COVID-19 Vaccination Among Individuals With Inflammatory Bowel Disease: Perception, Efficacy, and Safety

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Abstract: The COVID-19 pandemic, caused by SARS-CoV-2, has been the most significant global health crisis of the past century. The development of safe and effective vaccines has led to a reduction in COVID-19–related hospitalizations and deaths; however, the clinical trials that led to US Food and Drug Administration Emergency Use Authorization and/or approval of the vaccines in the United States did not include individuals with inflammatory bowel disease (IBD). Because individuals with IBD are commonly treated with immunosuppressive medications, there had been concern for reduced vaccine efficacy in this population. This article provides an overview of the peer-reviewed literature addressing COVID-19 vaccination in individuals with IBD; details the perceptions of patients with IBD of COVID-19 vaccines, including how gastroenterologists can help to reduce vaccine hesitancy; and describes the humoral immune response to COVID-19 vaccines, with a majority of patients with IBD seroconverting following complete vaccination regardless of medication exposure. Additionally, low rates of IBD flare and similar rates of vaccine-related adverse events to those in the general population are described. Finally, the article provides current recommendations from the Centers for Disease Control and Prevention for COVID-19 vaccination in individuals with IBD.

The COVID-19 pandemic, caused by SARS-CoV-2, is the most significant global health crisis of the past century. To date, over 530 million people worldwide have been infected with COVID-19, with nearly 6.3 million dying from this infection.¹ The development of safe and effective vaccines has significantly reduced COVID-19–related hospitalizations and deaths.² In the United States, both messenger RNA (mRNA) and adenovirus vector vaccines have been granted US
Food and Drug Administration (FDA) Emergency Use Authorization (EUA) and/or approval. The mRNA vaccinations, including BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna/National Institutes of Health), as well as the adenovirus vector vaccine Ad26.COV2.S (Johnson & Johnson) were found to be 95%, 94.1%, and 66.9% effective, respectively, against the development of COVID-19 infection in clinical trials that led to EUA.3-5 Through its receptor-binding domain (RBD), the spike protein of SARS-CoV-2 engages with angiotensin-converting enzyme 2, which allows viral entry into the host cell.6 All 3 vaccines available in the United States encode the prefusion-stabilized conformation of SARS-CoV-2 full-length spike protein, which more closely mimics the intact virus.3,5,7 mRNA vaccines induce human cells to translate the mRNA into SARS-CoV-2 spike protein that stimulates an immune response to that specific protein.8 Similarly, after administration of Ad26.COV2.S, a replication-incompetent adenovirus delivers SARS-CoV-2 spike protein to induce a protective immune response.5

The primary mRNA vaccine series includes 2 doses of BNT162b2 given 3 weeks apart or 2 doses of mRNA-1273 given 4 weeks apart. Ad26.COV2.S is a single-dose vaccine. Updated recommendations for additional primary vaccine doses for moderately to severely immunocompromised patients and boosters are outlined in more detail in the Figure.

Individuals with inflammatory bowel disease (IBD), including Crohn’s disease and ulcerative colitis, are frequently treated with immunosuppressive medications. Since the start of the COVID-19 pandemic, there have been questions regarding COVID-19 vaccine efficacy and safety in this population given its exclusion from the clinical trials that led to FDA EUA and/or approval of the vaccines. This article outlines the peer-reviewed literature to date, including IBD patients’ perceptions of COVID-19 vaccines; efficacy of COVID-19 vaccines in individuals with IBD, including humoral and T-cell immune responses; rates of vaccine-associated adverse events (AEs) and IBD flares; and evidence-based COVID-19

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**Figure.** Recommendations for COVID-19 vaccination in nonimmunosuppressed patients with inflammatory bowel disease (A) and moderately to severely immunosuppressed patients with inflammatory bowel disease (B).

vaccination recommendations for patients with IBD in the United States.

**Recommendations for COVID-19 Vaccination in the Inflammatory Bowel Disease Population**

In January 2021, the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) provided expert guidance that all patients with IBD should be vaccinated at the earliest opportunity against SARS-CoV-2. The IOIBD stated that COVID-19 vaccination should not be delayed because of treatment with immunosuppressive therapies but did caution that vaccine efficacy may be blunted in patients receiving systemic corticosteroids. Recommendations emphasized the safety of both mRNA vaccines and replication-incompetent adenovirus, stressing the importance of referring vaccinated patients with IBD to vaccine registries to better understand the effects of vaccination in the IBD population.

Similarly, the British Society of Gastroenterology strongly recommended COVID-19 vaccination for individuals with IBD with any approved vaccine, discussing the potential for diminished vaccine response in those on immunosuppression but affirming the safety of COVID-19 vaccination regardless of medication exposure.

The Crohn's & Colitis Foundation also released several position statements on COVID-19 vaccination, including an update on recommendations for additional vaccine doses for individuals on immunosuppression. The initial statement echoed similar sentiments by the IOIBD and British Society of Gastroenterology. Based upon recommendations from the Centers for Disease Control and Prevention (CDC), the Crohn's & Colitis Foundation recommended against checking antibody levels following vaccination outside a research study.

