID-19 complications. Over the last year, the international registry of patients with IBD and COVID-19 (the SECURE-IBD registry) has attempted to determine if this is in fact the case. Reassuringly, existing data have demonstrated that IBD alone does not appear to increase the risk of developing severe SARS-CoV-2 infection.[4] As with the wider population, host-related factors, including increasing age and comorbidities, are the main factors associated with an increased risk of severe COVID-19.[4-6] (Table 1) While biologic monotherapy has not been associated with the development of severe COVID-19, thiopurines and baseline corticosteroid use are both risk factors.[4-6] The evidence regarding 5-aminosalicylates (5ASAs) and risk of severe COVID-19 is mixed. Danish registry data failed to demonstrate an association,[14] while SECURE-IBD data were suggestive of an increased risk in comparison to those exposed to anti-TNF and other medical therapies, but not in comparison to those receiving no medical therapy and there is no discernible dose-response.[5] Further large cohort data are required, but the risk is postulated to be driven by confounders.[14]

3.2 | SARS-CoV-2 vaccines and immunity

An exhaustive discussion of the SARS-CoV-2 vaccine mechanism is beyond the scope of this review. In brief, available vaccines target various pathways of SARS-CoV-2 infection, aiming to induce an immune response mimicking that induced by exposure to the virus itself. COVID-19 enters the cell via its spike protein (glycoprotein S), which contains a receptor-binding domain (RBD). This domain interacts with ACE-2 receptors on the human cell surface, permitting cellular entry.[15] Humoral immune response to the viral surface glycoproteins is key to achieving immunity. Preventing viral protein and cellular receptor interaction with neutralising antibodies enables viral clearance.[16] The T cell response to SARS-CoV-2 is also critical. Anti-viral cytokines are released by SARS-CoV-2 specific CD4+ T helper 1 (TH1) cells, including interferon (IFN)-gamma and

TNF-alpha. Cytotoxic CD8+ T cells additionally directly kill virally infected cells. T helper cells provide stimulation for ongoing B cell-mediated antibody response to viral surface antigens. Thus, an effective vaccination must induce both a humoral and T cell response to provide durable immunisation.[16] Successful SARS-CoV-2 vaccination formats have demonstrated both T and B cell response, as measured via antibody response and IFN-gamma production respectively.[17]

3.3 | SARS-CoV-2 vaccine mechanisms of action

The vaccine platforms most commonly being implemented include mRNA, viral vector-based, inactivated vaccines, and recombinant protein formats.[18] These include the 12 vaccines available internationally at the time of writing.[19]

3.3.1 | mRNA Vaccines (Pfizer-BioNTech BNT162b2 and Moderna mRNA-1273)

mRNA vaccines (Pfizer-BioNTech and Moderna) employ nanoparticles containing synthetised pseudo-nucleotides mimicking the RNA that encodes for the COVID-19 spike "S" protein. Once injected, this non-replicating mRNA is released enabling transient protein synthesis of the "S" protein in the host cellular cytoplasm. Correspondingly, "S" protein antibodies and reactive T-cells are elicited to protect the host from SARS-CoV-2.[18,20]

3.3.2 | Non-Replicating Viral Vector Vaccines (Oxford/ AstraZeneca AZD1222, Gamaleya Sputnik V, Janssen/ Johnson&Johnson Ad26.COV2.S, CanSino Ad5-nCoV)

The non-replicating viral vector vaccinations utilise adenovirus vectored to the genetic code (double-stranded DNA) of the SARS-CoV-2 spike protein. The adenovirus in these vaccines is engineered so that it can invade the host cell but cannot make copies of itself. Once inside the host cell, the DNA is released into the nucleus and the spike protein is produced. This induces both B and T cell responses to this protein inducing immune protection.[21]

3.3.3 | Recombinant Protein Vaccines (Novovax NVX-CoV2373, FBRI EpiVacCorona)

The recombinant protein vaccination (Novovax) employs a recombinant nanoparticle vaccine constructed from the wild type full-length SARS-CoV-2 S protein and a Matrik-M1 adjuvant to enhance antibody and immune response.[22,23] These nanoparticles mimic the molecular structure of SARS-CoV-2 spike protein to induce an immune response and protect the host cell from SARS-CoV-2 invasion.

TABLE 1 Vaccines with regulatory approval or undergoing Phase 3 trials

Developer	Vaccine Name	Form	Mode of action	Route & Schedule	Storage	Current availability	Trial phase published	Trial population Location	Age	Number of participants	Key exclusion related to IBD / immunosuppression	Efficacy/effectiveness against Severe COVID-19 or Hospitalisation	Mortality	Efficacy
Pfizer-BioNTech[25]	BNT162b2 COMIRNATY	mRNA	Lipid nanoparticle formulation encapsulated mRNA	IM; Day 0, 21	−70°C until thawed, then stable for 120 hours at 2-8°C 6 hours room temp after reconstitution	Approved in 70 countries including Australia, the UK and the US[19,26]	3	United States, Argentina, Brazil South Africa, Germany, Turkey	16+	43,448	Immunocompromised or treatment with immunosuppressive therapy	Not reported in phase 3 RCT[27]. In real world Israeli data, 7 days following second dose vaccine effectiveness 87% (95% CI, 55 to 100) for hospitalisation and 92% (95% CI, 75 to 100) for severe disease[28]	From 21-27 days post the first dose, vaccine effectiveness 84% (95% CI, 44 to 100) for death[28]	95% against symptomatic COVID-19 after two doses
Moderna[25]	mRNA-1273	mRNA	Lipid nanoparticle-encapsulated mRNA	IM; Day 0, 28	Distribution and storage at −20°C for up to 6 months. Protected from moisture and light until ready for preparation. Stable for up to 30days with refrigeration 2-8°C and room temperature for 24hours. 6 hours room temp after reconstitution	Approved in 40 countries[19]	3	United States	18+	30,420	Immunosuppressive or immunodeficiency state, use of immunosuppressants for >14 days in total within 6 months	100% effective at preventing severe COVID-19[30] participants in placebo group had severe COVID-19. None in vaccine arm	100%	94.1% (95% CI, 89.3 to 96.8) against symptomatic COVID-19 ≥ 14 days after the second dose
Oxford-AstraZeneca[29]	ChAdOx1 nCoV-19 (AZD1222)	Non-replicating viral vector	Chimpanzee adenovirus vectored vaccine displaying Spike protein on its surface	IM; day 0, 28	Stored up to 6 months at 2-8°C 6 hours refrigerated after reconstitution	Approved in Australia, the EU and by the WHO for use in low-income countries. In total, 74 countries[19,31]	3	United Kingdom, Brazil, South Africa	18+	23,848	Any autoimmune conditions, confirmed or suspected immunosuppressive or immunodeficient state, use of immunosuppressant medication within past 6 months	Severe COVID-19:100% Hospitalisations due to COVID-19:100% (after the 21-day initial exclusion period)[30]	100%	66.7% (95% CI 57.4-74.0) efficacy against virologically confirmed symptomatic COVID-19 disease ≥14 days after the second dose[30] Greater efficacy when ≥12 weeks between doses in both standard dose and low plus standard dose groups [81.3% (95% CI 60.3 to 91.2) and 80.0% (95% CI 65.2 to 88.5)].[30]

(Continues)

TABLE 1 (Continues)

Developer	Vaccine Name	Form	Mode of action	Efficacy	Route & Schedule	Storage	Current availability	Trial phase published	Trial population Location	Age	Number of participants	Key exclusion related to IBD / immunosuppression	Severe COVID-19 or Hospitalisation	Mortality
Gamaleya Research Institute[15]	Sputnik V	Viral vector	rAd26 + rAd5 expressing Spike protein	91.6% (95% CI 85.6 to 95.2) PCR confirmed COVID-19 ≥ 21 days after first dose	IM; D0, 21 (two slightly different formulations)	Liquid form stored and distributed at −18°C for up to 6 months [freeze dried or lyophilised formulation stored at 2-8°C]	Approved in 51 countries[19]	3	Russia	18+	21,977	Immunosuppression within 3 months	100% (95% CI 94.4 to 100.0) efficacy against moderate to severe COVID-19[32]	>99% 2 COVID-19 related deaths (developed COVID-19 symptoms days 4 and 5 after first vaccination dose and likely infected prior to vaccination despite negative PCR)[32]
Janssen/Johnson and Johnson[33]	Ad26 CovS1	Viral vector	Adenovirus serotype 26 expressing Spike protein	72% by neutralising antibody responses	IM; single dose vs 2 dose at Day 0, 28	Stored and distributed at refrigerator temperature (2 to 8°C) for up to 3 months 6 hours refrigeration after reconstitution	Approved in 34 countries	1/2	Belgium, United States	18+	405	Autoimmune disease; chronic or recurrent use of systemic corticosteroids or immunomodulating agents within 6 months	N/A	N/A
CanSino Biologics[34]	Ad5-nCoV	Viral vector	Adenovirus vector with Spike protein	67.7% (from Phase 2) by neutralising antibody responses	IM; single dose	Stored and distributed at refrigerator temperature (2 to 8°C) Avoid light	Approved in 3 countries—China, Mexico and Pakistan[19]	2	China	18+	508	Prior administration of immunosuppressant or corticosteroids in last 6 months	N/A	N/A
Beijing Institute of Biological Products[35,36]	BBIBP-CorV	Inactivated vaccine	vaccine-induced neutralising antibodies	79.34% by neutralising antibody responses	IM; Day 0, 21	Stored and distributed at refrigerator temperature (2 to 8°C)	Approved in 20 countries[19]	1/2	China	18+-85	448	Diagnosis with autoimmune disease; receiving immunotherapy or inhibitor therapy within 3 months	N/A	N/A

