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Vaccinations in kidney transplant recipients: Clearing the muddy waters

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Abstract

Vaccine preventable diseases account for a significant proportion of morbidity and mortality in transplant recipients and cause adverse outcomes to the patient and allograft. Patients should be screened for vaccination history at the time of pre-transplant evaluation and vaccinated at least four weeks prior to transplantation. For non-immune patients, dead-vaccines can be administered starting at six months post-transplant. Live attenuated vaccines are contraindicated after transplant due to concern for infectious complications from the vaccine and every effort should be made to vaccinate prior to transplant. Since transplant recipients are on life-long immunosuppression, these patients may have lower rates of serological conversion, lower mean antibody titers and waning of protective immunity over shorter period as compared to general population. Recommendations regarding booster dose in kidney transplant recipients with sub-optimal serological response are lacking. Travel plans should be part of routine post-transplant assessment and pre-travel vaccines and counseling should be provided. More studies are needed on vaccination schedules, serological response, need for booster doses and safety of live attenuated vaccines in this special population.

Key words: Immunizations; Kidney transplant; Vaccines; Transplant outcomes; Serological response

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Core tip: Vaccine-preventable disease can cause adverse patient and allograft outcomes

in kidney transplant recipients. Patients should be screened for vaccinations pre-transplant and catch up immunization should be provided at least four weeks prior to transplantation. For non-immune patients, catch-up immunization should start six months post-transplantation. Live attenuated vaccines are contra-indicated in transplant patients. There is limited data that suggests safety of live vaccines in selective population on low immunosuppression. Travel plans should be part of routine post-transplant assessment and pre-travel vaccines and counseling should be provided.

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BACKGROUND

With advancements in medicine and improved patient survival, there is a growing population of solid organ transplant (SOT) recipients^[1]. Advanced immunosuppressive regimens have emerged and acute rejection rates have substantially declined^[2]. Infection prophylaxis and rapid diagnosis of infectious complications have allowed patients to tolerate these more intense immunosuppressive regimens, yet vaccine preventable diseases still account for a significant proportion of morbidity and mortality in transplant recipients^[3]. The Centers for Disease Control and Prevention (CDC) estimates that each year there are roughly 40000 cases and 4000 deaths attributable to invasive pneumococcal disease, which occurs in organ transplant recipients at a rate 25 times greater than in the general population^[3]. It is estimated that the percentage of high-risk adults aged 18-64 vaccinated against pneumococcal disease to be only 21%^[4]. Despite the burden of illness in this population, approved and recommended vaccinations remain underutilized^[5,6].

The prevention of infection through vaccination is of paramount importance and of near equal importance is the timing of vaccination in relation to kidney transplantation (KT). Ideally, KT recipients (KTRs) should be vaccinated as early as possible as the response to vaccines is diminished in end-organ failure and in states of immunosuppression. In 2013, the guidelines of vaccination of adult solid organ transplant candidates and recipients were updated by the American Society of Transplantation (AST) and the Infectious Disease Society of America. They specify that vaccination is the responsibility of the primary care provider as well as the specialist or nephrologist. The vaccination status should be documented at the pre-transplant clinic and necessary immunizations must be administered as soon as possible thereafter^[7,8]. When pre-transplant immunization is not possible, inactivated vaccines are generally considered safe after transplant. This review summarizes current evidence on the use of vaccination before and after KT, serological conversion rates in the setting of immunosuppression and the effect of vaccinations on kidney transplant outcomes.

