*Ther Adv Gastroenterol*

2023, Vol. 16: 1–11

DOI: 10.1177/
17562848231174295



# SARS-CoV-2 breakthrough infections after COVID-19 vaccination in patients with inflammatory bowel disease: a systematic review and meta-analysis

**Natasja van de Pol, Qiuwei Pan, Lauranne A. A. P. Derikx, Linda Bakker, C. Janneke van der Woude and Annemarie C. de Vries**

***Abstract***

**Background:** Patients with inflammatory bowel disease (IBD) have an attenuated serologic response to COVID-19 vaccination. It is unclear whether an impaired immune response in vaccinated IBD patients impacts the susceptibility to SARS-CoV-2 infection and occurrence of severe COVID-19.

**Objectives:** To evaluate SARS-CoV-2 breakthrough infection rates and the disease course of COVID-19 in vaccinated IBD patients.

**Design:** A systematic literature search and meta-analysis was performed.

**Data sources and methods:** The search was performed in Embase, Medline, Web of Science Core Collection, Cochrane Central Register of Controlled Trials and CINAHIL. The articles were independently screened and selected by two reviewers. A random-effects model was used to calculate the pooled relative risk for breakthrough infections in vaccinated IBD patients and controls.

**Results:** A total of 16 studies were included, with study periods ranging from January 2020 to October 2021 and follow-up time from 3 weeks to 6 months. The breakthrough infection rates range from 0 to 37.4% in vaccinated IBD patients. The disease course of COVID-19 was generally mild, with low hospitalization and mortality rates (0–8.7% and 0–4.3%, respectively). Vaccinated IBD patients had a significantly lower relative risk of breakthrough infection rate compared to unvaccinated controls (risk ratio: 0.07, 95% CI: 0.03–0.18). No difference was observed between IBD patients and non-IBD controls, and between partially and fully vaccinated IBD patients. The impact of immunosuppressive therapy on breakthrough infection rates differs between studies. Most studies showed no impact from immunosuppressive treatment, anti-tumour necrosis factor alpha or corticosteroids and other biologics; one study reported higher rates for patients treated with infliximab *versus* vedolizumab.

**Conclusion:** Vaccination is effective to prevent COVID-19 infections in patients with IBD. Breakthrough infections do occur, but the disease course is generally mild. Available data seem to suggest a declining trend of breakthrough infections during calendar time.

**Registration:** The protocol was published in the PROSPERO database (CRD42021292853).

***Keywords:*** COVID-19, SARS-CoV-2, breakthrough infection, Inflammatory Bowel Disease

Received: 7 December 2022; revised manuscript accepted: 20 April 2023.

Correspondence to:
**Annemarie C. de Vries**
Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Dr. Molewaterplein 40, Rotterdam 3015 CE, The Netherlands
**a.c.devries@erasmusmc.nl**

**Natasja van de Pol**
**Qiuwei Pan**
**Lauranne A. A. P. Derikx**
**Linda Bakker**
**C. Janneke van der Woude**
Department of Gastroenterology and Hepatology, Erasmus MC, University Medical Centre, Rotterdam, The Netherlands

## Introduction

Since the start of the coronavirus disease (COVID-19) pandemic caused by SARS-CoV-2 infection, multiple vaccination programmes with both messenger RNA (mRNA) and viral vector vaccines were implemented. Initial concerns on an increased risk of COVID-19 infections and a more severe course for patients with inflammatory

bowel disease (IBD) have been refuted.[1–3] The overall incidence as well as the incidence of severe COVID-19 infections in patients with IBD is comparable to the general population.[1–3]

Risk factors for severe COVID-19 in IBD patients comprise a higher age, comorbidity and corticosteroid use. No association between severe COVID-19 and IBD medication, including biologicals, has been observed.[4] On the contrary, a beneficial effect of anti-inflammatory drugs has been suggested. Hypothetically these drugs protect patients from a cytokine storm associated with COVID-19, thereby reducing the expression of angiotensin-converting enzyme 2 receptors necessary for viral entry of COVID-19, which influences both the incidence and severity of COVID-19.[5] Contradictory to this hypothesis, the serologic response to infection was shown to be attenuated in patients with anti-tumour necrosis factor alpha (anti-TNF-α) treatment when compared with vedolizumab .[6,7]

An impaired immune response following hepatitis A and B, pneumococcal and influenza vaccinations was demonstrated in IBD patients on immunosuppressive therapy.[8–11] Given a reduced serologic response following COVID-19 infection, a reduced vaccination response following COVID-19 vaccination might be expected. A recent meta-analysis demonstrated that vaccinated IBD patients had slightly lower seroconversion rates after COVID-19 vaccination than healthy controls. Most importantly, a fast decay in antibody response to vaccination after 4weeks was demonstrated, which was most pronounced in patients treated with anti-TNF-α, immunomodulators or combination therapy.[12]

Although an impaired immune response has been demonstrated following COVID-19 vaccination in IBD patients, it is unclear whether this impacts the rate of (severe) SARS-CoV-2 infections. In this systematic review and meta-analysis, we aim to assess the rate of (severe) SARS-CoV-2 breakthrough infections after vaccination for patients with IBD. In addition, we describe the course of the breakthrough infections after COVID-19 vaccination and evaluate epidemiological and disease-specific risk factors.

## Methods

### *Search strategy*

This systematic review and meta-analysis was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions,[13] in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The protocol for this systematic review was published at PROSPERO (CRD42021292853). An expert librarian conducted a literature search on 11 March 2022 in multiple databases such as Embase, Medline, Web of Science Core Collection, Cochrane Central Register of Controlled Trials and CINAHIL (Supplemental Table 1). No restrictions in time, geography or language were made. References in the eligible articles were cross-checked by hand for additional literature.

