Vaccinations in pediatric kidney transplant recipients

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Abstract

Pediatric kidney transplant (KT) candidates should be fully immunized according to routine childhood schedules using age-appropriate guidelines. Unfortunately, vaccination rates in KT candidates remain suboptimal. With the exception of influenza vaccine, vaccination after transplantation should be delayed 3–6 months to maximize immunogenicity. While most vaccinations in the KT recipient are administered by primary care physicians, there are specific schedule alterations in the cases of influenza, hepatitis B, pneumococcal, and meningococcal vaccinations; consequently, these vaccines are usually administered by transplant physicians. This article will focus on those deviations from the normal vaccine schedule important in the care of pediatric KT recipients. The article will also review human papillomavirus vaccine due to its special importance in cancer prevention. Live vaccines are generally contraindicated in KT recipients. However, we present a brief review of live vaccines in organ transplant recipients, as there is evidence that certain live virus vaccines may be safe and effective in select groups. Lastly, we review vaccination of pediatric KT recipients prior to international travel.

Keywords Children · Kidney · Solid organ transplantation · Transplantation · Kidney transplantation · Immunization · Vaccination

Introduction

The medical management of the pediatric kidney transplant (KT) recipient is becoming increasingly complex, and the responsibility of care is usually split between the transplant teams and primary care physicians. Pediatric KT recipients are at higher risk of infections and malignancies compared to their healthy peers. Proper delivery of immunizations is important for prevention of infectious diseases and human papillomavirus (HPV)-related cancers. The introduction of

routine childhood immunizations has dramatically lowered morbidity and mortality due to infection [1]. Many vaccine-preventable diseases have either been completely eliminated or are seen at such a low frequency that the lay community may doubt the necessity of ongoing vaccination efforts [1]. In the USA, vaccination rates in children and adolescents have increased in recent years and remain high (>90%) for the majority of recommended vaccines, though rates for specific immunizations in certain age groups continue to be inadequate despite concerted efforts to improve coverage. In young children, vaccination rates remain high for most vaccines. From 2012 to 2016, >90% of children aged 19–35 months received at least three doses of diphtheria/tetanus/acellular pertussis (DTaP), pneumococcal conjugate, and inactivated poliovirus (IPV) vaccines, along with at least one dose each of measles/mumps/rubella (MMR) and varicella vaccine [2]. However, in this age group, completion of hepatitis A vaccine was more problematic: in 2016, only 60.6% of children aged 19–35 months had received the recommended two doses [2]. In the adolescent age group, vaccination rates are high for MMR and varicella, near 90.0%. Other vaccination rates are definitely improving, such as tetanus/diphtheria/acellular pertussis (Tdap), which, in 2016, reached 88.0% coverage. Finally,

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other vaccination rates in adolescents, while slowly improving, continue to be suboptimal. For example, in 2016, the quadrivalent meningococcal vaccine (MenACWY) reached 39.1% coverage, while HPV vaccine rates were 49.5% for adolescent females and 37.5% for adolescent males [3].

Non-immune and unvaccinated children and adults receive the indirect benefits of herd immunity from their vaccinated peers. Depending upon the specific vaccine and pathogen, a large population of immune individuals can shelter the susceptible hosts. The proportion of unvaccinated children remains low in the USA (<1%), but vaccination rates can vary based on geographic location, socioeconomic status, and race/ethnicity [2, 3]. When vaccination rates drop below a certain threshold, the benefits of herd immunity for the susceptible child are compromised. This is particularly relevant to the solid organ transplant (SOT) recipient, in whom vaccine immunogenicity may be reduced and certain vaccines may be contraindicated. The importance of herd immunity is highlighted by a series of 159 measles cases in four outbreaks reported by the Centers for Disease Control and Prevention (CDC) from January 4 through April 2, 2015 [4]. Two-dose measles vaccine is highly effective and, in the USA, led to the elimination (i.e., interruption of year-round endemic transmission) of measles in 2000 [4]. However, poor vaccine coverage in certain communities can lead to clusters of lost herd immunity and highly contagious pathogens like measles can rapidly spread in a short period of time. Over 80% of cases in this series occurred in individuals who were unvaccinated or who had unknown vaccination status [4]. Although many (40%) of the unvaccinated cases had not received MMR vaccine due to ineligibility (i.e., too young or presence of certain medical contraindications), 43% claimed philosophical or religious objections to vaccination, 4% were missed opportunities, and 13% had “other” reasons for not being vaccinated [4].

Routine childhood vaccines in KT candidates and recipients are more likely to be administered by primary care providers, while other vaccines, such as ones that lie outside of routine schedules, are more likely to be administered by transplant providers. Therefore, it is important for both primary care and transplant providers to be aware of the most recent guidelines for childhood immunizations in SOT recipients, including KT recipients. In addition, it is important to keep close communication between the two teams in order to ensure an ongoing fully immunized status for pediatric KT candidates and recipients.

