Received: 15 March 2021 | Accepted: 19 April 2021

DOI: 10.1111/petr.14031

PERSONAL VIEWPOINT

WILEY

COVID-19 vaccination in pediatric solid organ transplant recipients—Current state and future directions

Arnaud G. L'Huillier[1] | Monica I. Ardura[2] | Abanti Chaudhuri[3] | Lara Danziger-Isakov[4] | Daniel Dulek[5] | Michael Green[6] | Marian G. Michaels[6] | Klara M. Posfay-Barbe[1] | Luciola Vàsquez[7] | Christian Benden[8]

[1]Faculty of Medicine, Children's Hospital of Geneva, Geneva University Hospitals, Geneva, Switzerland

[2]Nationwide Children's Hospital, The Ohio State University, Columbus, OH, USA

[3]Stanford University, Palo Alto, CA, USA

[4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

[5]Vanderbilt University Medical Center, Nashville, TN, USA

[6]UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, USA

[7]Hospital Guillermo Almenara Irigoyen, Lima, Peru

[8]Faculty of Medicine, University of Zurich, Zurich, Switzerland

Correspondence
Arnaud G L'Huillier, Pediatric Infectious Diseases Unit, Geneva University Hospitals and Faculty of Medicine, 6 rue Willy-Donzé, 1205 Geneva, Switzerland.
Email: arnaud.lhuillier@hcuge.ch

Abstract

Background: Population-level COVID-19 immunization will play a key role in slowing down the SARS-CoV-2 pandemic on a global scale and protect the most at-risk individuals. Thanks to a formidable universal effort, several SARS-CoV-2 vaccines have been marketed less than a year since the first documented COVID-19 case, with promising safety, efficacy, and immunogenicity results in adults. As children were not included in the initial trials, no vaccine is currently approved for individuals <16 years of age. Similarly, immunosuppressed individuals, such as solid organ transplant recipients, were excluded from initial vaccine trials, limiting the understanding of vaccine immunogenicity and safety in this at-risk population. Thus, data regarding COVID-19 vaccination in pediatric solid organ transplantation recipients are currently lacking.

Methods: Members of the International Pediatric Transplant Association review the current general status of COVID-19 vaccines focusing on pediatric-specific issues.

Results: This review provides an overview of COVID-19 vaccines in pediatric SOT recipients and highlights the current paucity of data in both pediatric and transplant settings in terms of safety, immunogenicity, and clinical efficacy.

Conclusions: Vaccine trials including children and transplant recipients are underway and will be necessary to characterize COVID-19 vaccine safety, immunogenicity, and efficacy, which will determine potential future research directions.

KEYWORDS
children, COVID-19, immunization, SARS-CoV-2, solid organ transplantation, vaccine

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged at the end of 2019 and continues as a worldwide pandemic more than a year later, with 100 million confirmed cases and over 2 million coronavirus disease-2019 (COVID-19)-related deaths to date according to the World Health Organization (WHO). With limited treatment options, vaccination strategies will be key to prevent severe COVID-19. Thirty COVID-19 vaccines were in various stages of development stages by the summer of 2020.[1] Six months on, and a year after the first cases of SARS-CoV-2 were confirmed outside China, several vaccines had sufficient clinical safety and efficacy data to obtain approval by the regulatory health authorities, for example, in the European Union, in the United States of America, and

Abbreviations: AEs, Adverse events; AST, American Society of Transplantation; CDC, Centers for Disease Control and Prevention; COVAX, COVID-19 Vaccines Global Access; COVID-19, Coronavirus disease-2019; IGRA, Interferon-gamma release assay; IPTA, International Pediatric Transplant Association; ISHLT, International Society for Heart and Lung Transplantation; RBD, Receptor-binding domain; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SOT, Solid organ transplantation; TB, Tuberculosis; TST, TB skin test; UK, United Kingdom; WHO, World Health Organization; yo, years old.

in the United Kingdom (UK); an astonishing feat due to collaboration between governments, industry, and academia. However, so far, no vaccine has been approved for use in individuals <16 years old (yo) as children were not included in the initial clinical trials. Further, immunosuppressed individuals including solid organ transplantation (SOT) recipients were excluded from initial clinical vaccine trials, limiting our understanding of both immunogenicity and safety in this at-risk population. Based on previous data in inactivated vaccines, various transplant societies such as the *American Society of Transplantation* (AST) and *The International Society for Heart and Lung Transplantation* (ISHLT) have encouraged SOT recipients to get vaccinated against COVID-19.[2-4] Here, members of the *International Pediatric Transplant Association* (IPTA) review the current general status of COVID-19 vaccines focusing on pediatric-specific issues and provide an outlook on COVID-19 vaccination after pediatric SOT and potential future vaccine research directions. As an international group of pediatric transplant specialists from across different continents, we emphasize the overall importance of a collaborative international effort to tackle this global pandemic for the benefit of our patients across the globe.[5] For the purpose of this commentary, pediatric patients refer to individuals <18 years. As additional data emerge in pediatric immunocompromised patients, recommendations may change.

