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September 2021 update

INTRODUCTION

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic continues to cause excess morbidity and mortality in the United States and worldwide. Hematopoietic cell transplant (HCT) and chimeric antigen receptor T (CAR T) cell recipients are at higher risk for serious complications from the virus, including hospitalization, ICU admission and death from COVID-19 [1-4]. These patients are also burdened with other comorbidities associated with COVID-19–related mortality, including older age, cardiovascular disease, renal dysfunction, and high-level immunosuppression, among many others that further deepen and drive worse outcomes.

In the United States, two novel messenger RNA (mRNA) vaccines and one novel adenovirus vector-based vaccine have been either formally approved by the Food and Drug Administration (FDA) or are approved under the FDA's Emergency Use Authorization (EUA; Table 1). 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 [5,6]. 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 [7]. 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.

Despite varied approaches to local allocation of vaccines among states and U.S. territories, HCT and CAR T cell recipients should be amongst the first patients to receive vaccination, when available, although data on vaccine safety and efficacy are scarce for HCT or CAR T cell recipients and the vaccine immune response is likely to be blunted compared to healthy individuals [8,9]. However, despite the scarcity of data, the high level of protection afforded to those vaccinated in the clinical trials and overall safety of the vaccine in clinical trials and post-EUA experience, the **American Society of Transplantation and Cellular Therapy (ASTCT) and the American Society of Hematology (ASH) strongly support early access to vaccines for these vulnerable patients, along with their caregivers, family, and household contacts when and if vaccine supply permits.**

This document will be updated periodically when new data become available. **All current guidance and responses are based on opinions of the ASTCT/ASH COVID-19 Vaccine expert panel.** Furthermore, the expert panel recognizes that vaccine supply varies between states due to federal and state allocation, and our opinion is not meant to supersede vaccine eligibility as determined by the state or federal government.

Table 1. List of currently formally approved COVID-19 vaccines or under Emergency Use Authorization in the United States

Platform	Vaccine	Manufacturing Company	Age Limit (years)	Number of Doses/Intervals (weeks)
mRNA	BNT162b2*	Pfizer and BioNTech	≥ 12	2 doses/ 3 weeks apart
mRNA	mRNA-1273	Moderna	≥ 18	2 doses/ 4 weeks apart
Recombinant adenovirus vector	Ad26.COV2.S	Johnson & Johnson/Janssen	≥ 18	1 dose

**** Received formal FDA only for ages 16 years and up approval on 8/23/21, 12-15 years of age remain under EUA***

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

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

HCT or CAR T cell recipients are often immunosuppressed for months afterwards due to conditioning regimens, maintenance therapies, immunosuppressive drugs, hypogammaglobinemia, or development of graft-versus-host disease (GvHD, in allogeneic HCT recipients); these factors may lead to a blunted immune response and affect vaccine efficacy [10-12]. Yet by delaying immunizations, these patients are at risk of severe and life-threatening COVID-19 if they acquire the infection [1-4]. Based on prior antigen-based vaccine trials in allogeneic HCT recipients, initiating vaccination series three months versus six months after transplantation did not affect induction of immunogenicity [11,13-15]. Clinical trial data to determine the optimal time to initiate vaccinations in HCT and CAR T cell recipients is unfortunately lacking but is of high priority. One potential concern is the efficacy of the Ad26.COV2.S (Johnson & Johnson/Janssen) vaccine in patients with prior adenovirus infection. This was noted with the use of recombinant adenovirus serotype 5 (Ad5) [16]. As adenovirus serotype 26 (Ad26) does not commonly circulate in the general population, pre-existing antibodies to this strain are unlikely. It was also reported in the phase I trial for Ad26.COV2.S (Johnson & Johnson/Janssen) vaccine that levels of Ad26 neutralizing antibodies did not correlate with vaccine efficacy [17]. On another note, the different currently available COVID-19 vaccines were not evaluated head-to-head with each other, making it improper to compare vaccine effectiveness based only on phase III trial data that compared each vaccine to a placebo.

