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SYSTEMATIC REVIEWS AND META-ANALYSES

Siddharth Singh, Section Editor

Effectiveness and Durability of COVID-19 Vaccination in 9447 Patients With IBD: A Systematic Review and Meta-Analysis

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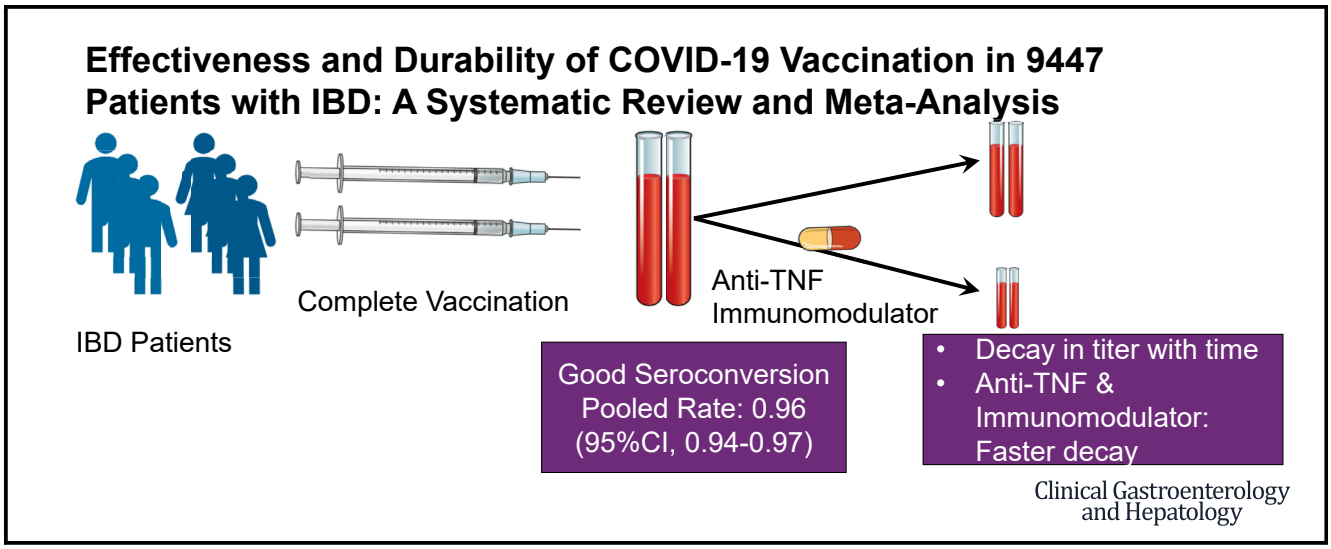
This article has an accompanying continuing medical education activity, also eligible for MOC credit on page e1525. Upon completion of this assessment, successful learners will be able to counsel patients with inflammatory bowel disease about COVID-19 vaccination.



BACKGROUND AND AIMS: The serological responses after severe acute respiratory syndrome coronavirus 2 vaccination may be attenuated in immunocompromised individuals. The study aimed to systematically evaluate the seroconversion rates after complete vaccination for coronavirus disease 2019 (COVID-19) in patients with inflammatory bowel disease (IBD).

METHODS: Electronic databases were searched to identify studies reporting response to COVID-19 vaccination in IBD. Pooled seroconversion rates after complete vaccination were calculated. Subgroup analysis for vaccine types was also performed. Pooled seroconversion rates for various drugs or classes were also estimated. The pooled rates of breakthrough infections in vaccinated IBD patients were estimated. The pooled neutralization rates after complete vaccination were also estimated. The studies reporting durability of titers were systematically assessed.

RESULTS: A total of 46 studies were included. The pooled seroconversion rate for complete vaccination (31 studies, 9447 patients) was 0.96 (95% confidence interval [CI], 0.94–0.97; $I^2 = 90\%$). When compared with healthy control subjects, the pooled relative risk of seroconversion was lower (0.98; 95% CI, 0.98–0.99; $I^2 = 39\%$). The pooled seroconversion rates were statistically similar among various drug classes. The pooled positivity of neutralization assays (8 studies, 771 participants) was 0.80 (95% CI, 0.70–0.87; $I^2 = 82\%$). The pooled relative risk of breakthrough infections in vaccinated IBD patients was similar to vaccinated control subjects (0.60; 95% CI,

Abbreviations used in this paper: AAV, adeno-associated virus; CD, Crohn's disease; CI, confidence interval; COVID-19, coronavirus disease 2019; IBD, inflammatory bowel disease; IMID, immune-mediated inflammatory disease; mRNA, messenger RNA; RR, relative risk; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF, tumor necrosis factor; UC, ulcerative colitis.

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0.25–1.42; $I^2 = 79\%$). Most studies suggested that titers fall after 4 weeks of COVID-19 vaccination, and the decay was higher in patients on anti-tumor necrosis factor alone or combination with immunomodulators. An additional dose of COVID-19 vaccine elicited serological response in most nonresponders to complete vaccination.

CONCLUSIONS: **Complete COVID-19 vaccination is associated with seroconversion in most patients with IBD. The decay in titers over time necessitates consideration of additional doses in these patients.**

Keywords: Ulcerative Colitis; Crohn's Disease; Immunization; Anti-IL12/23; Thiopurines; Infliximab; Adenoviral Associated Virus; mRNA; Decay; Anti-TNF.

Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been the main strategy for the control of coronavirus disease 2019 (COVID-19) pandemic across the globe. A number of vaccines have been approved in different countries. The mechanisms of action of various vaccines differ substantially but the major approved vaccines (messenger RNA [mRNA], adeno-associated virus [AAV], and inactivated) have demonstrated good immune responses and protection from severe disease in clinical trials.[1] However, the clinical trials typically exclude patients with immune-mediated inflammatory diseases (IMIDs) including inflammatory bowel disease (IBD).[2]

IBD is a state of altered immune function—partly owing to the underlying disease and partly to the immune-modifying therapies. A subset of patients with IBD may have worse outcomes in SARS-CoV-2 infection. Vaccination is an important strategy to reduce infections and adverse outcomes due to COVID-19.[3] Previous data have shown that the seroconversion rates in patients with solid organ transplants and malignancies are suboptimal raising concerns about the efficacy of COVID-19 vaccines in immunocompromised individuals.[4,5] A previous systematic review in patients with IMIDs suggested that certain subsets (especially those on B cell–depleting therapies) may be at a risk of inadequate serological response to COVID-19 vaccination. This systematic review had limitations including the fact that it included multiple IMIDs with varying patients and drug therapies.[2] Responses to certain traditional vaccines including influenza and hepatitis B may be attenuated in patients with IBD, especially those on systemic immunosuppression.[6,7] In addition to possibly reduced seroconversion rates with COVID-19 vaccination in IBD, there are concerns about the potential accelerated rate of decay in antibody titers with certain therapies. This may potentially reduce efficacy of the vaccine over time, especially in wake of emergence of newer variants of concern.[8]

A number of studies which report on seroconversion after COVID-19 vaccination in IBD have been published. However, these studies have different populations (type of IBD, drugs treatment) and differing vaccination schedules (single or 2 doses, type of vaccine [ie, mRNA or AAV]). Therefore, we performed a systematic review regarding the efficacy and seroconversion rates with the use of COVID-19 vaccination in IBD to help inform clinical practice in patients with IBD. We also systematically assessed the durability of the antibody responses with time. Further, we assessed the evolving data on responses to an additional dose of COVID-19 vaccination after complete initial series.

Materials and Methods

The present systematic review has been conducted as per the guidance provided by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and the MOOSE group.[9,10]

Search

We searched electronic databases (PubMed and Embase) on January 19, 2022, to identify studies reporting on the seroconversion and efficacy of COVID-19 vaccination in patients with IBD using the keywords "Inflammatory bowel disease," "Crohn's disease," "ulcerative colitis" combined with "SARS-CoV-2," "COVID-19," and "immunisation" and "vaccination." Additional articles were identified by search of preprint servers (bioRxiv, medRxiv, Research Square) and abstracts of various conferences in 2021 and 2022. The detailed search strategy is shown in Supplementary Table 1. All the titles were combined and duplicates were removed. The title and abstract screening were performed by 2 authors (A.J., V.S.) to identify full texts for further screening. The differences were resolved by consensus.

Selection of Studies

We included all studies that reported the use of COVID-19 vaccination in patients having underlying IBD and providing information on the (1) frequency of seroconversion after incomplete or complete COVID-19 vaccination (Supplementary Table 2) with respect to anti-spike antibodies or as determined by neutralization assays; (2) protection from COVID-19 infection after complete vaccination when compared with similarly vaccinated healthy control subjects; (3) T cell responses after COVID-19 vaccination in patients with IBD; (4) decay in antibody titers after complete vaccination; and (5) response to an additional dose (after complete vaccination) of COVID-19 vaccination in patients with IBD.

The studies were included irrespective of the publication type, type of vaccine used, doses of vaccination, or the language of publication. We excluded studies that reported only the mean or median titers of antibodies or did not provide relevant categorical data on seroconversion. The studies reporting on <5 patients, those reporting only data on adverse effects or case series reporting only on the subset who did not have seroconversion were excluded. If the total number of possible events in respect to a particular outcome was <5, the study was excluded from the relevant analysis. For multiple publications out of a single cohort, we used the highest numbers available from the cohort for each analysis.

Data Extraction

The data from studies were extracted on a predefined form that contained information about the vaccine type, number of doses, and the duration after which the response was estimated. We separately extracted data from studies about response after incomplete or complete vaccination. We also extracted the corresponding seroconversion rates for healthy control subjects. For studies that reported the breakthrough infections after complete vaccination in IBD patients, we also extracted data if corresponding data in vaccinated control subjects were provided. We extracted data regarding seroconversion rates after complete vaccination in respect to the current IBD therapies. The positivity rates of neutralization assays were also extracted when available. The T cell response rates were also extracted and qualitatively summarized. The studies reporting measurement of antibody titers at multiple time periods were assessed to look for durability or any decay in the antibody titers. For each of the eligible studies, we also included details regarding the publication (authors, geographic location of study, specific cohort, type of publication), underlying IBD (numbers, age, sex, ulcerative colitis, or Crohn's disease), and current drug treatment.

Outcomes

We estimated the pooled seroconversion rates (positivity of anti-spike or anti-receptor binding domain antibodies as defined in individual studies) after COVID-19 vaccination in IBD. We calculated seroconversion rates after incomplete or complete vaccination depending on the type of vaccine. The pooled relative risk (RR) for seroconversion in IBD patients as compared with healthy control subjects calculated. The overall pooled seroconversion rates were also calculated for each of the drug types separately by pooling data from relevant studies. We made a pooled estimate only if at least 3 studies with a minimum of 5 participants reported the seroconversion rates for a particular therapy. The pooled breakthrough infection rates in completely vaccinated IBD patients was calculated and pooled RR in comparison with vaccinated control subjects was also determined. We also calculated the pooled positivity of neutralization assays in patients with IBD and RR of neutralization positivity as compared

What You Need to Know

Background

We searched PubMed, Embase, conference abstracts, and preprint servers for previous meta-analyses on responses to coronavirus disease 2019 (COVID-19) vaccination in patients with inflammatory bowel disease (IBD). We identified 2 systematic reviews and meta-analyses that focused on seroconversion in patients with immune mediated inflammatory diseases but none in the setting of IBD. These systematic reviews identified certain therapies that could attenuate responses to COVID-19 vaccination including B cell–depleting agents and ant-CTLA-4 agents. These agents are, however, not typically used in IBD.

Findings

Our study provides the first estimates on the seroconversion rates after complete COVID-19 vaccination in IBD patients. Through this systematic review, comprising 46 studies, we report about the pooled seroconversion rates, positivity of neutralization assays, and breakthrough infections in IBD patients and compare them with the control groups. Based on 31 studies with 9447 participants, the overall seroconversion after complete vaccination was good (0.96; 95% confidence interval, 0.94–0.97) but slightly lower than that of the control subjects (0.98; 95% confidence interval, 0.98–0.99). The positivity of neutralization assays was lower in IBD patients as compared with the control subjects. Certain drugs like steroids and combination of anti-tumor necrosis factor (TNF) with immunomodulators were associated with numerically (but not statistically) lower rates of seroconversion in contrast to excellent seroconversion amongst patients on no treatment or those on anti-TNF alone, vedolizumab, ustekinumab, or JAK inhibitors. The studies reporting on durability suggested that titers begin declining 4 weeks after complete vaccination, and the decay may be faster with anti-TNF, immunomodulators, and combination of these 2.

Implications For Patient Care

Our findings suggest that complete COVID-19 vaccination has good seroconversion in patients with IBD. However, durability of these responses is a concern, especially with anti-TNF and immunomodulators. In the subset of nonresponders to initial series of complete vaccination, an additional dose helps achieve serological response in most of them.

with the control population. The presence of neutralizing antibodies was as per the definitions used in individual studies.

Data Analysis

We used R statistical software version 4.0.1 for the analysis and used the meta and metafor packages in addition to the base package.[11] We used the random effects model with inverse variance approach to report the pooled seroconversion rates and Mantel and Haenszel method for the pooled RR. Logit transformations were made for the individual seroconversion rate before computing pooled summary. I^2 and P values were used for the assessment of heterogeneity. We planned to address any significant heterogeneity (>50%) using subgroup analysis for the vaccine type. We also planned to use the Baujat plot to identify studies contributing to heterogeneity and if a biologically plausible reason could explain the heterogeneity and guide a subgroup analysis.

