Update on COVID-19 vaccination in pediatric solid organ transplant recipients

Dulek, Daniel E; Ardura, Monica I; Green, Michael; Michaels, Marian G; Chaudhuri, Abanti; Vasquez, Luciola; Danziger-Isakov, Lara; Posfay Barbe, Klara; McCulloch, Mignon I; L'Huillier, Arnaud; Benden, Christian

How to cite

DULEK, Daniel E et al. Update on COVID-19 vaccination in pediatric solid organ transplant recipients. In: Pediatric transplantation, 2022, vol. 26, n° 5, p. e14235. doi: 10.1111/petr.14235

This publication URL: https://archive-ouverte.unige.ch/unige:173845

Publication DOI: 10.1111/petr.14235

Received: 15 November 2021 | Revised: 6 January 2022 | Accepted: 7 January 2022

DOI: 10.1111/petr.14235

MINI REVIEW

WILEY

Update on COVID-19 vaccination in pediatric solid organ transplant recipients

Daniel E. Dulek[1] | Monica I. Ardura[2] | Michael Green[3] | Marian G. Michaels[3] | Abanti Chaudhuri[4] | Luciola Vasquez[5] | Lara Danziger-Isakov[6] | Klara M. Posfay-Barbe[7] | Mignon I. McCulloch[8] | Arnaud G. L'Huillier[7] | Christian Benden[9]

[1]Vanderbilt University Medical Center, Nashville, Tennessee, USA

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

[3]UPMC Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania, USA

[4]Stanford University, Palo Alto, California, USA

[5]Hospital Guillermo Almenara Irigoyen, Lima, Peru

[6]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA

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

[8]Red Cross War Memorial Children's Hospital, University of Cape Town, Cape Town, South Africa

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

Correspondence
Daniel E. Dulek, Vanderbilt University Medical Center, Nashville, TN, USA.
Email: daniel.dulek@vumc.org

Abstract

Background: COVID-19 vaccination has been successful in decreasing rates of SARS-CoV-2 infection in areas with high vaccine uptake. Cases of breakthrough SARS-CoV-2 infection remain infrequent among immunocompetent vaccine recipients who are protected from severe COVID-19. Robust data demonstrate the safety, immunogenicity, and effectiveness of several COVID-19 vaccine formulations. Importantly, Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine studies have now included children as young as 5 years of age with safety, immunogenicity, and effectiveness data publicly available. In the United States, emergency use authorization by the Federal Drug Administration and approval from the Centers for Disease Control/Advisory Committee on Immunization Practices have been provided for the 5- to 11-year-old age group.

Methods: Members of the International Pediatric Transplant Association (IPTA) provide an updated review of current COVID-19 vaccine data with focus on pediatric solid organ transplant (SOT)-specific issues.

Results: This review provides an overview of current COVID-19 immunogenicity, safety, and efficacy data from key studies, with focus on data of importance to pediatric SOT recipients. Continued paucity of data in the setting of pediatric transplantation remains a challenge.

Conclusions: Further studies of COVID-19 vaccination in pediatric SOT recipients are needed to better understand post-vaccine COVID-19 T-cell and antibody kinetics and determine the optimal vaccine schedule. Increased COVID-19 vaccine acceptability, uptake, and worldwide availability are needed to limit the risk that COVID-19 poses to pediatric solid organ transplant recipients.

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

Abbreviations: ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; EUA, emergency use authorization; FDA, Food and Drug Administration; IPTA, International Pediatric Transplant Association; MIS-C, multisystem inflammatory syndrome in children; RBD, receptor-binding domain; SOT, solid organ transplant.

1 | INTRODUCTION

Since our prior review of the landscape of COVID-19 vaccination in children with focus on implications for pediatric SOT recipients, several key advances have been made. These include initiation of pediatric COVID-19 vaccination in children down to age 5 years, evidence demonstrating the safety and immunogenicity of COVID-19 vaccination in adult SOT recipients, and recognition of the importance of a three-dose primary series for immunocompromised adults due to sub-optimal antibody responses. Despite these advances, key data gaps remain with regard to COVID-19 vaccination in children. We therefore review the current state of available data and highlight continued areas of need for future study.