In August 2021, the CDC Advisory Committee on Immunization Practices recommended an additional dose of mRNA COVID-19 vaccine to complete the primary mRNA vaccine series for moderately to severely immunocompromised individuals. From an IBD perspective, this included treatment with high-dose systemic corticosteroids (≥20 mg prednisone), anti–tumor necrosis factor (TNF) biologics, and immunomodulators such as thiopurines and methotrexate. Specific recommendations were not provided for the biologics vedolizumab (Entyvio, Takeda) and ustekinumab (Stelara, Janssen) or the small molecules ozanimod (Zeposia, Bristol Myers Squibb) and tofacitinib (Xeljanz, Pfizer). The additional or third dose of mRNA vaccine should be given at least 28 days after the second vaccine dose. A booster mRNA vaccine dose is also recommended at least 3 months after the additional dose.

More recently, the CDC provided guidance for individuals who received Ad26.COV2.S. The CDC now recommends that these individuals receive an additional dose of mRNA vaccine (BNT162b2 or mRNA-1273) at least 4 weeks after their first vaccine dose. A booster dose of mRNA vaccine is also recommended at least 2 months after the second vaccine dose for moderately to severely immunocompromised individuals. A visual representation of vaccine recommendations for patients with IBD can be seen in the Figure.

**Perceptions of COVID-19 Vaccination Among Individuals With Inflammatory Bowel Disease**

Several studies have evaluated the perceptions of COVID-19 vaccination among individuals with IBD. Generally, most individuals reported intent to receive the vaccine when available, but many expressed hesitancy to receive the vaccine for reasons outlined here.

Dalal and colleagues surveyed patients with IBD regarding intent to receive the COVID-19 vaccine soon after it became available in the United States. Of 906 respondents, 236 were recruited locally in Boston and 670 via social media. Over 80% of local participants and 60% of social media participants reported intent to receive COVID-19 vaccination. Among the vaccine-hesitant participants, the most common concerns included unknown long-term safety of the vaccine, desire to see how others tolerated the vaccine first, and desire for IBD-specific data with regard to COVID-19 vaccine safety and efficacy. On multivariable analysis, factors significantly associated with willingness to receive a vaccine included age 50 years and older and having a bachelor’s degree for local participants, and White race, bachelor’s degree, current use of biologic therapy, and prior COVID-19 infection for social media participants. Other US-based studies found that concerns regarding vaccine efficacy and safety, prior vaccine refusal, younger age, underrepresented minority group status, and neighborhood socioeconomic disadvantage were associated with COVID-19 vaccine hesitancy. Similarly, a French study of 104 patients with IBD reported 54.8% intent to receive the COVID-19 vaccine. The rationale for proceeding with vaccination included protection against SARS-CoV-2 infection, protecting vulnerable individuals, and returning to a normal life, and the most commonly cited concerns among the vaccine-hesitant participants included unknown long-term effects of the vaccine, fear about vaccine-related AEs, and development time of the vaccine.

In addition to these survey studies, a group of gastroenterologists in Italy aimed to better define rates of COVID-19 vaccine uptake in their patients with IBD...
who were treated with a biologic and/or azathioprine.\textsuperscript{18} During clinic visits, 29 out of 56 individuals (51.8\%) reported having already been vaccinated, and 25 out of 27 unvaccinated individuals agreed to undergo vaccination at the time of the clinic visit. Access to vaccination in the clinic immediately following physician counseling may have led to increased vaccine uptake.

Walldorf and colleagues evaluated the perceptions of individuals with IBD (n=1032) in Germany vs a non-IBD control cohort (n=410) with regard to acceptance of mRNA COVID-19 vaccines.\textsuperscript{19} Although patients with IBD received annual influenza vaccinations more frequently than non-IBD controls, they were significantly less likely to report intention to receive the COVID-19 vaccine as soon as possible or to report having already been vaccinated compared with non-IBD controls (58.5\% vs 65.1\%; \(P=.013\)). Additionally, patients with IBD were significantly more likely than non-IBD controls to prefer a vaccine type other than mRNA vaccines or stated that they would postpone their vaccine for at least 6 months to obtain more information regarding potential AEs (25.1\% vs 18.5\%; \(P=.007\)). Factors associated with vaccine intent included male sex, 1 or more severe SARS-CoV-2 infections among family or friends, history of hypertension, and receipt of influenza vaccine during the 2019 to 2020 or 2020 to 2021 influenza seasons. This study suggests that patients with IBD were generally not opposed to vaccinations, as evidenced by higher influenza vaccine uptake compared with the non-IBD cohort; however, there were lower rates of COVID-19 vaccine uptake and higher rates of vaccine hesitancy in this German IBD population.

Crispino and colleagues developed an anonymous web-based questionnaire that was sent to patients to evaluate uptake of the annual influenza vaccine, willingness to receive the COVID-19 vaccine, and vaccine-related concerns.\textsuperscript{20} A total of 276 out of 450 questionnaires (61.3\%) were completed. Less than one-half of the study population (47.1\%) received their annual influenza vaccine. A majority of participants (148; 53.6\%) reported willingness to receive the COVID-19 vaccine, and at the time of the survey, 110 out of those 148 participants (74.3\%) had already received dose 1 (D1) of the COVID-19 vaccine. Only 25 out of the 276 participants (9\%) stated that they would definitely refuse the COVID-19 vaccine, whereas 103 participants (37.3\%) were uncertain but likely to change their stance after receiving additional safety information about the vaccine. Similar to other studies, motivations for becoming vaccinated included collective responsibility and desire to return to a normal life. Individuals opposed to vaccination cited fear of side effects and possible flare of IBD as reasons for declining vaccination. On multivariate analysis, the authors found that receipt of the influenza vaccine during previous year (odds ratio [OR], 3.78; 95\% CI, 2.22-6.44; \(P<.0001\)), recommendation from gastroenterologist (OR, 3.30; 95\% CI, 1.77-6.17; \(P=.001\)), and household member age greater than 65 years (OR, 2.22; 95\% CI, 1.20-4.10; \(P=.01\)) were predictors of COVID-19 vaccine acceptance. This study suggests that counseling by gastroenterologists may be effective at improving vaccine uptake, particularly among vaccine-hesitant patients.

