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Vaccination in Kidney Transplant Candidates

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Background: Kidney transplant (KT) candidates have historically low immunization rates against recommended vaccines. A retrospective single-center study of contemporary KT candidates was conducted to assess vaccination rates and vaccine uptake. **Methods:** All KT candidates ≥18 y evaluated between January 1, 2020, and December 31, 2020, were retrospectively reviewed for history of prior vaccination against tetanus, diphtheria, and pertussis; 13-valent pneumococcal conjugate vaccine; 23-valent pneumococcal polysaccharide vaccine; and recombinant zoster vaccine. Positive hepatitis A IgG total, hepatitis B surface antibody, measles, mumps, rubella, and varicella IgG were assessed as surrogate markers of immunity. Vaccine uptake among vaccine-eligible candidates was also assessed. **Results:** Among 150 KT candidates, the rate of prior vaccination against tetanus, diphtheria, and pertussis; 13-valent pneumococcal conjugate vaccine; 23-valent pneumococcal polysaccharide vaccine; and recombinant zoster vaccine (latter among patients ≥50 y) was found to be as low as 11%. Hepatitis A IgG total, hepatitis B surface antibody, measles, mumps, rubella, and varicella IgG seropositivity rates were 30%, 66%, 88%, 78%, 90%, and 96%, respectively. Only 7 (5%) of 150 patients had complete immunization or seropositivity. Five (3%) of 143 vaccine-eligible patients declined vaccination. Hepatitis A vaccine declination was relatively common with 15 (16%) of 94 vaccine-eligible patients declining it. **Conclusions:** KT candidates have low baseline rates of prior immunization/seropositivity against most recommended vaccines. Overall vaccine uptake among eligible candidates was high.(Transplantation Direct 2023;9: e1544; doi: 10.1097/TXD.0000000000001544.)

Kidney transplant (KT) recipients remain on lifelong immunosuppressive therapy and are at an increased risk of infection in the posttransplant period.[1] Vaccination can prevent certain infections in this population. Ideally, vaccination should be done before transplantation when the immune system is relatively intact.[2-4] Vaccine efficacy decreases in the posttransplant period due to the compromised immune system.[5-7]

The American Society of Transplantation recommends vaccination against influenza, tetanus, diphtheria, and pertussis (Tdap), *Streptococcus pneumoniae*, and hepatitis B virus, in addition to other age-appropriate vaccines in all potential KT candidates.[8] Vaccination is also recommended against hepatitis A virus, especially in patients with liver disease or at risk of acquiring hepatitis A infection, but can be offered to any adult who wishes to get vaccinated.[9] Similarly, recombinant zoster vaccine (RZV), which used to be recommended in adults ≥50 y old, is now recommended in all adults ≥19 y if they are immunocompromised or expected to be immunocompromised soon.[10] Live vaccines against measles, mumps, rubella (MMR), and varicella are also indicated, if no contraindications, in unvaccinated KT candidates. Despite these recommendations, vaccination rates in KT candidates remain low, and there are limited data on contemporary vaccination rates, vaccine uptake, and refusal in KT candidates.[11-14]

The primary objective of the study was to assess vaccination rates among contemporary KT candidates against Tdap, *S. pneumoniae* (using 13-valent pneumococcal conjugate vaccine [PCV13] and 23-valent pneumococcal polysaccharide vaccine [PPSV23]), and RZV and to assess immunity against hepatitis A, hepatitis B, MMR, and varicella. The secondary objective was to evaluate vaccine uptake among vaccine eligible candidates during pretransplant evaluation.

MATERIALS AND METHODS

In our center, all KT candidates ≥18 y are referred to the Transplant Infectious Disease (TID) clinic for pretransplant evaluation. In this single-center study, all consecutive KT candidates between January 1, 2020, and December 31, 2020, were retrospectively reviewed for rates of prior immunization against Tdap (in the last 10 y), PCV13, PPSV23, and RZV. For the latter 3, the patients could have received vaccination at any time before evaluation to be

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considered immunized, except PPSV23 in patients ≥65 y, who are recommended to have 1 dose of PPSV23 after they turned 65 y, and at least 5 y after the last dose if they had received it before 65 y old. Some patients had received >1 dose of PPSV23, but complete information was not available on the number of doses received, and for the study purpose, only the last dose was counted. For RZV, receipt of 2 doses among patients ≥50 y was considered immunized. Additional data on immunization against tetanus and diphtheria (Td) and live zoster vaccination were also collected. Rates of positive hepatitis A IgG total (HepAIgG), hepatitis B surface antibody (HepBsAb), MMR, and varicella IgG were assessed as surrogate markers of immunity and/or prior vaccination.

Data on vaccine uptake among eligible candidates were collected from electronic medical records. Verbal recollection of vaccination was accepted if the patients appeared to be confident of their vaccination status (except for MMR and varicella). Denominators with missing data were not reflected in the calculation of percentages in Tables 1 and 2.