(Continues)

TABLE 1 (Continues)

Developer	Vaccine Name	Form	Mode of action	Efficacy	Route & Schedule	Storage	Current availability	Trial phase published	Trial population			Key exclusion related to IBD / immunosuppression	Efficacy/effectiveness against	
									Location	Age	Number of participants		Severe COVID-19 or Hospitalisation	Mortality
Sinovac Biotech[37]	CoronoVac	Inactivated vaccine	vaccine-induced neutralising antibodies	50.38% by seroconversion of antibodies, defined as a change from seronegative at baseline to seropositive or a four-fold titre increase if the participant was seropositive at baseline	IM; Day 0, 14	Stored and distributed at refrigerator temperature (2 to 8°C)	Approved in 17 countries[19]	1/2	China	18-59	600	Autoimmune disease or immunosuppression; immunosuppressive therapy in the past 6 months	N/A	N/A
Bharat Biotech and Ocugen[38]	Covaxin	Inactivated vaccine	Whole virion inactivated	80.6% by neutralising antibody responses	IM; Day 0, 14 (phase I) Day 0, 28 (phase II)	Stored and distributed at refrigerator temperature (2 to 8°C)	Approved in three counties— India, Iran and Zimbabwe[19]	1/2	India (Bharat Biotech) and US (Ocugen)	18-55	375 (phase 1) 380 (phase 2)	Immunosuppression as a result of an underlying illness or treatment with immunosuppressive or cytotoxic drugs, or use of anticancer chemotherapy or radiation therapy within the preceding six months (nasal and topical steroids are allowed). Long-term use (> 2 weeks) of oral or parenteral steroids or high-dose inhaled steroids within the preceding six months 36 months.	N/A	N/A
Novavax[39]	NVX-COV2373	Recombinant nanoparticle	Trimeric spike glycoproteins and Matrix-M1 adjuvant	Data not yet available	IM; day 0, 21	Distribution and storage at 2-8°C for 6 months; 24 hours at room temperature	N/A—in phase 3 trials	1/2	Australia	18-59	134	Any autoimmune condition; chronic administration of immunosuppressant >14 days or anticipation of need for immunosuppressive treatment within 6 months after last vaccination	N/A: Nil phase 3 data available	N/A

Abbreviations: NAAT, Nucleic acid amplification test; SOB, Shortness of breath.

Based on virus-neutralising geometric mean antibody titres (NGMATs). NB – two additional vaccines have been approved, *Sinopharm (Wuhan) Inactivated (Vero Cells) and FBRI EpiVacCorona* that are not included above, as trial data is not available at the time of writing, with availability limited to China and the UAE, and Russia respectively.[19]

Table 2. Efficacy of SARS-CoV-2 vaccine in studied populations Modified from Chung, J. Y., Thone, MN, Kwon, Y. J. Advanced Drug Delivery Reviews 170 (2021) 1-25.[18]

3.3.4 | Inactivated Vaccines (Bharat Biotech Covaxin, Sinovac CoronaVac, Sinopharm (Beijing) BBIBP-CorV, Sinopharm (Wuhan) Inactivated (Vero Cells))

The inactivated vaccines (Covaxin, CoronaVac, BBIBP-CorV) deliver whole inactivated viruses. In these inactivated vaccines the genetic material has been destroyed, thereby precluding replication, but the structure of the virus is maintained. Most of the inactivated viruses contain an aluminium hydroxide-based adjuvant to augment immune response and, as in the above-mentioned vaccines, "S" protein antibodies and reactive T cells are elicited to protect the host from SARS-CoV-2.[24]

3.4 | Efficacy of SARS-CoV-2 vaccine in studied populations

Table 1 summarises the most commonly employed vaccines currently available globally, their current trial phase of, route and schedule, storage and efficacy and where available, the incidence of severe COVID-19, hospitalisation and mortality.

The primary and secondary endpoints and definitions utilised in the vaccination trials described in the table above differ, which is important to note when interpreting the results.[29,39]

Broadly speaking, the quality of evidence appears to be of the highest quality with respect to prevention of symptomatic, PCR confirmed COVID-19, particularly for those vaccines subject to phase 3 trials (see above table).[40,41] Furthermore, the rapidity with which the vaccines have been developed and implemented has meant a period of time to optimise vaccination schedule, from both a dosage and timing perspective, has not been possible. For example, there was a discrepancy in dose efficacy reported in the Oxford/AstraZeneca vaccine interim results from two of the four randomised trials in the UK and Brazil, which included 11,636 participants with four months follow-up at the time of publication. Participants received either a single standard (SD) or low dose (LD) vaccine at day 0 followed by standard dose or control at day 28. Vaccine efficacy (reported as no COVID-19 infection 14 days after the second vaccination) was 70.4% (95% CI 54.8 to 80.6). Efficacy of the LD/SD schedule was higher (90.0% [95% CI 67.4 to 97.0]) vs the SD/SD schedule (62.1% [95% CI 41.0 to 75.7]).[21] Subsequent to this, further data have been published with respect to dosing intervals. When the Oxford/AstraZeneca vaccine doses are separated by 12 as opposed to four weeks, vaccine efficacy is increased to 81.3% (95% CI 60.3-91.2) vs 55% (33.0-69.9).[29] Similarly, the Sinovac whole inactivated virus vaccine may increase neutralising antibody titres when the interval at which it is provided is extended from two to four weeks.[36] Consequently, providers and regulatory agencies worldwide must remain cognisant of the fact that evidence regarding both the overall efficacy of and optimal schedule for providing the available SARs-CoV-2 vaccinations is continually evolving.

3.5 | Vaccination efficacy and SARS-CoV-2 variants

Concern has been raised that variants of COVID-19 may escape current vaccines. There is limited evidence that this may be the case. A pre-print article reported that the AstraZeneca vaccine (ChAdOx1-nCoV19) efficacy against mild-moderate COVID-19 from the B.1.351 South African escape variant was only 10.4% compared to an efficacy of 75% for non-B.1.351 variants.[38] Notably, the study was not powered to look at the vaccine efficacy for the prevention of severe COVID-19 due to B.1.351. The novovax phase 2b clinical trial also reported reduced efficacy in South Africa where the majority of COVID-19 was secondary to the B.1.351 strain, with a vaccine efficacy for preventing mild-moderate COVID-19 of approximately 60% compared to 89% efficacy in their UK trial where the variant was not present.[42] Of note, one-third of patients enrolled in the trial were seropositive at baseline, with the prior infection postulated to not offer protection against subsequent infection with the South African variant.

Despite these findings, the demonstrable efficacy in preventing severe COVID-19 remains reassuring.[38,42] Evidence is also accumulating on the behaviour of the United Kingdom variant, B.1.1.7, a strain that has up to 10 amino acid mutations in the spike (S) protein. Researchers from BioNTech demonstrated equivalent neutralising titres to both the Wuhan and lineage B.1.1.7 variants.[43] Conversely, a team at the University of Cambridge demonstrated that there was reduced neutralising antibody response to B.1.1.7 in vaccine and convalescent sera compared to the wild-type virus.[44] Reassuringly, vaccine developers have indicated that rapid redesign and deployment of both mRNA and viral vector platforms would be possible within a short timeframe to counter immune escape if required.