2 | GENERAL IMPORTANCE OF PEDIATRIC SARS-COV-2 VACCINATION

Since the start of the pandemic, children and adolescents infected with SARS-CoV-2 have represented a small percentage of confirmed infections and have generally presented with less severe COVID-19 and related complications than adults. By mid-2021 and coincident with increasing circulation of the SARS-CoV-2 Delta (B.1.617.2) variant, pediatric COVID-19 infections and associated hospitalizations in the United States increased exponentially.[1,2] As of October 21, 2021, >6.2 million children in the United States have laboratory-confirmed SARS-CoV-2 infection, for an overall rate of 8, 364 per 100 000 children in the population and accounting for 1.6%–4.3% of hospitalizations.[3] These increased pediatric infection rates are likely in part due to the inability of children <12 years of age to receive any COVID-19 vaccine at that time. Indeed, it is important to highlight that pediatric hospitalization rates were 10 times higher among unvaccinated than fully vaccinated adolescents 12–17 years of age.[2] Though data are still emerging, it seems that other variables of severity (e.g., intensive care admission, mechanical ventilation, death) in children have remained the same as reported earlier in the pandemic, pre-Delta.[1,2] Although most infected children are asymptomatic or have mild illness, there have been over 600 pediatric deaths attributed to COVID-19 in the United States since the start of the pandemic, a number surpassing historical mortality rates from other vaccine-preventable infections such as influenza.[4] Globally, from the 82 countries with age disaggregated data available in the COVerAGE database, over 11 7000 reported COVID-19 deaths (0.4% of total reported deaths) have occurred in children and adolescents under 20 years of age.[5,6] Importantly, these metrics do not describe the global burden of COVID-19 on children, including its socioeconomic impact on children in less well-resourced countries and impacts on malnutrition, access to health care, and overall safety.[7–9] Yet, many eligible children remain under-vaccinated, due to lack of access to vaccines in some countries and vaccine hesitancy in others.

The direct benefits of pediatric COVID-19 vaccination at the individual and population-based level are expected to mirror those seen in adults. As vaccination protects against SARS-CoV-2 infection, it may also provide some protection against the development of post-COVID-19 sequelae in children, including post-COVID-19 syndrome (also called "long COVID") and immune-mediated multisystem inflammatory syndrome in children (MIS-C).[10,11] In addition, some preliminary modeling data suggest that vaccinating children against SARS-CoV-2 could indirectly positively impact adult outcomes including hospitalizations and deaths, a benefit similarly seen with other vaccines (e.g., pneumococcal).[12]

3 | UPDATED COVID-19 VACCINE DATA INCLUDING CURRENT PEDIATRIC COVID-19 VACCINE DATA

Phase 3 safety, immunogenicity, and efficacy data for the Pfizer-BioNTech BNT162b2 (Comirnaty) mRNA COVID-19 vaccine in healthy adolescents were published in May 2021.[13] In this study of 2260 participants aged 12–15 years, neutralizing antibody titers measured after a 2-dose series met noninferiority criteria compared with 16- to 25-year-old participants. Further, overall observed vaccine efficacy was 100% with no COVID-19 cases occurring after more than 7 days following the second dose. These data led to emergency use authorization (EUA) of this vaccine for children aged 12–15 years of age in the United States in May 2021. More recently, the vaccine effectiveness of 2 doses of Pfizer-BioNTech BNT162b2 mRNA vaccine in children 12–18 years of age was documented to be 93% (95% CI 83%–97%) during a period of B.1.6.17.2/Delta variant circulation.[14] Currently, COVID-19 vaccines from Moderna and from Johnson&Johnson/Janssen are not approved for individuals under 18 years of age in the United States, although data for the Moderna vaccine have been submitted to the FDA for evaluation. The Moderna vaccine is approved down to age 12 years in Europe.[15] Other vaccines, notably adenoviral vector-based vaccines, are currently not authorized in children in the USA or Europe based on the lack of pediatric-specific safety and immunogenicity data.

On October 29, 2021, the United States Food and Drug Administration (FDA) authorized administration of a 2-dose series of Pfizer-BioNTech BNT162b2 vaccine to children aged 5–11 years old based on data from 1518 vaccine recipients and 750 placebo recipients.[16] According to released data, the Pfizer vaccine met pre-determined criteria for vaccine success including both geometric mean neutralizing antibody titers and seroresponse frequency compared with a subset of 16- to 25-year-old participants from the prior efficacy trial. Importantly, 10 μg mRNA per dose for those 5–11 years was used compared with the 30μg mRNA per dose authorized for children ≥12 years of age and adults. Descriptive efficacy data demonstrated an observed vaccine efficacy of 90.7% (95% CI: 67.4%–98.3%) for overall COVID-19 infection with no severe COVID-19 cases reported in either the vaccine or the placebo groups.

Currently, the Pfizer-BioNTech BNT162b2 vaccine is fully FDA approved in the United States for persons ≥16 years of age[17] and available under EUA for children 5–11[6,18] and 12–15 years.[19] In

addition, the Advisory Committee on Immunization Practices (ACIP) within the US Center's for Disease Control (CDC) recently provided interim recommendations for use of this vaccine in children aged 5–11 years.[20] In Europe, the Pfizer-BioNTech BNT162b2 COVID-19 vaccine is approved for individuals ≥12 years of age.[21] Regarding the Moderna vaccine (Spikevax®), there are currently no published data regarding safety among children younger than 18 years. This vaccine is currently available under an EUA only for individuals ≥18 years in the United States,[22] but has been administered in several states in individuals starting at 12 years of age.[23] In Europe, the Moderna vaccine is approved for children ≥12 years of age based on unpublished data from a study of 3732 children aged 12–17 years.[24] A brief review of vaccine approval for children in countries outside of the United States and Europe is included at the end.

