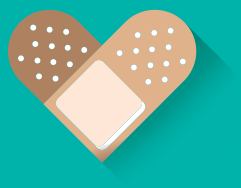

Addressing Concerns of People Who Are Immunocompromised

The Issue

People with compromised immune systems have been disproportionately affected by the COVID-19 pandemic: they are both more susceptible to SARS-CoV-2 infection and more vulnerable to severe COVID-19 illness and death. Unfortunately, messaging that COVID-19 vaccination is ineffective for immunocompromised persons or cannot work in that population may have caused some people to question the value of COVID-19 vaccines. Confusing and changing guidance and terminology left many patients and pharmacists unsure about recommendations for the primary COVID-19 vaccination series and booster dosing in immunocompromised persons.

Sound Bites

- People who are moderately or severely immunocompromised (have a weakened immune system) have an increased risk of severe COVID-19 illness (e.g., hospitalization, admission to the intensive care unit, intubation or mechanical ventilation) and death.
- The immune response to COVID-19 vaccination in people who are immunocompromised may not be as strong as in people who are not immunocompromised. However, the vaccines still provide important protection against severe COVID-19 illness and death.
- Immunocompromised persons are protected best from severe COVID-19 illness and death when they stay up to date with their COVID-19 vaccines, which includes getting all recommended boosters when eligible.
- People are allowed to self-attest to their moderately or severely immunocompromised status. This means they do not need any documentation of their status to receive COVID-19 vaccine doses for which they are eligible, wherever they are offered.
- Many immunocompromised persons are eligible for Evusheld (tixagevimab co-packaged with cilgavimab), co-administered monoclonal antibodies used in addition to vaccination to help prevent SARS-CoV-2 infection (pre-exposure prophylaxis). Evusheld is available to eligible patients at little to no cost (the medication itself is free, but there may be an associated administration fee).

Questions for Exploring Patient Concerns

- What do you know about the effectiveness of COVID-19 vaccines in people with weakened immune systems?
- What concerns you most about getting a COVID-19 vaccine?
- What would have to be true for you to think it was important to get a COVID-19 vaccine?
- What if I told you…? (Provide information relevant to the patient's concerns.)

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What We Know

The first COVID-19 vaccines were authorized in December 2020, less than 1 year after the genetic blueprint of the novel coronavirus SARS-CoV-2 was identified. This unprecedented timeline was achieved in part because phase 3 trials were conducted during a time of very high community transmission, making it possible for researchers to tell within months whether a vaccine was effective in protecting the vaccinated groups (compared with the placebo groups).

Because those phase 3 trials had to be completed as quickly as feasible and were focused on determining vaccine efficacy and safety in the general adult population, they excluded nearly all people with compromised immune systems (e.g., patients with cancer, patients with rheumatological disorders, organ transplant recipients). And because vaccines work by harnessing the capability of a fully competent immune system, there was concern about the immune response to COVID-19 vaccines in immunocompromised persons and the level of protection vaccination would offer.

Early data were not promising. An analysis of a convenience sample of 436 solid organ transplant recipients who received a first dose of an mRNA vaccine between December 16, 2020, and February 5, 2021, found that less than 20% mounted appreciable antispike antibody responses.1 A follow-up to that study showed some improvement in antispike antibody responses after a second vaccine dose compared with dose 1, but the gains were relatively modest. Of the 658 transplant recipients included in that analysis (396 of whom were part of the first study), 98 (15%) had measurable antibody response after dose 1 and dose 2; 301 (46%) had no antibody response after dose 1 or dose 2; and 259 (39%) had no antibody response after dose 1 but subsequent antibody response after dose 2.2 A systematic review and meta-analysis confirmed significantly lower seroconversion rates and antibody titers after COVID-19 vaccination in immunocompromised patients than immunocompetent individuals.[3] Organ transplant recipients showed the lowest rates of seroconversion; patients with solid tumors showed the highest.

These data have been particularly concerning because people who are moderately or severely immunocompromised are at higher risk for severe illness from COVID-19.[4] The Centers for Disease Control and Prevention (CDC) defines “severe illness” as hospitalization, admission to the intensive care unit, intubation or mechanical ventilation, or death. People are considered to be moderately or severely immunocompromised due to conditions and treatments that include[5]:

- Active treatment for solid tumor and hematologic malignancies.
- Receipt of solid-organ transplant and taking immunosuppressive therapy.
- Receipt of chimeric antigen receptor T-cell therapy or hematopoietic cell transplant (within 2 years of transplantation or taking immunosuppressive therapy).
- Moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome).
- Advanced or untreated HIV infection (people with HIV and CD4 cell counts less than 200 cells/mm3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV).
- Active treatment with high-dose corticosteroids (i.e., 20 mg or more of prednisone or equivalent per day when administered for 2 or more weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor necrosis factor blockers, and other biologic agents that are immunosuppressive or immunomodulatory.