### *Study selection*

Two authors (NP and LB) independently screened all titles and abstracts. Subsequently, full-text articles (if available) were read for definitive study inclusion. Articles were selected according to the inclusion criteria: (a) observational cohort studies, (b) patients with IBD, (c) vaccination with COVID-19 vaccine, including mRNA and viral vector vaccine, and (d) reported SARS-CoV-2 breakthrough infection rates or disease course. Abstracts which met the inclusion criteria were included. Case reports and systematic reviews were excluded. Discrepancies between reviewers were resolved through consensus with a third author (AV).

### *Data extraction and quality assessment*

Data extraction was independently performed by two authors (NP and LB). The collected data existed of (a) study characteristics, that is, first author name, type of article, year of publication, inclusion time period, follow-up time, study country and sample size; (b) intervention characteristics, that is, type vaccination, number of vaccinations, vaccination interval, follow-up time and prior SARS-CoV-2 infection; (c) epidemiological and disease-specific characteristics, that is, age, sex, ethnicity, body composition, comorbidities, IBD diagnosis and current medication and (d) breakthrough infection rates, symptoms, hospitalization and mortality rates. The quality of the studies was assessed with the Newcastle Ottawa Scale for nonrandomized studies.[14]

### *Outcomes and comparisons*

Primary outcome was the SARS-CoV-2 breakthrough infection rate after vaccination in patients

with IBD. Breakthrough infection rates were compared with non-IBD controls, partially vaccinated and unvaccinated IBD patients. Furthermore, comparisons were made between IBD subgroups based on IBD type, medical therapy and vaccination type. Secondary outcome was the COVID-19 breakthrough infection severity, including symptomatic disease, hospitalization, intensive care unit (ICU) admission and all-cause mortality.

### *Data synthesis and analysis*

A meta-analysis on the breakthrough infection rates of fully vaccinated IBD patients in comparison with vaccinated non-IBD controls, unvaccinated and partially vaccinated IBD patients was performed. We used a random-effects model and the Mantel-Haenszel method. Continuity correction of 0.5 was used in studies with zero cell frequencies. To assess heterogeneity, DerSimonian-Laird estimator was used for $\tau^2$. We critically appraised the available data for other outcome measures and did not perform a meta-analysis for other outcome measurements due to lack of data. A two-sided $p$-value $<0.05$ was considered statistically significant.

## Results

### *Eligible studies*

The initial literature search revealed 663 articles potentially eligible for inclusion (Figure 1). After full-text screening, 16 articles were included in the systematic review. No additional articles were found through citation search.

### *Quality assessment*

Details of the quality assessment are shown in Supplemental Table 2. Eleven articles comprised a control group, including healthy controls ($n=1$),[15] non-IBD patients ($n=4$),[16–19] unvaccinated IBD patients ($n=3$),[20–22] IBD patients after a SARS-CoV-2 infection ($n=1$),[23] irritable bowel syndrome (IBS) patients ($n=1$)[24] and an unspecified control group ($n=1$).[25] Eight studies were of high quality (7–9 stars)[16–21,23,26] and eight studies were of moderate quality (4–6 stars)[15,22,24,25,27–30] due to no selection of a control group,[26–30] no selection of a matched control group,[15,22,24,25] no demonstration that patients did not have a SARs-CoV-2 infection at the start of the study[22,24,25,29,30] or unclear follow-up time.[24]

### *Study characteristics*

The characteristics of the included articles are summarized in Table 1. Included studies were performed between January 2020 and October 2021 with a follow-up time ranging from 30 days to 6 months. All articles included patients which were fully vaccinated,[15–30] three articles included an additional subgroup of patients who were partially vaccinated[20,21,30] and none of the articles included patients who received three or more vaccinations. Fully vaccinated is defined as either after a second dose in a two-dose series (e.g. Pfizer-BioNTech; Moderna ) or after a first dose in a single-dose series (e.g. Janssen/Johnson & Johnson).[31] In 14 available studies, 36,109 patients and 41,624 controls received the mRNA vaccine with mRNA-1273 (Moderna)[17,21–25,27,28,30] or BNT162b2 (Pfizer-BioNTech).[15–17,19–25,27–30] In four studies, 315 patients and 95 controls received the adenovirus vector vaccine with Ad26.CoV2.S (Janssen, Johnson & Johnson),[22–24,30] ChAdOx1 nCoV-19 (Oxford-AstraZeneca),[22,24] GAM-COVID-Vac (Sputnik)[22] or Ad5-nCoV-S (CanSino).[22] In one study, six patients received the inactivated SARS-CoV-2 vaccine with CoronaVac (Sinovac).[22] Four studies (patients: $n=13{,}030$; controls: $n=11{,}676$) did not specify the type of vaccination.[17,18,25,26]

### *Breakthrough infections*

Fifteen studies assessed the breakthrough infection rate. The majority of studies reported breakthrough infection rates below 6% within the study follow-up time, although rates vary between 0% and 37.4% (Figure 2).[15–21,23–30] A calculated pooled breakthrough infection rate was not possible due to differences in follow-up time and period of included studies. Seven studies compared the breakthrough SARS-CoV-2 infection rate between IBD patients and non-IBD controls. Meta-analysis of these studies showed a risk ratio (RR) of 1.01 (95% CI: 0.92–1.10) (Figure 3).[15–19,24,25] Furthermore, the pooled relative risk of breakthrough infections in vaccinated IBD patients was significantly lower than the risk of infection in unvaccinated IBD patients (RR: 0.07, 95% CI: 0.03–0.18, Figure 4). Heterogeneity was significantly present ($I^2=83\%$, $p<0.01$).[19–21]

