Alimentary Pharmacology & Therapeutics

WILEY

AP&T Alimentary Pharmacology & Therapeutics

ORIGINAL ARTICLE OPEN ACCESS

Consensus Statements on Assessments and Vaccinations Prior to Commencement of Advanced Therapies for the Treatment of Inflammatory Bowel Diseases

Rupert W. Leong[1,2,3] | Anthony Sakiris[3,4] | Arteen Arzivian[2] | John David Chetwood[1,3] | Thanaboon Chaemsupaphan[1,5] | Miles P. Sparrow[6] | Michael A. Kamm[7,8] | Viraj Kariayawasam[1,2,9] | For the Australian IBD Consensus Working Group

[1]Gastroenterology and Liver Services, Concord Repatriation General Hospital, Sydney, New South Wales, Australia | [2]Faculty of Medicine and Health Sciences, Macquarie University, Sydney, New South Wales, Australia | [3]Faculty of Medicine and Health, University of Sydney, Sydney, New South Wales, Australia | [4]Department of Gastroenterology and Hepatology, Westmead Hospital, Sydney, New South Wales, Australia | [5]Division of Gastroenterology, Department of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand | [6]Department of Gastroenterology, School of Translational Medicine, Monash University and Alfred Health, Melbourne, Victoria, Australia | [7]Department of Medicine, University of Melbourne, Melbourne, Victoria, Australia | [8]Department of Gastroenterology, St Vincent's Hospital, Melbourne, Victoria, Australia | [9]Blacktown Clinical School, Western Sydney University, Sydney, New South Wales, Australia

Correspondence: Rupert W. Leong (rupertleong@outlook.com)

Received: 29 July 2024 | **Revised:** 21 August 2024 | **Accepted:** 20 September 2024

Handling Editor: Richard Gearry

Funding: The authors received no specific funding for this work.

Keywords: advanced therapy | adverse event | Crohn's disease | infection | inflammatory bowel disease | screening | thromboembolism | ulcerative colitis | vaccination

ABSTRACT

Background: Given the introduction of new advanced therapies for inflammatory bowel diseases (IBDs), expanded risk mitigation strategies are essential.

Aims: To create a comprehensive set of statements on assessment procedures and vaccinations before starting monoclonal antibodies, Janus kinase (JAK) inhibitors or sphingosine-1-phosphate (S1P) modulators for IBD.

Methods: We examined literature, guidelines and drug product information regarding vaccination and assessment recommendations for initiating advanced IBD therapies. Using a modified Delphi approach, delegates voted anonymously on the acceptability of these statements prior to and following consensus discussion.

Results: We developed eight statements on the domains of infectious diseases screening, vaccinations and assessments prior to commencing JAK inhibitors and S1P modulators. Six statements received agreement. Pre-advanced therapy screening for infectious diseases was established, and the vaccination protocol was revised. Malignancy, cardiovascular and thromboembolic risk assessments are necessary before initiating JAK inhibitors. Those starting S1P modulators need cardiac and ophthalmic assessments.

Abbreviations: BP, blood pressure assessment; CMV, cytomegalovirus; CXR, chest X-ray; DTP, diphtheria tetanus pertussis; EBV, Epstein–Barr virus; ECG, electrocardiography; FBC, full blood count; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; IBD, inflammatory bowel disease; IGRA-TB, interferon-gamma release assay for tuberculosis; LFT, liver function test; MMR, measles, mumps, and rubella; S1P, sphingosine 1 phosphate; UEC, urea, electrolytes and creatinine; VTE, venous thromboembolism; VZV, varicella-zoster virus.

Conclusions: These consensus statements combine vaccination and assessments on the currently available advanced therapies for IBD as a single comprehensive document that may reduce IBD complications associated with use of advanced therapies. Knowledge gaps identified during the consensus process will provide further research opportunities.

1 | Introduction

Inflammatory bowel diseases (IBDs), encompassing Crohn's disease (CD) and ulcerative colitis (UC), are chronic incurable conditions that are increasingly prevalent worldwide [1]. Increasingly, IBD disproportionately affects an ageing population, in whom complications such as infections and malignancies are of concern [2, 3]. The therapeutic options for managing IBD have expanded. In addition to tumour necrosis factor alpha inhibitors (TNFi), integrin receptor blockers and p-40 subunit interleukin (IL)-12/23 inhibitors, the new treatments p19-subunit IL-23 inhibitors, oral small molecules Janus kinase (JAK) inhibitors and sphingosine-1-phosphate (S1P) modulators, have been introduced. Vedolizumab, ustekinumab and p-19 subunit IL-23 inhibitors risankizumab and mirikizumab have favourable safety profiles with lower risks of infection and malignancy [4, 5]. However, TNFi increases the risk of infections and related hospitalisations [6]. The JAK inhibitors filgotinib, tofacitinib and upadacitinib have the potential to induce infections, malignancy, major adverse cardiac events (MACE) and thrombosis. The S1P-modulators ozanimod and etrasimod may precipitate hypertension, bradycardia and macular oedema [7].

Because the newer treatment classes have unique adverse effect profiles, modification to established screening guidelines might be required. The 2021 European Crohn Colitis Organisation guidelines [8] advised on the prevention and treatment of infections. Upadacitinib, S1P modulators and specific IL-23 inhibitors, however, had not been introduced at that time. The ORAL Surveillance study [9] compared the JAK inhibitor tofacitinib versus TNFi in older patients with rheumatoid arthritis. By refuting non-inferiority compared with TNFi therapy for the occurrence of MACE (hazard ratio, HR: 1.33, 95% confidence interval; CI: 0.91–1.94) or malignancy (HR 1.48; 95% CI 1.04–2.09), tofacitinib may be associated with an increased risk of harm versus TNFi. As such, boxed warnings stipulated by the FDA in the United States, EMA in Europe and TGA in Australia affect all patients prescribed this therapeutic class across all therapeutic indications [10]. While JAK inhibitors are only prescribed to bio-exposed patients with prior advanced therapy treatment failure in the United States, it may be prescribed to bio-naive individuals in Europe and Australia. Cardiac complications of small molecules have also been reviewed in IBD [10]. Prior to commencing S1P inhibitors, electrocardiography (ECG) screening for bradyarrhythmia and heart block is recommended for both ozanimod and etrasimod. Additional baseline tests include serum lipid profile, liver function and creatine kinase (CK).

Given the immunosuppressive effect of advanced therapies, an ageing IBD population and global pandemics [11], it was also timely to review the IBD vaccination protocol. Since the publication of IBD therapeutic guidelines [8], the recombinant herpes zoster vaccine Shingrix has become available, accompanied by the withdrawal of the live varicella-zoster virus (VZV) vaccine. Other viral infections of note include coronavirus COVID-19, respiratory syncytial virus (RSV) and dengue fever [12]. Reviewing these infections, including their vaccinations and relevance to an IBD population was considered a priority.

Failure, intolerance or non-persistence of IBD treatments [13, 14] may result in the need to commence or initiate out-of-class switching of advanced therapies. Risk mitigation strategies, therefore, are applicable to all IBD patients, ideally, before commencing an advanced therapy. We aimed to update IBD clinical practice guidelines applicable to all currently available advanced therapies, with the goal of improving patient safety.

2 | Materials and Methods

2.1 | Development of Statements and Selection of Delegates

The development of statements was carried out through an online platform, with steering committee members (R.W.L. and V.K.) identifying potential safety issues associated with the use of all approved IBD advanced therapies. A focus group, consisting of gastroenterologists and consumer representation, further expanded on these topics. Delegates, chosen for leadership roles in IBD societies, clinical positions, academic contributions and attendance availability, participated in a face-to-face meeting in Sydney, Australia. The process was divided into three domains: updating infectious disease screening, vaccination protocol and specific tests for TNFi, JAK inhibitors and S1P receptor modulators. Gastroenterology fellows (A.A., A.S., and J.D.C.) conducted unbiased literature searches for these domains.

2.2 | Voting

A modified Delphi process [15] was used to determine the level of agreement on the statements and grade their evidence. Delegates cast anonymous online votes using a dedicated platform, with the option to offer feedback. Well-established practices, unchanged in recent times, were combined into composite statements to enable *en bloc* voting, streamlining the process. This allowed delegates to concentrate on recent advancements, which were voted on individually. Disagreements identified through online voting or commentary were crafted into individual statements for thorough discussion at the in-person meeting. Additional time was allocated for presenting and discussing these statements, particularly those not covered in previous guidelines or with notable disagreements. Despite online voting outcomes, all statements underwent review, discussion and anonymous voting at the face-to-face meeting. Consensus was deemed achieved if $\geq 80\%$ of delegates either strongly agreed or agreed with the statements. Conversely, if $\geq 80\%$ of delegates disagreed or strongly disagreed with a statement, it was rejected. Statements that did not meet either consensus could be debated, literature reviewed, wording modified and anonymous

re-voting conducted afterwards. One reiteration was permitted, and if consensus was not achieved, the statement was then rejected. Every statement was then graded to indicate the quality of evidence and classification of recommendations according to the National Health and Medical Research Council, Australia (NHMRC) [16]. The finalised statements were presented to a group of community gastroenterologists for feedback and acceptability.