Based on the current evidence of high efficacy and safety in the general patient population, including individuals with underlying conditions, the current mRNA SARS-CoV-2 vaccines could be offered as early as three months to HCT and CAR T cell recipients to prevent infection and severe disease, though efficacy may not be optimal as suggested in situations of influenza community outbreaks [15]. At this time, no preference of vaccine formulation is recommended, and patients are encouraged to receive whichever formulation is available.

When should delay of vaccination be considered 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 but may contribute to poor vaccine immune response [18]. Patients scheduled for such therapy should complete their SARS-CoV-2 vaccination when feasible prior to initiation or between cycles of cytotoxic or B-cell–depleting therapies if possible. Based on a phase I trial of the mRNA SARS-CoV-2 vaccines, peak neutralizing antibodies developed seven to 14 days after the second dose of the vaccine series in patients without prior infection[19]. Similarly, a rise in neutralizing antibodies was seen 15 days after a single-dose recombinant, replication-incompetent adenovirus serotype 26 vector-based vaccine in phase I studies [17,20]. **HCT and CAR T recipients scheduled to undergo cytotoxic or B-cell–depleting therapies could be offered the COVID-19 vaccine prior to therapy and allowed at least two weeks to pass after the second dose to allow memory T cell formation prior to giving cytotoxic or B-cell–depleting therapies if feasible.**

Human intravenous immunoglobulins (IVIGs) are often given to patients with hypogammaglobinemia due to poor B-cell function. As SARS-CoV-2 becomes more widespread, immunoglobulins to SARS-CoV-2 may be detectable in pooled IVIG. Theoretically, the immunoglobulins would mask the antigens and dampen the immune response to the vaccines and cross react with serologic testing; for this reason, IVIG recipients were excluded from the phase III mRNA COVID-19 vaccine trials[5-7]. **However, based on recent Centers for Disease Control and Prevention (CDC) recommendations, no delay in vaccination is recommended for patients who are receiving IVIGs. These recommendations may change when more data are available.**

When should an additional COVID-19 vaccine dose be considered in HCT or CAR T cell recipients?

A third dose of either of the mRNA vaccines has been approved by both the FDA and CDC on 8/12/21 for immunocompromised patients at least 28 days from the 2nd dose; the third dose is considered a part of the original vaccination series and not a booster dose. The recommendation was based on waning protective antibodies over time in immunocompromised individuals including transplant recipients, and concern that without a 3rd dose, these patients would be at high risk for COVID-19 infection [21]. Further data has suggested that patients over the age of 60 would also benefit from an additional third dose of the COVID-19 vaccination [22]. Recently, an expert FDA panel has recommended that individuals above the age of 65 or at high risk for severe disease should be considered for a booster dose 6 months after their second dose. The expert panel also recommended that health workers and others who could be at high risk of exposure to the virus on the job may get booster doses; this was endorsed by the CDC/ACIP on September 23, 2021.

Recent press release on phase 3 clinical trial for Ad26.COV2.S (Johnson & Johnson/Janssen) showed that second shot of the vaccine at 2 months provided 94% protection (CI 58%-100%) against symptomatic COVID-19 and the antibody levels rose 4-6 times higher than after single shot. The company is seeking authorization for a booster and data has been submitted to the FDA.

Should we revaccinate HCT or CAR T cell recipients regardless of whether they were partially or fully vaccinated prior to transplantation or cellular therapy?

In patients who underwent COVID-19 vaccination prior to HCT or CAR T cell therapy, there is major concern for loss of immunity. Despite the lack of data on COVID-19 vaccines, we can extrapolate from

prior experience with other preventable infections post transplantation to predict the loss in immunity after HCT [13]. It has already been demonstrated that the protection conferred by childhood vaccinations, such as MMR, are often not retained post transplantation necessitating the need for revaccination post transplantation [23]. Multiple professional societies recommend repeating all vaccinations post-transplantation, regardless of patient's vaccination status prior to transplantation [24,25]. The ASTCT, Center for International Blood and Marrow Transplant Research (CIBMTR) and the National Marrow Donor Program (NMDP) strongly recommend SARS-CoV-2 revaccination following HCT or CAR T therapy.