3.6 | SARS-CoV-2 vaccine – emerging real-world data

As vaccination programmes are instituted internationally, further phase 3 data and subsequent real-world data are becoming available. Of note, a single dose of the Oxford/AstraZeneca vaccine was found to provide vaccine efficacy of 76% (95% CI 59.3-85.9) against primary symptomatic COVID-19 in the first 90 days post, while additionally demonstrating efficacy against NAAT positive infection at 63.9% (46.0%-75.9%).[29] This holds significance when considering the potential to reduce transmission of SARS-CoV-2. Similarly, real-world cohort data have demonstrated efficacy with a single dose of the Pfizer vaccination, resulting in a four-fold decrease in the rate of asymptomatic positive PCR results in health care workers.[45] As described in the above table, real work data from Israel reports estimated effectiveness in preventing death from COVID-19 of 72% (95% CI 19-200) for days 14 to 20 following the first dose, while effectiveness was 46% for documented COVID-19 infection, 57% for symptomatic COVID-19, 74% for hospitalisation and 62% for severe disease.[27] Using mathematical modelling, a further real-world Israeli study has identified effectiveness for prevention of severe

cases and hospitalisation of 82%-83% utilising the Pfizer vaccine, which increases to a 98% reduction following the second dose. A 72% reduction in symptomatic and asymptomatic cases in the first two weeks following the first dose was also identified.[46]

United States real-world data for the efficacy of SARS-CoV-2 vaccination with the Pfizer/BioNtech or Moderna vaccines have confirmed overall efficacy of 88.7% (95% CI 68.4%-97.1%) in preventing infection. An associated decrease in 14-day hospitalisation rate in those who were vaccinated and subsequently diagnosed with COVID-19 was also appreciable when compared to propensity-matched unvaccinated COVID-19–infected individuals at 3.7% compared to 9.2% respectively, with a relative risk of 0.4; $P = 0.007$.[47] In the UK, a multicentre prospective cohort study reported on staff working in public-funded hospitals undergoing regular asymptomatic testing. It found that the Pfizer/BioNtech vaccine had an efficacy of 72% (95% CI 58-86) 21 days following the first dose and 86% (95% CI 76-97) seven days following the second dose for preventing combined symptomatic and asymptomatic infection in the previously antibody negative cohort.[48]

An English study evaluated the real-world effectiveness of the Pfizer/BioNtech vaccine and Oxford/AstraZeneca vaccine in adults aged 70 and older.[49] The primary endpoint of the study following exposure to either one of two doses of the Pfizer/BioNtech vaccine or one dose of the Oxford/AstraZeneca Vaccine was symptomatic PCR confirmed SARS-CoV-2 infection. Hospitalisation and COVID-19-related death were additionally analysed. In individuals aged 80 or more, effectiveness was reported to be 70% (95% CI 59%-78%) from 28 to 34 days following the initial dose of the Pfizer/BioNtech vaccine. Effectiveness increased to 89% (95% CI 85%-93%) 14 days subsequent to the second Pfizer/BioNtech dose. With the Oxford/AstraZeneca Vaccine in adults aged 70 and over, an effectiveness of 73% (95% CI 27%-90%) was identified from more than 35 days post the initial dose. Furthermore, individuals vaccinated with one dose of the Pfizer/BioNtech had a 43% (95% CI 33%-52%) reduction in the risk of emergency hospitalisation, and 51% (95% CI 37%-62%) reduction in the risk of death. The authors concluded that a single dose of either vaccine is approximately 80% effective in this age group at preventing hospitalisation, while a single dose of the Pfizer/BioNtech vaccine is 85% effective at preventing COVID-19–related death.[49]

3.7 | SARS-CoV-2 vaccine efficacy in patients with IBD

Data regarding the efficacy of available SARS-CoV-2 vaccinations in immunosuppressed or immunocompromised patients, including those with IBD, are limited but emerging. All clinical trials evaluating vaccine efficacy excluded patients with immunosuppression within three to six months. When extrapolating from data for other parenterally administered vaccines, patients receiving corticosteroids, anti-TNF or immunomodulators including calcineurin inhibitors may have an attenuated SARS-CoV-2 vaccine response.[50,51] In regards to response to COVID-19 vaccines, a recently published cohort study on 436 transplant recipients evaluated for antibody production to

the SARs-CoV-2 S1 domain of the spike protein when vaccinated with the Pfizer-BioNTech (52%) and Moderna (48%) vaccines.[52] 86% of patients were receiving tacrolimus, 54% corticosteroid, 66% mycophenolate, 9% azathioprine, 4% sirolimus and 2% everolimus. Those patients exposed to anti-metabolites, including azathioprine, were less likely to develop antibodies in response to vaccination, at 37% vs 63% in those not receiving anti-metabolites: adjusted incidence rate ratio [IRR], 0.22 [95% CI, 0.15-0.34], $P < 0.001$. With regards to the entire exposed cohort, the antibody response was higher in those receiving Moderna as opposed to the Pfizer-BioNTech (69% vs 31%, respectively: adjusted IRR, 2.15 [95% CI, 1.29-3.57], $P = 0.003$).

Specific to IBD, a multicentre prospective observational cohort study, the CLARITY IBD study, evaluated serological response to SARS-CoV-2 infection in 6935 patients receiving either vedolizumab, anti-TNF therapy or immunomodulators.[53] Rates of symptomatic and proven SARS-CoV-2 infection were similar between groups, however, antibody seroprevalence was lower in infliximab-treated than vedolizumab-treated patients (3.4% (161/4685) vs 6.0% (134/2250), $P < 0.0001$). Infliximab and immunomodulator use were independently associated with lower rates of seropositivity in comparison to vedolizumab, with OR 0.66 ((95% CI 0.51 to 0.87), $P = 0.0027$) and OR 0.70 ((95% CI 0.53 to 0.92), $P = 0.012$) respectively. In patients with confirmed SARS-CoV-2 infection, seroconversion was also observed in fewer infliximab-treated than vedolizumab-treated patients (48% (39/81) vs 83% (30/36), $P = 0.00044$) and the magnitude of anti-SARS-CoV-2 reactivity was lower (median 0.8 cut-off index (0.2-5.6) vs 37.0 (15.2-76.1), $P < 0.0001$), implying a blunted response.[53] However, the clinical implications of this are unknown. As an extension to this data, the same group evaluated the seroconversion rates to the Pfizer/BioNtech and AstraZeneca vaccines in 865 infliximab-exposed patients, compared to a reference cohort of 428 vedolizumab-treated patients without prior evidence of infection.[54] Antibody responses were assessed at weeks 3 to 10 following vaccination. Older age, immunomodulator use, Crohn's disease (vs UC or IBD unclassified), and current smoking were associated with lower anti-SARS-CoV-2 antibody concentrations irrespective of the vaccine received. As predicted by the original CLARITY IBD data, anti-SARS-CoV-2 antibody levels and rates of seroconversion were lower following primary (first dose) vaccination with both the Pfizer/BioNtech and AstraZeneca vaccines in patients with IBD treated with infliximab compared to vedolizumab. Importantly, however, after two vaccines only 18% of infliximab exposed and 8% of vedolizumab-exposed patients failed to mount an adequate serological response.[54] Thus, ensuring the complete vaccine schedule is completed in a timely fashion is important in biologic-exposed patients.

The ICARUS-IBD working group from Mount Sinai New York have published interim results of their similarly designed study, evaluating serological response to the Pfizer/BioNtech and Moderna vaccines.[55] Sera from 48 patients, were tested for "SARS-CoV-2 anti-RBD total immunoglobulins and IgG (Siemens COV2T and sCOVG assays), anti-Spike IgG (in-house ELISA), and

anti-nucleocapsid antibodies (Roche)" following one or two vaccinations. Thirty-three and 15 with IBD completed one and two doses respectively. In the latter group of patients, all produced antibody responses considered adequate to qualify for convalescent plasma donation. This included five patients on anti-TNF monotherapy, nine on vedolizumab monotherapy and two on no therapy. Vedolizumab exposure was associated with lower COV2T anti-RBD total Ig (0.02) and anti-S IgG ($P = 0.0043$) levels than observed in controls.[55]

Thus overall, although vaccination response is attenuated by exposure to immunomodulators, anti-TNFs, and potentially also vedolizumab, an adequate response can be achieved in the vast majority of patients with two vaccinations. Further data for those managed with immunomodulator monotherapy is needed. Given the potential risk of an attenuated response, in particular following a single vaccine dose, those patients who are immunosuppressed and have undergone vaccination are advised to maintain behavioural precautions to minimise infection exposure, and should also ensure they receive their second dose of vaccine in a timely fashion.

3.8 | Effect of IBD and IBD medications on vaccination efficacy

The various medications employed in the management of IBD impart differing degrees of immunosuppression. Live vaccines are contraindicated in the setting of high-level immunosuppression. Occasionally certain select live (ie VZV) vaccination may be considered in those with low-level immunosuppression after discussion with the treating physician.[56] Importantly, this is not a reflection of expected vaccine efficacy. Rather, this directive is driven by safety. None of the currently available SARS-CoV-2 vaccines is considered "live" in the classical sense. Those SARS-CoV-2 vaccines composed of a live viral vector lack replicative capacity.

3.8.1 | 5-Aminosalicyltes

Sulfasalazine and the 5-ASA medications are used as first-line induction and maintenance treatment for UC. 5-aminosalicylates have very mild immunosuppressive activity and are often well tolerated with minimal side effects. There are no reports of these medications being associated with reduced vaccination response or increased side-effects with similar immune response seen to influenza vaccination and pneumococcal vaccination compared to the general population.[57,58] Their use should not affect the decision to vaccinate patients against COVID-19.

