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Frequently Asked Questions on Coronavirus Disease 2019 Vaccination for Hematopoietic Cell Transplantation and Chimeric Antigen Receptor T-Cell Recipients From the American Society for Transplantation and Cellular Therapy and the American Society of Hematology

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A B S T R A C T

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), disproportionately affects immunocompromised and elderly patients. Not only are hematopoietic cell transplantation (HCT) and chimeric antigen receptor (CAR) T-cell recipients at greater risk for severe COVID-19 and COVID-19–related complications, but they also may experience suboptimal immune responses to currently available COVID-19 vaccines. Optimizing the use, timing, and number of doses of the COVID-19 vaccines in these patients may provide better protection against SARS-CoV-2 infection and better outcomes after infection. To this end, current guidelines for COVID-19 vaccination in HCT and CAR T-cell recipients from the American Society of Transplantation and Cellular Therapy Transplant Infectious Disease Special Interest Group and the American Society of Hematology are provided in a frequently asked questions format.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may now be endemic in the United States and worldwide [1]. Hematopoietic cell transplant (HCT) and chimeric antigen receptor T (CAR T)-cell recipients remain at higher risk for severe complications from the virus, including hospitalization, (intensive care unit) admission, and death from coronavirus disease 2019 (COVID-19) [2–5]. HCT and CAR T-cell recipients also have other comorbidities associated with COVID-19–related mortality, including older age, cardiovascular disease, chronic lung disease, diabetes, renal dysfunction, and high-level immunosuppression [6].

In the United States, 2 novel messenger RNA (mRNA) vaccines, 1 novel adenovirus vector-based vaccine and 1 protein subunit vaccine, have been either formally approved by the Food and Drug Administration (FDA) or approved under an FDA Emergency Use Authorization (EUA). BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) COVID-19 vaccines have shown in large phase III clinical trials involving

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immunocompetent subjects to be more than 90% effective at preventing laboratory-confirmed, symptomatic, and severe COVID-19 [7,8]. 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 efficacy of 66% (72% in the United States) in a phase III clinical trial [9]. The protein subunit vaccine, NVX-CoV2373 (Novavax vaccine), prevent new COVID-19 infections with an efficacy of 89.7% [10]. With the emergence of new SARS-CoV-2 variants, such as the Delta and Omicron variants [11], the efficacy of the COVID-19 vaccines has decreased. This has led to the recent development of the bivalent mRNA vaccines that target the Omicron variant and subvariants BA.4 and BA.5 and has replaced the monovalent (ancestral strain) boosters for patients 12 years and older who have received one of the mRNA vaccines as a primary series. Multiple studies in HCT or CAR T-cell recipients compared to healthy individuals have shown attenuated humoral (antibody) responses in response to vaccination [12,13].

Given the high level of protection afforded to those vaccinated in the clinical trials and the overall safety profile of the COVID-19 vaccines as demonstrated in both the clinical trials and the post-EUA/licensure experience [14], vaccination of this vulnerable patient population is of utmost importance and highly recommended, as is vaccination of caregivers, family members, and household contacts. This guidance document, in the form of frequently asked questions (FAQs), addresses current knowledge and directions for COVID-19 vaccination in HCT and CAR T-cell recipients.

RECOMMENDATIONS ON TIMING OF COVID-19 VACCINE IN HCT AND CAR T-CELL RECIPIENTS AND CONSIDERATIONS FOR DELAY

FAQ1: When is the recommended time to administer COVID-19 vaccines to autologous HCT, allogeneic HCT, and CAR T-cell recipients?

HCT or CAR T-cell recipients are often immunosuppressed for months because of conditioning regimens, maintenance therapies, immunosuppressive drugs, hypogammaglobulinemia, or the development of graft-versus-host disease (GvHD) in allogeneic HCT recipients requiring further immunosuppression. These factors may lead to a diminished immune response and affect vaccine efficacy [15–17]. However, delaying immunization places these patients at risk of severe and life-threatening COVID-19 [2–5]. Based on prior trials of antigen-based vaccines for other diseases in allogeneic HCT recipients, initiating vaccination series 3 months versus 6 months after transplantation did not affect the induction of immunogenicity [16,18-20].