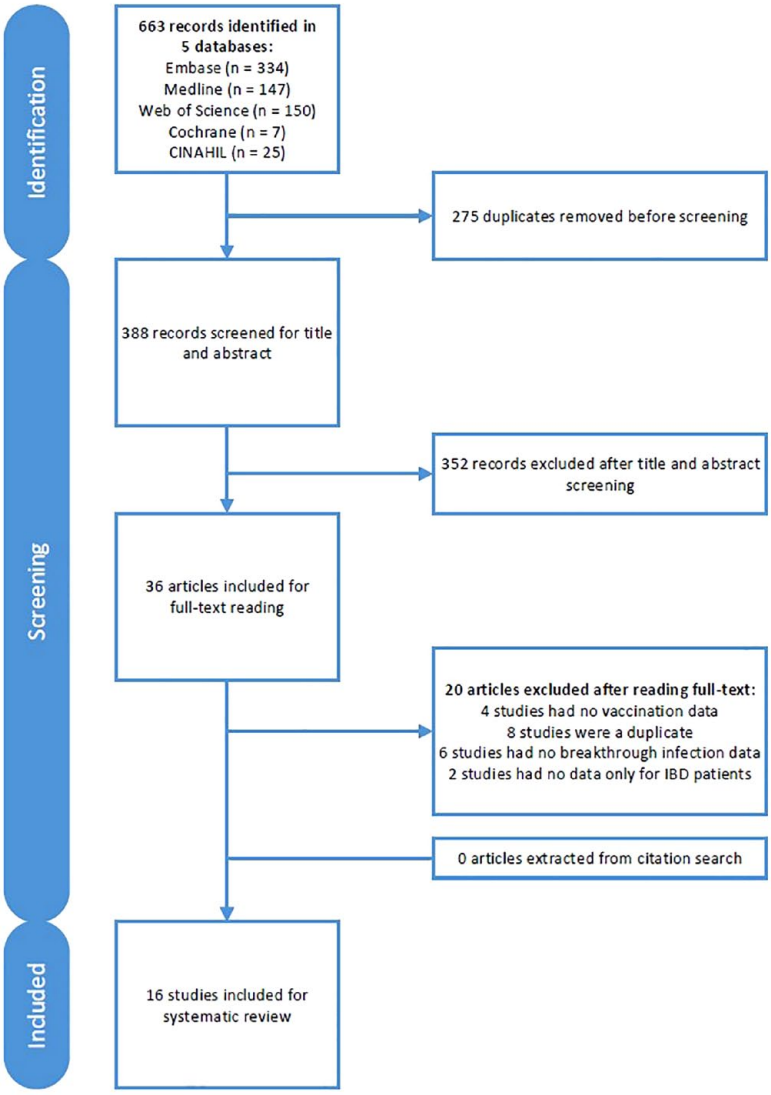


**Figure 1.** Flowchart of the study selection process according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

No differences were found between fully and partially vaccinated IBD patients (RR: 0.67, 95% CI: 0.38–1.18, Figure 5).[20,21,30]

Subgroup analyses in one study revealed no significant difference in breakthrough infection rates between Pfizer-BioNTech and Moderna.[21] One comparative study assessed the risk of breakthrough infections per IBD subtype compared to healthy controls. According to this study, both patients with CD and UC were not at increased risk of breakthrough infections ($p = 0.055$ and $p = 0.310$, respectively).

When comparing the IBD subtypes, patients with CD showed higher infection rates after >7 days (HR: 3.56; 95% CI: 1.29–9.83; $p = 0.01$) and >14 days (HR: 3.38; 95% CI: 1.07–10.64; $p = 0.04$) when compared to patients with UC.[16] In addition, one study showed that patients with infliximab had higher rates of breakthrough infections than patients with vedolizumab ($p = 0.0039$),[26] whereas other studies showed no difference between immunosuppressive treatment (immunomodulators and biologics) *versus* no treatment ($p = 0.45$),[16] between anti-TNF-α/corticosteroids *versus* without anti-TNF-α/corticosteroids ($p = 0.25$) and between

**Table 1.** Baseline characteristics of the included studies.

| Author | Type | Year | Country | Type of vaccination (%) | IBD patient group size (*N*) | Controls group size (*N*) and description | Sex (% men) | Age (y), mean (SD) or median (IQR) | IBD diagnosis (%) | Current medication (%) | Follow-up time, median (IQR) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ben-Tov[16] | Original article | 2021 | Israel | Pfizer-BioNTech 100 | 12,213 | 36,254 matched healthy participants | Patients 50.1, controls 50 | Patients 47 (17), controls 47 (17) | CD 44.4, UC 51.9, IBD-U 3.7 | 5-ASA or none 72.6, steroids 3.7, anti-TNF-α 10.8, UST 1.8, VDZ 3.7, MTX 1.4, thiopurines 4.8, thiopurines and anti-TNF-α combination therapy 1.1 | 71 days (52–80) |
| Charilaou[27] | Original article | 2021 | USA | Pfizer-BioNTech 63.1, Moderna 36.9 | 176 | | 67.6 | 47.3 (16.0) | CD 64.6, UC 36.4 | No biologic/small molecule 31.3, IFX/ADA/CTZ 26.7, UST 26.7, VDZ 11.4, TOFA 4, prednisone 4, IM 10.2, anti-TNF-α + IM 8.5 | 126 days (89–162) |
| Dailey[23] | Original article | 2021 | USA | Pfizer-BioNTech 63.6, Moderna 21.2, Johnson & Johnson 15.2 | 33 | 44 IBD patients after infection | | Patients 21 (16–27) | | | mRNA 3.3 weeks (1–10) or AVV 3.1 weeks (1.6–3.6) |
| Edelman-Klapper[15] | Original article | 2022 | Israel | Pfizer-BioNTech 100 | 185 | 73 healthy participants | Patients 60.6, controls 27.4 | Patients 37.9 (14.3), controls 36.6 (12.4) | CD 65.9, UC 28.6, IPAA 3.2, IBD-U 2.2 | Non-anti-TNF-α/no medication 36.2, anti-TNF-α 63.8 | 30 days (28–33) |
| Frey[28] | Original article | 2022 | USA | Pfizer-BioNTech 57.3, Moderna 42.7 | 75 | | 26.7 | 45 (38–58) | | Hydroxychloroquine 1.3, mycophenolate 1.3, MTX 6.7, thiopurine 14.7, anti-TNF-α 50.7, anti-TNF-α monotherapy 32, TOFA 2.7, UST 22.7, VDZ 8, budesonide 8, systemic corticosteroids 22.4, anti-TNF-α + thiopurine/MTX 10.7, anti-TNF-α + systemic corticosteroids 13.3, other combination therapy 14.7 | 179 (165–202) |
| Hadi[17] | Original article | 2021 | USA | Pfizer-BioNTech 27.9, Moderna 6.9, not specified 65.2 | 5561 | 5561 non-IBD pre-matched | Patients 41.3, controls 41.4 | Patients 57.3 (17.5), controls 57.4 (17.4) | CD 47.3, UC 52.7 | Biologics/thiopurines 52.8 | 30 days |
| Julton[18] | Abstract | 2021 | USA | Unspecified Pfizer-BioNTech, Moderna or Johnson & Johnson | 6108 | 6107 non-IBD pre-matched | | Patients and controls 18–90 | | Biologics/small molecules 21.5, IM 58.8, other therapies 19.6 | 3–6 months |
| Khan[21] | Original article | 2021 | USA | Pfizer-BioNTech 45.2, Moderna 54.8 | 7321 | 7376 IBD patients unvaccinated | Patients 92.6, controls 91.7 | Patients 71 (60–75), controls 64 (47–73) | Patients: CD 37.5, UC 62.5 Controls: CD 38.9, UC 61.1 | Patients: mesalamine 54.9, thiopurine 10.8, anti-TNF-α monotherapy 18.8, anti-TNF-α + IM 4.2, VDZ 7.2, UST 1, TOFA 0.7, MTX 2.3, steroids 6.8 Controls: mesalamine 54.6, thiopurine 10.5, anti-TNF-α monotherapy 20.9, anti-TNF-α + IM 4, VDZ 6, UST 1.1, TOFA 0.8, MTX 2, steroids 5.6 | 38 days (20–55) |