With advancing medical care, pediatric KT recipients enjoy a better quality of life, making them more likely to travel internationally. Unfortunately, SOT recipients do not always seek pre-travel advice, even when provided by travel medicine experts [5]. Population vaccination rates are lower and the prevalence of vaccine-preventable diseases is higher in developing countries. SOT recipients are at heightened risk of many of these infections depending on the destination; therefore,

clinicians caring for the traveling SOT recipient should be aware of current recommendations for immunizations pertaining to international travel.

Vaccination strategies pre-KT: current recommendations, status, and trends

The Infectious Diseases Society of America (IDSA) and the American Society of Transplantation (AST) recommend that pediatric SOT candidates be immunized prior to transplantation using age-appropriate guidelines [6, 7]. The CDC provides updated age-based immunization schedules (<https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html>). Children behind on vaccinations prior to transplantation can follow an expedited schedule according to the CDC’s catch-up schedule (<https://www.cdc.gov/vaccines/schedules/hcp/imz/catchup.html>). Transplant candidates, although often unable to mount an ideal immune response compared to the general population [8], have better immune responses compared to patients after transplantation [9]. Furthermore, live vaccines are generally contraindicated post transplantation [6], so ensuring that all eligible vaccines are given before transplant surgery is critical [7]. A suggested immunization list for pediatric KT candidates is included in Table 1 [10]. Regarding the live-attenuated vaccines MMR and varicella, waiting a minimum of 4 weeks between vaccine administration and transplantation is recommended, given the theoretical risk of developing disease from the vaccine strain [6]. MMR and varicella are normally given at 12 months of age but can be administered to children as young as 6 months [6]. However, vaccine efficacy at this age can be impeded by maternal antibodies; therefore, if MMR and varicella vaccines are given early, they should be repeated at 12 months of age if organ transplantation has not yet occurred. MMR and varicella vaccines can be given together, but if they are not, their administrations need to be separated by at least 28 days [6].

Patients undergoing transplant evaluation may be receiving or have recently received immunosuppressive therapies and/or immunoglobulin (IG) therapy, whether standard or disease-specific, which can affect the response to vaccines. Rituximab is an anti-CD20 monoclonal antibody that can inhibit the immune response to vaccines. The ability of vaccines to stimulate humoral immunity after receipt of rituximab can be impaired for as long as 12 months, although the maximum effect occurs within the first 6 months [11]. As a general recommendation, most sources suggest delaying vaccination for at least 6 months after rituximab in order to make the administration of inactivated vaccines effective and live vaccines safe [12]. Delaying live virus vaccines for at least 4 weeks in patients receiving 14 days or more of high-dose corticosteroids (≥ 2 mg/kg/day of prednisone or ≥ 20 mg/day in patients over 10 kg) is generally recommended, although the evidence to

Table 1 Recommended vaccines for pediatric kidney transplant candidates and recipients and recommendations for monitoring vaccine titers after transplantation

Vaccine	Inactivated/live-attenuated (I/LA)	Recommended for candidates	Recommended for recipients	Monitor vaccine titers
Influenza	I	Yes	Yes	No
Influenza	LA	No	No	No
Hepatitis B	I	Yes	Yes	Yes
Hepatitis A	I	Yes	Yes	Yes ¹
Pertussis	I	Yes	Yes	No
Diphtheria	I	Yes	Yes	No
Tetanus	I	Yes	Yes	Yes
IPV	I	Yes	Yes	No
<i>H. influenzae</i>	I	Yes	Yes	Yes
PCV13	I	Yes	Yes	Yes
PPSV23	I	Yes	Yes	Yes
MenACWY	I	Yes	Yes	No
HPV	I	Yes	Yes	No
Varicella	LA	Yes	No ²	Yes
Rotavirus	LA	Yes	No	No
Measles	LA	Yes	No	Yes
Mumps	LA	Yes	No	Yes
Rubella	LA	Yes	No	Yes

Adapted with permission from Danziger-Isakov and Kumar [7]

¹ Monitoring only if ongoing risk of exposure, for example with planned travel to high-risk areas

² May be considered for select transplant recipients. See text for more details

support this recommendation is scarce [13]. For immunosuppressive medications such as mycophenolate, tacrolimus, cyclosporine, cyclophosphamide, and azathioprine, there are even fewer data to guide the proper time interval between medication cessation and safe live vaccine administration. In the rheumatology literature, based on only level D evidence, it is generally considered that a period of 3 months is required for immune status to be completely restored after the cessation of these medications and therefore before live vaccines can be safely administered [14]. The immune responses to inactivated and toxoid vaccines are not meaningfully affected by IG, but receipt of IG can interfere with the responses to certain live vaccines such as MMR and varicella vaccines. The responses to other live vaccines—yellow fever, oral polio virus (OPV; not given in the USA and most developed countries), rotavirus, and live-attenuated influenza vaccines (LAIVs)—are not significantly impacted by IG. MMR and varicella vaccines should be delayed at least 2 weeks before and up to 11 months after receipt of IG [15]. The period of delay is proportional to the dose of IG given. For example, those given a 400 mg/kg dose should delay MMR and varicella vaccines by 8 months. Receipt of doses of 1600 to 2000 mg/kg requires an 11-month deferral [15]. Postponement of MMR and varicella vaccines is also required after receipt of other passive immunizations as well, such as

tetanus, hepatitis B, varicella, and rabies-specific IG [15]. In addition, MMR and varicella vaccines should also be delayed in patients who have received blood products. For example, those receiving packed red blood cells (10 ml/kg) or platelets/plasma (10 ml/kg) should wait 5 and 7 months, respectively, before receiving these vaccines [15].