> Treatment with 5-ASA therapy should continue during the vaccination period in IBD patients
> Treatment with 5-ASA therapy should not affect vaccine efficacy or side-effects

3.8.2 | Corticosteroids

Corticosteroids are non-selective, broad immunosuppressive agents used to induce rapid remission in patients with IBD. Importantly, due to their varied but significant side effects, they do not have a role in maintenance therapy.[59] Corticosteroid dose at the time of, or preceding, vaccination determines whether live vaccinations are considered safe. High-level immunosuppression is defined as treatment with greater than 20 mg of oral prednisolone or equivalent for more than two weeks, and within three months of having ceased analogous therapy. Doses of less than this or for a shorter duration are deemed to impart low-level immunosuppression,[60] but may reduce vaccine efficacy.

The response to hepatitis B vaccination is reduced in the setting of high dose (>10 mg/day) corticosteroid exposure in patients with IBD.[61] The same is observed with doses >20 mg/day with polysaccharide pneumococcal vaccination.[62] Importantly the response to HPV, conjugate and polysaccharide pneumococcal, influenza, yellow fever and herpes zoster vaccines is preserved in the presence of low dose corticosteroid.[10] Importantly, the latter two vaccines are live vaccines, and are not recommended in the setting of corticosteroid use.[56]

> - Vaccines are efficacious in patients receiving corticosteroids at doses of <10 mg prednisolone equivalent/day.
> - If commencing a higher dose of corticosteroid, consider SARS-CoV-2 vaccination two weeks prior to commencement where treatment delay is safe.
> - To maximise vaccine efficacy, when patients are on high dose corticosteroids consider delaying SARS-CoV-2 vaccination until patients are receiving <20 mg prednisolone equivalent/day when on a weaning regimen. It is important to note that evidence to guide this recommendation is lacking and must be weighed against the community prevalence and risk of COVID-19 acquisition.

3.8.3 | Immunomodulators

Methotrexate and thiopurines, including azathioprine, mercaptopurine and tioguanine, are commonly used agents in the management of IBD.[63] Individuals receiving doses of methotrexate exceeding 0.4 mg/kg/week, azathioprine exceeding 3.0mg/kg/day, or mercaptopurine exceeding 1.5 mg/kg/day, should not receive any live vaccinations as they are considered to be highly immunosuppressed.[56,60,64] Vaccine responses in patients exposed to immunomodulators are variably affected... Although the serological response to influenza,[65] hepatitis B[10,66] and pneumococcal vaccination[67,68] is reduced in the presence of immmunomodulators compared to healthy controls, overall vaccination responses in IBD are deemed to be adequate.[69]

In the CLARITY IBD study,[54] the use of immunomodulators was independently associated with lower rates of seroconversion following the first dose of SARS-COV-2 vaccination

(BNT162b2 and ChAdOx1 nCoV-19). This finding is similar to that of transplant recipients receiving an anti-metabolite (mycophenolate and azathioprine) who have comparatively low rates of antibody production in response to the first dose of mRNA vaccine.[52] However, only a small proportion of patients did not mount an antibody response after the second SARS-COV-2 dose in the CLARITY IBD study. This supports the recommendation for IBD patients on immunomodulators to proceed with and complete SARS-COV-2 vaccination as per schedule.[70]

> The antibody response to the first dose of SARS-COV-2 vaccination may be lower in IBD patients receiving immunomodulators; however, the overall antibody response is adequate after completing the vaccination schedule.
> Treatment with immunomodulators should not deter patients from SARS-CoV-2 vaccination.

3.8.4 | Anti-Tumour Necrosis Factor (TNF)

Anti-TNF-alpha therapies are considered to be highly immunosuppressive. Therefore, live attenuated vaccines are contraindicated within the subsequent three months of exposure and during therapy.[11,60]

Data regarding the efficacy of vaccines in patients receiving anti-TNF are conflicting. An attenuated response to hepatitis A and hepatitis B vaccines has been cited.[10,66,71-74] Combination therapy results in an attenuated and less durable pneumococcal vaccination response, but efficacy with anti-TNF monotherapy is preserved.[3,67,68,73,75-78] However, this latter statement was contradicted by a single study identifying a reduced response to the 23-valent polysaccharide vaccine with both combination and monotherapy anti-TNF. The timing of polysaccharide vaccination in relation to anti-TNF dosage and treatment duration does not alter the pneumococcal vaccination response.[3] Combination therapy with an immunomodulator and anti-TNF also have lower rates of seroprotective response to influenza vaccination compared to non-immunosuppressed patients.[79-81] This does not vary with the timing of vaccine and anti-TNF schedule,[80] but may be overcome with high dose vaccination. Booster dosing has not been shown to be effective in enhancing vaccine efficacy.[82,83]

As discussed previously, data from the CLARITY-IBD study suggest those exposed to anti-TNF may have an attenuated serological response to both SARS CoV-2 vaccination and infection.[53,54] However, protective antibody titre levels can be obtained, and are common following completion of a two-dose vaccine schedule.[58,65,84] The same is observed with hepatitis A vaccination, with 86% of anti-TNF treated IBD patients achieving adequate seroprotection with two vaccine doses.[74]

> - Vaccine efficacy may be decreased by anti-TNF therapy, particularly in combination with an immunomodulator, although data are conflicting.
> - A seroprotective vaccine response is still achieved with the majority of vaccines.
> - Recent data suggest seroprotection may be reduced with SARS-CoV-2 vaccines following a single dose however patients responded appropriately after their second dose; therefore, prompt administration of the second dose where relevant should be instigated. Anti-TNF therapy commencement should be delayed two weeks post SARS-CoV-2 vaccination to optimise efficacy where safe to do so.
> - Treatment with anti-TNF should not be interrupted to vaccinate with non-live or non-replicative viral vector vaccines including SARS-CoV-2 vaccines.

3.8.5 | Ustekinumab

Ustekinumab, an IL12/23p40 subunit antibody, is a well-established therapeutic option in CD, with evidence and experience accumulating in UC.[85] Live vaccines are contraindicated in the setting of ustekinumab exposure, including in the three months post medication cessation.[11,60]

Data regarding vaccine efficacy in patients with IBD treated with ustekinumab are limited. Ustekinumab does not impair pneumococcal or tetanus vaccine response in patients with psoriasis[86] nor influenza vaccination response in IBD patients.[87] Further studies are required before more definitive recommendations can be made, but such studies provide a degree of reassurance.

> Vaccines are efficacious in IBD patients receiving ustekinumab, although data are limited.
> Treatment with ustekinumab should not be interrupted to vaccinate with non-live or non-replicative viral vector vaccines including SARS-CoV-2 vaccines.

3.8.6 | Vedolizumab

Vedolizumab, a fully humanised monoclonal IgG-1 antibody, inhibits α4β7 integrin on lymphocytes and thereby prevents their translocation to the gastrointestinal tract.[88] Consequently, vedolizumab has minimal impact on systemic inflammatory pathways. Recommendations regarding the safety of live vaccines in those managed with vedolizumab are conflicting and largely based on low-level evidence. Vedolizumab is deemed to be a high-level immunosuppressive, and hence live vaccination is contraindicated during therapy and in the three months subsequently.[60] However, this recommendation has been disputed more recently by a Swiss working group, stating vedolizumab should not be withheld prior to the provision of live vaccination.[11] The risk vs benefit of vaccination should be considered when making this assessment on an individual patient basis, as stated in the marketing information.[64]

Due to its gut-specific mechanism of action, the effects of vedolizumab on parenteral vaccination response are unlikely to be marked. A recent study in patients receiving vedolizumab was inconclusive with respect to influenza vaccination efficacy on the basis of high baseline influenza antibody titres.[89] Parenteral hepatitis B vaccination response in healthy controls receiving a dose of vedolizumab, compared to those receiving placebo are equivalent.[89,90] In comparison to anti-TNF therapy, the CLARITY-IBD study demonstrated more robust antibody responses to SARS-CoV-2 vaccination, but the ICARUS-IBD study identified a lower antibody response to mRNA vaccination in vedolizumab-exposed patients in comparison to healthy controls.[54,55]

> Parenteral vaccinations are efficacious in IBD patients receiving vedolizumab, although data are limited.
> SARS-CoV-2 vaccination may be attenuated by vedolizumab exposure in comparison to healthy controls.
> Treatment with vedolizumab should not be interrupted to vaccinate with non-live or non-replicative viral vector vaccines including SARS-CoV-2 vaccines

3.8.7 | Tofacitinib

Tofacitinib, an oral Janus kinase inhibitor, is effective for inducing remission in moderate to severe UC[91] and is considered to be relatively heavily immunosuppressive. Live vaccinations should consequently be avoided, however, recommendations with respect to this are limited. An attenuated response to pneumococcal polysaccharide vaccine is observed in RA patients treated with tofacitinib, while the response to influenza vaccination is preserved.[92] Vaccination against herpes zoster using a live vaccine is efficacious in RA patients receiving tofacitinib in the subsequent three weeks,[93] but was complicated by disseminated zoster in one patient without pre-existing VZV antibodies, and is thus discouraged. Additionally, the doses utilised in RA differ from those commonly employed in UC. 10 mg BD tofacitinib is employed as an induction dose in UC, while 5 mg BD is used in RA. Hence, direct inferences of vaccine efficacy from the RA population to UC patients may be invalid.