Tailored education may play a role in decreasing vaccine hesitancy. In a recent study, unvaccinated individuals with IBD were shown a video in which a gastroenterologist described the rationale for COVID-19 vaccination, including the safety and efficacy of the vaccine in patients with IBD.\textsuperscript{21} After watching the video, 43 out of 45 participants reported that they were certain or very likely to receive the COVID-19 vaccine, and 35 participants found the content at least somewhat helpful for making an informed decision to receive the vaccine.

Taken together, these findings suggest that gastroenterologists should play an active role in increasing COVID-19 vaccine uptake among individuals with IBD. When recommending a vaccine, gastroenterologists should acknowledge the patient's concerns and normalize hesitancy, presume openness to receiving a vaccine, discuss the risks of COVID-19 infection and benefits of vaccination, and ultimately provide a strong recommendation that all patients with IBD should receive the COVID-19 vaccine.\textsuperscript{22} Gastroenterologists can also dispel common myths and misconceptions regarding the COVID-19 vaccine by educating about the excellent safety and efficacy of the available vaccines.\textsuperscript{21}

**Clinical Effectiveness of COVID-19 Vaccines Among Individuals With Inflammatory Bowel Disease**

Ben-Tov and colleagues were the first to describe real-world vaccine effectiveness of BNT162b2 in a large Israeli population, including 12,231 vaccinated patients with IBD and 36,254 matched patients without IBD.\textsuperscript{23} They described very low rates of breakthrough infection in both cohorts at 7 days (0.19\% IBD vs 0.15\% non-IBD) and 14 days (0.14\% IBD vs 0.10\% non-IBD) after completion of the vaccine series. Of the 23 patients with IBD with a positive SARS-CoV-2 polymerase chain reaction test more than 7 days following vaccination, 9 were asymptomatic, 2 were hospitalized, and 1 died.

Real-world effectiveness of the COVID-19 vaccine was also described in a US Veterans Affairs cohort of 14,697 patients with IBD, including 7321 patients who received at least 1 dose of the COVID-19 vaccine.\textsuperscript{24} Complete vaccination (but not partial vaccination) was significantly associated with reduced rates of COVID-19
infection (hazard ratio, 0.31; 95% CI, 0.17-0.56; \( P < .001 \)), which corresponded to 80.4% effectiveness against development of COVID-19 infection. IBD medication classes were not associated with increased risk of COVID-19 infection following vaccination.

A large study from Israel showed similar COVID-19 vaccine effectiveness among patients with IBD and non-IBD controls. Specifically, the study did not find higher rates of SARS-CoV-2 infection among individuals on systemic corticosteroids or biologics, including TNF inhibitors, up to 22 weeks following vaccination.

**Humoral Immune Response to COVID-19 Vaccines**

Many studies have evaluated the humoral immune response to COVID-19 vaccines in individuals with IBD. Data from these studies are summarized here and in the Table. The vast majority of patients with IBD were able to mount a humoral immune response following completion of the COVID-19 vaccine series. Lower antibody levels have been noted in patients with IBD compared with non-IBD controls; however, a specific antibody threshold that confers protection against COVID-19 infection and/or hospitalization has not been identified. Regarding medication classes, lower antibody titers have been seen in individuals who are treated with anti-TNF monotherapy and combination therapy, tofacitinib, and systemic corticosteroids.

In the CLARITY IBD study, researchers described an attenuated humoral immune response to a single dose of COVID-19 vaccine (BNT162b2 or ChAdOx1 nCoV-19 [Oxford-AstraZeneca]) in patients with IBD who were treated with infliximab (n=328) or infliximab combination therapy (n=537) compared with those treated with vedolizumab (n=428). The study found that age 60 years or greater, immunomodulator use, and smoking were associated with lower anti-spike antibody concentrations. This study reaffirmed the need for complete COVID-19 vaccination, particularly for individuals treated with immune-modifying therapies. A follow-up study evaluated anti-RBD antibody levels 2 to 10 weeks following dose 2 (D2), rate of antibody decay following vaccination, and risk of breakthrough COVID-19 infection in 2306 infliximab-treated patients and 1045 vedolizumab-treated patients. The study found lower anti-RBD antibody levels, shorter antibody half-lives, and more frequent breakthrough COVID-19 infections (5.8% vs 3.9%) in patients treated with infliximab vs patients treated with vedolizumab. Additionally, individuals vaccinated with BNT162b2 had significantly higher anti-RBD antibody concentrations than those vaccinated with ChAdOx1 nCoV-19, and higher anti-RBD antibody levels following D2 were protective against breakthrough COVID-19 infection. These researchers also aimed to determine if specific immunosuppressive medications impacted humoral immune response to the COVID-19 vaccine. In a cohort of 370 patients with IBD and 120 healthy controls (HCs) who received 2 doses of ChAdOx1 nCoV-19, mRNA-1273, or BNT162b2, the authors found lower anti-RBD antibody concentrations in individuals treated with infliximab, infliximab plus thiopurine, and tofacitinib compared with HCs. There was no difference in anti-RBD antibody levels between HCs and thiopurine-treated, ustekinumab-treated, or vedolizumab-treated patients with IBD. On multivariable analysis, the mRNA vaccines were associated with higher anti-RBD antibody levels than the adenovirus vector vaccine.

