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Effectiveness and safety of SARS-CoV-2 vaccine in Inflammatory Bowel Disease patients: a systematic review, meta-analysis and meta-regression

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Abstract

Introduction: There are concerns regarding the effectiveness and safety of SARS-CoV-2 vaccine in inflammatory Bowel Disease (IBD) patients. This systematic review and meta-analysis comprehensively summarises the available literature regarding the safety and effectiveness of SARS-CoV-2 vaccine in IBD.

Methods: Three independent reviewers performed a comprehensive review of all original articles describing the response of SARS-CoV-2 vaccines in patients with IBD. Primary outcomes were (1) pooled seroconversion rate SARS-CoV-2 vaccination in IBD patients (2) comparison of breakthrough COVID-19 infection rate SARS-CoV-2 vaccination in IBD patients with control cohort and (3) pooled adverse event rate of SARS-CoV-2 vaccine. All outcomes were evaluated for one and two doses of SARS-CoV-2 vaccine. Meta-regression was performed. Probability of publication bias was assessed using funnel plots and with Egger's test.

Results: Twenty-one studies yielded a pooled seroconversion rate of 73.7% and 96.8% in IBD patients after one and two doses of SARS-CoV-2 vaccine respectively. Sub-group analysis revealed non-statistically significant differences between different immunosuppressive regimens for seroconversion. Meta-regression revealed that the vaccine type and study location independently influenced seroconversion rates. There was no statistically significant difference in breakthrough infection in IBD patients as compared to control after vaccination.

Conclusion: In summary, the systematic review and meta-analysis suggest that SARS-CoV-2 vaccine is safe and effective in IBD patients.

As part of AP&T's peer preview process, a technical check of this meta-analysis was performed by Dr. Y. Yuan. The Handling Editor for this article was Dr Cynthia Seow, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Corona Virus Disease 19 (COVID-19), caused by Severe Acute Respiratory Syndrome-COronaVirus-2 (SARS-CoV-2), has been associated with greater than 2 million deaths worldwide as well as significant economic and social upheaval.[1] One of the most significant efforts to reduce SARS-CoV-2 infections and COVID-19 morbidity has been the development of SARS-CoV-2 vaccines. Pharmaceutical companies and academic institutes have rapidly generated several vaccine candidates after sequencing the SARS-CoV-2 virus.[2,3] In December 2020, two messenger RNA (mRNA) vaccines (BNT 162b2 and mRNA-1273) and one adenovirus vector vaccine (JNJ-78436735) were approved for use in the United States and multiple other countries. The safety and efficacy of ChAdOx1 nCoV-19 vaccine, based on replication-incompetent chimpanzee adenovirus vector expressing the spike protein, was first described in 2020.[4] Since then, there are indications that these vaccines could play a substantial role in curbing the SARS-CoV-2 pandemic, and decrease morbidity and mortality among those with breakthrough infections.

Inflammatory Bowel Disease (IBD), chronic inflammatory diseases of the intestinal tract with two major phenotypes, Crohn's disease (CD) and ulcerative colitis (UC), is increasing in incidence and prevalence worldwide.[5] IBD can significantly impact the quality of life of those affected, and also have marked effects on societies and healthcare systems as a whole.[6,7] Immunosuppressive therapies are commonly used in the management of IBD and promote an increased risk of infections.[8] Despite this, current evidence demonstrates that patients with IBD do not have an increased risk of developing SARS-CoV-2 infection.[9–11] However, a significant proportion of the IBD patients have comorbidities (eg pulmonary, cardiovascular and thromboembolic diseases) that can increase the risk of adverse outcomes from COVID-19.[11] Therefore, current professional society guidelines recommend that patients with IBD should receive two doses of SARS-CoV-2 vaccination along with an additional booster dose regardless of immune-modifying therapy.[12–14]

The efficacy of the SARS-CoV-2 vaccines has been demonstrated in several clinical trials; however, patients with IBD or those treated with immunosuppressive medications were excluded from these studies.[15] Therefore, multiple questions regarding the effectiveness of the SARS-CoV-2 vaccination in IBD have emerged. For example, it is unknown if the underlying immune dysregulation characteristic of IBD, or the immunosuppressive therapies used in IBD management, cause an attenuated response to the SARS-CoV-2 vaccination.[16] While several studies have reported the effectiveness of the SARS-CoV-2 vaccine in IBD patients,[17–21] the majority of the studies had a small sample size and are underpowered to accurately predict outcomes. This systematic review and meta-analysis summarises the available evidence regarding the effectiveness of SARS-CoV-2 vaccination in patients with IBD to fill this knowledge gap. A subgroup analysis was also performed to evaluate the impact of immunosuppressive medications on the effectiveness of the two-dose SARS-CoV-2 vaccination schedule.

2 | METHODS

The study has been performed in accordance with the Preferred Reporting Items for systematic reviews and meta-analyses statement (PRISMA statement).[22] The PRISMA Checklist has been added as a supplementary file. The protocol was not registered publicly.

2.1 | Search strategy

The search strategy was designed and conducted by the authors (A.B, H.R.M, V.B.). Three reviewers independently and in duplicate searched PubMed MEDLINE, CINAHL and Cochrane CENTRAL from December 1st, 2019 until December 25th, 2021 evaluating the response of SARS-CoV-2 vaccines in patients with IBD using a combination of keywords and medical subject headings. The detailed search strategy for PubMed is shown in Figure S1.

All titles and abstracts were identified by the authors and screened to accrue potentially eligible studies. A manual search of the references of the included studies was also performed to supplement the electronic search. Then, the same reviewers independently assessed all selected full-text manuscripts for eligibility. Disagreements between two reviewers were resolved through consensus and after input from the third reviewer and the principal investigator.

2.2 | Eligibility criteria

The specific inclusion criteria for the systematic review and meta-analysis were as follows: (1) all randomised control trials (RCTs) or prospective studies or retrospective studies of patients with IBD undergoing SARS-CoV-2 vaccination; (2) studies describing the seroconversion after SARS-CoV-2 vaccination (one and two doses) in IBD patients; (3) all studies with information available to evaluate the incidence of seroconversion and SARS-CoV-2 breakthrough infection after vaccination; (4) full-text articles available in English language and (5) studies with at least 10 IBD patients to avoid bias from small sample size. Only peer reviewed and published data from the studies were utilised for analysis. The data analysed were publicly available and therefore exempt from institutional review board (IRB).

2.3 | Study characteristics and quality assessment

Non-randomised studies were evaluated using the preferred ROBINS-I tool.[23] For each non-randomised study, we assessed the study and ascertained the risk of bias due to confounding, selection of participants, classification of interventions, bias due to missing data measurement of outcomes, bias in reported results and overall risk of bias.

The NIH study quality assessment Tool was used for measuring the risk of bias in case control studies and cohort studies.[24] Appraisal

of individual study quality was based on tailored quality assessment tools developed jointly by methodologists from NHLBI and Research Triangle Institute International. The tools were based on quality assessment methods, concepts and other tools developed by researchers in the Agency for Healthcare Research and Quality (AHRQ) Evidence-Based Practice Centers, the Cochrane Collaboration, the USPSTF, the Scottish Intercollegiate Guidelines Network and the National Health Service Centre for Reviews and Dissemination, as well as consulting epidemiologists and others working in evidence-based medicine, with adaptations by methodologists and NHLBI staff for this project.[24]

Quality assessments were also conducted independently by the reviewers (A.B, V.B, H.R.M, S.A), and discrepancies were resolved by consensus.

2.4 | Outcome measures

All the studies describing the effectiveness and safety of SARS-CoV-2 vaccine in IBD patients were evaluated. Primary outcomes were (1) pooled seroconversion rate after SARS-CoV-2 vaccination in IBD patients after one and two doses of the vaccine (seroconversion was defined as positivity of anti-spike or anti-receptor binding domain antibodies as defined in individual studies) and (2) comparison of breakthrough SARS-CoV-2 infection rate (all infections regardless of symptoms) after SARS-CoV-2 vaccination in patients with IBD and control cohort (defined as non-IBD population and IBD population without vaccination) and (3) pooled adverse event rate after one and two doses. Both seroconversion and breakthrough infection were evaluated at least 2 weeks after the administration of the second dose of SARS-CoV-2 vaccine. Seroconversion and breakthrough infections were considered as markers of the effectiveness of SARS-CoV-2 vaccine. Subgroup analysis was performed to evaluate the seroconversion rate on the basis of immunosuppression.

The pooled adverse event rate after the first and second dose of SARS-CoV-2 vaccine was evaluated. Severe adverse events were defined as acute myocardial infarction, anaphylaxis, facial nerve palsy, coagulopathy, deep vein thrombosis, pulmonary embolism, Guillain-Barré syndrome, transverse myelitis, immune thrombocytopenia, disseminated intravascular coagulation, myocarditis, pericarditis, haemorrhagic stroke, non-haemorrhagic stroke, appendicitis, narcolepsy and encephalomyelitis or severe adverse events as reported by the primary studies. Other adverse events such as myalgia, arthralgia, febrile episode, injection site reaction and headache were evaluated separately for each dose of SARS-CoV-2 vaccine.

2.5 | Data extraction

Four reviewers (A.B., H.R.M., V.B., A.G.) independently reviewed and abstracted data on seroconversion rate, breakthrough infection and adverse event rate for each eligible study. The authors attempted to obtain an adjusted hazard ratio when feasible and adjusted ratios were considered to be equivalent to the unadjusted ratios, and therefore were pooled together. If there were multiple reports stemming from a specific study database, data from the most robust study were extracted with other studies contributing only towards the bibliography. The reviewers sorted the data separately in all stages of study collection, data extraction and quality assessment. All discrepancies found between the three reviewers were resolved with consensus and inputs from other authors.