Unfortunately, incompletely vaccinated children often receive transplants. A nationwide survey of pediatric SOT centers in the USA reported that 82% of providers would list a child who was not vaccinated for medical reasons and 47% would list a child whose parents had refused vaccinations. Only 4% reported that their programs had policies regarding parental vaccination refusal. The authors recommend the development of written guidelines to unify programs' assessments of incompletely vaccinated pediatric SOT candidates [16]. The actual vaccination rates in pre-SOT patients remain suboptimal even when parental refusal is excluded. A study that surveyed immunization practices in 18 centers looking at pediatric candidates for lung transplantation found that monitoring of response to prior vaccination was performed inconsistently: varicella serologic status was most commonly tested (88%), followed by serologic evaluation for rubella (50%), measles (50%), mumps (38%), and hepatitis B (38%) [17]. In pediatric KT candidates, a retrospective study reported inactivated influenza vaccine (IIV) rates of only 55% [18].

Despite these discouraging data, immunization rates have been improving. A survey of all the United Network for Organ Sharing-certified KT centers in the USA, conducted over two decades, showed an improvement in provider IIV recommendation over time (94.5 vs. 84.4%, $P=0.02$) [19]. This is likely a result of nationwide efforts to improve quality measures. For example, to improve pneumococcal vaccination rates in a tertiary care facility, a multifaceted intervention (nurse-screening tool, storage of the vaccine in automated dispensing cabinets, creation of a tracking system) was implemented. The rate of pneumococcal vaccine administration significantly improved post implementation (74.2 vs. 19.1%, respectively, $P<0.001$) [20]. Continuous efforts are needed to improve vaccination rates in pediatric KT candidates.

Vaccination strategies post transplantation: current recommendations, status, and trends

The international organization Kidney Disease Improving Global Outcomes (KDIGO) recommends giving KT recipients all standard non-live vaccines according to routine immunization schedules [21]. There are specific recommendations in transplant recipients that deviate from the routine schedule, namely for hepatitis B vaccine (HBV), pneumococcal vaccines, and MenACWY. These particularities are discussed below. The importance of HPV in cancer prevention is highlighted. Live vaccines are generally contraindicated in SOT recipients due to the risk of developing disease from the vaccine strain [6, 7, 21]. A brief review of the use of live vaccines in SOT recipients is presented, as there are data showing that in select circumstances, they may be safely used. With the exception of IIV, it is recommended to wait for 3–6 months after transplantation and until maintenance immunosuppression levels are achieved before starting vaccination in order to maximize the chances of an adequate immune response [6, 7, 21]. For the same concern, except for IIV, vaccinations should be withheld from SOT recipients during intensified immunosuppression, such as 2–6 months after treatment of acute rejection episodes [6]. Unfortunately, providers often do not follow vaccine recommendations in SOT recipients. A cross-sectional national survey among Dutch adult nephrologists to assess vaccination adherence to the KDIGO guidelines showed that reported immunization rates were 90.8% for IIV, but only 27.3% for HBV. The most frequently perceived barrier to guideline adherence was expectation of low effectiveness [22]. Currently, the majority of vaccinations are administered by primary care providers [23]. Improvement of vaccination rates in pediatric KT recipients will depend on a more active role of the transplant providers, particularly for those vaccines that require alterations of the routine schedules.

Influenza vaccine

Inactivated influenza vaccine is recommended yearly to pediatric KT recipients, healthcare givers, and household contacts [6, 7]. Influenza-related morbidity and mortality and graft loss can be prevented with the use of vaccine [24]. Several case reports and small series reported a possible correlation between IIV and graft rejection, but larger studies have not confirmed this [25]. In a study of adult SOT recipients, no development of de novo donor-specific antibodies was observed after IIV administration [6].

The Advisory Committee on Immunization Practices (ACIP) recommended against the use of LAIV in children for the 2017–2018 influenza season, based upon consistently poor effectiveness against influenza A H1N1 and influenza B [26]. Furthermore, LAIV is contraindicated in SOT recipients. If LAIV is inadvertently given to a SOT recipient, antiviral therapy and vaccination with IIV can be given [7].

In pediatric KT recipients, early studies showed no differences in seroconversion rates, percentage of patients achieving protective hemagglutination-inhibition titers, or change in geometric mean titers from pre to post vaccination between study groups and controls [27]. One month post IIV, 82% achieved protective titers of antibodies to influenza A and 60% to influenza B, rates similar to controls [28]. More recently, a study compared the response to IIV in children with KT on steroid-free versus steroid-based immunosuppression. Both KT groups seroconverted less frequently than controls for A/H1N1 but were not different from controls for B. For A/H3N2, the steroid-free group had the poorest seroconversion rate, possibly due to mycophenolate-enhanced exposure [29]. Indeed, different immunosuppression protocols can have different influences on the antibody response. In a study on adult KT recipients, mycophenolate decreased the response to IIV to the point that there was zero seroconversion for the B strain [30]. Similar differences in the immune response have been noted in other SOT recipients; therefore, SOT patients might benefit from modified regimens, such as either an augmented dose or a booster dose. A recent randomized, controlled, open-label clinical trial conducted in Spain (TRANSGRIPE 1–2) looked at long-term immunity in a large number of adult SOT recipients who received a booster dose of IIV 5 weeks after the standard vaccination. Researchers showed that the booster is safe and effective and induces an increased antibody response compared to standard single-dose influenza vaccination [31].