Thus, we recommend repeating the COVID-19 vaccination series at least 3 months after HCT or CAR T cell therapy regardless of vaccination status prior to transplantation or cellular therapy. Repeating the vaccination series with the same type of vaccine the patient received pre transplantation is recommended but with some exceptions such as access to the same type of vaccine.

Due to the limited data on safety of these vaccines beyond 2 doses, we strongly recommend reporting any suspected adverse events in immunocompromised patients through the vaccine adverse events reporting system (VAERS) (https://vaers.hhs.gov/reportevent.html).

When should HCT and CAR T cell recipients receive their second dose of the COVD-19 vaccine if they become infected with SARS-CoV-2 between doses?

If COVID-19 vaccinees become infected prior to the second dose, the CDC recommends delaying the second dose of either the Moderna or Pfizer series. However, these patients were originally restricted from receiving the second dose in the phase III clinical trials [5,6]. Further analysis of patients with asymptomatic infection between doses is ongoing. **Based on data from patients previously infected with COVID-19 prior to mRNA vaccination series, HCT and CAR T cell recipients infected with COVID-19 between the first and the second doses could be offered the second dose of their respective vaccines once symptoms have resolved and isolation precautions are discontinued, as there is no indication so far of vaccine-associated enhanced disease (VAED) or other serious adverse events.**

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

No safety and efficacy data have been published on the use of mRNA SARS-CoV-2 vaccines after receipt of SARS-CoV-2 monoclonal antibodies or convalescent plasma in patients as part of their COVID-19 treatment; these patients were specifically excluded from the phase III mRNA COVID-19 vaccine trials [5,6]. CDC guidelines recommend delaying vaccination for 90 days based on the half-life of the COVID-19–specific antibodies and based on the evidence that reinfection after natural infection is uncommon within three months [26,27]. **Currently, we recommend delaying COVID-19 vaccination for 90 days in HCT and CAR T cell recipients if they received either SARS-CoV-2 monoclonal antibodies or COVID-19 convalescent plasma, in alignment with the CDC recommendations.**

Can SARS-CoV-2 monoclonal antibodies be given to HCT and CAR T cell recipients who develop COVID-19 after receipt of mRNA COVID-19 vaccines?

If SARS-CoV-2 infection is acquired after receiving the COVID-19 vaccine, **these patients are still eligible for monoclonal antibodies under EUA guidance or convalescent plasma as part of treatment of COVID-19.**

Casirivimab and imdevimab (REGEN-COV) is the only monoclonal combination therapy approved for post exposure prophylaxis in patients from 12 years of age and older who are at high risk of severe COVID-19 if infected and are not fully vaccinated or are predicted to mount a poor response to the vaccine (such as immunocompromised patients with poor B cell function). The role of REGEN-COV for pre exposure prophylaxis is yet to be studied for immunocompromised patients. **Using monoclonal antibodies for pre-exposure prophylaxis in HCT and CAR T cell recipients is not recommended at the present time outside clinical trials**

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

Has the mRNA SARS-CoV-2 and recombinant adenovirus vaccines platform previously been investigated in the immunocompromised patient population?

While there are no other licensed mRNA vaccines in the United States, mRNA-vaccine platforms have been studied in the treatment of cancer and other infections, such as influenza, Zika, rabies, and cytomegalovirus [28,29]. With the ongoing mRNA SARS-CoV-2 vaccine uptake, data in immunocompromised patients became available [8,9,30]. One study involving cancer patients with either solid tumors or hematologic malignancies, demonstrated poor antibody response after a single dose of the Pfizer mRNA vaccine. A more pronounced antibody response was seen after the second dose in solid tumor patients [9]. Another study from the University of Pittsburg showed that 46% of hematologic malignancy patients did not produce antibodies after 2 doses of the mRNA vaccines [30]. Similar results were described in a study of solid organ transplant recipients [8]. Despite the suboptimal antibody responses in this immunocompromised population, no major safety events were reported after the use of mRNA vaccines. These studies did not report clinical outcomes of the vaccinated patients and were unable to correlate vaccination with reduced risk of COVID-19.