Recent studies have evaluated serologic responses after 2 or 3 doses of the COVID-19 vaccines in HCT and CAR T-cell recipients. Vaccinations were administered as early as 3 months after transplantation or CAR T-cell infusion in a number of observational studies [21–23]. After 2 doses of either mRNA vaccine, neutralizing antibodies were detected in 30% to 77% of patients [21–23]. Humoral responses were affected by timing from transplantation [24,25], relapsed disease [24], GvHD [23,24], lymphopenia [25], immunosuppressive therapy [23,25], and B-cell aplasia [26,27]. A third dose was associated with increased serologic responses [25]. Maillard et al. [25] reported that among HCT or CAR T-cell recipients with no prior response to 2 doses of an mRNA COVID-19 vaccine, 41% developed a serologic response after the third dose. The humoral response in HCT and CAR T-cell recipients is lower after a primary vaccination series, although not significantly, compared to immunocompetent recipients [23,24]. Of note, the mRNA vaccines are preferable to adenovirus-vector vaccines for primary and booster vaccination; it is unclear whether the protein subunit vaccine may provide a similar, enhanced or less-robust response.

FAQ 2: When should COVID-19 vaccination be delayed in HCT or CAR T-cell recipients?

Cytotoxic or B-cell–depleting therapies after HCT or CAR T-cell therapy are often used for maintenance therapy and may contribute to poor vaccine immune responses [28]. If possible, patients scheduled for such therapy should complete their COVID-19 vaccination series when feasible before initiation or between cycles of cytotoxic or B-cell–depleting therapies. Based on a phase I trial of the SARS-CoV-2 mRNA vaccines, peak neutralizing antibodies developed 7 to 14 days after the second dose of the vaccine in individuals without prior infection [29]. Similarly, a rise in neutralizing antibodies was seen 15 days after a single dose of the Johnson & Johnson/Janssen adenovirus vector–based vaccine in phase I studies [30,31]. HCT and CAR T-cell recipients scheduled to undergo cytotoxic or B-cell–depleting therapies could be offered COVID-19 vaccination and, if feasible, allowed at least 2 weeks after the second dose for memory T-cell formation before initiation of cytotoxic or B-cell–depleting therapies/conditioning.

FAQ 3: What is the currently recommended vaccination schedule for HCT or CAR T-cell recipients?

We recommend the primary vaccination and booster schedule approved by the FDA [32] and recommended by the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) [33] for immunocompromised patients (Table 1). The CDC now considers the primary series for immunocompromised patients to be 3 doses of an mRNA vaccine or 1 dose of the adenovirus vector-based vaccine, followed by a dose of an mRNA vaccine; all doses after the primary series are considered booster doses.

After receipt of the original 2-dose series of either mRNA vaccine, a third dose is recommended 28 days or more after the second dose. Furthermore, the recommended time between the third dose and the booster dose (fourth dose) was reduced from 5 to 3 months for recipients of the mRNA vaccines in the general public. Individuals who received the Ad26.COV2.S vaccine are eligible to receive a second dose of an mRNA vaccine 28 days or more after the first dose, followed by a booster dose 2 months after the second dose. The booster can be either the Ad26.COV2.S (Johnson & Johnson/Janssen) vaccine or an mRNA vaccine. These recommendations were based on observations of waning protective antibodies over time in immunocompromised individuals, including transplant recipients, and the concern that without a fourth and fifth dose, these patients would be at high risk for severe COVID-19 [34]. Currently, only a 2-dose primary series with the protein subunit vaccine is approved by FDA EUA.

Recently, bivalent COVID-19 mRNA vaccines have been approved and have replaced the prior monovalent mRNA vaccines as boosters [35]. Patients who are due for a booster after completing their 3-dose primary series with the monovalent COVID-19 mRNA vaccines, or patients who had previously received boosters with the monovalent COVID-19 mRNA vaccines should receive the new bivalent COVID-19 mRNA vaccine booster 3 months after their last COVID-19 mRNA vaccines.

Table 1
Recommended COVID-19 Vaccination Schedule for Individuals With Moderate or Severe Immunocompromising Conditions Based on CDC Recommendations [33]

Primary Vaccination	Age Group	Number of Primary Vaccine Doses	Number of Booster Doses	Interval Between 1st and 2nd Dose	Interval Between 2nd and 3rd Dose	Interval Between 3rd and 4th Dose
Pfizer-BioNTech	6 months to 4 years	3	0	3 weeks	≥8 weeks	NA
Pfizer-BioNTech	5 to 11 years	3	1	3 weeks	≥4 weeks	≥3 months*
Pfizer-BioNTech	≥12 years	3	2	3 weeks	≥4 weeks	≥3 months*
Moderna	6 months to 11 years	3	0	4 weeks	≥4 weeks	NA
Moderna	12 years to 17 years	3	0	4 weeks	≥4 weeks	≥3 months*
Moderna	≥18 years	3	2	4 weeks	≥4 weeks	≥3 months*
Janssen	≥18 years	1 Janssen, followed by 1 mRNA	1	4 weeks	≥2 months	≥4 months
Novavax	≥18 years	2	0	3 weeks	NA	NA

NA indicates not applicable.
* Monovalent mRNA vaccines were replaced by bivalent mRNA vaccines.

