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ORIGINAL ARTICLE

Return to School and COVID-19 Vaccination for Pediatric Solid Organ Transplant Recipients in the United States: Expert Opinion for 2021-2022

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The COVID-19 pandemic continues to generate challenges for pediatric solid organ transplant (SOT) recipients and their families. As rates of COVID-19 fluctuate, new SARS-CoV-2 variants emerge, and adherence to and implementation of mitigation strategies vary from community to community, questions remain about the best and safest practices to prevent COVID-19 in vulnerable patients. Notably, decisions about returning to school remain difficult. We assembled a team of specialists in pediatric infectious diseases, transplant infectious diseases, public health, transplant psychology, and infection prevention and control to re-address concerns about school re-entry, as well as COVID-19 vaccines, for pediatric SOT recipients in the United States in 2021. Based on available literature and guidance from national organizations, we generated expert statements specific to pediatric SOT recipients focused on school attendance in 2021.

Key words: coronavirus; COVID-19 vaccines; masks; pediatric transplant; return to school; SARS-CoV-2; vaccination.

Despite the hopes of many, the coronavirus disease 2019 (COVID-19) pandemic continues to create substantial hardships for children and their families. Nearly 18 months after the United States first closed schools and businesses to limit the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), parents still face difficult decisions about what is best and safest for their children's return to school. During the 2020-2021 school year, the physical, emotional, and developmental well-being of children of all ages were negatively impacted by school closures and disruptions, as well as the myriad of health and financial effects that the pandemic had on families [1, 2]. Remote learning resulted in poorer educational outcomes for students, particularly those of color [3]. In addition to the negative educational consequences, the loss of in-person education has resulted in reduced mental and physical health for students [4], has limited access to basic needs such as school-provided nutrition and health care, and has reduced opportunity for intervention for abuse and neglect [5].

Highly effective and safe COVID-19 vaccines have been authorized for use in individuals 12 years and older throughout the United States [6]. These vaccines substantially reduce the risk of severe COVID-19 in recipients and have the potential to decrease the risk of transmission of SARS-CoV-2 virus in school settings [7], providing a level of protection for school staff and older students that was non-existent at the beginning of the 2020-2021 school year. Although COVID-19 vaccines are not yet authorized for younger school-aged children, there is hope that these vaccines will add to the safety of in-person education. However, disinformation and misunderstanding of the risks and benefits of COVID-19 vaccines have led to substantial variability in vaccine uptake in communities across the country [8]. This has contributed to surges in cases in under-vaccinated locales, driven largely by SARS-CoV-2 variants. Furthermore, despite the recommendation by the American Academy of Pediatrics (AAP) for universal masking of students and staff in schools this year [9], and the recent revision of Centers for Disease Control

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(CDC) guidelines to suggest the same [10], decisions about masking ultimately remain in the hands of states and individual school districts and may not be routinely followed. As a result, questions remain about the safety of returning to school for unvaccinated children and for those in whom vaccine effectiveness may be impaired, such as solid organ transplant (SOT) recipients [11].

For recipients of SOT, age and underlying comorbidities have been major drivers of disease severity and mortality [12]. So, while mortality among unvaccinated adult SOT recipients is high [12], most infections in the pediatric SOT population have had a mild course [13–16]. According to data from the Pediatric Heart Transplant Society registry as of August 2, 2021, only 18% of 313 reported cases required hospitalization, 7% required intensive care unit admission, and less than 1% died [17]. Similarly, none of the 47 pediatric liver transplant recipients with COVID-19 in the NASPGHAN/SPLIT SARS-CoV2 registry died [15]. Among 24 COVID-19-positive pediatric kidney transplant recipients reported by the Improving Renal Outcomes Collaborative (IROC), 8 (33%) required hospitalization (2 in intensive care unit) with no respiratory failure, deaths, or allograft loss [18]. Thus, while pediatric SOT recipients are considered a higher risk group compared to other children, their risk of severe or fatal outcomes from COVID-19 has been substantially lower than adult SOT patients. Notably, these data derive mainly from cases that occurred in 2020 and early 2021, prior to emergence of the Delta variant; severity of the Delta variant among pediatric SOT recipients is not well understood. Regardless, despite the lower risk of severe outcomes, the pandemic has contributed to tremendous stress, worry, mood disturbances, and poor sleep among pediatric SOT recipients and their families [19, 20].

The goal of this document is to provide expert guidance to help inform return to school decisions in the United States for pediatric SOT recipients in 2021. We also aim to provide information about COVID-19 vaccines in this population. The consensus statements that were generated and published last year by this authorship group [21] focused on the key determinants of safe return to school for pediatric SOT recipients and remain valid. However, updated recommendations are warranted in light of a better understanding of COVID-19 in pediatric SOT recipients, the availability of vaccines in older children and young adults, varying vaccine uptake and case counts across communities, and uncertain mask requirements and usage in school settings. As with the previous iteration of this document, these recommendations are based on expert opinion and current information and should not be viewed as a guideline or systematic review. In addition, with the emergence of SARS-CoV-2 variants both presently and in the future, recommendations may be subject to change.