Assessment of Risk of Bias

Two investigators made independent assessments of methodological rigor and risk of bias in the included studies using the relevant Joanna Briggs Institute Critical Appraisal Checklist. The Joanna Briggs Institute tool for prevalence studies was used to assess the studies that described the response to vaccines without any control group or any comparison with a nonvaccinated cohort.[12] This includes assessment of appropriateness of the included population, and the sampling, description of subjects, and if vaccine response was assessed appropriately and similarly in all individuals. The appraisal tool for cohort studies was used in studies in which control groups were present, and the tool included questions about similarities in groups and assessment of exposure (vaccine) and outcomes (response to vaccine).[13] Publication bias was assessed using a funnel plot and the Egger test.[14]

Results

Study Selection

Of the 617 records identified after database search, 128 were duplicates. Of the 489 titles which underwent initial screening, 449 were removed for various reasons and 40 articles underwent full text screening. An additional 27 articles were identified from conference abstracts. Eventually, 46 articles were included in the meta-analysis. The full PRISMA flow chart of study selection is depicted in Figure 1. Table 1 shows the details of the 46 included studies with the study type, type of population and the information provided.[15–60]

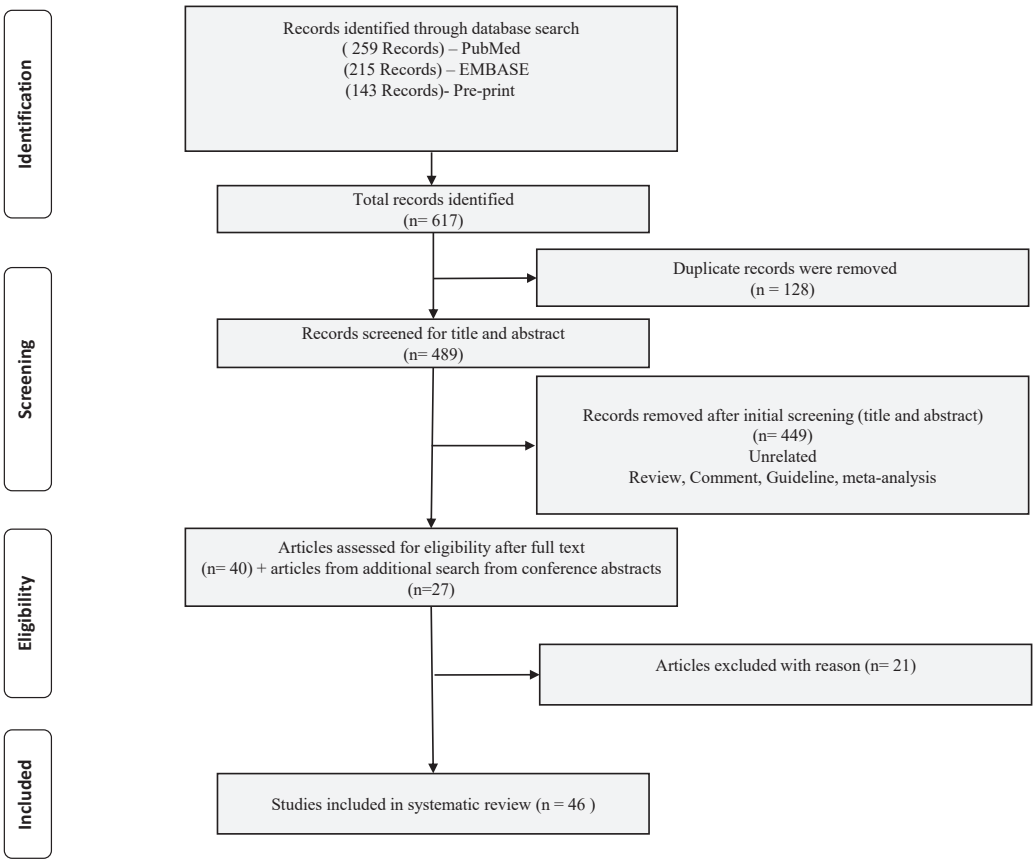

Figure 1. PRISMA flowchart showing the process of screening and selection of studies

Table 1. Characteristics of Studies Included in the Meta-Analysis Along With Details on Participants and Vaccination

Author	Type	Country	Vaccine	Number of Patients	Age and Sex	Response	Response With Various Drugs	Response Tested at	Definition of Response	Factors Associated With Low Response	Durability	Number With Neutralization	Breakthrough Infections
Alexander et al (VIP)[15]	Abstract	United Kingdom	mRNA and AAV (2 doses of ChAdOx1 nCoV-19, BNT162b2 or mRNA1273)	IBD (n = 357) Control subjects (n = 90)	—	—	Anti TNF (44/49), Anti-TNF + thiopurine (49/56), anti-integrin (50/50), ustekinumab (47/49), JAK inhibitor (19/19), thiopurine (64/64)	53–92 d after second vaccine dos	Ab responses (defined cutoff anti-S concentration 15 U/mL, which correlated with 20% viral neutralization)	Antibody responses are significantly reduced with infliximab, or tofacitinib and to a lesser extent with ustekinumab	—	—	—
Ben-Tov et al[16]	Research Letter	Israel	mRNA Second dose complete vaccination	IBD (n = 12,213) (UC: 6339, CD: 5422, Unspecified: 452) Control (36,254)	Mean age 47 ± 17 y in both groups 50.0% female in both groups	—	—	—	—	—	—	—	IBD: 23/12,213, Control subjects: 55/36,254
Caldera et al (HERCULES)[17]	Brief communication	United States	mRNA Pfizer (n = 60) Moderna (n = 62) complete vaccination	IBD (n = 122) (CD: 85, UC: 37) Control subjects (n = 60)	Median : 40 (33–52) y Male: 64 (22%)	IBD: 118/122, Control subjects: 60/60	—	28–35 d after second dose in patients 30 d in healthy control subjects	Spike protein S1 receptor-binding domain– specific IgG antibodies	Immune-modifying therapy had lower antibody concentrations compared with no treatment/5-ASA/vedolizumab	—	—	—
Cerna et al[18]	Original article	Czech	mRNA BNT162b2 (n = 101), mRNA CX-024414 (n = 212) and vector ChAdOx1 nCoV-19 (n = 189)	IBD (n = 602) (CD: 415, UC: 187) Control (n = 168)	Median age: 38.5 (22;49.5) y, Females (n = 365) Median age: 42.0 (26.5–51.9) y, females (n = 92)	IBD: 450/461 Control (128/128)	—	8 wk after second dose	Detection of serum anti-SARS-CoV-2 IgG antibodies by chemiluminescent microparticle immunoassay	TNF-α inhibitors with concomitant immunosuppressive treatment Median anti-SARS-CoV-2 IgG levels were lower with ChAdOx1 nCoV-19 compared with other vaccines	—	—	—

Table 1. Continued

Author	Type	Country	Vaccine	Number of Patients	Age and Sex	Response	Response With Various Drugs	Response Tested at	Definition of Response	Factors Associated With Low Response	Durability	Number With Neutralization	Breakthrough Infections
Chen et al (COVARIPAD)[19]	Original article	United States	mRNA complete vaccination	IBD (n = 31): CD-all, Control (n = 25)	—	—	—	3 mo after second dose	—	—	—	IBD: 19/31, Control subjects: 23/25 tested against delta strain	—
Charilaou et al[20]	Research letter	United States	mRNA (BNT162b2 n = 111, mRNA-1273 n = 65) complete vaccination	IBD (n = 195) Control subjects (n = 128)	—	IBD: 172/176 Control subjects: 128/128	—	126 d (89: 162)	—	Anti-TNF ± IMM had lower titres than vedolizumab/ ustekinumab/ 5-ASA/ budesonide/ no treatment	Significant decay observed in group 2 (anti-TNF ± immuno-modulators) Significantly faster than group 1 (vedolizumab/ ustekinumab/ mesalamine/ budesonide/ no therapy)	—	IBD: 1/176
Classen et al (COKA)[21]	Original article	Germany	Mixed Pfizer (n = 64), Moderna (n = 4), AstraZeneca (n = 1) complete vaccination	IBD (n = 72)	Mean age: 48.4 ± 15.236 y Females (n = 38)	IBD: 61/61 (mRNA)	—	56.4 ± 31.485 d	Presence of IgG SARS-CoV2 antibodies against RBD-S protein using immunoassays Elecsys Anti-SARS-CoV-2S (Roche Diagnostics)	Elderly have poor response	—	—	—
Dailey J et al[22]	Original article	United States	mRNA (n = 28), AAV (n = 5) complete vaccination	IBD (n = 33)	Mean age 17 y, range 2–26 y, 58% male	IBD: 33/33	Anti-TNF: 22/22, Anti-TNF+IMM: 3/3, vedolizumab: 4/4	3.1 wk (range, 1.6–3.6 wk)	SARS-CoV-2 S-RBD IgG antibodies	—	—	Pseudo-type virus neutralization assay Seen in 33 of 33 patients	0/33
Deepak et al (COVARIPAD)[23]	Original article	United States	mRNA (n = 43+53) complete vaccination	IBD (n = 43) (UC: 18, CD: 21) Control subjects (n = 53)	—	IBD: 42/43 (UC: 18/18 CD: 20/21) Control subjects: 53/53	No drug: 16/16, Steroids: 1/1, Anti-TNF: 10/11, Anti-TNF + thiopurines: 2/2, JAK inhibitor: 2/3, Thiopurines: 3/3	within 14 d after vaccination	Detection of Anti–SARS-CoV-2 spike (S) IgG^{+} binding using ELISA	—	—	—	—
Doherty et al (VARIATION)[24]	Abstract	Ireland	Mixed	IBD (n = 270) Control subjects (n = 116)	—	IBD: 265/270 Control subjects: 116/116	—	—	—	viral-vector vaccine use and anti TNF use	IgG SP antibody levels reduced rapidly during follow-up	—	—

Table 1. Continued

Author	Type	Country	Vaccine	Number of Patients	Age and Sex	Response	Response With Various Drugs	Response Tested at	Definition of Response	Factors Associated With Low Response	Durability	Number With Neutralization	Breakthrough Infections
Edelman-Klapper et al (RECOVER)[25]	Original article	Israel	mRNA first dose (Pfizer) mRNA complete vaccination (Pfizer)	IBD (n = 185): UC: 53 and CD: 122, IBDU: 1, Control subjects (n = 73)	Mean age IBD 37.9 ± 14.3 y and control 36.6 ±12.4 y, Males: 60.6% IBD and 27.4% in control group	IBD: 172/185, Control subjects: 73/73 IBD: 185/185, (UC: 53/53 CD: 122/122) Control subjects: 73/73	— No treatment: 38/38, steroid (8/8), anti-TNF (67/67), anti-integrin (26/26), ustekinumab (5/5), JAK (3/3), 5-ASA (42/42)	21 (IQR, 20-21) d 30 (IQR 28–33) d	binding IgG antibodies to SARS-CoV-2 spike (S) antigen	—	—	— IBD: 161/179, Control subjects: 68/70	IBD: 3/185 Control subjects: 2/73 IBD: 3/182, Control subjects: 2/73
Frey S et al[26]	Original article	United States	mRNA complete vaccination	IBD (n = 75)	Median age of 45 (IQR, 38–58) y 55 were female	IBD: 75/75 Low positive: 16/75 High positive: 59/75	Thiopurine (11/11), TNF inhibitor: 24/24, JAK inhibitor: 2/2, vedolizumab: 6/6, ustekinumab: 17/17, steroid: 17/17, budesonide: 6/6, Anti-TNF + thiopurine: 6/6	179 (165, 202) d	Roche Elecsys anti-RBD pan Ig >0.8 units/mL for seroconversion Low-positive antibody response >anti-RBD pan Ig 0.8–50 units/mL. High-positive antibody response : anti-RBD pan Ig >50 units/mL.	—	Most patients (37/45) with high antibody response at 1 mo, maintained high antibody response at 6 mo	—	IBD: 1/75 reported at 2 mo after second dose
Garrido et al[27]	Letter to editor	Portugal	mRNA AAV	IBD (n = 115) (UC: 26, CD: 89)	Median age of 51 (IQR, 38–59) y Female (n = 60)	IBD: 85/87, I BD: 21/28	Anti-TNF: 76/83, Anti-integrin: 14/14, Ustekinumab: 16/18	61 (IQR, 44–76) d after complete vaccination	Anti-RBD >10 and/or Anti-spike Ab >10 IU/mL	—	—	—	—
Kappelman et al (PREVENT)[28]	Abstract	United States	Mixed third dose	IBD (n = 659)	—	After second dose: IBD: 613/659 After third dose- IBD: 656/659	—	— 6 wk	—	—	—	—	—

Table 1. Continued

Author	Type	Country	Vaccine	Number of Patients	Age and Sex	Response	Response With Various Drugs	Response Tested at	Definition of Response	Factors Associated With Low Response	Durability	Number With Neutralization	Breakthrough Infections
Kappelman et al (PREVENT)[29]	Original article	United States	mRNA 2 doses Pfizer (1123) Moderna (692) AAV (JJ) 1 dose	IBD-mRNA group (n = 1815) UC: 469, CD: 1050 IBD AAV group (n = 94) UC: 25, Unclassified: 9, CD: 60	Mean age :44 y Female (n = 1332) Mean age: 43.5 y Female (54/63)	IBD mRNA: 1748/1815 UC: 459/469, CD: 1005/1050 IBD AAV: 76/94 UC: 19/25, Unclassified: 7/9, CD: 50/60	No treatment: 114/117, steroids: 71/77, anti-TNF: 634/660, anti-TNF+IMM: 176/202, IMM: 158/160, 5-ASA: 385/391, budesonide (69/74), vedolizumab:210/212 ustekinumab:270/272 tofacitinib: 29/30 Steroids: 1/4, Anti-TNF: 24/31,Anti-TNF+IMM: 5/8, IMM: 4/4, 5-ASA: 18/23, budesonide:4/6, vedolizumab:10/12 ustekinumab:17/18 tofacitinib: 1/2	67.2 d after mRNA 2 doses 91.3 d after 1 dose	Anti-receptor binding domain IgG antibodies at 8 wk after second dose LabCorp Cov2Quant IgG assay. Results of 1.0 μg/mL (lower limit of quantitation) or greater suggest vaccination	Older patients, anti-TNF and immuno-modulator	—	—	—
Kennedy et al (CLARITY 1)[30]	Original Article	United Kingdom	mRNA AAV First dose	IBD -mRNA group (n = 589), IBD-AAV group (n = 704)	43.8 (32.8–57.6) y Males: 50.7% (653/1288)	IBD mRNA : 262/589, IBD AAV: 232/704	Infliximab: 103/328, vedolizumab: 218/330, infliximab + thiopurine: 125/537, vedolizumab + thiopurine: 48/98	3–10 wk	Seroconversion rates (a cutoff of 15 U/mL)	—	—	—	—
Khan et al[31]	Abstract	Qatar	mRNA complete vaccination (Pfizer)	IBD (n = 469) Control subjects (n = 465)	—	—	—	—	—	—	—	—	IBD: 6/469 Control subjects: 40/465
Khan et al[32]	Original article	United States	mRNA complete vaccination Pfizer (n = 2873) Moderna (n = 3380)	IBD (n = 6253)	—	—	—	—	—	—	—	—	IBD: 7/6253