PRE-TRANSPLANT VACCINATIONS

Patients with advanced chronic kidney disease (CKD) and dialysis dependent end stage renal disease (ESRD) on kidney transplant waitlist have high rates of infectious complications secondary to their already compromised immune systems. In this population, serological response to vaccinations may not be as optimal as in healthy individuals, but it is still better compared to post-transplant immunization. Hence, it is recommended to vaccinate patients with CKD, not requiring dialysis, so that they can mount an optimal immunological response. There is no consensus on the stage of CKD that would be ideal for administering vaccines. Too early-on administration might lead to "unnecessary" immunizations as many of these patients may never progress to ESRD. Dukes *et al*^[9] conducted a prospective study in pre-dialysis patients (with serum creatinine > 2 mg/dL, mean serum creatinine 4.5 mg/dL) and found a favorable response to hepatitis B vaccine with subsequent booster dose as compared to dialysis patients historically^[9]. Another prospective cohort study looked at rates of

seroconversion after hepatitis B immunization in CKD patients with mean serum creatinine of 3.4 ± 1.5 mg/dL and mean estimated glomerular filtration rate (GFR) of 20 mL/min. They concluded that patient at higher GFR levels are more likely to respond to hepatitis B vaccination^[10].

Some experts have recommended additional doses and/or boosters to improve serological response in CKD patients. García-Agudo *et al*^[11] measured serological response in 155 CKD patients prospectively with two cycles of four double doses of conventional hepatitis B vaccine (at 0, 1, 2 and 6 mo), and additional four 20 mg dose of adjuvant vaccine in non-responders. Serological response was improved to 93.8% after the eighth dose compared to 75.9% after the fourth dose. Studies have shown that the humoral response to influenza vaccine is similarly better in hemodialysis patients compared to KTRs^[12,13].

POST-TRANSPLANT VACCINATIONS

For those patients who are unable to obtain vaccinations pre-transplant, inactivated vaccines are considered safe when administered after kidney transplant. The optimal time for vaccination is not known but most transplant centers generally agree to wait at least 3-6 mo after transplantation or when patients are on stable maintenance levels of immunosuppressants. AST guidelines suggest avoiding all vaccinations, except influenza, within the first 6 mo post KT. Live-attenuated vaccinations (LAV) are contraindicated in KTRs due to risk of infection but family members of these patients can consider LAVs when appropriate to help provide herd immunity.

INFLUENZA VACCINE

Influenza is a common viral disease post-transplant and is associated with higher morbidity and mortality in immunosuppressed patients compared to a healthy host. Furthermore, influenza has been associated with increased risk of acute rejection after KT^[14]. Although generally recommended to administer vaccination 3-6 mo after KT, the influenza vaccine may be given earlier than this time period if the transplantation occurs during the influenza season. Immunological response may be suboptimal with early vaccination; so patients may be revaccinated in the 3-6 mo period post KT if epidemiological risk for influenza exists based on the time of the year^[7]. Thereafter, influenza vaccination should be offered yearly. Despite recommendations and safety profile of the influenza vaccine, this mode of protection against influenza is underutilized. Hurst *et al*^[14] identified 51730 Medicare first-time KTRs from 2000 to 2006, of which 18.7% patients had influenza vaccination within the first year post-transplant and 43% of these patient received vaccines within the first 6 mo post-transplant. Multivariate analysis demonstrated that vaccination within the first year after transplant was associated with lower risk of allograft loss and death with adjusted hazard ratio of 0.77 ($P < 0.001$) and 0.82 ($P < 0.001$), respectively. Vaccination in the first 6 or 12 mo after transplant was not associated with increased risk for acute rejection^[14].

Influenza vaccine preparations vary but both quadrivalent and trivalent vaccines can be used after KT. Only the LAV (FluMist) is contraindicated in transplant recipients and household members of transplant patients. One study investigated whether high-dose intradermal (ID) influenza vaccination would provide superior immunity to transplant patients compared to standard-dose intramuscular (IM) vaccine^[15]. No significant difference was found in serological conversion rates between the high-dose ID and standard-dose IM vaccines. Similarly, there was no difference found in adverse effects between the two vaccines besides significantly higher rates of local adverse events including erythema, induration, tenderness, and pruritus with the ID vaccine^[15].