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

In the separate studies that led to FDA and CDC/ACIP approval of the Pfizer-BioNTech BNT162b2 vaccine, safety and adverse event frequencies in individuals 5–11 years and 12–15 years of age were similar both within these younger age groups and compared to 16–25-year-old vaccine recipients.[13,18] While local injection site pain was very common, severe injection site pain was infrequent, occurring in only 0.3% of 5–11-year-olds, 1.5% of 12–15-year-olds and 3.4% of 16–25-year-olds.[13,20] Common systemic reactogenicity events in the 5–11- and 12–15-year-old groups included fatigue (5–11 years: dose 1%–33%, dose 2%–39.4%; 12–15 years: dose 1%–60%, dose 2%–66%), headache (5–11 years: 22.4%, 28%; 12–15 years: 55%, 65%), chills (5–11 years: 4.6%, 9.8%; 12–15 year: 28%, 42%), and myalgia (5–11 years: 9.1%, 11.7%; 12–15 years: 24%, 32%).[13,20] Vaccine-related adverse events occurred in 3% of vaccine recipients and 2% of placebo recipients in the 12–15-year-old age group compared with 6% in the 16–25-year-old vaccine recipients.[13] In the 5–11-year-old age group, vaccine recipients had increased frequency of lymphadenopathy (0.9%) compared with placebo recipients (0.4%), though this difference was not noted in an expanded safety cohort.[20] No vaccine-related serious adverse events were identified in the study.

Importantly, mRNA vaccines described above have been associated with a risk of myopericarditis. This rare SAE has a favorable outcome in most cases and mainly affects males <30 years with an estimated incidence of <10/100 000 persons following the second dose of vaccine.[25–27] Based on this incidence, the frequency of post-vaccine myopericarditis is 5–10-fold less frequent when compared with the incidence of myopericarditis following SARS-CoV-2 infection.[28] Recently, data from the United States and Canada reported relatively higher rates of myopericarditis following the Moderna vaccine when compared to the Pfizer vaccine,[29,30] prompting several regions and countries to preferentially recommend the Pfizer-BioNTech BNT162b2 vaccine in young persons.[31,32]

In the transplant setting, acute allograft rejection episodes have anecdotally been documented following mRNA vaccines.[33–36] Moreover, in one small series of adult kidney transplant recipients, mRNA COVID-19 vaccine did not alter panel reactive antibody or flow cytometry cross-match.[37] To our knowledge, there are no reports of post-COVID vaccine myopericarditis in adult or pediatric SOT recipients.

5 | CURRENT COVID-19 VACCINE DATA IN ADULT SOT RECIPIENTS

Current recommendations in the United States are for adult SOT recipients to receive vaccination against SARS-CoV-2 using locally approved vaccines.[38] Early data following the use of mRNA vaccines demonstrated poor immunogenicity in adult SOT recipients following a single dose of mRNA COVID vaccine.[39–41] Subsequent studies demonstrated improved immunogenicity and continued safety with the full two-dose series with detection frequency of anti-spike IgG as high as 54% following the second vaccine.[33,42,43]

Two studies have evaluated a third dose of mRNA COVID vaccine as part of a primary series in adult SOT recipients.[36,44] In a randomized controlled trial of 120 adult SOT recipients receiving either placebo or a 3rd dose of Moderna mRNA-1273, 55% of 3rd dose recipients had above threshold anti-receptor-binding domain (RBD) antibody concentrations compared with only 18% of recipients receiving placebo.[44] In addition, neutralizing antibody frequency was significantly increased in recipients receiving 3 doses compared with recipients receiving 2 vaccine doses. These data were supported by a non-randomized series of adult SOT recipients in France receiving three mRNA COVID vaccine doses.[36] Importantly, serologic response to the three-dose regimen appears to be at least partly dependent on immunosuppression regimen and time post-transplant.[45]

Supporting the importance of a three-dose primary COVID-19 vaccine series for immunocompromised adults, a recent CDC study using a 9-site surveillance network demonstrated 2-dose vaccine effectiveness against COVID-19-associated hospitalization to be 77% (95% CI: 74%–80%) for immunocompromised adults compared with 90% (95% CI: 89%–91%) for immunocompetent adults.[46] While early data suggested infrequent occurrence of breakthrough infection in vaccinated adult SOT recipients, a more recent retrospective, multicenter study demonstrated a breakthrough infection rate of 0.83% among 18 215 fully vaccinated adult SOT recipients compared with the 0.0102% breakthrough infection rate reported by the CDC in fully vaccinated adults in the United States.[47–50]

Importantly for understanding vaccine-mediated protection from COVID in the absence of vaccine-induced serologic response, several studies of adult SOT recipients have demonstrated that COVID-19-specific T-cell responses to vaccination develop with greater frequency than and even in the absence of humoral responses.[51,52] In one cohort of 40 adult SOT recipients receiving either homologous or heterologous prime-boosting with mRNA-1273 and/or adenovirus vectored vaccine, the frequency of detectable

