# COVID-19 vaccine use in immunocompromised patients: A commentary on evidence and recommendations

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**Purpose.** While COVID-19 vaccine emergency use authorization (EUA) deemed the vaccines to be effective and safe for public use, the phase 3 trials leading to EUA predominantly excluded patients with immunocompromising conditions. Immunocompromised patients make up a significant proportion of the population, and in light of recent mass vaccination efforts, we aim to review current evidence and recommendations of COVID-19 vaccines in 4 patient populations with immunocompromising disorders or conditions: human immunodeficiency virus (HIV) infection, solid organ transplantation, rheumatoid arthritis, and inflammatory bowel disease.

**Summary.** Given the evolving data on the safety and efficacy of the approved COVID-19 vaccines in the immunocompromised population, it is vital that pharmacists and other immunizing providers understand the current data and recommendations and provide the public with accurate information. To date, the only immunocompromised subgroup included in phase 3 COVID-19 vaccine trials have been those with HIV infection. However, recent retrospective trials have provided reassuring data on the safety of the COVID-19 vaccine in immunocompromised patients, and the interim analysis of the Moderna phase 3 trial produced promising data on efficacy in HIV-infected patients. Presently, the US Centers for Disease Control and Prevention, British Society for Immunology, and various other governmental and professional societies and organizations endorse COVID-19 vaccination in the immunocompromised population.

**Conclusion.** While additional data is needed to determine the effects of immunocompromising medical conditions and immunosuppressing medications on the efficacy of the vaccine, the benefits of vaccination is anticipated to outweigh theoretical risks. Thus, COVID-19 vaccination is recommended for immunocompromised patients at this time, and providers should make efforts to decrease vaccine hesitancy in this population through education and reassurance.

**Keywords:** COVID-19 vaccines, HIV, immunocompromised, inflammatory bowel disease, rheumatoid arthritis, solid organ transplant

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Coronavirus disease (COVID-19), which was first identified in December 2019, is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and transmitted from person to person through respiratory droplets. Most cases are self-limited, with a wide range of symptoms such as fever, chills, cough, shortness of breath, headache, fatigue, body aches, new loss of smell or taste, nausea, vomiting, and diarrhea.[1] As of June 2021, there had been over 33 million COVID-19 cases with almost 600,000 deaths in the United States alone, thus prompting the need for an effective and safe vaccine to reduce COVID-19 spread and complications.[2]

In May 2020, the US government announced Operation Warp Speed to accelerate the development, production, and distribution of COVID-19

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vaccines.[3] Currently, there are 3 vaccines granted emergency use authorization (EUA), which facilitates the availability and use of medical products not yet approved by the US Food and Drug Administration (FDA) during public health emergencies, such as the current COVID-19 pandemic.[4] In December 2020, both the Pfizer-BioNTech and Moderna COVID-19 vaccines were granted EUA by FDA. Both of these vaccines contain nucleoside-modified messenger RNA (mRNA) formulated in lipid particles, which enable delivery into the host cells to allow expression of the SARS-CoV-2 spike protein. As a result, an immune response to the spike protein is elicited, which protects against COVID-19.[5,6] In February 2021, FDA issued an EUA for the Janssen COVID-19 vaccine. This vaccine is composed of a recombinant, replication-incompetent human adenovirus type 26 vector that enters human cells to allow expression of the spike protein without virus propagation; as with the mRNA vaccines, the spike protein then elicits an immune response, which protects against COVID-19.[7] Since neither the mRNA nor viral vector vaccines contain live virus, the development of COVID-19 as a result of vaccine administration is not possible.