2 | GENERAL STATUS OF COVID-19 VACCINES AND CURRENT PEDIATRIC DATA ON COVID-19 VACCINES

Current vaccines employ a range of strategies and include mRNA-based, subunit with or without adjuvants, replication-deficient viral vectors, inactivated or live virus, and DNA platforms. Broad variability exists across the globe in the assessment, approval, and availability of potential vaccines (Table 1). There are 70 vaccines in human clinical trials and 181 in preclinical development to date.[6,7] Efficacy ranges from 65 to 95% depending on the formulation, dosing, and outcomes assessed. Prevention of symptomatic or serious COVID-19 functioned as the primary outcome in most studies, and prevention of asymptomatic infection remains under investigation. For example,

TABLE 1 COVID-19 vaccines platforms, efficacy and approval status as of March 15, 2021

Platform	Producer	Efficacy	Approval
mRNA	Pfizer-BioNTech[8]	95% in 43 548 participants	USA, Canada, Mexico, UK, Israel, Bahrain, Kuwait, Saudi Arabia, Chile, Panama, Ecuador, Costa Rica, E.U., Norway
	Moderna[9]	94.5% in 30 400 participants	USA
Replication defective adenovirus vector	Oxford-AztraZeneca[59]	70% in 11 636 participants	Brazil, South Africa, UK
	Johnson & Johnson[10]	66% overall for moderate to severe disease in 44 325 participants	USA
	Gamaleya Research Institute[60]	91.6% in 19 866 participants	Russia, Hungary
	CanSinoPharma	Under Investigation	China
Protein Subunit (with or without adjuvant)	Novovax Sanofi-GSK; Clover-GSK-Dynavax Vector Institute; Medicago; Anhui Zhifei Longcom and the Chinese Academy of Medical Sciences (CAMS)	Under Investigation	Vector Institute: Russia
Inactivated Virus	Sinopharm Wuhan Institute Beijing Institute Sinovac Institute of Medical Biology at CAMS Bharat Biotech and Indian Council of Medical Research and the National Institute of Virology	Under investigation Preliminary press release: Sinopharm Beijing 86% in 31,000 participants (press release)	Sinopharm: China, UAE, Bahrain Sinovac: China

vaccine efficacy in preventing symptomatic COVID-19 in adults after two COVID-19 mRNA-based vaccine doses has proven to be quite robust (95% Pfizer, 95% confidence interval [CI] 90.3–97.6% and 94.1% Moderna, 95%CI 89–96.8).[8,9] The replication-deficient adenoviral vector vaccine from Johnson & Johnson was 66% effective in prevention moderate to severe disease.[10] Initial studies have neither included children nor individuals receiving immunosuppression (including SOT recipients), leaving pending questions on immunogenicity, efficacy, and safety in these populations. The landscape of COVID-19 vaccines trials that include children is currently less robust, despite requests by pediatric societies and parents call for timely inclusion of children.[11,12]

Inequities are even more apparent in many countries such as in South America, where social inequalities as well as diverse and deficient healthcare systems have created a new epicenter for the pandemic.[5] The arrival of COVID-19 vaccines brought hope in many countries, with Argentina being the first country to initiate vaccination in South America. So far, South-American countries have been supplied with various vaccines,[13] but vaccination campaigns have been restricted to adults. Several South-American vaccines, such as Cuba's Soberana 2, are currently being evaluated clinically. Thus far, the cumulative vaccine rate is below 4% (0.1–3.8%) of the population, except for Chile, which reports 17.5%.[13] Some countries are still awaiting vaccine receipt through the COVID-19 Vaccines Global Access (COVAX) Facility to start vaccination campaigns.

At the writing of this manuscript, one COVID-19 mRNA-based vaccine is approved for individuals 16–17 years and there are approximately ten clinical studies evaluating COVID-19 vaccination in children registered in clinicaltrials.gov (accessed 2/25/2021) (Table 2). Pfizer has completed enrolment of 2000 children 12–15 yo, with plans for age de-escalation enrollment down to 5 yo.[14] Both safety and immunogenicity data are expected in Q2 to Q3 of 2021. Similarly, Moderna continues enrolling individuals 12–17 yo,[15] and the Oxford-AstraZeneca trial has started enrolling children down to 6 yo in the UK.[16] Additional studies are under consideration including children as young as 6 months old, but these are in the planning stages. Pediatric immunocompromised patients and SOT recipients were not included in these studies.