In the PREVENT-COVID cohort, more than 95% of individuals with IBD, including those taking immunosuppressive medications, mounted a detectable antibody response to COVID-19 mRNA vaccines. This cohort included 1909 participants with IBD who received Ad26.COV2.S (n=94) or 2 doses of BNT162b2 (n=1123) or mRNA-1273 (n=692). On multivariable analysis, factors associated with lack of antibody response included older age, time from D2, BNT162b2 vs mRNA-1273 (OR, 2.1; 95% CI, 1.0-3.9), and anti-TNF combination therapy (OR, 4.2; 95% CI, 2.4-7.3). Individuals treated with mesalamines (OR, 0.3; 95% CI, 0.1-0.8) and ustekinumab (OR, 0.2; 95% CI, 0.05-0.8) were less likely to lack antibody response. Given the small number of individuals who received Ad26.COV2.S, these data were analyzed separately from mRNA vaccines. Only 76 out of 94 (81%) individuals who received Ad26.COV2.S had detectable anti-RBD antibodies 3 months following vaccination, with a median antibody level of 2.7 µg/mL (vs median antibody level of 17 µg/mL among mRNA vaccine recipients). Although the vast majority of patients with IBD were able to mount an antibody response to COVID-19 vaccines, older individuals as well as those treated with anti-TNF combination therapy may benefit most from an additional dose of COVID-19 vaccine.