While the EUA of COVID-19 vaccines allowed for timely dissemination and public use, the trials informing the EUA largely excluded patients with immunocompromising conditions, leading to concerns about vaccine efficacy and potential effects of new vaccine technology among this patient population. Per the 2013 National Health Interview Survey, nearly 3% of US adults self-reported being immunosuppressed, and this proportion is expected to have increased due to greater life expectancy as a result of treatment advancements.[8] Vaccine misperceptions and hesitancy in this population could greatly hinder the efforts to get a majority of the US population vaccinated. Here we review current recommendations and evidence of vaccination in the immunocompromised population to help optimize COVID-19 immunization rates.

## KEY POINTS

- The US Centers for Disease Control and Prevention, British Society for Immunology, and various other government and professional organizations with expertise in specific immunocompromised conditions have endorsed COVID-19 vaccination in these populations.
- More data is needed to determine the effects of immunosuppressing medications on the efficacy of COVID-19 vaccines, but the benefit of vaccination is expected to outweigh the risks.
- It is vital that pharmacists and other immunizing providers understand current data and recommendations for COVID-19 vaccines to optimize immunization rates and minimize vaccine hesitancy among immunocompromised patients.

## General recommendations regarding vaccines in the immunocompromised population

The Advisory Committee on Immunization Practices (ACIP) has published *General Best Practice Guidelines for Immunization*, which includes a section regarding immunizations in individuals with altered immunocompetence. This guidance is applicable to patients with primary (eg, congenital) immunodeficiency and secondary immunodeficiency acquired as a result of a disease process or its therapy (eg, human immunodeficiency virus [HIV] infection, hematopoietic malignancies, radiation therapy, and treatment with immunosuppressive medications). In general, live vaccines in this patient population are commonly deferred until immune function has improved, given safety concerns relating to uninhibited growth of attenuated live virus vaccine. Conversely, administration of vaccines containing inactivated virus may need to be repeated due to suboptimal efficacy.[9]

In regards to COVID-19 vaccines, all 3 products with EUA in the United States contain warnings that "immunocompromised persons, including those receiving immunosuppressant therapy," may have a diminished immune response to the COVID-19 vaccine.[5-7] However, both the Centers for Disease Control and Prevention (CDC) and the British Society for Immunology (BSI) have released statements regarding their recommendations for COVID-19 vaccination in this population. CDC acknowledges limited data is available to establish COVID-19 vaccine safety and efficacy in this patient population but recognizes the population's increased risk for severe COVID-19. Since the 3 currently authorized COVID-19 vaccines are not live, CDC confirms these vaccines can be safely administered to immunocompromised individuals. However, data to inform optimal timing of COVID-19 vaccination among those planning to receive immunosuppressive therapy is lacking; thus, CDC recommends following the *General Best Practice Guidelines for Immunization* by completing vaccination ideally at least 2 weeks prior to initiation of immunosuppressive therapies. If that is not possible, patients on immunosuppressive therapy may still receive the COVID-19 vaccine. CDC does not recommend antibody testing to assess for immunity to SARS-CoV-2 following vaccination, as the clinical utility of postvaccination testing has not been established. Additionally, revaccination is not recommended in the setting of low antibody titers or if patients regain immune competence.[10]

The statement released by BSI echoes these sentiments, stating that all COVID-19 vaccines approved for use in the United Kingdom (the

Pfizer-BioNTech, AstraZeneca/Oxford, and Moderna vaccines) are safe for use in immunocompromised patients, as none contain active SARS-CoV-2. The BSI notes that vaccination may provide a lower level of protection in this population but will still offer a certain amount of protection against the virus. Additionally, BSI notes that those who may be severely immunocompromised or undergoing organ or stem cell transplant should consult their medical team about the most suitable time for COVID-19 vaccination.[11]