SARS-CoV-2-specific T-cell immunity was greater than detectable humoral immunity following both 1st (23.7% cellular vs. 5.3% humoral) and 2nd (64.7% cellular vs. 25.3% humoral).[51] Though the comparison was limited by small subcategorization cohorts, SOT recipients who received vector vaccine priming followed by mRNA vaccine boosting appeared to have the most robust induction of SARS-CoV-2-specific antibodies and CD4+ T cells compared with either homologous vaccine strategy. Similarly, in a subcohort of 48 adult SOT recipients who received two doses of mRNA-1273 vaccine, 46.2% of patients who did not have detectable anti-RBD had a detectable SARS = CoV-2-specific CD4+ T-cell response post-vaccine.[52] While the degree of protection provided by T-cell immunity in the absence of detectable SARS-CoV-2 antibodies is not known, these studies provide rationale for continued vaccination of SOT recipients despite impaired humoral immune responses.

Recommendations from national health authorities regarding the number of primary series vaccinations and the number and timing of booster doses for immunocompromised patients have been rapidly evolving over the past several months and vary by country. Therefore, we are not reviewing current booster recommendations in detail and advise transplant physicians to follow national health agencies within their country of practice.

6 | CURRENT COVID-19 VACCINE DATA IN PEDIATRIC SOT RECIPIENTS

Current data addressing the immunogenicity of COVID-19 vaccines in children are sparse. However, two small studies suggest that immunogenicity to mRNA-based COVID-19 vaccines may be similar to that seen in adult SOT recipients. In a study of 25 fully vaccinated pediatric kidney transplant recipients with median age of 19 years (IQR 18–20) who were 5 years (IQR 4–9) post-transplant, 52% were seropositive for spike antibody following 2 doses of SARS-CoV-2 vaccine (one subject received the mRNA-1273 Moderna vaccine).[53] Vaccine responders were less likely to be receiving mycophenolate mofetil compared with vaccine-nonresponders. Importantly, this study is limited by small sample size and by its consisting of a nearly adult-aged cohort.

In a prospective cohort study, 52 pediatric SOT recipients aged 12–18 years of age and without prior SARS-CoV-2 infection or seropositivity received a two-dose series of the Pfizer-BioNTech BNT162b2 vaccine.[54] Following the first vaccine dose, 56.8% of the 37 subjects with antibody testing performed were seropositive using the Roche Elecsys anti-SARS-CoV-2 S enzyme immunoassay. Among 45 subjects who had antibody testing performed 4 weeks after receipt of vaccine dose 2, seropositivity was identified in 73.3% which is higher that in many adult organ transplant cohorts. Risk factors for lack of seroresponse included SOT receipt in the preceding 3 years, receiving multiple immunosuppressive medications, and use of antimetabolite immunosuppression. Two subjects developed SARS-CoV-2 infection during the study period. One subject developed mild infection between 1st and 2nd vaccines. The second subject was seronegative following both doses of vaccine and developed infection 46 days after the second vaccination. No data are provided regarding the severity of this subject's illness. Mild-to-moderate injection site pain and fatigue were common occurring in 83.5% and 39.5% of 57 subjects, respectively. No episodes of allergic reaction, myopericarditis, or post-vaccine rejection occurred.

Thus, these two studies demonstrate modestly increased COVID-19 mRNA vaccine immunogenicity compared with that seen in adult SOT recipients though still less than seen in otherwise healthy children. Moreover, there is a suggestion of similar risk factors for vaccine non-response, especially the impact of mycophenolate mofetil. However, these studies are limited by small size, and therefore, future studies focusing on pediatric SOT recipients are urgently needed. In addition, currently, there are no published data determining the T-cell immune response to COVID-19 vaccination in pediatric SOT recipients.

7 | GLOBAL PERSPECTIVE ON COVID-19 VACCINE IN PEDIATRIC RECIPIENTS

At the time of writing this paper, many less well-resourced countries (particularly in Africa) have not had enough vaccine supply to vaccinate their high-risk adult populations. Emphasizing this discrepancy, in many countries only 3% of high-risk adults have received at least 1 dose.[55] Rates of completed vaccination in selected countries are as follows: Brazil 51.6%, India 21.4%, South Africa 18.4%, Bangladesh 11.8%, Egypt 7.4%, Malawi 2.7%, and Nigeria 1.4%.[55] In addition to vaccine supply limitations, vaccine hesitancy has been a significant challenge in many regions worldwide.[56]