2.3 | Funding and Conflict of Interest

This project was not funded or influenced by sponsors. Neither delegates nor steering committee members received payment. Meetings occurred online and opportunistically at a Sydney scientific exchange meeting, organised independently and without honoraria. Delegates disclosed conflicts of interest on the virtual platform, at the meeting venue and in the co-authorship document.

3 | Results

Nineteen delegates convened in Sydney in October 2023 to vote on eight consensus statements. These statements are listed in accordance with the domains of (1) infectious disease screening; (2) vaccinations; and (3) assessments prior to commencing JAK inhibitors and S1P modulators. Of these statements, 6 of 8 reached consensus (Table 1 and Figure 1).

3.1 | Infectious Disease Screening

Statement 1: For patients with IBD under consideration for advanced therapy, Epstein–Barr virus (EBV), VZV, cytomegalovirus (CMV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), human Immunodeficiency virus (HIV) serology, chest X-ray and interferon-gamma release assay (IGRA) should be considered.

(*NHMRC*: *Level of Evidence III-3, Grade of Recommendation B. Statement Agreement—100%*)

Given the risk of lymphoproliferative diseases and hemophagocytic syndrome developing in immunosuppressed patients following acute EBV infection, primarily in those on thiopurines, screening for EBV should be considered prior to the commencement of immunosuppressive therapies [17]. Younger subjects are most at risk of EBV seronegative status. VZV serology should also be performed especially if prior chickenpox, shingles or vaccination status is unknown. This is crucial, as several studies have shown a higher risk of herpes zoster in IBD patients, particularly those receiving new advanced therapies, including JAK inhibitors and S1P modulators [18, 19]. Although it is unlikely to influence acute management, CMV reactivation may occur in immunosuppressed patients [20]. Baseline HAV serology should be performed due to the risk of severe hepatitis in immunosuppressed patients with IBD. Similarly, HBV status should be ascertained due to potential viral reactivation. Testing for hepatitis B surface antigen (HBsAg), antibodies to surface antigen (anti-HBs) and core antigen (anti-HBc) is recommended [21]. Vaccination to HAV and HBV is recommended in seronegative subjects. HCV screening should also be performed prior to commencing advanced therapy, with HCV RNA testing in HCV Ab positive patients to differentiate active infection from prior seroconversion from viral clearance. Patients with HCV infection may be at risk of deteriorating liver function due to the immunosuppressive effects of advanced therapy [21]. IBD patients under consideration for advanced therapy should undergo HIV screening. Infective sequelae are less likely to occur in patients with HIV who receive highly active antiretroviral therapy (HAART) than in those who do not [21]. The requirement for immunosuppression and biologic therapy may be lower in patients with HIV [22]. JAK inhibitors and S1P modulators lack data on EBV reactivation risk. Hemophagocytic lymphohistiocytosis or increased risk of lymphoproliferative disorders have not been reported to date. There remains a need to screen for EBV exposure prior to commencing thiopurines. Patients commencing advanced therapies for IBD should have chest X-ray and tuberculosis (TB) IGRA such as QuantiFERON-TB Gold performed. IGRAs effectively screen latent TB and are effective in patients with prior BCG vaccinations in combination with epidemiological exposure risk assessment in addition to chest imaging [23]. While there is clear evidence of an increased risk of TB reactivation following TNFi [24], there have been only rare cases of TB reactivation following exposure to anti-IL12/23 [25] and JAK inhibitors in rheumatoid arthritis patients [26]. However, patients failing non-TNFi advanced therapies may need to switch to TNFi treatment. As such, prior TB screening remains relevant before the commencement of an advanced therapy.

Patients who test positive for IGRA should be evaluated for active TB by risk assessment, history and chest imaging. If active TB were excluded, latent TB infection treatment should precede commencement of immunosuppressive therapies. In the event of indeterminate result, often due to concurrent immunosuppressive medications or underlying disease activity, a repeat IGRA and/or Tuberculin Skin Test depending on local practice should be performed after reducing the dose of immunosuppressants or once the disease flare has resolved [27]. For patients with a negative screening test, annual TB testing should be considered while continuing immunosuppressive therapy, particularly for those living in endemic areas. The consensus group discussed that even though TB prevalence is low in Western societies, immunosuppressed IBD patients may travel to TB-endemic countries risking inadvertent exposure. In addition to vaccination (see below), risk avoidant behaviour is strongly recommended for exposure to infectious agents with travel and specific counselling is recommended on a case-by-case basis. This counselling is beyond the scope of our current project.

Statement 2: For patients with IBD under consideration for an advanced therapy, measles, mumps and rubella (MMR) serology should be performed in the absence of complete vaccination or documented past infection.

(*NHMRC*: *Level of Evidence IV, Grade of Recommendation C. Statement Agreement—84%*)

Given the potential severity of MMR outbreaks in immunosuppressed patients, we recommend performing MMR serology before initiating advanced therapy in IBD patients if the patient

TABLE 1 | Assessments and vaccinations prior to commencing advanced therapy for the treatment of IBD.

Statements		Consensus vote percentage				
		Strongly agree	Agree	Neither	Disagree	Strongly disagree
1	For patients with IBD under consideration for advanced therapy, Epstein–Barr virus (EBV), varicella-zoster virus (VZV), cytomegalovirus (CMV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) serology, chest X-ray and interferon-gamma release assay (IGRA) should be considered	84	16	0	0	0
2	For patients with IBD under consideration for an advanced therapy, measles, mumps, and rubella (MMR) serology should be performed in the absence of complete vaccination or documented past infection	17	67	16	0	0
3	For patients with IBD under consideration for advanced therapy, John Cunningham (JC) virus serology should be performed	0	0	0	0	100
4	For patients with IBD under consideration for advanced therapy, vaccination for VZV, influenza, COVID-19 and pneumococcal and human papillomavirus (HPV) (if < 26 years old, or ≥ 26 with risk factors) should be undertaken	100	0	0	0	0
5	A diphtheria, tetanus and pertussis (DTP) booster and HBV vaccination may be recommended to all patients who have not received these previously. Hemophilus, meningococcus, HAV, Yellow fever, and MMR vaccination may be recommended for specific circumstances based on the risk exposure prior to the commencement of advanced therapy in IBD	12	82	6	0	0
6	In addition to the full blood count, renal and liver function tests required for all patients with IBD considered for advanced therapy, those under consideration for JAK inhibitors should undergo a fasting lipid profile, cardiovascular and venous thromboembolism risk assessment and age-appropriate cancer screening prior to commencement	83	17	0	0	0
7	In addition to the above, patients with IBD under consideration for Janus kinase (JAK) inhibitors should undergo creatine kinase (CK) level testing prior to commencement	0	26	37	37	0
8	In addition to the full blood count, renal and liver function tests required for all patients with IBD considered for advanced therapy, those under consideration for S1P modulators should undergo hypertension screening, electrocardiography (ECG) and ophthalmic screening	65	35	0	0	0

Note: Consensus for agreement was achieved. Consensus for agreement was not achieved. Consensus for disagreement was achieved.

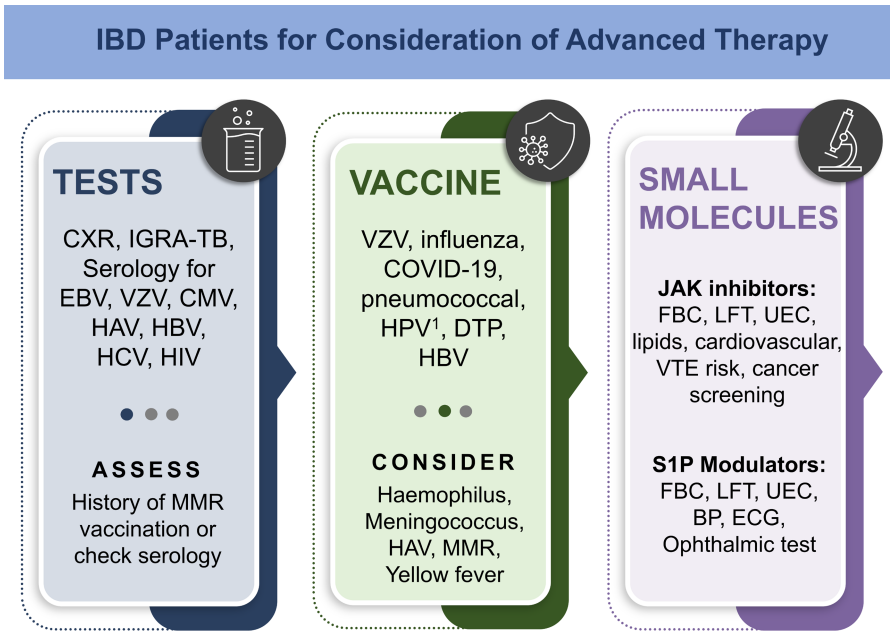

FIGURE 1 | Assessments and vaccinations prior to commencing advanced therapy for the treatment of IBD. [1]HPV vaccination: Indicated in patients < 26 years old, or if ≥ 26 years old with risk factors.

has not completed two doses of the vaccine, documentation of vaccination is unavailable or there is no documented history of infection. If the patient has immunity or prior vaccination status is known, MMR serology is not required. The MMR vaccine remains effective in the setting of IBD immunosuppressive treatment and advanced therapies [28]. Patients with IBD who are non-immune to MMR or confirmed not to be vaccinated against MMR should receive vaccination. MMR as a live attenuated vaccine should not be administered concurrently with advanced therapy [29]. Pregnant IBD patients should not receive the MMR live vaccine. Vaccination testing and administration should not defer commencement of IBD treatment in those with severe disease [11].