*(Continued)*

**Table 1.** (Continued)

| Author | Type | Year | Country | Type of vaccination (%) | IBD patient group size (*N*) | Controls group size (*N*) and description | Sex (% men) | Age (y), mean (SD) or median (IQR) | IBD diagnosis (%) | Current medication (%) | Follow-up time, median (IQR) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Khan[20] | Abstract | 2022 | Qatar | Pfizer-BioNTech 100 | 476 | 476 IBD patients unvaccinated | | | | | >14 days (total 23,289 p-d) |
| Lev-Tzion[19] | Original article | 2022 | Israel | Pfizer-BioNTech 100 | 4946 | 4946 non-IBD pre-matched | Patients 49, controls 49 | Patients 51 (16), controls 51 (16) | CD 49, UC 51 | Mesalamine monotherapy 54.9, corticosteroid 4, IM 6, anti-TNF-α 10, VDZ 4, UST 2, TOFA 1, | 22 weeks (4–24) |
| Lin[26] | Original article | 2022 | UK | Unspecified Pfizer-BioNTech or AstraZeneca | 5123 | | | | | | 5.7 weeks (3.7–7.7) |
| Sciberras[24] | Abstract | 2022 | Malta | Pfizer-BioNTech 50, Moderna 3.5, Johnson & Johnson 4, AstraZeneca 42.5 | 250 | 250 IBS patients | Patients 56.4, controls 21.6 | Patients 40.7 (15.7), controls 40.6 (11.99) | | IFX 62.8, ADA 24.8, VDZ 10, UST 2.4 | |
| Spiera[22] | Original article | 2022 | USA | Pfizer-BioNTech 65.9, Moderna 13.6, Sinovac 6.8, AstraZeneca 8, Sputnik 3.4, CanSino 1.1, Johnson & Johnson 1.1 | 88 | 2317 IBD patients unvaccinated | Patients 45.3 | Patients 40.1 (16.7) | CD 59.1, UC 38.6, IBD-U 2.3 | Mesalamine/sulfasalazine 21.6, corticosteroids 5.7, TOFA 1.1, IM monotherapy 3.4, biologic monotherapy 58, anti-TNF-α monotherapy 38.6, anti-integrin monotherapy 6.8, IL12/23-i monotherapy 11.4, monotherapy unspecified 1.1, combination therapy 21.6, other therapies 4.5, no therapy 6.8 | |
| Viazis[29] | Abstract | 2022 | Greece | Pfizer-BioNTech 100 | 2940 | | | | | | |
| Watanabe[25] | Abstract | 2022 | Japan | Pfizer-BioNTech 73.5, Moderna 10.5 | 679 | 204 controls unspecified | Patients 52.4, controls 23.5 | | CD 38.4, UC 61.6 | Oral 5-ASA 76.7, systemic corticosteroids 8.7, IM 36.6, anti-TNF-α 37.4, VDZ 8.7, UST 17.1, TOFA 6.1 | 6 months |
| Weaver[30] | Original article | 2022 | USA | Pfizer-BioNTech 57.5, Moderna 37.6, Johnson & Johnson 4.9 | 3316 | | 27.7 | 43.7 (15.1) | CD 54.6, UC 45.4 | Oral/parenteral steroids 4.6, oral budesonide 4.2, oral mesalamine 18.8, sulfasalazine 3, thiopurine 16.7, MTX 5.4, IFX 24.3, ADA 18.9, CTZ 1.7, golimumab 0.8, VDZ 12.1, UST 14.7, TOFA 1.8, cyclosporine 0.1, tacrolimus 0.5 | 30 days |