IIV can safely be given as early as 1 month post transplantation. A multicenter prospective cohort study in adult SOT recipients assessed the immunogenicity and safety of IIV when given earlier than 6 months versus beyond 6 months post transplantation. Seroprotection was similar in both groups: 73.1 vs. 76.5% for A/(H1N1) ($P=0.49$), 67.5 vs. 74.1% for A/H3N2 ($P=0.17$), and 84.2 vs. 85.2% for

influenza B ($P=0.80$) [32]. No cases of rejection were seen, suggesting that during an influenza epidemic or pandemic, IIV is safe and effective in recent SOT recipients. However, some experts recommend that if IIV is administered early after transplantation, consideration should be given to revaccinate 3 to 6 months post KT if the influenza season is ongoing [7].

Hepatitis B virus vaccine

Ideally, KT recipients should receive the complete HBV series before transplantation. Although KT recipients can mount HBV-specific T cell responses [33], they are suboptimal. In a study performed by the Southwest Pediatric Nephrology Study Group, a smaller percentage of children immunized post KT reached protective hepatitis B surface antibody (HBsAb) levels of ≥ 10 mIU/ml (66.7%) compared to those pre-KT patients pre dialysis or those on dialysis (96.4%) [34]. In addition, there is a considerable decrease in antibody levels over time. In a study looking at adult KT recipients, after 12 months, 25% of patients had lost protective HBsAb titers [35]. Since 2013, AST has recommended serial HBsAb titers every 6–12 months after pediatric SOT to assess ongoing immunity [7]. KDIGO proposed annual anti-HBsAb titers and revaccination if the titer falls below 10 mIU/ml [21, 36]. To improve vaccine immunogenicity, intradermal administration was found to achieve a greater number of high-dose vaccine responders (subjects achieving an anti-HBsAb titer > 1000 mIU/ml) when used in children with celiac disease [37]. Third-generation HBVs are more immunogenic, containing one or two additional envelope proteins that have been developed in transfected mammalian cells [38]. In a study examining the evolution of HBsAb titers during the first year post KT in adult subjects, protective titers of ≥ 10 mIU/ml at month 12 persisted in 93% of patients with an initial titer ≥ 100 mIU/ml, compared to 33% with 10–100 mIU/ml titer ($P<0.0001$) [35]. In addition, a retrospective cohort study examined post-transplant hepatitis B reactivation in adult KT patients who had evidence of resolved infection at the time of transplant. While 6.5% of the patients experienced reactivation, in patients with a HBsAb titer above 100 mIU/ml, no reactivation was observed [39]. The authors of both of these studies recommended maintaining HBsAb levels above 100 mIU/ml rather than the traditional 10 mIU/ml. More research is needed to optimize continued hepatitis B immunity in pediatric KT recipients. The official recommendation remains to monitor annual HBsAb titers and to revaccinate if the titer falls below 10 mIU/ml [21, 36].

Pneumococcal vaccines

Solid organ transplant recipients should be immunized with the pneumococcal conjugate vaccine 13-valent (PCV13) according to routine immunization schedules [40]. For

previously unimmunized KT recipients, there are catch-up recommendations for children over age 2 based on algorithms, taking into account the patient's age, prior immunization history, and the interval between doses [40, 41]. It should be noted that catch-up schedules for high-risk children, including SOT recipients, are different from those for healthy children (Fig. 1) [41]. Despite this vaccination strategy, KT recipients remain at risk of invasive pneumococcal disease. In a study that prospectively followed pediatric SOT recipients, invasive pneumococcal disease was significantly more common than in healthy children [42]. Therefore, it is recommended that pediatric SOT, including KT recipients, also receive the pneumococcal polysaccharide vaccine 23-valent (PPSV23) for expanded serotype coverage, provided that they are at least 2 years of age. PCV13 should always be given before PPSV23 to enhance immunogenicity. PPSV23 should be given at a minimum of 8 weeks after PCV13 (Fig. 1) [7, 40, 41].

PCV13 and PPSV23 are proven safe and immunogenic in pediatric SOT recipients [43] and in adult KT recipients [44]. However, it is unclear how persistent the anti-pneumococcal antibody titers remain over time. One study found a significant decrease in anti-pneumococcal antibody titers at 1 year after KT in adults [45], while another study found persistently high antibody concentrations at 15 months [46]. After 3 years, the antibody titers declined significantly in adult KT recipients [47]. Therefore, for high-risk children, including SOT recipients, it is recommended to administer one additional dose of PPSV23 after 5 years (Fig. 1) [41].

