General Principles of COVID-19 Vaccines for Immunocompromised Patients

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Please see specific FAQ for guidance on vaccination in patients who have received HCT or CAR T cells. Please see the FAQ dedicated to adverse effects related to adenoviral vector vaccines for the most up-to-date recommendations related to vaccines and clotting risk.

In the United States, two novel messenger RNA (mRNA) vaccines and one novel adenovirus vector-based vaccine have been approved through the U.S. Food and Drug Administration’s (FDA’s) Emergency Use Authorization (EUAs; Table). The BNT162b2 (Pfizer/BioNTech) and the mRNA-1273 (Moderna) COVID-19 vaccines have both been shown in large phase III clinical trials to be more than 90 percent effective at preventing lab-confirmed COVID-19 illness and severe infections.1,2 The single-dose recombinant, replication-incompetent adenovirus serotype 26 vector-based vaccine (Ad26.COV2.S; Johnson& Johnson/Janssen) reduced the incidence of symptomatic COVID-19 with a reported overall efficacy of 66.1 percent (72% in the United States) based on data from the phase III clinical trial.3 The overall lower efficacy was thought to be due to the newly emerging SARS-CoV-2 variant arising from South Africa (20H/501Y.V2 variant [B.1.351]), which was the predominant strain circulating in South Africa at the time of the clinical trial and accounted for 95 percent of the sequenced isolates.3 Data on efficacy of vaccines in additional variants is accumulating.

Table. List of currently approved COVID-19 vaccines under Emergency Use Authorization in the United States

<table>
<thead>
<tr>
<th>Platform</th>
<th>Vaccine</th>
<th>Manufacturing Company</th>
<th>Age Limit (years)</th>
<th>Number of Doses/Intervals (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRNA</td>
<td>BNT162b2</td>
<td>Pfizer and BioNTech</td>
<td>≥ 12</td>
<td>2 doses/ 3 weeks apart</td>
</tr>
<tr>
<td>mRNA</td>
<td>mRNA-1273</td>
<td>Moderna</td>
<td>≥ 18</td>
<td>2 doses/ 4 weeks apart</td>
</tr>
<tr>
<td>Recombinant adenovirus vector</td>
<td>Ad26.COV2.S</td>
<td>Johnson &amp; Johnson/Janssen</td>
<td>≥ 18</td>
<td>1 dose</td>
</tr>
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What are mechanisms of action for the leading candidate SARS-CoV-2 vaccines?

Leading SARS-CoV-2 vaccine candidates use either conventional or novel mechanisms of action to elicit an immune response in patients. Conventional methods include administration of attenuated inactivated (killed) virus4 or recombinant viral protein4 vaccines to develop immunity. Novel approaches include replication-deficient, adenovirus vector-based vaccines that contains the SARS-CoV-2 spike protein5,6 and mRNA-based vaccines that encode for a SARS-CoV-2 spike protein.7,8 Based on phase I/II studies, candidate SARS-CoV-2 vaccines elicited both humoral and cellular immune responses.

How are the SARS-CoV-2 vaccines administered and what challenges exist for vaccination?
All except one of the vaccine candidates being tested require two separate inoculations separated by three to four weeks. Current challenges for an approved SARS-CoV-2 vaccine include manufacture to scale, distribution, storage conditions, reconstitution, and administration, particularly for the lipid nanoparticle mRNA-based vaccines, which require low temperatures for adequate vaccine preservation. Most importantly, the public must be willing to receive the vaccine.

**What SARS-CoV-2 vaccines are approved for use in immunocompromised patients?**

Despite several vaccine candidates being in phase II/III clinical trials, data on vaccine efficacy and safety in immunocompromised patients remains scarce; there are ongoing trials at this time. Definitive efficacy and safety of a SARS-CoV-2 vaccine has not been established in the different immunocompromised patient populations. There are no data that preferentially support one vaccine over another in this or any population.

**Why might some hematology patients not respond to vaccines?**

In order to generate optimal protective immunity following vaccination, intact host immunity is needed, particularly with respect to antigen presentation, B- and T-cell activation, and plasma B cell antibody generation. Therefore, hosts lacking functional adaptive immune cells may be unable to generate a fully protective immune response to a SARS-CoV-2 vaccine approved for use in the general population.