METHODS

A team of specialists in pediatric infectious diseases (ID), infection prevention and control, public health, and transplant psychology from the United States was convened. Team members met via webinar weekly from July to August 2021. Clinical questions were drafted based on discussion of the most common clinical questions raised by patients, families, primary and transplant providers. Only questions pertaining to school attendance in US schools or COVID-19 vaccination with vaccines authorized/approved as of August 2021 in the United States were considered; however, guidance in this document may be applicable to other countries, as well.

A non-systematic review of the literature was performed to collate data relating to each key question. This process consisted of PubMed and internet searches to identify pertinent published studies, preprint manuscripts, editorials, and publicly available state policy documents. Based on the available literature, the team drafted recommendations, which were then voted upon by the full group to ensure consensus. To be considered a consensus statement, each had to be approved by all 10 team members.

The statements and recommendations included in this manuscript were reviewed and endorsed by the Pediatric Infectious Diseases Society (PIDS), as well as Advanced Cardiac Therapies Improving Outcomes Network (ACTION), the Improving Renal Outcomes Collaborative (IROC), the Pediatric Heart Transplant Society (PHTS), the Society of Pediatric Liver Transplantation (SPLIT), the Starzl Network for Excellence in Pediatric Transplantation, and Transplant Families, who collectively specialize in pediatric solid organ transplantation, with the sole purpose of providing guidance for these vulnerable patients and their families based on available data.

RESULTS

The following key questions and statements reflect the topics that were felt to be most frequently addressed as of August 2021 by pediatric transplant ID providers.

School Attendance

What factors should be considered when assessing individual risk/benefit associated with in-person school attendance?

- *Individual risk is dependent on numerous patient-, community-, and school-related factors that, in combination, influence the risk/benefit balance of attending school (Table 1).*

All activities that involve interaction with other people carry some risk for immunocompromised individuals. This was true prior to the COVID-19 pandemic and remains true now. Fortunately, children have fared relatively well when infected

Table 1. Risk Stratification for Pediatric SOT Recipients Returning to In-Person Education

Potential Risk Category	Higher Potential Risk	Moderate Potential Risk	Lower Potential Risk
Patient factors			
Level of immunosuppression	SOT recipients within early months post-transplant (ie, first 3-6 months), who are escalating or not yet tapering immunosuppression	SOT recipients on stable maintenance immunosuppression beyond the first 3-6 months following transplant or who are tapering immunosuppression	Low-level immunosuppressive monotherapy (eg, tacrolimus) or not receiving any immunosuppression
Stability of graft function and underlying disease indication for transplantation	Unstable graft function, increased likelihood of requiring augmented immunosuppression for rejection or other medical interventions to preserve graft function	Stable or improving graft function with low likelihood of requiring augmented immunosuppression for rejection or other medical interventions	Stable graft function
Comorbidities	Presence of comorbidities associated with risk of severe COVID-19, including: • Obesity • Diabetes mellitus • Chronic lung disease • Cardiac dysfunction • Neurologic disease Presence of another concurrent condition leading to immunocompromise	Single medical comorbidity that is medically stable or improving and not requiring frequent adjustment of medical management; this may include a high-risk comorbidity that is well-controlled, if applicable	No potentially high-risk comorbidities
Developmental and behavioral readiness to adhere to precautions in school setting	SOT recipient who would otherwise be categorized as "moderate potential risk" but due to developmental readiness, does not consistently demonstrate the ability to adhere to optimal hygiene, face covering, and physical distancing practices AND Low likelihood that school personnel would be able to consistently support adherence to precautions	SOT recipient who would otherwise be categorized as "low potential risk" but due to developmental readiness, does not consistently demonstrate the ability to adhere to optimal hygiene, face covering, and physical distancing practices AND Low likelihood that school personnel would be able to consistently support adherence to precautions	SOT recipient demonstrates the ability to adhere consistently to optimal hygiene, face covering, and physical distancing practices OR SOT recipient has an individualized plan in place such that school personnel can consistently support adherence to optimal hygiene, face covering, and physical distancing practices
Vaccination status of the SOT recipient	Unvaccinated or incomplete vaccine series	Completion of vaccine series	Based on uncertainty regarding vaccine effectiveness in SOT population, we would not consider any SOT recipients low risk strictly based on vaccine status
Community- and virus-related factors			
Level of community transmission[a]	Viral transmission in the community is substantial or high	Viral transmission in the community is moderate	Viral transmission in the community is low
Vaccine rates in the community[b]	Community-level vaccination is low (<50% of vaccine-eligible individuals have completed vaccine series)	Community-level vaccination is moderate (50%-70% of vaccine-eligible individuals have completed vaccine series)	Community-level vaccination is high (>70% of vaccine-eligible individuals have completed vaccine series)
Contact tracing	No contact tracing is performed.	School relies on public health authority but cooperates to identify students who are close contacts of an infectious case	School/community performs contact tracing and school excludes students who are close contacts of an infectious case
School factors			
Mask requirements for other students	Masks not required or worn by students or staff	Masks required indoors for all unvaccinated students and staff at all times	Masks required indoors for all students and staff at all times
Social distancing of other students	No minimum distancing requirements enforced	3-6 feet social distancing required	6 feet social distancing required
Cohorting	No cohorting performed	Students are kept in large cohorts (ie, grades)	Students are kept in small cohorts (ie, individual classes) and no mixing is permitted