FAQ 4: Should we revaccinate HCT or CAR T-cell recipients regardless of whether they were partially or fully vaccinated before transplantation or cellular therapy?

In patients who underwent COVID-19 vaccination before HCT or CAR T-cell therapy, there is a significant concern for the loss of immunity after HCT or cellular therapy. Despite a lack of data specifically on COVID-19 vaccines, we can extrapolate from prior experience with other preventable infections to predict loss of immunity after HCT [18]. For instance, the protection conferred by childhood vaccinations, such as the measles-mumps-rubella vaccine, is often not retained after transplantations, necessitating revaccination [36]. A small study focused on CAR T-cell recipients demonstrated that there is some retained vaccine-induced COVID-19 immunity after CAR T-cell therapy, but there is no clear clinical correlation [37]. Multiple professional societies recommend repeating all vaccinations after patients undergo HCT or CAR T-cell therapy, regardless of the patient's vaccination status before the transplantation [38,39].

Recipients of HCT or CAR T-cell therapy who received 1 or more doses of COVID-19 vaccine before or during treatment should be revaccinated (i.e., complete primary vaccination and any recommended additional and booster doses). Table 1 depicts recommended vaccination intervals in immunocompromised patients. The mRNA vaccine is preferred for revaccination, regardless of which vaccine was administered before transplantation or administration of cellular products. In alignment with CDC/ACIP recommendations, revaccination with the primary series followed by the booster shots should start at least 3 months (12 weeks) after transplantation or CAR T-cell therapy. However, a patient's clinical team is best positioned to determine the appropriate timing of revaccination based on the degree of immune compromise and the individual's need for revaccination.

In summary, we recommend repeating the COVID-19 vaccination series, which is a primary series of 3 doses, as described above, and 1 bivalent mRNA booster dose at least 3 months after HCT or CAR T-cell therapy regardless of the patient's vaccination status before transplantation or cellular therapy. Repeating the primary and booster vaccination series with an mRNA vaccine is recommended for patients vaccinated before HCT and CAR T-cell therapy.

FAQ 5: When should HCT and CAR T-cell recipients receive an additional dose of the COVD-19 vaccine or continue the original series if they become infected with SARS-CoV-2 between scheduled doses?

If COVID-19 vaccinees become infected before a scheduled next dose, the CDC recommends delaying the scheduled dose of either mRNA vaccine until symptoms resolve and isolation precautions or quarantine are discontinued [40]. Patients may also consider delaying their next dose by 3 months based on CDC recommendations [40].

Based on data from patients who had COVID-19 before receiving an mRNA vaccine, HCT and CAR T-cell recipients who develop COVID-19 between vaccine doses can resume their respective vaccine series once symptoms resolve and isolation precautions are discontinued [7,8]. Vaccine-associated enhanced disease or other serious adverse events have thus far not been reported [41,42]. Because HCT and CAR T cell recipients are at high risk for breakthrough COVID-19 after vaccination [43,44], we strongly recommend resuming patient's respective series once symptoms resolve and isolation precautions are discontinued.

FAQ 6: When can the current COVID-19 vaccines be given after receiving SARS-CoV-2 monoclonal antibodies or convalescent plasma in HCT and CAR T-cell recipients?

Limited safety and efficacy data are published on mRNA SARS-CoV-2 vaccines after receipt of SARS-CoV-2 monoclonal antibodies or convalescent plasma as part of COVID-19 treatment. As such patients were specifically excluded from the phase III trials of the mRNA COVID-19 vaccines [7,8]. Despite early reports that monoclonal antibodies may reduce serologic responses from vaccines, there is no clear clinical benefit in delaying vaccination due to the recent receipt of monoclonal antibodies [45]. Based on the CDC recommendations [46], COVID-19 vaccination should not be deferred after receipt of convalescent plasma or monoclonal antibodies directed at SARS-CoV-2 for pre-exposure or post-exposure prophylaxis or treatment. On the other hand, owing to the EUA restrictions for tixagevimab/cilgavimab (Evusheld), its administration should be delayed for 2 weeks after vaccine administration [46].