Despite these recommendations, pneumococcal vaccination rates in pediatric KT recipients remain low, in part due to patient care being split between the primary care providers and the transplant teams and in part due to the complexity of these vaccination schedules, particularly for the catch-up schedule. However, it appears that the pneumococcal vaccination rates can be significantly increased by quality improvement initiatives, such as in a recent study that applied a simplified vaccine algorithm [48].

Meningococcal vaccines

Pediatric KT recipients should be vaccinated against meningococcal disease according to the routine immunization guidelines [7]. In general, this consists of one dose of MenACWY (for protection against serogroups A, C, W, and Y) at age 11 with a booster dose at age 16 [49]. Serogroup B meningococcal vaccine (MenB) can be considered starting at age 16, especially during outbreaks and for students living in residency halls [50]. There is very little information on the immunogenicity of meningococcal vaccines in SOT recipients. In one study in adults with KT and liver transplants, only 50% of patients mounted an immune response to MenACWY [51]. One small study in Europe using a conjugate meningococcus C vaccine in pediatric SOT recipients showed a

The flowchart illustrates the timing of PCV13 and PPSV23 for different groups of kidney transplant (KT) recipients. The groups are defined by age and transplant status:

- KT recipient Age < 24 months:**
 - PCV13 x 4 (2, 4, 6 and 12-15 months - routine)
- KT recipient Age 2-6 years:**
 - Received 0, 1 or 2 doses of PCV13 before age 2:
 - PCV13 (8 weeks) → PCV13 (8 weeks) → PPSV23
 - Received 3 doses of PCV13 before age 2:
 - PCV13 (8 weeks) → PPSV23
 - Received all 4 doses of PCV13 before age 2:
 - PPSV23 (8 weeks) → PPSV23
- KT recipient Age 6-18 years:**
 - Received 0 doses of PCV13:
 - PCV13 (8 weeks) → PPSV23
 - Received 1, 2, 3 or 4 doses of PCV13:
 - PPSV23 (5 years) → PPSV23

The final outcome for all groups is PPSV23, which is administered 5 years after the initial PCV13 or PPSV23 dose.

Among pediatric KT recipients, it is important to identify those patients with specific risk factors for invasive meningococcal infections, as they will require different interventions. This category includes KT recipients with persistent complement component deficiencies due to C3 glomerulopathy or atypical hemolytic uremic syndrome, patients receiving eculizumab (an anti-C5 monoclonal antibody used for treatment of complement-mediated glomerular diseases) and patients with human immunodeficiency virus (HIV). Such patients should receive meningococcal vaccines earlier than standard schedules [53]. High-risk children aged 2 through 18 months should receive MenACWY at ages 2, 4, 6, and 12 to 15 months along with the other routine immunizations in infancy. If MenACWY is administered to infants, it should be given before or at the same time as DTaP. High-risk children older than 7 months who have not yet initiated MenACWY should receive two doses of MenACWY separated by 12 weeks. High-risk children older than 10 years should additionally receive MenB [54]. Patients receiving eculizumab should receive both MenACWY and MenB at the initiation of treatment [50]. KT candidates and recipients who are at high risk of invasive meningococcal infections should receive boosters of MenACWY every 5 years [53]. Very little data is available regarding immunogenicity of the meningococcal vaccines in high-risk populations, but the risk/benefit ratio favors their use [55].

Kidney transplant recipients have a 14-fold increased risk of cervical cancer and a 100-fold increased risk of anal cancers, the majority of which are caused by high-risk HPV types [56]. Cervical carcinoma, the second most common cancer in

Live-attenuated vaccines in solid organ transplant recipients

Three live-attenuated virus vaccines are part of the routine immunization schedule in children: varicella, MMR, and rotavirus vaccines. Diseases caused by these pathogens can be more severe in SOT recipients [62]. Waning herd immunity due to inadequate vaccination of the population places SOT recipients at increasing risk [10]. Disease from primary infection is usually worse than disease from reactivation, and SOT