2.6 | Quantitative data synthesis

All outcomes were analysed by the Comprehensive Meta-Analysis software package (Biostat, Englewood, NJ, USA).[25] The final pooled risk estimates were obtained using random effects models. No transformation was necessary for random effects model. Inverse variance method was utilised for pooled ratios. To explore differences between studies that might be expected to influence the effect size on seroconversion after two doses of SARS-CoV-2 vaccines, we performed random effects (maximum likelihood method) univariate and multivariate meta-regression analyses. The potential sources of variability defined a priori included vaccine type and study location. Covariates were selected for further modelling if they significantly ($p < 0.05$) influenced the outcomes. Subsequently, preselected covariates were included in a manual backward and stepwise multiple meta-regression analysis with $p = 0.05$ as a cutoff point for removal. Sensitivity analysis was performed on the basis of study design (retrospective vs prospective study vs survey-based design). The Cochrane Q and the I^2 statistics were calculated to assess heterogeneity between studies. $p < 0.10$ for chi-square test and $I^2 > 30\%$ were interpreted as significant heterogeneity.[26] The probability of publication bias was assessed using funnel plots and with Egger's test.

3 | RESULTS

The initial library search identified 278 potentially relevant citations from PubMed MEDLINE, CINAHL and Cochrane CENTRAL. Subsequently, 27 duplicates were removed. Two hundred and twenty-six articles were excluded after title and abstract reviews, including articles that did not report the outcomes of seroconversion or breakthrough COVID-19 infection after SARS-CoV-2 vaccination, review articles, opinions, editorials and all articles not in the English language. The remaining 25 manuscripts were scrutinised further and an additional four studies were excluded because they did not meet inclusion criteria. Thus, 21 studies were included in their entirety as shown in Table 1. These included 11 prospective studies, seven retrospective studies and three survey-based studies.[16–21,27–41] The PRISMA Flow chart is shown in Figure 1. The study details are shown in Table 1.

TABLE 1 Characteristics of the studies describing the effectiveness and safety of *SARS-CoV-2* vaccines in inflammatory Bowel Disease (IBD) patients

Authors	Study design	Study location	Study sample	Study inclusion criteria	*SARS-CoV-2* vaccines	SARS-CoV-2 antibodies measured
Kennedy et al,2021	Multicentre, prospective observational cohort	United Kingdom	1293 consecutive patients from 92 National Health Service hospitals between September 2020 and December 2020	Age 5 years and over with diagnosis of IBD and current treatment with infliximab or vedolizumab for 6 weeks or more.	BNT 162b2 and ChAdOx1n vaccines	anti-SARS-CoV-2 anti-spike (S) protein receptor-binding protein antibodies using Roche Elecsys Anti-SARS-CoV-2 spike (S) immunoassay13 and the nucleocapsid (N) immunoassay.
Ben Tov et al,2021	Multicentre, retrospective cohort	Israel	Data from Maccabi Healthcare services between December 2020 and March 2021 including 12,231 IBD patients	Age ≥ 16 years with diagnosis of IBD based on the registry	BNT 162b2 Vaccine	Anti-receptor binding domain IgG antibodies specific to SARS-CoV-2 using the LabCorp Cov2Quant IgG assay
Hadi et al,2021	Multicentre, retrospective cohort	United States	Data from TriNetX research network with 5562 IBD patients who received SARS-CoV-2 vaccination until April 30,2021	Age ≥ 16 years with diagnosis of IBD based on ICD-9-CM and ICD-10-CM Codes with an IBD-specific medication	BNT 162b2 Vaccine and mRNA-1273 vaccine	n/a
Kappelman et al,2021	Prospective, observational cohort	United States	Survey-based study of 317 IBD patients recruited via social media, education and outreach efforts of Crohn's and Colitis foundation	Age ≥ 16 years with diagnosis of IBD diagnosis with receipt of 1 or more doses of SARS-CoV-2 vaccines and followed up to 18 months	BNT 162b2 Vaccine and mRNA-1273 vaccine	Anti-receptor binding domain IgG antibodies specific to SARS-CoV-2 using the LabCorp Cov2Quant IgG assay
Khan et al,2021	Multicentre, retrospective cohort	United States	14,697 IBD patients in 170 Veterans Health Administrations centres between December 2020 and April 2021	Age ≥ 18 years with IBD and no prior *CoV-19* infection and taking IBD medication	BNT 162b2 Vaccine and mRNA-1273 vaccine	n/a
Pozdnyakova et al,2021	Prospective registry	United States	353 IBD patients participating in prospective nationwide vaccine registry	All IBD patients in the registry without prior *CoV-19* infection and who had completed a full vaccine regimen	BNT 162b2 Vaccine; mRNA-1273 vaccine; Ad26.CoV2.S vaccine	Antibodies to the viral spike protein receptor binding domain using the SARS-CoV-2 IgG-II assay (Abbott Labs, Abbott Park, IL)

(Continues)

TABLE 1 (Continued)

Authors	Study design	Study location	Study sample	Study inclusion criteria	*SARS-CoV-2* vaccines	SARS-CoV-2 antibodies measured
Wong et al,2021	Single centre, serosurvey	United States	48 IBD patients at Mount Sinai, NY, US between December 2020 and February 2021	All IBD patients who had self-reported at least 1 vaccination	BNT 162b2 Vaccine; mRNA-1273 vaccine	Siemens Healthineers SARS-CoV-2 Total (COV2T) & SARS-CoV-2 IgG (sCOVG) assays testing for IgG to receptor binding domain of the SARSCoV-2 S protein and Roche assay for antibodies to nucleocapsid protein
Classen et al, 2021	Single-centre retrospective cohort	Germany	65 patients included in the COVID-19 Registry (COKA)	All adult IBD patients who had received the SARS-CoV-2 vaccine in the COKA registry	BNT 162b2 Vaccine; mRNA-1273 vaccine; Ad26. CoV2.S vaccine	SARS-CoV-2 antibodies (IgG) against the receptor-binding domain (RBD) of the spike protein (S) using immunoassays Elecsys® Anti-SARS-CoV-2S (Roche Diagnostics, Germany)
Shehab et al, 2021	Multicentre, prospective cohort	Kuwait	58 IBD patients at two tertiary care centres recruited between August and September 2021	All patients ≥18 years of age with diagnosis of IBD on IBD-related medications	BNT 162b2 vaccine	SARS-CoV-2-specific IgG and IgA antibodies by enzyme-linked immunosorbent assay (ELISA) kit (SERION ELISA agile SARSCoV-2 IgG and IgA SERION Diagnostics, Wüzburg, Germany
Caldera et al, 2021	Prospective cohort	United States	122 IBD patients reporting adverse events after SARS-CoV-2 vaccination	IBD patients who had received SARS-CoV-2 vaccination between June and July 2021	BNT 162b2Vaccine; mRNA-1273 vaccine	Nucleocapsid and spike protein S1 receptor-binding domain–specific IgG antibodies using Labcorp Assay
Charilaou et al, 2021	Single centre, prospective cohort	United States	195 IBD patients who underwent antibody level testing between April and October 2021	IBD who received both doses of SARS-CoV-2	BNT 162b2 Vaccine; mRNA-1273; JNJ-78436735 vaccine	Anti-Spike Total Antibody titre test

TABLE 1 (Continued)

Authors	Study design	Study location	Study sample	Study inclusion criteria	*SARS-CoV-2* vaccines	SARS-CoV-2 antibodies measured
Melmed et al, 2021	Multicentre, prospective cohort	United States	582 patients referred to a single-tertiary care centre for antibody titres from 18 gastroenterology practices and a social media campaign (January to July 2021)	Patients with IBD diagnosis who had undergone SARS-CoV-2 vaccination	BNT 162b2 Vaccine; mRNA-1273; JNJ-78436735 vaccine	Antibodies to the receptor-binding domain of the spike protein S1 subunit (IgG(S)) and to the viral nucleocapsid protein (IgG(N)) using the SARS-CoV-2 IgG-II and SARS-CoV-2 IgG assays, respectively (Abbott Labs).
Cerna et al, 2021	Single centre, prospective cohort	Czech Republic	602 IBD patients who underwent SARS-CoV-2 vaccination between January and June 2021	IBD patients at the single centre. Patients on steroids were excluded.	BNT 162b2 Vaccine; CX-024414 (Moderna); ChAdOx1 n	IgG antibodies to the receptor-binding domain of the S1 subunit of the spike protein of SARS-CoV-2 using SARS-CoV-2 IgG II Quant antibody test (Abbott, USA)
Weaver et al, 2021	Multicentre, prospective observational cohort	United States	Partnership to Report Effectiveness of Vaccination in populations Excluded from iNitial Trials of COVID (PREVENT-COVID): a prospective, observational, cohort study of patients with 3316 IBD in the United States who have received any SARS-CoV-2 vaccine	IBD patients who completed baseline and 30-day post-enrollment surveys prior to July 8, 2021	BNT 162b2 Vaccine; mRNA-1273 vaccine; Ad26.CoV2.S vaccine	n/a
Reuken et al, 2021	Single centre, prospective cohort	Germany	Single centre study including 28 IBD patients	IBD patients treated at one centre and followed after SARS-CoV-2 vaccination	BNT 162b2 Vaccine; mRNA-1273 vaccine; Ad26.CoV2.S vaccine	IgG antibodies against SARS-CoV-2-specific trimeric spike glycoprotein using Liaison SARSCoV-2 Trimerics IgG CLIA on the LiaisonXL (DiaSorin, Saluggia, Italy)