> Vaccine efficacy may be decreased with the use of tofacitinib although data are limited.
> Delaying SARS-CoV-2 vaccination until patients have completed tofacitinib induction and are receiving maintenance doses of 5 mg BD is recommended where this will not be expected to delay vaccination excessively.
> Tofacitinib commencement should be delayed two weeks post-vaccination to optimise efficacy where safe to do so.
> Tofacitinib therapy should not be interrupted to vaccinate with non-live or non-replicative viral vector vaccines including SARS-CoV-2 vaccines

3.9 | Safety of SARS-CoV-2 vaccinations in patients with IBD

Broadly speaking, inactivated vaccinations are considered safe and advocated for in IBD, while the use of live vaccinations in immuno-suppressed patients is contraindicated.[3,11,94,95] Specifically, mRNA vaccines like the Pfizer-BioNTech and Moderna COVID-19 vaccines do not carry a risk of causing the viral disease and the Canadian Association of Gastroenterology (CAG) concluded: "it was biologically implausible for mRNA vaccines to cause catastrophic harm in patients with IBD on or not on immunosuppressive therapy and other serious harms highly unlikely".[96]

Currently, the only CDC mandated contraindications to SARS-CoV-2 vaccination include previous severe allergic reactions or anaphylaxis to the vaccine or its components. There are no medical illnesses that preclude COVID vaccination on the basis of existing, albeit limited, data.[97] This is important when considering widely publicised complications associated with other coronavirus vaccine development. The original Severe Acute Respiratory Syndrome (SARS) coronavirus vaccine success was hindered by immune complications.[98] Fortunately, a more recent randomised, controlled trial of a Middle Eastern Respiratory Syndrome (MERS) coronavirus vaccine reported no severe adverse events. Inflammatory complications with the presently approved SARS-CoV-2 vaccines have been extremely uncommon and not clearly causally associated.[25,99,100]

3.10 | Counselling regarding potential adverse events of SARS-CoV-2 vaccination

When counselling prior to vaccination, patients must be informed of the relatively common incidence of mild injection site tenderness and systemic flu-like reactions. Fatigue and headache were reported in 59% and 54% respectively of young vaccine recipients following the second dose of the Pfizer-BioNTech vaccine,[25] as opposed to 23% and 24% respectively in the placebo group. This is comparable to the side effect profile of commonly utilised vaccines.[12] Similarly, injection site tenderness was reported in over 60% of patients receiving the AstraZeneca vaccine. Myalgia, chills, malaise, arthralgia and fever were also common.[99] Given the paucity of safety data regarding the administration of any SARS-CoV-2 vaccine and other vaccines in conjunction, including the influenza vaccine, it is prudent to ensure a 14-day interval is maintained.[101]

More recently, concern regarding the risk of vaccine provoked thrombotic events (specifically cerebral venous thrombosis and splanchnic thrombosis with a concomitant thrombocytopenia, defined as the "Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)" or "Vaccine-Induced Prothrombotic Immune Thrombocytopenia (VIPIT)" syndrome) has arisen with the adenovirus-vectored vaccine, namely the AstraZeneca vaccine. This syndrome mimics heparin-induced thrombocytopenia with detection of anti-platelet factor 4 (PF4) antibodies,

occurring within four to 20 days of the first dose in the majority of cases.[102] Although rare, the incidence of this highly morbid and frequently mortal (at the time of writing (18/86))[102,103] adverse event was seven times the expected rate in a German population, with a plausible connection to vaccination.[104] The majority of cases have occurred in women under the age of 50 with no associated co-morbidities. The European Medicines Agency (EMA) has formally recognised the association but presently suggests the benefits of vaccination outweigh the risks. However, specific government directives in each country must be considered and are highly variable in accordance with the risk of SARS-CoV-2 acquisition.[105,106] Practitioners must remain cognisant of such recommendations.[106]

Anaphylaxis has been reported rarely with the Pfizer-BioNTech vaccine and has not yet been reported with the AstraZeneca vaccine.[25,99] Following the provision of almost two million first doses of the Pfizer-BioNTech COVID-19 in the United States, anaphylaxis was seen in 11.1 cases per million doses.[107] The majority of cases occurred in individuals with a prior history of anaphylaxis or allergic reactions and almost all reactions occurred within 30 minutes of receiving the vaccine. The reaction is postulated to be caused by an allergy to polyethylene glycol (PEG) 2000 that is in both the Moderna and Pfizer-BioNTech vaccines.[108] Therefore previous anaphylaxis to PEG 2000, to an injectable medication or to prior vaccine warrants specialist opinion regarding the safety of vaccination.[108] Additionally, a degree of cross-reactivity between the PEG 2000 and polysorbate 80 may occur. Thus, the use of an alternative vaccination format following anaphylaxis to a specific SARS-CoV-2 vaccination formulation may not be entirely without risk, and medical consultation must be sought.[108109]

Specific to IBD, the prospective nationwide registry Coronavirus Risk Associations and Longitudinal Evaluation-IBD (CoraleIBD) the study reported on 246 patients with IBD and on immune-based therapies vaccinated with at least one dose of either the Pfizer-BioNtech or Moderna vaccines.[110] The overall frequency of adverse events was 39% following dose 1, and 62% following dose 2. This mimics that of the general population, again with mild localised injection site reactions, fatigue and malaise, fevers and chills commonly reported. Three and two patients were hospitalised following dose one and two respectively, the majority with fevers, chills and headaches. Adverse events occurred more commonly in patients less than 50 years of age (47% vs 29% after D1, $P = 0.011$; 73% vs 45% after D2, $P = 0.003$), those with a prior history of COVID-19 (78% vs 37% after D1, $P = 0.04$) and in those with UC as opposed to CD (78% vs 55% after D2, $P = 0.038$). Patients receiving biologic therapies were less likely to report adverse events (36% vs 47% after D1, $P = 0.17$; 54% vs 82% after D2, $P = 0.013$), as were those receiving any immunomodulating therapy versus unmedicated patients (37% vs 48% after D1; $P = 0.22$; 54% vs 86% after D2; $P = 0.012$). The adjusted analysis confirmed the reduced odds ratio of adverse events following second dose vaccine with biologic exposure (OR 0.32, 95%

CI 0.10-0.94; $P = 0.049$).[110] Whether the reduction in rates of adverse events reflects the reduced serologic response to vaccination observed in existing cohort studies[54,55] is uncertain, but theoretically plausible.

3.11 | SARS-CoV-2 vaccination in special populations

3.11.1 | Pregnancy and Breastfeeding

Pregnancy poses an increased risk for severe COVID-19, thus immunisation must be considered particularly in those at high risk of SARS-CoV-2 acquisition or with additional risk factors for severe disease.[12,111,112] This includes pregnant, immunosuppressed patients with IBD, particularly those receiving corticosteroids, thiopurines or combination anti-TNF therapy. There is a distinct lack of evidence regarding the safety of existing SARS-CoV-2 vaccines in pregnancy, with pregnant patients excluded from the seminal trials.[25,100] Currently, it is recommended that SARS-CoV-2 vaccination be offered to pregnant and lactating women with IBD if they would otherwise be offered the vaccine (ie if they did not have IBD).[13] Registry data will inform future practice, including from the v-safe registry. This is established and maintained by the CDC as an electronic reporting tool for outcomes subsequent to SARS-CoV-2 vaccination, has thus far included more than 30,000 self-reported pregnant women. The majority of women were vaccinated in the first trimester and with the Pfizer-BioNTech vaccine. Thus far, there has been no signal for any pregnancy-specific safety concerns, with the observed miscarriage rate comparable to that of the background population.[113] While this is reassuring, specific guidance from regulatory agencies is awaited.

Like in the setting of pregnancy, data specific to the safety of SARS-CoV-2 vaccination in breastfeeding women is extremely limited.[114] The British Royal College of Obstetricians and Gynaecologists recommends that breastfeeding women be offered the SARS-CoV-2 vaccination if they otherwise would be, following informed discussion with respect to the lack of specific safety data. [115] Of interest, a pre-print study of six women who received a COVID-19 mRNA vaccine while lactating, found that following vaccination the breast milk transmissible SARS-CoV-2 immunoglobulins which potentially may be protective for infants.[116]

3.11.2 | Paediatric

Most of the existing SARS-CoV-2 vaccines are not approved in children younger than 16 years old, due to exclusion from initial trials. Fortunately, paediatric IBD patients appear to be at low risk of severe COVID-19 irrespective of medication exposures.[117] Vaccination trials are ongoing in the paediatric population. The use of the Pfizer vaccine in a cohort of 2260 children aged 12-15 had

been demonstrated to be 100% effective with no concerning or un-expected safety signals, and there has been recent emergency use authorisation for this vaccine in this age group.[118] A phase 1/2/3 trial in 6 months to 11-year-olds has recently commenced.[118]

3.12 | Summary of recommendations

All patients with IBD should be vaccinated against pneumococcal and influenza in accordance with pre-existing international society guidelines, regardless of IBD medical therapy.