The CORALE-IBD cohort included 582 vaccinated patients with IBD (342 received BNT162b2 and 240 received mRNA-1273), a majority of whom were treated with biologic and/or small molecule therapy. The authors found that 49%, 92%, and 99% of patients had positive antibody titers following D1 (5 days after D1 until the day of D2), D2 (2-13 days after D2), and 2 weeks following completion of the vaccine series, respectively. The authors described findings similar to PREVENT-COVID, with the lowest antibody levels in patients treated with anti-TNF combination therapy and systemic corticosteroids, and the highest antibody levels in individuals who are not...
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Participants With IBD and Vaccines Received</th>
<th>Assay Used and Time of Collection</th>
<th>Antibody Levels</th>
<th>Seroconversion Rate</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Lin et al³⁰</td>
<td>3351 participants</td>
<td>Roche Elecsys anti-SARS-CoV-2 spike immunoassay</td>
<td>Antibody levels lower in IFX-treated patients vs VDZ-treated patients</td>
<td>IFX: 94.1% VDZ: 98.7%</td>
<td>Study population included 2306 IFX-treated patients vs 1045 VDZ-treated patients</td>
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<td>• 1355 BNT162b2</td>
<td>• 2-10 weeks after D2</td>
<td>BNT162b2: IFX 567.3 U/mL vs VDZ 4601.1 U/mL</td>
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<td>• 1996 ChAdOx1 nCoV-19</td>
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<td>ChAdOx1 nCoV-19: IFX 183.9 U/mL vs VDZ 789.4 U/mL</td>
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<td>Antibody levels lower in IFX-treated patients vs VDZ-treated patients</td>
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<td>ChAdOx1 nCoV-19: IFX 183.9 U/mL vs VDZ 789.4 U/mL</td>
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<td>Kappelman et al²⁷</td>
<td>1909 participants</td>
<td>LabCorp Cov2Quant IgG assay</td>
<td>Mean 29.8 µg/mL</td>
<td>96% Values ≥1.0 µg/mL suggest vaccination and/or prior infection. A value of 1.0 µg/mL is equivalent to 25 IU/mL of the WHO International Standard</td>
<td>Values ≥1.0 µg/mL</td>
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<td>• 1123 BNT162b2</td>
<td>• 8 weeks after completion of vaccine series</td>
<td>Median • Either mRNA vaccine: 17 µg/mL • Ad26.COV2.S: 2.7 µg/mL</td>
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<td>• 692 mRNA-1273</td>
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<td>• 94 Ad26.COV2.S</td>
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<tr>
<td>Cerna et al³⁷</td>
<td>602 participants</td>
<td>SARS-CoV-2 IgG II assay (Abbott Laboratories)</td>
<td>Similar antibody titers in IBD and HC groups for both BNT162b2 and mRNA-1273 vaccines</td>
<td>100% in those with prior COVID-19 infection</td>
<td>Values ≥50 AU/mL are considered positive</td>
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<td></td>
<td>• 101 BNT162b2</td>
<td>• Before vaccination</td>
<td>Lower antibody titers in IBD cohort vs HCs in those who received ChAdOx1 nCoV-19</td>
<td>97.8% in those without history of COVID-19 infection</td>
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<td>• 212 mRNA-1273</td>
<td>• 8 weeks after completion of vaccine series</td>
<td>Higher antibody titers in individuals with prior COVID-19 infection</td>
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<td>• 289 ChAdOx1 nCoV-19</td>
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<td>168 HCs</td>
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<td>• 48 BNT162b2</td>
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<td>• 54 mRNA-1273</td>
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<td>• 66 ChAdOx1 nCoV-19</td>
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<td>Melmed et al³⁷</td>
<td>582 participants</td>
<td>SARS-CoV-2 IgG II assay (Abbott Laboratories)</td>
<td>Mean antibody levels</td>
<td>49% after D1 92% after D2 99% 2 weeks after D2</td>
<td>Values ≥50 AU/mL are considered positive</td>
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<td></td>
<td>• 342 BNT162b2</td>
<td>• After D1 (113)</td>
<td>• D1: 50 AU/mL • D2: 2042 AU/mL • 2 weeks: 10,233 AU/mL • 8 weeks: 3236 AU/mL • 16 weeks: 1445 AU/mL</td>
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<td>• 240 mRNA-1273</td>
<td>• After D2 (89)</td>
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<td>• 2 weeks after D2 (115)</td>
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<td>• 8 weeks after D2 (366)</td>
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<td>• 16 weeks after D2 (171)</td>
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<td>Pozdnyakova et al³³</td>
<td>353 participants</td>
<td>SARS-CoV-2 IgG II assay (Abbott Laboratories)</td>
<td>Log_{10} anti-spike antibody levels higher in those who received BNT162b2 and mRNA-1273 vaccines</td>
<td>100% Values ≥50 AU/mL are considered positive</td>
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<td>• 193 BNT162b2</td>
<td>• 2 weeks after complete vaccination</td>
<td>Mean antibody levels</td>
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<td>• 148 mRNA-1273</td>
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<td>• D1: 50 AU/mL • D2: 2042 AU/mL • 2 weeks: 10,233 AU/mL • 8 weeks: 3236 AU/mL • 16 weeks: 1445 AU/mL</td>
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<td>• 12 Ad26.COV2.S</td>
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<tr>
<td>Alexander et al³⁶</td>
<td>287 participants</td>
<td>Roche Elecsys anti-SARS-CoV-2 spike immunoassay</td>
<td>HCs: 1578.3 U/mL IFX: 156.8 U/mL IFX + thiopurine: 111.1 U/mL Thiopurine: 1019.8 U/mL Tofacitinib: 429 U/mL UST: 582.4 U/mL</td>
<td>96% overall HCs: 100% IFX: 90% IFX + thiopurine: 88% Thiopurine: 100% Tofacitinib: 100% UST: 96% VDZ: 100%</td>
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<td>• 112 BNT162b2</td>
<td>• 53-92 days after D2</td>
<td>HCs: 1578.3 U/mL IFX: 156.8 U/mL IFX + thiopurine: 111.1 U/mL Thiopurine: 1019.8 U/mL Tofacitinib: 429 U/mL UST: 582.4 U/mL</td>
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<td>• 171 ChAdOx1 nCoV-19</td>
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<td>88 HCs</td>
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<td>Charilaou et al⁴⁰</td>
<td>185 participants</td>
<td>Anti-spike total antibody titer test</td>
<td>Mean 306 µ/mL</td>
<td>98% Various antibody tests were used for this study</td>
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<td></td>
<td>• 111 BNT162b2</td>
<td>• Not at predetermined time following vaccination; anytime between 4/15/21 and 10/19/21</td>
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<td>• 65 mRNA-1273</td>
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<td>• 9 Ad26.COV2.S</td>
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<th>Study</th>
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<th>Antibody Levels</th>
<th>Seroconversion Rate</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Edelman-Klapper et al³⁶      | 185 participants with IBD  
   • 185 BNT162b2  
   • 73 HCs  
   • 73 BNT162b2 | SARS-CoV-2 IgG II assay (Abbott Laboratories)  
   • Prevaccine  
   • 14-21 days after D1  
   • 21-35 days after D2 | D1  
   • Anti-TNF IBD: 340 AU/mL  
   • Non–anti-TNF IBD: 710 AU/mL  
   • HCs: 1039 AU/mL  
   D2  
   • Anti-TNF IBD: 3787 AU/mL  
   • Non–anti-TNF IBD: 8320 AU/mL  
   • HCs: 10,979 AU/mL | 100% HCs and 93% with IBD after D1  
   100% of all participants after D2 | Antibody levels 2- to 3-fold lower in those treated with anti-TNF vs non–anti-TNF–treated patients after D1 and D2 |
| Caldera et al³⁵             | 122 participants with IBD  
   • 59 BNT162b2  
   • 62 mRNA-1273  
   • 7 BNT162b2  
   • 52 mRNA-1273  
   • 1 unknown | LabCorp Cov2Quant IgG assay  
   • 4 weeks after D2 | Median 31 µg/mL  
   Lower antibody titers in those with IBD vs HCs: median 31 vs 118 µg/mL  
   Higher antibody titers in those who received mRNA-1273 vs BNT162b2 | 97% | Values ≥1.0 µg/mL suggest vaccination and/or prior infection. A value of 1.0 µg/mL is equivalent to 25 IU/mL of the WHO International Standard |
| Garrido et al³⁴             | 115 participants  
   • 64 BNT162b2  
   • 23 mRNA-1273  
   • 16 Ad26.COV2.S  
   • 12 ChAdOx1 nCoV-19 | BioPlex 2200 SARS-CoV-2 IgG Panel (Bio-Rad)  
   • 8 weeks after completion of vaccine series | 92.2% overall  
   BNT162b2: 96.9%  
   mRNA-1273: 100%  
   ChAdOx1 nCoV-19: 91.7%  
   Ad26.COV2.S: 62.5% | Values ≥10 U/mL are considered positive |
| Frey et al³¹                | 75 participants  
   • 43 BNT162b2  
   • 32 mRNA-1273 | Roche Elecsys anti-SARS-CoV-2 enzyme immunoassay  
   • 1, 3, and 6 months after completion of vaccine series | Mean/median values not reported. 59/75 (78.7%) with high-positive antibody response and 16/75 (21.3%) with low-positive antibody response | 100% at 6 months | Values ≥0.8 U/mL are considered positive. Low-positive is 0.8-50 U/mL and high-positive is >50 U/mL |
| Wong et al³⁸                | 48 participants, including 26 who received 2 doses of mRNA vaccine  
   • 23 BNT162b2  
   • 25 mRNA-1273 | Siemens Healthineers  
   SARS-CoV-2 Total (COV2T) and SARS-CoV-2 IgG (sCOVG) assays  
   • Specimens collected at infusions and clinic appointments, not timed to vaccination dates | 100% in those who received 2 doses of mRNA vaccine |                              |                                |
| Spencer et al³²             | 20 pediatric participants  
   • 14 BNT162b2  
   • 5 mRNA-1273  
   • 1 Ad26.COV2.S | COVID-SeroKlir semiquantitative SARS-CoV-2 IgG assay (Kantaro Biosciences)  
   • Specimens collected at infusions and clinic appointments, not timed to vaccination dates | 18/20 (90%) with high-titer antibodies | 100% | High titer or strongly positive is defined as ≥960 titer or >40 AU/mL. Moderately positive is defined as 320-960 titer or 16-39 AU/mL. Weakly positive is defined as 80-160 titer or 5-15 AU/mL |