(Continues)

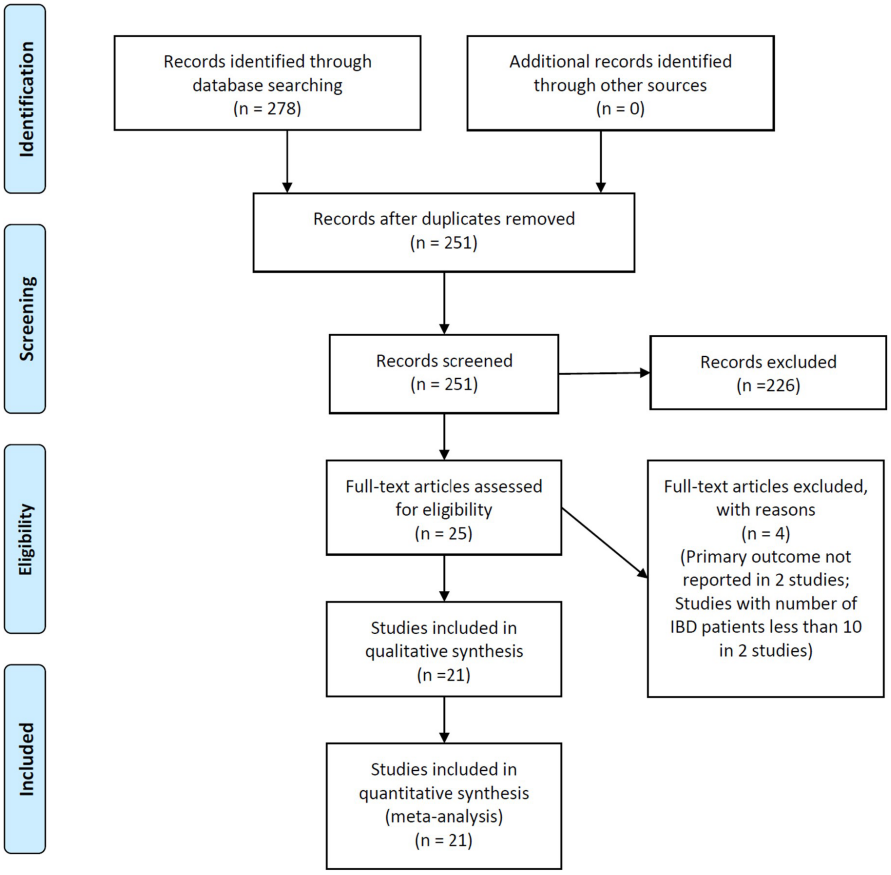
TABLE 1 (Continued)

Authors	Study design	Study location	Study sample	Study inclusion criteria	*SARS-CoV-2* vaccines	SARS-CoV-2 antibodies measured
Spencer et al,2021	Single centre, retrospective cohort	United States	340 paediatric IBD patients at Mount Sinai, NY, US	All patients younger than 21 years of age who underwent *CoV-19* IgG antibody assay	BNT 162b2 Vaccine; mRNA-1273; JNJ-78436735 vaccine	COVID-SeroKlir (Kantaro Biosciences, LLC, New York, NY) semiquantitative SARS-CoV-2 IgG antibody assay, an enzyme-linked IgG antibody to SARS-CoV-2 spike protein
Cannatelli et al, 2021	Single centre, prospective cohort	Italy	488 IBD patients who underwent SARS-CoV-2 vaccination at a single centre	IBD patients who underwent SARS-CoV-2 vaccination between June and July 2021	BNT 162b2 Vaccine; mRNA-1273 vaccine; Ad26. CoV2.S vaccine	n/a
Garrido et al, 2021	Single centre, prospective cohort	Portugal	Survey to assess adverse events after SARS-CoV-2 vaccination among 301 IBD patients	Adult IBD patients undergoing biological therapy	BNT 162b2 Vaccine; mRNA-1273 vaccine; Ad26. CoV2.S vaccine	n/a
Lev-Tzion et al, 2021	Multiple national Insurance carriers, retrospective cohort	Israel	12,109 IBD patients from 4 national Health Maintenance Organisations between December 2020 and June 2021	All IBD patients undergoing SARS-CoV-2 vaccination without prior infection	BNT 162b2 Vaccine	n/a
Edelman-Klapper et al,2021	Prospective multicentre Israeli study	Israel	185 IBD patients evaluated in a prospective, observational multicentre study	Patients obtained through referral; All IBD patients more than 18 years of age	BNT 162b2 vaccine	Immunoglobulin [Ig] G antibodies to SARS-CoV-2 spike [S] antigen and neutralising and inhibitory antibodies using the Abbott architect i2000sr platform and EUROIMMUN assay, Lubeck, Germany
Levine et al, 2021	Single-centre retrospective	United States	19 patients with IBD at a single centre	IBD patients undergoing SARS-CoV-2 vaccination	BNT162b2 vaccine; mRNA-1273 vaccine	ELISA assay for both the COVID-19 nucleocapsid and spike domain antibodies (Roche)

3.1 | Seroconversion rate after SARS-CoV-2 vaccination

A summary of the studies reporting on seroconversion after SARS-CoV-2 vaccination is shown in Table 2. The pooled seroconversion rate in IBD patients after one dose of SARS-CoV-2 vaccine was 73.7% (95% CI 38.1–92.7). As shown in Figure 2A, there was significant heterogeneity in the analysis ($I^2 = 96.4\%$). Further analysis was performed to evaluate the seroconversion rate of individual vaccines in IBD patients. The pooled seroconversion rater after a single-dose

FIGURE 1 PRISMA flow chart



ofBNT162b2 vaccine was 76.3% (95% CI 19.5–97.7) in IBD patients. One study reported seroconversion rate of 42.1% (95% CI 37.7–46.6) after a single dose of ChAdOx1 vaccine dose in IBD patients.

The pooled seroconversion rate in IBD patients after two doses of SARS-CoV-2 vaccine was 96.8% (95% CI 94–98.3). As shown in Figure 2B, there was significant heterogeneity in the analysis (I^2 = 78%). There was a statistically significant difference between seroconversion rate after one dose and two doses of all SARS-CoV-2 vaccines in IBD patients (p = 0.005). A subgroup analysis was performed to evaluate the seroconversion rate of two doses of individual SARS-CoV-2 vaccines in IBD patients. One study reported the seroconversion rate of 90% (95% CI 53.3–98.6) after two doses of Ad26.CoV2.S vaccine in IBD patients. The pooled seroconversion rate after two doses of BNT162b2 vaccine was 98.7% (95% CI 96.4–99.6). The pooled seroconversion rate after two doses of mRNA-1273 vaccine was 96% (95% CI 73.4–99.5). There was no statistical difference between seroconversion rate after two doses of mRNA-1273 and BNT162b2 vaccines (p = 0.34). The seroconversion rates stratified by vaccine type and dose are shown in Figure 2C.

The meta-regression revealed that the vaccine type and location of the study explained 90% of the between-study heterogeneity in the seroconversion rate after two doses of SARS-CoV-2 vaccination. Twelve studies were included in the meta-regression model. BNT162b2 vaccine was the reference group for the vaccine type. The study location was coded with four codes in meta-regression analysis. The scatter plots, coefficients and the resulting equation are shown in Figures S2 and S3.

Subgroup analysis was performed to evaluate the impact of treatment with immunosuppressive medications on seroconversion rate after SARS-CoV-2 vaccination (Figure 3A). Patients on no medications for IBD, or 5-aminosalicylic acid (5-ASA)-based therapy, had a pooled seroconversion rate of 95.6% (95% CI 91.3–97.8). The pooled seroconversion rate in the patients treated with anti-Tumour Necrosis Factor alpha (anti-TNF α) therapy was 95.4% (95% CI 88.9–98.1) compared to 97.2% (95% CI 93.3–98.9) with anti-integrin therapy. There was no statistically significant difference in seroconversion rates of patients on anti-TNF **α** therapy and anti-integrin therapy (p = 0.43). The pooled seroconversion rate was 96.2% (95% CI 89.6–98.7) with anti-interleukin 12/23 therapy (compared to anti-TNF α therapy, p = 0.77; compared to anti-integrin therapy, p = 0.66). The pooled seroconversion rate was 92.2% (95% CI 68.9–98.4) with Janus Kinase Inhibitor therapy (compared to anti-TNF α, p = 0.57; compared to anti-integrin therapy, p = 0.26). Immunomodulator therapy alone (azathioprine, mercaptopurine, or methotrexate) had a pooled seroconversion rate of 96.5% (95% CI 88.7–99).). The pooled seroconversion rate was 95.6% (95% CI 80.8–99.1) with corticosteroid therapy in a relatively small sample size from the two included studies. There was a moderate level of heterogeneity (I^2 = 43.1%).

Additional subgroup analysis compared the seroconversion rates in patients on immunosuppression combination therapy vs those on immunosuppression monotherapy, as shown in Figure 3B.