## Recommendations and data for COVID-19 vaccination in specific immunocompromised populations

Guidance regarding the use of COVID-19 vaccines in specific immunocompromised conditions has been published by many professional societies, but few studies on vaccine safety and efficacy in these specific populations exist. Given our clinical practice areas and the small number of COVID-19 vaccine studies available for certain conditions at the time of writing (March through May 2021), we aimed to review current recommendations and data for 4 specific immunocompromised populations: HIV-infected patients ("patients with HIV" hereafter), solid organ transplant recipients (SOTRs), patients with inflammatory bowel disease (IBD), and patients with rheumatoid arthritis (RA). To identify studies beyond the COVID-19 vaccine phase 3 trials, we conducted a literature search of PubMed using the following keywords: *COVID-19 vaccine, SARS-CoV-2 vaccines, human immunodeficiency, organ transplantation, transplant recipients, inflammatory bowel disease, rheumatoid arthritis,* and *immunocompromised*. All English-language articles on relevant clinical studies were assessed and reviewed if appropriate. Additionally, for the immunocompromised populations not included in our paper, we have provided links to resources relating to COVID-19 vaccine recommendations for these populations in Table 1.

**HIV-infected patients.** Patients with HIV are the only immunocompromised patient population thus far to be included in the phase 3 COVID-19 vaccine studies. The Pfizer-BioNTech vaccine was studied in patients with stable HIV infection, defined as those who had a CD4 count of >200 cells/mm$^3$, had an undetectable viral load, and were on stable antiretroviral therapy for at least 6 months prior to enrollment. Patients with HIV comprised 0.3% of the study population (121 patients in total) but were not included in the primary efficacy and safety analysis.[12] The Moderna vaccine study included a slightly larger number of patients with stable HIV infection (159, or 0.06% of the total study population). Stable HIV infection in this study was defined as a CD4 count of >350 cells/mm$^3$ and undetectable viral load within 1 year.[13] Based on a report from the December 2020 FDA Vaccines and Related Biological Products Advisory Committee meeting, no patients with HIV developed COVID-19 between 14 days following the second Moderna vaccine dose and for a median of 2 months after.[14] The Janssen vaccine study included the largest number of patients with HIV thus far: 1,218, or 2.8% of study participants[15] Similar to the Pfizer-BioNTech vaccine study, patients with HIV were also not included in the primary safety and efficacy analysis of the Janssen vaccine.

Although patients with HIV were included in the COVID-19 vaccine studies, there is limited published data on this population from these studies. The National Institutes of Health (NIH) Office of Acquired Immunodeficiency Syndrome Research Advisory Council has published interim guidance for COVID-19 and patients with HIV.[16] In this NIH guidance, it is recommended that all people with HIV be vaccinated against COVID-19 regardless of CD4 count or viral load, as the potential benefits are perceived to outweigh potential risks. The advisory council notes that patients with HIV who are well controlled on antiretroviral therapy historically respond well to other vaccines administered in clinical practice. However, the guidance recognizes that the safety and efficacy of the COVID-19 vaccine specifically in this population have not been fully reported.

**Patients with solid organ transplant history.** Patients with a history of solid organ transplant were excluded from phase 3 studies of all 3 COVID-19 vaccines currently available in the United States. However, a small, nonrandomized, observational study was conducted to evaluate the safety of the first COVID-19 vaccine dose in SOTRs receiving immunosuppression treatment. This study included 187 SOTRs who received their first dose of vaccine, with 50% receiving the Pfizer-BioNTech and 50% receiving the Moderna vaccine. The median time since transplantation was 6 years, and patients were recipients of kidney (52%), liver (19%), heart (14%), lung (9%), kidney/pancreas (3%), or multiorgan (3%) transplants. In an online questionnaire completed 1 week post vaccination, there were no self-reported cases of polymerase chain reaction (PCR)–confirmed COVID-19 diagnosis. Additionally, no patients reported acute organ rejection, neurological diagnoses (Bell's palsy, Guillain-Barre syndrome, or neuropathy), or allergic reactions requiring epinephrine. Adverse events were largely consistent with expected vaccine reactogenicity and reported at rates similar to rates in non-SOTRs in phase 3 trials (mild injection site pain, 61%; fatigue, 38%; headaches, 32%; myalgias, 15%; chills, 9%; and fever, 4%).[17] Although limited because it did not evaluate COVID-19 vaccine efficacy, this study provided early, reassuring safety data in the SOTR population.