The following immunocompromised patient populations could have attenuated or absent response to SARS-CoV-2 vaccines:

- a. Primary and secondary immunodeficiencies involving adaptive immunity
- b. Splenectomy or functional asplenia.
- c. B cell directed therapies (e.g., blocking monoclonal antibodies against CD20 or CD22, bispecific agents like blinatumomab, CD19 or CD22-directed chimeric antigen receptor T cell [CAR-T] therapies, Bruton tyrosine kinase [BTK] inhibitors)
- d. T-cell-directed therapies (e.g., calcineurin inhibitors, antithymocyte globulin, alemtuzumab)
- e. Many chemotherapy regimens
- f. High-dose corticosteroids (>2 mg/kg/day daily prednisone for greater than two weeks, or equivalent)
- g. Hematopoietic cell transplantation (HCT), especially within the first three to six months after autologous HCT and often longer after allogeneic HCT
- h. Underlying aberrant immunity (e.g., graft-vs.-host disease, graft rejection, absent or incomplete immune reconstitution, neutropenia ANC <500/μL, lymphopenia ALC <200/μL)

**What are the current recommendations for providing a third vaccination dose in immunocompromised individuals?**
On August 12, the FDA amended the emergency use authorizations (EUAs) for both the Pfizer-BioNTech COVID-19 Vaccine and the Moderna COVID-19 Vaccine to allow for the use of an additional dose of the same vaccine in certain immunocompromised individuals, specifically, solid organ transplant recipients or those who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

The FDA evaluated information on the use of a third dose of the Pfizer-BioNTech or Moderna Vaccines in these individuals and determined that the administration of third vaccine doses may increase protection in this population. Supporting the decision was a randomized trial of 120 solid organ transplant (SOT) patients receiving similar immunosuppression and having similar lymphocyte counts at the time of study enrollment. Specifically, 55% (30/60) patients receiving a third mRNA-1273 versus 18% (10/57) patients receiving placebo had anti-RBD antibody above 100 U/mL (arbitrary threshold). In addition, after the third dose of mRNA-1273, median percent virus neutralization was 71% in the vaccine versus 13% in the placebo group; and 60% of third vaccine administered patients versus 25% placebo patients achieved 30% threshold for neutralizing antibody positivity. Furthermore, median SARS-CoV-2-specific T cell induction measured after third dose mRNA-1273 was greater than in placebo patients (432 vs 67 cells per million CD4+ T cells, 95% CI 46-986). Lastly, third mRNA dose was associated with more, but not severe, local and systemic events compared to placebo. Taken together, the data suggested that a third dose of mRNA vaccine was safe and induced more immunogenicity in SOT patients. An earlier publication from the French National Authority for Health also showed similar higher induction of anti-SARS-CoV-2 antibody titers following a third dose of mRNA vaccine BNT162b2 in SOT patients.

Importantly, however, not all immunocompromised patients responded with higher titers after additional mRNA vaccine administration and some patients receiving two doses of vaccination may have favorable antibody induction.

On August 13, the CDC vaccine advisory panel endorsed the FDA recommendation.

**Who are candidates for the third dose of mRNA vaccine?**

The third dose of the COVID-19 mRNA vaccine has been recommended for moderately or severely immunocompromised individuals. There are no definitive guidelines from CDC describing which patients would meet such criteria, however, we would consider the following patients groups to be among those eligible:

- Patients actively treated for hematologic malignancy
- Patients who at the time of their primary vaccine series were within 12 months of treatment with an agent known to cause prolonged B cell aplasia or lymphopenia (CD19, CD20 antibodies, BTKis, Alemtuzumab etc)
- Patients actively treated for solid tumors with agents classified as moderate to severely immunosuppressive
- CLL (regardless of treatment)
- Asplenia
- CAR-T cell recipients (within two years)
- Hematopoietic stem cell transplant recipient (within two years). There is debate about the risk/benefit in patients with active GVHD.
Primary immunodeficiency disorders (example, DiGeorge syndrome, Wiskott-Aldrich syndrome).