3 | PEDIATRIC-SPECIFIC SAFETY ISSUES ON COVID-19 VACCINATION

So far, only the Pfizer vaccine is approved in patients <18 yo, with a lower age limit of 16 yo. In the large-scale phase 3 placebo-controlled trial, adverse events (AEs) in vaccinees were mostly mild to moderate, with serious AEs only rarely reported.[8] Local AEs mainly consisted of pain at injection site, whereas systemic AEs mainly consisted of fatigue, headache, and muscle pain, with respective rates of 78–83%, 47–59%, 42–52%, and 21–37% in participants 16–55 yo.[8] In general, local and systemic AEs were more frequent in patients <55 yo than in older patients.[8] Regarding anaphylaxis, early reports suggested an incidence of 1/100 000 doses; however, with expanded administration, it appears to be similar to other vaccinations with 2–3 events per 1 000 000 doses.[17,18]

Although SOT recipients have been excluded from recently published COVID-19 vaccine trials, very early data indicate that mRNA-based COVID-19 vaccines are safe in adult SOT recipients.[19] This agrees with the generally similar safety profile of inactivated vaccines in immunocompromised and immunocompetent individuals.[20] As with any recently marketed vaccine, concerns about vaccine-induced allograft rejection or induction of donor-specific antibodies arise although no currently marketed vaccine has been clearly associated with allograft rejection.[21,22] Indeed, among 187 SOT patients who received the mRNA-based COVID-19 vaccine, none developed acute cellular rejection.[19] Altogether, the overall safety profile as well as the potential associations with allograft rejection will have to be carefully evaluated in SOT recipients receiving COVID-19 vaccines.

Based on experience with other inactivated vaccines, mRNA-based vaccines are anticipated to be as safe in children as in individuals ≥16-18 yo.

4 | PEDIATRIC-SPECIFIC IMMUNOGENICITY OF COVID-19 VACCINES

Based on experience with other inactivated vaccines, the mRNA-based vaccines are expected to be as immunogenic in children as in individuals ≥16 yo. COVID-19 vaccines have been successful at both eliciting a robust SARS-CoV-2-specific immune response and preventing overall and severe COVID-19,[8,9,23,24] but data on healthy children, pediatric SOT recipients, or otherwise immunocompromised children are lacking.[25] Importantly, transplanted children demonstrate decreased immunogenicity to various vaccines compared with healthy children.[26] Therefore, it is very likely that transplanted children will have diminished immune responses to COVID-19 vaccines, although the extent of this impairment is currently unknown. Impaired antibody development following confirmed COVID-19 illness in one study of adult SOT recipients highlights the concern that SOT-associated COVID-19 vaccine immunogenicity impairment will be a challenge.[27]

Determining correlates of protection after both acute COVID-19 or vaccination and threshold values for these correlates will be useful for reliably evaluating COVID-19 vaccine immunogenicity in future studies of transplanted children.[28] It will also facilitate the design and completion of vaccine clinical trials in pediatric SOT recipients given the challenges of enrolling sufficient participants to perform efficacy trial(s). In addition, initial immunobridging data from adult SOT cohorts may provide additional context for pediatric recommendations.

With the high concentrations of neutralizing antibodies generated by COVID-19 vaccines in non-immunocompromised adults, there may still be sufficient immunogenicity in pediatric SOT recipients even accounting for immunosuppression and chronic-disease induced immune impairment. Given the development of SARS-CoV-2 variants, eliciting high-level, functionally neutralizing

TABLE 2 Registered clinical studies evaluating COVID-19 vaccination in children as of March 15, 2021

Producer	Ages (y)	Enrollment	Sites
Pfizer/BioNTech	12–17	2000 (enrollment completed)	US
Moderna	12–17	3000	US
CanSino	6+	481	China
Sinovac	3–17	552	China
Bharat Biotech and Indian Council of Medical Research and the National Institute of Virology	12–65	755	India

antibody responses to COVID-19 vaccines in pediatric SOT recipients will likely be critical to enable these children to stay ahead of the viral evolution game.

5 | GENERAL IMPORTANCE OF APPROPRIATE VACCINATION IN PEDIATRIC SOT CANDIDATES

SARS-CoV-2 generally causes a milder disease in children, and COVID-19-associated morbidity and mortality are lower in children compared with adults. However, severe disease, including respiratory failure or shock during acute infection and the post-infectious, immune-mediated multi-system inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 underscore that COVID-19 and its sequelae can also be severe in children.[29-32] Children account for approximately 13% of all COVID-19 cases in the United States, with an overall rate of 4,030 cases/100,000 children, and contribute to 1.2–3% of all hospitalizations.[33] As of February 2021, cumulative COVID-19-related mortality in children surpassed the record influenza-related deaths during the 2019–20 season.[33-35] Furthermore, regardless of disease severity, children are susceptible to SARS-CoV-2 and likely contribute to virus transmission under certain circumstances. Thus, preventing SARS-CoV-2 infection could prevent severe disease and post-infectious complications, potentially reducing hospitalizations and providing some relief for already overburdened healthcare systems.