Table 1. Continued

Author	Type	Country	Vaccine	Number of Patients	Age and Sex	Response	Response With Various Drugs	Response Tested at	Definition of Response	Factors Associated With Low Response	Durability	Number With Neutralization	Breakthrough Infections
Knezevic et al[33]	Abstract	Serbia	mRNA (Pfizer), Vero cell Vaccine and SPUTNIK V Gam-COVID-Vac	IBD (n = 328) UC: 125 CD: 202	Mean age 55.7 ± 15.1 y Males (n = 176)	IBD: 110/160	Vedolizumab: 34/63, anti-TNF: 52/98	—	ELISA anti-spike protein-based serology (INEP, Belgrade, Serbia) with cutoff level of, 15 as negative, 15–20 intermediate, and >20 as positive	—	—	—	—
Levine et al[34]	Letter to editor	United States	mRNA second dose (Pfizer: 11, Moderna: 8)	IBD (n = 19)	Mean age: 50 (27–80) y Females: 47%	IBD: 18/19	Anti-TNF: 9/10, anti-integrin: 2/2 JAK inhibitor: 1/1, 5-ASA: 0/1, Thiopurine: 1/1	—	ELISA assay for both the COVID-19 nucleocapsid and spike domain antibodies (Roche) >0.80 U/mL indicating positive results.	—	—	—	—
Lev-Tzion et al[35]	Original article	Israel	mRNA complete vaccination	IBD (n = 4946) CD: 2447 UC: 2499 Control subjects (n = 4946)	Mean age 51 ± 16 y, male (n = 2412) Mean age 51 ± 16) y Males (n = 2412)	—	—	—	—	—	—	—	IBD: 15/4946 Control subjects: 15/4946
Li et al[36]	Preprint	United States	mRNA both doses Pfizer (n = 90), Moderna (n = 68)	IBD (n = 158)	Females (n = 88)	T cell response matrices, mean Clonal breadth: 2.03e-04 ± 1.55e-04 Clonal depth: 76.13 ± 111.82 Clonal breadth spike: 5.04e-05 ± 6.74e-05 Clonal depth spike: 5.86 ± 41.77	—	—	—	Reduced T cell clonal depth was associated with chronologic age, male sex, and immuno-modulator treatment	—	—	—

Table 1. Continued

Author	Type	Country	Vaccine	Number of Patients	Age and Sex	Response	Response With Various Drugs	Response Tested at	Definition of Response	Factors Associated With Low Response	Durability	Number With Neutralization	Breakthrough Infections
Lin S et al (CLARITY 2)[37]	Preprint	United Kingdom	mRNA, 2 doses AAV 2 doses	IBD-mRNA group (n = 1327), IBD-AAV group (n = 1983)	39.8 (30.9–49.7) y Females: 41.8% (118/282)	IBD-mRNA group: 1277/1327 T cell response: 54/67 IBD-AAV group: 1886/1983 T cell response: 45/56	Infliximab: 347/356, infliximab + thiopurine: 525/558, vedolizumab: 328/335, vedolizumab + thiopurine: 77/78 Infliximab: 557/596, infliximab + thiopurine: 716/769, vedolizumab: 479/483, vedolizumab + thiopurine: 479/483	2–10 wk	Seroconversion threshold of 15 U/mL following 2 doses of SARS-CoV-2 vaccine	—	Half-lives shorter in patients with infliximab than vedolizumab, after -mRNA group; 26.8 d (95% CI, 26.2–27.5] vs 47.6 d (45.5–49.8], $P < .0001$ -AAV group; 35.9 d (34.9 –36.8] vs 58.0 d (55.0–61.3], P value $<.0001$)	—	After >2 wk after second dose (infliximab: 202/3467, vedolizumab: 66/1691)
López Marte et al[38]	Abstract	Puerto Rico	mRNA (Pfizer and Moderna)	IBD (n = 32) Control subjects (n = 32)	—	IBD: 32/32 Control subjects: 18/18	Anti-TNF: 17/17, vedolizumab:4/4, ustekinumab: 5/5 Anti TNF + thiopurine: 1/1	2 wk 6 wk	Anti-spike protein RBD IgG levels SARS-CoV-2 surrogate virus neutralization test >30% is positive for effective viral inhibition	—	—	>60% neutralizing antibody detection after 14 and 60 d of the second vaccine dose	—
Martin Arranz et al[39]	Abstract	Spain	Mixed Pfizer (n = 154), Astra Zeneca (n = 80), Moderna (n = 19), Janssen (n = 13)	IBD (n = 252)	Females (n = 134)	IBD: 233/252	—	2–4 wk	Detection in Siemens Atellica Anti-SARS-CoV-2 (N) and Vircell Virclia (S and N) electro-chemilumine scence immunoassay	Immuno-suppressive or biologic drugs (except vedolizumab) and Ad26.CoV2.S (Janssen) vaccine	—	—	—
Mayorga Ayala et al[40]	Abstract	Spain	mRNA	IBD (n = 148)	—	IBD: 148/148 T cell response: 129/148	Anti-TNF: 57/57, anti-TNF+IMM: 53/53, IMM: 38/38	6 ±2 wk	Positive Antibodies to the Spike (S) SARS-CoV-2 protein were analyzed by CLIA	—	—	—	—

Table 1. Continued

Author	Type	Country	Vaccine	Number of Patients	Age and Sex	Response	Response With Various Drugs	Response Tested at	Definition of Response	Factors Associated With Low Response	Durability	Number With Neutralization	Breakthrough Infections
Melmed et al (CORALE)[41]	Brief communication	United States	mRNA second dose (Pfizer: 342 Moderna: 240)	IBD (n = 552) (UC: 197, CD: 385)	Mean age: 44.4 (14.6) y, Male: 34.3%	IBD: 545/552	Vedolizumab: 75/76, ustekinumab: 113/114, JAK inhibitor: 7/7, IMM: 12/12, no treatment: 85/87, steroids: 26/27, anti-TNF: 175/175, anti-TNF+IMM: 49/49	2 (14–29 d) wk	IgG(S) and IgG(N) using the SARS-CoV-2 IgG-II and SARS-CoV-2 IgG assays, respectively (Abbott Labs). IgG(S) level >50 AU/mL positive result.	—	After dose 2, GMT: 2042 (1348–3090); 2 wk after GMT: 10,233 (7762–13,490), 8 wk after GMT: 3236 (2818–2715) 16 wk after, GMT: 1445 (1148–1820)	—	—
Otten et al[42]	Abstract	Netherlands	Mixed	IBD (n = 312) UC: 140 CD: 172	—	IBD: 307/312		2–10 wk	Anti-SARS-CoV-2 spike (S) antibody concentrations, measured using CMIA Titer of >50 AU/mL	TNF and steroid use			
Pozdnyakova et al (CORALE)[43]	Research Letter	United States	Double doses of mRNA AAV	IBD-mRNA (n = 264), IBD-AAV group (n = 10)	mean age, 51 y, 62% were female)	IBD-mRNA: 263/264, IBD-AAV: 9/10	—	2 wk (14–29 d)	Positive anti-Spike IgG value (>50 AU/mL) at least 2 wk after regimen completion.	—	—	—	—
Quan et al[44]	Abstract	Canada	Mixed Pfizer (n = 275), Moderna (n = 51), Astra Zeneca (n = 7)	IBD (n = 464) UC/indeterminate: 128 CD: 336	Mean age: 49.9 (14.7) y, Males (n = 215)	IBD: 278/283 IBD: 82/87	No treatment: 32/32, vedolizumab: 47/48, ustekinumab: 66/66, Anti TNF: 95/97, IMM: 15/15, Anti-TNF+IMM: 31/33, Steroids: 4/7	2: 8 wk 8–18 wk	Seroconversion defined as IgG levels of >50 AU/mL	—	GMT levels significantly increased ($P < .0001$) from first dose (1679 AU/mL) to second dose at 2–8 wk (7943 AU/mL) but fell significantly (<.0001) to 3565 AU/mL at 8–18 wk	—	—

Table 1. Continued

Author	Type	Country	Vaccine	Number of Patients	Age and Sex	Response	Response With Various Drugs	Response Tested at	Definition of Response	Factors Associated With Low Response	Durability	Number With Neutralization	Breakthrough Infections
Rabinowitz et al (RECOVER)[45]	Abstract	Israel	mRNA	IBD (n = 130) Control (n = 60)	—	—	—	176 d (IQR, 166–186)	—	—	Serologic response at 176 (IQR, 166–186) d and compared with, 4 wk after, first dose significantly declined in all 3 groups, but was lowest in the anti-TNFα group	—	—
Reuken et al[46]	Original Article	Germany	Mixed single dose	IBD (n = 28), (UC: 10,CD: 17, IBD unclassified: 1) Control (n = 27)	median age: 42 y	IBD: 20/28, Control subjects: 23/27	—	3 wk	Liaison SARS-CoV-2 Trimerics IgG CLIA on the LiaisonXL (DiaSorin, Saluggia, Italy)	—	—	—	—
			mixed double dose	IBD (n = 12), Control subjects (n = 12)		IBD: 11/12, Control subjects: 12/12	—		Cut-off of 33.8 BAU/mL	—	—	—	—
Rodríguez-Martinó et al[47]	Original article	Puerto Rico	mRNA first dose	IBD (n = 17) (CD: 17, UC: 7), Control (n = 21)	—	IBD : 12/17, Control subjects: 21/21	—	2 wk	Detectable SARS-CoV-2 IgG antibodies	—	—	Neutralization seen in all IBD and control patients	—
			mRNA second dose	IBD (n = 19), Control (n = 21)	Mean age: 34 y (22–59), Males: 10	IBD: 19/19, Control (21/21)	Anti-TNF: 18/18, Thiopurine: 1/1			—	—		—
Schell et al (HERCULES)[48]	Preprint	United States	mRNA complete vaccination, Pfizer (n = 48) Moderna (n = 37) Third dose Pfizer (n = 72), Moderna (n = 67)	IBD (n = 139) UC: 43 CD: 96 IBD (n = 85) UC: 30 CD: 55	Median age = 41 (34–52) y, Males (n = 71) Median age = 48 (38–60) y, Males (n = 38)	After second dose IBD: 135/139 After third dose IBD: 85/85	—	28–35 d after complete vaccination 28–65 d after third dose	Detectable antibody concentrations: SARS-CoV-2 anti-spike IgG	—	—	—	—
Shehab et al[49]	Original article	Kuwait	mRNA complete vaccination	IBD (n = 58) CD seen in 60% cases Control (n = 58)	Mean age: 33.2 y, Males: 56%	IBD: 47/58, Control subjects: 58/58	Anti-TNF + thiopurine: 47/58	4–10 wk	SARS-CoV-2–specific IgG antibodies measured by SERION ELISA Values >31.5 BAU/mL positive	—	—	IBD: 43/58, Control subjects: 58/58	—

Table 1. Continued

Author	Type	Country	Vaccine	Number of Patients	Age and Sex	Response	Response With Various Drugs	Response Tested at	Definition of Response	Factors Associated With Low Response	Durability	Number With Neutralization	Breakthrough Infections
Shehab et al[50]	Original article	Kuwait	First dose mRNA or AAV Second dose mRNA AAV	IBD (n = 24) IBD-mRNA group (n = 77), IBD-AAV group (n = 25)	mean age: 31 y; male : 60%	IBD: 18/24 IBD-mRNA (64/77), IBD-AAV (19/25)	- Anti-TNF: 57/75, Anti-integrin: 13/14, Ustekinumab: 13/13	3–6 wk after first dose 4–10 wk after second dose	SARS-CoV-2–specific IgG antibodies measured by SERION ELISA Values >31.5 BAU/mL positive	— —	— —	— IBD-mRNA: 60/77, IBD-AAV: 18/25	— —
Simon et al[51]	Original article	Germany	mRNA complete vaccination	IBD (n = 8), Control (n = 182)	—	IBD: 182/182, Control subjects: 8/8	—	39 d	IgG antibodies against the S1 domain of the spike protein of commercial ELISA from Euroimmun (Lübeck, Germany) A cutoff of ≥0.8 (OD 450 nm): positive.	—	—	—	—
Spencer et al[52]	Original article	United States	Mixed Complete vaccination	IBD (n = 20) (CD: 15, UC: 5)	Median age: 18 (17–20) y, Male: 60%	IBD: 20/20 UC: 5/5 CD: 15/12	Anti-TNF: 9/9, Ustekinumab: 10/10, JAK inhibitor: 2/2	14–37 d	Semiquantitative SARS-CoV-2 IgG antibody assay, ELISA measuring IgG antibody to spike protein >5–15 AU/mL	—	—	—	—
Viazis et al[53]	Abstract	Greece	mRNA complete vaccination (Pfizer)	IBD (n = 2940)	—	—	—	—	—	—	—	—	IBD: 46/2940 CD: 32 UC: 14
Vollenberg et al[54]	Original article	Germany	mRNA Pfizer (n = 89) Moderna (n = 6)	IBD (n = 95) UC: 35 CD: 60 3 mo cohort IBD (n = 60) Control subjects (n = 11) At 6 mo IBD (n = 4) Control subjects (n = 7)	Median age: 46 (IQR, 33–55) y Males (n = 50)	At 3 mo IBD: 59/60 Control subjects: 11/11 At 6 mo IBD (3/4) Control subjects (7/7)	At 3 mo Anti TNF: 33/33, vedolizumab: 9/10, ustekinumab: 11/11	3 mo 6 mo	IgG assay (Abbott Diagnostics, Wiesbaden, Germany). Values at or above the cutoff (50.0 AU/mL) denoting seropositivity	—	At 3 mo, Sero-conversion rate IBD (59/60) Control (11/11) At 6 mo, sero-conversion rate IBD (3/4) Control (7/7)	—	—
Watanabe et al (J-COMBAT)[55]	Abstract	Japan	mRNA Pfizer (n = 476) Moderna (n = 69) Pfizer: 86.9%, Moderna: 12.1%	IBD (n = 679) CD: 261 UC: 418 Control subjects (n = 203)	Female (n = 323) Females (n = 156)	—	—	4 wk	—	Age and most immuno-modulators	—	—	IBD: 4/679 Control subjects: 2/203