SARS-CoV-2 vaccination is recommended for all adult non-pregnant individuals with IBD without contraindication, regardless of IBD medical therapy.

Individuals on immunosuppressive therapies for IBD including corticosteroids, immunomodulators and anti-TNFs may have reduced vaccine efficacy, in particular, to single-dose vaccination but this should not deter patients or practitioners from vaccinating and should encourage completion of a two-dose vaccination course.

Individuals receiving immunosuppressive medical therapies for IBD must continue to implement non-pharmaceutical practices to minimise the risk of SARS-CoV-2 acquisition due to the theoretical risk of reduced vaccine efficacy.

Data regarding the use of SARS-CoV-2 in pregnant individuals remain limited. Therefore, the relative risks and benefits of vaccination must be discussed with each patient individually.

SARS-CoV-2 vaccination cannot be recommended in individuals with IBD younger than 12 years of age presently, due to lack of efficacy and safety data and the relatively low risk of severe COVID-19 in this population, although data are emerging rapidly.

Individuals with a past history of anaphylaxis to medicines should consult with their medical practitioner prior to receiving a SARS-CoV-2 vaccine. SARS-CoV-2 vaccinations are contraindicated in individuals with a history of anaphylaxis to a SARS-CoV-2 vaccine or their components according to manufacturer recommendations. However, speciality immunologist review should be considered if the risks of COVID-19 in the individual outweigh the risks of medically supervised vaccination.

Women with IBD who are pregnant, or breastfeeding should be offered SARS-CoV-2 if they would otherwise be a candidate for it, with an individualised and collaborative risk-benefit analysis undertaken for each patient.

4 | CONCLUSION

The COVID-19 pandemic continues to evolve rapidly, with a need to prioritise the prevention of acquisition and progression to severe disease. These recommendations, based on the available evidence presently, will be modified as data specific to the immunosuppressed IBD population accumulates. Clinicians must focus on providing patients with sound, well-reasoned advice to support their decision to vaccinate. This is especially important in the setting of an immunosuppressive medical condition, where safety and efficacy concerns may be particularly anxiety-provoking.

AUTHORSHIP

Guarantor of the article: Britt Christensen.

Author contributions: RP, CR, EZ, DJ, AA, JH and BC reviewed the literature. RP, CR and EZ wrote the manuscript. JG, DJ, BC and AA critically edited and contributed to the writing of the content. RVB, JB, MW, SC, SG and PL reviewed the paper critically reviewed and approved the manuscript. All authors approved the final version of the manuscript. EZ is on a research IBD fellowship provided by Pfizer.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/ygh2.473.

ORCID

Ralley E. Prentice https://orcid.org/0000-0002-4331-9295
Aysha H. Al-Ani https://orcid.org/0000-0002-4735-5234
Eva Zhang https://orcid.org/0000-0003-4640-1291
Robert Bryant https://orcid.org/0000-0003-4229-3289
Jacob Begun https://orcid.org/0000-0001-5256-7672
Mark G. Ward https://orcid.org/0000-0002-2840-0108
Susan J. Connor https://orcid.org/0000-0001-5606-0270
Simon Ghaly https://orcid.org/0000-0003-2489-6430
Britt Christensen https://orcid.org/0000-0002-8746-4275

REFERENCES

1. Ghosh N, Premchand P. A UK cost of care model for inflammatory bowel disease. *Frontline Gastroenterol.* 2015;6:169-174.

2. Jeong DY, Kim S, Son MJ, et al. Induction and maintenance treatment of inflammatory bowel disease: A comprehensive review. *Autoimmun Rev.* 2019;18:439-454.

3. Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis.* 2014;8:443-468.

4. Brenner EJ, Ungaro RC, Gearry RB, et al. Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. *Gastroenterology.* 2020;159:481-491.e3.

5. Ungaro RC, Brenner EJ, Gearry RB, et al. Effect of IBD medications on COVID-19 outcomes: results from an international registry. *Gut.* 2021;70:725-732.

6. Khan N, Patel D, Xie D, Lewis J, Trivedi C, Yang Y-X. Impact of anti-tumor necrosis factor and thiopurine medications on the development of COVID-19 in patients with inflammatory bowel disease: a nationwide veterans administration cohort study. *Gastroenterology.* 2020;159:1545-6.e1.

7. Carvalho A, Alqusairi R, Adams A, et al. SARS-CoV-2 gastrointestinal infection causing hemorrhagic colitis: implications for detection and transmission of COVID-19 disease. *Am J Gastroenterol.* 2020;115:942-946.

8. Cheung KS, Hung IFN, Chan PPY, et al. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong Cohort: systematic review and meta-analysis. *Gastroenterology.* 2020;159:81-95.

9. Allez M, Fleshner P, Gearry R, Lakatos PL, Rubin DT. Care of the patient with IBD requiring hospitalisation during the COVID-19 pandemic. *J Crohns Colitis.* 2020;14:S774-S779.

10. Papp KA, Haraoui B, Kumar D, et al. Vaccination guidelines for patients with immune-mediated disorders on immunosuppressive therapies. *J Cutan Med Surg.* 2019;23:50-74.

11. Manser CN, Maillard MH, Rogler G, Schreiner P, Rieder F, Bühler S. Vaccination in patients with inflammatory bowel diseases. *Digestion.* 2020;101:58-68.

12. Alexander JL, Moran G, Gaya DR, et al. British society of gastroenterology inflammatory bowel disease section and IBD clinical research group position statement on SARS-CoV2 vaccination. 2020. https://www.bsg.org.uk/covid-19-advice/british-society-of-gastroenterology-inflammatory-bowel-disease-section-and-ibd-clinical-research-group-position-statement-on-sars-cov2-vaccination/

13. Siegel CA, Melmed GY, McGovern DPB, et al. SARS-CoV-2 vaccination for patients with inflammatory bowel diseases: recommendations from an international consensus meeting. *Gut.* 2021;70:635-640.

14. Attauabi M, Seidelin J, Burisch J. Association between 5-aminosalicylates in patients with IBD and risk of severe COVID-19: an artefactual result of research methodology? *Gut.* 2021;19:2021–324397.

15. Logunov DY, Dolzhikova IV, Zubkova OV, et al. Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia. *Lancet.* 2020;396:887-897.

16. Poland GA, Ovsyannikova IG, Kennedy RB. SARS-CoV-2 immunity: review and applications to phase 3 vaccine candidates. *The Lancet.* 2020;396:1595-1606.

17. Jarjour NN, Masopust D, Jameson SC. T cell memory: understanding COVID-19. *Immunity.* 2021;54:14-18.

18. Chung JY, Thone MN, Kwon YJ. COVID-19 vaccines: the status and perspectives in delivery points of view. *Adv Drug Deliv Rev.* 2020;170:1-25.

19. Basta NE, Moodie EEM. COVID19 vaccine tracker 2021. https://covid19.trackvaccines.org/vaccines/

20. Sahin U, Muik A, Derhovanessian E, et al. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. *Nature.* 2020;586:594-599.

21. Knoll MD, Wonodi C. Oxford-AstraZeneca COVID-19 vaccine efficacy. *Lancet.* 2021;397:72-74.

22. Keech C, Albert G, Cho I, et al. Phase 1–2 Trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine. *N Engl J Med.* 2020;383:2320-2332.

23. Bengtsson KL, Song H, Stertman L, et al. Matrix-M adjuvant enhances antibody, cellular and protective immune responses of a Zaire Ebola/Makona virus glycoprotein (GP) nanoparticle vaccine in mice. *Vaccine.* 2016;34:1927-1935.

24. Iversen PL, Bavari S. Inactivated COVID-19 vaccines to make a global impact. *Lancet Infect Dis.* 2021;21:746-748.

25. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med.* 2020;383:2603-2615.

26. Countries already using Pfizer coronavirus vaccine include UK, US, Canada and Singapore 2021. updated 16 Feb 2021. https://www.abc.net.au/news/2021-02-15/which-countries-already-have-the-pfizer-biontech-vaccine/13157332

27. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med.* 2021;384:1412-1423.

28. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet.* 2021;397:99-111.

29. Voysey M, Costa Clemens SA, Madhi SA, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *Lancet.* 2021;397:881-891.

30. AstraZeneca COVID-19 vaccine authorised for emergency use by the World Health Organization [press release]. 15 Feburary 2020 2021.

31. Logunov DY, Dolzhikova IV, Shcheblyakov DV, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. *Lancet.* 2021;397:671-681.

32. Sadoff J, Le Gars M, Shukarev G, et al. Interim results of a phase 1–2a trial of Ad26.COV2.S Covid-19 vaccine. *N Engl J Med.* 2021;384:1824-1835.

33. Zhu F-C, Li Y-H, Guan X-H, et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. *Lancet.* 2020;395:1845-1854.

34. Xia S, Zhang Y, Wang Y, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. *Lancet Infect Dis.* 2021;21:39-51.

35. Tumban E. Lead SARS-CoV-2 candidate vaccines: expectations from phase III trials and recommendations post-vaccine approval. *Viruses.* 2020;13:54.