Given concerns for impaired immunogenicity post-transplant, provision of COVID-19 vaccine to pediatric SOT candidates would be ideal when feasible. Ideally, COVID-19 vaccination should be completed at least 2–4 weeks before the projected start of any immunosuppression or SOT, as clinically feasible. When available, pediatric SOT candidates or recipients are encouraged to participate in COVID-19 vaccine clinical trials. In addition, cocooning measures should be encouraged, including offering household contacts of pediatric SOT candidates and recipients COVID-19 vaccination if available.

While attention has focused on SARS-CoV-2, pediatric SOT patients are vulnerable to other infections as well. The COVID-19 pandemic has led to disruptions in children's health maintenance and significant declines in routine childhood vaccinations globally.[36] School closures have also impacted vaccine delivery, particularly in countries where vaccines are delivered at school. It remains imperative that SOT candidates receive routine vaccines pre-SOT. Currently, mRNA-based COVID-19 vaccines are not recommended to be co-administered with other vaccines.[22] Instead, a 14-day minimum interval between COVID-19 vaccine and any other vaccine is suggested.[37] If, however, there is a tight timeline and benefits of vaccination outweigh potential risks of vaccine co-administration, a shorter dosing interval may be justified. Providers should consider combination vaccines, accelerated vaccine schedules, and vaccine pre-planning, including possible prioritization of vaccines (for example, measles-mumps-rubella and varicella) to optimize pre-SOT vaccination strategies. If the candidate is ineligible or unable to receive COVID-19 vaccine before SOT, reassessment of eligibility for COVID-19 vaccination at 1–6 months after SOT is advised,[3,38] with timing depending on induction and maintenance immunosuppression regimens.

The pre-SOT evaluation may also include assessment and testing for tuberculosis (TB) infection. COVID-19 vaccines are not expected to affect the intradermal tuberculin skin test (TST) or TB interferon-gamma release assays (IGRA). However, there are insufficient data regarding whether COVID-19 vaccination could affect the TST and IGRA results in the 4 weeks post-vaccination. Per current Centers for Disease Control and Prevention (CDC) recommendations, if the COVID-19 mRNA-based vaccine has been given, deferring the TST or IGRA testing for ≥4 weeks after completion of the 2-dose COVID-19 vaccine is preferred.[39] Prioritization of TB testing in candidates should be based on individual exposures, risk factors, and time to projected SOT and weighed against the importance of receiving COVID-19 vaccine.[39]

If the SOT candidate has a history of current or prior SARS-CoV-2 infection, then COVID-19 vaccination should be offered after full recovery from COVID-19 and isolation is discontinued.[3,37,38] If, however, the SOT candidate received adjunctive specific COVID-19 therapies such as convalescent plasma or monoclonal antibodies, then COVID-19 vaccination should be deferred for at least 90 days since last antibody dose to avoid potential effect on vaccine-induced immunogenicity. Individuals receiving non-COVID-19-specific antibody therapies (subcutaneous or intravenous immunoglobulin) may proceed with COVID-19 vaccine when eligible and available, without further delay. SOT candidates who have been exposed to SARS-CoV-2 but have not developed symptomatic infection may seek vaccination after quarantine completion. As current

recommendations state that COVID-19 vaccines should not be withheld from pregnant individuals, emerging data demonstrate transplacental antibody transfer, suggesting that young SOT candidates <6 months of age may be protected if their mothers suffered from COVID-19 or received COVID-19 vaccination during pregnancy, though extent and duration of protection are unknown.[40,41]

Currently, the extent and duration of vaccine-induced immunity are unknown. At this time, a booster COVID-19 vaccine is not recommended after the initial 2-dose primary mRNA-based vaccination. Nor is re-vaccination currently recommended after immune reconstitution in individuals who received one or both doses of mRNA-based COVID-19 vaccine while receiving immunosuppression. Lastly, since a serological correlate of immune protection has not been confirmed, no recommendations exist for antibody testing after COVID-19 vaccination at this time outside of a clinical study. Regardless of vaccine status and until additional data emerge, SOT candidates and recipients should continue to follow the well-known COVID-19 preventative measures during the pandemic.

6 | IDEAL FUTURE STUDIES ON COVID-19 VACCINES

In the near future, studies in pediatric candidates and SOT recipients are needed to guide preventive strategies for these vulnerable populations. As children receive many immunizations in early life, data on the immunologic impact of COVID-19 vaccines, including de-novo antibody formation post-transplant or implication of cross-match results pre-transplant, as well as safety of COVID-19 vaccine concurrent with other vaccines deserve a high priority. Specific safety and efficacy data on children before and after transplant are also of great importance. If immunogenicity is inferior compared with healthy children, studies evaluating possible booster doses would be beneficial.