Type of vaccination percentage is calculated on the number of vaccinated patients and controls. The type of vaccination is specified as CanSino, Ad5-nCoV-S; Johnson & Johnson, Ad26.CoV2.S; Moderna, mRNA-1273; Oxford-AstraZeneca, ChAdOx1 nCoV-19; Pfizer-BioNTech, BNT162b2 mRNA; Sinovac, CoronaVac; Sputnik, Gam-COVID-Vac.
5-ASA, 5-aminosalicylic acid; ADA, adalimumab; anti-TNF-α, anti-tumour necrosis factor alpha; AVV, adeno viral vector vaccine; AZA, azathioprine; CD, Crohn's disease; CTZ, certolizumab; IBD-U, inflammatory bowel disease undefined; IBS, irritable bowel syndrome; IFX, infliximab; IL12/23-i, interleukin 12/23 inhibitor; IM, immunomodulatory; IPAA, ileal pouch–anal anastomosis; IQR, interquartile range; JAK-i, Janus kinase inhibitor; mRNA, mRNA vaccines; MTX, methotrexate; N, number; p-d, person-days; SD, standard deviation; TOFA, tofacitinib; UC, ulcerative colitis; UST, ustekinumab; VDZ, vedolizumab; y, year.

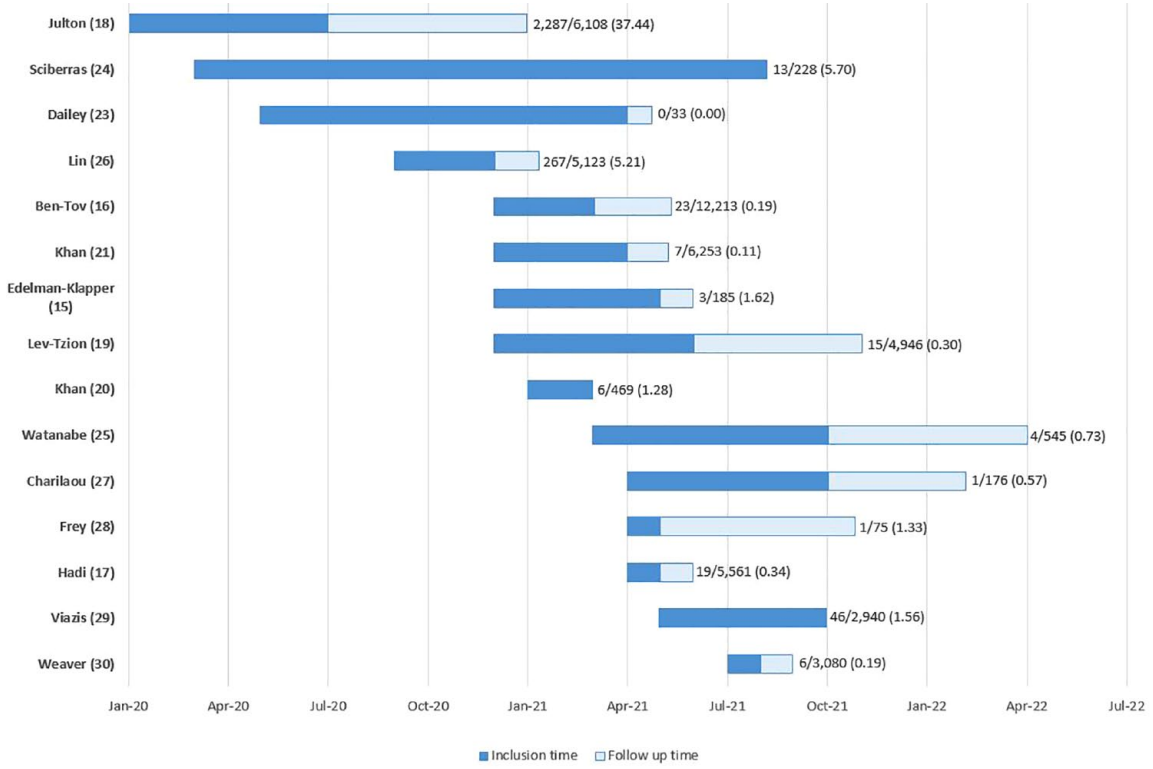


**Figure 2.** SARS-CoV-2 breakthrough infection rates in inflammatory bowel disease (IBD) patients within the study follow-up time.
The infection rates are described as number of infected patients/total number of patients (%).

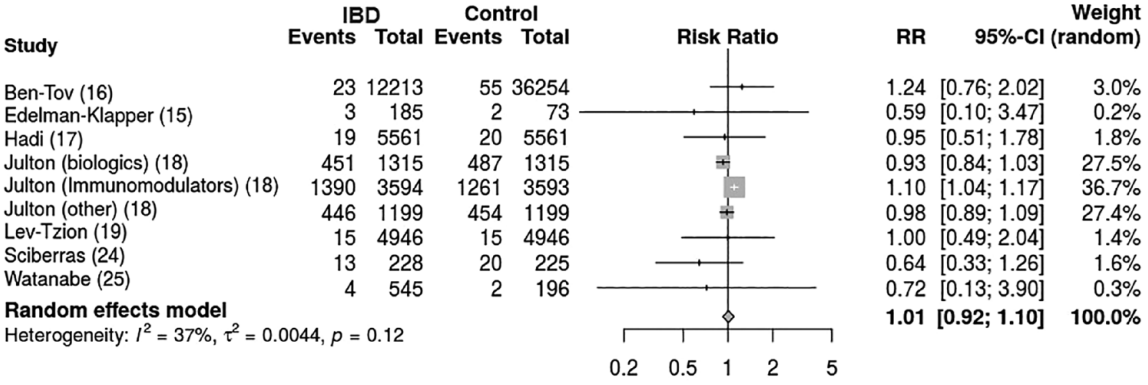


**Figure 3.** Meta-analysis of breakthrough SARS-CoV-2 infections in patients with IBD *versus* a control group (i.e. healthy control group, non-IBD group and IBS group).
IBD, inflammatory bowel disease; IBS, irritable bowel syndrome.