36. Zhang Y, Zeng G, Pan H, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis.* 2021;21:181-192.

37. Ella R, Vadrevu KM, Jogdand H, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial. *Lancet Infect Dis.* 2021;21:637-646.

38. Madhi SA, Baillie V, Cutland CL, et al. Safety and efficacy of the ChAdOx1 nCoV-19 (AZD1222) Covid-19 vaccine against the B.1.351 variant in South Africa. *medRxiv.* 2021:2021.02.10.21251247.

39. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384:403-416.

40. (ACIP) ACoIP. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Pfizer-BioNTech COVID-19 Vaccine. 2020. 10 December 2020.

41. (ACIP) ACoIP. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Moderna COVID-19 Vaccine. 2020. 20 December 2020.

42. Novavax COVID-19 Vaccine Demonstrates 89.3% Efficacy in UK Phase 3 Trial [press release]. GAITHERSBURG, Md.Jan 28, 2021 at 4:05 PM EST.

43. Muik A, Wallisch A-K, Sänger B, et al. Neutralization of SARS-CoV-2 lineage B.1.1.7 pseudovirus by BNT162b2 vaccine-elicited human sera. *bioRxiv*. 2021:2021.01.18.426984.

44. Collier DA, De Marco A, Ferreira IATM, et al. SARS-CoV-2 B.1.1.7 sensitivity to mRNA vaccine-elicited, convalescent and monoclonal antibodies. *medRxiv*. 2021:2021.01.19.21249840.

45. Weekes M, Jones NK, Rivett L, et al. Single-dose BNT162b2 vaccine protects against asymptomatic SARS-CoV-2 infection. *Authorea*. 2021;10:e68808. https://doi.org/10.7554/eLife.68808

46. Aran D. Estimating real-world COVID-19 vaccine effectiveness in Israel using aggregated counts. *medRxiv*. 2021:2021.02.05.21251139.

47. Pawlowski C, Lenehan P, Puranik A, et al. FDA-authorized mRNA COVID-19 vaccines are effective per real-world evidence synthesized across a multi-state health system. *Med*. 2021:2021.02.15.21251623. https://doi.org/10.1016/j.medj.2021.06.007

48. Hall VJ, Foulkes S, Saei A, et al. Effectiveness of BNT162b2 mRNA vaccine against infection and COVID-19 vaccine coverage in healthcare workers in england, multicentre prospective cohort study (the SIREN Study). *Preprints with THE LANCET*. 2021.

49. Bernal JL, Andrews N, Gower C, et al. Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England. *medRxiv*. 2021.

50. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497-506.

51. Howard J, Snowden J, Ashcroft J. COVID-19 Vaccine in patients with haematological disorders British Society for Haematology. 21st. December 2020 updated 21st December 2020. 1. https://b-s-h.org.uk/media/19195/haematology-covid-19-v10-vaccination-statement-231220.pdf. Accessed April 02, 2021.

52. Boyarsky BJ, Werbel WA, Avery RK, et al. Immunogenicity of a single dose of SARS-CoV-2 messenger RNA vaccine in solid organ transplant recipients. *JAMA*. 2021;325:1784-1786.

53. Kennedy NA, Goodhand JR, Bewshea C, et al. Anti-SARS-CoV-2 antibody responses are attenuated in patients with IBD treated with infliximab. *Gut*. 2021;70:865-875.

54. Kennedy NA, Lin S, Goodhand JR, et al. Infliximab is associated with attenuated immunogenicity to BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines. *medRxiv*. 2021:2021.03.25.21254335.

55. Wong S-Y, Dixon R, Martinez Pazos V, et al. Serologic response to messenger RNA coronavirus disease 2019 vaccines in inflammatory bowel disease patients receiving biologic therapies [published online ahead of print April 20, 2021]. *Gastroenterology*: 2021.03.17.21253848. https://doi.org/10.1053/j.gastro.2021. 04.025

56. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*. 2014;58:309-318.

57. Gabay C, Bel M, Combescure C, et al. Impact of synthetic and biologic disease-modifying antirheumatic drugs on antibody responses to the AS03-adjuvanted pandemic influenza vaccine: a prospective, open-label, parallel-cohort, single-center study. *Arthritis Rheum*. 2011;63:1486-1496.

58. Lu Y, Jacobson DL, Ashworth LA, et al. Immune response to influenza vaccine in children with inflammatory bowel disease. *Am J Gastroenterol*. 2009;104:444-453.

59. Dorrington AM, Selinger CP, Parkes GC, Smith M, Pollok RC, Raine T. The historical role and contemporary use of corticosteroids in inflammatory bowel disease. *J Crohns Colitis*. 2020;14:1316-1329.

60. Farshidpour M, Charabaty A, Mattar MC. Improving immunization strategies in patients with inflammatory bowel disease. *Ann Gastroenterol*. 2019;32:247-256.

61. Sempere L, Almenta I, Barrenengoa J, et al. Factors predicting response to hepatitis B vaccination in patients with inflammatory bowel disease. *Vaccine*. 2013;31:3065-3071.

62. Fischer L, Gerstel PF, Poncet A, et al. Pneumococcal polysaccharide vaccination in adults undergoing immunosuppressive treatment for inflammatory diseases – a longitudinal study. *Arthritis Res Ther*. 2015;17:151.

63. Herfarth HH, Kappelman MD, Long MD, Isaacs KL. Use of methotrexate in the treatment of inflammatory bowel diseases. *Inflamm Bowel Dis*. 2016;22:224-233.

64. Farraye FA, Melmed GY, Lichtenstein GR, Kane SV. ACG clinical guideline: preventive care in inflammatory bowel disease. *Am J Gastroenterol*. 2017;112:241-258.

65. Kapetanovic MC, Saxne T, Nilsson JA, Geborek P. Influenza vaccination as model for testing immune modulation induced by anti-TNF and methotrexate therapy in rheumatoid arthritis patients. *Rheumatology (Oxford)*. 2007;46:608-611.

66. Andrade P, Santos-Antunes J, Rodrigues S, Lopes S, Macedo G. Treatment with infliximab or azathioprine negatively impact the efficacy of hepatitis B vaccine in inflammatory bowel disease patients. *J Gastroenterol Hepatol*. 2015;30:1591-1595.

67. Kapetanovic MC, Saxne T, Sjöholm A, Truedsson L, Jönsson G, Geborek P. Influence of methotrexate, TNF blockers and prednisolone on antibody responses to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis. *Rheumatology (Oxford)*. 2006;45:106-111.

68. Kapetanovic MC, Roseman C, Jönsson G, Truedsson L, Saxne T, Geborek P. Antibody response is reduced following vaccination with 7-valent conjugate pneumococcal vaccine in adult methotrexate-treated patients with established arthritis, but not those treated with tumor necrosis factor inhibitors. *Arthritis Rheum*. 2011;63:3723-3732.

69. Dotan I, Werner L, Vigodman S, et al. Normal response to vaccines in inflammatory bowel disease patients treated with thiopurines. *Inflamm Bowel Dis*. 2012;18:261-268.

70. Wasan SK, Zullow S, Berg A, Cheifetz AS, Ganley-Leal L, Farraye FA. Herpes zoster vaccine response in inflammatory bowel disease patients on low-dose immunosuppression. *Inflamm Bowel Dis*. 2016;22:1391-1396.

71. Wong PKK, Bagga H, Barrett C, et al. A practical approach to vaccination of patients with autoimmune inflammatory rheumatic diseases in Australia. *Intern Med J*. 2017;47:491-500.

72. Hall V, Johnson D, Torresi J. Travel and biologic therapy: travel-related infection risk, vaccine response and recommendations. *J Travel Med*. 2018;25:1-17.

73. Park SH, Yang S-K, Park S-K, et al. Efficacy of hepatitis A vaccination and factors impacting on seroconversion in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2014;20:69-74.

74. Askling HH, Rombo L, van Vollenhoven R, et al. Hepatitis A vaccine for immunosuppressed patients with rheumatoid arthritis: a prospective, open-label, multi-centre study. *Travel Med Infect Dis*. 2014;12:134-142.

75. van Aalst M, Garcia Garrido HM, van der Leun J, et al. Immunogenicity of the currently recommended pneumococcal

vaccination schedule in patients with inflammatory bowel disease. *Clin Infect Dis*. 2020;70:595-604.

76. Fiorino G, Peyrin-Biroulet L, Naccarato P, et al. Effects of immunosuppression on immune response to pneumococcal vaccine in inflammatory bowel disease: a prospective study. *Inflamm Bowel Dis*. 2012;18:1042-1047.

77. Gelinck L, van der Bijl AE, Visser LG, et al. Synergistic immunosuppressive effect of anti-TNF combined with methotrexate on antibody responses to the 23 valent pneumococcal polysaccharide vaccine. *Vaccine*. 2008;26:3528-3533.