TABLE 2 Studies describing seroconversion after SARS-CoV-2 vaccination in inflammatory Bowel Disease patients

Authors	Vaccine type	Seroconversion after 1st dose of SARS-CoV-2 vaccine	Seroconversion after 2nd dose of SARS-CoV-2 vaccine	Seroconversion based on vaccine type
Kennedy et al,2021	BNT 162b2: 45.6%; ChAdOx1: 54.4%	**Overall: 41% (353/867)** Anti TNFα combination: 23.3% (125/537) Anti-Integrin Therapy: 69% (228/330)	**Overall:** 85.18% (23/27) Anti-TNFα therapy – 85% (17/20) Anti-Integrin therapy—85.7% (6/7)	**One dose** BNT 162b2: 189/406 ChAdOx1: 194/461 **Two doses:** not available
Kappelman et al,2021	BNT 162b2: 55%; mRNA-1273: 45%	**2 dose vaccine series reported**	**Overall:** 95% (300/317) Anti-TNFα monotherapy: 94% (101/108); anti-TNFα combination therapy: 88% (21/24) Anti-Integrin therapy: 100% (46/46) Anti IL12/23 therapy: 97% (38/39) Immunomodulator: 95% (19/20) 5 ASA/No medications: 94% (61/65)	**Not available**
Pozdnyakova et al,2021	BNT 162b2: 42%; mRNA-1273 vaccine: 55%; Ad26.CoV2.S:3%	**The analysis involved only two doses of SARS-CoV-2 vaccination**	**Overall:** 96.7% (272/281)	**Two doses seroconversion** mRNA-1273 – 100% (121/121) BNT162b2–99% (142/143) Ad26.CoV2.S-90% (9/10)
Wong et al,2021	BNT 162b2:47.9%; mRNA-1273 *Cov-19* vaccine:	**Overall:** 68.75% (11/16)	**Overall:** 100% (26/26) Anti-TNFα therapy: 100% (8/8) Anti-Integrin therapy: 100% (12/12) Anti-IL12/23 therapy: 100% (2/2) No medications: 100% (4/4)	**Not available**
Spencer et al,2021	BNT 162b2: 70%; mRNA-1273:25%; JNJ-78436735: 5	**Overall: 100% (2/2)**	**Overall:** 100% (18/18)	**One dose** JNJ-78436735 – 100% (1/1)BNT162b2–100% (1/1) **Two Doses** BNT162b2–100% (13/13) mRNA-1273 – 100% (5/5)
Classen et al, 2021	BNT 162b2 *CoV-19* Vaccine; mRNA-1273 Cov-19; ChAdOx1 n*CoV-19* vaccine	Data not available for calculations	**Overall:** 100% (72/72) Anti-TNFα monotherapy: 100% (1/1); anti-TNFα combination therapy: 100% (26/26) Anti-integrin therapy: 100% (19/19) Anti-IL12/23 therapy: 100% (14/14) 5-ASA therapy: 100% (5/5)	**Mixed vaccination**
Shehab et al, 2021	BNT162b2: 100%	**2 dose vaccine series reported**	**Overall**: anti-TNFα combination therapy: 81% (47/58)	**BNT162b2: 81% (47/58)**
Caldera et al, 2021	BNT 162b2:48%; mRNA-1273:51%	**2 dose vaccine series reported**	**Overall:** 97% (118/122)	**Not available**

TABLE 2 (Continued)

Authors	Vaccine type	Seroconversion after 1st dose of SARS-CoV-2 vaccine	Seroconversion after 2nd dose of SARS-CoV-2 vaccine	Seroconversion based on vaccine type
Melmed et al, 2021	BNT 162b2: 58.8%; mRNA-1273:41.2%	**2 dose vaccine series reported**	**Overall:** 98% (545/552) Anti-TNFα monotherapy: 99% (175/177); Anti-TNFα combination therapy: 100% (49/49) Anti-integrin therapy: 99% (75/76) JAK inhibitor therapy: 100% (7/7) Immunomodulator therapy: 100% (12/12) Corticosteroids: 96% (26/27) No therapies: 98% (85/87)	**Not available**
Charilou et al, 2021	BNT 162b2: 60%; mRNA-1273: 35.1%; JNJ-78436735: 4.6%	**2 dose vaccine series reported**	**Overall:** 97.7% (172/176)	**Not available**
Cerna et al, 2021	BNT 162b2:16.8%; CX-024414 (Moderna):35.2%; ChAdOx1 n*CoV-19*: 48%	**2 dose series reported**	**Overall**: 100% (602/602) Anti-TNFα monotherapy: 100% (162/162); Anti-TNFα combination therapy: 100% (130/130) Anti-Integrin monotherapy: 100% (91/91); Anti-Integrin combination therapy: 100% (15/15) Anti-Integrin with corticosteroids: 100% (6/6) Anti IL12/23 monotherapy: 100% (76/76); anti IL12/23 combination therapy: 100% (11/11); Anti IL12/23 and steroids: 100% (4/4) JAK Inhibitor therapy: 100% (7/7) Immunomodulator therapy: 100% (51/51) 5-ASA therapy or no meds: 100% (49/49)	**Not available**
Reuken et al, 2021	BNT 162b2; mRNA-1273 (35.8% mRNA vaccines); Ad26.CoV2.S (64.2%)	**Overall: 71.4% (20/28)**	**Overall**: 96.4% (27/28)	**Not available**
Edelman-Klapper et al, 2021	BNT162b2–100% (185/185)	**Overall: 93% (171/185)** Anti TNFα monotherapy: (54/58) Anti TNF combination therapy: (7/9) Anti-Integrin therapy: (25/26) Anti-IL 12/23: (4/5) JAK Inhibitors: (1/3) 5 ASA or no meds: (71/75)	**Overall: 100% (185/185)** Anti-TNFα monotherapy: 100% (58/58) Anti-TNFα combination therapy: 100% (9/9) Anti-Integrin therapy: 100% (26/26) Anti IL12/23 therapy: 100% (5/5) Immunomodulator: 100% (8/8) Corticosteroids alone: 100% (7/7) JAK inhibitors: 100% (3/3) 5-ASA or no meds: 100% (75/75)	**All patients with BNT162b2 vaccines** **Single dose 93% (171/185)** **Two doses 100% (185/185)**
Levine et al, 2021	BNT162b2- (11/19) mRNA-1273-(8/19)	**2 dose series reported**	**Overall – 95% (18/19)** Anti TNF α therapy – 90% (9/10) Anti-Integrin therapy – 100% (2/2) Anti IL12/23 therapy – 100% (5/5) JAK Inhibitor –100% (1/1) Immunomodulator –100% (1/1)	One dose – no data **Two doses** BNT162b2–100% (11/11) mRNA-1273 – (7/8)

Abbreviations: 5-ASA, 5-aminosalicylic acid; IL, Interleukin; JAK, Janus Kinase; TNFα, Tumour Necrosis Factor alpha.

Anti-TNFα monotherapy was noticed to have a similar seroconversion rate as compared to anti-TNFα combination therapy (98.3% vs 95%, p = 0.25). There was no significant heterogeneity (I^2 = 28%).

3.2 | Breakthrough infection after SARS-CoV-2 vaccination

Four studies reported breakthrough infection after SARS-CoV-2 vaccination in IBD patients.[27–29,39] This yielded a total of 29 breakthrough infections in 6765 IBD patients after one dose. Thirty-three breakthrough infections were reported in 12,674 IBD patients. The meta-analysis revealed that there was no statistically significant difference in breakthrough infection in IBD patients as compared to control cohort after one dose (OR 0.99, 95% CI 0.71–1.38; $p = 0.96$) or two doses (OR 0.72, 95% CI 0.29–1.77; $p = 0.48$) (see Figure 4). There was significant heterogeneity in the analysis (I^2 = 71%). A summary of the studies is shown in Table 3.

3.3 | Adverse events after SARS-CoV-2 vaccination

Seven studies reported adverse events after SARS-CoV-2 vaccination in IBD patients, as shown in Table 4.[18,19,21,28,37,38] The pooled severe adverse advent rate after one dose of SARS-CoV-2 vaccination was 2.2% (95% CI 1.4–3.6). The pooled severe adverse event rate after the second dose of COVID-19 vaccine was 0.09% (95% CI 0.01–0.091)(see Figure 5A). There was significant heterogeneity (I^2 = 95.52%). There was no significant difference in pooled severe adverse rates between one and two doses (p = 0.47).

Mild adverse events after one and second vaccine doses were analysed individually. The pooled rate of injection site reactions after one and two SARS-CoV-2 vaccine doses was 52.6% (95% CI 38.2–66.6) and 50.2% (95% CI 35.7–64.6) respectively with high heterogeneity (I^2 = 96.14%) (see Figure 5B). Pooled headache rate after one and two SARS-CoV-2 vaccine doses were 15.6% (95% CI 7.1–30.9) and 25.2% (95% CI 11–47.8), respectively, with high heterogeneity (I^2 = 98.45%). There was no significant difference in pooled headache rates between one and two doses ($p = 0.37$) (see Figure 5C). Pooled fatigue rate after one and two SARS-CoV-2 vaccine doses were 24.5% (95% CI 10.8–46.6) and 36.1% (95% CI 13.2–67.7), respectively, with high heterogeneity (I^2 = 98.81%). There was no significant difference in the pooled fatigue rates between one and two doses ($p = 0.50$) (see Figure 5D). Pooled febrile episode rate after one and two SARS-CoV-2 vaccine doses were 5.5% (95% CI 3.6–8.4) and 14.5% (95% CI 9.2–22), respectively, with high heterogeneity (I^2 = 97.97%). There was a significant difference in the pooled febrile rate rates between one and two doses ($p < 0.0001$) (see Figure 5E). Pooled arthralgia rate after one and two SARS-CoV-2 vaccine doses were 9.9% (95% CI 6.5–14.7) and 9.1% (95% CI 3.3–22.8) with high heterogeneity (I^2 = 97.12%) (see Figure 5F). There was no significant difference in pooled arthralgia rates between one and two doses ($p = 0.87$). Pooled myalgia rate after one and two SARS-CoV-2 vaccine doses were 15.9% (95% CI 9.9–24.4) and 20.5% (95% CI 8.8–40.8) with high heterogeneity (I^2 = 98.3%). There was no significant difference in pooled myalgia rates between one and two doses ($p = 0.34$) (see Figure 5G).