Table 1. Continued

Author	Type	Country	Vaccine	Number of Patients	Age and Sex	Response	Response With Various Drugs	Response Tested at	Definition of Response	Factors Associated With Low Response	Durability	Number With Neutralization	Breakthrough Infections
Wagner et al[56]	Preprint	Austria	mRNA complete vaccination Pfizer (n = 128), Moderna (n = 2)	IBD (n = 130) Control subjects (n = 66)	—	IBD: 130/130 Control subjects: 66/66	Mean age: 44.0 ± 14.4; (19–77) y, Females (n = 61) Mean age: 46.1 ± 15.1 y (20–78) y Females (n = 33)	4 wk	SARS-CoV-2–specific IgG antibodies S1 by ELISA (Quantivac, Euroimmun) iAntibody values above 35.2 BAU/mL were considered as positive	Anti-TNF	—	—	—
Weaver et al (PREVENT)[57]	Full article	United States	mRNA complete vaccination	IBD (n = 3080)	—	—	—	—	—	—	—	—	IBD: 6/3080
Wong et al (ICARUS)[58]	Brief Commu-nication	United States	mRNA complete vaccination	IBD (n = 48) CD: 23 UC: 25	Mean age : 49.1 (20.2) y, Females (n = 25)	IBD: 26/26	No treatment: 4/4, anti-TNF: 8/8, Anti-integrin: 12/12, ustekinumab: 2/2,	2–85 d	Total antibodies to the SARS-CoV-2 RBD of the S protein, and the Q9 EUA sCOVG is a semiquantitative assay for anti-RBD: index value of 1 equals a positive	—	—	—	IBD: 3/48 for 1-dose vaccine
Zacharopoulou et al[59]	Abstract	Greece	mRNA complete vaccination Pfizer (n = 340), Moderna (n = 150 AAV Complete vaccination AstraZeneca (n = 41), JJ (n = 6)	IBD (n = 403) IBD (n = 47)	Median age: 45 (35–56) y, Females (n = 188)	IBD: 351/355 IBD: 44/47	—	31 (IQR, 23–46) d	Anti-S1 IgG ≥11 RU/mL	Age, time since vaccination, and anti-TNF-α therapy	—	—	—

Table 1. Continued

Author	Type	Country	Vaccine	Number of Patients	Age and Sex	Response	Response With Various Drugs	Response Tested at	Definition of Response	Factors Associated With Low Response	Durability	Number With Neutralization	Breakthrough Infections
Zhang et al[60]	Abstract	Australia	Mixed Pfizer (n = 84) Oxford AstraZeneca (n = 4)	IBD (n = 88) UC: 28 CD: 60 Control subjects (n = 53)	—	IBD (88/88) Control subjects (53/53)	5-ASA: 6/6, IMM: 6/6, Anti-TNF: 14/14, TNF+IMM: 32/32, vedolizumab: 13/13, ustekinumab: 16/16, tofacitinib: 1/1	21–42 d after second dose	Antibodies to the S1/2 IgG subunit and RBD were measured	—	Mean anti-S1/2 antibody concentrations at 4 wk after second vaccination (V3) were significantly lower in IBD TNF treated patients (162.6± 1.7) compared with IBD non TNF treated patients (325.2± 1.3), and healthy control subjects	—	—

5-ASA, 5-aminosalicylates; AAV, adeno-associated virus; CD, Crohn's disease; CIMA, chemiluminescence microparticle immunoassay; ELISA, enzyme-linked immunosorbent assay; GMT, geometric mean titer; IBD, inflammatory bowel disease; mRNA, messenger RNA; RBD, receptor-binding protein; TNF, tumor necrosis factor; UC, ulcerative colitis.

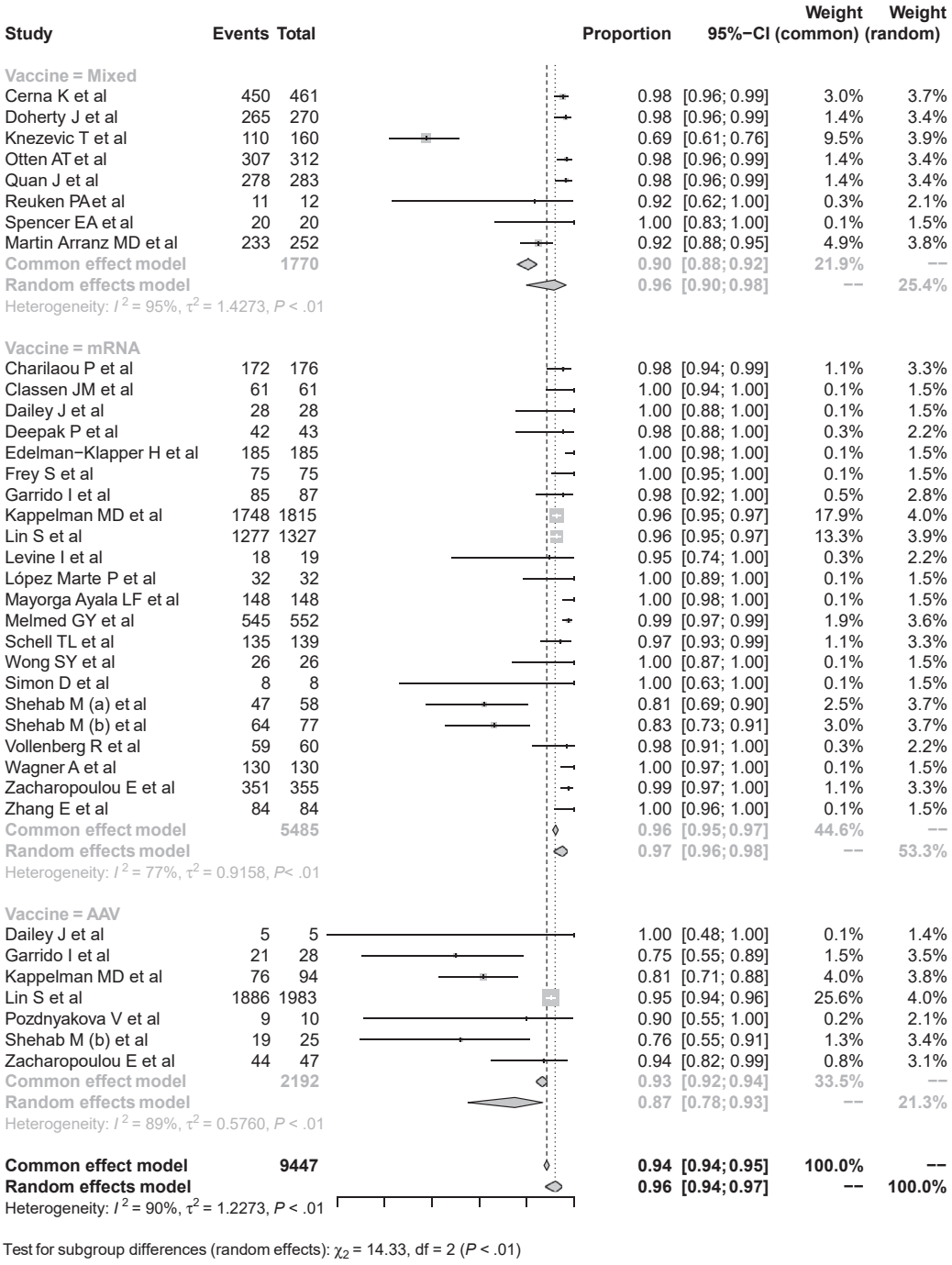

Figure 2. Forest plot depicting the pooled seroconversion rates after complete COVID-19 vaccination in patients with IBD

Supplementary Table 3 shows the excluded studies with reasons of exclusion.

Seroconversion After COVID-19 Vaccination

For the seroconversion after complete vaccination (Supplementary Table 2) of COVID-19 vaccination there were 31 eligible studies (9447 participants) reporting the serological response. The pooled seroconversion rate was 0.96 (95% confidence interval [CI], 0.94–0.97; I^2 = 90%) (Figure 2). When the subgroup analysis was done for the vaccine subtype, there were 22 studies (5485 participants) reporting about efficacy of mRNA vaccine. The pooled seroconversion rate after complete mRNA vaccination was 0.97 (95% CI, 0.96–0.98; I^2 = 77%). The pooled seroconversion rate after complete AAV vaccine (7 studies: 2192 participants) was lower (0.87; 95% CI, 0.78–0.93; I^2 = 89%) (Figure 2). The pooled seroconversion rates after complete vaccination with Pfizer, Moderna, Johnson and Johnson (Ad26.COV2.S), and AstraZeneca were 0.96 (95% CI, 0.93–0.98; I^2 = 77%), 0.98 (95% CI, 0.97–0.99; I^2= 0), 0.78 (95% CI, 0.65–0.88; I^2 = 23%), and 0.90 (95% CI, 0.72–0.97; I^2 = 86%),

respectively (Supplementary Figure 1). When compared with the healthy control subjects, the pooled RR (12 studies, 830 control subjects and 1469 IBD patients) of seroconversion in patients with IBD after complete COVID vaccination was lower (0.98; 95% CI, 0.98–0.99; $I^2 = 39\%$) but was similar for mRNA vaccine on subgroup analysis (0.99; 95% CI, 0.97–1.00; $I^2 = 50\%$) (Supplementary Figure 2). The definitions of seroconversion and the assays used in individual studies were variable and are shown in Supplementary Table 4.

For incomplete vaccination, there were 8 studies (2030 participants) that reported seroconversion after incomplete COVID-19 vaccination in patients with IBD. The pooled seroconversion rate was 0.76 (95% CI, 0.57–0.88; $I^2 = 98\%$) (Supplementary Figure 3). The pooled RR of seroconversion after incomplete COVID vaccination was lower in the IBD patients as compared with healthy control subjects (0.94; 95% CI, 0.89–0.99; $I^2 = 55\%$) (Supplementary Figure 4).

Neutralization Response After COVID-19 Vaccination

Overall, there were 8 studies (771 participants) that reported the positivity of neutralization assays after complete COVID vaccination. The pooled positivity rates were 0.80 (95% CI, 0.70–0.87; $I^2 = 82\%$) (Supplementary Figure 5). When compared with healthy control subjects, the positivity of neutralization assays post complete vaccination were lower in the IBD group (pooled RR, 0.85; 95% CI, 0.75–0.96; $I^2 = 77\%$) (Supplementary Figure 6). The definitions of positivity of neutralization assays with the duration at which they were measured as reported in individual studies are shown in Supplementary Table 5.

Seroconversion in Patients Stratified by Therapies

The pooled response rate after complete COVID-19 vaccination in IBD patients who were not on any treatment was 0.98 (95% CI, 0.95–0.99; $I^2 = 0\%$). The pooled seroconversion rate with the use of steroids was 0.93 (95% CI, 0.75–0.99; $I^2 = 38\%$). The pooled seroconversion rate after complete vaccination in patients on 5-aminosalicylates was 0.98 (95% CI, 0.96–0.99; $I^2 = 0$). The pooled seroconversion rates in patients on immunomodulator monotherapy was 0.99 (95% CI, 0.97–1.00; $I^2 = 0\%$). The pooled seroconversion rate in patients on anti-tumor necrosis factor (TNF) monotherapy was 0.98 (95% CI, 0.94–0.99; $I^2 = 89\%$). With the use of a combination therapy of anti-TNF with thiopurines, the pooled seroconversion rate was 0.94 (95% CI, 0.83–0.98; $I^2 = 79\%$). The pooled seroconversion rates in patients on vedolizumab (0.98; 95% CI, 0.93–0.99; $I^2 = 90\%$) and ustekinumab (0.99; 95% CI, 0.98–0.99; $I^2 = 0\%$) were good. The pooled seroconversion rate in patients on JAK inhibitors was 0.97 (95% CI, 0.87–0.99; $I^2 = 0$) (Figure 3). The pooled RR of seroconversion was similar in the combination group as compared with anti-TNF alone (pooled RR, 0.98; 95% CI, 0.95–1.01; $I^2 = 69\%$) (Supplementary Figure 7) in 8 included studies.

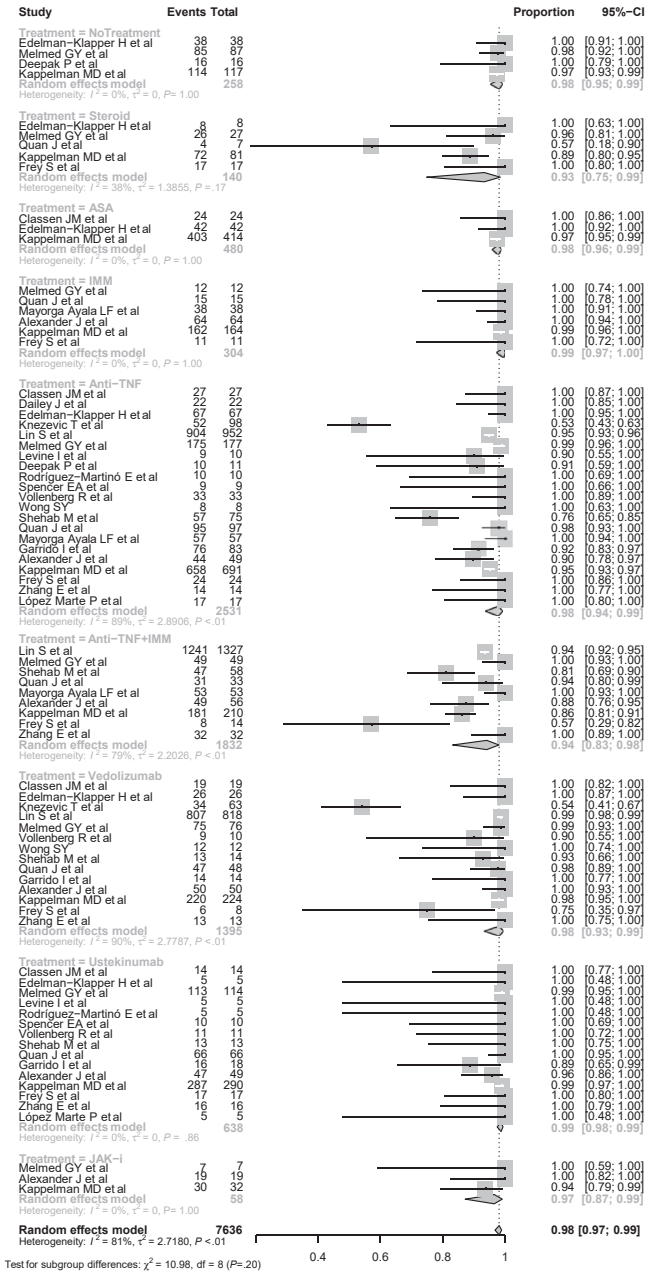

Figure 3. Forest plot depicting the pooled seroconversion rates after complete COVID-19 vaccination in patients with IBD depending on the underlying treatment.

T Cell Responses

Five studies reported T cell responses after COVID-19 vaccination, of which 4 reported SARS-CoV-2–specific responses. Two studies suggested that T cell responses could be attenuated with the use of immunomodulators while one study suggested that anti-TNF agents could

augment T cell responses. Two studies suggested that the antibody response and T cell responses could be decoupled from each other (Supplementary Table 6).