Another, more recent study in the SOTR population evaluated COVID-19 vaccine efficacy. This study included 436 transplant recipients across the United States, none with a prior PCR-confirmed diagnosis of COVID-19, who received their first dose of COVID-19 vaccine (52% the Pfizer-BioNTech vaccine and 48% the Moderna vaccine). Patients provided blood samples,

**Table 1.** Government and Professional Organizations Endorsing COVID-19 Vaccine Administration in Immunocompromised Populations

| Organization | Web Resources |
|---|---|
| US Centers for Disease Control and Prevention | https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html<br>See "Immunocompromised People"section |
| British Society for Immunology | https://www.immunology.org/news/bsi-statement-covid-19-vaccines-for-patients-immunocompromised-immunosuppressed |
| Human Immunodeficiency Virus Medicine Association | https://www.hivma.org/globalassets/idsa/public-health/covid-19/covid-19-vaccines-hiv-faq-.pdf |
| US Department of Health and Human Services | https://clinicalinfo.hiv.gov/en/guidelines/covid-19-and-persons-hiv-interim-guidance/interim-guidance-covid-19-and-persons-hiv?view=full<br>https://www.hiv.gov/hiv-basics/staying-in-hiv-care/other-related-health-issues/coronavirus-and-hiv-faqs |
| International Society of Heart and Lung Transplantation | https://ishlt.org/covid-19-information |
| American Society of Transplant Surgeons | https://asts.org/advocacy/covid-19-resources#.YLpAdNVKipo |
| American Society of Transplantation | https://www.myast.org/statement-covid-19-vaccination-solid-organ-transplant-recipients<br>https://www.myast.org/covid-19-vaccine-faq-sheet |
| Crohn's and Colitis Foundation | https://www.crohnscolitisfoundation.org/coronavirus/vaccines |
| International Organization for the Study of Inflammatory Bowel Disease | https://ioibd.org/sars-cov-2-vaccination-for-patients-with-inflammatory-bowel-diseases-recommendations-from-an-international-consensus-meeting/ |
| American College of Rheumatology | https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf<br>https://www.rheumatology.org/Portals/0/Files/ACR-Information-Vaccination-Against-SARS-CoV-2.pdf |
| National Multiple Sclerosis Society | https://www.nationalmssociety.org/coronavirus-covid-19-information/multiple-sclerosis-and-coronavirus/covid-19-vaccine-guidance |
| National Comprehensive Cancer Network | https://www.nccn.org/covid-19 |
| American Society of Clinical Oncology | https://www.asco.org/asco-coronavirus-resources/covid-19-vaccines-patients-cancer |
| American Cancer Society | https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/low-blood-counts/infections/covid-19-vaccines-in-people-with-cancer.html |
| Immune Deficiency Foundation | https://primaryimmune.org/news/covid-19-update-vaccines-treatment-options |

which were tested using an enzyme immunoassay to detect antibodies to the SARS-CoV-2 spike protein. At a median of 20 days after the first dose of vaccine, antibodies were detectable in 17% of participants. Transplant recipients receiving antimetabolite maintenance immunosuppression therapy (eg, mycophenolate, azathioprine) were less likely to develop an antibody response than those not receiving such therapy (37% vs 63%; adjusted incidence rate ratio [IRR], 0.22 [95% CI, 0.15-0.34], $P < 0.001$). Additionally, those receiving the Moderna vaccine were more likely to develop antibody response than those receiving the Pfizer-BioNTech product (69% vs 31%; adjusted IRR, 2.15 [95% CI, 1.29-3.57], $P = 0.003$). Lastly, older transplant recipients were less likely to develop a response (adjusted IRR, 0.83 [95% CI, 0.73-0.93] per 10 years, $P = 0.002$). Given that this study lacked a concurrent immunocompetent control group and represented the humoral response to only the first dose in a 2-dose vaccine series, conclusions to be drawn regarding immunologic response in the immunocompromised population are limited.[18] However, the same investigators conducted an additional study to assess antibody response after the second dose of a SARS-CoV-2 mRNA vaccine in 658 transplant recipients (of whom 396 were participants in the original study). None of these participants had previously experienced COVID-19 per PCR analysis. At a median of