While adenoviral vectors have been tested in far more people than the mRNA vaccines prior to COVID-19, no adenoviral vector vaccines have demonstrated prevention of diseases in humans, nor are any licensed for use in the United States. There are limited data regarding adenovirus vector-based vaccines in immunocompromised patients. Further investigation is warranted to study the immunogenicity and durability of protection from these vaccines among this population. The adenovirus vector (Ad26) used in the Janssen vaccine is replication incompetent and should not pose a safety concern for immunocompromised hosts.

As previously mentioned, we strongly recommend reporting any suspected adverse events in immunocompromised patients through the vaccine adverse events reporting system (VAERS) (https://vaers.hhs.gov/reportevent.html).

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

The mRNA SARS-CoV-2 vaccines were administered to nearly 70,000 study participants, and safety profile at two months median follow-up has not raised any significant concerns [5,6,31,32]. HCT and CAR T cell recipients were excluded from these trials; however, individuals with well-controlled HIV infection and CD4>350 were included. Similar to other vaccines, short-term adverse effects included local injection site reactions, fever, fatigue, and headache, and they typically resolved within one to two days. Adults older than 55 years experienced decreased frequency and severity of local injection site reactions

and systemic adverse effects. Serious adverse effects were seen in 0.5 to 1.5 percent of study participants across the three reported trials with similar distribution in control and vaccine arms. Although extrapolation of safety data in the HCT and CAR T cell recipients can be challenging, significant adverse effects beyond the early post-vaccination period are not anticipated, and the benefits from vaccines may outweigh any short-term or long-term adverse effects. Close monitoring for early and late post-vaccination effects is warranted. Any adverse events should be reported to the vaccine adverse events reporting system (VAERS) and is strongly recommended in immunocompromised patients (https://vaers.hhs.gov/reportevent.html).

What is known about the safety of the recombinant adenovirus vector SARS-CoV-2 vaccine?

The three recombinant adenovirus vector vaccines in clinical trials 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, 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 EUA by the FDA. Provided information is limited to the AD26.COV2.S vaccine.

A total of 44,325 people were enrolled onto the phase III trial for AD26.COV2.S from eight different countries, including the United States [7]. Of those, 22,174 received the vaccine [7]. 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 effects were pain at the injection site, headaches, fatigue, muscle pain, nausea, and fevers. Serious adverse effects were seen in 0.7% of individuals who received the vaccine [7]. A hypersensitivity event was reported in one case, and although no cases of anaphylaxis were reported initially, two cases were subsequently reported to the FDA. The FDA fact sheet also notes that the vaccine may have lower efficacy in immunocompromised patients, but no data is cited [33]. Additionally, numerical imbalances were noted for certain unsolicited adverse effects such as thromboembolic events, seizures, and tinnitus [7]. Please see below for more details regarding thrombosis associated with recombinant adenovirus mRNA vaccines below. It is again challenging to extrapolate safety to HCT and CAR T cell recipients from the available data, and prior to administration, potential risks and benefits should be weighed. Close monitoring for early and late postvaccination effects is warranted.

What is the safety of mRNA and recombinant adenovirus vector SARS-CoV-2 vaccines in patients with unknown prior SARS-CoV-2 exposure?

Based on prior studies in severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and Middle East respiratory syndrome (MERS), there is a theoretical concern that formation of low titer neutralizing antibodies can precipitate a VAED [34,35]. Although there were no HCT or CAR T cell recipients enrolled in the current clinical trials, there were no concerns for VAED among the general population, including a small number of patients who had a history of cancer (< 3%) and 1,218 individuals with stable HIV. These trials included a subset of study participants who were seropositive for SARS-CoV-2 at time of study entry (9.6% had evidence of previous infection) and participants who developed COVID-19 in the vaccine arm.