recipients vaccinated prior to transplant have less severe clinical courses compared to naïve patients who acquire infection after transplantation [63]. Ensuring completion of vaccinations prior to transplantation is important but can be more difficult in pediatric patients since many undergo transplant surgery prior to completion of the vaccine series. As soon as organ transplantation is discussed as an option in the care of the child's underlying condition, every effort should be made to complete the recommended live virus vaccinations prior to surgery, as immunogenicity is poorer following transplantation [64]. Additionally, most live vaccines are contraindicated after transplantation due to the potential for disease from the vaccine strain, which could lead to severe illness and death [6, 7]. Although live vaccines remain generally contraindicated after SOT, there are several reports demonstrating safety and efficacy of MMR and varicella vaccines in select non-immune renal and liver transplant recipients [65]. Based on these studies, IDSA allows providers to consider varicella vaccine under very specific select clinical circumstances, as delineated below. Two studies from Japan are worth noting. Kawano et al., in a prospective interventional study, administered varicella and MMR vaccines to 39 pediatric living donor liver transplant recipients [66]. Strict criteria were applied to vaccine recipients to reduce the likelihood of adverse events and included the following: > 1 year after transplantation in stable condition, no use of systemic steroids for acute rejection within 6 months, exclusive use of tacrolimus for immune suppression and with serum troughs < 5 ng/ml, and no severe immunosuppression based on serum immunoglobulin levels, lymphocyte numbers, and T cell functional assays. No serious adverse events were seen in this study. One patient developed varicella disease 30 days after receipt of varicella vaccine and responded to a 7-day course of valacyclovir. Serologic response in study patients was variable: rubella (70%), measles and mumps (50%), and varicella (32%). Some improvement was seen after a second dose. Those who had received MMR prior to organ transplant had better responses post transplantation. Unfortunately, significant waning immunity was seen. Shinjoh et al. report a series of 48 pediatric living donor liver transplant recipients who received a total of 196 MMR and varicella vaccines from 2002 to 2014 [67]. Criteria for receipt of vaccines were similar to those from Kawano et al. They included the following: negative/borderline vaccine titers, > 2 years post transplantation, stable liver function tests and no rejection within 6 months, no immune globulin or systemic steroid receipt within 6 months, low serum troughs for tacrolimus (< 5 ng/ml) and cyclosporine (< 100 ng/ml), and no significant immunosuppression based on IgG level and lymphocyte numbers and function. Much better rates of seroconversion were seen as compared to Kawano et al. Seroconversion after first vaccine was 100% for measles and rubella, 75% for mumps, and 70% for varicella. Waning immunity was minimal for rubella but significant for measles,

mumps, and varicella. Three patients who received varicella vaccine developed breakthrough disease but had mild clinical courses. Adverse events were minimal and not serious.

Varicella vaccine

Varicella in SOT recipients, after primary infection or secondary reactivation, can lead to severe disseminated disease and allograft rejection [68], and community exposures are often unrecognized [69]. The attenuated varicella virus contained in the vaccine can replicate and cause disease in the immunocompromised patient, and reports of clinical disease in SOT recipients due to vaccine virus have been reported [70]. Despite the concern for dissemination of vaccine virus, several studies in pediatric SOT recipients have reported that varicella vaccine is safe and effective following SOT. A recent review examined seven prospective studies of varicella vaccine in pediatric SOT recipients published between 1994 and 2012 [65]. A total of 128 children received the vaccine after transplantation. Adverse events were common but not serious. Vesicular rash was seen in 25% in one study but was not due to vaccine virus [71]. Serologic response was variable, ranging from 65 to 100% [65]. In a study from Switzerland of 36 pediatric liver transplant recipients who received varicella vaccine a median of 1 year after transplantation, five patients experienced a vaccine-associated rash, but there were no serious adverse effects and none had breakthrough disease [72]. One hundred percent of patients seroconverted, and all but one maintained immunity after a median of 1.7 years of follow-up. Similar to the results achieved with seroconversion, patients in this study had substantially increased varicella virus-specific CD4+ T cells following vaccination, a marker of specific cellular immunity to varicella.

The Infectious Disease Society of America states that varicella vaccine can be *considered* for varicella non-immune kidney or liver transplant recipients, as long as they are receiving long-term, low-level immune suppression and are without any recent episodes of organ rejection [6]. The decision to administer varicella vaccine to the KT recipient should be based on the patient's serologic status, likelihood of infection, and probability of vaccine adverse effects. Transplant recipients who received no varicella vaccines pre surgery and are exposed to varicella are at highest risk of infection. The probability of adverse effects from varicella vaccine, namely the development of disease due to vaccine virus, is likely related to factors such as time from transplant, rejection episodes, and degree of immunosuppression. Varicella vaccine should only be considered for those non-immune transplant recipients who are stable, several months out from surgery, not receiving systemic corticosteroids, without any significant episodes of rejection, and receiving only low-level immunosuppression. Limited studies to date suggest that varicella vaccine is safe in

patients meeting these criteria, but providers and patients should be aware that significant adverse events are possible.

Measles-mumps-rubella vaccine

Recent outbreaks of these vaccine-preventable diseases reveal that despite widespread vaccination efforts, these viruses continue to be a threat, especially to vulnerable populations [73]. Measles virus infection in SOT recipients can cause organ rejection [74] and severe disease and can present with more atypical clinical findings such as absence of rash [75]. Less is known about the disease course of mumps and rubella in SOT recipients, but cases of severe disease are reported in the literature, including an adult KT recipient who developed graft failure due to interstitial nephritis from mumps virus [76]. Compared to varicella vaccine, fewer studies are available of MMR in SOT recipients, but existing evidence suggests that it too may be safe in these patients. Four prospective studies on MMR in pediatric SOT recipients are available in the literature, all in liver transplant recipients. Seventy-six children in total received MMR at least 1 year after liver transplant [65]. No vaccine-attributable serious adverse events were reported. Serologic response was variable (39–100%). Duration of immunity may be problematic after organ transplant. Rand et al. reported that only four of 14 patients maintained protective titers 6 months after receipt of vaccine [77]. IDSA states that existing data are insufficient to recommend MMR after organ transplant, and therefore it remains contraindicated in SOT recipients.