78. Crnkic Kapetanovic M, Saxne T, Truedsson L, Geborek P. Persistence of antibody response 1.5 years after vaccination using 7-valent pneumococcal conjugate vaccine in patients with arthritis treated with different antirheumatic drugs. *Arthritis Res Ther*. 2013;15:R1.

79. Cullen G, Bader C, Korzenik JR, Sands BE. Serological response to the 2009 H1N1 influenza vaccination in patients with inflammatory bowel disease. *Gut*. 2012;61:385-391.

80. deBruyn J, Fonseca K, Ghosh S, et al. Immunogenicity of influenza vaccine for patients with inflammatory bowel disease on maintenance infliximab therapy: a randomized trial. *Inflamm Bowel Dis*. 2016;22:638-647.

81. Mamula P, Markowitz JE, Piccoli DA, Klimov A, Cohen L, Baldassano RN. Immune response to influenza vaccine in pediatric patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2007;5:851-856.

82. Caldera F, Hillman L, Saha S, et al. Immunogenicity of high dose influenza vaccine for patients with inflammatory bowel disease on anti-TNF monotherapy: a randomized clinical trial. *Inflamm Bowel Dis*. 2020;26:593-602.

83. Matsumoto H, Ohfuji S, Watanabe K, et al. Booster influenza vaccination does not improve immune response in adult inflammatory bowel disease patients treated with immunosuppressives: a randomized controlled trial. *J Gastroenterol*. 2015;50:876-886.

84. Gelinck LB, van der Bijl AE, Beyer WE, et al. The effect of anti-tumour necrosis factor alpha treatment on the antibody response to influenza vaccination. *Ann Rheum Dis*. 2008;67:713-716.

85. Sandborn WJ, Feagan BG, Danese S, et al. Safety of ustekinumab in inflammatory bowel disease: pooled safety analysis of results from phase 2/3 studies. *Inflamm Bowel Dis*. 2021;27:994-1007.

86. Brodmerkel C, Wadman E, Langley RG, et al. Immune response to pneumococcus and tetanus toxoid in patients with moderate-to-severe psoriasis following long-term ustekinumab use. *J Drugs Dermatol*. 2013;12:1122-1129.

87. Doornekamp L, Goetgebuer RL, Schmitz KS, et al. High immunogenicity to influenza vaccination in crohn's disease patients treated with ustekinumab. *Vaccines (Basel)*. 2020;8:455.

88. Scribano ML. Vedolizumab for inflammatory bowel disease: From randomized controlled trials to real-life evidence. *World J Gastroenterol*. 2018;24:2457-2467.

89. Harrington JE, Hamilton RE, Ganley-Leal L, Farraye FA, Wasan SK. The immunogenicity of the influenza, pneumococcal, and hepatitis B vaccines in patients with inflammatory bowel disease treated with vedolizumab. *Crohn's & Colitis 360*. 2020;2.

90. Wyant T, Leach T, Sankoh S, et al. Vedolizumab affects antibody responses to immunisation selectively in the gastrointestinal tract: randomised controlled trial results. *Gut*. 2015;64:77.

91. Singh S, Murad MH, Fumery M, Dulai PS, Sandborn WJ. First- and second-line pharmacotherapies for patients with moderate to severely active ulcerative colitis: an updated network meta-analysis. *Clin Gastroenterol Hepatol*. 2020;18:2179-91 e6.

92. Winthrop KL, Silverfield J, Racewicz A, et al. The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. *Ann Rheum Dis*. 2016;75:687.

93. Winthrop KL, Wouters AG, Choy EH, et al. The safety and immunogenicity of live zoster vaccination in patients with rheumatoid arthritis before starting tofacitinib: a randomized phase II trial. *Arthritis Rheumatol*. 2017;69:1969-1977.

94. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut*. 2019;68:s1-s106.

95. Ward M, Dv L, Alex G, Andrews JM, Bell S, Connor S, et al. Clinical Update for General Practitioners and Physicians Inflammatory Bowel Disease. The Gastroenterological Society of Australia (GESA) Level 1, 517 Flinders Lane | Melbourne | VIC 30002018. https://www.gesa.org.au/public/13/files/Professional/2018_IBD_Clinical_Update_May_update.pdf

96. Tse F, Moayyedi P, Waschke KA, et al. COVID-19 vaccination in patients with inflammatory bowel disease: communiqué from the canadian association of gastroenterology. *J Canadian Assoc Gastroenterol*. 2021;4:49.

97. Prevention CfDCa. Interim Clinical Considerations for Use of mRNA COVID-19 Vaccines Currently Authorized in the United States 2021 updated 6/1/2020. https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html

98. Maslow JN. Vaccines for emerging infectious diseases: lessons from MERS coronavirus and Zika virus. *Hum Vaccin Immunother*. 2017;13:2918-2930.

99. Knoll MD, Wonodi C. Oxford–AstraZeneca COVID-19 vaccine efficacy. *The Lancet*. 2021;397:72-74.

100. Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA Vaccine against SARS-CoV-2 — Preliminary Report. *N Engl J Med*. 2020;383:1920-1931.

101. (ATAGI) ATAGoI. Clinical guidance on use of COVID-19 vaccine in Australia in 2021. 2021. [updated 05/02/2021. 1. https://www.health.gov.au/sites/default/files/documents/2021/02/covid-19-vaccination-atagi-clinical-guidance-on-covid-19-vaccine-in-australia-in-2021.pdf

102. Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 6-9 April 2021 [press release]. 9/4/2021 2021.

103. COVID-19 Vaccine AstraZeneca: benefits still outweigh the risks despite possible link to rare blood clots with low blood platelets [press release]. March 18th 2021 2021.

104. FAQ - Termporary Suspension of COVID-19 vaccine AstraZeneca [press release]. Paul-Ehrlich-Stabe 51-59 63225 Langen Germany16 March 2021.

105. MHRA issues new advice, concluding a possible link between COVID-19 Vaccine AstraZeneca and extremely rare, unlikely to occur blood clots [press release]. London 2021.

106. ATAGI statement on AstraZeneca vaccine in response to new vaccine safety concerns [press release]. Canberra, Australia. 8 April 2021.

107. Administration CC-rtFaD. Allergic reactions including anaphylaxis after receipt of the first dose of pfizer-BioNTech COVID-19 vaccine — United States, December 14–23, 2020. *MMWR Morb Mortal Wkly Rep*. 2021;70:46-p51.

108. Banerji A, Wickner PG, Saff R, et al. mRNA vaccines to prevent COVID-19 disease and reported allergic reactions: current evidence and suggested approach. *J Allergy Clin Immunol Pract*. 2021;9:1423-1437.

109. Oxford University/AstraZeneca COVID-19 vaccine approved. The new vaccine has been approved after meeting the required safety, quality and effectiveness standards. [press release]. GOV.UK, 30 December 2020 2020.

110. Botwin GJ, Li D, Figueiredo J, et al. Adverse events following SARS-CoV-2 mRNA vaccination among patients with inflammatory bowel disease. *medRxiv*. 2021:2021.03.30.21254607.

111. Riley LE, Beigi R, Jamieson DJ, et al. Vaccinating Pregnant and Lactating Patients Against COVID-19 Practice Advisory. 2020. updated December 21 2020. 1:[A Practice Advisory is a brief, focused statement issued within 48 hours in response to evolving information on an emergent clinical issue.]. https://www.acog.org/

clinical/clinical-guidance/practice-advisory/articles/2020/12/vaccinating-pregnant-and-lactating-patients-against-covid-19

112. Joint Committee on Vaccination and Immunisation: advice on priority groups for COVID-19 vaccination. 2020 [cited 2021 9th January]. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/950113/jcvi-advice-on-priority-groups-for-covid-19-vaccination-30-dec-2020-revised.pdf

113. COVID-19 vaccine safety update Advisory Committee on Immunization Practices (ACIP). March 1, 2021 [press release]. CDCMarch 2021.

114. Prevention CfDCa. Vaccination Considerations for People who are Pregnant or Breastfeeding. 2021 updated 12/02/2021. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html

115. Gynacologists RCoOa. COVID-19 vaccines, pregnancy and breastfeeding. 2021 [updated 05/02/2021; cited 2021 9th March]. https://www.rcog.org.uk/en/guidelines-research-services/coronavirus-covid-19-pregnancy-and-womens-health/covid-19-vaccines-and-pregnancy/covid-19-vaccines-pregnancy-and-breastfeeding/

116. Baird JK, Jensen SM, Urba WJ, Fox BA, Baird JR. SARS-CoV-2 antibodies detected in human breast milk post-vaccination. *medRxiv*. 2021:2021.02.23.21252328.

117. Brenner EJ, Pigneur B, Focht G, et al. Benign evolution of SARS-Cov2 infections in children with inflammatory bowel disease: results from two international databases. *Clin Gastroenterol Hepatol*. 2021;19:394-396.e5.

118. Pfizer-biontech announce positive topline results of pivotal COVID-19 vaccine study in adolescents [press release]. 31 March 2021.