(Table continues on following page)
immunosuppressed as well as individuals taking vedolizumab and ustekinumab. CORALE-IBD also evaluated humoral immune response to the Ad26.COV2.S vaccine (n=12) vs mRNA-1273 (n=148) or BNT162b2 (n=193) 2 weeks or longer after complete vaccination.33 Positive anti-spike antibodies were present in 100%, 99%, and 90% of patients receiving the mRNA-1273, BNT162b2, and Ad26.COV2.S vaccines, respectively. Anti-spike antibody levels were significantly higher at 2 and 8 weeks postvaccination among individuals who received mRNA vaccines than those who received Ad26.COV2.S, similar to PREVENT-COVID findings.27,33 Additionally, a smaller study that evaluated seroconversion rates following COVID-19 vaccination found that individuals who received Ad26.COV2.S had significantly lower rates of seroconversion compared with other vaccines (Ad26.COV2.S, 62.5%; BNT162b2, 96.9%; mRNA-1273, 100%; ChAdOx1 nCoV-19, 91.7%; P<.001).34 These data suggest that mRNA vaccines may be more effective in individuals with IBD.

Studies out of Israel and the Czech Republic have also reported significantly lower anti-spike antibody levels in patients treated with anti-TNF monotherapy or anti-TNF combination therapy, and recipients of ChAdOx1 nCoV-19.36,37 There was no correlation between biologic drug levels at time of vaccination and serologic response to the COVID-19 vaccine.36 Several small studies also evaluated humoral immune response to COVID-19 vaccines among individuals with IBD, with results summarized in the Table.38-42

At this time, there are only 2 peer-reviewed studies evaluating humoral immune response to an additional dose of a COVID-19 vaccine after completion of the initial vaccine series. Long and colleagues described 659 participants in PREVENT-COVID who had anti-RBD antibody levels checked 8 weeks following the initial vaccine series and 3 to 8 weeks after an additional COVID-19 vaccine dose.43 Following the additional vaccine, 99.5% of participants had a detectable antibody titer. Among 47 individuals with undetectable antibodies after the initial vaccine series, 45 individuals seroconverted with an additional vaccine dose; however, the median antibody level recipients (median of 22 µg/mL vs 38 µg/mL; P<.001). Similar to other studies, significantly lower antibody levels were observed in patients taking immunosuppressive medications vs no treatment or treatment with aminosalicylates or vedolizumab (median of 26 µg/mL vs 59 µg/mL; P=.003).

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The HERCULES study evaluated the humoral immune response to mRNA-199-19 vaccines among 122 individuals with IBD compared with 60 HCs.35 All HCs and 97% (118/122) of patients with IBD developed anti-RBD antibodies after COVID-19 vaccination; however, antibody levels were significantly lower in patients with IBD than in HCs (median of 31 µg/mL vs 118 µg/mL; P<.001) and in BNT162b2 vs mRNA-1273

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<td>17/19 (89%) had highest measurable levels on Roche assay</td>
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<td>28 participants with IBD4</td>
<td>LIAISON SARS-CoV-2 Trimerics IgG CLIA</td>
<td>D1: IBT: 57.2 BAU/mL; HCs: 105.0 BAU/mL</td>
<td>D1: IBD: 71.4%; HCs: 85.1%</td>
<td>D2: IBD: 91.7%; HCs: 100%; Values ≥13 AU/mL or ≥33.8 BAU/mL are defined as seropositive</td>
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Ad26.COV2.S, Johnson & Johnson COVID-19 vaccine; AU, activity units; BAU, binding antibody units; BNT162b2, Pfizer-BioNTech COVID-19 vaccine; ChAdOx1 nCoV-19, Oxford-AstraZeneca COVID-19 vaccine; CLIA, Clinical Laboratory Improvement Amendments; D1, vaccine dose 1; D2, vaccine dose 2; HCs, healthy controls; IBD, inflammatory bowel disease; IFX, infliximab; IgG, immunoglobulin G; mRNA-1273, Moderna/National Institutes of Health COVID-19 vaccine; TNF, tumor necrosis factor; UST, ustekinumab; VDZ, vedolizumab; WHO, World Health Organization.