Durability of Serological Response

The durability of serological response was reported in 9 studies at variable times after the complete vaccination (Table 2). Most of the studies suggested that titers fall after 4 weeks of COVID-19 vaccination. There was variability in the rate of decay with some of the studies clearly suggesting that the decay was faster in those treated with anti-TNF agents, immunomodulators, or their combination.

Response to Additional Dose After Complete Vaccination

Only 2 studies reported response to the third dose after the initial series of complete vaccination.[29,48] Both studies reported that a majority of nonresponders seroconverted after the third dose. Further, the antibody titers also increased after the third dose (Supplementary Table 7).

Breakthrough Infections

A total of 12 studies reported breakthrough infections after COVID-19 vaccination in patients with IBD; however, only 5 provided corresponding breakthrough infections in vaccinated control subjects. The pooled rate of breakthrough infections (12 studies, 36,207 patients) was 0.01 (95% CI, 0.00–0.01; $I^2 = 98\%$) (Figure 4*A*). The pooled RR of breakthrough infections in vaccinated patients with IBD was similar to vaccinated control subjects (pooled RR, 0.60; 95% CI, 0.25–1.42; $I^2 = 79\%$) (Figure 4*B*)

Risk of Bias

The visual assessment of the funnel plot (Supplementary Figure 8) and the Egger test ($t = 1.09$, $P = .2822$) did not suggest presence of publication bias. Few studies had concern regarding description of the selected sample size with lack of clear details (Supplementary Tables 8 and 9). While certain studies did not look into the confounding factors of vaccine breakthrough infections. As the Joanna Briggs Institute guidance suggests against using a score cutoff for quality assessment, we also did not score the studies.

Heterogeneity

The Baujat plot (Supplementary Figure 9) constructed for studies reporting seroconversion after 2 doses of COVID-19 vaccines suggested that studies by Knezevic et al[33] and Kappelman et al[29] contributed highest to the heterogeneity. The report by Knezevic et al is published as a conference abstract from Serbia and reports seroconversion after 2 doses of multiple types of vaccines including mRNA (Pfizer-BioNTech), AAV (AstraZeneca/ChAdOxl nCoV-l9 COVISHIELD), and inactivated (SARS-CoV-2 Vero Cell, SPUTNIK V Gam-COVID-Vac) vaccines.[33] The seroconversion rates after inactivated vaccines were particularly low. Subgroup analysis with vaccine subtypes showed lesser heterogeneity for analysis of Ad26.COV2.S (Janssen) and mRNA-1273 (Moderna) vaccines but high for the ChAdOx1-S (AstraZeneca) and BNT162b2 (Pfizer) types (Supplementary Figure 1).

Discussion

This systematic review provides the estimates of seroconversion after complete vaccination for COVID-19 in patients with IBD. We have also provided the pooled seroconversion rates among individual vaccines. The present study also reports about the durability of complete vaccination as well as efficacy of vaccination in preventing breakthrough infections. The overall data suggest that the seroconversion rates after 2 doses of COVID-19 vaccination in the IBD population was slightly lower than healthy control subjects. With mRNA vaccines, the pooled rates of seroconversion were similar in patients of IBD to those of control subjects. The findings provide reassurance to patients with IBD and clinicians treating them regarding the seroconversion after complete vaccination for most vaccines.[61,62]

The other important finding is the impact of drugs on seroconversion rates: the rates of seroconversion were statistically similar among various drugs. The pooled seroconversion rates were numerically lower for steroids and combination of anti-TNF with immunomodulator. However, even these were >90% after complete vaccination. Anti-TNF agents, vedolizumab, ustekinumab, and JAK inhibitors were associated with good seroconversion rates with complete vaccination. The impact of anti-TNF agents on efficacy of COVID-19 vaccination has been under increasing scrutiny because of lower titers achieved in patients on these drugs and an early decay of titers.[30,37] Recent data also suggest that the antibody titers may be lower in JAK inhibitors.[63] Interestingly, our analysis did not demonstrate any decreased seroconversion with the use of combination of anti-TNF with immunomodulators as compared with anti-TNF alone. This finding contrasts with results of a previous systematic review in the setting of IMIDs.[2] There could be many possible reasons for this finding: low number of studies and differences in the immunomodulator use in IBD as compared with other IMIDs.

The durability of antibody response following COVID-19 complete vaccination is a matter of ongoing

Table 2. Studies Reporting Durability of COVID Vaccination in IBD

Author	Number of Patients with IBD	Vaccination	Follow-Up	Finding	Factors for Decay
Charilaou et al	Group 1 n = 74 (anti integrin/5-ASA/ budesonide/not on treatment) Group 2 n = 42 (anti-TNF ± IMM)	mRNA (complete vaccination)	6 mo	Large numerical differences in those who mounted anti-S total without reaching statistical significance -Significant decay observed in group 2 (EDC 1.8%/d; $P = .012$; estimated half-life, 38 d) -Significantly faster (Δ-slope P 1⁄4 .045) than group 1 ($P = .058$; EDC 0.05%/ d; estimated half-life, 153 d),	Significant decay in those on anti-TNF alone and on combination with IMMs
Lin et al	mRNA group (n = 1327) AAV group (n = 1983)	mRNA (complete vaccination) AAV (complete vaccination)	Decay calculated from antibody test carried out between 1 and 70 d after second vaccine dose	Half-lives shorter in patients with infliximab than vedolizumab, after -mRNA group; 26.8 d [95% CI, 26.2–27.5] vs 47.6 d [45.5–49.8], $P < .0001$ -AAV group; 35.9 d [34.9–36.8] vs 58.0 d [55.0–61.3], $P < .0001$)	Faster fall in anti-S RBD antibody in -Infliximab compared with vedolizumab treatment -Current smoking -White ethnicity Minimal decay in prior COVID infection
Doherty et al	IBD (n = 270) Healthy control subjects (n = 116)	Mixed		IgG SP antibody levels in the IBD cohort reduced rapidly during follow-up	
Frey et al	IBD (n = 75)	mRNA	6 mo	Serological positivity seen in all patients High positive (59/75), Low positive titres (16/75)	
	In 45 patients, paired 1-mo and 6-mo analysis was done	mRNA	1.6 mo	At 1 mo, High positive (45/45), Low positive (nil) At 6 mo, High positive (37/45), Low positive (8/45)	
Melmed et al	IBD (n = 89)	mRNA	After dose 2	GMT: 2042 (1348–3090)	
	IBD (n = 115) IBD (n = 366) IBD (n = 171)	mRNA mRNA mRNA	2 wk after 8 wk after 16 wk after	GMT: 10,233 (7762–13,490) GMT: 3236 (2818–2715) GMT: 1445 (1148–1820)	

Table 2. Continued

Author	Number of Patients with IBD	Vaccination	Follow-Up	Finding	Factors for Decay
Quan et al	IBD (n = 283)	Mixed	2–8 wk	Seroconversion rate (278/283)	GMT levels significantly increased ($P < .0001$) from first dose (1679 AU/mL) to second dose at 2–8 wk (7943 AU/mL) but fell significantly ($P < .0001$) to 3565 AU/mL at 8–18 wk
	IBD (n = 87)	Mixed	8–18 wk	Seroconversion rate (82/87)	
Rabinowitz et al	IBD (n = 130) Control (n = 60)	mRNA	6 mo	Serologic response at median 176 (IQR, 166–186) d and compared with, 4 wk after, first dose significantly declined in all 3 groups, but was lowest in the anti-TNF-α group	Older age was an additional predictor of lower serologic response
Zhang et al	IBD (n = 88) Control subjects (n = 53)	Mixed		Mean anti-S1/2 antibody concentrations at 4 wk after second vaccination (V3) were significantly lower in IBD TNF-treated patients (162.6 $\pm$ 1.7) compared with IBD non–TNF-treated patients (325.2 $\pm$ 1.3), and healthy control subjects	
Vollenberg et al	IBD (n = 60) Control (n = 11)	mRNA	3 mo	Seroconversion rate IBD (59/60) Control (11/11)	
	IBD (n = 4) Control (n = 7)	mRNA	6 mo	Seroconversion rate IBD (3/4) Control (7/7)	

AAV, adeno-associated virus; 5-ASA, 5-aminosalicylates; EDC, exponentiated decay coefficient; GMT, geometric mean titer; IBD, inflammatory bowel disease; IMM, immunomodulator; IQR, interquartile range; mRNA, messenger RNA; TNF, tumor necrosis factor.

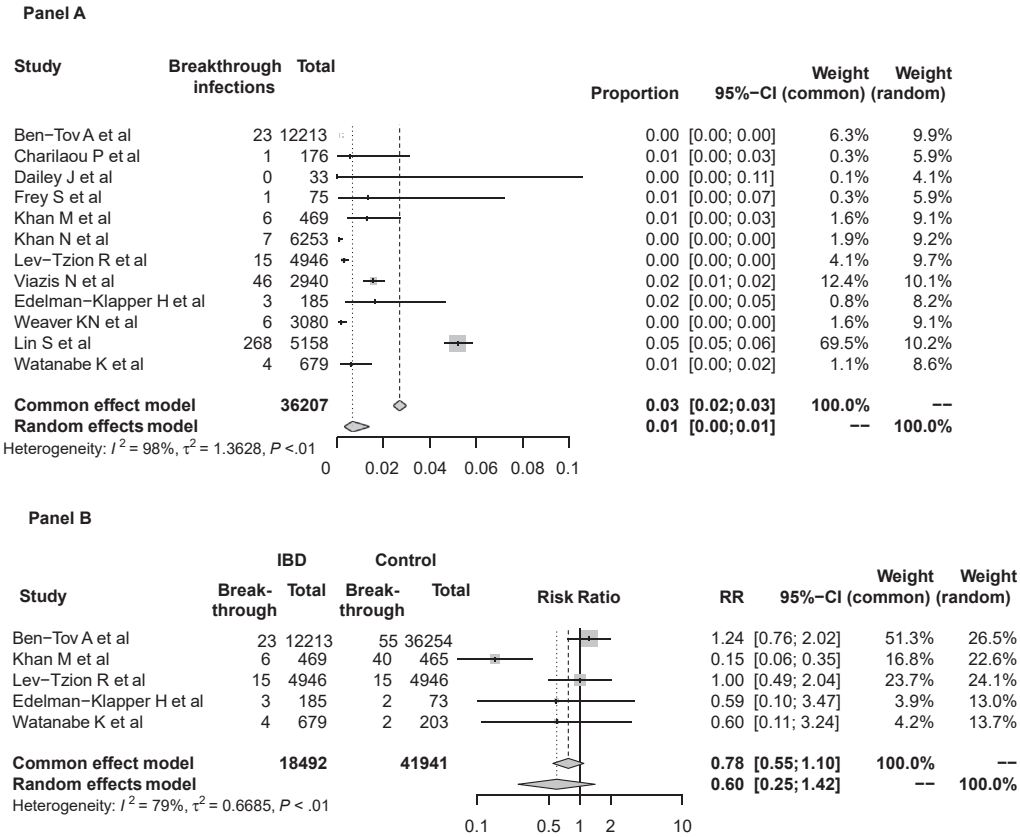

Figure 4. Forest plot depicting (*A*) the pooled rate of breakthrough infections after 2 doses of COVID-19 vaccination in patients with IBD and (*B*) the pooled RR of breakthrough infection in IBD patients as compared with vaccinated control subjects.

evaluation. The systematic review suggested that there is decay in antibody responses after COVID-19 vaccination in patients of IBD. The decay was faster in those treated with anti-TNF agents, immunomodulators, or their combination. [20,37,45,60] The biology behind this waning immunity needs further study of the mechanisms involved. The analysis on breakthrough infections suggested that the breakthrough infections could occur but the overall frequency was likely to be similar to the general population. This finding, along with the fact that the majority of breakthrough infections did not require hospitalization, is reassuring to IBD patients and carers.[32]

There has been considerable debate about whether seroconversion is a proxy indicator of protection from breakthrough infections and severe COVID-19. In this regard, functional assays to detect neutralizing antibodies have been considered as surrogates of protection. These tests could be viral neutralization assays, pseudovirus neutralization assays, or competitive viral neutralization tests. The pooled rates of positivity in neutralization assays after complete vaccination were also lower in patients of IBD as compared with healthy control subjects. Because of the lower number of participating studies, a subgroup analysis regarding the impact of various IBD therapies on neutralization was not possible.

T cell responses are believed to be an important component of protective response against SARS-CoV-2 infection. These responses have been associated with protection from infection and severe disease. It is believed that they may be responsible for protection from emerging variants, even in situations where neutralizing response is not robust.[64] The importance of T cell response may be particularly important in individuals with decaying antibody titers and these may afford durable protection.[65] Interestingly, the T cell response could be discordant to the antibody responses.[36] Unexpectedly, anti-TNF therapy seemed to augment T cell responses, suggesting that even though these individuals may have attenuated antibody response, the protection may not be compromised.[36]

There were only limited studies reporting the response rates of additional doses of COVID-19 vaccine in IBD. There is some evidence to suggest those who did not have seroconversion following complete vaccination did so after a booster dose. The seroconversion as well durability of antibody responses following the additional dose requires further studies.

With the third dose of BNT162b2 vaccine having good neutralization against newer variants like Omicron in the general population, it would be worthwhile to see for responses in patients of IBD.[66] Chen et al reported reduction in neutralizing antibodies and Fc effector

functions capacity in patients with anti-TNF therapy.[19] They found reduced neutralization of BNT162b2 mRNA vaccine against B.1.617.2 (Delta strain) as compared with B.1.351 (Beta strain) in a cohort of chronic inflammatory diseases that included a subset of patients with Crohn's disease.[19]

Our meta-analysis has certain limitations including a significant amount of heterogeneity. The multitude of factors that impact the seroconversion could be responsible for the high heterogeneity: differences in populations (type of IBD, age, drug therapies, disease activity and severity), type of vaccine (AAV, mRNA, or both), definition or assessment of seroconversion, and the timing of determination of outcomes (time of follow-up for breakthrough infections, time from vaccination to the estimation of antibody responses). We attempted to address the heterogeneity by doing a subgroup analysis for the vaccine type and drug-specific analysis. Other limitations include the small number of studies for some of the analysis (comparison of seroconversion with healthy control subjects, breakthrough infections and positivity of neutralization assays when compared with control subjects). Due to the small number of available studies, the T cell responses could not be analyzed quantitatively. Another limitation is that not all the data are from peer-reviewed publications; preprints and conference abstracts have been included to include all the relevant information. Even with the limitations, the analysis includes a significant number of studies and provides, for the first time, the information on neutralizing antibodies, T cell response, durability of response, and pooled breakthrough infections.