Statement 3: For patients with IBD under consideration for an advanced therapy, John Cunningham (JC) virus serology should be performed. [STATEMENT REJECTED]

(*NHMRC*: *Level of Evidence III—2, Grade of Recommendation B. Statement Agreement—0%*)

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease secondary to the reactivation of the JC virus [30]. JC virus prevalence is 40%–90% in the community and remains latent but risks reactivation in settings of significant immunosuppression [31]. Natalizumab is the commonest immunosuppressive medication associated with PML [32]. Notably, natalizumab is not a routinely utilised advanced therapy for IBD following the availability of newer advanced therapies. Vedolizumab alone has not demonstrated evidence for the development of PML [20]. Although rare cases of PML have been reported in patients with multiple sclerosis treated with S1P modulators, particularly fingolimod [33], there is a lack of data with ozanimod and etrasimod for the treatment IBD. Furthermore, JC virus seropositivity alone has a low positive-predictive value in the development of PML [34]. Based on this, we do not recommend routine JC virus serology screening prior to initiating advanced therapy in the absence of additional risk factors such as prior exposure to natalizumab or active HIV infection.

3.2 | Vaccinations

Statement 4: For patients with IBD under consideration for advanced therapy, vaccination for varicella-zoster, influenza, COVID-19 and pneumococcal and human papillomavirus (HPV) (if under 26 years old, or if 26 and older with risk factors) should be undertaken.

(*NHMRC*: *Level of Evidence III-2, Grade of Recommendation B. Statement Agreement—100%*)

Primary VZV infection is often more severe in adults than children [35, 36]. Typically, VZV seroconversion is almost universal by late childhood. Additionally, many countries have childhood VZV vaccination schedules [35]. Reports of primary VZV infection in adults with IBD including instances of severe disease, post-herpetic neuralgia and rarely deaths have been reported. Immunosuppressed adult IBD patients, who are VZV-seronegative, may receive post-exposure prophylaxis in the event of VZV exposure [8, 37]. Patients with IBD on systemic immunosuppressive therapy are more susceptible to VZV reactivation and may develop a more severe disease course from viral reactivation [38]. The risk of reactivation is associated with older age, Asian ethnicity and those on corticosteroids, TNFi, JAK inhibitors and S1P modulators [8]. Comorbidities such as rheumatoid arthritis, active haematological malignancies and monogenic IBD germline mutations are also at elevated risk [39]. VZV vaccination is effective in

preventing VZV reactivation and associated complications, such as post-hepatic neuralgia and hospitalisation, and is therefore recommended [40, 41]. The recombinant VZV vaccine (Shingrix) is ideal in patients soon to commence or already on advanced therapies. Live VZV vaccines have been withdrawn in many markets.

Influenza is a ubiquitous and seasonal infection. Patients with IBD are at higher risk of acquiring influenza and suffer a higher 30-day influenza-related hospitalisation rate compared with non-IBD patients. Corticosteroid usage conveys an independent additional risk [42, 43]. Vaccination effectively prevents influenza-related sequelae. Some therapies such as TNFi can attenuate the immunologic response to vaccination, though patients on vedolizumab appear to show a similar response to controls [8, 44, 45].

Patients with IBD generally experience a similar rate of severe outcomes and mortality from COVID-19 infection to the general population, regardless of their IBD therapy such as TNFi, JAK inhibitor, ustekinumab or vedolizumab. The exception to this is observed in patients with uncontrolled IBD disease activity and corticosteroid use, which are associated with increased odds of severe COVID-19, hospitalisation and death [46–48]. The protective effect of vaccination, measured by anti-SARS-CoV-2 spike (S1 receptor binding domain) antibody concentration, is attenuated with infliximab and tofacitinib [48]. Furthermore, patients on TNFi experience more rapid antibody decay after vaccination [49]. Anti-S antibodies correlate with both neutralising antibody titres and T-cell response, and the initial titre response has been suggested to positively impact long-term immunity [50–52]. These data, therefore, support both COVID-19 vaccination in IBD, as well as the provision of additional vaccine doses for those subgroups at risk of suboptimal vaccination response. Immunosuppressed IBD patients that develop symptomatic COVID-19 infection should be considered for early antiviral therapy irrespective of prior vaccination status.

Patients with IBD are at increased risk of developing invasive *Streptococcal pneumoniae* infection [53]. Previous trials demonstrated the efficacy of Prevnar 13 and Pneumovax 23 vaccines and confirmed a lower risk of severe pneumococcal disease in IBD patients who receive pneumococcal vaccines compared to those who did not [54].

At least 13 of more than 100 known HPV genotypes can cause 6 types of cancers, and HPV is responsible for over 90% of anal and cervical cancers [8, 55]. Childhood vaccination schedules have been implemented in many countries [56]. IBD patients on immunosuppressant medication are also at particular risk of cervical high-grade dysplasia or cancer compared to the general population [57], and patients with chronic perianal CD are at substantial risk of developing squamous cell carcinoma (SCC) or adenocarcinoma from the fistula-lining epithelium, as well as SCC or adenocarcinoma arising from chronic anorectal ulcerations or strictures [58]. HPV vaccination effectively protects against HPV-related sequelae including malignancy [59]. Due to the epidemiological risk of HPV acquisition, vaccination is recommended for those under 26 years old, and patient-centred discussions are advised for those 26 years old and over with specific behavioural or medical risk factors for HPV infection, including immunosuppression [8, 60].

Statement 5: Diphtheria, tetanus, and pertussis (DTP) booster and HBV vaccination may be recommended to all patients who have not received these previously. Hemophilus, meningococcus, HAV, yellow fever and MMR vaccination may be recommended for specific circumstances based on the risk exposure prior to the commencement of advanced therapy in IBD.

(*NHMRC*: *Level of Evidence IV, Grade of Recommendation B. Statement Agreement—94%*)

Diphtheria, tetanus and pertussis (DTP) and MMR vaccinations are part of the routine vaccination schedule in many countries. The immunocompromised state represents a significant risk factor for severe disease with measles [61]. There is no specific evidence indicating a higher risk of disease nor a protective effect of MMR and DTP vaccination in patients with IBD than in healthy populations, possibly because of the very low prevalence of these diseases in high-income settings and/or the uneven distribution of cases [62]. However, given the protective effect in the general population, vaccination is still recommended for patients with IBD who have not received these previously, particularly as the serological response to vaccination seems unaffected by both the presence of IBD and irrespective of immunosuppressive therapy, and since MMR administration is contraindicated once systemic immunosuppressive therapy is instituted.

HBV rates vary worldwide, with high prevalences reported in low socio-demographic index (SDI) countries, whereas a relatively low prevalence in high SDI countries [63]. Though antiviral prophylaxis is effective in preventing HBV-related sequelae in chronic infection, HBV reactivation with resultant acute liver failure after immunosuppression has been reported in patients with IBD who were not on antiviral prophylaxis [64]. Immunosuppression also conveys and increases risk for chronic infection after acute exposure [65]. HBV vaccination against HBsAg is effective in preventing infection and sequelae such as liver cirrhosis, liver cancers and mortality and has been incorporated into many childhood vaccination schedules as well as for at-risk adults [66]. HBV vaccination in patients with IBD seems to induce a lower anti-HBs titre than in those without IBD, though the clinical significance is uncertain [67–69]. While some systemic immunosuppressive agents such as corticosteroids, TNFi and thiopurines attenuate the serological response to vaccination [67], vedolizumab does not appear to affect HBV seroprotection [70]. The assessment of prior vaccination status via serology can be problematic as anti-HBs titre can decline to undetectable levels after vaccination, even though this does not convey a risk for chronic HBV infection after exposure [71, 72]. Nonetheless, HBV infection has been documented in vaccinated immunocompromised non-IBD patients [73]. The risk of repeated HBV booster vaccinations appears low, though is ultimately uncertain [74]. Thus, HBV vaccination prior to systemic immunosuppression represents an opportune moment to initiate vaccination in those who are otherwise suitable. This is particularly important as a patient's risk factor status can change over time, IBD and immunosuppressive therapy can reduce

the response to HBV vaccination and long-term outcomes of infection can be life-threatening. However, there remain unanswered questions regarding the impact of anti-HBs serology testing in patients with IBD.