Variation in the available formulations, approved ages, and timing of approval exists regarding childhood COVID-19 vaccination throughout the world. Where COVID-19 vaccines are available, mRNA vaccines often are not accessible and instead the following have been used: Johnson&Johnson, Astra-Zeneca, and/or Sinovac. South Africa became one of the first African countries to make one dose of Pfizer-BioNTech BNT162b2 vaccine available to children 12–17 years old (including those with co-morbidities such as SOT on October 20, 2021). Underscoring the complexities of vaccination policy, the Children's Act of South Africa also made allowance for children 12–17 years old to make their own decisions about receiving COVID-19 vaccination without their parents' permission, provided the child understands the benefits and risks.[55]

In Central and South America, Brazil and Costa Rica have initiated teenage vaccinations (12–17 years of age) using the Pfizer-BioNTech vaccine whereas Columbia and Argentina have made both the Moderna and the Pfizer-BioNTech formulations available to this age group. In Chile, the CoronaVac (Sinovac) inactivated whole virus vaccine was authorized in September 2021 for children ≥6 years of age. In contrast, Bolivia, Nicaragua, and Mexico have not yet approved COVID-19 vaccination in children.[57]

In Asia, the regulatory agency for vaccine approval in India recently approved COVID-19 vaccination for children aged

2–17 years using an inactivated whole virus vaccine (Covaxin, Bharat Biotech). This approval adds to the previously approved vaccine for children aged 12–17 years in India (either inactivated vaccine or DNA vaccine formulations) (personal communication and[58]). China approved CoronaVac for children in June 2021 but only recently began providing the vaccine to children aged 6–11 years in September 2021.[59] A recently published Phase 1/2 RCT of CoronaVac in children aged 3–17 years demonstrated a 96.8% seroconversion rate for the 1.5 μg formulation and 100% for the 3.0 μg formulation.[60] Injection site pain was observed with similar frequency between the two-dose formulations and was significantly more frequent than in the alum-only placebo group (16%, 16%, and 2%, respectively). No vaccine-attributable serious adverse events occurred in this study.

8 | IMPACT OF COVID-19 VARIANTS ON VACCINE PROTECTION

With the emergence and spread of the B.1.6.17.2/Delta variant, early concerns focused on whether currently available COVID-19 vaccine formulations would provide adequate protection against this variant of concern. Despite these initial concerns, mechanistic and clinical studies have shown that vaccination continues to provide very good protection against severe COVID-19 due to the Delta variant with vaccine effectiveness exceeding 90% against severe COVID-19 due to the Delta variant.[14,59,61–63]

More recently, the emergence of the SARS-CoV-2 B.1.1.529 (Omicron) variant has revealed the limitations of current COVID-19 vaccines in providing protection against novel SARS-CoV-2 variants with a broader array of mutations than prior variants. The Omicron variant, first detected and identified in South Africa, has rapidly spread worldwide and possesses a heavily mutated spike protein compared with prior-prevalent SARS-CoV-2 strains, including the Delta variant.[64,65] Accordingly, in vitro studies and current clinical evidence demonstrate increased infectivity by Omicron and decreased protection provided by currently available COVID-19 vaccines against the Omicron variant.[66–68] Despite this decreased protection from infection imparted by prior COVID-19 vaccination, Omicron variant infections may be less likely to result in severe illness or hospitalization.[64,65,69] Studies are needed to better understand the impact of Omicron on SOT recipients and to optimize vaccine strategies for SARS-CoV-2 variants that emerge in the future.

9 | CONCLUSIONS AND KEY QUESTIONS FOR FUTURE STUDIES IN PEDIATRIC SOT RECIPIENTS

Since our prior publication reviewing COVID-19 vaccinations in the context of pediatric SOT recipients, robust immunogenicity and safety data in immunocompetent children have been released or published in children as young as 5 years of age. Data specifically evaluating COVID-19 vaccine in pediatric SOT recipients remain limited, but extensive studies in adult SOT recipients have characterized vaccine immunogenicity and safety. COVID-19 vaccination of eligible pediatric SOT candidates and recipients and their household contacts is critical for limiting individual infections and their associated morbidity and for the prevention of COVID-19 at the population level. Future studies are needed to determine optimal COVID-19 vaccination strategies including the most immunogenic vaccine formulation and/or dose and the number and timing of initial and booster vaccine doses, and to understand the duration of humoral and cellular immunity in pediatric SOT recipients. Further study is also needed to ensure rare adverse events are identified and understood in the context of transplant-associated immunosuppression. Filling in these knowledge gaps for COVID-19 vaccination of pediatric SOT recipients will optimize both the health and outcomes of our patients and also enhance knowledge of vaccination strategies in pediatric SOT recipients.

AUTHOR CONTRIBUTION

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

DATA AVAILABILITY STATEMENT

There is no data statement for this manuscript as no data were generated.