7 | EMERGING VARIANTS

RNA viruses like SARS-CoV-2 predictably experience mutations on a regular basis.[42] Given the widespread presence of SARS-CoV-2 with more than 100 million people infected worldwide, the development of clinically significant virus variants potentially containing multiple sites of mutation was inevitable. Depending upon where on the viral genome the mutations occur, their presence may lead to enhanced infectivity, enhanced virulence, and possibly the ability to escape pre-existing immunity derived from prior infection or vaccine.[43] While awareness of the presence of these variants has been increasingly recognized recently, it is worth noting that the emergence of the D614G variant identified in early 2020 was thought to account for a substantial increase in spread through increased replication efficiency and transmissibility.[44]

To date, three major SARS-CoV-2 variants have drawn attention. In August 2020, the so-called UK variant, also known as B.1.1.7 (N501Y), was initially recognized and has been associated with increased transmissibility.[45] While there has been speculation of increased virulence, this has not been confirmed at this time.[46] Moreover, this variant does not appear at present to "escape" antibody-mediated immunity from prior COVID-19 infection or immunization.[47] Immune sera from persons previously vaccinated with mRNA-based COVID-19 vaccine maintained neutralizing titers against the B.1.1.7 lineage.[48] In addition, although B.1.1.7 (as of January 25, 2021) was associated with either imported cases or community spread in a total of 70 countries across all 6 WHO regions,[49] evidence at this time has not been confirmed to result in worse outcomes or lack of protection from COVID-19 vaccines that are nearing or already approval.

Of greater concern at present is the South African variant, also known as B.1.351 (N501Y.V2). This variant contains many more mutations than D614G or B.1.1.7, including those that involve the receptor-binding domain (RBD).[44] While more recently recognized, its presence appears associated with a notable increase in recognized cases. Importantly, this variant does not appear to impact disease severity. However, there is evidence that B.1.351 evades, at least partly, antibody responses to prior SARS-CoV-2 infection and/or immunization. Evaluation of sera containing antibody against SARS-CoV-2 obtained from patients who had received one of the two mRNA-based vaccines demonstrated a reduction in neutralization of B.1.351 in vitro.[50,51] Additionally, data from clinical trial of the Novavax protein sub-unit COVID-19 vaccine in South Africa found a reduced (~50%) efficacy compared with the nearly 90% efficacy for patients in their clinical trial enrolled in the UK.[52] Moreover, therapeutic anti-spike protein monoclonal antibodies demonstrate absent neutralization activity against B.1.351.[53] These early findings raise significant concerns about the potential for this and future SARS-CoV-2 variants to initiate an immunologic arms race between vaccine development and variant selection.

Finally, the Brazilian variant, also known as P.1 or B.1.1.26, which has a mutation pattern similar to B.1.351 is the most recent variant to draw attention, the first identified case in the USA occurred in late January 2021. While less is known about this variant, it is thought to be closely related to B.1.351 and will likely share its properties.[54]

With continued global SARS-CoV-2 circulation in association with high rates of infection, additional variants will continue to emerge, evolve, and spread.[55,56] Of major concern is the ongoing potential for the development of escape mutations against immunity derived from prior infection with older strains or from vaccine. In addition, immunocompromised hosts, potentially including SOT recipients, may serve as source for development of SARS-CoV-2 variants.[57] Areas of uncertainty include the relative contribution of T-cell responses to conserved peptide epitopes amongst SARS-CoV-2 variants and whether these conserved responses could mitigate the loss of antibody responsiveness described above.[58] Increased vigilance and use of molecular sequencing to fully characterize these mutations combined with the ability of newer vaccine platforms to rapidly generate updated vaccines for use as boosters for those previously vaccinated or in combination with the initial vaccines for those not

yet vaccinated, does provide hope to minimize the impact of these variants. In the meantime, prevention strategies are the best way to limit the spread of these variants and to slow the emergence of new ones.

8 | CONCLUSION

So far, data are still lacking about safety, efficacy, and immunogenicity of COVID-19 vaccine in pediatric SOT candidates and recipients. However, excellent efficacy data, associated with robust vaccine-associated immune responses and a good vaccine safety profile in healthy adults, are promising signals that the currently available vaccines will be safe and effective in the pediatric transplant population. Pediatric- and transplant-specific vaccine trials are rapidly needed to confirm the findings generated in the general population.

AUTHOR CONTRIBUTION

Paragraphs were divided between authors, with at least two authors contributing to one paragraph. Each author group performed at least one nonsystematic review of the available literature and drafted the paragraph(s) accordingly. All authors critically reviewed the final version of the manuscript.

DATA AVAILABILITY STATEMENT

No original data in this manuscript.