3.4 | Quality of the studies

The quality of the non-randomised studies was assessed using ROBINS-I tool and NIH Quality assessment. Selection bias in survey-based studies included in the analysis. The homogeneous IBD patient cohort in the study by Khan et al (Veterans Affairs Cohort) may have introduced a baseline confounding effect.[29] These results are shown in Figures S4–S5 and Table S1.

3.5 | Sensitivity analysis

Sensitivity analysis was performed on the basis of study design (retrospective vs prospective study vs survey-based design) for the seroconversion rate after one and two doses of SARS-CoV-2 vaccination. The pooled seroconversion rate in prospective studies after one and two doses of SARS-CoV-2 vaccine was 73.2% (95% CI 27–95.3) and 96.6% (93.1–98.4) respectively. The pooled seroconversion rate in retrospective studies after one and two doses of SARS-CoV-2 vaccine was 83.3% (95% CI 19.4–99) and 97.4% (95% CI 90–99.3) respectively. The pooled seroconversion rate in survey-based design after one and two doses was 68.8% (95% CI 43.3–86.4) and 98.1% (95% CI 76.4–99.9). There was high heterogeneity in the analysis (I^2 = 97%). These are shown in Figure S6.

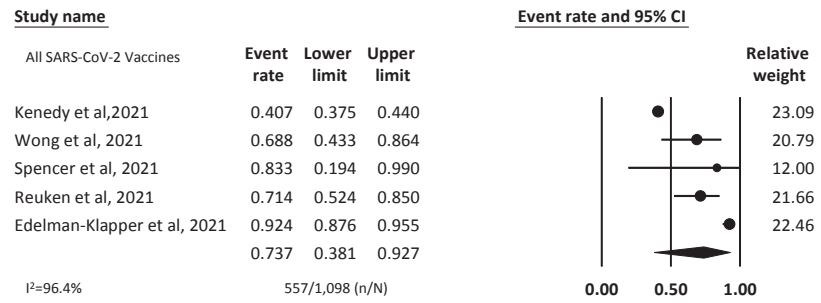
3.6 | Publication bias

Visual inspection of the standard error plots for the severity analysis also suggests symmetry without an underrepresentation of studies of any precision. However, in Egger's regression test the null hypothesis of no small study effects was rejected at p < 0.05 (estimated bias coefficient = 1.56 ± 1.03SE). The funnel plot is shown in Figure S7.

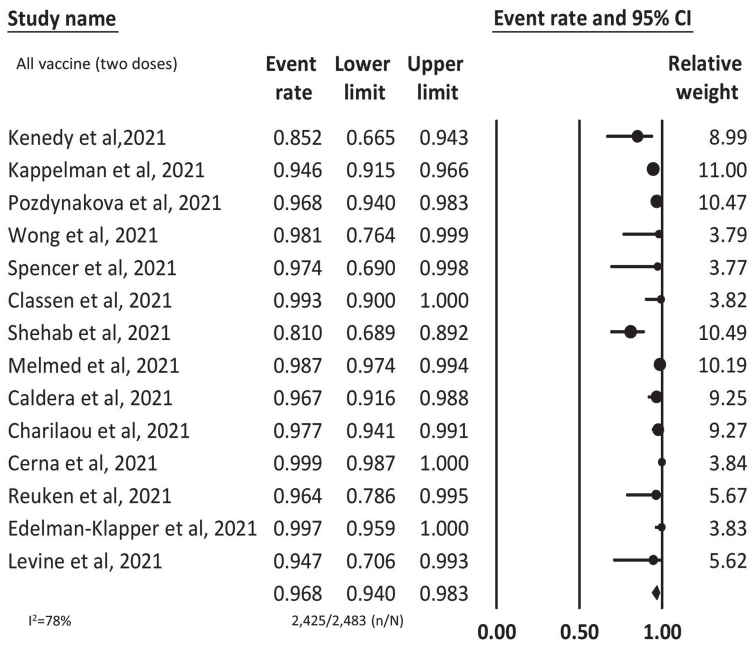
4 | DISCUSSION

The COVID-19 pandemic is an ongoing, global public health challenge with millions of people reported infected.[1] Vaccine development and strategies for widespread vaccine administration are considered important steps in curbing the pandemic. The IBD patient population is theoretically at a greater risk for SARS-CoV-2 infection and complications due to a combination of dysregulated mucosal immunity and the frequent need for immunosuppressive medical therapies. As a result, professional societies have recommended SARS-CoV-2 vaccination in the IBD population.[12,14] There have been numerous studies reporting the effectiveness and safety of the SARS-CoV-2 vaccine in

(A) Pooled overall seroconversion rate after one dose SARS-CoV-2 vaccination in IBD patients



(B) Pooled seroconversion rate after second dose of SARS-CoV-2 vaccine in IBD patients



(C) Seroconversion rate stratified by SARS-CoV-2 vaccine type in IBD patients

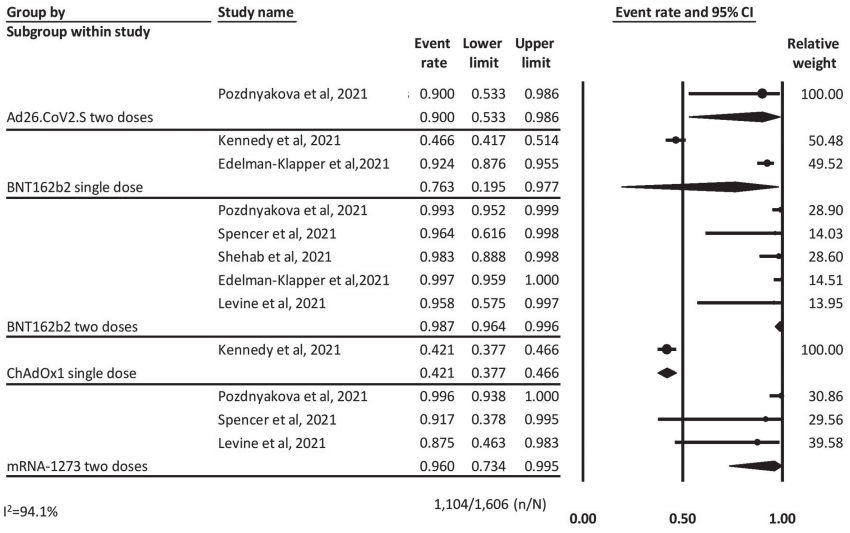
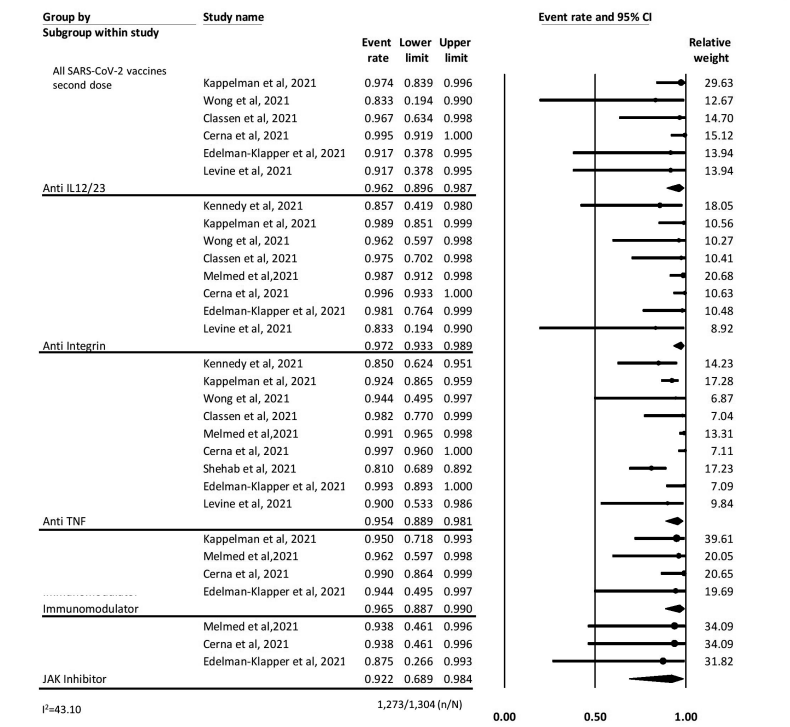


FIGURE 2 (A) Seroconversion rate after one dose of SARS-CoV-2 vaccine in IBD. (B) Seroconversion rate after two doses of SARS-CoV-2 vaccine in IBD. (C) Seroconversion rate stratified by SARS-CoV-2 vaccine type in IBD