Hemophilus influenzae type B (Hib) is an obligate human pathogen and an important cause of invasive bacterial infections predominantly in unvaccinated children. As such, it is included in the childhood vaccination schedule in many countries [8, 74]. Hib vaccination programs are efficacious in preventing severe invasive disease and morbidity [75]. However, invasive Hib disease has not yet been eliminated in countries with low vaccine coverage, and periodic outbreaks of Hib infection still occur in countries with high vaccine coverage [76]. In adults, the majority of *Hemophilus*-related morbidity is caused by non-typable *Hemophilus influenzae*, whilst invasive Hib infection is rare, and there are questions about the cost-effectiveness of adult vaccination [74]. Although there are no paediatric IBD data, one cohort study found that adults with IBD had an increased adjusted odds ratio (aOR) of being hospitalised for Hib-related pneumonia (aOR: 1.34, 95% CI: 1.16–1.55) compared to non-IBD controls, though this did not translate into increased mortality and there have been criticisms of the study design [42]. Furthermore, the pathogenicity of encapsulated bacteria such as Hib is increased with hyposplenism, and IBD is associated with a spectrum of hyposplenism from mild functional hyposplenism to frank splenic atrophy though the exact frequency and severity in patients with IBD remains uncertain [77]. Hib vaccination seems to induce an appropriate serological response in adults with IBD on thiopurines [78]. The current recommendations therefore reflect the limited evidence base, and that vaccination advice should be personalised and discussed with the patient in this context.

Neisseria meningitides is a gram-negative encapsulated bacterium, of which 6 serogroups cause most diseases worldwide [79]. Though a rare event, epidemiological data suggest that IBD patients appear to be at increased risk of meningococcal disease [80]. Furthermore, as mentioned before, IBD is associated with hyposplenism, which conveys an increased resultant risk of severe disease from infection with encapsulated bacteria such as *Neisseria meningitides* [77]. Though the risk of invasive meningococcal disease can be catastrophic, the absolute risk is low in IBD patients and the benefit of vaccination uncertain. Considering this, the consensus group recommends vaccination for those at specific risk (such as adolescents, the elderly, or those who travel to endemic areas) [79], after a patient-centred discussion.

The mortality rate from fulminant HAV infection is estimated to be around 2.1% in adults over 40 years old, but with a higher rate suggested in immunosuppressed patients [81]. Although HAV vaccination is generally effective in patients with IBD, the seroconversion rate is lower in patients receiving anti-TNF agents and ≥ 2 immunosuppressants [82]. Due to the faecal-oral transmission of HAV, the risk of acquisition is related to endemicity, sanitation and hygiene measures, as well as specific behaviours such as the ingestion of contaminated filter-feeders such as shellfish [83, 84]. Though HAV infection in low-endemicity countries is rare, there is some evidence that the rate is increasing [84]. However, there is insufficient evidence to recommend universal HAV vaccination for all IBD patients, hence it should be limited to those planning to visit endemic countries or used opportunistically when combined with HBV vaccination.

Yellow fever is an arbovirus transmitted to humans primarily by the bites of infected *Aedes* and *Hemagogus* spp. mosquitoes and is found in areas of Africa, Central and South America [85]. However, there are concerns that global endemicity patterns for arboviruses may change with climate change [86, 87]. Currently, yellow fever transmission has not been described outside endemic areas, though the Aedes aegypti mosquito that transmits the disease is found widely distributed in such areas as northern Queensland in Australia, south-eastern United States, the Middle East, south-east Asia and the Pacific Islands [88]. Yellow fever live vaccination administration is contraindicated for patients on immunosuppression [89]. Though case reports and case series have reported the safety of administration after low-dose methotrexate or TNFi [90–92], fatalities after IBD-related immunosuppression have also been reported [93]. Due to the lack of transmission of yellow fever in Australia and lack of proven benefit after vaccination in IBD, routine vaccination is not recommended but should be discussed with patients who are not on systemic immunosuppression and may have specific risk factors such as travel to endemic areas.

3.3 | Assessments Prior to Commencing JAK Inhibitors and S1P Receptor Modulators

Statement 6: In addition to the full blood count, renal and liver function tests required for all patients with IBD considered for advanced therapy, those under consideration for JAK inhibitors should undergo a fasting lipid profile, cardiovascular and venous thromboembolism (VTE) risk assessment and age-appropriate cancer screening prior to commencement.

(*NHMRC*: *Level of Evidence II, Grade of Recommendation B. Statement Agreement—100%*)

Safety data of 1157 patients on tofacitinib for UC followed up to 7.8 years reported anaemia in 6.7%, lymphopenia in 3.8%, neutropenia in 0.9% and acute renal impairment in 0.9% [94]. In the open-label long-term extension of the OCTAVE trial, 26 patients out of 944 had derangement of liver function tests and were assessed for drug-induced liver injury related to tofacitinib [95]. Filgotinib may be associated with a lower risk of adverse events. Upadacitinib use was associated with similar blood parameter changes [96]. All these adverse events were mild and reversible on cessation of treatment.

A reversible increase in total cholesterol, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol was reported as early as week 8 of treatment with tofacitinib in UC. The increased lipid levels were sustained but not worsening on long-term follow-up [97]. Tofacitinib was associated with a higher risk of VTE, MACE and malignancies compared to TNFi in patients with rheumatoid arthritis who are above 50 years of age with one or more risk factors [9]. The incidence of VTE, cardiovascular and malignant complications arising in UC and CD studies, however, are low [98, 99]. Findings from the ORAL Surveillance study

led to the issuance of a boxed warning from several regulatory agencies [9]. However, the generalizability of these results to IBD patients has not been confirmed given the high baseline cardiovascular risk in the study population. The real-world evidence on this issue in IBD and long-term clinical trial data to date have been reassuring. The decision to prescribe JAK inhibitors should be made through careful discussions, considering individual cardiovascular risk factors. We acknowledge that not all risk factors carry the same weight; therefore, utilising locally validated cardiovascular risk calculators (e.g., Atherosclerotic Cardiovascular Disease; ASCVD risk [100]) may help guide risk stratification. For patients with known or high cardiovascular risk according to the ASCVD risk score who require JAK inhibitors, we recommend comprehensive cardiovascular assessment alongside the continuation of lipid-lowering agents with regular monitoring when initiating JAK inhibitors. Additionally, prioritising lifestyle modifications, such as smoking cessation and weight reduction, is essential to mitigate overall cardiovascular risk. The addition of antiplatelet or anticoagulant therapy may be considered based on high-risk profiling and on an individualised basis.

Data from clinical trials and long-term extension studies have shown no elevated cancer risk in IBD patients using tofacitinib. However, findings from the ORAL Surveillance study reported a higher overall incidence of malignancies, particularly lung cancer and lymphoma [9]. In light of this, we recommend that in addition to regular colonoscopy for colorectal cancer surveillance, patients should undergo age-appropriate cancer screening, which should align with national guidelines, such as biennial mammograms and cervical screening tests every 5 years for women at average risk. Additionally, annual skin checks by a general practitioner or dermatologist should be considered, along with other cancer screenings as appropriate.

Statement 7: In addition to the above, patients under consideration for JAK inhibitors should undergo creatine kinase level testing prior to commencement. [STATEMENT REJECTED]

(*NHMRC*: *Level of Evidence III-1, Grade of Recommendation B. Statement Agreement—26%*)

Creatine kinase (CK) elevation was a frequent laboratory abnormality reported in patients with UC treated with tofacitinib (12.3%). However, there was no significant clinical weakness, muscle pain and documented rhabdomyolysis. The mean CK level increase from induction to the end of 52 weeks of maintenance tofacitinib therapy was between 90.3 and 115.6 U/L and was not associated with adverse clinical sequel [94]. The U-ACHIEVE maintenance trial of upadacitinib therapy for UC reported CK elevation in 6% of patients on upadacitinib 15 mg daily and 8% in patients on 30 mg daily, with 1 patient discontinuing treatment due to muscle pain [96]. In the absence of clinical significance and the lack of specificity, the need for CK universal testing and follow-up was deemed unnecessary by the consensus group. However, CK testing is required in those that develop muscle pain.

Statement 8: In addition to the full blood count, renal, and liver function tests required for all patients with IBD considered for advanced therapy, those under consideration for S1P modulators should undergo hypertension screening, ECG and ophthalmic screening.