ORCID

Arnaud G. L'Huillier https://orcid.org/0000-0001-9230-7285
Monica I. Ardura https://orcid.org/0000-0002-2853-2581
Abanti Chaudhuri https://orcid.org/0000-0003-0302-0739
Lara Danziger-Isakov https://orcid.org/0000-0002-5691-5221
Michael Green https://orcid.org/0000-0002-6011-2894
Marian G. Michaels https://orcid.org/0000-0002-2556-0544
Klara M. Posfay-Barbe https://orcid.org/0000-0001-9464-5704
Luciola Vàsquez https://orcid.org/0000-0002-6881-3660
Christian Benden https://orcid.org/0000-0002-8409-5646

REFERENCES

1. Sharma O, Sultan AA, Ding H, Triggle CR. A review of the progress and challenges of developing a vaccine for COVID-19. *Front Immunol*. 2020;11:585354. https://doi.org/10.3389/fimmu.2020.585354
2. Aslam S, Goldstein DR, Vos R, et al. COVID-19 vaccination in our transplant recipients: The time is now. *J Heart Lung Transplant*. 2021;40(3):169-171. https://doi.org/10.1016/j.healun.2020.12.009.
3. American Society of Transplantation. COVID-19 Vaccine FAQ Sheet [cited Mar 15, 2021]. Available from https://www.myast.org/covid-19-vaccine-faq-sheet
4. International Society of Heart and Lung Transplantation. Guidance from the International Society of Heart and Lung Transplantation regarding the SARS CoV-2 pandemic. [Cited Mar 15, 2021]. Available from https://ishlt.org/ishlt/media/documents/SARS-CoV-2_Guidance-for-Cardiothoracic-Transplant-and-VAD-center.pdf
5. Feldman AG, Beaty BL, Curtis D, Juarez-Colunga E, Kempe A. Incidence of hospitalization for vaccine-preventable infections in children following solid organ transplant and associated morbidity, mortality, and costs. *JAMA Pediatr*. 2019;173(3):260-268. https://doi.org/10.1001/jamapediatrics.2018.4954
6. World Health Organization. COVID-19: Landscape of novel coronavirus candidate vaccine development worldwide. [Cited 15 Mar, 2021]. Available from https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines
7. Bloomberg's COVID Vaccine Tracker. [Cited 15 Mar, 2021]. Available from https://www.bloomberg.com/graphics/covid-vaccine-tracker-global-distribution/
8. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. 2020;383(27):2603-2615. https://doi.org/10.1056/NEJMoa2034577
9. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. 2021;384(5):403-416. https://doi.org/10.1056/NEJMoa2035389
10. National Institutes of Health. Janssen Investigational COVID-19 Vaccine: Interim Analysis of Phase 3. [Cited 15 Mar, 2021]. Available from https://www.nih.gov/news-events/news-releases/janssen-investigational-covid-19-vaccine-interim-analysis-phase-3-clinical-data-released
11. American Academy of Pediatrics. News Release: COVID vaccine trials should begin including children now. [Cited 15 Mar, 2021]. Avaialble from https://services.aap.org/en/news-room/news-releases/aap/2020/covid-vaccine-trials-should-begin-including-children-now-says-american-academy-of-pediatrics/
12. Anderson EJ, Campbell JD, Creech CB, et al. Warp speed for COVID-19 vaccines: why are children stuck in neutral? *Clin Infect Dis*. 2020. https://doi.org/10.1093/cid/ciaa1425
13. Our World in Data. Coronavirus (COVID-19) Vaccinations. [Cited 15 Mar, 2021]. Available from https://ourworldindata.org/covid-vaccinations
14. CNBC. Pfizer says its COVID vaccine trial for kids ages 12 to 15 is fully enrolled. [Cited 15 Mar, 2021]. Available from https://www.cnbc.com/2021/01/22/pfizer-says-its-covid-vaccine-trial-for-kids-ages-12-to-15-is-fully-enrolled.html
15. Moderna. Moderna Announces First Participants Dosed in Phase 2/3 Study of COVID-19 Vaccine Candidate in Adolescents. [Cited Dec 10, 2020]. Available from https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-first-participants-dosed-phase-23-study-covid
16. COVID-19 Oxford Vaccine Trial. [Cited 15 Mar, 2021]. Available from https://covid19vaccinetrial.co.uk/
17. CDC. COVID-19 Response team & food and drug administration. allergic reactions including anaphylaxis after receipt of the first dose of pfizer-BioNTech COVID-19 vaccine - USA. *MMWR Morb Mortal Wkly Rep*. 2021;70(2):46-51. https://doi.org/10.15585/mmwr.mm7002e1
18. CDC. COVID-19 Response team and food and drug administration. allergic reactions including anaphylaxis after receipt of the first dose of moderna COVID-19 Vaccine - USA. *MMWR Morb Mortal Wkly Rep*. 2021;70(4):125-129. https://doi.org/10.15585/mmwr.mm7004e1
19. Boyarsky BJ, Ou MT, Greenberg RS, et al. Safety of the first dose of SARS-CoV-2 vaccination in solid organ transplant recipients. *Transplantation*. 2021;105(5):e56-e57. https://doi.org/10.1097/TP.0000000000003654
20. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*. 2014;58(3):e44-100. https://doi.org/10.1093/cid/cit684
21. Dos Santos G, Haguinet F, Cohet C, et al. Risk of solid organ transplant rejection following vaccination with seasonal trivalent inactivated influenza vaccines in England: A self-controlled case-series.