Some studies have shown improved immunogenicity with higher doses of antigen in transplant recipients. Natori *et al*^[16] showed significantly increased immunogenicity with high dose (60 mg) as compared to standard dose of influenza vaccine in SOT recipients. Since, high dose vaccine is not commercially available outside of North America, Mombelli *et al*^[17] recently compared efficacy of double dose (30 mg) versus standard dose (15 mg) of inactivated trivalent influenza vaccine in SOT recipients and found a trend towards increased vaccine response and significantly higher rates of seroprotection with double dose, without any increase in vaccine-related serious adverse events. Another strategy that has been shown to be effective is to administer a booster dose five weeks after initial dose that led to significantly increased seroconversion rates to all strains of influenza^[18].

PNEUMOCOCCAL VACCINE

Infections from *Streptococcus pneumoniae* occur in SOT patients at an incidence rate of 146 infections per 100000 persons per year. Comparatively, the incidence rate of pneumococcal infections in the general population is 11.5 per 100000 persons per year^[19]. There are two vaccines against *Pneumococcus*; the pneumococcal conjugate vaccine 13-valent vaccine (Pneumovax 13® or PCV13) and the 23-valent polysaccharide vaccine (Pneumovax® or PPSV23). The CDC currently recommends administering PCV 13 followed by PPSV23 eight weeks later for immunocompromised patients including those with CKD, nephrotic syndrome, and SOT^[20]. A booster dose of PPSV23 should be given at least five years after the first dose. If this booster dose is given before the age of 65, then a final dose of PPSV23 may be administered after 65 years of age, provided five years have elapsed since the previous dose. In the event, PPSV23 is administered prior to PCV 13; one should wait at least a year before giving PCV 13. Subsequent booster doses of PPSV23 may be administered as outlined earlier^[21].

There have been no studies to date examining serological response or durability of response of PCV13 followed by PPSV23 in KTRs. However, some small randomized studies have explored the impact of the pneumococcal conjugate 7-valent (Pneumovax-7 or PCV7) vaccine compared to PPSV23 in KTRs and did not find any improvement in duration of immune response^[22,23]. Tobudic *et al*^[24] found that immunogenicity was not improved when PPSV23 was boosted with PCV7. In this study, 62 patients were randomly assigned to PCV7 followed by PPSV23 after one year versus two doses of PPSV23 given one year apart. Immunogenicity of pneumococcal vaccination was not significantly different between the two strategies (87.5% for PCV7 *vs* 87.1% for PPSV23)^[24].

DIPHTHERIA, TETANUS, PERTUSSIS VACCINE

Whooping cough, or pertussis, is a highly contagious infection caused by *Bordetella pertussis*. Recent outbreaks of pertussis are thought to be caused by waning pertussis immunity in adulthood. Therefore, a single dose of tetanus, diphtheria toxoid, and pertussis vaccine should be administered for all adults over the age of 18 to boost immunity to pertussis. Otherwise, tetanus and diphtheria is recommended every 10 years as an adult or when one sustains serious wounds including punctures, bites, scrapes, and burns^[25].

HEPATITIS B VACCINE

Reactivation of hepatitis B after solid organ transplantation can rapidly cause severe hepatitis in the presence of potent immunosuppression^[26]. Currently, the Advisory Committee on Immunization Practices (ACIP) recommends all hemodialysis (HD) patients be vaccinated for hepatitis B and to revaccinate this population when anti-HBs titers decrease to under 10 IU/mL^[27]. Therefore, the majority of KTRs have been vaccinated to hepatitis B prior to transplant. The universal vaccination of HD patients has created an opportunity to expand the pool of possible deceased donor kidneys to include hepatitis B surface antigen (HBsAg) positive donors^[28]. KTRs that are immune to hepatitis B either through vaccination or previous infection can be considered for HBsAg positive organs if the recipients' anti-HBs titers are above 10 IU/mL. There are several recent reports that showed patient and graft survival were similar to recipients with HBsAg-negative donors, with normal liver function and no evidence of HBV transmission^[29,30]. Patients who receive living kidney transplants and preemptive transplants may require primary vaccination of hepatitis B after transplant^[28,31-34].