Table 1. Continued

Potential Risk Category	Higher Potential Risk	Moderate Potential Risk	Lower Potential Risk
Symptom screening	No symptom screening performed	School policy requires that symptomatic students stay home, but no formal procedures in place to screen	Students/staff are actively screened for symptoms and excluded from school if symptomatic
Ventilation	Rooms are unventilated	Standard ventilation is in place	Advanced ventilation is in place
Hand hygiene	Hand hygiene is at the discretion of the student	Hand hygiene is encouraged but not scheduled	Scheduled opportunities for hand hygiene are included in the day

Abbreviation: SOT, solid organ transplant.

This table was developed to inform risk for an individual within each category (row). No single category should determine an individual's risk. For example, a child who is unvaccinated is at higher risk than another child who has completed the full vaccine series, but this does not, in itself, make an unvaccinated child high risk. Information from all categories should be taken together to assess risk.

[a]Low community transmission is defined as 0-9 cases per 100 000 persons in the past 7 days; moderate transmission: 10-49 cases per 100 000 persons in the past 7 days; substantial transmission: 50-99 cases per 100 000 persons in the past 7 days; high transmission: ≥100 cases per 100 000 persons in the past 7 days. Level of community transmission based on CDC COVID Data Tracker groupings, https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-people-fully-percent-pop12.

[b]Low, moderate, and high designations based on CDC COVID Data Tracker groupings, https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-people-fully-percent-pop12.

with SARS-CoV-2, with far fewer cases of severe COVID-19 compared with adults [22]. As mentioned above, age and underlying comorbidities are important risk factors for severe COVID-19 [12]. Consequently, most infections in children who have received organ transplants are mild [13–15]. Despite this, pediatric SOT recipients should continue to be viewed as a higher risk population compared to immune-competent children. Amongst pediatric SOT recipients, those receiving higher amounts of immunosuppressive medications or having other comorbidities may be at greater risk for the development of severe COVID-19 (Table 1). Thus, caregivers and transplant providers must assess each patient's unique medical history to determine the safety and timing of in-person schooling.

Community- and school-related factors should also be considered when making individual risk assessments. During the 2020-2021 school year, substantial knowledge was gained about the safe operation of in-person learning [23]. When schools have opened with a layered approach to mitigation strategies (ie, engineering controls, space reconfiguration, masking, distancing, cleaning, and disinfection, etc.), there has been little evidence of school-based transmission of SARS-CoV-2 [24]. Even in areas with very high levels of community transmission, there has been minimal evidence of student-to-student transmission when strict procedures are in place to limit the spread of infection [25–27]. In fact, the effect of prevention measures extended beyond SARS-CoV-2 and had a profound impact on decreasing other seasonal respiratory viruses [28, 29].

Key features of school-based mitigation measures/strategies are outlined in Table 1. The degree to which these strategies need to be applied will depend on the level of community transmission, as well as the level of vaccine-specific immunity in the community. During times of widespread community transmission and low vaccine-specific immunity among students and staff, multiple mitigation strategies should be deployed to ensure the safe and uninterrupted operation of schools (CDC, AAP) [9, 10]. Schools should carefully track data on cases and transmissions in the school environment and be prepared to adapt school policies as necessary. Surveillance testing may not be practical or feasible in all educational environments but could be utilized in certain circumstances to enhance the safety of student activities [30].

The mental/behavioral health and individualized learning needs of each student are also important considerations when planning for school this fall. While some students thrived in the virtual/remote schooling environment, emerging research has identified increased anxiety, loneliness, stress, sadness, and frustration in children and teens as a result of school closures [31]. Mental health has the potential to impact transplant health and medication adherence [32]. Furthermore, access to school-based special education services, physical and mental health care services, and nutritional programs decreased substantially for most remote learners in the last academic year. Remote learning may not be feasible for some families due to caregiving, employment, or financial demands. Therefore, families and clinicians must thoughtfully weigh these additional, individual considerations alongside the patient health-, community-, and school-specific considerations.

Should masks be worn by SOT recipients this fall?