FAQ 7: After receipt of COVID-19 vaccines, can SARS-CoV-2 monoclonal antibodies be given to HCT and CAR T-cell recipients who develop COVID-19?

Patients who are exposed to or develop SARS-CoV-2 infection after receiving a COVID-19 vaccine are eligible for monoclonal antibodies that retain neutralizing activity against the circulating variant(s) for postexposure prophylaxis or treatment of COVID-19. However, the EUA status of multiple COVID-19 monoclonal antibodies has been suspended owing to their reduced efficacy considering emerging SARS-CoV-2 variants, namely Omicron. Currently, monoclonal antibodies that are active to the most common circulating variant in the

Table 2
SARS-CoV-2 Monoclonal Antibodies: Indications and Status

Indication	Monoclonal Antibody	Efficacy Against COVID-19 Variants [47]	Comments
Treatment	Bamlanivimab and etesevimab	Reduced efficacy against Omicron variants and subvariants	Due to lack of efficacy against circulating variants, distribution has been paused in the USA since June 2021.
	Bebtelovimab	Active against Omicron variants, including BA.2. May have efficacy against BA.4/BA.5 [48]	Currently no clinical efficacy data. Indicated for patients at high risk for progression of COVID-19, unable to receive other FDA-approved treatments, and in an outpatient setting [49].
	Casirivimab plus imdevimab	Reduced efficacy against Omicron variants	Due to lack of efficacy against Omicron variants, distribution has been paused in the USA since June 2021.
	Sotrovimab	Active against the Omicron BA.1 and BA.1.1 subvariants but reduced efficacy against BA.2 and BA.4/5 [48] variants	Due to lack of efficacy against the Omicron BA.2 variant, distribution has been paused in the USA since April 2022.
Prophylaxis	**Tixagevimab plus cilgavimab**	After increasing the dosage to 600 mg (300 mg of tixagevimab and 300 mg of cilgavimab), the efficacy against Omicron was improved in vitro.	Approved for pre-exposure prophylaxis for uninfected patients who are immunocompromised and unable to undergo vaccination due to allergies or unlikely to respond to vaccination due to an immunocompromised state [50].

United States (Omicron and its subvariants) are available for pre-exposure prophylaxis or treatment of COVID-19 (Table 2).

COVID-19 VACCINE SAFETY IN HCT AND CAR T-CELL RECIPIENTS

FAQ 8: What is known about the safety of SARS-CoV-2 mRNA vaccines?

The SARS-CoV-2 mRNA vaccines were administered to nearly 70,000 study participants, and the safety profile at 2 months median follow-up has not raised any significant concerns [7,51,52]. HCT and CAR T-cell recipients were excluded from these trials, but individuals with well-controlled HIV infection and CD4+ T-cell counts greater than 350 cells/mm^3 were included. Like other vaccines, short-term adverse effects included local injection site reactions, fever, fatigue, and headache, typically resolved within 1 to 2 days. Adults older than 55 years experienced less-frequent and -severe local injection site reactions and systemic adverse effects. Serious adverse effects were seen in 0.5% to 1.5% of study participants across the 3 reported trials, with similar distribution in the control and vaccine arms [7,8]. Data regarding safety beyond 2 months have been published, with 5% of patients reporting severe adverse reactions [53].

Both the BNT162b2 (Pfizer/BioNTech) and the mRNA-1273 (Moderna) vaccines have been associated with increased risk of myocarditis in infants, adolescents, and young adult males [54]. However, the incidence is low, with a reported rate of 40.6 cases per million second doses of mRNA vaccines administered to males aged 12 to 29 years and 2.4 cases per million second doses administered to males aged ≥30 years [54,55]. Notably, the development of cardiac toxicity, including myocarditis, after COVID-19 occurs at higher rates than vaccine-associated myocarditis [54]. Many patients with COVID-19-related myocarditis presented with cardiogenic shock that progressed to death, according to data from systematic reviews [56]. Because of the low occurrence of these adverse events after vaccination and the high probability of severe COVID-19 in unvaccinated individuals, individuals are strongly encouraged to undergo vaccination.