What are the risks of serious allergic reactions from mRNA and recombinant adenovirus vector SARS-CoV-2 vaccines?

For individuals with a history of anaphylaxis to other vaccines, counselling for a potential similar reaction is recommended and should be monitored for 30 minutes if vaccinated. All individuals who receive the vaccine need to be monitored on site immediately following vaccination for at least 15 minutes. It is still recommended for individuals with drug or food allergies to receive the SARS-CoV-2 vaccine. The potential for anaphylaxis to either mRNA vaccine is 2.5 to 4.7 cases per million doses [36].

The risk of anaphylaxis reported after the AdV26.Cov2.S (Johnson & Johnson/Janssen) vaccine is extremely low. The only contraindication to this vaccine is an immediate severe allergic reaction to one of the components of the AdV26.Cov2.S (Johnson & Johnson/Janssen) or known allergy to polysorbate. Individuals with history of anaphylaxis to other vaccines, drugs or foods can safely receive the vaccine with close monitoring. Patients who are allergic to ingredients in the mRNA vaccines or those with a known allergy to polyethylene glycol should consider getting the recombinant adenovirus vector SARS-CoV-2 vaccine or AD26.COV2.S, and vice versa [27]. The CDC also recommends that those who cannot get the second dose of the mRNA SARS-CoV-2 vaccine due to contraindications (such as allergic reaction to the first dose), may consider the single-dose recombinant adenovirus vector SARS-CoV-2 vaccine after at least 28 days have passed after the first dose. The CDC website provides detailed guidance on vaccine ingredients and triaging candidates based on their history of allergic reactions.

Is it safe to combine routine post-transplant vaccines with SARS-CoV-2 vaccines?

Previously, it was recommended that SARS-CoV-2 vaccines should be administered alone, and at least 14 days separate from routine post-transplant vaccines**. However, this restriction was recently lifted by the CDC and 14 days wait time is no longer needed between vaccinations.**

Is it safe to use COVID-19 vaccines for treatment of an acute COVID-19 in HCT and CAR T cell recipients?

Although data from vaccine clinical trials have demonstrated safety in patients previously infected with COVID-19, neither the mRNA SARS-CoV-2 nor the recombinant adenovirus vector vaccines are a replacement for therapy. HCT or CAR T cell therapy recipients with recent COVID-19 should be offered the vaccine once symptoms resolve. The vaccines should not be used for treatment of COVID-19.

What are some considerations or concerns post–COVID-19 vaccination among HCT and CAR T cell recipients?

A study in immunocompetent individuals (<56 years of age) showed that COVID-19 vaccine BNT162b1 elicits CD4+ and CD8+ T cell responses, with TH1 cell responses and increased production of IFNγ, IL-2, and IL-12 [37]. Similarly, the phase I data for the recombinant adenovirus vector SARS-CoV-2 vaccine reported an increase in IFNγ ELISPOT responses, with no IL-4 response, favoring a TH1 cell response [20]. As no transplant recipients were enrolled in the vaccine phase II/III trials, it remains unknown whether postvaccination inflammatory reactions could incite risk for GvHD, hemophagocytic lymphohistiocytosis, and transplant-associated thrombotic microangiopathy. Close monitoring and reporting of such events are strongly advised.

What are the clotting risks associated with administration of the COVID-19 vaccine, in particular the AZD1222 (AstraZeneca) and AD26.COV2.S (Janssen) vaccines?