- *In alignment with CDC and AAP, we support universal masking for all children 2 years of age or older in schools this year, including pediatric SOT recipients.*
- *In situations where universal masking does not occur, medical-grade face masks should be worn by all pediatric SOT recipients who attend school, regardless of vaccination status.*

SARS-CoV2 is transmitted primarily by inhalation of respiratory droplets, which are generated during coughing or sneezing, but also when singing or during normal speech [33–35]. Over the course of the pandemic, and especially now with the emergence of more easily transmissible SARS-CoV2 variants such as B.1.617.2 (Delta), the use of face masks indoors in communities

with substantial or high transmission has been recommended by CDC, regardless of vaccination status [36]. Masking has continued to be recommended in indoor settings for all unvaccinated individuals, which at the time of this printing includes all children 2-12 years of age who do not yet qualify for authorized vaccines [37]. The main benefit of universal masking occurs by reducing the number of respiratory droplets with virus particles emitted from an infected mask-wearer to others ("source-control") [35]. If adherence is high with masks worn correctly and consistently, universal masking indoors can lead to substantially decreased spread of virus among students. Several studies during the 2020-2021 school year demonstrated that children who attend in-person school, while adhering to mitigation measures including consistent universal masking, have lower risk of SARS-CoV2 infection even when community transmission is high [24, 26, 38]. For schools this fall, universal indoor masking for all students, staff, and visitors is recommended, regardless of vaccination status. [9, 10]. Masks should also be encouraged for all SOT recipients during outdoor activities (recess, afterschool sports, etc.) where the recipient will have prolonged close contact with another person [39].

While a mask's ability to filter fine droplets varies by material and fit, in general, masks are also effective at reducing inhalation of droplets by the uninfected wearer ("filtration for wearer protection"). A case-control study from Thailand showed that wearing a mask, independent of mask type (non-medical vs medical-grade), for the duration of exposure to a person infected with SARS-CoV2 was associated with a lower risk of infection regardless of whether the infected patient also wore a mask [40]. A meta-analysis demonstrated that use of a medical-grade face mask (3-ply disposable, "surgical", or similar) was associated with significant protection against viral infection compared with no mask [41]. Given these data, we reaffirm our stance that pediatric SOT recipients would benefit from wearing a medical-grade mask in schools, especially in situations where universal masking does not occur. In situations where a medical-grade mask cannot be obtained/used, wearing a cloth mask with at least 3 layers that fits snugly across the nose and under the chin would also offer protective benefit to the pediatric SOT recipient. Using aluminum nasal bridges, knotting ear loops, or securing the ear loops behind the head are examples of techniques to improve mask fit, thereby enhancing a mask's ability to filter virus-laden droplets [42, 43]. SOT recipients who cannot wear a mask due to age, developmental, or anatomic reasons should discuss risk/benefit of school attendance with their transplant provider. Finally, COVID-19 variants continue to circulate widely in the community and the extent to which SOT recipients are protected by COVID-19 vaccines is not fully understood. Therefore, pediatric SOT recipients who have received COVID-19 vaccination should continue to mask in indoor public places, including schools, regardless of what other students may be doing.

Is it safe for my child to go back to school if they are the only one masking?

- *For most pediatric SOT recipients, attendance of in-person school will be appropriate. This decision should be individualized based on patient-specific factors as well as the level of COVID-19 activity in the community and whether or not the school has implemented other mitigation strategies besides masking.*

For school districts not requiring masking, parents of pediatric SOT recipients will be faced with the question of if it is safe for their child to attend school when others are not masked. As noted above (and in Table 1), these decisions should consider patient-specific factors as well as the status of COVID-19 cases in the child's community. Children in the first 3- to 6-month post-transplant are typically more immunosuppressed than those out longer from transplant. These children have often not yet been released to attend school this early after transplant, even prior to the COVID-19 pandemic. Children requiring higher levels of immune suppression because of a recent history of rejection should be considered on a case-by-case basis. A lack of mask mandate in a community with substantial to high levels of transmission might be a reason to seek alternative educational options. Further, it should be considered that children who have undergone lung transplantation, and those with substantial comorbidities, may be at risk for worse outcomes if they were to become infected, as with other respiratory viral infections [44].

For children greater than 3-6 months following transplant who are on baseline immune suppression, benefits of school attendance using a hospital-grade mask may outweigh risks, even in communities with substantial or high levels of SARS-CoV-2 activity. The safety of this approach will be enhanced if schools are using other mitigation strategies (eg, distancing, contact tracing). Unfortunately, there are insufficient data to support that any non-N95 masks confer adequate protection against acquisition of SARS-CoV-2 virus in a high-risk setting (ie, prolonged close contact with infected individual). The benefits of mask-wearing are optimized when all individuals are wearing masks, limiting spread of droplets. Thus, the risk-benefit ratio of returning to in-person schooling when masks are not being worn by all students and staff should be individualized.

Are there situations/settings where special accommodations should be made for SOT recipients?