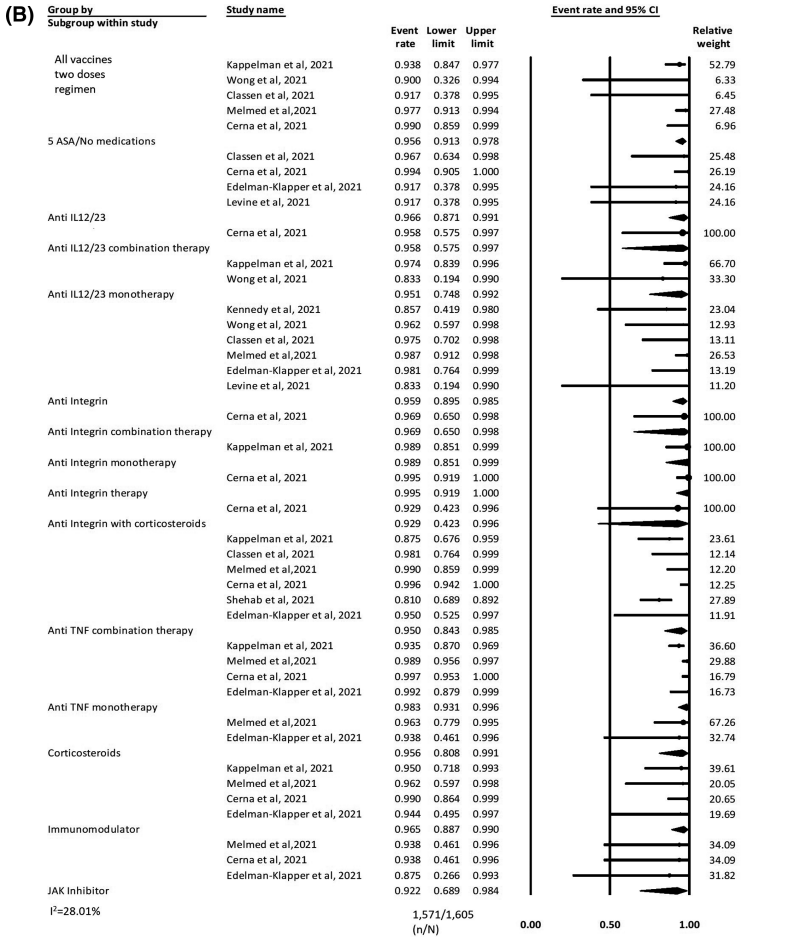


FIGURE 3 (A) Seroconversion rate stratified by immunosuppression after SARS-CoV-2 vaccination in IBD. (B) Pooled seroconversion rate after two doses of SARS-CoV-2 vaccination in IBD stratified by monotherapy and combination therapy

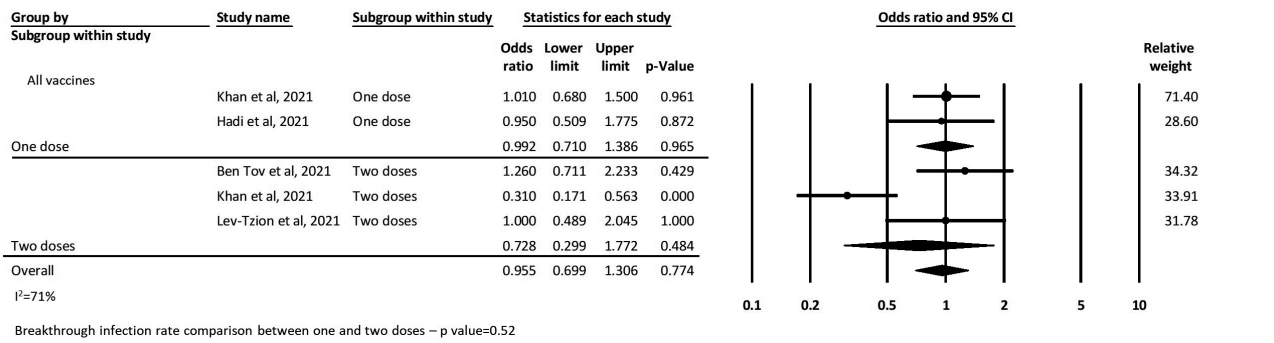


FIGURE 4 Breakthrough CoV-19 infection rate stratified by number of SARS-CoV-2 vaccine doses in IBD

TABLE 3 Outcomes of studies describing breakthrough CoV-19 infection in vaccinated inflammatory Bowel Disease (IBD) patients

Authors	Vaccine used	Breakthrough infections	Comparison to control cohort	Details of the control cohort
Ben Tov et al,2021	BNT 162b2:100%	0.14% (17/12,213) at 2 weeks Immunosuppressive therapy aHR: 0.67 (0.2–2.03); p = 0.45	RR for breakthrough infection >7 days after two doses (1 patient in a sample size of 17) 1.21 (95% CI 0.74–1.97) RR for breakthrough infection >14 days (7 patients out of 16 patients) 1.26 (95% CI 0.71–2.23)	Individual matching was performed based on sex, birth year, coexisting comorbidities, and month of the first vaccination dose
Hadi et al,2021	BNT 162b2: 55.8%; mRNA-1273:13.7%; not reported: 30.5%	0.36% (19/5562) 4 weeks after 1st dose	RR for SARS-CoV-2 infection at 4 weeks 0.95 (95% CI 0.51–1.78)	General population without IBD
Khan et al,2021	BNT 162b2 *CoV-19* (45.2%) Vaccine and mRNA-1273 *Cov-19* vaccine (54.8%)	14 *CoV-19* Infection in partially vaccinated IBD patients 4 weeks after 1st dose	aHR for SARS-CoV-2 infection (partial vaccine): 1.01 (0.68–1.50) (14 out of 7112)aHR for SARS-CoV-2 infection (full vaccine): 0.31 (0.17–0.56) (7 out of 6253) aHR for severe SARS-CoV-2 infection (partial vaccine): 0.91 (0.39–2.14) aHR for severe SARS-CoV-2 infection (full vaccine): 0.51 (0.19–1.36)	IBD patients without vaccination
Lev-Tzion et al, 2021	BNT 162b2:100%		OR 1 (95% CI 0.49–2.05)	Non-IBD controls matched with age, sex

Notes: Adjustment for aHR was performed for—immunosuppressive mediations, steroids, vaccine manufacturer.
Data from >7 days was selected for analysis.
Abbreviations: aHR, adjusted Hazard Ratio; OR, odds ratio; RR, relative risk.

the IBD population,[16,19,21,28,32] however, majority of the studies were underpowered. This is the first systematic review and meta-analysis of the current data regarding the effectiveness of SARS-CoV-2 vaccines in patients with IBD, and indicates that the SARS-CoV-2 vaccination is safe and effective in eliciting a serological response in that patient population.

The meta-analysis revealed a pooled seroconversion rate of 73% after one dose and increased significantly to 96% after two doses of SARS-CoV-2 vaccination in the IBD population. The seroconversion rates are reported in immune-mediated diseases (69.3%, 95% CI 52.4–82.3 and 83.1%, 95% CI 74.9–89 after one and two doses of SARS-CoV-2 vaccine respectively) and general population (99%)[42–44] These findings support that two doses regimen in the IBD patients as recommended by the professional societies. These findings indicate that the antibody response to the SARS-CoV-2 vaccines is not attenuated in IBD patients despite a high prevalence of immunosuppressive

TABLE 4 Studies describing adverse events after SARS-CoV-2 vaccine in IBD patients

Authors	Frequency of adverse events
Wong et al,2021	80.5% (29/36) after any dose of SARS-CoV-2 vaccine (not specified whether 1st or 2nd dose) (0/36 severe reactions; 19/36 local injection site reaction; 12/36 myalgia.; 14/36 fatigue; 1/36 arthralgia)
Classen et al, 2021	58.3% (42 symptoms total) after the 1st dose of SARS-CoV-2 vaccine (15 with muscle pain, 3 with fever, 7 with joint pain, 31 with injection site pain, 4 with redness, 22 fatigue, febrile episode 3/42) 55.4% (31 symptoms total) after the 2nd dose of SARS-CoV-2 vaccine (0/31 severe reactions; 14/31 local injection site reaction; 9/31 myalgia; 20/31 fatigue; 6/31 arthralgia, 5/31)
Hadi et al, 2021	2% (113/5561) severe adverse reactions after a dose of SARS-CoV-2 vaccine (defined as acute myocardial infarction, anaphylaxis, facial nerve palsy, coagulopathy, deep vein thrombosis, pulmonary embolism, Guillain-Barré syndrome, transverse myelitis, immune thrombocytopenia, disseminated intravascular coagulation, myocarditis, pericarditis, haemorrhagic stroke, non-haemorrhagic stroke, appendicitis, narcolepsy, and encephalomyelitis) 0.95% (53) had hospitalisations after a dose of SARS-CoV-2 vaccination
Weaver et al, 2021	3% (86) reported severe systemic reaction with 9/3316 requiring hospitalisation after 1st dose of SARS-CoV-2 vaccine (2183/3316 reported injection site pain, 385/3316 reported redness, 673/3316 reported myalgias, arthralgia 412/3316, headache 1054/3316, febrile episode 204/3316) 11% (352/3080) severe adverse reactions after 2nd dose of SARS-CoV-2 vaccine with 5/3080 hospitalisations (1995/3080 local injection site pain; 1318 /3080 myalgia; 822/3080 arthralgia; 2085/3080 fatigue; 1570/3080 headache, febrile episode 776/3080)
Cannatelli et al, 2021	0% with severe adverse reaction after 1st dose (n = 55) (12.9% with headache, 4% myalgia; 3% arthralgia, 10% fatigue, 9% febrile episode) 0% (0/433) severe adverse reactions after 2nd dose (186/433 local injection site reaction.; 19.70% [85/433] had headaches, 14% fatigue, 7% arthralgia, 21% febrile episode)
Garrido et al, 2021	Overall:56.8% adverse events after 1st dose (n = 66) (55% local injection site reaction, 10% myalgias; arthralgias 1%,9% headache, 20% fatigue, 4% febrile episode) 74.2% (128/173) adverse reactions after the 2nd dose of SARS-CoV-2 vaccine (51% (88/173) local injection site reaction; 15% (26/173) myalgia; 23% (40/173) fatigue, 3% (5/173) with arthralgia, 8% febrile episode)
Edelman-Klapper et al, 2021	Adverse events after 1st dose (134/185 with injection site reaction, headache 23/185, fatigue 19/185, myalgias 17/185, arthralgias 11/185, febrile episode 3/185) Adverse events after 2nd dose (128/185 with injection site reaction, headache 46/185, fatigue 45/185, myalgias 27/185, arthralgias 8/185, febrile episode 13/185)

therapy use. Further analysis revealed that high rates of seroconversion were also noticed in patients independent of use of as well as class of immunosuppressive regimens. The seroconversion rates did not statistically differ between different immunosuppressive agents such as anti-TNFα, anti-integrin therapy, anti IL12/23 or JAK inhibitors. Further studies will be important to evaluate the impact of a booster dose on seroconversion of these patients. Only two studies evaluated of corticosteroid use in IBD patients undergoing SARS-CoV-2 vaccination[34,40] and as corticosteroids are considered to have strong effects on seroconversion after vaccination, and hence further studies are needed address this potentially important variable in responses to vaccination among IBD patients. Furthermore, additional studies are necessary to evaluate T-cell response, also an important component of response to SARS-CoV-2 vaccine.[45]

An important measure of the effectiveness of SARS-CoV-2 vaccines is the incidence of breakthrough infection after COVID-19 vaccination. This meta-analysis showed that there was no statistical difference in the risk of developing a breakthrough infection after SARS-CoV-2 vaccine in IBD patients as compared to the control cohort. However, there were only four studies evaluating breakthrough infection after SARS-CoV-2 infection and thus, further studies are necessary to evaluate the risk of breakthrough infections in IBD patients.