Vaccine. 2016;34(31):3598-3606. https://doi.org/10.1016/j.vaccine.2016.05.016
22. Danziger-Isakov L, Kumar D. Practice AICo. Vaccination of solid organ transplant candidates and recipients: Guidelines from the American society of transplantation infectious diseases community of practice. *Clin Transplant*. 2019;33(9):e13563. https://doi.org/10.1111/ctr.13563
23. Anderson EJ, Rouphael NG, Widge AT, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. *N Engl J Med*. 2020;383(25):2427-2438. https://doi.org/10.1056/NEJMoa2028436
24. Walsh EE, Frenck RW Jr, Falsey AR, et al. Safety and immunogenicity of two RNA-Based Covid-19 vaccine candidates. *N Engl J Med*. 2020;383(25):2439-2450. https://doi.org/10.1056/NEJMoa2027906
25. Kamidani S, Rostad CA, Anderson EJ. COVID-19 vaccine development: a pediatric perspective. *Curr Opin Pediatr*. 2021;33(1):144-151. https://doi.org/10.1097/MOP.0000000000000978
26. Dulek DE, de St MA, Halasa NB. Vaccines in pediatric transplant recipients-Past, present, and future. *Pediatr Transplant*. 2018;22(7):e13282. https://doi.org/10.1111/petr.13282
27. Burack D, Pereira MR, Tsapepas DS, et al. Prevalence and predictors of SARS-CoV-2 antibodies among solid organ transplant recipients with confirmed infection. *Am J Transplant*. 2021. https://doi.org/10.1111/ajt.16541
28. Jin P, Li J, Pan H, Wu Y, Zhu F. Immunological surrogate endpoints of COVID-2019 vaccines: the evidence we have versus the evidence we need. *Signal Transduct Target Ther*. 2021;6(1):48. https://doi.org/10.1038/s41392-021-00481-y
29. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med*. 2020;383(4):334-346. https://doi.org/10.1056/NEJMoa2021680
30. Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA*. 2020;324(3):259-269. https://doi.org/10.1001/jama.2020.10369
31. Gotzinger F, Santiago-Garcia B, Noguera-Julian A, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. *Lancet Child Adolesc Health*. 2020;4(9):653-661. https://doi.org/10.1016/S2352-4642(20)30177-2
32. Leidman E, Duca LM, Omura JD, Proia K, Stephens JW, Sauber-Schatz EK. COVID-19 trends among persons aged 0–24 Years - USA. *MMWR Morb Mortal Wkly Rep*. 2021;70(3):88-94. https://doi.org/10.15585/mmwr.mm7003e1
33. American Academy of Pediatrics. Children and COVID-19: State-level Data Report. [Cited 15 Mar, 2021]. Available from https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/
34. Centers for Disease Control. Influenza-Associated Pediatric Mortality. [Cited 15 Mar, 2021]. Available from https://www.cdc.gov/flu/weekly/index.htm#S3
35. CDC COVID Data Tracker. [Cited 20 Feb, 2021]. Available from https://covid.cdc.gov/covid-data-tracker/#demographics
36. Feldman AG, O'Leary ST, Isakov LD. The risk of resurgence in vaccine preventable infections due to COVID-related gaps in immunization. *Clin Infect Dis*. 2021. https://doi.org/10.1093/cid/ciab127
37. Centers for Disease Control and Prevention. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States. [Cited 15 Mar, 2021]. Avaialble from https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html
38. The Transplantation Society. TID COVID-19 Guidance Focused Review: SARS-CoV-2 Vaccines in Transplant Recipients. [Cited 15 Mar, 2021]. Avaialble from https://tts.org/index.php?option=com_content&view=article&id=850&Itemid=140.
39. Centers for Disease Control and Prevention. TB tests and mRNA COVID-19 vaccines. [Cited 15 Mar, 2021]. Avaialble from https://www.cdc.gov/tb/publications/letters/covid19-mrna.html
40. Flannery DD, Gouma S, Dhudasia MB, et al. Assessment of maternal and neonatal cord blood SARS-CoV-2 antibodies and placental transfer ratios. *JAMA Pediatr*. 2021. https://doi.org/10.1001/jamapediatrics.2021.0038
41. Joseph NT, Dunlop AL, Patel RM, et al. LB01 Maternal antibody response and placental antibody transfer following asymptomatic and symptomatic SARS-CoV-1 infection. *Am J Obs Gynecol*. 2021;224(2):S722. https://doi.org/10.1016/j.ajog.2020.12.1203