- *While not necessary for all SOT recipients, an Individualized Education Plan (IEP) or 504 Plan may be helpful to ensure accommodations are provided to promote academic success and a safer learning environment.*

Some SOT recipients may benefit from additional accommodations in school settings. These individuals are likely to qualify for

504 plans or IEPs under the criterion of "Other Health Impaired." Such plans are often encouraged for SOT recipients, especially those who may have significant or frequently unexpected medical needs. Given the dynamic nature of the COVID-19 pandemic, excused absences when supported by health care team, flexible learning instruction (ie, transitioning from in-person vs remote learning based on local risk), opportunities to make up missed work, and access to less crowded learning and eating spaces (ie, eating lunch outside of cafeteria) are accommodations to consider.

Special considerations may also be warranted for siblings or close household contacts of a transplant recipient. Siblings of transplant recipients who attend school are also at risk for infection and should follow similar mitigation strategies as a transplant recipient, including masking, social distancing, and hand-washing. We also encourage families to inform siblings' teachers and schools of their child's transplant history so that they can be notified promptly upon identification of sick contacts in the classroom.

COVID-19 Vaccination

Should eligible SOT recipients receive COVID-19 vaccinations?

- *COVID-19 vaccination is strongly recommended for all eligible individuals, including SOT candidates and recipients. Once the vaccines are authorized by the Food and Drug Administration (FDA) for children <12 years of age, vaccination of younger SOT recipients will also be encouraged.*
- *Ideally, eligible children awaiting transplant should complete COVID-19 vaccination at least 2 weeks prior to transplantation to maximize immunologic response.*
- *Household members and other close contacts around SOT recipients should receive COVID-19 vaccinations as soon as they are eligible to help further ensure the protection of the SOT recipient.*
- *A third dose of mRNA COVID-19 vaccines has been authorized for use in immunocompromised individuals in the United States, including SOT recipients; families/patients should discuss this additional dose with their transplant providers.*

On December 11, 2020, the US FDA issued the first emergency use authorization (EUA) for what would be the first of 3 vaccines available now in the United States to prevent COVID-19 infection and on August 23, 2021, the FDA approved the first COVID-19 vaccine, Pfizer-BioNTech's mRNA vaccine for individuals 16 years of age and older (Table 2) [45–48]. Currently available COVID-19 mRNA vaccines, which are the predominantly used vaccines in pediatric patients 12 years of age and older, have shown significant efficacy in reducing COVID-19 infection and in preventing severe disease [49, 50]. Among immunocompetent individuals, antibody titers after vaccination persist for at least 6 months [51], and particularly noteworthy is the finding that younger immunocompetent individuals have higher antibody levels than adults [50].

Table 2. Current COVID-19 Vaccines Available in the United States

Vaccine	Type	Age Authorized for Use in the United States	Comments
BNT162b2 (tozinameran; Comirnaty) [Pfizer Inc and BioNTech]	mRNA	12 years of age and above; approved for use in individuals 16 years of age and above	EUA in the United States, EU, and other countries Approved in the United States, Canada, and other countries 2 shots, 21 days apart
mRNA-1273 (Spikevax) [ModernaTx Inc]	mRNA	18 years of age and above	EUA in the United States, EU, and other countries, Approved in Canada and Switzerland 2 shots, 28 days apart
JNJ-78326735/ Ad26.COV2.S [Janssen/ Johnson & Johnson]	Replication-defective adenoviral vector	18 years of age and above	EUA in the United States, EU, Canada, and other countries 1 shot

Abbreviation: EUA, emergency use authorization.

Various studies have evaluated antibody titers after vaccination with mRNA vaccines in SOT recipients [52–56]. While studies in adult SOT recipients have demonstrated lower antibody levels post-vaccination compared to immunocompetent adults, many individuals in these studies did develop adequate antibody titers after the second vaccine dose. Furthermore, recent studies have shown a boost from a third dose compared to those who received placebo for the third dose [57]. Despite a reduced immunogenicity compared to immunocompetent adults, vaccination is effective for most SOT recipients. In a study of 2151 adults SOT recipients, vaccination led to an almost 80% reduction in the incidence of symptomatic COVID-19 compared to unvaccinated SOT recipients [49]. Meanwhile, in one large study of 18 215 adult SOT recipients, 0.83% developed an infection after completing all recommended vaccine doses [58]. Studies in pediatric SOT recipients are limited. A recent study of 57 pediatric SOT recipients found that 73% had positive antibody responses after 2 doses of mRNA vaccine [59], higher than most reports following a 2-dose series in adults. However, post-vaccine cellular immune responses, as well as the rate and severity of infection after vaccination in SOT recipients, have not yet been fully evaluated.

SOT recipients often have lower or waning antibody titers to other vaccines such as influenza or pneumococcal vaccines, but these vaccines continue to provide substantial protection against infection and severe disease despite modest immune responses [49]. These vaccines are therefore routinely recommended prior to and after transplantation. Based on this existing experience with other vaccines, COVID-19 vaccination of all eligible SOT recipients is strongly recommended given the potential

for protection against severe disease in this vulnerable population. SOT recipients should receive any of the currently available COVID-19 vaccines based on age of eligibility. The full series should be completed for mRNA vaccines, and routine testing of antibody titers to assess the immune response or determine the need for a subsequent dose is not recommended.