ORCID

Daniel E. Dulek https://orcid.org/0000-0002-1821-6657
Monica I. Ardura https://orcid.org/0000-0002-2853-2581
Michael Green https://orcid.org/0000-0002-6011-2894
Marian G. Michaels https://orcid.org/0000-0002-2556-0544
Abanti Chaudhuri https://orcid.org/0000-0003-0302-0739
Luciola Vasquez https://orcid.org/0000-0002-6881-3660
Lara Danziger-Isakov https://orcid.org/0000-0002-5691-5221
Klara M. Posfay-Barbe https://orcid.org/0000-0001-9464-5704
Mignon I. McCulloch https://orcid.org/0000-0003-2876-4785
Arnaud G. L'Huillier https://orcid.org/0000-0001-9230-7285
Christian Benden https://orcid.org/0000-0002-8409-5646

REFERENCES

1. Siegel DA, Reses HE, Cool AJ, et al. Trends in COVID-19 cases, emergency department visits, and hospital admissions among children and adolescents aged 0–17 years - United States, august 2020-august 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(36):1249-1254.
2. Delahoy MJ, Ujamaa D, Whitaker M, et al. Hospitalizations associated with COVID-19 among children and adolescents - COVID-NET, 14 States, march 1, 2020-august 14, 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(36):1255-1260.
3. American Academy of Pediatrics (AAP). Children and COVID-19: state-level data report. September 9, 2021. Available at: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infec

tions/children-and-covid-19-state-level-data-report/. Accessed September 18, 2021.
4. Center for Disease Control and Prevention. National center for health statistics. weekly updates by select demographic and geographic characteristics. Available at: https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm#SexAndAge. Accessed September 18, 2021.
5. Riffe T, Acosta E. Team TC-D. Data resource profile: COVerAGE-DB: a global demographic database of COVID-19 cases and deaths. *Int J Epidemiol*. 2021;50(2):390-f.
6. Available at: https://data.unicef.org/resources/covid-19-confirmed-cases-and-deaths-dashboard/. Accessed November 10, 2021.
7. Unicef. COVID-19 and children. unicef data hub. Available at: https://data.unicef.org/covid-19-and-children/. Accessed September 18, 2021.
8. Headey D, Heidkamp R, Osendarp S, et al. Impacts of COVID-19 on childhood malnutrition and nutrition-related mortality. *Lancet*. 2020;396(10250):519-521.
9. UNICEF data: child mortality and COVID-19. Available at: https://data.unicef.org/topic/child-survival/covid-19/. Accessed September 18, 2021.
10. Radtke T, Ulyte A, Puhan MA, Kriemler S. Long-term symptoms after SARS-CoV-2 infection in children and adolescents. *JAMA*. 2021;326(9):869.
11. Molteni E, Sudre CH, Canas LS, et al. Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2. *Lancet Child Adolesc Health*. 2021;5(10):708-718.
12. GOV.UK. Department of Health & Social Care. Independent Report: JCVI statement on COVID-19 vaccination of children and young people aged 12 to 17 years. Published August 4. 2021. Available at: https://www.gov.uk/government/publications/jcvi-statement-august-2021-covid-19-vaccination-of-children-and-young-people-aged-12-to-17-years/jcvi-statement-on-covid-19-vaccination-of-children-and-young-people-aged-12-to-17-years-4-august-2021. Accessed September 18, 2021.
13. Frenck RW Jr, Klein NP, Kitchin N, et al. Safety, immunogenicity, and efficacy of the BNT162b2 Covid-19 vaccine in adolescents. *N Engl J Med*. 2021;385(3):239-250.
14. Olson SM, Newhams MM, Halasa NB, et al. Effectiveness of pfizer-BioNTech mRNA vaccination against COVID-19 hospitalization among persons aged 12–18 years — United States, June–September 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(42):1483-1488.
15. Available at: https://www.ema.europa.eu/en/news/covid-19-vaccine-spikevax-approved-children-aged-12-17-eu. Accessed November 9, 2021
16. Committee VaRBPA. EUA amendment request for Pfizer-BioNTech COVID-10 Vaccine for use in children 5 through 11 years of age, 2021. October 26, 2021.
17. Food and Drug Administration. FDA approves first COVID-19 vaccine. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine
18. Walter EB, Talaat KR, Sabharwal C, et al. Evaluation of the BNT162b2 Covid-19 vaccine in children 5 to 11 years of age. *N Engl J Med*. 2022;386(1):35-46.
19. Food and Drug Administration, Food and Drug Administration. Coronavirus (COVID-19) Update: FDA Authorizes Pfizer-BioNTech COVID-19 Vaccine for Emergency Use in Adolescents in Another Important Action in Fight Against Pandemic. Released May 10,2021; Accessed November 10, 2021. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use
20. Woodworth KR, Moulia D, Collins JP, et al. The advisory committee on immunization practices' interim recommendation for use of Pfizer-BioNTech COVID-19 vaccine in children aged 5–11 years - United States, November 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(45):1579-1583.
21. European Medicine Agency. Cominarty. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty
22. Food and Drug Administration. Moderna COVID-19 Vaccine. Available at: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/moderna-covid-19-vaccine
23. The Boston Globe. R.I. approves Moderna COVID-19 vaccine for teens ahead of FDA authorization. Available at: https://www.bostonglobe.com/2021/07/13/metro/ri-approves-moderna-covid-19-vaccine-teens-ahead-fda-authorization-will-continue-administer-johnson-johnson-doses/
24. European Medicine Agency. Spikevax. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/spikevax
25. Mevorach D, Anis E, Cedar N, et al. Myocarditis after BNT162b2 mRNA vaccine against Covid-19 in Israel. *N Engl J Med*. 2021;385(23):2140-2149.
26. Witberg G, Barda N, Hoss S, et al. Myocarditis after Covid-19 vaccination in a large health care organization. *N Engl J Med*. 2021;385(23):2132-2139.
27. Simone A, Herald J, Chen A, et al. Acute myocarditis following COVID-19 mRNA vaccination in adults aged 18 years or older. *JAMA Intern Med*. 2021;181(12):1668.
28. Singer ME, Taub IB, Kaelber DC. Risk of myocarditis from COVID-19 infection in people under age 20: a population-based analysis. *medRxiv*. 2021. doi:10.1101/2021.07.23.21260998
29. National Advisory Committee on Immunization (NACI). Recommendation on the use of mRNA COVID-19 vaccines in adolescents 12 to 17 years of age. Publication Date: August 27, 2021. Available at: https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/recommendations-use-covid-19-vaccines/mrna-adolescents.html#b6
30. Shimabukuro T. *OVID-19 Vaccine safety updates [slides presented at Advisory Committee on Immunization Practices (ACIP) meeting] [Internet]*. Centers for Disease Control and Prevention (CDC); 2021. Jun 23. Available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/03-COVID-Shimabukuro-508.pdf
31. Reuters. Finland joins sweden and denmark in limiting moderna COVID-19 vaccine. https://www.reuters.com/world/europe/finland-pauses-use-moderna-covid-19-vaccine-young-men-2021-10-07/
32. Ontario's Ministry of Health. COVID-19 Vaccine Information Sheet: For Youth (age 12-17). Available at: https://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/vaccine/COVID-19_vaccine_information_sheet_youth.pdf
33. Ou MT, Boyarsky BJ, Motter JD, et al. Safety and reactogenicity of 2 doses of SARS-CoV-2 vaccination in solid organ transplant recipients. *Transplantation*. 2021;105(10):2170-2174.
34. Del Bello A, Marion O, Delas A, Congy-Jolivet N, Colombat M, Kamar N. Acute rejection after anti-SARS-CoV-2 mRNA vaccination in a patient who underwent a kidney transplant. *Kidney Int*. 2021;100(1):238-239.
35. Werbel WA, Boyarsky BJ, Ou MT, et al. Safety and immunogenicity of a third dose of SARS-CoV-2 vaccine in solid organ transplant recipients: a case series. *Ann Intern Med*. 2021;174(9):1330-1332.
36. Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients. *N Engl J Med*. 2021;385(7):661-662.
37. Kumar D, Kimball P, Gupta G. COVID-19 vaccine does not alter panel reactive antibody or flow cytometric cross match in kidney transplant candidates. *Transpl Immunol*. 2021;69:101469.
38. Available at. https://www.myast.org/covid-19-vaccine-faq-sheet. Accessed October 29, 2021.

39. Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody response to 2-dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. *JAMA*. 2021;325(21):2204-2206.
40. Boyarsky BJ, Werbel WA, Avery RK, et al. Immunogenicity of a single dose of SARS-CoV-2 messenger RNA vaccine in solid organ transplant recipients. *JAMA*. 2021;325(17):1784-1786.
41. Yi SG, Knight RJ, Graviss EA, et al. Kidney transplant recipients rarely show an early antibody response following the first COVID-19 vaccine administration. *Transplantation*. 2021;105(7):e72-e73.
42. Peled Y, Ram E, Lavee J, et al. BNT162b2 vaccination in heart transplant recipients: clinical experience and antibody response. *J Heart Lung Transplant*. 2021;40(8):759-762.
43. Narasimhan M, Mahimainathan L, Clark AE, et al. Serological response in lung transplant recipients after two doses of SARS-CoV-2 mRNA vaccines. *Vaccines (Basel)*. 2021;9(7):708.
44. Hall VG, Ferreira VH, Ku T, et al. Randomized trial of a third dose of mRNA-1273 vaccine in transplant recipients. *N Engl J Med*. 2021;385(13):1244-1246.
45. Chavarot N, Morel A, Leruez-Ville M, et al. Weak antibody response to three doses of mRNA vaccine in kidney transplant recipients treated with belatacept. *Am J Transplant*. 2021;21(12):4043-4051.
46. Embi PJ, Levy ME, Naleway AL, et al. Effectiveness of 2-dose vaccination with mRNA COVID-19 vaccines against COVID-19-associated hospitalizations among immunocompromised Adults - Nine States, January-September 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(44):1553-1559.
47. Malinis M, Cohen E, Azar MM. Effectiveness of SARS-CoV-2 vaccination in fully vaccinated solid organ transplant recipients. *Am J Transplant*. 2021;21(8):2916-2918.
48. Anjan S, Natori Y, Fernandez Betances AA, et al. Breakthrough COVID-19 infections after mRNA vaccination in solid organ transplant recipients in Miami, Florida. *Transplantation*. 2021;105(10):e139-e141.
49. Wadei HM, Gonwa TA, Leoni JC, Shah SZ, Aslam N, Speicher LL. COVID-19 infection in solid organ transplant recipients after SARS-CoV-2 vaccination. *Am J Transplant*. 2021;21(10):3496-3499.
50. Qin CX, Moore LW, Anjan S, et al. Risk of breakthrough SARS-CoV-2 infections in adult transplant recipients. *Transplantation*. 2021;105(11):e265-e266.
51. Schmidt T, Klemis V, Schub D, et al. Cellular immunity predominates over humoral immunity after homologous and heterologous mRNA and vector-based COVID-19 vaccine regimens in solid organ transplant recipients. *Am J Transplant*. 2021;21(12):3990-4002.
52. Hall VG, Ferreira VH, Ierullo M, et al. Humoral and cellular immune response and safety of two-dose SARS-CoV-2 mRNA-1273 vaccine in solid organ transplant recipients. *Am J Transplant*. 2021;21(12):3980-3989.
53. Crane C, Phebus E, Ingulli E. Immunologic response of mRNA SARS-CoV-2 vaccination in adolescent kidney transplant recipients. *Pediatr Nephrol*. 2021. doi:10.1007/s00467-021-05256-9. Online ahead of print.
54. Qin CX, Auerbach SR, Charnaya O, et al. Antibody response to 2-dose SARS-CoV-2 mRNA vaccination in pediatric solid organ transplant recipients. *Am J Transplant*. 2021. doi:10.1111/ajt.16841. Online ahead of print.
55. Mathieu E, Ritchie H, Ortiz-Ospina E, et al. A global database of COVID-19 vaccinations. *Nat Hum Behav*. 2021;5(7):947-953.
56. Sallam M. COVID-19 vaccine hesitancy worldwide: a concise systematic review of vaccine acceptance rates. *Vaccines (Basel)*. 2021;9(2):160.
57. Available at: https://www.as-coa.org/articles/are-kids-all-right-look-vaccine-age-eligibility-latin-america. Accessed November 8, 2021.
58. Available at: https://www.reuters.com/world/india/india-recommends-emergency-use-bharat-biotechs-covid-19-shot-kids-2021-10-12/. Accessed October 30, 2021.
59. Dyer O. Covid-19: US and China prepare for mass vaccination of children under 12. *BMJ*. 2021;375:n2631.
60. Han B, Song Y, Li C, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy children and adolescents: a double-blind, randomised, controlled, phase 1/2 clinical trial. *Lancet Infect Dis*. 2021;21(12):1645-1653.
61. Cevik M, Grubaugh ND, Iwasaki A, Openshaw P. COVID-19 vaccines: keeping pace with SARS-CoV-2 variants. *Cell*. 2021;184(20):5077-5081.
62. Pouwels KB, Pritchard E, Matthews PC, et al. Effect of delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. *Nat Med*. 2021;7(12):2127-2135.
63. Tang P, Hasan MR, Chemaitelly H, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the SARS-CoV-2 Delta variant in Qatar. *Nat Med*. 2021;27(12):2136-2143.
64. Team CC-R. SARS-CoV-2 B.1.1.529 (Omicron) variant - United States, December 1-8, 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(50):1731-1734.
65. Abdullah F, Myers J, Basu D, et al. Decreased severity of disease during the first global omicron variant covid-19 outbreak in a large hospital in Tshwane, South Africa. *Int J Infect Dis*. 2021;116:38-42.
66. Laurie MT, Liu J, Sunshine S, et al. SARS-CoV-2 variant exposures elicit antibody responses with differential cross-neutralization of established and emerging strains including Delta and Omicron. *J Infect Dis*. 2022:jiab635. https://doi.org/10.1093/infdis/jiab635. Online ahead of print.
67. Dejnirattisai W, Shaw RH, Supasa P, et al. Reduced neutralisation of SARS-CoV-2 omicron B.1.1.529 variant by post-immunisation serum. *Lancet*. 2021;399(10321):234-236.
68. Lu L, Mok BW, Chen LL, et al. Neutralization of SARS-CoV-2 Omicron variant by sera from BNT162b2 or Coronavac vaccine recipients. *Clin Infect Dis*. 2021:ciab1041.
69. Ledford H. How severe are omicron infections? *Nature*. 2021;600(7890):577-578.

How to cite this article: Dulek DE, Ardura MI, Green M, et al. Update on COVID-19 vaccination in pediatric solid organ transplant recipients. *Pediatr Transplant*. 2022;26:e14235. doi:10.1111/petr.14235