29 days after the second dose of the vaccine, antibody was detectable in 357 participants (54%; 95% CI, 50%-58%). Of the overall study population, 15% had measurable antibody response after both doses, 46% had no antibody response after both doses, and 39% had measurable but low antibody response after the second dose only. Among the 473 patients receiving antimetabolites, 43% had an antibody response after both doses, whereas in patients not receiving antimetabolites, 83% had a response after both doses. Limitations of this study included lack of (1) an immunocompetent control group and (2) assessment of COVID-19 incidence post vaccination. Nonetheless, the investigators concluded that while there was an improvement in antibody responses after dose 2 compared to dose 1, transplant recipients may remain at risk for COVID-19 after being fully vaccinated.[19]

To date, various transplant societies have endorsed COVID-19 vaccinations in this population. The International Society of Heart and Lung Transplantation (ISHLT) encourages COVID-19 vaccination in those awaiting or post cardiothoracic transplantation, stating that the potential advantage outweighs concerns for reduced vaccine efficacy or perceived lack of safety. Specifically, ISHLT recommends delaying vaccination at least 1 month from transplant surgery and 3 to 6 months from use of T cell–depleting agents such as antithymocyte globulin or specific B cell–depleting agents such as rituximab.[20] The American Society of Transplant Surgeons (ASTS) released vaccine recommendations in December 2020, deeming the Pfizer-BioNTech and Moderna vaccines to be safe for the transplant population, but noted that vaccination consequences are unknown. The American Society of Transplantation (AST) released COVID-19 vaccination guidance in February 2021, encouraging that pre- and posttransplant patients get vaccinated, as benefits outweigh any unproven risks. At the time of this guidance, only the Pfizer-BioNTech and Moderna vaccines were available. Guidance on timing of vaccination was similar to ISHLT guidance, with recommendations that patients should ideally be vaccinated at least 2 weeks prior to transplant or 1 month after transplant surgery.[21]

Finally, a joint statement from numerous transplant organizations regarding the recent published studies examining the response to COVID-19 vaccines in SOTRs was released in May 2021. The statement acknowledged the reduced antibody response to the COVID-19 vaccines in SOTRs but noted that this population historically has lower rates of immune responses to vaccines in general. Additionally, the organizations stressed that further studies are needed to assess vaccine effectiveness for protection against severe COVID-19, an important clinical endpoint. They strongly cautioned against concluding that low antibody response rates would lead to reduced clinical effectiveness and emphasized the need for additional studies. For example, transplant patients historically have had low antibody response to influenza vaccination, yet they have experienced reduced influenza-related lower respiratory tract infections and hospitalizations post vaccination. Presently, various transplant societies recommend pretransplant vaccination of all solid organ transplant candidates when feasible, vaccinations in SOTRs, and maintenance of protective measures such as wearing a mask and following social distancing regardless of vaccination status.[22]

**Patients with IBD.** Patients with IBD or on immunotherapy for IBD were also excluded from the COVID-19 vaccine phase 3 trials. However, multiple groups have released position statements guided by expert opinion for this patient population. The Crohn's and Colitis Foundation noted in its January 2021 position statement that currently approved vaccines and those known to be in phase 3 testing do not contain live virus particles, thus these vaccine products are safe for patients regardless of their IBD treatments. The foundation also stressed that although patients on specific types of immune-modifying treatments may have a reduced vaccine response, vaccination should not be deferred solely because of such therapy.[23] Additionally, the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) met in December 2020 to develop consensus statements for COVID-19 vaccination in patients with IBD. The panel recommended vaccination for all patients with IBD as soon as they are able to receive the vaccine, regardless of immune-modifying therapies. However, patients vaccinated while receiving systemic corticosteroids should be counseled that vaccine efficacy may be decreased. The panel also noted the vaccines currently available are safe to administer in this population, given that the vaccines do not contain live virus.[24]