Pediatric SOT recipients who may not have an adequate immune response to COVID-19 vaccination or are too young to be vaccinated can be more optimally protected from developing COVID-19 infection if all vaccine-eligible households and other close contacts are vaccinated. Eligible SOT recipients themselves should ideally receive the full vaccine series prior to transplantation, if possible, but deferral of transplantation to complete the series is not recommended. The optimal time to initiate vaccination or complete the vaccine series after transplantation is unclear. Experts generally recommend waiting at least 1-month post-SOT to enable a more robust immune response [60]. While we do not advocate for any specific COVID-19 vaccine type, all experience and data regarding the safety and efficacy in pediatric SOT recipients 12-17 years of age have been with mRNA vaccines.

The FDA has recently expanded the EUA to include administration of an additional (third) vaccine dose for age-eligible SOT recipients who have completed their primary, 2-dose mRNA COVID-19 vaccine series. The third dose should be given no sooner than 28 days after completion of the second dose in the vaccine series and the same vaccine product (Pfizer-BioNTech or Moderna) should be used for all doses, when clinically possible. Although there are no specific data to guide the optimal timing of third doses in age-eligible pediatric SOT recipients, we would suggest administration of the third dose at least 28 days following dose 2 but as close to that dose as is feasible and deemed safe by the transplant team. The goal of the third dose is to ensure adequacy of the primary immune response to vaccination rather than boosting of waning protection. Parents and pediatric SOT recipients should discuss a third dose of vaccine with their providers. Currently, most data on third doses are from adult studies.

Further, monoclonal antibodies (mAb) are adjunctive therapies that have been authorized by the FDA for use in individuals at highest risk for severe COVID-19. Patients and families should be aware of the potential availability of mAb for children 12 years of age and older weighing more than 40 kg in the outpatient setting for the treatment of mild-to-moderate COVID-19 and as post-exposure prophylaxis [61]. Given the limited data on mAb in pediatric SOT recipients, families should discuss their use with their local transplant team. COVID-19 vaccines can be provided to eligible children who receive monoclonal antibodies 90 days after the last mAb dose.

Pediatric SOT recipients should also be encouraged to complete all other age-appropriate vaccinations, including inactivated influenza vaccine (IIV). Given the lack of significant influenza transmission in 2020-2021, it will be difficult to predict the severity of influenza this season. Additionally, influenza and other respiratory viruses can mimic COVID-19, and prevention of respiratory illnesses will help schools to remain open and in-person this fall and winter. Similarly, household contacts of pediatric SOT candidates and recipients should receive IIV before there is influenza in the community.

If a child has had COVID-19 infection, does he/she still need a vaccination?

- *COVID-19 vaccination is recommended for all eligible SOT recipients, including those with a history of prior COVID-19 infection.*
- *Children who have COVID-19 infection can pursue vaccination once they have recovered and no longer require isolation.*
- *It is currently recommended to wait 90 days to initiate vaccination in individuals treated with COVID-19 monoclonal antibodies.*

Immunization against COVID-19 has been a critical addition to interventions such as masking, symptom screening, frequent hand-washing, and physical distancing for control of the spread of SARS-CoV-2. Populations with higher vaccination rates have experienced decreases in COVID-19 cases, hospitalizations, and deaths [62, 63]. Although individuals with prior SARS-CoV-2 infection develop some degree of protective immunity against the virus [64], responses vary from 1 person to another and are generally lower than those stimulated by vaccination, as measured by antibodies against the Spike protein that mediate infection [65]. The duration of any protection generated by natural infection is also not clear. A recent study of individuals with prior SARS-CoV-2 infection found that reinfection rates were more than twice as high in individuals who were not vaccinated after their primary infection compared to those who were vaccinated [66].

Importantly for children, adolescents who were not immunocompromised who received an mRNA-based vaccine against SARS-CoV-2 generated even higher antibody levels than adults [50], suggesting that these vaccines may work even better in preventing infection and disease in younger individuals. Adult SOT recipients have lower antibody levels than adults without immune compromise [52, 67]; although it is reasonable to suspect this will also be the case in pediatric SOT recipients, this is still under evaluation. Importantly, vaccination stimulates immune protection against the dominant circulating variants, including the Delta variant [68, 69]. This is likely mediated by T cell responses, which in addition to antibodies are also generated by the currently authorized vaccines [70]. Taken together, the current data support recommendations to complete a full vaccine series to protect against SARS-CoV-2 disease, even in individuals who have had prior infection [71].

Are mRNA COVID-19 vaccines safe for pediatric SOT recipients?