(*NHMRC*: *Level of Evidence III-1, Grade of Recommendation B. Statement Agreement—100%*)

The interim analysis of the ongoing True North open-label extension assessing the long-term safety of 3 years of ozanimod in moderately to severely active UC [101] reported lymphopenia in 15.6% of the patients, anaemia in 10.4%, alanine aminotransferase derangement in 9% and gamma-glutamyl transferase derangement in 6%. Lymphocyte counts usually return to normal within 12–18 weeks and did not lead to drug discontinuation. Hypertension was reported in 6%. In the ELEVATE UC trial, the incidence of hypertension was also higher in patients treated with etrasimod compared to those receiving placebo, necessitating the need for blood pressure monitoring during treatment and appropriate management [102]. S1P receptor signalling, which plays a role in cardiovascular function, may cause bradycardia and atrioventricular block when using S1P modulators. In the ozanimod trial, bradycardia risk was low (0.6%) with gradual dose titration, primarily occurring during the induction phase and typically resolving spontaneously [103]. No serious bradycardia events were reported in the etrasimod trial, which did not use dose titration [102]. An ECG is recommended before initiating S1P modulators to identify any pre-existing cardiac conduction abnormalities, and the use of this class of medication is contraindicated in patients with high-degree atrioventricular block [104]. No increased signal for ischemic heart disease or thromboembolic events was identified with long-term use of ozanimod [101, 105]. Macular oedema was reported as a rare event of 0.6% in ozanimod and 0.3% in etrasimod trials, primarily in patients with risk factors such as diabetes mellitus, uncontrolled hypertension, history of uveitis or retinal disease [102, 103, 105]. The likely mechanism involves S1P modulators reducing pericytes and disrupting tight junctions between endothelial cells, leading to increasing vascular permeability at the blood–retina barrier [106]. According to the USA summary of product characteristics, it is recommended to perform ophthalmic examination in all patients being considered for S1P modulators. In contrast, the Australian TGA advises ophthalmic exam only in patients at risk for macular edema. This discordance extends to European guidance, where the EMA recommends ophthalmic exams in high-risk patients prior to initiating ozanimod but advises exams for all patients when starting etrasimod. In settings with delayed ophthalmology consultation, the consensus group advised optometrist-led screening, ideally using optical coherence tomography.

3.3.1 | Knowledge Gaps

Respiratory syncytial virus (RSV) and dengue fever, for which vaccination schedules exist, along with rabies, Ross River, Barmah Forest virus and tick-borne diseases, were discussed at the focus group. Limited data exist specific to IBD patients, necessitating case-by-case individualisation possibly in collaboration with infectious disease physicians. Additional mitigation strategies, such as avoiding travel to endemic regions, vector avoidance and post-exposure treatment, were deemed relevant, but require individualisation. The inclusion of thiopurine and

corticosteroid harm minimisation strategies did not reach sufficient prioritisation over focused coverage of the new advanced therapies. Pregnancy and breastfeeding considerations have recently received specific attention [98].

4 | Discussion

Arising from the increased complexity of IBD therapeutics, we developed eight harm minimisation recommendations for patients requiring advanced therapy for IBD. These recommendations encompass assessments and vaccinations prior to initiating monoclonal antibodies, JAK inhibitors and S1P modulators. We incorporated considerations for new vaccines and changes to vaccination schedules. Following the consensus process, two statements regarding JC virus exposure testing and baseline serum CK testing were regarded as unnecessary. The statements were considered useful when assessed by a second cohort of community gastroenterologists. Additional knowledge gaps were identified for future meetings.

Establishing a comprehensive checklist of pre-treatment assessments and vaccinations before initiating immunosuppressive therapies is considered standard practice across various treatment indications [107]. Checklists provide cognitive prompts or reminders for the completion of evidence-based practices and engender a culture of safety that may reduce harm to patients. Risk mitigation is essential for all IBD patients, regardless of their initial advanced therapy, due to the unpredictability of long-term treatment efficacy. Primary non-response, secondary loss of response, intolerance and adverse events result in the limited persistence of all IBD drugs [13]. Most IBD patients will, therefore, be eventually exposed to several therapeutic classes. In cases of severe disease relapse, patients may require treatments associated with greater risks, such as JAK inhibitors and TNFi. Completing vaccination schedules before immunosuppression and having baseline test results available can aid in selecting appropriate treatments, reducing delays and minimise complications.

The strengths of this project are, firstly, that we established well-defined, output-focused goals encompassing patient-centric safety concerns and improving prescriber confidence. Secondly, we confirmed that the statements could be generalised from community-based prescribers to highly specialised IBD units. Thirdly, the unbiased literature review process incorporated not only established guidelines but also other studies and drug product information. Fourthly, we focused on the recent changes and additions to our formulary that demanded greater attention. Finally, we used a well-established voting process by expert clinicians including ample opportunities for virtual and live discussion. The fact that only six out of eight statements were endorsed supports the process as robust. We aimed to keep the list of risk mitigation strategies brief to encourage quality-prescribing of medicines, rather than to discourage the use of advanced therapies through over-complication.

There are caveats to this consensus process. The perspectives and recommendations presented are based on the Australian healthcare system, which may not fully reflect practices in other countries. Nevertheless, Australia's universal insurance allows all IBD patients to commence and continue advanced therapies indefinitely without a specified hierarchy [13]. With high use of advanced therapies, therefore, these risk mitigation strategies become even more relevant. Another limitation is the dynamic nature of IBD treatment, necessitating future updates with new treatments or once new adverse events are uncovered. We have identified knowledge gaps that may inform dedicated future research. In conclusion, we recommend adopting a clear checklist that aims to promote quality use of advanced therapies in IBD.

Author Contributions

Rupert W. Leong: conceptualisation, writing – review and editing, writing – original draft, methodology, investigation, supervision. **Anthony Sakiris:** data curation, investigation, writing – original draft. **Arteen Arzivian:** data curation, investigation, writing – original draft. **John David Chetwood:** data curation, investigation, writing – original draft. **Thanaboon Chaemsupaphan:** data curation, writing – review and editing, investigation, writing – original draft. **Miles P. Sparrow:** data curation, writing – review and editing. **Michael A. Kamm:** data curation, writing – review and editing. **Viraj Kariayawasam:** data curation, writing – review and editing, conceptualisation, methodology.

Acknowledgements

Open access publishing facilitated by The University of Sydney, as part of the Wiley - The University of Sydney agreement via the Council of Australian University Librarians.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. A. Pudipeddi, J. Liu, V. Kariyawasam, et al., "High Prevalence of Crohn Disease and Ulcerative Colitis Among Older People in Sydney," *Medical Journal of Australia* 214, no. 8 (2021): 365–370.

2. A. Pudipeddi, V. Kariyawasam, C. Haifer, B. Baraty, S. Paramsothy, and R. W. Leong, "Safety of Drugs Used for the Treatment of Crohn's Disease," *Expert Opinion on Drug Safety* 18, no. 5 (2019): 357–367.

3. W. Fries, G. Basile, F. Bellone, G. Costantino, and A. Viola, "Efficacy and Safety of Biological Therapies and JAK Inhibitors in Older Patients With Inflammatory Bowel Disease," *Cells* 12, no. 13 (2023): 1722.

4. W. Chan, V. C. Kariyawasam, S. Kim, et al., "Gastroenterologists' Preference and Risk Perception on the Use of Immunomodulators and Biological Therapies in Elderly Patients With Ulcerative Colitis: An International Survey," *European Journal of Gastroenterology & Hepatology* 32, no. 8 (2020): 976–983.

5. N. Khan, T. Pernes, A. Weiss, et al., "Incidence of Infections and Malignancy Among Elderly Male Patients With IBD Exposed to Vedolizumab, Prednisone, and 5-ASA Medications: A Nationwide Retrospective Cohort Study," *Advances in Therapy* 38, no. 5 (2021): 2586–2598.

6. N. Khan, D. Patel, C. Trivedi, et al., "The Impact of IBD Medications on Risk of Pneumonia and Pneumonia-Related Hospitalisation: A Nationwide Cohort Study of 56 410 IBD Patients," *Alimentary Pharmacology & Therapeutics* 55, no. 1 (2022): 64–72.

7. B. Clement, K. De Felice, and A. Afzali, "Indications and Safety of Newer IBD Treatments in the Older Patient," *Current Gastroenterology Reports* 25, no. 7 (2023): 160–168.

8. T. Kucharzik, P. Ellul, T. Greuter, et al., "ECCO Guidelines on the Prevention, Diagnosis, and Management of Infections in

Inflammatory Bowel Disease," *Journal of Crohn's & Colitis* 15, no. 6 (2021): 879–913.

9. S. R. Ytterberg, D. L. Bhatt, and C. A. Connell, "Cardiovascular and Cancer Risk With Tofacitinib in Rheumatoid Arthritis. Reply," *New England Journal of Medicine* 386, no. 18 (2022): 1768.

10. P. A. Olivera, J. S. Lasa, G. Peretto, S. Zuily, S. Danese, and L. Peyrin-Biroulet, "Review Article: Risk of Cardiovascular Events in Patients With Inflammatory Bowel Disease Receiving Small Molecule Drugs," *Alimentary Pharmacology & Therapeutics* 57, no. 11 (2023): 1231–1248.

11. J. Reich, S. K. Wasan, and F. A. Farraye, "Vaccination and Health Maintenance Issues to Consider in Patients With Inflammatory Bowel Disease," *Gastroenterology Hepatology* 13, no. 12 (2017): 717–724.