anti-TNF-α/corticosteroids *versus* other biologics ($p = 1.0$).[19]

### *COVID-19 disease course*

The majority of patients reported mild constitutional and respiratory symptoms, including fatigue, anosmia/ageusia, fever, cough, myalgia, hoarse voice, confusion and chest pains.[16,20,26,29,30] The rates for hospitalization (0–8.7%), severe SARS-CoV-2 infections (0.05–3.4%), ICU admission or mechanical ventilation (0) and all-cause mortality (0–4.3%) were low (Table 2).[16,20–22,26,29,30] One article defined severe SARS-CoV-2 infections as

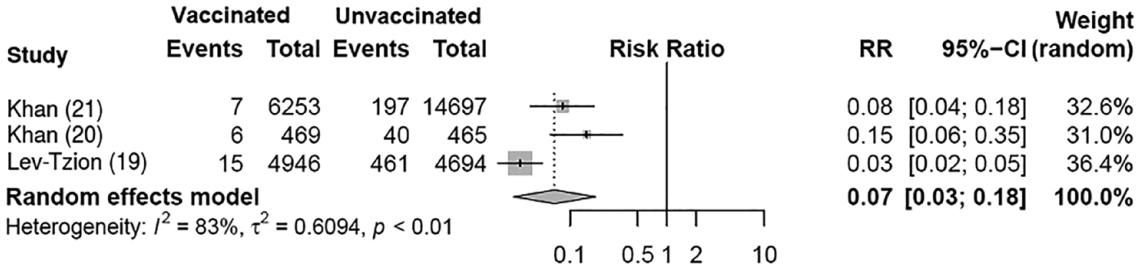


**Figure 4.** Meta-analysis of SARS-CoV-2 infections in vaccinated and unvaccinated inflammatory bowel disease (IBD) patients.

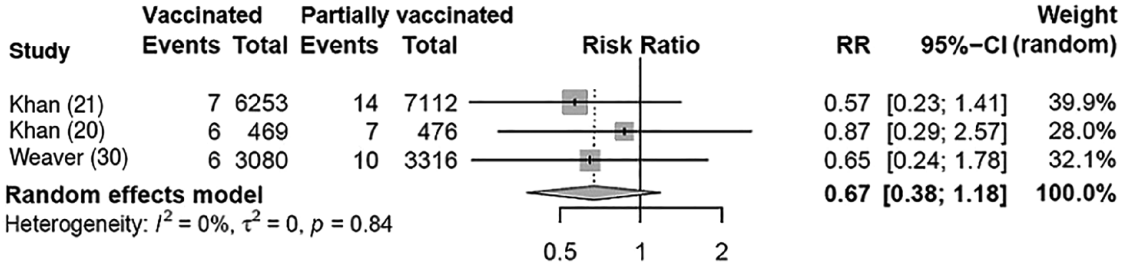


**Figure 5.** Meta-analysis of SARS-CoV-2 infections in vaccinated and partially vaccinated inflammatory bowel disease (IBD) patients.

**Table 2.** Secondary outcomes.

| Author | Breakthrough infection rates, n/N (%) | Symptomatic infection, n/N (%)+ | Severe SARS-CoV-2 infection, n/N (%)+ | Hospitalization, n/N (%) | ICU admission or mechanical ventilation, n/N (%) | All-cause mortality, n/N (%) |
|---|---|---|---|---|---|---|
| Ben-Tov[16] | 23/12,213 (0.19) | 9/23 (39.1) | | 2/23 (8.7) | | 1/23 (4.3) |
| Khan[21] | 7/6253 (0.11) | | 3/6253 (0.05)++ | | | 2/6253 (0.03)++ |
| Khan[20] | 6/469 (1.28) | 4/6 (66.7) | | 0/474 (0) | 0/469 (0) | 0/469 (0) |
| Lin[26] | 267/5123 (5.21) | 238/267 (89.2) | | 3/253 (1.2) | | |
| Spiera[22] | 88* | | 3/88 (3.4) | 5/88 (5.7) | | 1/88 (1.1) |
| Viazis[29] | 46/2940 (1.56) | 40/46 (87.0) | | 2/46 (4.3) | 0/46 (0) | |
| Weaver[30] | 6/3080 (0.19) | 15/16 (93.8)** | | 0/6 (0) | | |

Rates are described as *n/N* (%).
+Defined as COVID-19-related hospitalization or death[21] or as ICU admission, mechanical ventilation or death.[22]
++Described this only within all vaccinated patients.
*Only mentioned the total infection rate within vaccinated IBD patients.
**Described the symptomatic infection rate as a total of infected patients after first and second vaccinations.
ICU, intensive care unit; *n/N*, number/total number.

COVID-19-related hospitalization or death, and no differences were found for severe SARS-CoV-2 infection and all-cause mortality rates between fully vaccinated and unvaccinated IBD patients ($p = 0.18$ and $p = 0.11$, respectively).[21] Another article defined severe SARS-CoV-2

infection as ICU admission, mechanical ventilation and/or death, and it showed that all IBD patients with a severe SARS-CoV-2 infection used combination therapy and were significantly older (mean age 59 years *versus* 39 years, $p = 0.03$) . Higher hospitalization rates were observed in patients on combination therapy (15.8%) compared to biological (2.0%) or immunomodulatory monotherapy (0%) ($p = 0.08$), and hospitalized patients were significantly older (mean age 53 years *versus* 39 years, $p = 0.04$) . Vaccine type showed no difference in disease severity and hospitalization rates.[22]

## Discussion

This systematic review and meta-analysis provides an overview of SARS-CoV-2 breakthrough infection rates and COVID-19 disease severity following COVID-19 vaccinations. Breakthrough infections after COVID-19 vaccination do occur in fully vaccinated IBD patients, though at a similar rate as compared to non-IBD controls. Data suggest a declining trend of breakthrough infections during calendar time. Furthermore, the relative risk of breakthrough infections in vaccinated IBD was lower than the risk of infection in unvaccinated IBD patients. The course of breakthrough infections is generally mild, and hospitalization and mortality rates are in line with the rates in non-IBD patients. Potential risk factors associated with a severe course of breakthrough infections include combination therapy with both anti-TNF and an immunomodulator and older age at infection.