- *Overall, mRNA COVID-19 vaccines are well tolerated; the safety profiles of COVID-19 vaccines are similar in SOT recipients when compared with the general population. Vaccine safety data in adolescents are emerging that suggest a significant benefit over risk.*

Concerns about safety and possible side effects after COVID-19 vaccination are frequently cited reasons for deferring COVID-19 vaccine among individuals prioritized for early vaccination [72, 73]. Safety data from adult SOT recipients, who were excluded from the initial phase II and III COVID-19 vaccine clinical trials, are emerging. Preliminary results from small observational cohort studies in adult SOT recipients report that COVID-19 vaccines are well tolerated overall, and these limited data do not suggest a major safety signal [57, 74]. Adverse events in adult SOT recipients, both local and, less frequently, systemic reactions, were consistent with expected vaccine reactogenicity, with rare episodes of graft rejection reported soon after receiving 2 or 3 doses of mRNA COVID-19 vaccines [57, 74–77]. Additional studies are needed to continue to assess both the short- and long-term safety profile of the multiple vaccines being used and underdevelopment in immunocompromised individuals [78, 79].

COVID-19 vaccination rates in children are variable across the globe. As such, the majority of pediatric COVID-19 vaccine safety data currently available are derived from immunocompetent children 12-17 years of age receiving the Pfizer-BioNTech mRNA COVID-19 vaccine, as it was the first COVID-19 vaccine to be recommended for EUA in children [45, 80]. As of August 4, 2021, in the United States, more than 10 million children 12-17 years of age have received at least 1 mRNA COVID-19 vaccine dose, and 7 million of them have completed a 2-dose series [81, 82]. The side effects most frequently reported to the US Vaccine Adverse Events Reporting System (VAERS) after mRNA COVID-19 vaccination in children 12-17 years of age were local vaccine site reactions, followed by systemic reactions, including headache, myalgia, fever, enlarged lymph nodes; these were usually mild to moderate in severity, self-resolving within a few days after vaccination [83]. Serious adverse events requiring medical care were reported among <1% of children 12-17 years, with 0.04% (4 per 10 000) requiring hospitalization [83].

What serious adverse events have been reported in pediatric SOT recipients after receipt of mRNA COVID-19 vaccines?

- *Serious adverse events, including myopericarditis, have very rarely been reported after mRNA COVID-19 vaccination among immunocompetent children.*
- *Children who receive COVID-19 vaccines are encouraged to participate in vaccine safety reporting strategies.*

The answer to this question is not completely known at this time given the small number of pediatric SOT recipients receiving COVID-19 vaccination. In most individuals, mRNA COVID-19 vaccines are safe, and serious adverse events are very rare [84]. As COVID-19 vaccines became more readily available to children and young adults, reports of myopericarditis arose among immunocompetent children and young adults that had not been described in the initial pediatric vaccine clinical trials and at a rate higher than would be the expected in children <18 years of age [85]. Post-vaccination myopericarditis cases occurred more frequently after the second than first dose of COVID-19 mRNA vaccine, most often in adolescent males who presented with acute onset of chest pain and fatigue [86–91]. Laboratory tests revealed elevated serum troponin concentrations and ST-segment changes on electrocardiography. Notably, symptoms resolved relatively quickly with supportive care, though a few children received additional therapies [86].

The exact pathophysiology of post-vaccination myopericarditis is unknown. At the time of this manuscript, the CDC estimates an overall incidence of post-COVID-19 mRNA vaccination myocarditis to be 3.5 per 1 million vaccine doses, with risk varying by age and sex [92, 93]. In young adult males (12-29 years), that risk may be as high as 40.6 per million after the second mRNA vaccine dose [94]. This risk must be weighed against myocarditis caused by acute SARS-CoV-2 infection, which itself affects the cardiovascular system and the post-infectious hyperinflammatory syndrome known as multisystem inflammatory syndrome (MIS-C), where children can present with shock and ventricular dysfunction 2-6 weeks after acute SARS-CoV-2 infection [85, 95–98]. After review of available data, the Advisory Committee on Immunization Practices (ACIP) concluded that the benefits of COVID-19 vaccination continue to outweigh the risks of possible post-vaccine myopericarditis, even in adolescents and young adults. And, the American Heart Association continues to recommend vaccination against COVID-19 for all eligible heart transplant recipients [99]. Transplant centers and clinicians should familiarize themselves with the myocarditis case definitions and discuss the EUA vaccine fact sheet with patients/families before vaccination [95]. In addition, education to patients and parents regarding possible symptoms will be important to ensure prompt recognition and medical evaluation. To date, there are no published cases of myopericarditis among COVID-19 vaccinated SOT recipients.

How frequent are serious adverse events after other, non-mRNA COVID-19 vaccines?

- *Serious adverse events, including Guillain-Barre syndrome (GBS) and thrombosis with thrombocytopenia syndrome (TTS), have been very rarely reported among non-SOT adults who received other, non-mRNA COVID-19 vaccines.*

Rare, serious adverse events have been reported with the Janssen Johnson & Johnson Ad26.COV2.S (J&J) COVID-19 vaccine that is currently authorized for use in individuals ≥18 years of age. Based on initial VAERS reporting data, 143 cases of GBS have occurred 4-6 weeks following vaccination among the 12.5 million J&J vaccine doses administered; 95 individuals required hospitalization [100, 101]. Though causality has not been proven, rates of GBS occurrence after J&J vaccine were higher than expected to occur in the general population and when compared with rates after receipt of mRNA COVID-19 vaccines. GBS is estimated to occur in 7.8 cases per million vaccine doses in adults. Thus, the FDA announced revisions to the Janssen vaccine fact sheets for providers and vaccine recipients to include a warning about a possible association [47, 102]. Health care providers should educate patients to seek medical care should they develop muscle weakness, paresthesias, oculobulbar symptoms, or bowel or bladder incontinence after receipt of this vaccine.