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Uncertainty and confusion about how best to protect moderately or severely immunocompromised persons from COVID-19 were exacerbated when discussions about the likely need for an additional vaccine dose in that population occurred around the same time as discussions about booster doses for the general population. Because the vast majority of people in the United States had received an mRNA vaccine, discussions about boosters often used the term "third shot" (or "third dose"). The "third shot" booster dose was intended to enhance or restore waning immunity after the initial two-dose primary vaccine series. But it was becoming increasingly clear that moderately or severely immunocompromised persons needed a different kind of "third shot"—a third dose as part of the primary vaccine series to improve the initial immune response.[6] When immunocompromised persons became eligible for a COVID-19 vaccine booster, it usually represented a fourth dose of vaccine. Some immunocompromised people who qualified for that "fourth shot" were initially turned away by providers who were unaware that anyone was entitled to a fourth vaccine dose.

To help avoid confusion and clarify recommendations, the CDC maintains a dedicated web page with specific COVID-19 vaccine guidance for moderately or severely immunocompromised people. The CDC emphasizes that immunocompromised people are best protected against serious COVID-19 illness, hospitalization, and death when they stay up to date with COVID-19 vaccines. As of August 2022, "up to date" could include as many as five doses of an mRNA vaccine (three doses in the primary series plus two boosters). In September 2022, these patients also became eligible for the bivalent booster vaccine. Current recommendations are summarized in the CDC COVID-19 Vaccination Schedule for People Who Are Moderately or Severely Immunocompromised.

The CDC allows people to self-attest to their moderately or severely immunocompromised status. This means they do not need any documentation of their status to receive COVID-19 vaccine doses for which they are eligible, wherever those doses are offered.[6]

Immunocompromised persons should be reassured that COVID-19 vaccines do indeed work by providing robust protection against severe illness. In a case-control analysis using surveillance data from 21 hospitals across the United States (the Influenza and Other Viruses in the Acutely Ill Network, or IVY Network), vaccine effectiveness for three mRNA vaccine doses to prevent hospital admission was high for both immunocompetent persons (97%; 95% CI 95%–98%) and immunocompromised persons (87%; CI 78%–92%) when the Delta variant was dominant (July 4 to December 25, 2021).7 Another case-control analysis using IVY Network data evaluated vaccine effectiveness against the most severe outcomes of COVID-19 hospitalizations: invasive mechanical ventilation and in-hospital death.8 Across the surveillance period (March 2021 to January 2022), vaccine effectiveness was 92% (CI 91%–94%) among immunocompetent persons and 74% (CI 64%–81%) among adults with immunocompromising conditions. However, of the 123 vaccinated COVID-19 case patients with immunocompromising conditions, only 17 (14%) had received three vaccine doses and were considered fully vaccinated.

People who are moderately or severely immunocompromised may not be aware that they also likely are eligible for Evusheld (tixagevimab co-packaged with cilgavimab), which has emergency use authorization as pre-exposure prophylaxis (PrEP) for prevention of COVID-19. Tixagevimab and cilgavimab are two long-acting recombinant human IgG1κ monoclonal antibodies that can simultaneously bind to non-overlapping regions of the SARS-CoV-2 spike protein, blocking the spike protein from interacting with the SARS-CoV-2 receptor and preventing the virus from attaching to and entering human cells. (Evusheld is not authorized for individuals to treat COVID-19 or for the post-exposure prevention of COVID-19.)

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Evusheld is used in addition to—not as a substitute for—COVID-19 vaccination. It is administered during a single visit as two separate consecutive intramuscular injections (one injection per monoclonal antibody, given in immediate succession). In clinical trials, Evusheld reduced the incidence of symptomatic COVID-19 illness by 77% compared with placebo.[9] Repeat doses may be administered every 6 months.

Evusheld is available to eligible patients at little to no cost (the drug is free to eligible individuals, but there may be an associated administration fee). Patients should talk with their health care provider to determine whether Evusheld is an appropriate pre-exposure prevention option for them. The U.S. Department of Health and Human Services maintains an Evusheld information page for health care professionals.

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