Recent single-center studies have demonstrated short-term safety and no clear association with the development of post-vaccination GvHD [14]. Although extrapolation of safety data in HCT and CAR T-cell recipients can be challenging, significant adverse effects beyond the early postvaccination period are not anticipated, and the benefits from vaccines may outweigh any short-term or long-term adverse effects [14]. Any adverse events, particularly in immunocompromised patients, should be reported to the Vaccine Adverse Events Reporting System [57].

FAQ 9: What is known about the safety of the recombinant adenovirus vector and protein subunit SARS-CoV-2 vaccines?

The 4 recombinant adenovirus vector vaccines currently available make use of different adenovirus serotypes: the Ad5-nCoV (CanSino) vaccine uses the human-derived serotype 5 (Ad5), the ChAdOx1 (AstraZeneca) vaccine uses the chimpanzee-derived serotype AZD1222, Gam-COVID-Vac (Sputnik V) vaccines uses both Ad25 and Ad6 serotypes, and the AD26.COV2.S (Johnson & Johnson/Janssen) vaccine uses human-derived serotype 26 (Ad26). To date, only AD26.COV2.S (Johnson & Johnson/Janssen) has received FDA EUA, and thus the following information is limited to the latter.

A total of 44,325 people were enrolled onto the phase III trial for AD26.COV2.S from 8 different countries, including the United States [9]. Of those, 22,174 received the vaccine [9]. Patients with controlled HIV were included as well, but a separate analysis of this population was not released. Like the mRNA vaccines, the most common adverse events were pain at the injection site, headaches, fatigue, muscle pain, nausea, and fevers. Serious adverse events were seen in 0.7% of individuals who received the vaccine [9]. A hypersensitivity event was reported to the FDA in 1 case and anaphylaxis in 2 cases. The FDA fact sheet also notes that the vaccine may have lower efficacy in immunocompromised patients, but no data are cited [58].

Additionally, numerical imbalances were noted between the control and vaccine groups for specific unsolicited adverse effects, such as thromboembolic events, seizures, and tinnitus [9]. Please see below for more details regarding thrombosis associated with recombinant adenovirus vaccines. It is challenging to extrapolate from the available safety data to HCT and CAR T-cell recipients. Potential risks and benefits should be weighed, and decision-making should be shared with the patient; the CDC recommends preference for the mRNA vaccines in many instances [59]. Recent single-center studies have demonstrated short-term safety and no clear association with the development of GvHD after vaccination [14]; however, close monitoring is warranted.

The NVX-CoV2373 (Novavax) vaccine was approved by the FDA under EUA on July 13, 2022, and has the least safety data

available because of limited experience in immunocompromised patients. Based on the phase 3 data, local side effects occurred in 79.6% of vaccine recipients, and systemic side effects occurred in 64.0% of vaccine recipients [10]. The most common side effects included pain at the injection site, headaches, muscle pain, and fatigue [10,60]. One case of myocarditis was reported in a vaccine recipient after the second dose [10]. A dedicated subanalysis also determined that the NVX-CoV2373 (Novavax) vaccine can be co-administered with the influenza vaccination without significant side effects noted [61].

FAQ 10: What are the risks of severe allergic reactions from SARS-CoV-2 mRNA, recombinant adenovirus vector and protein subunit vaccines?

All individuals who receive the COVID-19 vaccines need to be monitored on-site for at least 15 minutes immediately after vaccination. The potential for anaphylactic reactions to either of the mRNA vaccines is 2.5 to 4.7 cases per million doses [62]. The risk of anaphylaxis reported after the AdV26.COV2.S (Johnson & Johnson/Janssen) and NVX-CoV2373 (Novavax) vaccines is also extremely low [59]. For individuals with a history of anaphylaxis to other vaccines, counselling for a potential similar reaction is recommended. These individuals should be monitored for 30 minutes after receipt of the vaccine. There is no contraindication to receipt of COVID-19 vaccines for individuals with drug or food allergies [63].

The only contraindication to the AdV26.COV2.S (Johnson & Johnson/Janssen) vaccine is an immediate severe allergic reaction to one of its components or a known allergy to polysorbate; similarly. Individuals with a history of anaphylaxis to other vaccines, drugs, or foods can safely receive the vaccine with close monitoring. Patients allergic to ingredients in the mRNA vaccines or those with a known allergy to polyethylene glycol should consider getting the recombinant adenovirus vector vaccine (AD26.COV2.S), and vice versa [64]. The CDC also recommends that those who cannot get the second dose of an mRNA vaccine because of contraindications (such as severe allergic reaction to the first dose) may be given a single dose of the recombinant adenovirus vector vaccine 28 days or more after the first dose of the mRNA vaccine [63]. The CDC website provides detailed guidance on vaccine ingredients and triaging candidates based on their history of allergic reactions [65].