Previously, cases of thrombosis at unusual sites (e.g., sinus or cerebral vein thrombosis) and cases of disseminated intravascular coagulation had been observed within four to 16 days after vaccination with the AZD1222 (AstraZeneca) vaccine in countries outside the United States. Affected individuals were mostly women younger than 55 years. Initial reports stated that the vaccine was unlikely linked to these cases [7], however, updated incidence of atypical clotting was 1 in 100,000 vaccine recipients; some of these events led to death [38]. The mechanisms of these clotting events were similar to heparin-induced thrombocytopenia and thrombosis (HITT) due to the presence of IgG antibodies against PF4 [38,39]. As these thrombotic events occurred in younger individuals, many European countries are now offering this vaccine to older populations. AZD1222 (AstraZeneca) vaccine is not available in the USA.

Similar thrombotic events were also noted with the AD26.COV2.S vaccine (Johnsons & 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 reported in the findings of the phase 3 trial but were not clearly linked to the vaccine [7]. However, antibodies against PF4 were detected in few cases [40]. After 6 cases of cerebral venous sinus thrombosis were reported to the FDA, administration and distribution of this vaccine were halted in the US on April 13th, 2021. On April 23rd, the CDC 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 18-49. 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.

SECTION C: RECOMMENDATIONS FOR SPECIAL HCT AND CAR T CELL RECIPIENT POPULATIONS

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 current COVID-19 vaccines available under EUA are 12 years or older for the BNT162b2 (Pfizer) vaccine, and 18 years or older for the mRNA-1273 (Moderna) and Ad26.Cov2.S (Johnson & Johnson/Janssen) vaccines. The lower age limit for the BNT162b2 (Pfizer) vaccine was reduced from 16 to 12 based on phase III trial submitted to the FDA for EUA amendment [41]. Pfizer has recently announced that the results from their Phase 2/3 trial were promising and showed favorable safety and efficacy in children between the age of 5 and 11 years based on immunological markers of protection[42]; FDA review is currently pending . Moderna has also announced that their trial (TeenCOVE), which enrolled children from the age of 12 to 17, has met its endpoint analysis and they plan to submit their results to the FDA [43]. Table 1 lists the approved ages for the different COVID-19 vaccines. As in adults, there are no specific data on safety or efficacy available for pediatric HCT and CAR T cell recipients. Recommendations for timing of vaccine administration **and revaccinating HCT and CART cell recipients (lower age limit of 12 and 16 years for Pfizer and Moderna, respectively) regardless of their vaccination status prior to transplantation** could be similar to those in adults.". Considerations for vaccination of household contacts, use of serologic assays, use of monoclonal antibodies in the context of vaccination, and co-administration with other vaccines, are the same as in adults.

Should HCT or CAR T cell candidates receive the COVID-19 vaccination to prevent severe disease post-HCT or post–CAR T cell therapy? Should stem cell donors receive the COVID-19 vaccination to prevent disease in transplant recipients?

To enhance vaccine immune response in HCT recipients, some vaccination strategies have attempted to initiate the vaccine series prior to transplantation, which has shown some success in autologous HCT recipients who receive the first dose of a vaccine series prior to transplantation [44-46]. However, these vaccine series included up to three doses after transplantation. The current EUAs for the COVID-19 vaccines restrict the use to 3 doses at specific alternative times only, and attempts to deviate from the established EUAs' criteria are discouraged by the FDA and other societies [47]. **However, we recommend that transplant and CAR T cell therapy candidates who received the mRNA SARS-CoV 2 vaccines prior to transplantation or CAR T cell therapy, should repeat the two doses of the same mRNA vaccine preferably, 3 months or later after transplantation or CAR T cell therapy.**

Vaccinating stem cell donors prior to stem cell harvesting has not been shown to benefit HCT recipients in prior studies [48,49]. It is also difficult and not feasible in cases of unrelated donors. **Stem cell donors should not be offered the COVID-19 vaccine for the sole purpose of benefiting the HCT recipient unless under a research protocol. However, if the donor has been vaccinated, it may be desirable to wait at least two weeks after the second vaccine dose before stem cell donation (if possible) as it may provide some protective effect to the recipient.**

How effective are the COVD-19 vaccines in preventing infection from SARS-CoV-2 variants in HCT and CAR T cell recipients?