HERPES ZOSTER VACCINE

Immunosuppression increases the incidence of herpes zoster infection approximately 7- fold compared to the immunocompetent host^[35]. Until recently, the only vaccine available was a live-attenuated varicella zoster vaccine (Zostavax® or ZVL) which was contraindicated in KTRs. ZVL is FDA approved for prevention of herpes zoster in patients ≥ 50 years of age^[36], however due to concerns about durability of the response, the ACIP recommends vaccination in ≥ 60 years of age. Comparatively, Shingrix® is a dead, recombinant zoster vaccine (RZV) which is approved to prevent

herpes zoster in patients ≥ 50 years^[37]. RZV is a two dose vaccination given 2-6 mo apart and reduces the risk of shingles by more than 90%. Studies in healthy, non-transplant patients have demonstrated continued efficacy for three years post vaccination with 84.7% prevention of herpes zoster and reduced post-herpetic neuralgia in patients by 91.2%^[38]. A Phase III randomized clinical trial found that humoral immunogenicity was significantly increased two months after vaccination in adult KTRs who received the RZV compared to placebo^[39]. Further studies are required to determine the long term efficacy and safety of this vaccine in KTRs.

HPV VACCINE

Human papillomavirus (HPV) is a common sexually transmitted viral disease that is associated with cancers of the anus, penis, cervix, and vulva. Almost 14 million people are infected with HPV each year^[40]. Three inactive HPV vaccines have been FDA approved for use in the United States. Both Gardasil® (4 valent vaccine) and Gardasil 9® (9-valent vaccine) are approved for use in females and males between 9 and 26 years of age^[41,42]. Cervarix® is a bivalent HPV vaccine that is approved for use in females between the age of 9 and 25 years^[43]. In the United States, only the 9-valent vaccine is currently available. The ACIP currently recommends that all patients with history of primary or secondary immunocompromising conditions, including SOT recipients, should receive a three dose series of HPV vaccine at months 0, 1-2, and 6 mo^[40]. Serological and durability of immunological response post vaccination is unknown after kidney transplant.

MENINGOCOCCAL VACCINE

Menigococcal vaccine is indicated for KTRs who are travelling to highly endemic areas such as Sub-saharan Africa, Saudi Arabia or patients with history of splenectomy. It is also indicated for patients with atypical hemolytic uremic syndrome or antibody mediated rejection who are receiving eculizumab which is a complement inhibitor^[44]. Effort should be made to administer meningococcal vaccine at least two weeks prior to the first dose of eculizumab. Patients should receive vaccination against meningococcal serogroups A, C, Y and W1235 by either Menactra or Menveo as well as vaccination against meningococcal serogroup B with either Trumemba or Bexsero. Menactra or Menveo should be administered twice, at least 2 mo apart, with concurrent Trumemba or Bexsero vaccination. When Trumemba is given, three doses are required at 0, 1-2, and 6 mo while Bexsero is a two-dose series administered at least 1 mo apart. Vaccination should be repeated every 5 years for group A, C, Y, and W1235 with either Menactra or Menveo^[21]. Immunogenic response to polysaccharide meningococcal vaccine is only 40% in SOT recipients with low titer antibodies developing only to meningococcus C. With conjugate vaccine, about half of the SOT recipients develop low antibody titers at least against one of the serogroups including A, C, Y and W-135. Two doses of conjugated quadrivalent meningococcal vaccine is recommended, followed by a booster every five years^[45].