Rotavirus vaccine

Rotavirus vaccine in SOT recipients has not been studied, but because it is a live vaccine, there are theoretical risks of severe disease in these patients and it is therefore contraindicated [6]. Rotavirus vaccine can be safely given to infant contacts of the SOT recipient, but because the virus is shed in the infant's stool [78], SOT recipients should avoid changing the vaccine recipient's diapers for at least 28 days following receipt of vaccine. If this is unavoidable, strict hand hygiene should be enforced [6].

Vaccination of family members and close contacts

Eligible family members and close contacts of SOT recipients can safely receive MMR and varicella vaccines. Transmission of vaccine virus to susceptible hosts is rare. However, varicella vaccine recipients who develop rash after vaccination should be isolated from the SOT recipient or at a minimum cover all affected areas and avoid direct contact [6].

Travel-related vaccinations

International travel is increasing worldwide, and as the morbidity in patients with immunocompromising conditions declines with advancing medical care, this population will likely participate with higher frequency in foreign travel, placing them at unique risks of infection [79]. Unfortunately, SOT recipients often do not seek advice pre travel and many will get sick while abroad [80]. This is particularly true of “visiting friends and relatives” travel as these individuals and their families are less likely to seek pre-travel advice due to an underestimation of risks and are therefore more likely to experience adverse events. Delaying international travel is recommended in the first year after SOT [81]. SOT recipients experiencing complications such as organ rejection or infection should consider delaying unnecessary travel at any point after transplant. Clinicians should be intimately involved in pre-travel preparation, which includes counseling, dispensing of certain additional medications, and administering vaccinations. It is highly recommended that patients seek the advice of a travel medicine expert and do so at least 3 months prior to expected travel [79]. The recommended vaccines based on travel destination can be found on the CDC travel website (www.cdc.gov/travel).

Hepatitis A vaccine

Hepatitis A virus is highly contagious and transmitted by person-to-person contact or through contaminated food and water. SOT recipients are at particularly high risk of severe disease. All parts of the world are considered intermediate or high risk of infection to travelers except the USA, Canada, Western Europe and Scandinavia, Japan, New Zealand, and Australia (www.cdc.gov/hepatitis/hav/). Unvaccinated or non-immune SOT recipients should receive two doses of the hepatitis A vaccine separated by 6 months prior to travel [79]. If only a single dose can be given prior to travel, at least a 2-week time is needed for antibody response. However, it is important that SOT recipients receive the complete two-dose series, as highlighted in a study of liver and KT recipients where seroconversion rates following a single dose were 41 and 24% in liver and KT recipients, respectively; antibody response increased to 97 and 72% following a second dose of vaccine [82]. Immunogenicity is often suboptimal in SOT recipients. In a study of 85 immunocompromised travelers receiving hepatitis A vaccine, six of ten SOT recipients developed immunity [83]. In addition, waning antibody response has prompted some experts to recommend revaccination after 2 years in SOT recipients with ongoing risk of exposure [84].

Poliovirus vaccine

Despite eradication efforts, infection with wild poliovirus continues to be a problem in select countries, and non-immune travelers are at risk. IPV is safe and immunogenic in SOT recipients [85]. OPV is a live virus vaccine and is used in many resource-limited countries. It is contraindicated in SOT recipients. It is also contraindicated in patient contacts due to the transmissibility of vaccine virus. When patients seek pre-travel advice, clinicians should be aware of current polio outbreaks, understanding that sporadic polio outbreaks continue to occur worldwide (www.cdc.gov/polio). SOT recipients are also at risk of disease from vaccine-derived poliovirus during travel to countries where oral poliovirus vaccine is used. SOT recipients with ongoing travel to polio endemic areas should receive a booster dose of IPV every 10 years [7].

Meningococcal vaccine

Children as young as 2 months can receive MenACWY prior to travel to areas with endemic disease (e.g., Sub-Saharan Africa) or active outbreaks [49]. A combination conjugate vaccine that provides protection against meningococcus serogroups C and Y and *Haemophilus influenzae* type B was developed but is not currently available in the US. MenB is not included in MenACWY and should be considered in SOT recipients ≥ 10 years of age prior to travel to areas with significant activity of meningococcus serotype B [79].

Rabies vaccine

Rabies is a viral infection of the central nervous system that is almost always fatal. Infection is most often acquired from the bite of an infected animal, but most cases in SOT recipients have occurred after receipt of a graft from a patient with undiagnosed rabies infection [79]. The efficacy of pre-exposure vaccination (i.e., receipt of vaccine prior to travel) is unclear in SOT recipients [81]. Pre-exposure vaccination is a three-dose series and can be considered for select patients based on duration of travel, specific activities to be performed abroad, and expected high risk of animal exposures [79]. In the USA and other developed countries, rabies is most often transmitted by non-canine mammals (e.g., bats, raccoons, and skunks). While dogs uncommonly transmit rabies to humans in the USA, they are the most common vector of disease to humans worldwide. Travelers to most areas of Africa, Asia, and Central and South America are at risk of rabies from dog bites. Prompt medical care is important after exposure, as post-exposure prophylaxis should be given as soon as possible with a five-dose vaccine series (instead of the typical four doses in immunocompetent individuals) along with rabies immunoglobulin. It is important for travelers to realize that contrary

to the situation in the USA, the availability of rabies vaccine and immunoglobulin is often limited in other countries. An emergency evacuation plan should be made before travel in case an expedient return is necessary, such as after a bite from a high-risk animal in an area where vaccine and immunoglobulin are not readily available.