SARS-CoV-2 variants have emerged due to the inherent mutagenesis of the virus itself and the continued viral prevalence throughout the United States (CDC Viral Variant Tracker), reflecting low herd immunity. The mRNA COVID-19 vaccine BNT162b2 (Pfizer) effectiveness in preventing COVID-19 against the variants B.1.1.7 and B.1.351 was 89.5% and 75.0% respectively [50] and prevention of severe disease due to these 2 variants was higher (up to 97.4%). However, the vaccine effectiveness against COVID-19 variants was lower than what was previously reported in the prior phase III trials and live experience from Israel and the USA [51]. The AD26.COV2.S (Janssen vaccine) was also less effective in South Africa and Brazil where the B.1.135 and P.1 variants were widespread, respectively [7]. Yet, the results of the phase III trials still exceeded 50% effectiveness in preventing COVID-19 infection, the FDA EUA threshold. It is not certain how effective the vaccines are in immunocompromised patients. Based on antibody studies post COVID-19 vaccination in immunocompromised patients [8,9], the current COVID-19 vaccines may not be sufficient to prevent COVID-19 nor severe COVID-19 in HCT or CAR T cell recipients. Yet studies are needed to determine whether COVID-19 infections, despite vaccination in HCT and CAR T cell recipients, are due to specific variants and their impact on clinical outcomes. Furthermore, mechanisms for vaccine-induced immunity are still under investigation and may impact duration and level of protection needed to protect against SARS-CoV-2.

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

What is the appropriate timing and the role of serologic testing for COVID-19 after COVID-19 vaccination?

Neutralizing antibodies against the receptor binding domain (RBD) of the spike protein are considered protective against reinfection, in contrast to antibodies against the nucleocapsid, which are not thought to be protective [52]. Available vaccines will only produce antibodies to the spike protein. In healthy individuals who had mild to moderate COVID-19 infections, high titers of neutralizing antibodies lasted up to five months after initial infection, with robust antibody response occurring by day 30 post infection [53]. However, the correlation between COVID-19 antibodies and development of subsequent illness is not clear. Similarly, antibody response is expected with COVID-19 vaccination. Durability of response to COVID-19 mRNA-1273 vaccine was assessed in a subset of vaccine recipients [54]. Neutralizing antibody levels were detected in the entire subset at day 119 and 90 days after first and second dose of the vaccine, respectively [54]. Lower geometric mean titer was observed in vaccine recipients older than 71 years compared with those younger than 70 years [54]. There is limited COVID-19 antibody data in immunocompromised vaccine recipients [9]. In a British study comprising of 56 solid cancer patients, 44 hematologic malignancy patients and 34 healthy controls, anti-S protein was detected 21 days after the first dose of BNT162b2 in 38%, 18% and 94% vaccine recipients, respectively [9]. Of those, antibody data was available for 25 solid cancer patients and 6 hematologic malignancy patients 14 days after the second dose, and anti-S protein was detected in 95% and 60% respectively [9].

However, the antibody response (titer and durability) to the COVID-19 vaccine in HCT and CAR T cell recipients is not known. **As the role of serologic testing post-vaccination in HCT and CAR T cell recipients is not clear, we do not recommend routine testing with serology unless done under a research protocol.**

On the other hand, if serologic testing is desired by the patient or health care providers, we recommend testing for SARS-COV-2 antibodies against the spike protein anytime between 30 and 90 days after the second dose of the vaccine. Importantly, some of the commercially available serology assays test for antibodies against the nucleocapsid (N) protein, which are markers of prior natural infection from SARS-CoV-2 and not an indication of immune response to COVID-19 vaccines; thus, understanding which serologic assays are available at your disposal is of utmost importance. Additionally, with increasing prevalence of SARS-CoV-2 infections and vaccinations uptake across the United States, pooled immunoglobulin (IgG) may contain antibodies against SARS-CoV-2 spike and nucleocapsid proteins; thus, if serologic testing is desired, we do not recommended testing for SARS-CoV-2 antibodies within four weeks of IVIG infusion due to possible false-positive results.