42. Sevajol M, Subissi L, Decroly E, Canard B, Imbert I. Insights into RNA synthesis, capping, and proofreading mechanisms of SARS-coronavirus. *Virus Res*. 2014;194:90-99. https://doi.org/10.1016/j.virusres.2014.10.008
43. Weisblum Y, Schmidt F, Zhang F, et al. Escape from neutralizing antibodies by SARS-CoV-2 spike protein variants. *Elife*. 2020;9: https://doi.org/10.7554/eLife.61312
44. Korber B, Fischer WM, Gnanakaran S, et al. Tracking changes in SARS-CoV-2 Spike: evidence that D614G increases infectivity of the COVID-19 virus. *Cell*. 2020;182(4):812-827. https://doi.org/10.1016/j.cell.2020.06.043
45. Davies NG, Abbott S, Barnard RC, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. *Science*. 2021. https://doi.org/10.1126/science.abg3055
46. Horby P, Huntley C, Davies N, et al. NERVTAG note on B.1.1.7 severity. SAGE meeting report2021.
47. Wang P, Nair MS, Liu L, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. *Nature*. 2021. https://doi.org/10.1038/s41586-021-03398-2
48. Muik A, Wallisch AK, Sanger B, et al. Neutralization of SARS-CoV-2 lineage B.1.1.7 pseudovirus by BNT162b2 vaccine-elicited human sera. *Science*. 2021. https://doi.org/10.1126/science.abg6105
49. World Health Organization. Program for monitoring emerging diseases (ProMED). 2020. Accessed 73, 103
50. Chen RE, Zhang X, Case JB, et al. Resistance of SARS-CoV-2 variants to neutralization by monoclonal and serum-derived polyclonal antibodies. *Nat Med*. 2021;27(4):717-726. https://doi.org/10.1038/s41591-021-01294-w
51. Wang Z, Schmidt F, Weisblum Y, et al. mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. *Nature*. 2021;27(4):717-726. https://doi.org/10.1038/s41586-021-03324-6
52. Mahase E. Covid-19 Novavax vaccine efficacy is 86% against UK variant and 60% against South African variant. *BMJ*. 2021;372:n296. https://doi.org/10.1136/bmj.n296
53. Tada T, Dcosta BM, Zhou H, Vaill A, Kazmierski W, Landau NR. Decreased neutralization of SARS-CoV-2 global variants by therapeutic anti-spike protein monoclonal antibodies. *bioRxiv*. 2021. https://doi.org/10.1101/2021.02.18.431897
54. Jangra S, Ye C, Rathnasinghe R, et al. The E484K mutation in the SARS-CoV-2 spike protein reduces but does not abolish neutralizing activity of human convalescent and post-vaccination sera. *medRxiv*. 2021. https://doi.org/10.1101/2021.01.26.21250543
55. Mascola JR, Graham BS, Fauci AS. SARS-CoV-2 viral variants-tackling a moving target. *JAMA*. 2021;325(13):1261. https://doi.org/10.1001/jama.2021.2088
56. Zhang W, Davis BD, Chen SS, Sincuir Martinez JM, Plummer JT, Vail E. Emergence of a novel SARS-CoV-2 variant in Southern California. *JAMA*. 2021;325(13):1324. https://doi.org/10.1001/jama.2021.1612
57. McCarthy KR, Rennick LJ, Nambulli S, et al. Recurrent deletions in the SARS-CoV-2 spike glycoprotein drive antibody escape. *Science*. 2021;371(6534):1139-1142. https://doi.org/10.1126/science.abf6950

58. Redd AD, Nardin A, Kared H, et al. CD8+ T cell responses in COVID-19 convalescent individuals target conserved epitopes from multiple prominent SARS-CoV-2 circulating variants. *medRxiv*. 2021. https://doi.org/10.1101/2021.02.11.21251585
59. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet*. 2021;397(10269):99-111. https://doi.org/10.1016/S0140-6736(20)32661-1
60. Logunov DY, Dolzhikova IV, Shcheblyakov DV, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. *Lancet*. 2021;397(10275):671-681. https://doi.org/10.1016/S0140-6736(21)00234-8

How to cite this article: L'Huillier AG, Ardura MI, Chaudhuri A, et al. COVID-19 vaccination in pediatric solid organ transplant recipients—Current state and future directions. *Pediatr Transplant*. 2021;25:e14031. https://doi.org/10.1111/petr.14031