12. O. Kaiwan, Y. Sethi, N. Khehra, et al., "Emerging and Re-Emerging Viral Diseases, Predisposing Risk Factors, and Implications of International Travel: A Call for Action for Increasing Vigilance and Imposing Restrictions Under the Current Threats of Recently Emerging Multiple Omicron Subvariants," *International Journal of Surgery* 109, no. 3 (2023): 589–591.

13. Y. Ko, S. Paramsothy, Y. Yau, and R. W. Leong, "Superior Treatment Persistence With Ustekinumab in Crohn's Disease and Vedolizumab in Ulcerative Colitis Compared With Anti-TNF Biological Agents: Real-World Registry Data From the Persistence Australian National IBD Cohort (PANIC) Study," *Alimentary Pharmacology & Therapeutics* 54, no. 3 (2021): 292–301.

14. A. Pudipeddi, Y. Ko, S. Paramsothy, and R. W. Leong, "Vedolizumab has Longer Persistence Than Infliximab as a First-Line Biological Agent but not as a Second-Line Biological Agent in Moderate-to-Severe Ulcerative Colitis: Real-World Registry Data From the Persistence Australian National IBD Cohort (PANIC) Study," *Therapeutic Advances in Gastroenterology* 15 (2022), https://doi.org/10.1177/17562848221080793.

15. P. Nasa, R. Jain, and D. Juneja, "Delphi Methodology in Healthcare Research: How to Decide its Appropriateness," *World Journal of Methodology* 11, no. 4 (2021): 116–129.

16. T. Merlin, A. Weston, R. Tooher, et al., *NHMRC Levels of Evidence and Grades for Recommendations for Developers of Guidelines. National Health and Medical Research Council (NHRMC)* (Canberra, ACT: Australian Government, 2009).

17. H. Zhang, S. Zhao, and Z. Cao, "Impact of Epstein-Barr Virus Infection in Patients With Inflammatory Bowel Disease," *Frontiers in Immunology* 13 (2022): 1001055.

18. M. Ham, G. Cullen, and A. S. Cheifetz, "Varicella Zoster Virus Infection in Patients With Inflammatory Bowel Disease," *Gastroenterology Hepatology* 9, no. 1 (2013): 56–58.

19. P. A. Olivera, J. S. Lasa, S. Bonovas, S. Danese, and L. Peyrin-Biroulet, "Safety of Janus Kinase Inhibitors in Patients With Inflammatory Bowel Diseases or Other Immune-Mediated Diseases: A Systematic Review and Meta-Analysis," *Gastroenterology* 158, no. 6 (2020): 1554–1573.e12.

20. C. A. Lamb, N. A. Kennedy, T. Raine, et al., "British Society of Gastroenterology Consensus Guidelines on the Management of Inflammatory Bowel Disease in Adults," *Gut* 68, no. Suppl 3 (2019): s1–s106.

21. J. F. Rahier, F. Magro, C. Abreu, et al., "Second European Evidence-Based Consensus on the Prevention, Diagnosis and Management of Opportunistic Infections in Inflammatory Bowel Disease," *Journal of Crohn's & Colitis* 8, no. 6 (2014): 443–468.

22. L. Guillo, M. Uzzan, L. Beaugerie, et al., "Impact of HIV Infection on the Course of Inflammatory Bowel Disease and Drug Safety Profile: A Multicenter GETAID Study," *Clinical Gastroenterology and Hepatology* 20, no. 4 (2022): 787–797.e2.

23. G. Andrisani, A. Armuzzi, A. Papa, et al., "Comparison of Quantiferon-TB Gold Versus Tuberculin Skin Test for Tuberculosis Screening in Inflammatory Bowel Disease Patients," *Journal of Gastrointestinal and Liver Diseases* 22, no. 1 (2013): 21–25.

24. R. Lorenzetti, A. Zullo, L. Ridola, et al., "Higher Risk of Tuberculosis Reactivation When Anti-TNF is Combined With Immunosuppressive Agents: A Systematic Review of Randomized Controlled Trials," *Annals of Medicine* 46, no. 7 (2014): 547–554.

25. S. Ghosh, B. G. Feagan, E. Ott, et al., "Safety of Ustekinumab in Inflammatory Bowel Disease: Pooled Safety Analysis Through 5 Years in Crohn's Disease and 4 Years in Ulcerative Colitis," *Journal of Crohn's & Colitis* 18, no. 7 (2024): 1091–1101.

26. K. L. Winthrop, S. H. Park, A. Gul, et al., "Tuberculosis and Other Opportunistic Infections in Tofacitinib-Treated Patients With Rheumatoid Arthritis," *Annals of the Rheumatic Diseases* 75, no. 6 (2016): 1133–1138.

27. B. J. Qumseya, A. N. Ananthakrishnan, S. Skaros, et al., "QuantiFERON TB Gold Testing for Tuberculosis Screening in an Inflammatory Bowel Disease Cohort in the United States," *Inflammatory Bowel Diseases* 17, no. 1 (2011): 77–83.

28. F. Caldera, E. A. Misch, S. Saha, et al., "Immunosuppression Does Not Affect Antibody Concentrations to Measles, Mumps, and Rubella in Patients With Inflammatory Bowel Disease," *Digestive Diseases and Sciences* 64, no. 1 (2019): 189–195.

29. G. Syal, M. Serrano, A. Jain, et al., "Health Maintenance Consensus for Adults With Inflammatory Bowel Disease," *Inflammatory Bowel Diseases* 27, no. 10 (2021): 1552–1563.

30. J. R. Berger, A. J. Aksamit, D. B. Clifford, et al., "PML Diagnostic Criteria: Consensus Statement From the AAN Neuroinfectious Disease Section," *Neurology* 80, no. 15 (2013): 1430–1438.

31. D. W. Raisch, J. A. Rafi, C. Chen, and C. L. Bennett, "Detection of Cases of Progressive Multifocal Leukoencephalopathy Associated With New Biologicals and Targeted Cancer Therapies From the FDA's Adverse Event Reporting System," *Expert Opinion on Drug Safety* 15, no. 8 (2016): 1003–1011.

32. M. Fayyaz and S. S. Jaffery, "Natalizumab-Associated Progressive Multifocal Leukoencephalopathy in Patients With Multiple Sclerosis: A Mini Review," *Cureus* 10, no. 8 (2018): e3093.

33. S. Sriwastava, D. Chaudhary, S. Srivastava, et al., "Progressive Multifocal Leukoencephalopathy and Sphingosine 1-Phosphate Receptor Modulators Used in Multiple Sclerosis: An Updated Review of Literature," *Journal of Neurology* 269, no. 3 (2022): 1678–1687.

34. G. Bloomgren, S. Richman, C. Hotermans, et al., "Risk of Natalizumab-Associated Progressive Multifocal Leukoencephalopathy," *New England Journal of Medicine* 366, no. 20 (2012): 1870–1880.

35. K. Bollaerts, M. Riera-Montes, U. Heininger, et al., "A Systematic Review of Varicella Seroprevalence in European Countries Before Universal Childhood Immunization: Deriving Incidence From Seroprevalence Data," *Epidemiology and Infection* 145, no. 13 (2017): 2666–2677.

36. A. M. Arbeter, "Clinical Trials of Varicella Vaccine in Healthy Adolescents and Adults," *Infectious Disease Clinics of North America* 10, no. 3 (1996): 609–615.

37. G. Cullen, R. P. Baden, and A. S. Cheifetz, "Varicella Zoster Virus Infection in Inflammatory Bowel Disease," *Inflammatory Bowel Diseases* 18, no. 12 (2012): 2392–2403.

38. M. D. Long, C. Martin, R. S. Sandler, and M. D. Kappelman, "Increased Risk of Herpes Zoster Among 108 604 Patients With Inflammatory Bowel Disease," *Alimentary Pharmacology & Therapeutics* 37, no. 4 (2013): 420–429.

39. R. Nambu, N. Warner, D. J. Mulder, et al., "A Systematic Review of Monogenic Inflammatory Bowel Disease," *Clinical Gastroenterology and Hepatology* 20, no. 4 (2022): e653–e663.

40. A. Mwakingwe-Omari, N. Lecrenier, A. Naficy, D. Curran, and I. Posiuniene, "Recombinant Zoster Vaccine in Immunocompetent and Immunocompromised Adults: A Review of Clinical Studies," *Human Vaccines & Immunotherapeutics* 19, no. 3 (2023): 2278362.

41. R. E. Harris, L. Curtis, V. Hegde, et al., "A Decade of Varicella Screening Within a Paediatric Inflammatory Bowel Disease Population," *Journal of Crohn's & Colitis* 14, no. 5 (2020): 608–616.

42. D. J. Stobaugh, P. Deepak, and E. D. Ehrenpreis, "Hospitalizations for Vaccine Preventable Pneumonias in Patients With Inflammatory Bowel Disease: A 6-Year Analysis of the Nationwide Inpatient Sample," *Clinical and Experimental Gastroenterology* 6 (2013): 43–49.