In conclusion, complete COVID-19 vaccination is associated with seroconversion in most patients with IBD. The RR of breakthrough infections in vaccinated patients with IBD was similar to vaccinated control subjects. The decay in titers over time necessitates consideration of additional doses in patients particularly on certain therapies.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2022.02.030.

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Reprint Requests
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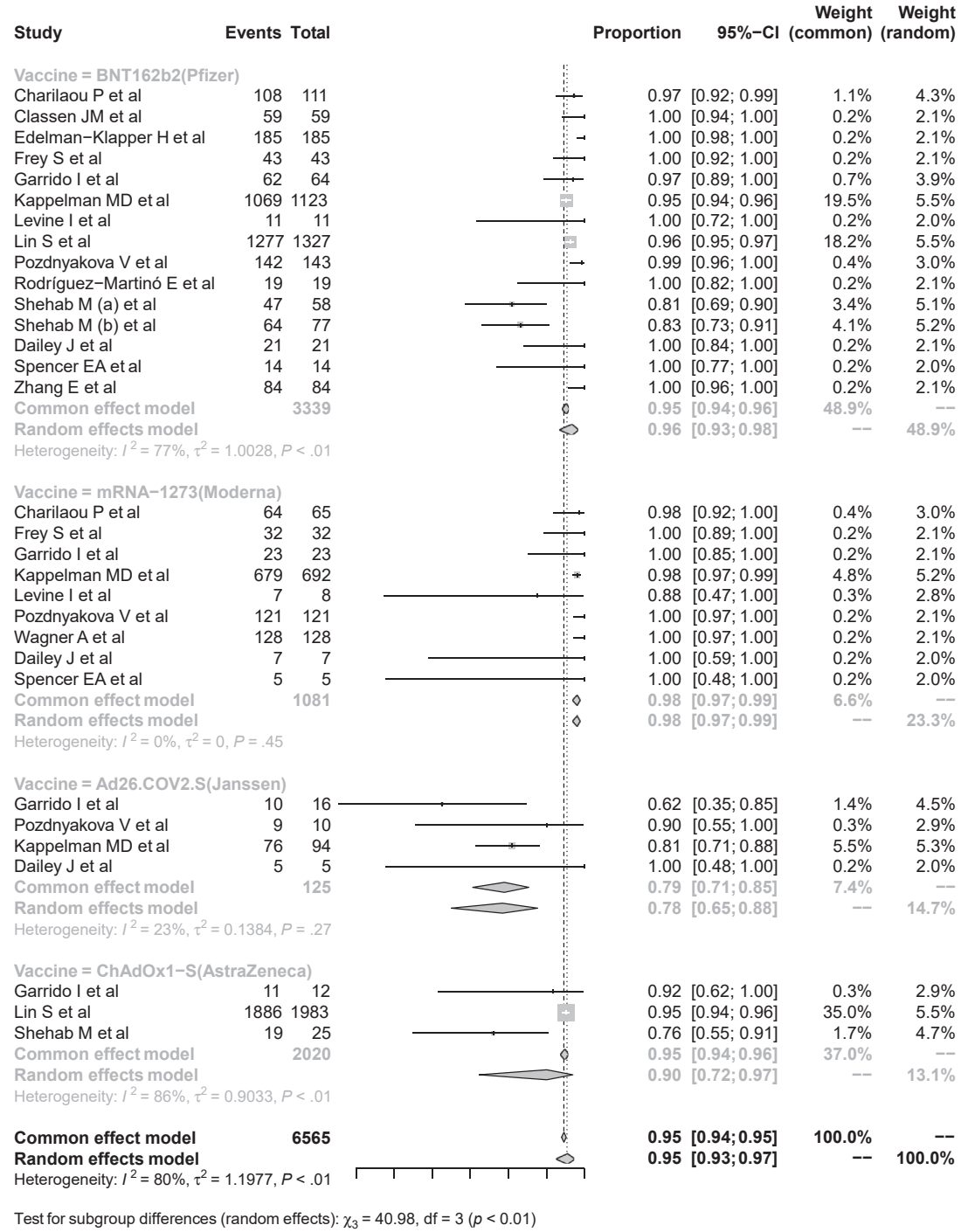
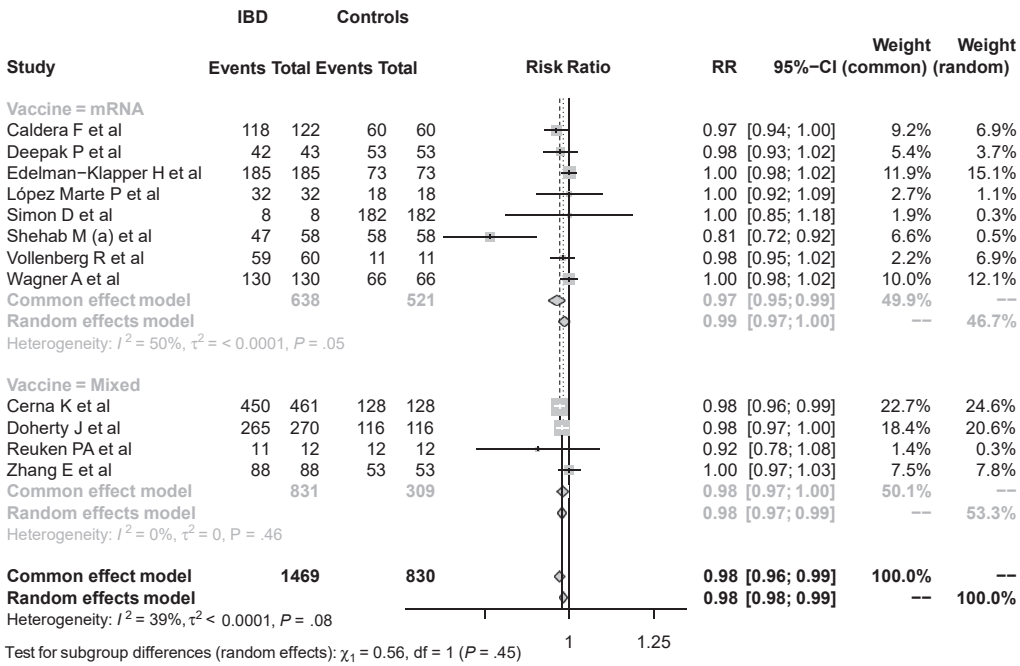
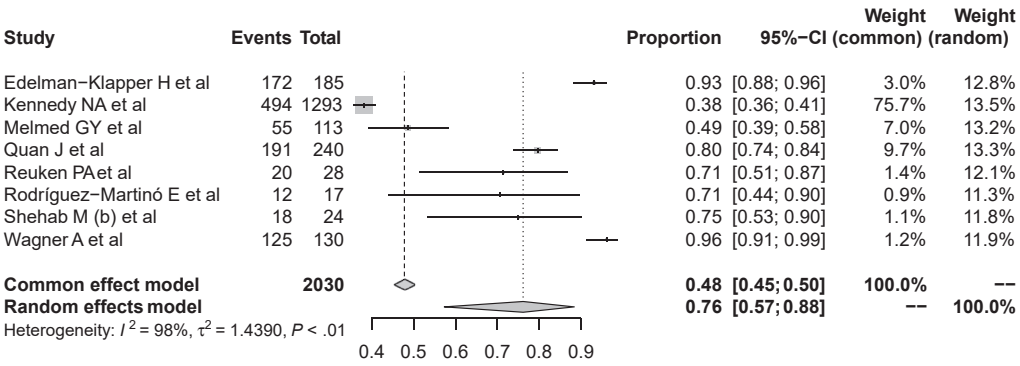
Conflicts of interest
The authors disclose no conflicts.



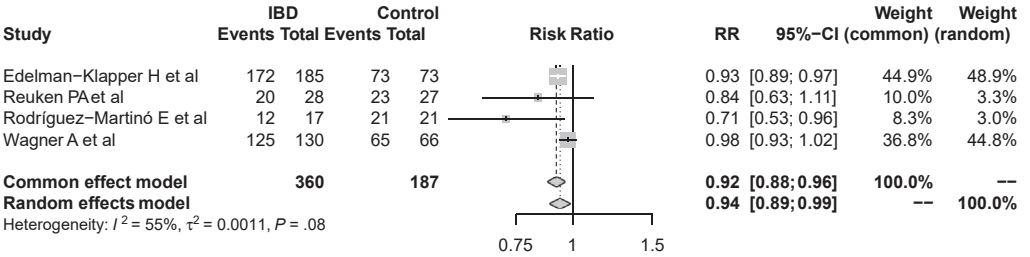
Supplementary Figure 1. Pooled seroconversion rates after complete coronavirus disease 2019 (COVID-19) vaccination in patients with inflammatory bowel disease (IBD) as per the individual vaccine types. CI, confidence interval; RR, relative risk.



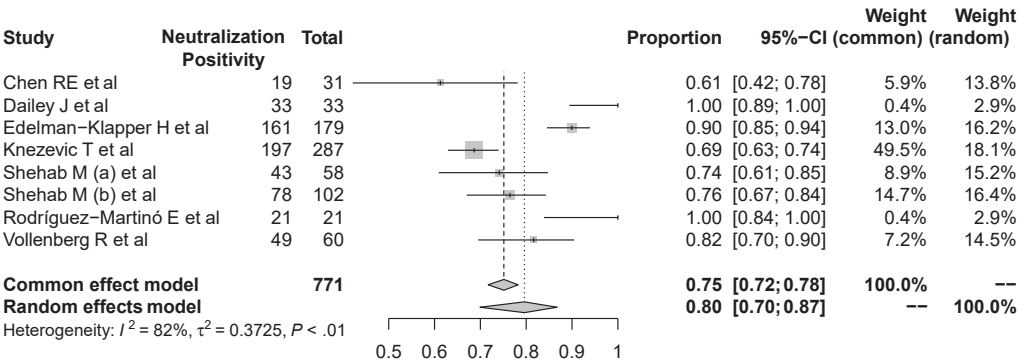
Supplementary Figure 2. Pooled RR of seroconversion after complete COVID-19 vaccination in patients with IBD as compared with healthy control subjects with subgroup analysis.



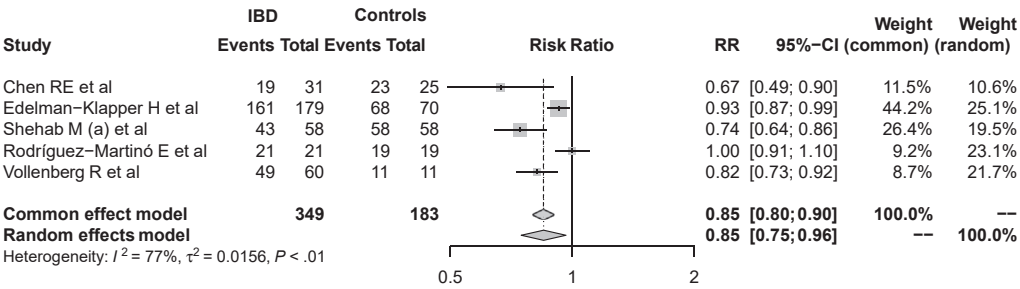
Supplementary Figure 3. Pooled seroconversion rates after incomplete COVID-19 vaccination in patients with IBD.



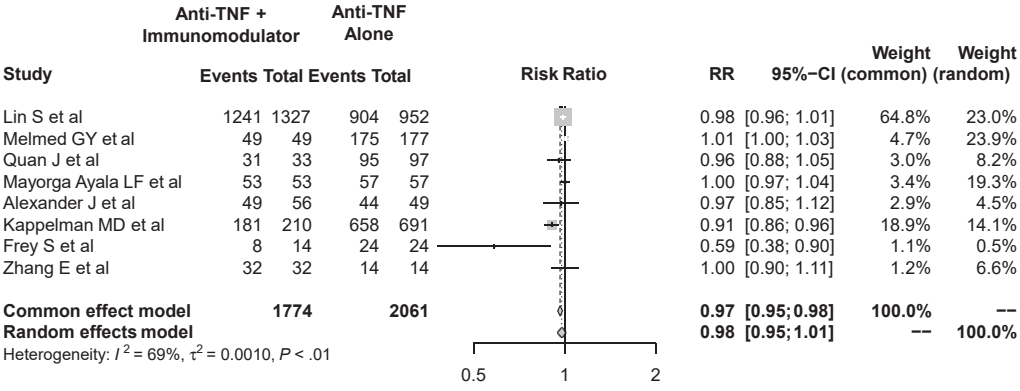
Supplementary Figure 4. Pooled RR of seroconversion after incomplete COVID-19 vaccination in patients with IBD as compared with healthy control subjects.