- Active or untreated HIV infection (CD4<200 /uL)
- Active high-dose steroid use (equivalent of prednisone ≥ 20 mg/day for >2 weeks)
- Use of biologic agents such as TNF antagonists.

Of note, many cancer patients are not undergoing treatments that substantially damage the immune system and would not be recommended to receive a third vaccination dose. These would include those who have undergone surgery for cancer treatment, radiation therapy, hormonal therapy, many “targeted” treatments and immune checkpoint inhibitors. The clinical team is best able to assess immune competence based on past, current, and future treatment and determine vaccine timing for optimal immune response.

Even with a third dose of the vaccine, a significant amount of individuals may not mount a sufficient antibody response, and therefore should be cautioned to maintain social distancing and other mitigation measures. The panel has not yet clarified whether antibody levels need to be tested prior to prescribing a third dose of vaccine.

**Are pediatric patients eligible to receive the third vaccine dose?**

The expanded EUA applies to patients 12 and older for Pfizer vaccine and 18 or older for Moderna.

There is, potentially, a low risk for myopericarditis in adolescent patients, usually occurring after receiving second dose BNT162b2 mRNA vaccine. Whether additive risk for cardiotoxicity occurs in patients receiving cardiotoxic chemotherapeutics like anthracyclines or after receiving additional mRNA vaccine dosing is unknown at this time.

**Which vaccines can be used for a third dose?**

Only patients who completed the primary series with either the Pfizer or Moderna vaccine can receive the third dose.

Mixing vaccines or heterologous vaccination is not recommended at this time. Currently the CDC is recommending that a third dose of the same mRNA vaccine should be used. A person should not receive more than three mRNA vaccine doses.

CDC has not made any recommendations for J&J (adenoviral vector) vaccinated individuals at this time—this might change in the coming weeks.

**What is the minimum dosing interval between the second and third dose for eligible patients?**

The third dose should be administered at least 28 days after the second mRNA dose.

**Should I use serological testing to decide if my patient should receive the third vaccine dose?**

Serological testing before the third dose is not recommended at this time. The currently available assays are non-standardized, and the clinical thresholds of protection are not known.

**My patient’s serological test is positive for anti-spike antibodies. Should they receive the third dose?**
The third dose should be administered regardless of serological results or antibody levels if the patient meets eligibility criteria.

**Should patients with breakthrough infection receive the third dose?**

The safety of the third dose in patients with breakthrough infection is not known. Infection boosts immunity, and due to the potential higher risk of reactogenicity, third doses are not recommended. Exception: patients who were within 6 months of HCT or CD-20 therapy at the time of primary vaccine series should receive the third dose after a breakthrough infection.

**Are patients who received monoclonal antibody (mAb) for post-exposure prophylaxis eligible to receive the third dose of the vaccine?**

Yes, but a minimum of 90 days should have elapsed after the mAb treatment.

**Should patients who are diagnosed with COVID-19 or exposed to someone with COVID-19 receive Mab if they have already received three doses of the vaccine?**

Yes, mAb should be administered regardless of previous vaccination or number of doses received.

**What is known about the safety and efficacy of protein-based or killed (inactivated virus) vaccines in immunocompromised patients?**

Vaccine safety encompasses acute and long-term adverse effects associated with a vaccine. Based on experience with other recombinant protein-based and inactivated (killed) virus-based vaccines, no major adverse effects or unique adverse effects have been reported in immunocompromised patients. Common acute adverse effects associated with candidate SARS-CoV-2 vaccines reported to date include low-grade fever, myalgias, headache, nausea, fatigue, and soreness/redness at the injection site. These acute adverse effects were more pronounced after the booster dose (2nd vaccine dose) in some of the trials. Long-term adverse effects have not been defined for SARS-CoV-2 vaccines and will be available once phase III trials have completed long term follow up in healthy volunteers. Initial data on safety will be available for at least two months from vaccine administration based on EUA minimum standards. A national monitoring system exists for reporting vaccine-related adverse events.