Multiple studies to evaluate the COVID-19 vaccine efficacy and safety in the IBD population are currently ongoing, such as the Partnership to Report Effectiveness of Vaccination in Populations Excluded from Initial Trials of COVID (PREVENT COVID) study, which is currently enrolling patients 18 years of age or older with IBD who live in the United States and received a first COVID-19 vaccine dose in the preceding 60 days. Surveys will be disseminated for the study duration, and antibody response will be assessed to determine COVID-19 vaccine efficacy and safety.[25] Most recently, a study by Kennedy et al[26] evaluating whether patients with IBD treated with infliximab generated attenuated serological responses to a single dose of either the Pfizer-BioNTech or AstraZeneca vaccine was published. In comparison to patients treated with vedolizumab ($n$ = 428), patients receiving infliximab ($n$ = 865) had lower mean anti–SARS-CoV-2 antibody concentrations within 3 to 10 weeks following the first COVID-19 vaccine dose. Combination therapy with an immunomodulator further attenuated immunogenicity to both vaccines in the infliximab-treated group. Being 60 years of age or older or a current

smoker was also independently associated with lower anti–SARS-CoV-2 antibody concentrations post vaccine administration. However, seroconversion rates after a single dose of either vaccine were higher in patients with prior SARS-CoV-2 infection in both infliximab- and vedolizumab-treated patients. Vaccine response was also assessed in 27 patients without serological evidence of prior infection following both doses of the Pfizer-BioNTech vaccine. After second doses, 17 of 20 infliximab-treated patients (85%) and 6 of 7 vedolizumab-treated patients (86%) seroconverted. Thus, this study provided similar evidence of attenuated immunogenicity after the first COVID-19 vaccination dose (as discussed previously in reference to transplant patients) but also provides initial reassurance that most patients seroconvert after their second dose. However, the investigators noted that study limitations included inability to investigate whether timing of the biological infusion or drug level with respect to vaccine administration influenced antibody responses, and limited assessment of the effects of 2 immunodulating medications without an immunocompetent control group.

**Patients with RA.** Like patients with IBD, those with RA were also excluded from phase 3 COVID-19 vaccine trials. The American College of Rheumatology (ACR) has created a COVID-19 vaccine clinical guidance summary for patients with rheumatic and musculoskeletal diseases, which was last updated in April 2021.[27] Similar to guidance for other immunocompromised patient populations, the ACR notes there is no direct evidence about COVID-19 vaccine safety and efficacy in this population but endorses the stance that harms would very unlikely outweigh the benefits. Thus, there was a moderate level of consensus among the task force that patients with RA should receive COVID-19 vaccination and a strong level of consensus that antibody tests should not be routinely ordered to assess immunity to COVID-19 post vaccination. Additionally, the task force provided guidance related to the use and timing of immunomodulator therapies in relation to COVID-19 vaccination, which is outlined in Table 2.[27]

## Current implications

Initially, due to issues of vaccine availability, CDC provided recommendations regarding COVID-19