VACCINATION AGAINST CYTOMEGALOVIRUS

Cytomegalovirus (CMV) is a double-stranded DNA virus that is ubiquitous with very high sero-prevalence. The virus can cause significant morbidity and mortality in immune-compromised organ transplant recipients. Anti-viral therapy currently used for CMV prophylaxis in SOT recipients is associated with adverse events including neutropenia. Hence, there is an unmet need for developing treatments with new mechanisms of action including effective vaccines. Earlier studies have shown variable impact on CMV immunogenicity with different vaccines administered pre transplant^[46,47]. ASP0113 is a first-in-class bivalent DNA-based vaccine developed for preventing CMV infection in immuno-compromised transplant recipients. It contains equal quantities of the plasmids VCL-6365 and VCL-6368 encoding for glycoprotein B and phosphoprotein 65^[48]. A phase I study demonstrated the immunogenicity and safety of ASP0113 in healthy adults^[49]. In another randomized, double-blind placebo-controlled phase II study in allogeneic hematopoietic cell transplant (HCT) recipients, ASP0113 significantly reduced the occurrence and recurrence of CMV viremia with improved time to event and similar adverse events when compared to placebo^[50]. A recently published phase-II placebo-controlled study randomized 149 CMV seronegative recipients of kidneys from seropositive donors in a 1 : 1 manner to either 5

doses of ASP0113 or placebo on days 30, 60, 90, 120, 150 post-transplant. All patients received prophylactic valganciclovir/ganciclovir on days 10-100 after transplant. In this study, ASP0113 was not effective in preventing CMV viremia from day 100 through year one after first study vaccine injection but had a safety profile similar to placebo^[51]. One possible reason for the lack of vaccine efficacy observed in this study could be related to the post-transplant administration of the vaccine when patients are heavily immunosuppressed resulting in a weak T-cell response. Future studies should follow a protocol that mandates pre-transplant use of ASP0113 when recipients likely have more robust T-cell response. Currently, an ongoing phase III study is evaluating the safety and efficacy of ASP0113 in CMV-seropositive allogeneic HCT recipients (NCT01877655).

LIVE ATTENUATED VACCINES

Despite several advantages of live-attenuated vaccines (LAV), it is not recommended to use these in immunocompromised host secondary to risk of vaccine-virus induced disease and uncontrolled replication of vaccine virus. There is scant data on safety of LAV in transplant recipients with stringent criteria such as need for minimal immunosuppression, with stable immunological parameters^[52-54]. Live mumps, measles, rubella (MMR) vaccine is not recommended in KTRs. MMR serology should be checked prior to transplantation and non-immune patients should be vaccinated. If non-immune patients have exposure to measles, normal human immunoglobulin should be administered within six days of exposure^[55,56]. When living KT is scheduled, pre-transplant non-immune patients should be vaccinated against Varicella Zoster using LAV with two doses at least 4-6 wk and 2-4 wk prior to transplant^[57]. Generally, Herpes zoster vaccine Zostavax is contraindicated in KTRs secondary to risk of disseminated disease; however there is some data on the safety of Zostavax in pediatric patients with liver transplant^[58,59]. In non-immune patients with risk exposure, administer Varicella zoster immunoglobulin within 96 h along with valacyclovir for 7 to 10 d^[60].

While there are small studies suggesting no significant side effects with live attenuated yellow fever vaccines in transplant recipients traveling to sub-Saharan Africa and South America, it is still contraindicated post-transplantation secondary to risk of encephalitis^[61-63]. In such patients, it is recommended to administer yellow fever vaccine pre-transplant in anticipation of travel to endemic areas. Other live vaccines to avoid in KTRs include oral typhoid vaccine, Bacille Calmette-Guerin vaccine and attenuated intra-nasal influenza vaccine^[6,64-66].

INTERNATIONAL TRAVEL

A large number of immunocompromised patients including KTRs travel internationally to high risk destinations every year without adequate pre-travel advice and vaccinations^[67-70]. These patients are at heightened risk of acquiring infections that could even lead to allograft rejection. Pre-travel vaccines could help in disease prevention or decrease the severity of disease in KTRs^[64].

Preferably, patients should receive key vaccinations at least four weeks prior to undergoing transplantation but it may not be practical for area-specific travel vaccines for endemic diseases, especially, if travel plans are made post-transplantation. Some experts recommend restriction of travel within the first 12 mo post-transplantation^[71]. During each physician encounter, specific questions should be asked about travel plans and referred to travel clinics ideally 12 wk prior to travel so that there is enough time for administration of required pre-travel vaccines, serological testing and additional boosters^[45]. If travel is anticipated to endemic areas, then the recommended vaccinations are given in addition to routine vaccinations as listed in Table 1^[45,64]. Since yearly influenza vaccine strains differ between different hemispheres and influenza seasons are in months of October-March in Northern hemisphere, April-September for southern hemisphere and all-year round in tropics, the ACIP recommends two vaccinations with hemisphere-specific trivalent influenza vaccines four weeks apart in immunocompromised patients crossing the hemispheres^[72].