4Only 12 participants with IBD and 12 HCs received D2.

### Table. (Continued) Studies Evaluating the Humoral Immune Response to Initial COVID-19 Vaccine Series Among Individuals With IBD

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4Only 12 participants with IBD and 12 HCs received D2.
in this group was significantly lower compared with participants with initially detectable antibodies (13 µg/mL vs 51 µg/mL; \(P=0.017\)). Anti-TNF combination therapy was associated with a reduction in anti-RBD antibody titers. Although both BNT162b2 and mRNA-1273 additional vaccines were associated with a significant increase in antibody titers compared with baseline, the highest increases in antibody titers were observed following an additional dose of mRNA-1273. Schell and colleagues described 85 participants with IBD who received an additional dose of COVID-19 vaccine and underwent antibody measurement after a median of 37 days.\(^4\) In their cohort, 100% of participants had detectable anti-RBD antibodies, with a median antibody concentration of 68 µg/mL following receipt of a third dose of COVID-19 vaccine. The authors also observed higher antibody concentrations among patients who received 3 doses of mRNA-1273 vaccine vs BNT162b2.

**T-cell Response to COVID-19 Vaccination**

Many studies have evaluated the humoral immune response to COVID-19 vaccination in patients with IBD; however, less is known about the cellular or T-cell response to vaccination in this patient population. Reuken and colleagues compared the cellular immune response, including interferon-\(\gamma\) and TNF-\(\alpha\) response, of 28 patients with IBD with 27 matched non-IBD controls.\(^4\) Following D1, 71.8% of patients with IBD had detectable antibodies; however, even in the absence of antibodies, individuals with IBD had similar T-cell responses compared with controls. Furthermore, the T-cell response was not influenced by the various classes of immunosuppressive medications used to treat IBD. Similarly, a study by Li and colleagues reported that all patients with IBD (\(n=303\)) demonstrated a T-cell response following vaccination.\(^4\) Specifically, the study described a preserved T-cell response among patients on anti-integrin and anti-interleukin 12/23 therapies, whereas patients treated with anti-TNF biologics demonstrated an augmented T-cell response.

In the CLARITY IBD study, antibody concentrations following D2 of BNT162b2 and ChAdOx1 nCoV-19 were lower in patients treated with infliximab (\(n=2306\)) vs vedolizumab (\(n=1045\)); however, there were no differences in anti-spike T-cell responses between the 2 groups after 1 or 2 doses of BNT162b2 or ChAdOx1 nCoV-19.\(^3\)

Mayorga Ayala and colleagues evaluated the anti-spike antibody level and T-cell response via interferon-\(\gamma\) release assay 6 weeks following D2 of a COVID-19 mRNA vaccine among patients with IBD treated with an anti-TNF biologic and/or thiopurine.\(^4\) Anti-spike antibodies were detectable in the entire cohort, and T-cell response was evident in 92% treated with anti-TNF monotherapy, 87% with thiopurine monotherapy, and 83% with anti-TNF combination therapy. Despite immunosuppression, a vast majority of these patients demonstrated both humoral and cellular immune response to the mRNA COVID-19 vaccines.

**Safety and Adverse Events Following COVID-19 Vaccination**

The clinical trials that led to FDA EUA and/or approval of COVID-19 vaccines showed low rates of AEs but did not include individuals with IBD. As a result, many patients with IBD have expressed concerns regarding IBD flare following vaccination or development of vaccine-related AEs. The following summarizes the literature supporting the excellent safety profile and tolerability of COVID-19 vaccination among individuals with IBD.

Hadi and colleagues described the safety of COVID-19 vaccination in patients with IBD vs the general population, including AEs within 1 day of vaccination and AEs of special interest per the CDC up to 30 days after vaccination.\(^4\) Of the 864,575 individuals who received the COVID-19 vaccination during the study period, 5562 individuals had a preexisting diagnosis of IBD (52.8% were treated with a biologic or immunomodulator). Fewer than 10 individuals with IBD developed an immediate reaction to the COVID-19 vaccine. Additionally, 113 AEs of special interest were reported in this group; however, when patients with IBD were compared with a non-IBD matched cohort, there were no significant differences in AEs, AEs of special interest, or 30-day hospitalization rates following COVID-19 vaccination between the 2 groups. There was also no difference between rates of AEs of special interest among patients with or without biologic or immunomodulator use (2.2% vs 1.67%; relative risk, 1.32; 95% CI, 0.85-2.06).