The efficacy of protein-based or inactivated (killed) SARS-CoV-2 vaccines in immunocompromised patients has yet to be studied. Prior experience with inactivated or killed virus vaccines have demonstrated some efficacy in immunocompromised patients, leading some societies to recommend vaccination of this population. Vaccine responses are influenced by the underlying disease and the type and timing of recent therapy. The adjuvanted recombinant (protein-based) zoster vaccine was safe and elicited robust humoral and cellular immune responses across patients with hematologic malignancies when administered during or up to six months after immunosuppressive therapy. However, response rates in patients with chronic lymphocytic leukemia (CLL) or non-Hodgkin lymphomas, many likely treated with anti-CD20 containing regimens, were lower than in the rest of the hematologic malignancies.

Flu vaccines using killed virus are safe and can elicit humoral immune responses in immunocompromised patients, but response rates appear to be highly variable, reported between 15 and 63 percent of CLL patients not actively treated, and in 7 to 26 percent in patients on BTK inhibitor (ibrutinib) therapy.
The immune response to varicella zoster is a memory response, as the vast majority of people have formed antibodies against varicella zoster virus in childhood. Similarly, response to influenza is, at least in part, a memory response. In contrast, response to SARS-CoV-2 will require a de novo immune response and much less is known about how well immunocompromised patients will be able to generate such a response.

Potential considerations for testing prior to administration of SARS-CoV-2 vaccine in an immunocompromised patient include complete blood count with differential, peripheral blood B- and T-cell immunophenotype, quantitative immunoglobulins (IgG, IgM, IgA), and tetanus and pneumococcal titers, to determine if a patient is likely to mount a protective immune response. The impact of these parameters on responses to SARS-CoV-2 vaccines is unknown.

What is known about the safety and efficacy of attenuated live vaccines in immunocompromised patients?

Live attenuated vaccines carry the risk of converting to pathogenic strains with particular risk in immunocompromised patients. It is unclear if a live attenuated SARS-CoV-2 vaccine will have the same major risk, but due to the theoretical concerns, a live vaccine should be avoided in immunocompromised patients. Another potential risk from live-attenuated vaccines in general is the possible transmission of the virus to close contacts of the vaccinees. The only live SARS-CoV-2 vaccines are in production in India and Turkey.

What is known about the safety and efficacy of the mRNA vaccines in immunocompromised patients?

Pfizer’s BNT162b2 and Moderna’s mRNA-1273 mRNA vaccines have been approved in the United States under EUA since December 11, 2020 and December 18, 2020, respectively. Since then, safety data regarding the two mRNA vaccines during the vaccination roll outs have been released. Based on the phase II/III clinical trials of the vaccines, the most common adverse effects include pain at the injection site, fever, headache, fatique, and joint pain. A rare adverse effect reported is Bell’s palsy; both BioNTech/Pfizer and Moderna reported four and three cases, respectively, of Bell’s palsy in the vaccine recipients who participated in their phase III trials, respectively. Anaphylaxis due to vaccination with either the Pfizer or Moderna vaccine has been reported at a rate of 4.7 cases/million doses and 2.5 cases/million doses, respectively.

In immunocompromised patients, data are limited, but some reports have been published for cancer patients and solid organ transplant recipients; vaccine efficacy ranged from 43 percent to 95 percent after the second dose of the mRNA vaccine based on antibody assays. In cancer patients, side effects were mostly mild and included injection site pain, flu-like symptoms, fever, and headaches; similar findings were seen in solid organ transplant recipients. Data regarding safety in hematopoietic cell transplant recipients is beginning to emerge. (Add citation linked)

What is known about the safety and efficacy of the adeno-viral vector vaccines in immunocompromised patients?

The only adenovirus vector–based vaccine approved under EUA in the Unite States is Johnson & Johnson/Jansenn’s Ad26.COV2.S vaccine. The vaccine received EUA from the FDA on Feb 27, 2021, and has the least experience in the general public. Like the mRNA vaccines, the most common adverse effects were pain at the injection site, headaches, fatigue, muscle pain, nausea, and fever. Two cases
of anaphylaxis were reported to the FDA after the vaccine received EUA. There are limited data regarding safety in immunocompromised patients.