Lastly, rare events of thrombosis with TTS have been observed after receipt of Janssen J&J and AstraZeneca (not available in the United States) adenoviral vector-based COVID-19 vaccines in the United States and Europe. In total, 39 confirmed cases of TTS among ≥13 million J&J vaccine doses have been reported, occurring within 8 days (range 6-15) after vaccination, more frequently in younger (<50 years of age) adult females presenting with thrombocytopenia and thromboses, including more unusual locations including cerebral venous sinus thrombosis [93, 103]. Vaccine-induced prothrombotic immune thrombocytopenia events are rare but are thought to be a type of platelet-activating anti-PF4/heparin disorder, similar to heparin-induced thrombocytopenia [104].

Despite these rare adverse events, ongoing population-based assessments continue to demonstrate that the benefits of COVID-19 vaccination far outweigh potential risks. The AAP and CDC continue to recommend vaccination for all individuals ≥12 years of age; in addition, given the increasing number of SARS-Co-V2 infections being reported in children, the AAP strongly advocates for more timely authorization of COVID-19 vaccines in younger children based on preliminary safety data and encourages vaccine clinical trials in children as young as 6 months of age [81, 105]. Providers should encourage both COVID-19 vaccination and for patients to participate in the v-safe program. Clinicians should report all serious adverse events to VAERS, including any hospitalizations following COVID-19 vaccination and any clinically significant adverse event, regardless of causality [106, 107]. Better understanding of vaccine-associated adverse events and safety concerns will be paramount to allay individual vaccine hesitancy and to the overall success of ongoing COVID-19 vaccine efforts.

Should SOT recipients utilize antibody testing against SARS-CoV-2 when assessing personal risk for COVID-19?

- *At the current time, antibody testing following vaccination should not be routinely used to guide clinical decision making in pediatric SOT recipients.*

In general, routine antibody testing following vaccination is not recommended by the FDA and most transplant societies. Several factors related to the properties of commercially available tests as well as understanding of correlates of protection weigh in this recommendation. To begin, most commercially available tests do not examine the neutralizing antibody to spike protein receptor-binding domain (RBD) that is correlated with protection against infection and disease. Additionally, tests are either qualitative or the analytical cutoff values for antibody detection have not been validated as clinically relevant. Therefore, there is no commonly agreed antibody titer that has been defined as protective against COVID-19 infection or disease. The impact of cellular responses in conjunction with and independent of antibody responses has not yet been fully elucidated.

Individualized decisions to perform antibody testing should be informed by appropriate discussion between patients and providers regarding the limitations and interpretation of testing results in the context of local COVID-19 prevalence, emerging variants, personal situations, immunosuppressive medications, and household vaccination. The presence of antibodies after COVID-19 infection or vaccination does not guarantee protection from future infection. Therefore, continue vigilance and safety measures should be maintained regardless of the results of such testing.

DISCUSSION

The COVID-19 pandemic continues to create many questions about returning to school for pediatric SOT recipients and their families. No single answer is going to be appropriate for every child after SOT, as decisions regarding the risk/benefit of in-person school must weigh many factors. But, the academic, social, and mental health benefits of in-person school are unquestioned and we support in-person attendance at school, in conjunction with application of all optimal risk mitigation measures.

This document has been composed to help provide education and guidance for pediatric SOT recipients, their families,

and transplant providers. The statements and supporting paragraphs were developed based on current knowledge of COVID-19 and its impact on the SOT community. However, the COVID-19 pandemic has been, and likely will continue to be, dynamic. New SARS-CoV-2 variants, such as Delta (B.1.617.2), are continually emerging. With each new variant comes varying and unpredictable transmissibility and severity risks. Thus, while recommendations from our group may be appropriate now, the accuracy and applicability of these statements may change over time.

We expect that authorization for COVID-19 vaccines will be granted for younger children in the coming months, which should include pediatric SOT recipients. Vaccination is the most powerful tool available to combat SARS-CoV-2 and authorization/approval of COVID-19 vaccines in all children is paramount to lessen the impact of the pandemic on pediatric health. However, the effectiveness of COVID-19 vaccines against future SARS-CoV-2 variants cannot be anticipated. We are all hopeful that the widespread uptake of COVID-19 vaccines will lead to a reduction in infections and decrease the risk for pediatric SOT recipients and their families. Until that time, we all must continue to be vigilant and embrace public health guidance to prevent infection.

Notes

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