In this study, contradictory results were found regarding the impact of immunosuppressive therapy on the COVID-19 breakthrough infection rate in IBD patients. One article showed a negative impact of infliximab compared with vedolizumab, whereas other studies showed no impact of immunosuppressive treatment, anti-TNF-α or corticosteroids and other biologics. A higher rate of breakthrough infections may be explained by a combination of (a) lower seroconversion rates following COVID-19 vaccination in patients using steroids or combination therapy with anti-TNF-α and an immunomodulator, and (b) a faster antibody decay in patients treated with anti-TNF-α or immunomodulators.[12] Although one report showed a significantly lower geometric mean titre in patients with a confirmed breakthrough infection,[26] no cut-off values have been determined to identify patients at increased risk. This underlines the importance to advice full vaccination and revaccination for these specific subgroups.

The strength of this study: this is the first systematic review and meta-analysis which focused on breakthrough infection rates and the severity of COVID-19 infections. A comprehensive overview of breakthrough infection rates and performed multiple comparative subgroup analyses are provided. Nevertheless, some limitations should be taken into consideration. First, seasonal fluctuations in SARS-CoV-2 infection rates did not allow us to calculate a pooled breakthrough infection rate given differences in follow-up time and period of included studies.[32] Second, we were not able to perform more detailed subgroup analysis due to limited studies. Third, most articles included the mRNA vaccine (Pfizer or Moderna) questioning the generalizability of our results to the viral vector vaccinations (Johnson and AstraZeneca). Currently, the booster vaccination is introduced worldwide, and in this review, no studies reported the breakthrough infection rates after third or fourth vaccination.

In conclusion, this review and meta-analysis showed that vaccination is useful, considering the breakthrough infection rates in vaccinated IBD patients are significantly lower than the risk of infection in unvaccinated IBD patients. Although breakthrough infections do occur, severe SARS-CoV-2 infections, hospitalization, ICU admission or mechanical ventilation and all-cause mortality rates are low. Available data seem to suggest a declining trend of breakthrough infections during calendar time. The effect of IBD medication on the rate of breakthrough COVID-19 infections and disease course requires further elucidation.

## Declarations

### *Ethics approval and consent to participate*

Not applicable.

### *Consent for publication*

Not applicable.

### *Author contribution(s)*

**Natasja van de Pol:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Validation; Visualization; Writing – original draft; Writing – review & editing.

**Qiuwei Pan:** Writing – review & editing.

**Lauranne A. A. P. Derikx:** Writing – review & editing.

**Linda Bakker:** Conceptualization; Investigation; Methodology; Writing – review & editing.

**C. Janneke van der Woude:** Writing – review & editing.

**Annemarie C. de Vries:** Project administration; Supervision; Writing – review & editing.

*Acknowledgements*
We would like to thank W. M. Bramer, biomedical information specialist, for conducting the literature search.

*Funding*
The authors received no financial support for the research, authorship, and/or publication of this article.

*Competing interests*
CJW received grants and or fee for advisory boards and presentations from Pfizer, Abbvie, Celltrion, Falk Benelux, Takeda, Janssen and Ferring outside the submitted work; ACV has served on advisory boards for Takeda, Janssen, Bristol Myers Squibb, Abbvie, Pfizer and Galapagos and has received unrestricted research grants from Takeda, Janssen and Pfizer outside the submitted work; LAAPD has served on an advisory board for Sandoz and has received speaking fees from Janssen outside the submitted work; all other authors declare that they have no conflict of interest.

*Availability of data and materials*
Not applicable.

## ORCID iDs

Natasja van de Pol https://orcid.org/0000-0002-4699-6662
Lauranne A. A. P. Derikx https://orcid.org/0000-0002-4081-8451
Linda Bakker https://orcid.org/0009-0004-0121-8383
Annemarie C. de Vries https://orcid.org/0000-0002-3988-9201

## Supplemental material

Supplemental material for this article is available online.

## References

1. Allocca M, Fiorino G, Zallot C, *et al.* Incidence and patterns of COVID-19 among inflammatory bowel disease patients from the Nancy and Milan cohorts. *Clin Gastroenterol Hepatol* 2020; 18: 2134–2135.
2. Gubatan J, Levitte S, Balabanis T, *et al.* SARS-CoV-2 testing, prevalence, and predictors of COVID-19 in patients with inflammatory bowel disease in Northern California. *Gastroenterology* 2020; 159(3): 1141e2–1144e2.
3. Taxonera C, Alba C and Olivares D. What is the incidence of COVID-19 in patients with IBD in Western Countries? *Gastroenterology* 2021; 160: 1901–1902.
4. Brenner EJ, Ungaro RC, Gearry RB, *et al.* Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. *Gastroenterology* 2020; 159: 481e3–491e3.
5. Suria C, Bosca-Watts MM, Navarro P, *et al.* Management of patients with intestinal bowel disease and COVID-19: a review of current evidence and future perspectives. *Gastroenterol Hepatol* 2021; 45: 383–389.
6. Chanchlani N, Lin S, Chee D, *et al.* Adalimumab and infliximab impair SARS-CoV-2 antibody responses: results from a therapeutic drug monitoring study in 11422 biologic-treated patients. *J Crohns Colitis* 2021; 16: 389–397.
7. Kennedy NA, Goodhand JR, Bewshea C, *et al.* Anti-SARS-CoV-2 antibody responses are attenuated in patients with IBD treated with infliximab. *Gut* 2021; 70: 865–875.
8. Fiorino G, Peyrin-Biroulet L, Naccarato P, *et al.* Effects of immunosuppression on immune response to pneumococcal vaccine in inflammatory bowel disease: a prospective study. *Inflamm Bowel Dis* 2012; 18: 1042–1047.
9. Park SH, Yang SK, Park SK, *et al.* Efficacy of hepatitis a vaccination and factors impacting on seroconversion in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2014; 20: 69–74.
10. Pratt PK Jr., David N, Weber HC, *et al.* Antibody response to hepatitis B virus vaccine is impaired in patients with inflammatory bowel disease on infliximab therapy. *Inflamm Bowel Dis* 2018; 24: 380–386.
11. Shirai S, Hara M, Sakata Y, *et al.* Immunogenicity of quadrivalent influenza vaccine for patients with inflammatory bowel disease undergoing immunosuppressive therapy. *Inflamm Bowel Dis* 2018; 24: 1082–1091.