Numerical imbalances were noted in the phase III clinical trial for certain unsolicited adverse effects such as thromboembolic events, seizures, and tinnitus. Since receiving approval and undergoing widespread distribution, more cases of atypical clotting were reported to the FDA. After six cases of cerebral venous sinus thrombosis were reported to the FDA, administration and distribution of this vaccine were halted in the United States on April 13, 2021. On April 23, the Centers for Disease Control and Prevention and FDA made a joint announcement to resume distribution of the Johnsons & Johnson/Janssen SARS-CoV-2 vaccine after determination that the incidence of thrombosis is very low. A new warning was added for rare clotting events in women between the ages of 18 and 49. Individuals who report dizziness, headache, or other neurological symptoms that may suggest a sinus vein thrombosis or symptoms in accordance with other unusual thrombotic locations should undergo further medical evaluation to diagnose or rule out thrombotic events. It is not clear if the rate of clotting would be different in immunocompromised patients.

Are any trials of SARS-CoV-2 vaccines being done in immunocompromised populations?

Most SARS-CoV-2 phase II/III vaccine trials required patients to be off immunosuppression for a certain period to be eligible. This may not be feasible in patients who are receiving therapy for solid organ transplantation, graft-versus-host disease, or hematologic malignancy. It is unclear how the different SARS-CoV-2 vaccine candidates will specifically affect different forms of immune abnormalities. Given the diversity of various immunocompromised patient populations, it is possible that candidate SARS-CoV-2 vaccines may differ in their efficacy and safety for these patients. Clinical trials for immunocompromised patients are ongoing.

If immunocompromised patients were not included in the vaccine trials and are less likely to respond to a SARS-CoV-2 vaccine, should they still receive it? What is the timing in relation to chemotherapy, transplant, antibody therapy, splenectomy etc. Should higher vaccine doses or multiple vaccine types be used?

A full discussion of vaccination in patients undergoing stem-cell transplantation or CAR-T therapy is available in a separate FAQ. The risks and benefits for immunocompromised patients receiving a SARS-CoV-2 vaccine should be weighed on a case-by-case basis, with consideration of the incidence of infection in the community. This will depend on the approved vaccine formulation available, level of immunosuppression the patient has received, and the underlying reason for immunosuppressive therapy (e.g., cancer treatment, transplantation). If plans to proceed with the SARS-CoV-2 vaccine are made, vaccination is recommended at least two to four weeks prior to the planned immunosuppressive therapy, transplant, or splenectomy. If the patient is receiving or has received immunosuppressive therapy, consider vaccination six months after the patient has been taken off therapy to increase the likelihood of developing immunity (see potential laboratory testing). After hematopoietic cell transplantation, inactivated vaccines have generally shown low incremental risks and have not caused or worsened graft-versus-host disease; thus, inactivated vaccines are generally started after three to six months. If SARS-CoV-2 infection rates are low in a community and a given patient is expected to have improved immune status in upcoming months, clinical judgment is appropriate when weighing the desire for protection as early as possible versus delaying vaccination to give the best chance for response. These recommendations may change, based on the results of the approved vaccine trials.
Most experts recommend vaccination if the vaccine is safe for use, even if the expected protection rate is lower than the general population.

Importantly, vaccination does not change required precautionary behaviors such as masking, social distancing, and frequent hand hygiene. Influenza vaccination should also be administered to immunocompromised patients to reduce the burden of influenza infection and possible dual infection with SARS-CoV-2. Finally, all healthcare workers and household contacts should receive a SARS-CoV-2 vaccine when available to help protect immunocompromised patients, like the recommendations for influenza.

Whether or not an immunocompromised patient is known to have been previously infected with SARS-CoV-2 should not affect the decision of whether to vaccinate. Although some immunity is anticipated from experiencing a COVID-19 clinical infection, this immunity may be insufficient or wane, especially in immunocompromised hosts. However, increased adverse effects could be seen with vaccination, like what is observed with the second dose in a two-dose vaccine series.

Until more is known, different SARS-CoV-2 vaccines should not be given to the same patient. Although measuring titers may eventually be helpful to assess response, more information is needed. Giving more inoculations or higher doses of an approved SARS-CoV-2 vaccine is not recommended at this time.

References