In endemic areas, mosquito-borne infections such as malaria and dengue may precipitate acute allograft rejections^[73,74]. Traveler's diarrhea with organisms like *Escherichia coli*, *Campylobacter* sp, *Salmonella*, *Shigella*, *Giardia*, and *Entamoeba histolytica* are common especially in immunocompromised hosts. Patients should be advised to stay well hydrated as dehydration may also cause kidney dysfunction and calcineurin inhibitor toxicity. In addition to the pre-travel vaccines, KTRs should be counseled on

Table 1 Recommendations for various vaccines in kidney transplant recipients

Vaccine	Prior to transplant	After transplant	Prior to travel to endemic areas after transplant	Endemic areas	Antibody titers?
Hepatitis A	Yes	Yes	Yes		> 33 mIU/mL is protective
Hepatitis B	Yes	Yes	Yes		> 10 mIU/mL is protective
Pneumococcal	Yes	Yes	No		
Meningococcal	Yes	Yes	Yes	Sub-Saharan Africa, India, Philippines, Saudi Arabia	
Tdap	Yes	Yes	No		
Td	Yes	Yes	No		
MMR	Yes	No	No		
Varicella zoster	Yes	Only Shingrix may be given post-transplant	No		
Influenza	Yes	Yes - avoid live virus	No		
Rabies ¹ only upon exposure	No	No	No		
Diphtheria	No	No	Yes ¹	SE Asia, Hajj travelers to Saudi Arabia	
Tick-borne encephalitis	No	No	No (live)		Can follow antibody titers
Japanese encephalitis	No	No	Yes, day 0 and 28	South, South East, and East Asia and part of Western Pacific	
Cholera	No	No	Yes, oral killed vaccine	South and South East Asia	
Yellow fever	No	No	No,	Sub-Saharan Africa, South America	
Typhoid	No	No	Yes, 2 wk prior to travel	South and South East Asia, Africa, Caribbean, Central and South America	

¹Re-vaccination required if last vaccination was 10-15 years prior. MMR: Measles, mumps, rubella; Tdap: Tetanus toxoid, reduced diphtheria toxoid, acellular pertussis, Td: Tetanus diphtheria.

food and water hygiene measures, use of insect and mosquito repellants and safe sex practice. Chemoprophylaxis for malaria should be offered and anti-parasitic regimen(s) offered based on susceptibility pattern at destination site. Atovaquone-proguanil or doxycycline is commonly offered medications for malaria prophylaxis in areas with chloroquine resistance.

SEROLOGICAL RESPONSE IN KIDNEY TRANSPLANT RECIPIENTS

Since KTRs are on life-long immunosuppression, these patients may not mount comparable serological response to vaccinations with lower rates of seroconversion, lower mean antibody titers and waning of protective immunity over shorter period as compared to general population^[64,75]. Moreover, serological response might vary depending on type of immunosuppressive medications. Calcineurin inhibitors and mammalian target of Rapamycin (mTOR) inhibitors impair interleukin-2 dependent T-cell proliferation while mycophenolate mofetil and azathioprine inhibit antigen dependent T-and B-cell interaction and proliferation and response to vaccines^[15,76-79]. Further studies have shown that cyclosporine treated patients have poorer response post-influenza vaccination as compared to azathioprine treated patients, and patients on mTOR-inhibitors had lower immune response to H1N1 vaccination^[80,81]. Patients had decreased response rates if they had received anti-CD20 monoclonal antibody as a part of immunosuppression protocol^[82]. The issue becomes more complex with contemporary powerful immunosuppression including the depleting antibodies such

as Thymoglobulin and alemtuzumab.