12. Jena A, James D, Singh AK, *et al*. Effectiveness and Durability of COVID-19 Vaccination in 9447 Patients With IBD: A Systematic Review and Meta-Analysis. *Clin Gastroenterol Hepatol* 2022; 20: 1456.e18–1479.e18.
13. Higgins JPT TJ, Chandler J, Cumpston M, *et al*. Cochrane handbook for systematic reviews of interventions version 6.3 (updated February 2022): Cochrane. www.training.cochrane.org/handbook (2022, accessed March 2022).
14. Wells GA, Shea B, O'Connell D, *et al*. The newcastle-ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed June 2022).
15. Edelman-Klapper H, Zittan E, Bar-Gil Shitrit A, *et al*. Lower serologic response to COVID-19 mRNA vaccine in patients with inflammatory bowel diseases treated with anti-TNFα. *Gastroenterology* 2022; 162: 454–467.
16. Ben-Tov A, Banon T, Chodick G, *et al*. BNT162b2 messenger RNA COVID-19 vaccine effectiveness in patients with inflammatory bowel disease: preliminary real-world data during mass vaccination campaign. *Gastroenterology* 2021; 161: 1715.e1–1717.e1.
17. Hadi YB, Thakkar S, Shah-Khan SM, *et al*. COVID-19 vaccination is safe and effective in patients with inflammatory bowel disease: analysis of a large multi-institutional research network in the United States. *Gastroenterology* 2021; 161: 1336.e3–1339.e3.
18. Julton TC, Lauren S, Mouhammed S, *et al*. Impact of inflammatory bowel disease treatment and risk of COVID-19 infection after full immunization: a nationwide analysis. *Am J Gastroenterol* 2021; 116(SUPPL): S15.
19. Lev-Tzion R, Focht G, Lujan R, *et al*. COVID-19 vaccine is effective in inflammatory bowel disease patients and is not associated with disease exacerbation. *Clin Gastroenterol Hepatol* 2021; 20: e1263–e1282.
20. Khan M, Mushtaq K, Saddique M, *et al*. Safety and effectiveness of the BNT162B2 mRNA COVID-19 vaccine in a nationwide cohort of patients with inflammatory bowel disease. *Inflammatory Bowel Dis* 2022; 28(SUPPL 1): S12–S13.
21. Khan N and Mahmud N. Effectiveness of SARS-CoV-2 vaccination in a veterans affairs cohort of patients with inflammatory bowel disease with diverse exposure to immunosuppressive medications. *Gastroenterology* 2021; 161: 827–836.
22. Spiera E, Ganjian DY, Zhang X, *et al*. Outcomes of COVID-19 infections in vaccinated patients with inflammatory bowel disease: data from an international registry. *Inflamm Bowel Dis* 2022; 28: 1126–1129.
23. Dailey J, Kozhaya L, Dogan M, *et al*. Antibody responses to SARS-CoV-2 after infection or vaccination in children and young adults with inflammatory bowel disease. medRxiv 2021.
24. Sciberras N, Pisani A, Vassallo C, *et al*. The effect of COVID-19 infection and vaccination in patients with inflammatory bowel disease and irritable bowel syndrome. *J Crohn's Colitis* 2022; 16: i334.
25. Watanabe K, Hisamatsu T, Nakase H, *et al*. Japan prospective multicenter study for optimization of COVID-19 vaccinations based on the immune response and safety profile in Inflammatory bowel disease patients: interim analyses of the J-COMBAT trial. *J Crohn's Colitis* 2022; 16: i076.
26. Lin S, Kennedy NA, Saifuddin A, *et al*. Antibody decay, T cell immunity and breakthrough infections following two SARS-CoV-2 vaccine doses in inflammatory bowel disease patients treated with infliximab and vedolizumab. *Nat Commun* 2022; 13: 1379.
27. Charilaou P, Tricarico C, Battat R, *et al*. Impact of inflammatory bowel disease therapies on durability of humoral response to SARS-CoV-2 vaccination. *Clin Gastroenterol Hepatol* 2022; 20: e1493–e1499.
28. Frey S, Chowdhury R, Connolly CM, *et al*. Antibody response six months after SARS-CoV-2 mRNA vaccination in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2022; 20: 1609–1612.
29. Viazis N, Theodoropoulou A, Zampeli E, *et al*. The natural history of covid-19 in vaccinated inflammatory bowel disease patients. *J Crohn's Colitis* 2022; 16: i283–i284.
30. Weaver KN, Zhang X, Dai X, *et al*. Impact of SARS-CoV-2 vaccination on inflammatory bowel disease activity and development of vaccine-related adverse events: results from PREVENT-COVID. *Inflamm Bowel Dis* 2021; 28: 1497–1505.
31. Frequently Asked Questions about COVID-19 Vaccination. Centers for disease control and prevention. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/faq.html (accessed February 2023).
32. WHO coronavirus (COVID-19) dashboard. World health organization. https://covid19.who.int/ (accessed February 2023).