FAQ 11: Is it safe to combine routine post-transplantation vaccines with COVID-19 vaccines? What are some considerations or concerns after COVID-19 vaccination among HCT and CAR T-cell recipients?

Routine post-transplantation vaccines can be given concomitantly with COVID-19 vaccines. However, a study in immunocompetent individuals (<56 years of age) showed that the BNT162b1 (Pfizer/BioNTech) mRNA vaccine elicits CD4+ and CD8+ T-cell responses, TH1 cell responses, and increased production of IFNγ, IL-2, and IL-12 [66–68]. Similarly, the phase I data for the Ad26.COV2.S adenovirus vector vaccine showed an increase in IFNγ ELISPOT responses, but no IL-4 response, favoring a TH1 cell response [31]. This immune response may result in more side effects (such as pain and fever) or greater severity of adverse events. With the exclusion of transplant recipients from the phase II/III trials, it remains unknown whether postvaccination inflammatory reactions could increase the risk for GvHD, hemophagocytic lymphohistiocytosis, and transplant-associated thrombotic microangiopathy [69]. Thousands of doses have been administered in HCT and CAR T-cell recipients, and, up to now, there are limited reports of GvHD after vaccination [70]. Close monitoring and reporting of such events are strongly recommended.

FAQ 12: What are the clotting risks associated with the administration of the COVID-19 vaccine, particularly the AZD1222 (AstraZeneca) and AD26.COV2.S (Johnson & Johnson/Janssen) vaccines?

Cases of thrombosis at unusual sites (e.g., sinus or cerebral vein thrombosis) and cases of disseminated intravascular coagulation were observed within 4 to 16 days after vaccination with the AZD1222 (AstraZeneca) vaccine in individuals residing in countries outside the United States. Affected individuals to date, have been mostly women younger than 55 years of age. Based on updated data, the incidence of atypical clotting was 1 in 100,000 vaccine recipients, with some of these events leading to death [71]. The mechanisms of these clotting events were similar to heparin-induced thrombocytopenia and thrombosis because of the presence of immunoglobulin G (IgG) antibodies against platelet factor 4 [71,72]. As these thrombotic events occurred in younger individuals, many European countries now offer this vaccine only to older populations. AZD1222 is not available in the United States.

Similar thrombotic events were also noted with the AD26.COV2.S vaccine (Johnson & Johnson/Janssen). Cases of serious thromboembolic events (6 cases of deep venous thrombosis, 4 cases of pulmonary embolism, and 1 case of transverse sinus thrombosis) in the vaccine recipient group were initially reported from a phase III trial but were not clearly linked to the vaccine [9]. However, antibodies against platelet factor 4 were detected in a few cases [73]. After 6 cases of cerebral venous sinus thrombosis were reported to the FDA [74], administration and distribution of this vaccine was paused in the United States on April 13, 2021. Ten days later (April 23), the CDC and FDA made a joint announcement to resume distribution of the Ad26.COV2.S vaccine after determining that the incidence of thrombosis was very low and the benefit of the vaccination outweighed the risk [60]. 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 suggesting other unusual thrombotic locations should undergo further medical evaluation to diagnose or rule out thrombotic events. Given their risk for thrombosis, use of adenoviral-vector SARS-CoV-2 vaccines should only be considered if mRNA vaccines are unavailable and only in certain patient populations [75]. Notably, the CDC recommends preference for the mRNA vaccines in many instances [59].

RECOMMENDATIONS FOR DISTINCTIVE HCT AND CAR T-CELL RECIPIENT POPULATIONS

FAQ 13: What additional factors should be considered regarding COVID-19 vaccines for pediatric HCT and CAR T-cell recipients?