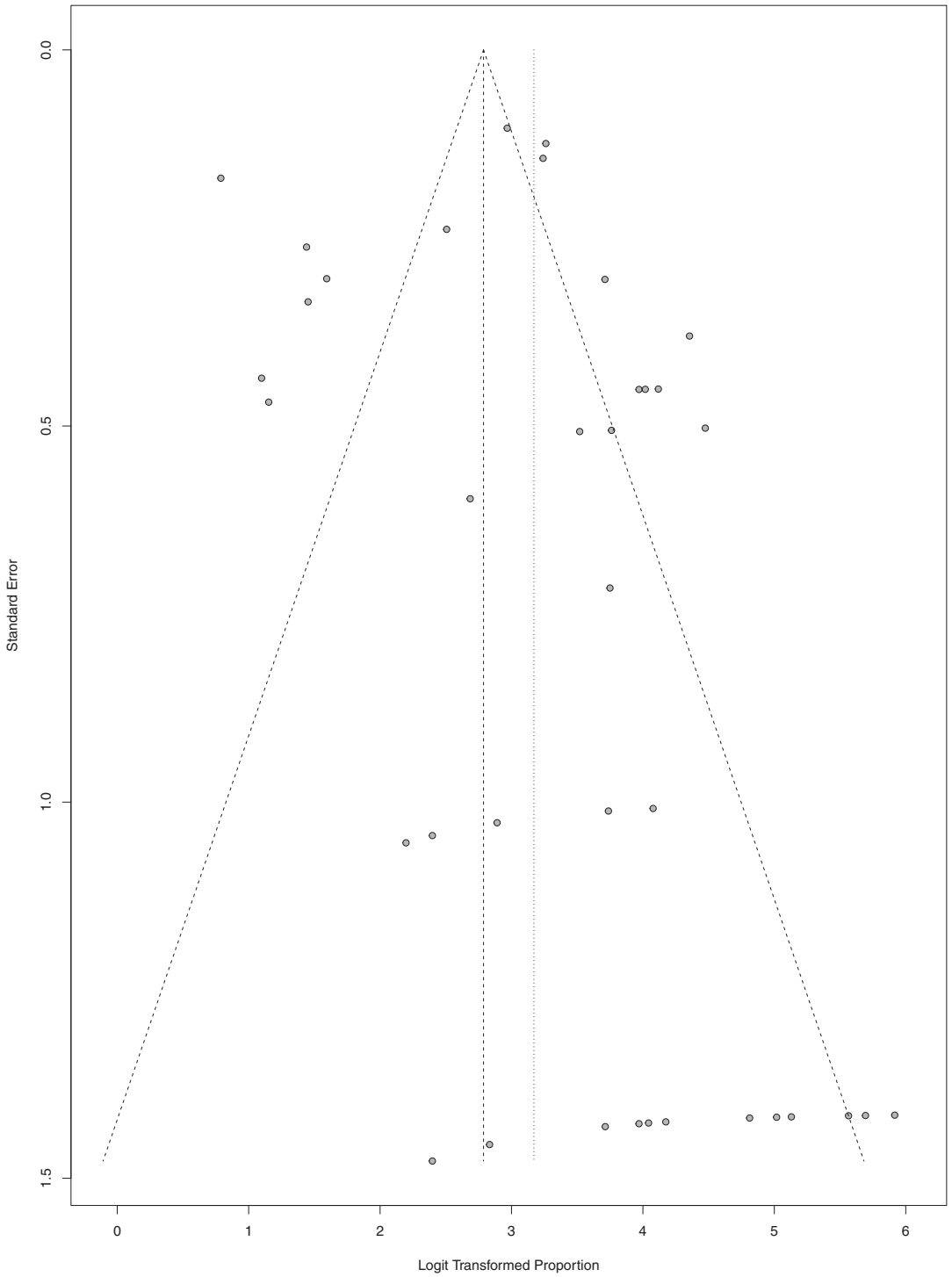
Supplementary Figure 5. Pooled positivity rates of neutralization assays after complete COVID-19 vaccination in patients with IBD.



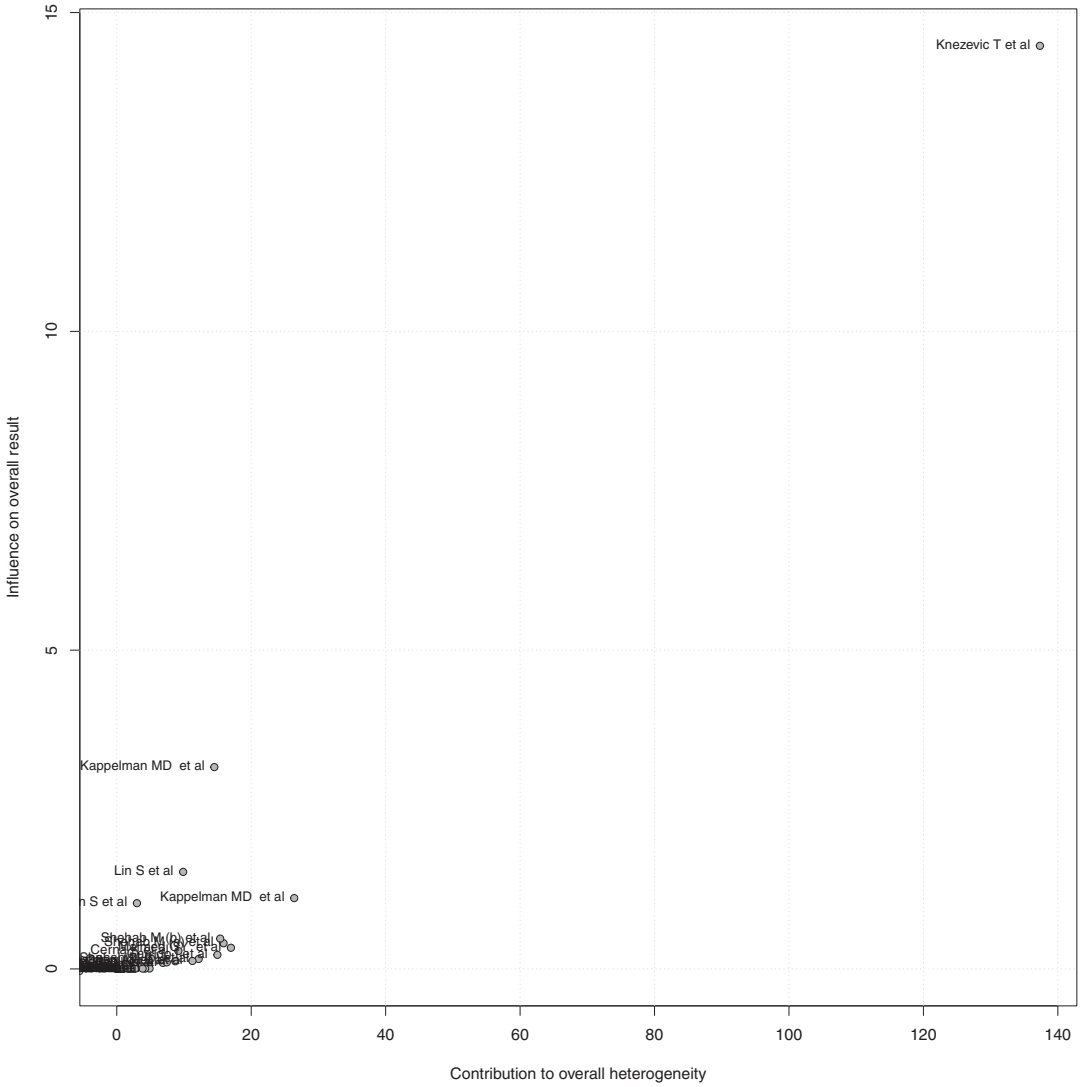
Supplementary Figure 6. Pooled RR of neutralization assay positivity after complete COVID-19 vaccination in patients with IBD as compared with healthy control subjects.



Supplementary Figure 7. Pooled RR of seroconversion after complete COVID-19 vaccination in patients on combination therapy (anti-tumor necrosis factor [TNF] plus immunomodulators) as compared with anti-TNF drugs alone.



Supplementary Figure 8. Funnel plot depicting the publication bias in studies reporting seroconversion after complete vaccination.



Supplementary Figure 9. Baujat plot depicting the studies contributing to heterogeneity.

Supplementary Table 1. Detailed Search Strategy for the Systematic Review

PubMed	19 January 2022	
#1	COVID-19 OR SARS-COV-2	218,613
#2	Vaccine OR Vaccination OR Immunization	1,542,538
#3	Ulcerative colitis OR Crohn's Disease OR Inflammatory Bowel Disease	128,232
#1 AND #2 AND #3		259
Embase	**19 January 2022**	
#1	'coronavirus disease 2019'/exp OR 'coronavirus disease 2019' OR 'severe acute respiratory syndrome coronavirus 2'/exp OR 'severe acute respiratory syndrome coronavirus 2'	198,170
#2	'vaccine'/exp OR vaccine OR 'vaccination'/exp OR vaccination OR 'immunization'/exp OR immunization	643,673
#3	'inflammatory bowel disease' OR 'Crohn disease' OR 'ulcerative colitis'	205,318
#1 AND #2 AND #3		215
Preprint Servers (medRxiv and bioRxiv)	COVID Vaccination Inflammatory bowel disease (full text)	143
Conference abstracts	Crohn's & Colitis Congress 2021 AGA Abstracts 2021 ACG Abstracts 2021 AIBD 2021 ECCO 2021 UEGJ 2021 ECCO Virtual 2022 Crohn's & Colitis Congress 2022	27

Supplementary Table 2. Various Vaccines Used in Patients of IBD With Regimen

Vaccine Name	Type	Age	Complete Vaccination	Booster/Additional Dose
Pfizer-BioNTech (BNT162b2)	mRNA	>5 y	2 doses 21 d apart	At 5 mo after last dose
Moderna (mRNA-1273)	mRNA	>18 y	2 doses 28 d apart	At 5 mo after last dose
AstraZeneca COVISHIELD (ChAdOx-nCov19)	Viral vector	>18 y	2 doses 8–12 wk apart	At 6–9 mo after last dose
Johnson & Johnson's Janssen (JNJ-78436725)	Viral vector	>18 y	Single dose	2 mo after single dose
SPUTNIK V Gam-COVID-Vac	Viral vector	>18 y	2 doses 3 wk apart	—
Sinopharm SARS-CoV2 Vero Cell (BBIBP-CorV)	Inactivated	>18 y	2 doses 3–4 wk apart	—
Sinovac-Coronavac	Inactivated	>18 y	2 doses 2–4 wk apart	—
COVAXIN (BBV152)	Inactivated	>15 y	2 doses 4 wk apart	At 6–9 mo after last dose

IBD, inflammatory bowel disease; mRNA, messenger RNA.

Supplementary Table 3. Studies That Were Not Included in Any Analysis and the Reasons for Exclusion

Study	Country	Reason of Exclusion
Al-Janabi et al[1]	United Kingdom	No data on vaccine response or break through infections
Botwin et al[2]	United States	No vaccine response data, Only adverse events data
Caldera et al[3]	United States	Duplicate overlapping data of HERCULES cohort with Schell et al
Cerna et al[4]	Czech Republic	Duplicate data as abstract
Farkas et al[5]	Hungary	No relevant data
Garrido et al[6]	Portugal	Duplicate data as abstract
Garza et al[7]	United States	No data on type of vaccine used
Hadi et al[8]	United States	No data on seroconversion No separate data on breakthrough post complete vaccination
Horvath et al[9]	Hungary	Only titers of response, No seroconversion numbers
Jørgensen et al[10]	Norway	No separate data of patients of IBD
Kappelman et al[11]	United States	Duplicate data as abstract of PREVENT COVID group
Kappelman et al[12]	United States	Overlapping data of PREVENT COVID group
Lev Zion et al[13]	Israel	Duplicate data
Macedo Silva et al[14]	Portugal	Only titers of response, No seroconversion numbers
Melgaco et al[15]	Brazil	Case report on twin
Sciberras et al[16]	Malta	No separate data for vaccinated IBD patients
Shire et al[17]	Canada	Only titers of response, No seroconversion numbers
Squire et al[18]	United States	No data on vaccine response or breakthrough infections
Seyahi et al[19]	Turkey	No data on vaccine response in IBD patients
Tomanguillo Chumbe et al[20]	United States	No separate data for breakthrough infections
Volkers et al[21]	Netherlands	No relevant seroconversion data

IBD, inflammatory bowel disease.

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Supplementary Table 4. Definition of Seroconversion Used in Various Studies With Respect to Anti-Spike or Anti-RBD Antibodies

Author	Time to Measurement of Serological Response	Definition of Seroconversion
Alexander et al[15]	53–92 d	Ab responses defined cutoff anti-S concentration 15 U/mL, which correlated with 20% viral neutralization
Cerna et al[18]	8 wk	Detection of Serum anti-SARS-CoV-2 IgG antibodies measured by chemiluminescent microparticle immunoassay
Charilaou et al[20]	126 d (89–162)	Detected with SARS-CoV-2 Semi-Quantitative Total Antibody Spike test (LabCorp test #164090, an electrochemiluminescence immunoassay)
Classen et al[21]	56.4 ± 31.485 d	Presence of SARS-CoV-2 antibodies (IgG) against the receptor-binding domain of the spike protein (S) using immunoassays Elecsys Anti-SARS-CoV-2S (Roche Diagnostics, Germany)
Dailey et al[22]	3.1 wk	Fluorescent bead-based immunoassay for SARS-CoV-2 wild-type S-RBD or K417N, E484K, N501 mutant S-RBD–specific IgG antibodies (Acro Biosystems) followed by flow cytometry (iQue Screener Plus; IntelliCyt, MI) and analysis by FlowJo (BD Biosciences). Titration curves for normalization of AUC used to calculate antibody titers
Deepak et al[23]	20 d	ELISA Anti-S IgG. Limit of detection defined as 1:30
Doherty et al[24]	—	Quantitative antibody responses after second dose
Edelman-Klapper et al[25]	4 wk	SARS-CoV-2 IgG II quantitative testing on Abbott architect i2000sr platform. Values ≥50 AU/mL considered positive
Frey et al[26]	179 (IQR, 165–202) d	Roche Elecsys anti-RBD pan Ig >0.8 units/mL
Garrido et al[27]	61 (IQR, 44–76) d	Anti-RBD >10 and/or Anti-spike Ab >10 IU/mL
Kappelman et al[28]	64 d	LabCorp's Cov2Quant IgG assay electrochemiluminescence immunoassay (quantitative measurement of IgG antibodies to SARS-CoV-2 RBD). Values ≥ 1.0 ug/mL considered positive
Knezevic et al[33]	—	ELISA anti-spike protein–based serology (INEP, Belgrade, Serbia) with cutoff level of, 15 as negative, 15–20 intermediate, and >, 20 as positive.
Lin et al[37]	14 and 70 d after second dose	Roche Elecsys Anti-SARS-CoV-2 spike (S) immunoassay and nucleocapsid (N) immunoassay. Electrochemiluminescence immunoassay. Values ≥ 15 U/mL considered positive
Levine et al[34]	—	ELISA assay for the COVID-19 spike domain antibodies (Roche). 0.79 U/mL considered negative and 0.80 U/mL considered positive
Lopez Marte et al[38]	2 and 6 wk	Detection on Siemens Atellica Anti-SARS-CoV-2 (N) and Vircell Virclia (S and N) electrochemiluminescence immunoassay
Mayorga Ayala et al[40]	6 ± 2 wk	Positive Antibodies to the Spike (S) SARS-CoV-2 protein were analyzed by CLIA
Martin Arranz et al[39]	2–4 wk	Detection in Siemens Atellica Anti-SARS-CoV-2 (N) and Vircell Virclia (S and N) electrochemiluminescence immunoassay
Melmed et al[41]	14–140 d	Antibodies to RBD of spike protein S1 subunit (IgG(S)) using the SARS-CoV-2 IgG-II and SARS-CoV-2 IgG assays, respectively (Abbott Labs). Values ≥50 AU/mL considered positive
Otten et al[42]	2–10 wk	Antibody titer of >50 AU/mL
Pozdnyakova et al[43]	2 wk (14–29 d)	IgG(S-RBD) using the SARS-CoV-2 IgG-II assay (Abbott Labs, Abbott Park, IL). Values >50 AU/mL considered positive
Quan et al[44]	2–8 wk	seroconversion defined as IgG levels of >50 AU/mL
Reuken et al[46]	—	LiaisonXL (DiaSorin, Saluggia, Italy), IgG against SARS-CoV-2–specific trimeric spike glycoprotein. Values ≥13 AU/mL or ≥33.8 BAU/mL considered positive
Rodríguez-Martinó et al[47]	2 wk	Total IgG titers, ELISA