At present, we have limited data on the timing, dosing and efficacy of vaccinations in organ transplant population. With the advent of new biologics as immunosuppressants and approval of newer vaccines, the waters have become muddier with respect to providing direction for vaccinations in KTRs. Beil *et al*^[83] followed antibody titers in 94 pediatric KTRs who had vaccinations and found that titers were low in 31% with tetanus, 25% with diphtheria and 68% with hepatitis B virus immunization. Eckerle *et al*^[82] systematically reviewed published data on the vaccination response in SOT recipients and found that they had 10%-16% less response rate as compared to general population. They found encouraging serological responder rates with tetanus, diphtheria, rabies, hepatitis A and polio vaccination, though antibody titers declined over time for diphtheria and hepatitis A vaccination. Efficacy of repeated hepatitis B vaccination is also reduced to 32%-36% as compared to 90%-95% in healthy controls^[84-86]. Recommendations regarding booster dose in pediatric or adult KTRs with sub-optimal serological response are lacking. L'Huillier *et al*^[87] published a strategy utilizing serology based immunization in pediatric liver transplant patients with some success.

HEALTHCARE WORKERS AND CLOSE CONTACTS OF TRANSPLANT RECIPIENTS

Since there is risk of transmission of infections in immunocompromised KTRs, it is of critical importance to fully immunize persons in close contact with KTRs. This helps in building herd immunity and protects KTRs from diseases. Annual influenza vaccination in all healthcare workers and all indicated age appropriate vaccinations including LAVs such as MMR, rotavirus vaccine and varicella vaccine should be administered to the children of transplant recipients^[44,82]. Since there is virus shedding post-vaccination, patients and contacts should be counseled about strict hand washing at least for two weeks after administration of live vaccines^[88-90]. Live oral polio vaccine is contra-indicated in close contacts; therefore, inactivated polio vaccine should be administered. Living-organ donors should avoid LAV at least 3-4 wk prior to transplantation^[53,91].

EFFECTS OF VACCINATIONS ON TRANSPLANT OUTCOMES

There have been concerns about adverse effects of influenza vaccination on allograft function by upregulation of human leukocyte antigen (HLA) alloantibodies after vaccination. During Influenza A/ H1N1 pandemic in 2009, some studies had demonstrated anti-HLA antibodies post vaccination with AS03-adjuvanted monoclonal H1N1 vaccine but this did not translate in adverse clinical outcomes^[92,93]. Many other clinical studies did not show increased risk of acute rejections or allograft dysfunction after influenza vaccination^[94-97]. In fact, Hurst *et al*^[14] had shown reduced risk of allograft loss if influenza vaccination is administered in the first post-transplant year. Influenza vaccination is deemed safe and should be recommended to all KTRs.

Lindemann *et al*^[98] showed no increase in HLA antibodies after pneumococcal vaccination in KTRs. Mulley *et al*^[99] recently published no effect on the development of de novo donor-specific antibodies and no increase in episodes of acute rejection or graft loss post-vaccination in SOT recipients based on a systematic review and meta-analysis of 90 studies involving 15645 vaccinated patients and 42924 controls. Further high-quality, controlled studies for assessing the post-vaccination outcomes in transplant recipients are needed.

CONCLUSION

KTRs are at increased risk of infectious complications in the setting of prolonged, chronic immunosuppression with increased morbidity and mortality. Awareness about vaccine-preventable diseases, administration of vaccines preferably prior to kidney transplantation and to close contacts could lower the burden of complications post-transplant. If the opportunity for pre-transplant primary vaccination is missed, patients should be offered immunization 6 mo post-transplantation. Patients should also be offered pre-travel endemic area specific vaccinations. LAVs are generally

contraindicated in KTRs. More studies are needed on vaccination schedules, serological response, need for booster doses and safety of LAVs in this special population. The emergence of newer data from such studies would enable transplant community to make more evidence based recommendations and further clear the muddy waters.

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