In the United States, the age limit for COVID-19 vaccines available under FDA EUAs or formal approval are 6 months or older for the BNT162b2 (Pfizer/BioNTech) vaccine and the mRNA-1273 (Moderna) mRNA vaccines, and greater than 18 years of age for the Ad26.COV2.S (Johnson & Johnson/Janssen) and NVX-CoV2373 vaccines. The lower age limit for the BNT162b2 vaccine under the FDA EUA was reduced first to 12 years and later to 6 months on the basis of phase III trials [76,77]. The age limit for the mRNA-1273 vaccine under the EUA was reduced to 6 months on the basis of an interim analysis from an ongoing phase II/III study [78]. As in adults, there

are no specific data on safety or efficacy available for pediatric HCT and CAR T-cell recipients; however, Moderna may be more efficacious for pediatric patients [78]. Recommendations for timing of vaccine administration and revaccinating HCT and CAR T-cell recipients (older than 6 months for the mRNA vaccines), regardless of their vaccination status before transplantation, are similar to those in adults. Considerations for vaccination of household contacts, use of monoclonal antibodies (age ≥12 years and weight ≥40 kg) in the context of vaccination, and co-administration with other vaccines are also the same as in adults.

FAQ 14: Should HCT or CAR T-cell candidates receive COVID-19 vaccination to prevent severe disease after HCT or CAR T-cell therapy? Should stem cell donors receive the COVID-19 vaccination with the goal of preventing COVID-19 in transplant recipients?

No currently reported literature has been published on the benefit of COVID-19 vaccination of candidates before HCT or cellular therapy in preventing severe COVID-19 after HCT or CAR T-cell therapy. Because the time required to complete the vaccine series and the loss of immunity after cellular therapy, using this approach solely to prevent potential severe disease may not be feasible or practical; thus it is not recommended. Instead, passive immunity can be conferred using a long-acting monoclonal antibody that is active against the circulating variant or subvariants [79].

No current studies demonstrate adoptive transfer of immunity from COVID-19–vaccinated donors to HCT or CAR T-cell recipients except for small sample size studies done in HCT donors have noted some benefits [80,81]. Vaccinating stem cell donors before stem cell harvesting has not been consistently shown to benefit HCT recipients in studies of other vaccines [82–84]. Stem cell donors should not be offered the COVID-19 vaccine for the sole purpose of benefiting HCT recipients unless under a research protocol.

FAQ 15: How effective are the COVD-19 vaccines in preventing infection from SARS-CoV-2 (sub)variants in HCT and CAR T-cell recipients?

SARS-CoV-2 (sub)variants have emerged because of the inherent mutagenesis of the virus itself and the continued viral transmission throughout the world. The World Health Organization has categorized the circulating SARS-CoV-2 variants as either variants of interest or variants of concern (VOCs) (Table 3). Because of the changes in SARS-CoV-2 VOCs, the efficacy of the different vaccines has changed over time [85]. The effectiveness of the BNT162b2 (Pfizer/BioNTech) mRNA vaccine in preventing infection from the variants B.1.1.7 and B.1.351 was 89.5% and 75.0%, respectively [86], and rates of prevention of severe disease caused by these two variants were higher (up to 97.4%). However, in real-world experience from Israel and the United States, vaccine efficacy against SARS-CoV-2 variants was lower than that reported in the phase III trials [87]. The AD26.COV2.S (Johnson & Johnson/Janssen) vaccine was less effective in South Africa and Brazil, where the B.1.135 and P.1 variants were widespread, respectively [9], yet exceeded the FDA EUA threshold of >50% effectiveness in preventing COVID-19. It is not certain how effective the vaccines are against variants in immunocompromised patients. Table 4 illustrates the efficacy of the SARS-CoV-2 vaccines available in the United States for different VOCs.

Table 3
WHO Categorization of Circulating Variants of SARS-CoV-2

Category	WHO Definition
Variant of concern	Increase in transmissibility or detrimental change in COVID-19 epidemiology; OR increase in virulence or change in clinical disease presentation; OR decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics.
Variant of interest	Genetic changes that are predicted or known to affect virus characteristics such as transmissibility, disease severity, immune escape, diagnostic or therapeutic escape; AND identified to cause significant community transmission or multiple COVID-19 clusters, in multiple countries with increasing relative prevalence alongside increasing number of cases over time, or other apparent epidemiological impacts to suggest an emerging risk to global public health.

WHO indicates World Health Organization.

The most recent (sub)variants, Omicron BA.4 and BA.5, have shown substantial immune evasion, with greater escape from vaccine-induced neutralizing antibodies than previous variants in in vitro studies [88,89]. Neutralizing antibody titers in serum of mRNA vaccine recipients were lower by a factor of 21 against BA.4 or BA.5 than against the original alpha strain [88]. Similar findings were noted with serum of individuals vaccinated with adenovirus vector–based vaccines [89].