43. A. Tinsley, S. Navabi, E. D. Williams, et al., "Increased Risk of Influenza and Influenza-Related Complications Among 140,480 Patients With Inflammatory Bowel Disease," *Inflammatory Bowel Diseases* 25, no. 2 (2019): 369–376.

44. F. Caldera, L. Hillman, S. Saha, et al., "Immunogenicity of High Dose Influenza Vaccine for Patients With Inflammatory Bowel Disease on Anti-TNF Monotherapy: A Randomized Clinical Trial," *Inflammatory Bowel Diseases* 26, no. 4 (2020): 593–602.

45. Y. Hagihara, S. Ohfuji, K. Watanabe, et al., "Infliximab and/or Immunomodulators Inhibit Immune Responses to Trivalent Influenza Vaccination in Adults With Inflammatory Bowel Disease," *Journal of Crohn's & Colitis* 8, no. 3 (2014): 223–233.

46. A. K. Singh, A. Jena, M. P. Kumar, V. Sharma, and S. Sebastian, "Risk and Outcomes of Coronavirus Disease in Patients With Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis," *United European Gastroenterology Journal* 9, no. 2 (2021): 159–176.

47. R. C. Ungaro, E. J. Brenner, M. Agrawal, et al., "Impact of Medications on COVID-19 Outcomes in Inflammatory Bowel Disease: Analysis of More Than 6000 Patients From an International Registry," *Gastroenterology* 162, no. 1 (2022): 316–319.e5.

48. E. Zhang, B. Christensen, F. A. Macrae, and R. Leong, "The Effects of the COVID Pandemic on Patients With IBD: Lessons Learned and Future Directions," *Journal of Clinical Medicine* 11, no. 23 (2022): 7002.

49. P. Charilaou, C. Tricarico, R. Battat, E. J. Scherl, R. S. Longman, and D. J. Lukin, "Impact of Inflammatory Bowel Disease Therapies on Durability of Humoral Response to SARS-CoV-2 Vaccination," *Clinical Gastroenterology and Hepatology* 20, no. 6 (2022): e1493–e1499.

50. L. Ni, F. Ye, M. L. Cheng, et al., "Detection of SARS-CoV-2-Specific Humoral and Cellular Immunity in COVID-19 Convalescent Individuals," *Immunity* 52, no. 6 (2020): 971–977.e3.

51. Y. Peng, A. J. Mentzer, G. Liu, et al., "Broad and Strong Memory CD4(+) And CD8(+) T Cells Induced by SARS-CoV-2 in UK Convalescent Individuals Following COVID-19," *Nature Immunology* 21, no. 11 (2020): 1336–1345.

52. Y. Wang, L. Zhang, L. Sang, et al., "Kinetics of Viral Load and Antibody Response in Relation to COVID-19 Severity," *Journal of Clinical Investigation* 130, no. 10 (2020): 5235–5244.

53. B. Kantso, J. Simonsen, S. Hoffmann, P. Valentiner-Branth, A. M. Petersen, and T. Jess, "Inflammatory Bowel Disease Patients Are at Increased Risk of Invasive Pneumococcal Disease: A Nationwide Danish Cohort Study 1977-2013," *American Journal of Gastroenterology* 110, no. 11 (2015): 1582–1587.

54. B. L. Love, C. J. Finney, and J. K. J. Gaidos, "Effectiveness of Conjugate and Polysaccharide Pneumococcal Vaccines for Prevention of Severe Pneumococcal Disease Among Inflammatory Bowel Disease Patients," *Journal of Crohn's & Colitis* 15, no. 8 (2021): 1279–1283.

55. C. Lin, S. Franceschi, and G. M. Clifford, "Human Papillomavirus Types From Infection to Cancer in the Anus, According to Sex and HIV Status: A Systematic Review and Meta-Analysis," *Lancet Infectious Diseases* 18, no. 2 (2018): 198–206.

56. S. Malik, R. Sah, K. Muhammad, and Y. Waheed, "Tracking HPV Infection, Associated Cancer Development, and Recent Treatment Efforts—A Comprehensive Review," *Vaccines (Basel)* 11, no. 1 (2023): 102.

57. J. R. Allegretti, E. L. Barnes, and A. Cameron, "Are Patients With Inflammatory Bowel Disease on Chronic Immunosuppressive Therapy at Increased Risk of Cervical High-Grade Dysplasia/Cancer? A Meta-Analysis," *Inflammatory Bowel Diseases* 21, no. 5 (2015): 1089–1097.

58. A. Wisniewski, J. F. Flejou, L. Siproudhis, L. Abramowitz, M. Svrcek, and L. Beaugerie, "Anal Neoplasia in Inflammatory Bowel Disease: Classification Proposal, Epidemiology, Carcinogenesis, and Risk Management Perspectives," *Journal of Crohn's & Colitis* 11, no. 8 (2017): 1011–1018.

59. D. L. Jacobson, A. Bousvaros, L. Ashworth, et al., "Immunogenicity and Tolerability to Human Papillomavirus-Like Particle Vaccine in Girls and Young Women With Inflammatory Bowel Disease," *Inflammatory Bowel Diseases* 19, no. 7 (2013): 1441–1449.

60. E. Meites, P. G. Szilagyi, H. W. Chesson, E. R. Unger, J. R. Romero, and L. E. Markowitz, "Human Papillomavirus Vaccination for Adults: Updated Recommendations of the Advisory Committee on Immunization Practices," *Morbidity and Mortality Weekly Report* 68, no. 32 (2019): 698–702.

61. S. R. Permar, D. E. Griffin, and N. L. Letvin, "Immune Containment and Consequences of Measles Virus Infection in Healthy and Immunocompromised Individuals," *Clinical and Vaccine Immunology* 13, no. 4 (2006): 437–443.

62. E. I. Benchimol, F. Tse, M. W. Carroll, et al., "Canadian Association of Gastroenterology Clinical Practice Guideline for Immunizations in Patients With Inflammatory Bowel Disease (IBD)-Part 1: Live Vaccines," *Journal of the Canadian Association of Gastroenterology* 4, no. 4 (2021): e59–e71.

63. Collaborators GBDHB, "Global, Regional, and National Burden of Hepatitis B, 1990-2019: A Systematic Analysis for the Global Burden of Disease Study 2019," *Lancet Gastroenterología y Hepatología* 7, no. 9 (2022): 796–829.

64. P. Lopez-Serrano, J. L. Perez-Calle, and M. D. Sanchez-Tembleque, "Hepatitis B and Inflammatory Bowel Disease: Role of Antiviral Prophylaxis," *World Journal of Gastroenterology* 19, no. 9 (2013): 1342–1348.

65. K. C. Hyams, "Risks of Chronicity Following Acute Hepatitis B Virus Infection: A Review," *Clinical Infectious Diseases* 20, no. 4 (1995): 992–1000.

66. C. J. Chiang, Y. W. Yang, S. L. You, M. S. Lai, and C. J. Chen, "Thirty-Year Outcomes of the National Hepatitis B Immunization Program in Taiwan," *Journal of the American Medical Association* 310, no. 9 (2013): 974–976.

67. H. Y. Jiang, S. Y. Wang, M. Deng, et al., "Immune Response to Hepatitis B Vaccination Among People With Inflammatory Bowel Diseases: A Systematic Review and Meta-Analysis," *Vaccine* 35, no. 20 (2017): 2633–2641.

68. A. Mishra, A. S. Puri, S. Sachdeva, and A. Dalal, "Efficacy of Hepatitis B Vaccination in Patients With Ulcerative Colitis: A Prospective Cohort Study," *Intestinal Research* 20, no. 4 (2022): 445–451.

69. B. E. Sands, C. Cuffari, J. Katz, et al., "Guidelines for Immunizations in Patients With Inflammatory Bowel Disease," *Inflammatory Bowel Diseases* 10, no. 5 (2004): 677–692.

70. T. Wyant, T. Leach, S. Sankoh, et al., "Vedolizumab Affects Antibody Responses to Immunisation Selectively in the Gastrointestinal Tract: Randomised Controlled Trial Results," *Gut* 64, no. 1 (2015): 77–83.

71. J. P. Gisbert, J. R. Villagrasa, A. Rodriguez-Nogueiras, and M. Chaparro, "Efficacy of Hepatitis B Vaccination and Revaccination and

Factors Impacting on Response in Patients With Inflammatory Bowel Disease," *American Journal of Gastroenterology* 107, no. 10 (2012): 1460–1466.

72. J. P. Gisbert, J. R. Villagrasa, A. Rodriguez-Nogueiras, and M. Chaparro, "Kinetics of Anti-Hepatitis B Surface Antigen Titers After Hepatitis B Vaccination in Patients With Inflammatory Bowel Disease," *Inflammatory Bowel Diseases* 19, no. 3 (2013): 554–558.

73. C. E. Stevens, H. J. Alter, P. E. Taylor, E. A. Zang, E. J. Harley, and W. Szmuness, "Hepatitis B Vaccine in Patients Receiving Hemodialysis. Immunogenicity and Efficacy," *New England Journal of Medicine* 311, no. 8 (1984): 496–501.