SECTION E: RECOMMENDATIONS FOR THE CLOSE CONTACTS OF HCT AND CAR T CELL RECIPIENTS REGARDING COVID-19 VACCINATION

Given the lack of published 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 [55], but especially to immunocompromised patients. Other close contacts include health care workers caring for immunocompromised patients, who are also at increased risk for exposure to COVID-19 in the community [56].**Vaccination of household members, close contacts, and health care providers caring for immunocompromised patients is a central strategy to reduce the risk of viral transmission to immunocompromised patients. All close contacts including health care workers are strongly encouraged to get vaccinated if they have access to COVID-19 vaccines.**

When should family members, caregivers and/or household contacts who interact with HCT and CAR T cell recipients be administered COVID-19 vaccines?

Although nosocomial transmission can occur and is associated with higher morbidity and mortality [57], community exposure is the most common source for many infections among cancer and transplant patients, including COVID-19. With the enhanced focus on infection control efforts in health care settings, including universal masking, social distancing, symptom screening, and frequent SARS-CoV-2 testing for these high-risk patients, hospital and clinic-based transmission is less frequent. However, family members, caregivers, and household contacts are more likely to be the source of SARS-CoV-2 transmission to HCT and CAR T recipients in the context of being unmasked for prolonged periods of time, especially in closed and/or poorly ventilated environments. In a recent meta-analysis of 54 studies with 77,758 participants, the estimated overall household secondary attack rate was 16.6 percent, with higher rates of transmission associated with a symptomatic household member [55]. Models suggest that more than 50 percent of all SARS-CoV-2 infections are a result of transmission from pre-symptomatic or asymptomatic infections [58]. Therefore, efforts to separate symptomatic contacts from high-risk immunocompromised patients, although still recommended, may not prevent transmission, particularly in home environments. Furthermore, when infected, prolonged viral shedding among immunocompromised patients can potentially put other family members and other close contacts at increased risk [59]. **We recommend that all close contacts of HCT and CAR T cell recipients receive COVID-19 vaccines as soon as possible, based on local allocation guidelines.**

To date, currently available vaccines are known to reduce the severity of COVID-19 disease and its complications, but data on prevention of primary infection or even transmission from those vaccinated have not been adequately demonstrated. Additionally, prior studies have demonstrated the spread of COVID-19 originating from vaccinated household members [60]. **For this reason, family members, caregivers, and other household members should continue to wear masks, practicing social distancing and following all current recommendations for preventing SARS-CoV-2 exposure and acquisition.**

Is there any foreseeable risk to HCT and CAR T cell recipients by vaccinating their close contacts with the available or soon-to-be-available COVID-19 vaccines?

Currently, approved mRNA vaccines (Pfizer-BioNTech, Moderna) under the FDA's EUA do not contain live virus; thus, these vaccines are safe to use in close contacts of immunocompromised patients. Similarly, the Johnson & Johnson/Janssen COVID-19 vaccine uses a replication-deficient adenovirus 26 vector that is nontransmissible to others. Other candidate vaccines are still in ongoing clinical trials or are under FDA review.

The AstraZeneca-Oxford vaccine consists of live simian adenovirus vector ChAdOx1, containing the full-length structural surface glycoprotein (spike protein) of SARS-CoV-2; but the virus has been modified to be replication-deficient, and it cannot be transmitted to others. This vaccine is currently not approved for use in the United States.[25] The Novavax vaccine candidate (NVX-CoV2373), a protein subunit vaccine delivered with an adjuvant (saponin-based Matrix-M™), is not a live-virus vaccine and is not yet approved for use in the United States [61]. **Therefore, when or if these vaccines become available for use in the United States, there is no foreseeable risk of SARS-CoV-2 transmission to immunocompromised patients or their close contacts.**

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