Based on serologic testing conducted after COVID-19 vaccination in immunocompromised patients [90,91], the current COVID-19 vaccines may not adequately prevent SARS-CoV-2 infection or even severe COVID-19 caused by currently circulating Omicron variants in HCT or CAR T-cell recipients. A prophylactic approach (pre-exposure) to prevent infection or severe disease in patients who are less likely to respond to vaccines is recommended, including the use of a long-acting SARS-CoV-2 monoclonal antibody with in vitro activity against the circulating variants (Table 2 for available monoclonal antibodies).

To better cover the Omicron variant and subvariants (BA 4/BA5), both Pfizer and Moderna have developed bivalent mRNA

Table 4
Vaccine Efficacy Against Symptomatic COVID-19 Associated With Selected Variants [10.93-98]

	SARS-CoV-2 variants		
	Alpha	Delta B.1.617.2	Omicron*
BNT162b2 Pfizer/BioNTech	91%-95% (2 doses)	51.9%-90% (2 doses) and 89.9%-92.3% (3 doses)	45.7%-66.9% (3 doses)
mRNA-1273 Moderna	93%-94% (2 doses)	73.7%-80.4% (2 doses) and 96.4% (3 doses)	66.3%-68.1% (3 doses)
Ad26.COV2.S Johnson & Johnson/Janssen	65%-81% (1 dose)	61%-74% (1 dose)	55%-74% (2 doses)
NVX-CoV2373 Novavax	86.3% (2 doses)	NA	NA

* No data are available for Omicron subvariants such as BA.4/BA.5.

vaccines for booster doses [92]. After FDA review of the mRNA bivalent COVID-19 vaccines, the CDC is recommending it as replacement of all the other available booster vaccines, after the primary series [35]. However, the monovalent mRNA vaccines are still recommended for primary vaccination.

POST-VACCINATION COVID-19 SEROLOGIC TESTING IN HCT AND CAR T-CELL RECIPIENTS

FAQ 16: What is the appropriate timing and role of serologic testing for COVID-19 after SARS-CoV-2 vaccination?

Some commercially available serology assays test for antibodies against the nucleocapsid (N) protein, which is a marker of prior natural infection with SARS-CoV-2 and not an indication of immune response to COVID-19 vaccines. In contrast, serology assay results suggesting immunogenicity of COVID-19 vaccines would measure anti-spike (S) IgG in the context of negative recent exposure to SARS-CoV-2 or previous infection with SARS-CoV-2. However, the levels of anti-S IgG that confer protection against SARS-CoV-2 infection have not been standardized. Therefore using serology testing alone is not recommended to determine vaccine efficacy, especially in immunocompromised patients who oftentimes cannot generate humoral immune responses to vaccines because of aberrant immunity caused by their underlying disease or disease-directed therapy.

Neutralizing antibodies against the receptor binding domain of the S protein are considered protective against reinfection in contrast to antibodies against the N protein [99]. In healthy individuals who had mild to moderate COVID-19, high titers of neutralizing antibodies lasted for up to 5 months after initial infection, with a robust antibody response occurring by day 30 after infection [100]. However, the correlation between levels of SARS-CoV-2 antibodies and development of subsequent illness is not clear.

Given the role of serologic testing after vaccination in HCT and CAR T-cell recipients is uncertain, we do not recommend routine testing with serology unless done under a research protocol. Additionally, with the increasing prevalence of SARS-CoV-2 infections and vaccination uptake across the United States, pooled IgG may contain antibodies against the SARS-CoV-2 S and N proteins. Therefore, if serologic testing is desired, we do not recommended testing for SARS-CoV-2 antibodies within 4 weeks of IVIG or COVID-19–directed monoclonal antibody infusions because of possible false-positive results.

FAQ 17: Given the scarce data on the safety and efficacy of the COVID-19 vaccines in immunocompromised patients, what is an effective vaccine strategy to reduce viral transmission to this group of patients?

Viral transmission from COVID-19–positive household contacts poses the highest risk of viral spread to any population [101], mainly to immunocompromised patients. Other close contacts [102] include health care workers caring for immunocompromised patients, who are also at increased risk for exposure to COVID-19 in the community [103]. Vaccination of household members, close contacts, and health care workers caring for immunocompromised patients is a central strategy for reducing the risk of viral transmission to this vulnerable patient population.

Q4 UNCITED REFERENCES

[93, 94, 95, 96, 97, 98]

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