Botwin and colleagues surveyed 246 vaccinated adults with IBD about postvaccination symptoms 8 days after each dose of COVID-19 vaccine.\(^4\) Fifty-seven percent had received BNT162b2 and 43% had received mRNA-1273, and a majority of patients (79.7%) were receiving biologics, small molecules/immunomodulators, and/or systemic corticosteroids at the time of vaccination. The rate of development of postvaccination AEs was 39% after D1 and 62% after D2, with fatigue as the most common systemic AE after both D1 (23%) and D2 (45%), followed by headache/dizziness and fevers/chills. The majority of AEs were nonsevere; however, 3 participants were hospitalized following D1 for fatigue and gastrointestinal symptoms, and 2 participants were hospitalized after D2 for fever, gastrointestinal symptoms, headache, and fatigue. Risk factors for the development...
of AEs included age less than 50 years (D1, D2), prior COVID-19 infection (D1), and ulcerative colitis diagnosis (D2). Individuals with IBD treated with biologic therapy were less likely to develop postvaccination AEs (36% vs 47% after D1, P=.17; 54% vs 82% after D2, P=.013).

In a larger cohort (n=3316), Weaver and colleagues described the development of localized and systemic AEs within 1 week of COVID-19 vaccine D1 or D2.05 Tenderness (68% after D1; 68% after D2) and pain (66% after D1; 65% after D2) at the injection sites were the most frequently reported localized AEs, and fatigue (46% after D1; 68% after D2) and headache (32% after D1; 51% after D2) were the most commonly reported systemic AEs. Systemic AEs were more common following D2 than following D1. A total of 16 participants (10 after D1; 6 after D2) visited the emergency department or were hospitalized owing to vaccine-related AEs.05 Prior COVID-19 infection was a risk factor for development of severe localized and systemic AEs after D1, and female sex, vaccine manufacturer, and anti-TNF use were associated with severe systemic reaction after D1. Higher rates of severe injection site reaction were seen after D2 of mRNA-1273 vs BNT162b2. Additionally, age less than 50 years, female sex, mRNA-1273 vaccine, anti-TNF use, and vedolizumab use were associated with severe systemic reactions after D2.

Limited data are available regarding vaccine-related AEs following an additional (third) dose of COVID-19 vaccine. A majority of participants in PREVENT-COVID tolerated the additional vaccine dose well, with 44% reporting no side effects and 24%, 25%, and 6% reporting mild, moderate, and severe side effects, respectively.43 In the studies by Botwin and colleagues and Weaver and colleagues,49,50 rates of AEs among individuals with IBD were similar to those reported in the COVID-19 vaccine clinical trials.3-5 No consistent risk factors for severe AEs were identified that would warrant a change in recommendations for COVID-19 vaccination in specific categories of patients with IBD.49,50

Rates of Inflammatory Bowel Disease Flare Following COVID-19 Vaccination

Several studies have evaluated for IBD flare or worsening gastrointestinal symptoms following COVID-19 vaccination. Hadi and colleagues described no difference in new corticosteroid prescriptions at 1 month following COVID-19 vaccination in a matched cohort of vaccinated and unvaccinated patients with IBD.48 Similarly, data from PREVENT-COVID demonstrated low rates of IBD flare, with 71 of 3316 participants (2.1%) reporting worsening IBD symptoms following COVID-19 vaccination.45 In this cohort, IBD flare was defined as worsening abdominal pain, bowel frequency, rectal bleeding, and/or extraintestinal manifestations following D1 or D2 and a need to change or add IBD medication owing to worsening symptoms within 1 month of vaccination. Additionally, results from the CORALE-IBD study reported low rates of gastrointestinal symptoms following vaccination, with 6% of participants describing symptoms after D1 and 11.5% after D2.45 Finally, Lev-Tzion and colleagues evaluated the impact of COVID-19 vaccination on IBD disease course in a stringently matched cohort of 707 vaccinated patients with IBD and unvaccinated patients with IBD with a median follow-up of 14 weeks.53 IBD flare was defined as need for escalation of treatment, start of corticosteroids or enema, or need for hospitalization. Rates of IBD flare were not significantly different between the 2 groups, with 29% of individuals in the vaccinated group meeting criteria for flare vs 26% in the unvaccinated group (P=.30). These data demonstrate low rates of IBD flare following COVID-19 vaccination.

Conclusion

COVID-19 vaccines are safe and effective in individuals with IBD, including those taking immune-modifying therapies. Rates of vaccine-related AEs are similar to those reported in the general population, and low rates of IBD flare have been described after vaccination. The vast majority of patients with IBD are able to mount a humoral immune response following completion of a COVID-19 vaccine series regardless of medication exposure; however, higher rates of seroconversion have been noted in patients with IBD who completed a mRNA vaccine series vs those who received an adnovirus vector vaccine. Because lower antibody concentrations have been described in older individuals as well as patients treated with anti-TNF monotherapy and combination therapy, tofacitinib, and systemic corticosteroids, these groups may benefit most from an additional dose of mRNA vaccine. Owing to the emergence of new COVID-19 variants and waning immunity from natural infection and vaccination over time, vaccine registries among patients with IBD will continue to help inform clinical practice.
Disclosures
Dr Weaver has consulted for AbbVie and Bristol Myers Squibb. Dr Kappelman has consulted for AbbVie, Janusen, Pfizer, and Takeda; is a shareholder in Johnson & Johnson; and has received research support from Pfizer, Takeda, Janssen, AbbVie, Eli Lilly, Genentech, Boehringer Ingelheim, Bristol Myers Squibb, Celtrion, and Arena Pharmaceuticals. Dr Long has received research support/gifts from Pfizer and has consulted for AbbVie, Bristol Myers Squibb, Celtrion, Eli Lilly, Genentech, Gilead Sciences, Janssen, Pfizer, Roche, Takeda, TARGET Pharma Solutions, and Theravance.

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