Even though the subgroup analysis of the type of SARS-CoV-2 vaccines did not reveal statistical differences for seroconversion rate after two doses, the meta-regression revealed that the between-study heterogeneity could be related to the SARS-CoV-2 vaccine type in the included studies. A higher frequency of the BNT162b2 vaccine was associated with a lower seroconversion rate in IBD patients in the included studies. Our results are in accordance with previous studies[46,47] and suggest that the mRNA1273 vaccine may be more effective in IBD patients as compared to BNT162b2 vaccine. However, further studies are needed to specifically address the question of vaccine-type effectiveness in IBD, as well as the effectiveness of different vaccines against SARS-CoV-2 variants. Additionally, further studies are necessary to evaluate the seroconversion rate of SARS-CoV-2 vaccination in IBD patients as compared to general population in a direct comparison study. The location of the study also likely contributed to heterogeneity in the analysis, which may have been due in part to differences in the predominant vaccine type used in a specific location. Both the BNT162b2 vaccine

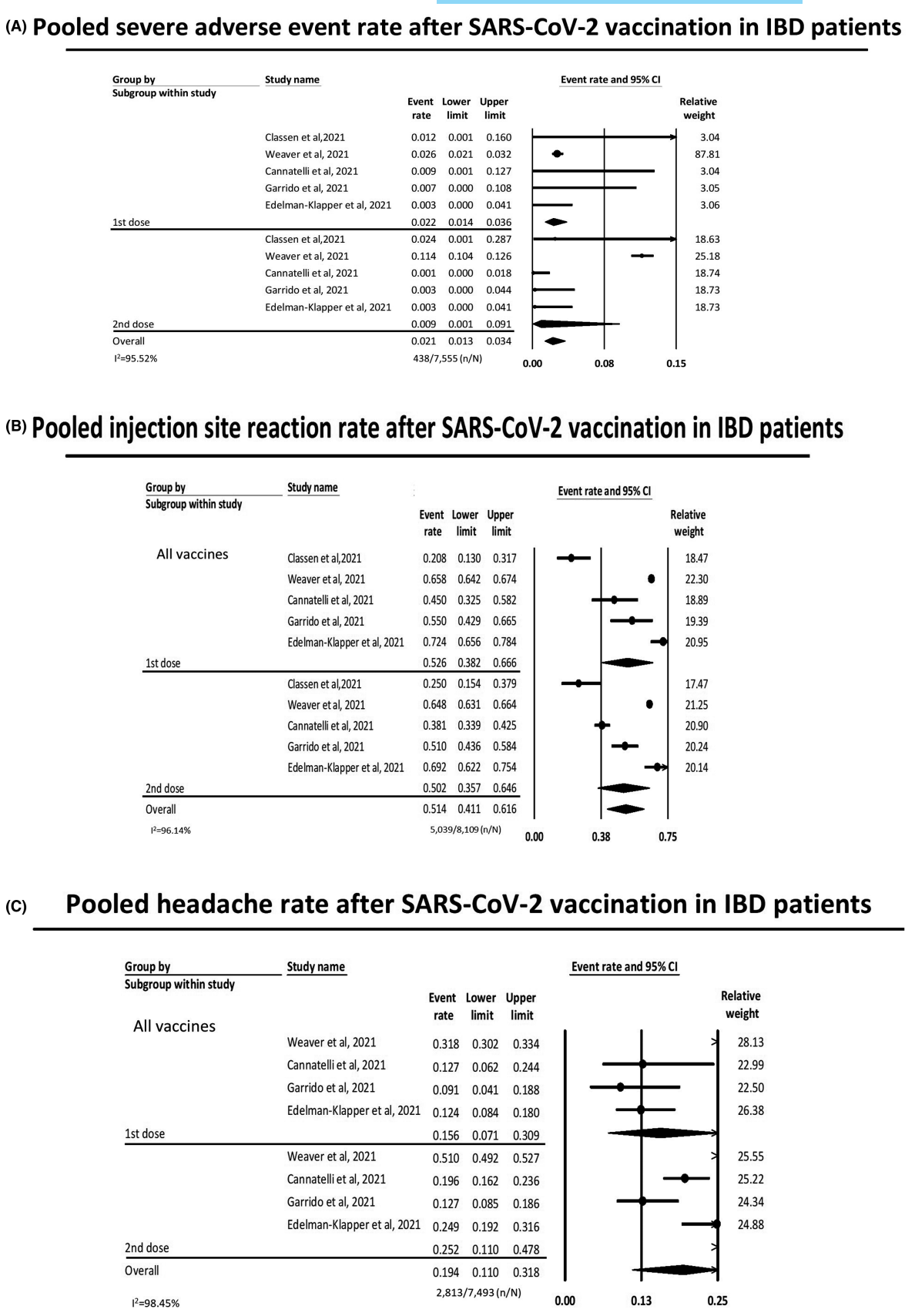
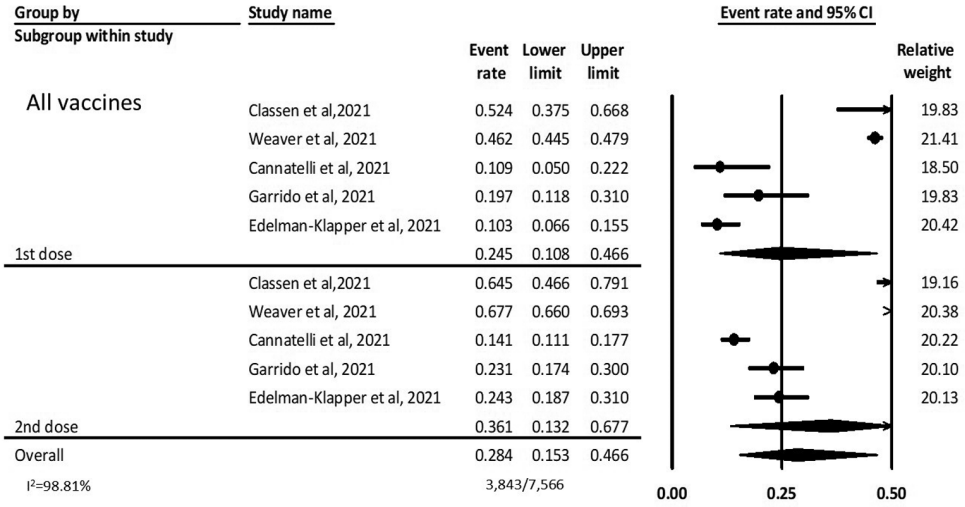
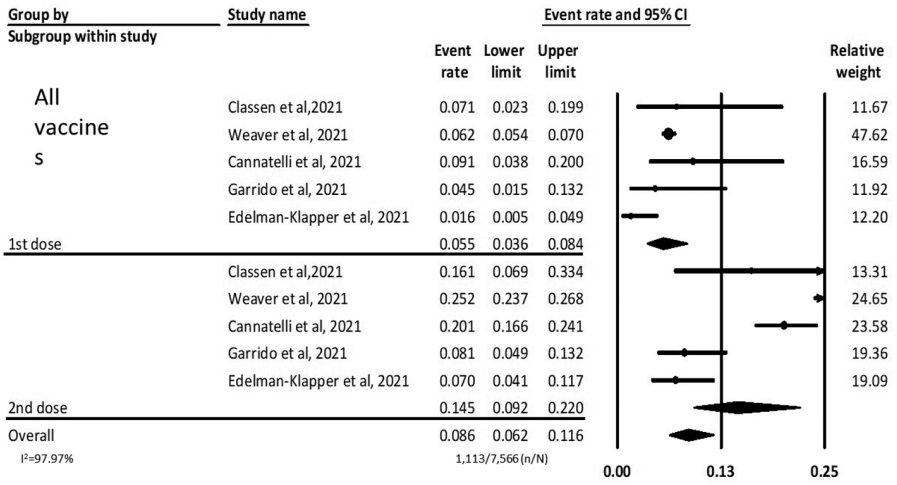


FIGURE 5 (A) Severe dose event rate stratified by number of SARS-CoV-2 vaccine doses in IBD. (B) Injection site reaction rate stratified by number of SARS-CoV-2 vaccine doses in IBD. (C) Headache rate stratified by number of SARS-CoV-2 vaccine doses in IBD. (D) Fatigue rate stratified by number of SARS-CoV-2 vaccine doses in IBD. (E) Febrile episode rate stratified by number of SARS-CoV-2 vaccine doses in IBD. (F) Arthralgia rate stratified by number of SARS-CoV-2 vaccine doses in IBD. (G) Myalgia rate stratified by number of SARS-CoV-2 vaccine doses in IBD