**Table 2.** Guidance Related to Timing of COVID-19 Vaccine Administration and Immunomodulatory Therapies in Patients with Rheumatologic Disorders[27]

| Medication | COVID-19 Vaccine Administration Timing | Immunomodulatory Therapy Timing |
|---|---|---|
| Abatacept (subcutaneous) | • Do not delay or adjust vaccine administration timing | • Hold for both 1 week prior to and after first vaccine dose only<br>• No interruption around second vaccine dose |
| Abatacept (intravenous) | • Time first vaccine dose for 4 weeks after entire abatacept infusion dosing interval | • Postpone subsequent infusion by 1 week (ie, give infusion 1 week after vaccine, with 5-week total gap between infusion doses)<br>• No medication adjustment for second vaccine dose |
| Acetaminophen, nonsteroidal anti-inflammatory drugs | • Do not delay or adjust vaccine administration timing | • Assuming that disease is stable, hold for 24 hours prior to vaccination<br>• No restrictions on use post vaccination to treat symptoms |
| Cyclophosphamide (intravenous) | • Do not delay or adjust vaccine administration timing | • Time cyclophosphamide administration so that it will occur approximately 1 week after each vaccine dose, when feasible |
| Janus kinase inhibitors | • Do not delay or adjust vaccine administration timing | • Hold for 1 week after each vaccine dose |
| Methotrexate | • Do not delay or adjust vaccine administration timing | • Hold for 1 week after each dose of the Pfizer-BioNTech or Moderna vaccine, for those with well-controlled disease<br>• Hold for 2 weeks after single-dose Janssen vaccine dose, for those with well-controlled disease |
| Mycophenolate | • Do not delay or adjust vaccine administration timing | • Assuming that disease is stable, hold for 1 week following each vaccine dose |
| Rituximab | • Initiate vaccine schedule approximately 4 weeks prior to next scheduled rituximab cycle(assuming COVID-19 risk is low or can be mitigated by preventative health measures) | • Delay rituximab for 2-4 weeks after second vaccine dose, if disease activity allows |

vaccine allocation and outlined a phased approach to vaccine administration based on patient risk. Phase 1c of the allocation comprised adults with medical conditions that increase the risk of severe COVID-19, which included those immunocompromised due to solid organ transplantation. Other immunocompromising conditions resulting from blood or bone marrow transplant, immune deficiencies, HIV infection, use of corticosteroids, or use of other immune-weakening medicines "might" put individuals at an increased risk, thus patients with these conditions were not considered in the phase 1c category.[28,29] These recommendations were guided by existing evidence, such as a recent retrospective cohort study conducted by Andersen et al[30] that evaluated 2,121 individuals, of whom 5% were on immunosuppressive medications at baseline, including prednisone, tacrolimus, and mycophenolate mofetil. After adjusting for potentially confounding covariates, no statistically significant differences in the risk of mechanical ventilation, in-hospital mortality, or increased length of stay among patients with and without chronic use of immunosuppressive medications were observed.

Now, due to increasing supply, COVID-19 vaccines are authorized and available to all adults age 18 or older, with the Pfizer-BioNTech vaccine available to children 12 or older. However, immunocompromised patients may be concerned about receiving the vaccine. In a study conducted by Brigham and Women's Hospital, 906 patients with IBD completed a survey assessing concerns and intentions regarding the COVID-19 vaccine.[31] Of the patients recruited nationwide through social media, 40% did not intend to receive the COVID-19 vaccine, most commonly citing "concern that long-term safety of the vaccine is unknown" and preference "to see how others tolerate the vaccine first" as reasons for hesitancy. Additionally, within this cohort, 70% desired data regarding vaccine safety and efficacy specifically in patients with IBD.[31] To acknowledge these hesitancies, it is vital that pharmacists and other providers understand current data and recommendations and are able to properly educate and inform the public. At this time, CDC recommends that immunocompromised populations continue to follow current guidance to protect against COVID-19, including wearing a mask, staying 6 feet apart from others not residing in the same household, and avoiding crowds, given the unknown vaccine efficacy in this population.[32]