74. J. L. Jones, F. Tse, M. W. Carroll, et al., "Canadian Association of Gastroenterology Clinical Practice Guideline for Immunizations in Patients With Inflammatory Bowel Disease (IBD)-Part 2: Inactivated Vaccines," *Journal of the Canadian Association of Gastroenterology* 4, no. 4 (2021): e72–e91.

75. G. Swingler, D. Fransman, and G. Hussey, "Conjugate Vaccines for Preventing Haemophilus Influenzae Type B Infections," *Cochrane Database of Systematic Reviews* 2 (2007): CD001729.

76. M. P. E. Slack, A. W. Cripps, K. Grimwood, G. A. Mackenzie, and M. Ulanova, "Invasive Haemophilus Influenzae Infections After 3 Decades of Hib Protein Conjugate Vaccine Use," *Clinical Microbiology Reviews* 34, no. 3 (2021): e0002821.

77. M. V. Lenti, C. Mengoli, M. Vernero, et al., "Preventing Infections by Encapsulated Bacteria Through Vaccine Prophylaxis in Inflammatory Bowel Disease," *Frontiers in Immunology* 11 (2020): 485.

78. I. Dotan, L. Werner, S. Vigodman, et al., "Normal Response to Vaccines in Inflammatory Bowel Disease Patients Treated With Thiopurines," *Inflammatory Bowel Diseases* 18, no. 2 (2012): 261–268.

79. C. Burman, J. Findlow, H. S. Marshall, and M. A. P. Safadi, "National and Regional Differences in Meningococcal Vaccine Recommendations for Individuals at an Increased Risk of Meningococcal Disease," *Expert Review of Vaccines* 22, no. 1 (2023): 839–848.

80. B. Kochar, Y. Jiang, and M. D. Long, "Patients With Inflammatory Bowel Diseases are at Higher Risk for Meningitis," *Journal of Clinical Gastroenterology* 55, no. 4 (2021): 350–354.

81. N. M. Kemmer and E. P. Miskovsky, "Hepatitis A," *Infectious Disease Clinics of North America* 14, no. 3 (2000): 605–615.

82. S. H. Park, S. K. Yang, S. K. Park, et al., "Efficacy of Hepatitis A Vaccination and Factors Impacting on Seroconversion in Patients With Inflammatory Bowel Disease," *Inflammatory Bowel Diseases* 20, no. 1 (2014): 69–74.

83. T. C. Sincero, D. B. Levin, C. M. Simoes, and C. R. Barardi, "Detection of Hepatitis A Virus (HAV) in Oysters (Crassostrea Gigas)," *Water Research* 40, no. 5 (2006): 895–902.

84. G. Cao, W. Jing, J. Liu, and M. Liu, "The Global Trends and Regional Differences in Incidence and Mortality of Hepatitis A From 1990 to 2019 and Implications for its Prevention," *Hepatology International* 15, no. 5 (2021): 1068–1082.

85. L. V. Simon, M. F. Hashmi, and K. D. Torp, *Yellow Fever* (Treasure Island, FL: StatPearls, 2024).

86. K. A. Gaythorpe, A. Hamlet, L. Cibrelus, T. Garske, and N. M. Ferguson, "The Effect of Climate Change on Yellow Fever Disease Burden in Africa," *eLife* 9 (2020): 9.

87. S. J. Ryan, C. J. Carlson, E. A. Mordecai, and L. R. Johnson, "Global Expansion and Redistribution of Aedes-Borne Virus Transmission Risk With Climate Change," *PLoS Neglected Tropical Diseases* 13, no. 3 (2019): e0007213.

88. M. K. Soumahoro, D. Fontenille, C. Turbelin, et al., "Imported Chikungunya Virus Infection," *Emerging Infectious Diseases* 16, no. 1 (2010): 162–163.

89. J. Chiodini, "The CDC Yellow Book App 2018," *Travel Medicine and Infectious Disease* 19 (2017): 75–77.

90. S. Buhler, V. K. Jaeger, G. Eperon, et al., "Safety and Immunogenicity of a Primary Yellow Fever Vaccination Under Low-Dose Methotrexate Therapy-a Prospective Multi-Centre Pilot Study1," *Journal of Travel Medicine* 27, no. 6 (2020): taaa126.

91. C. Ekenberg, N. Friis-Moller, T. Ulstrup, and C. Aalykke, "Inadvertent Yellow Fever Vaccination of a Patient With Crohn's Disease Treated With Infliximab and Methotrexate," *BML Case Reports* 2016 (2016): bcr2016215403.

92. E. R. Nash, M. Brand, and S. Chalkias, "Yellow Fever Vaccination of a Primary Vaccinee During Adalimumab Therapy," *Journal of Travel Medicine* 22, no. 4 (2015): 279–281.

93. K. Cheent, J. Nolan, S. Shariq, L. Kiho, A. Pal, and J. Arnold, "Case Report: Fatal Case of Disseminated BCG Infection in an Infant Born to a Mother Taking Infliximab for Crohn's Disease," *Journal of Crohn's & Colitis* 4, no. 5 (2010): 603–605.

94. W. J. Sandborn, G. R. D'Haens, B. E. Sands, et al., "Tofacitinib for the Treatment of Ulcerative Colitis: An Integrated Summary of up to 7.8 Years of Safety Data From the Global Clinical Programme," *Journal of Crohn's & Colitis* 17, no. 3 (2023): 338–351.

95. W. J. Sandborn, N. Lawendy, S. Danese, et al., "Safety and Efficacy of Tofacitinib for Treatment of Ulcerative Colitis: Final Analysis of OCTAVE Open, an Open-Label, Long-Term Extension Study With up to 7.0 Years of Treatment," *Alimentary Pharmacology & Therapeutics* 55, no. 4 (2022): 464–478.

96. W. J. Sandborn, S. Ghosh, J. Panes, et al., "Efficacy of Upadacitinib in a Randomized Trial of Patients With Active Ulcerative Colitis," *Gastroenterology* 158, no. 8 (2020): 2139–2149.e14.

97. B. E. Sands, P. R. Taub, A. Armuzzi, et al., "Tofacitinib Treatment is Associated With Modest and Reversible Increases in Serum Lipids in Patients With Ulcerative Colitis," *Clinical Gastroenterology and Hepatology* 18, no. 1 (2020): 123–132.e3.

98. M. D. Russell, C. Stovin, E. Alveyn, et al., "JAK Inhibitors and the Risk of Malignancy: A Meta-Analysis Across Disease Indications," *Annals of the Rheumatic Diseases* 82, no. 8 (2023): 1059–1067.

99. D. P. Misra, G. Pande, and V. Agarwal, "Cardiovascular Risks Associated With Janus Kinase Inhibitors: Peering Outside the Black Box," *Clinical Rheumatology* 42, no. 2 (2023): 621–632.

100. D. C. Goff, Jr., D. M. Lloyd-Jones, G. Bennett, et al., "ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines," *Journal of the American College of Cardiology* 63, no. 25 Pt B (2013): 2935–2959.

101. Long-Term Safety of 3 Years of Ozanimod in Moderately to Severely Active Ulcerative Colitis: An Interim Analysis of the True North Open-Label Extension," *Gastroenterol Hepatol (N Y)* 19, no. 7 Suppl 3 (2023): 3–4.

102. W. J. Sandborn, S. Vermeire, L. Peyrin-Biroulet, et al., "Etrasimod as Induction and Maintenance Therapy for Ulcerative Colitis (ELEVATE): Two Randomised, Double-Blind, Placebo-Controlled, Phase 3 Studies," *Lancet* 401, no. 10383 (2023): 1159–1171.

103. W. J. Sandborn, B. G. Feagan, G. D'Haens, et al., "Ozanimod as Induction and Maintenance Therapy for Ulcerative Colitis," *New England Journal of Medicine* 385, no. 14 (2021): 1280–1291.

104. B. E. Sands, S. Schreiber, I. Blumenstein, M. V. Chiorean, R. C. Ungaro, and D. T. Rubin, "Clinician's Guide to Using Ozanimod for the Treatment of Ulcerative Colitis," *Journal of Crohn's & Colitis* 17, no. 12 (2023): 2012–2025.

105. Long-Term Cardiac Safety of Ozanimod in a Phase 3 Clinical Program of Ulcerative Colitis and Relapsing Multiple Sclerosis," *Gastroenterol Hepatol (NY)* 18, no. 7 Suppl 2 (2022): 4–5.

106. N. Jain and M. T. Bhatti, "Fingolimod-Associated Macular Edema: Incidence, Detection, and Management," *Neurology* 78, no. 9 (2012): 672–680.

107. K. Harris and S. Russ, "Patient-Completed Safety Checklists as an Empowerment Tool for Patient Involvement in Patient Safety: Concepts, Considerations and Recommendations," *Future Healthcare Journal* 8, no. 3 (2021): e567–e573.