(D) Pooled fatigue rate after SARS-CoV-2 vaccination in IBD patients



(E) Pooled febrile episode rate after SARS-CoV-2 vaccination in IBD patients



(F) Pooled arthralgia rate after SARS-CoV-2 vaccination in IBD patients

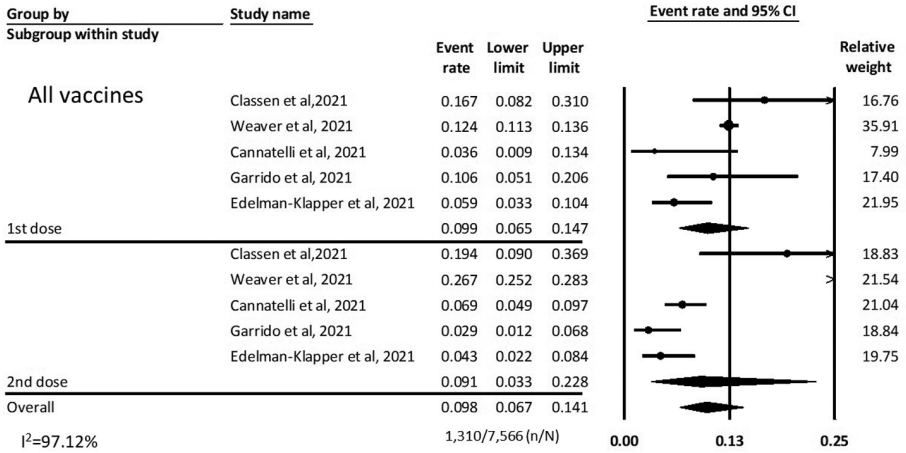


FIGURE 5 (Continued)

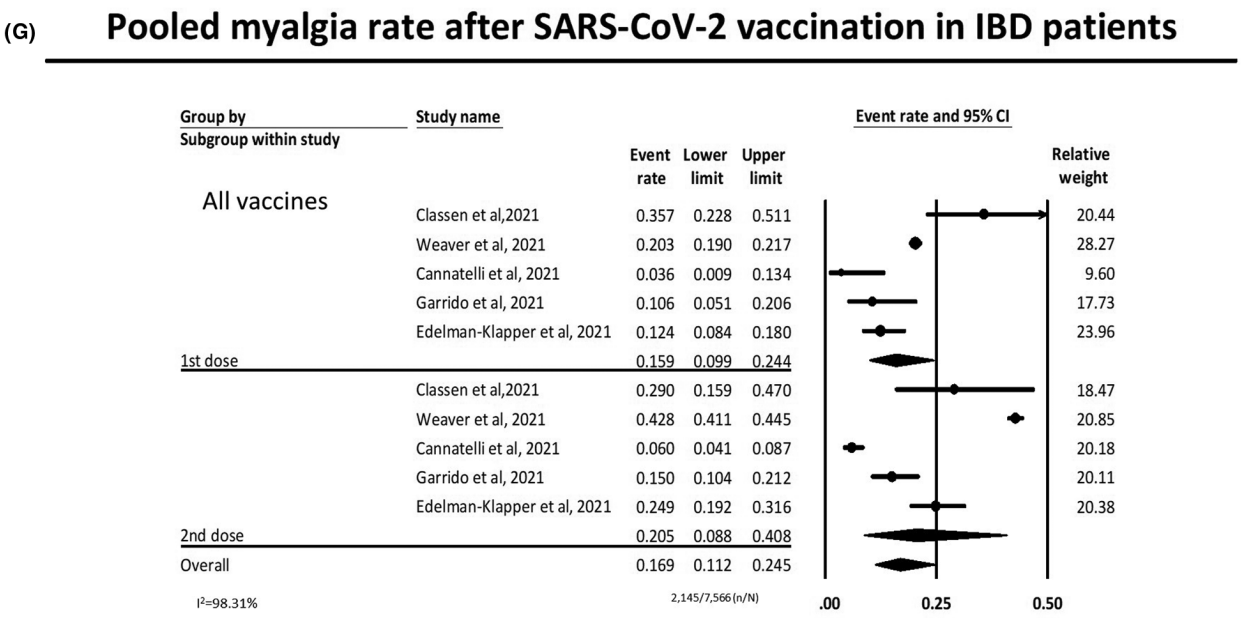


FIGURE 5 (Continued)

and mRNA1273 CoV-19 vaccine received emergency use authorisation from the United States Food and Drug Administration in December 2020[48] and have been utilised prominently. The majority of the studies included in the meta-analysis were conducted in the United States, and included data for both of the mRNA vaccines. Therefore, further studies are necessary to evaluate the influence of the country site with the seroconversion rate.

The meta-analysis revealed that the most common adverse event after the first and second dose of COVID-19 vaccine was injection site reaction occurring in more than 50% of patients. Injection site reaction has been reported in approximately 70% and 75.2% after one and two doses respectively.[49] Fatigue and myalgia were also frequently reported in the IBD patients after the second dose of COVID-19 vaccine. Prior study has reported fatigue rate of 30.9% and 53.9% after one and two doses of SARS-CoV-2 vaccination.[49] Similarly, myalgia rate of 19.4% and 44% after one and two doses of SARS-CoV-2 vaccination.[49] The overall pooled severe adverse event rate was around 2%. However, it is likely that this is an over-estimate due to suspected reporting bias as the majority of the studies evaluating adverse events were survey-based studies. Therefore, the current data indicate that the COVID-19 vaccine is safe in the IBD population, lending support to the current gastroenterological society recommendations noted above.

The strength of this study is the large number of patients included in the meta-analysis across a high number of prospective, well-designed studies. In addition, the subgroup analysis and sensitivity, and meta-regression, also added to the robust statistical design. There are also limitations to this meta-analysis. The heterogeneity in regard to immunosuppressive therapies and vaccine type indicates that certain outcomes could not be evaluated with certainty. We attempted to minimise the heterogeneity with regard to the immunosuppressive therapies and were able to explain 90% of the between-study heterogeneity. However, minimising heterogeneity in the evaluation of the adverse events was not feasible. This was due in part to the fact that survey-based studies, which were included for the evaluation of adverse events, have inherent limitations.[50] Additionally, there is a lack of randomised control group to evaluate the serious adverse events accurately in IBD population. It is also important to recognise that the studies utilised different assays to assess for the antibodies against SARS-CoV-2 which could also influence the outcomes. Even though, some of the assays are comparable,[51] further studies are necessary to compare the seroconversion rate between different assays for SARS-CoV-2 antibody measurement. The impact of booster dose and the seroconversion rate against SARS-CoV-2 variants (such as Omicron) also needs to be evaluated in patients with IBD. Additionally, it is important to note that breakthrough infections could still occur despite seroconversion after vaccination due to behavioural risk factors.[52] Therefore, further studies are necessary to accurately ascertain the adverse event rate, breakthrough infection and seroconversion rate with SARS-CoV-2 vaccine in IBD.

In summary, this systematic review and meta-analysis shows that the overall seroconversion rate after COVID-19 vaccination in IBD patients is high and improves with a second dose, with no statistical differences in antibody response associated with different immunosuppressive therapies. Even though, the rates of breakthrough SARS-CoV-2 infection after vaccination were low, further studies are necessary to accurately determine this risk. The pooled severe adverse events and mild adverse events after SARS-CoV-2 vaccination were low. These findings suggest that COVID-19 vaccination is safe and effective in IBD patients. Further studies regarding the effectiveness of these vaccines with the SARS-CoV-2 variants, determining the specific effects and possible confounding from concomitant steroid

use, as well as the impact of the third 'booster' dose of the mRNA vaccines specifically in IBD patients, would be of great value.

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Declaration of personal interests: We certify that we have no financial affiliation/interest (eg employment, stock holdings, consultant arrangements, honoraria in the subject matter, materials or products mentioned in this manuscript). The manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work

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AUTHOR CONTRIBUTIONS

Abhishek Bhurwal: Conceptualization (lead); data curation (lead); formal analysis (lead); investigation (lead); software (lead); writing – original draft (lead); writing – review and editing (lead). **Hemant Mutneja:** Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); software (equal); writing – original draft (equal); writing – review and editing (equal). **Vikas Bansal:** Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); project administration (equal); software (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal). **Akshay Goel:** Data curation (equal); formal analysis (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Shilpa Arora:** Data curation (equal); formal analysis (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Bashar M Attar:** Conceptualization (equal); formal analysis (equal); methodology (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal). **Carlos D Minacapelli:** Formal analysis (equal); methodology (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal). **Gursimran Kochhar:** Conceptualization (equal); methodology (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal). **Lea Ann Chen:** Conceptualization (equal); methodology (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal). **Steven Brant:** Conceptualization (equal); formal analysis (equal); methodology (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal). **Darren N Seril:** Conceptualization (equal); data curation (equal); investigation (equal); methodology (equal); project administration (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal).

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Guarantor of the article: Abhishek Bhurwal, MD

Author contributions: A. Bhurwal, H. Mutneja, S. Arora and V. Bansal designed the study. All authors participated in the search strategy and evaluated the articles for eligibility in the meta-analysis. A. Bhurwal, H. Mutneja, A.Goel and V. Bansal performed the statistical analysis and the authors have statistical expertise. A. Bhurwal, H. Mutneja, V. Bansal and D. Seril wrote the manuscript. All authors edited the manuscript.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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