Supplementary Table 4. Continued

Author	Time to Measurement of Serological Response	Definition of Seroconversion
Schell et al[48]	28–35 d	nucleocapsid and spike protein S1 receptor-binding domain (RDB)-specific IgG antibodies concentrations after 2 doses
Simon et al[51]	39 d	IgG antibodies against S1 domain of spike protein by ELISA (Euroimmun; Lübeck, Germany) using EUROIMMUN Analyzer I platform. Optical density ≥0.8 (optical density 450 nm) considered positive
Shehab et al (a)[50]	4–10 wk	SARS-CoV-2–specific IgG and IgA antibodies measured by enzyme-linked immunosorbent assay (ELISA) kit (SERION ELISA agile SARS-CoV-2 IgG and IgA SERION Diagnostics, Wurzburg, Germany) IgG levels <31.5 BAU/mL considered negative or nonprotective IgA levels <10 AU/mL considered negative or nonprotective
Shehab et al (b)[50]	4–10 wk	(ELISA) kit (SERION ELISA agile SARS-CoV-2 IgG; SERION Diagnostics, Würzburg, Germany). IgG levels <31.5 BAU/mL considered negative or non-protective
Spencer et al[52]	14–37 d	COVID-SeroKlir (Kantaro Biosciences, LLC, New York, NY) semiquantitative SARS-CoV-2 IgG antibody assay (ELISA) (full-length SARS-CoV-2 spike protein). High titer or strongly positive: ≥960 titer or >40 AU/mL, moderately positive: 320–960 titer or 16–39 AU/mL, weakly positive: 80–160 titer or 5–15 AU/mL
Vollenberg et al[54]	3 mo ± 7 d	RBD IgG (S-IgG) values at or above the cutoff (50.0 AU/mL) denoting seropositivity
Wagner et al[56]	4 wk	SARS-CoV-2–specific IgG antibodies S1 by ELISA (Quantivac, Euroimmun) iAntibody values above 35.2 BAU/mL were considered as positive
Wong et al[58]	2–85 d	Siemens COV2T chemiluminescence-based assay for total antibodies to the SARS-CoV-2 RBD of the S protein sCOVG (semiquantitative assay for anti-RBD IgG) – Index value = 1 considered positive. Roche assay for antibodies (IgG) to nucleocapsid protein. Values >100 considered positive and 4 titer increase from baseline as significant
Zacharopoulou et al[59]	31 (IQR, 23–46) d	Anti-S1 IgG ≥11 RU/mL
Zhang et al[60]	21–42 d	Antibodies to the S1/2 IgG subunit and receptor-binding protein (RBD) were measured

ELISA, enzyme-linked immunosorbent assay; IQR, interquartile range; S-RBD, spike protein-receptor binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Supplementary Table 5. Definition of Positivity of Neutralization Assays and the Duration of the Test as Used in Various Studies

Author	Details of Neutralization Assessment	Assessed at (After Complete Vaccination)
Chen et al[19]	SARS-CoV-2 Vero-TMPRSS2 focus reduction neutralization test using Delta B.1.617.2 spike antigens	3 mo after last dose
Dailey et al[22]	Pseudo-typed wild type/(alpha variant) lentiviruses on 293-ACE2 cells followed by flow cytometry using BD FACSymphony A5 analyzer	2 mo after last dose
Edelman-Klapper et al[25]	Pseudo-typed vesicular stomatitis virus (SΔ19-VSVGFPΔG) on HEP-293 cells focus reduction neutralization test	21–35 d after the second vaccine dose
Knezevic et al[33]	Presence of neutralization antibodies SARS-Cov-2 IgG response that was measured using ELISA anti-spike protein-based serology (INEP, Belgrade, Serbia) with cutoff level of, 15 as negative, 15–20 intermediate, and >20 as positive.	—
Shehab et al[49]	Neutralizing antibody levels <20% were considered negative or nonprotective. Assay not mentioned	4–10 wk after last dose
Shehab et al[50]	Neutralizing antibody levels <20% were considered negative or nonprotective. Assay not mentioned	4–10 wk after last dose
Rodríguez-Martinó et al[47]	Virus neutralization test % titers using ELISA	2 wk after last dose
Vollenberg et al[54]	Seroconversion as indicated by sVNT (inhibition > 30%)	3 mo after last dose

ELISA, enzyme-linked immunosorbent assay; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; sVNT, surrogate virus neutralization test.

Supplementary Table 6. Details of the Studies Reporting T Cell Responses After COVID-19 Vaccination in Patients of IBD

Author	Vaccine	Number of IBD Patients	Response	Interpretation	Method
Li et al (CORALE IBD)[36]	mRNA complete vaccination Pfizer (n = 90) Moderna (n = 68)	IBD (n = 158) Females (n = 88)	T cell response matrices Clonal breadth: 2.03e-04 ± 1.55e-04 Clonal depth: 76.13 ± 111.82 Clonal breadth spike: 5.04e-05 ± 6.74e-05 Clonal depth spike: 5.86 ± 41.77	Reduced T cell clonal depth was associated with chronologic age, male sex, and immunomodulator treatment No effect of interleukin-12/23 and integrins therapy Treatment with anti-TNF–augmented T cell responses	Immunosequencing of the CDR3 regions of human TCRβ chains was performed on blood genomic DNA using the immunoSEQ Assay (Adaptive 61 Biotechnologies), and quantitation of the corresponding T cell fractions by template count normalization
Lin et al (CLARITY IBD)[37]	mRNA complete vaccination AAV complete vaccination	IBD on infliximab or Vedolizumab (n = 67) IBD on infliximab or Vedolizumab (n = 56)	54/67 had T cell responses IBD: 45/56 had T cell responses	The proportion of patients failing to mount detectable T cell responses were similar in both groups (infliximab 19.6% vs vedolizumab 19.2%) Decoupling of antibody and T cell responses noted Minority (<5%) developed neither antibody nor T cell response	Anti-SARS-CoV-2 spike T cell responses: IFN-γ T cell ELISpot assays were performed using pre-coated plates (Mabtech 3420-2APT). A response below 2 SDs of the media only control wells was deemed to be a null response
Mayorga Ayala et al[40]	mRNA complete vaccination	IBD (n = 148) On thiopurines and/or anti-TNF	IBD: 129/148	T cell response in –92% of anti-TNF monotherapy, 87% of thiopurines and 83% in combination All had antibody response (anti-S antibody)	Specific T cell response to SARS-CoV-2 was determined by IGRA using Qiagen QuantiFERON SARS-CoV-2 RUO tubes

Supplementary Table 6. Continued

Author	Vaccine	Number of IBD Patients	Response	Interpretation	Method
Reuken et al[46]	Mixed vaccine type: first dose Second dose: mRNA	IBD (n = 28) Control subjects (n = 27)		IBD patients showed comparable T cell responses after first SARS-CoV-2 vaccination in respect to healthy control subjects, which was not influenced by different immunosuppressive regimens After second round of vaccination, the observed vaccine-related induction of SARS-CoV-2–reactive T helper cells did remain in IBD patients increase in the frequencies of IFN-γ producers among SARS-CoV-2–reactive T helper cells in the control subjects as well as in the IBD cohort	SARS-CoV-2–specific T helper cells among $CD45^{+}$ PBMCs, we incubated the PBMCs with 2 S-Protein–derived peptide mixes covering the whole sequence of the Spike protein (N- and C-terminally, S-Mix1 or S-Mix2, respectively).
Rodríguez-Martinó et al[47]	mRNA and AAV	IBD (n = 19)	There is a mild increase in mean CD4 count after the second vaccine dose Small progressive increase in mean CD8 counts after each vaccine dose	Both CD4 and CD8 mean levels showed an upward trend after vaccination	Cellular immunity (CD4+ and CD8+ T cell levels) with flow cytometry are measured at baseline and 2 wk after each vaccine dose However SARS-CoV-2 specific T cell responses were not evaluated
Wagner et al[56]	mRNA complete vaccination Pfizer (n = 2) Moderna (n = 128)	IBD (n = 130)		After the second dose, immune system of the IBD patients and the control subjects, mounted a clear T cell response upon stimulation with the peptide pool of the S1 subunit of the SARS-CoV-2 spike protein	T cell response by using a cytokine release assay after peptide stimulation of isolated PBMCs

AAV, adeno-associated virus; COVID-19, coronavirus disease 2019; IBD, inflammatory bowel disease; IFN, interferon; mRNA, messenger RNA; PBMC, peripheral blood mononuclear cell; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF = tumor necrosis factor.

Supplementary Table 7. Details of the Studies Showing the Response of the Third Dose of COVID-19 Vaccination in Patients of IBD

Author	Vaccine	IBD Patients	Response	Duration at Which Response Was Tested
Kappelman et al (PREVENT)[29]	Majority mRNA (except 1 patient) Additional dose same as initial vaccine in 98%	N = 659	Response after 2 dose (initial series): 613/659 (93%) Response after the third dose IBD: 656/659 (99.5%) 45/47 without initial response developed antibody response	6 wk
Schell et al (HERCULES Cohort)[48]	mRNA	N=85	Response after 2 doses (initial series) 135/139 (97.1%) Response after the third dose IBD: 85/85 (100%) Median antibody concentrations higher after third dose; titers were lower in those on steroids, anti-TNF, or combination therapy	28–65 d after third dose

COVID-19, coronavirus disease 2019; IBD, inflammatory bowel disease; mRNA, messenger RNA; TNF = tumor necrosis factor.

Supplementary Table 8. Risk-of-Bias Analysis of the Included Studies Using Joanna Briggs Institute Appraisal Guidance (Prevalence Studies)

Study	Was the Sample Frame Appropriate to Address the Target Population?	Were Study Participants Sampled in an Appropriate Way?	Was the Sample Size Adequate for Vaccine Response?	Were the Study Subjects and the Setting Described in Detail?	Was the Data Analysis Conducted With Sufficient Coverage of the Identified Sample?	Were Valid Methods Used for the Identification of Vaccine Response?	Was the Condition Measured in a Standard, Reliable Way for All Participants?	Was There Appropriate Statistical Analysis?	Was the Response Rate Adequate, and If Not, Was the Low Response Rate Managed Appropriately?
Cerna et al[18]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Charilaou et al[20]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chen et al[19]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Classen et al[21]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dailey et al[22]	Yes	Unclear	No	No	Yes	Yes	Yes	Yes	Yes
Deepak et al[23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Doherty et al[24]	NA	NA	Yes	NA	NA	NA	NA	NA	NA
Edelman-Klapper et al[25]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Frey et al[26]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Garrido et al[27]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear
Kappelman M et al[28]	Yes	NA	Yes	Yes	NA	NA	NA	NA	NA
Kappelman et al[29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kennedy et al[30]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Knezevic et al[33]	NA	NA	Yes	NA	NA	NA	NA	NA	NA
Levine et al[34]	Yes	Unclear	Yes	No	Unclear	Yes	Yes	Yes	Unclear
Li et al[36]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lin et al[37]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lopez Marte et al[38]	NA	NA	Unclear	NA	NA	NA	NA	NA	NA
Martin Arranz et al[39]	NA	NA	Yes	NA	NA	NA	NA	NA	NA
Mayorga Ayala et al[40]	NA	NA	Yes	NA	NA	NA	NA	NA	NA
Melmed et al[41]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Otten et al[42]	NA	NA	Yes	NA	NA	NA	NA	NA	NA
Pozdnyakova et al[43]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Quan et al[44]	Yes	NA	Yes	Yes	NA	NA	NA	NA	NA

Supplementary Table 8. Continued

Study	Was the Sample Frame Appropriate to Address the Target Population?	Were Study Participants Sampled in an Appropriate Way?	Was the Sample Size Adequate for Vaccine Response?	Were the Study Subjects and the Setting Described in Detail?	Was the Data Analysis Conducted With Sufficient Coverage of the Identified Sample?	Were Valid Methods Used for the Identification of Vaccine Response?	Was the Condition Measured in a Standard, Reliable Way for All Participants?	Was There Appropriate Statistical Analysis?	Was the Response Rate Adequate, and If Not, Was the Low Response Rate Managed Appropriately?
Reuken et al[46]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Rodríguez-Martinó et al[47]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Schell et al[48]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Shehab et al[49]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Shehab et al[50]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Simon et al[51]	Yes	Yes	Unclear	No	Unclear	Yes	Yes	Yes	Unclear
Spencer et al[52]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Vollenberg et al[54]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wagner et al[56]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Unclear
Wong et al[58]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Zacharopoulou et al[59]	NA	NA	Yes	Yes	NA	NA	NA	NA	NA
Zhang et al[60]	NA	NA	Yes	NA	NA	NA	NA	NA	NA

NA, not applicable

Supplementary Table 9. Risk-of-Bias Analysis of the Included Studies Using Joanna Briggs Institute Appraisal Guidance (Studies Reporting Breakthrough Infections With Control Group)

Study	Were the 2 Groups Similar and Recruited From the Same Population?	Were the Exposures Measured Similarly to Assign People to Both Exposed and Unexposed Groups?	Was the Exposure Measured in a Valid and Reliable Way?	Were Confounding Factors Identified?	Were Strategies to Deal With Confounding Factors Stated?	Were the Groups/ Participants Free of the Outcome at the Start of the Study (or at the Moment of Exposure)?	Were the Outcomes Measured in a Valid and Reliable Way?	Was the Follow-Up Time Reported and Sufficient to Be Long Enough for Outcomes to Occur?	Was Follow-Up Complete, and If Not, Were the Reasons to Loss to Follow-Up Described and Explored?	Were Strategies to Address Incomplete Follow-Up Utilized?	Was Appropriate Statistical Analysis Used?
Ben-Tov et al[16]	Yes	Yes	Unclear	Unclear	No	Yes	Yes	Yes	Unclear	Unclear	Yes
Charilaou et al[20]	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Edelman-Klapper et al[25]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Frey et al[26]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Khan et al[31]	Yes	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Khan et al[32]	Yes	Yes	Yes	Unclear	No	Yes	Yes	Yes	Yes	Unclear	Yes
Lev-Tzion et al[35]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lin et al[37]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Viazis et al[53]	Yes	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Watanabe et al[55]	Yes	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Weaver et al[57]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wong et al[58]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes

NA, not applicable.