Typhoid vaccine

Typhoid fever is a potentially fatal bacterial disease spread by contaminated food and water common in most of the world except the USA, Canada, Western Europe, Australia, and Japan. Travel to South Asia poses the greatest risk of acquisition [86]. An inactivated intramuscular vaccine is available and safe in SOT recipients aged 2 and older. Vaccine should be given at least 2 weeks before travel and repeated every 2 years if ongoing exposure is expected [5]. The live typhoid vaccine is contraindicated in SOT recipients.

Cholera vaccine

Cholera epidemics continue to occur worldwide, though travelers are at low risk of infection. A recently approved live cholera vaccine is available in the USA for adults, but its safety and efficacy in pediatric SOT recipients is unknown and therefore is not recommended in these patients. Several inactivated oral cholera vaccines are available outside the USA and may be considered if traveling to areas experiencing cholera outbreaks/epidemics [79].

Yellow fever vaccine

Yellow fever is a potentially fatal mosquito-borne viral infection endemic in tropical and subtropical South America and Africa. The vaccine contains live virus and is contraindicated in SOT recipients. Therefore, travel to countries highly endemic for yellow fever, especially during periods of peak disease, should be strongly discouraged in SOT recipients [5]. Prior to entry, many countries require documentation of receipt of yellow fever vaccine. Previously unvaccinated SOT recipients cannot receive the vaccine; therefore, individuals traveling to these countries need to travel with a medical waiver letter addressed to the embassy of the country being visited [81].

Japanese encephalitis virus vaccine

Japanese encephalitis virus (JEV) is a potentially life-threatening cause of encephalitis transmitted through the bite of a mosquito. It is endemic in India, East Asia, and the Western Pacific including Australia. The inactivated JEV vaccine is recommended in SOT recipients older than 2 months of age before travel to several countries in East Asia and certain

parts of Australia (CDC). Vaccination is typically only given if the duration of travel is more than 1 month and/or if significant time will be spent in rural areas, where transmission from the mosquito vector is more common. A two-dose series is given, separated by 28 days. Yearly revaccination should be considered if ongoing risk is expected [79]. A live vaccine is available in Asia, but it is contraindicated in SOT recipients.

Bacillus Calmette-Guerin vaccine

Bacillus Calmette-Guerin (BCG) is an attenuated live strain of *Mycobacterium bovis* given to infants in many countries for prevention of severe forms of tuberculosis. It is contraindicated in SOT recipients due to the risk of disseminated *M. bovis* disease [79].

Key summary points

1. Pediatric KT candidates should be fully immunized using age-appropriate guidelines.
2. A minimum of 4 weeks between live virus vaccine administration and transplantation should be allowed given the risk of developing disease.
3. There are specific alterations of the routine immunization schedule in KT patients in the cases of influenza, hepatitis B, pneumococcal, and meningococcal vaccination.
4. Live vaccines are generally contraindicated in KT recipients, except for varicella vaccine, which could be considered in very select non-immune children, recognizing the potential risks.
5. Pediatric KT physicians need to be aware of risks associated with international travel and work with travel medicine experts to provide immunizations.

Multiple choice questions (answers are provided following the reference list)

1. How long after administration of varicella vaccine can kidney transplantation surgery be safely performed?
 - a) Minimum 2 weeks.
 - b) Minimum 4 weeks.
 - c) Minimum 8 weeks.
 - d) It does not matter.
2. In a kidney transplant recipient who is fully immunized with PCV13 and who also received one dose of the PPSV23, what further action needs to be taken?
 - a) No further action.
 - b) Repeat the PPSV23 every 5 years.

- c) Repeat the PPSV23 once after 5 years.
- d) Restart the PCV13 and the PPSV23 vaccination series after 5 years.

3. Which of the following vaccines is contraindicated in pediatric KT recipients prior to international travel?
 - a) Hepatitis A vaccine.
 - b) Rabies vaccine.
 - c) Inactivated typhoid fever vaccine.
 - d) Yellow fever vaccine.
4. Vaccination against which pathogen(s) requires alterations of the standard immunization schedule when given to pediatric KT recipients?
 - a) Diphtheria, tetanus, and pertussis
 - b) HPV.
 - c) *Streptococcus pneumoniae*.
 - d) *Haemophilus influenzae* type b.
5. Which of the following statements regarding inactivated influenza vaccine (IIV) is FALSE?
 - a) After receipt in a KT candidate, one should wait 4 weeks before proceeding with transplantation.
 - b) It is recommended yearly for pediatric KT recipients.
 - c) It is recommended yearly for pediatric KT household contacts.
 - d) Patients on different immunosuppression regimens can have different immune responses to it.

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Compliance with ethical standards

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Answers to questions

1. b; 2. c; 3. d; 4. c; 5. a