## Conclusion

COVID-19 vaccine data and vaccination practices continue to evolve, especially in the immunocompromised population. This article is intended to provide guidance to pharmacists and other caregivers administering COVID-19 vaccinations. Currently, CDC, BSI, and various societies whose members include experts on specific immunocompromised conditions have endorsed COVID-19 vaccination in these populations, as the potential clinical benefits greatly outweigh the possible mild adverse effects of vaccination. While the limited number of efficacy studies available suggest a lower antibody response rate in immunocompromised patients, this is a surrogate endpoint and not a clinical endpoint. Further studies are needed to assess vaccine effectiveness in regards to protection against severe disease, hospitalization, or death in this population, as it is unclear at this time if low antibody response rate reduces clinical effectiveness. Additionally, longitudinal studies will be necessary to determine the potential need for vaccine booster doses and optimal administration timing in regard to immunosuppressive therapy. Presently, individuals who are recommending and administering COVID-19 vaccines should make efforts to optimize immunization rates and decrease vaccine hesitancy in immunocompromised individuals by staying up-to-date on current recommendations and providing proper education and reassurance.

Since the time of manuscript preparation, new guidance about COVID-19 vaccination in the immunocompromised population has become available. In mid-August 2021, FDA amended the EUA for both mRNA COVID-19 vaccines (the Pfizer-BioNTech and Moderna vaccines) to allow for use of an additional dose in certain immunocompromised individuals.[33] Shortly thereafter, CDC recommended that those who are moderately to severely immunocompromised receive an additional dose of the same mRNA COVID-19 vaccine at least 28 days after their second dose of a series. There are no CDC recommendations regarding an additional dose of the Janssen vaccine at this time. Per CDC guidance, moderate to severe immunocompromise includes the following situations and patients[34]:

- Active treatment for solid tumor and hematologic malignancies
- SOTRs on immunosuppressive therapy
- Receipt of a CAR-T cell or hematopoietic stem cell transplant (patients within 2 years of transplantation or taking immunosuppressive therapy)
- Moderate or severe primary immunodeficiency
- Advanced or untreated HIV infection
- Active treatment with high-dose corticosteroids (≥20 mg prednisone or equivalent per day), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor necrosis factor inhibitors, and other immunosuppressive or immunomodulatory biologic agents.

The above recommendation was based on mRNA vaccine effectiveness studies showing increased COVID-19 infection and symptomatic infection in vaccinated immunosuppressed individuals.[35] Additionally, a small study suggested that fully vaccinated immunocompromised patients accounted for 40% to 44% of hospitalized patients in breakthrough cases.[36] Lastly,

an emerging study in the transplant population highlighted that 44% of those who had no detectable antibody response to an initial mRNA vaccine series developed an antibody response with an additional mRNA vaccine dose.[37] Since this recommendation, the 2-dose series of the Pfizer-BioNTech COVID-19 vaccine has been approved by FDA for use in individuals age 16 or older, but both the Pfizer-BioNTech and Moderna vaccines remain available under EUA for administration of a third dose to immunocompromised individuals.[38]

Many professional societies have updated their stance on COVID-19 vaccination in the immunocompromised population. Currently, AST recommends a third dose in SOTRs, and ACR supports a third dose in patients receiving any immunosuppressive or immunomodulatory therapy except for hydroxychloroquine.[39,40] Additionally, ACR recommends withholding of all immunosuppressive therapy except for anticytokine therapies (due to lack of consensus) or glucocorticoids for 1 to 2 weeks after a supplemental dose.[40] Conversely, the Crohn's and Colitis Foundation notes that most patients with inflammatory bowel diseases are not considered immunosuppressed and therefore should not need an additional vaccine dose.[41] However, all 3 organizations still advise against testing to determine antibody response to vaccination outside of the research setting.

## Disclosures

Dr. Farraye is a consultant for BMS, Braintree Labs, Arena, GI Reviewers, Iterative Scopes, GSK, Innovation Pharmaceuticals, Janssen, Pfizer, and Sebela and sits on a data safety and monitoring board for Lilly and Theravance. Drs. Duly and Bhat have declared no potential conflicts of interest.

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