Patients were considered eligible for vaccination if they did not have contraindication to vaccination and

1. did not have history of prior immunization against PCV13, PPSV23, and 2 doses of RZV (latter for patients ≥50 y);
2. had negative HepAIgG;
3. had negative HepBsAb (< 11.99 mIU/mL) with no evidence of active hepatitis B infection and had not received 2 rounds of hepatitis B vaccine series; and
4. had negative measles (<13.5 AU/mL), mumps (< 9 AU/mL), rubella (<9 IU/mL), varicella IgG (<135 index), and no history of prior vaccination (1 dose for rubella and 2 doses for the other viruses).

TABLE 1.

Demographics of kidney transplant candidates

KT candidates (N = 150)	N (%)
Age (y)	Mean, 50.2; range, 19–73
Gender (M)	102 (68)
Race (N = 146)	
Black/African American	74 (51)
White	64 (44)
Others[a]	8 (5)
Ethnicity (N = 144)	
Non-Hispanic/Latino	137 (95)
Hispanic/Latino	7 (5)
US born (N = 144)	130 (90)
Etiology of kidney disease	
Diabetes	35 (23)
Hypertension	18 (12)
Diabetes and hypertension	16 (10)
Other[b]	81 (54)
Dialysis	103 (69)
Hemodialysis	69 (46)
Peritoneal dialysis	34 (23)
Prior transplant[c]	22 (15)
Prior transplant on immunosuppressants	16 (11)
Immunocompromising conditions[d]	30 (20)

[a] Asian = 7, Arab = 1.
[b] Polycystic kidney disease, focal segmental glomerulosclerosis, IgA nephropathy, HIV, APOL1, calcineurin inhibitor nephrotoxicity, Fabry disease, anti-glomerular basement membrane glomerulonephritis, lupus nephritis, chronic glomerulonephritis, nephrolithiasis/obstructive, nonsteroidal anti-inflammatory drugs, granulomatosis with polyangiitis, hepatorenal, hereditary nephritis, familial, hypoplastic, membranous glomerulonephritis, interstitial nephritis, mesangial proliferative glomerulonephritis-1, MPO glomerulonephritis, acute tubular necrosis, nodular glomerulosclerosis, reflux nephropathy, and thrombotic microangiopathy.
[c] Liver = 2, heart = 1, kidney = 19.
[d] HIV = 4, splenectomy = 2, lupus = 2, focal segmental glomerulosclerosis-1, steroid = 1, Gout = 1, Crohn's disease = 1, interstitial nephritis = 1, granulomatosis with polyangiitis = 1, and transplant = 16.
APOL1, apolipoprotein L1; KT, kidney transplant; M, male.

TABLE 2.

Kidney transplant candidates: vaccination and seropositivity

Kidney transplant candidates (N = 150)	N (%)
Tdap receipt (N = 146)	51 (35)
Tdap or Td receipt (N = 146)	58 (40)
PCV13 receipt	82 (55)
PPSV23 receipt	100 (67)
Positive hepatitis A IgG (N = 149)	44 (30)
Positive HepBsAb	99 (66)
Recombinant zoster (≥50 y) receipt[a] (N = 82)	9 (11)—2 doses
	13 (16)—1 dose
Live zoster (≥60 y) (N = 38)	7 (18)
Positive measles IgG (N = 148)	130 (88)
Positive mumps IgG[b] (N = 147)	114 (78)
Positive rubella IgG[c] (N = 144)	130 (90)
Positive varicella IgG (N = 149)	143 (96)
Positive measles, mumps, and rubella IgG (N = 141)	95 (67)

[a] One <50 y got the vaccine (not counted).
[b] One equivocal not counted.
[c] Five equivocal not counted.
HepBsAb, hepatitis B surface antibody; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; Td, tetanus and diphtheria; Tdap, tetanus, diphtheria, and pertussis.

The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study was approved by Atrium Health Institutional Review Board, which granted a waiver of consent from study subjects.

RESULTS

A total of 155 KT candidates were evaluated during the study period. Five were evaluated twice, and thus, a total of 150 patients were included in the study (Tables 1 and 2). One hundred three (69%) patients were on dialysis, and the rest had advanced chronic kidney disease (stage 4 or 5). Eleven patients were undergoing simultaneous kidney-pancreas transplant evaluation, 8 were undergoing simultaneous kidney-liver transplant evaluation, and the rest were being evaluated for KT alone. Twenty-two (15%) of 150 patients had a history of prior transplant (2 liver, 1 heart, and 19 KTs) with 16 on immunosuppressive medications. A total of 30 (20%) had immunocompromising conditions or were on immunosuppressive medications, including 16 patients with history of prior transplantation (Table 1).

Prior immunization rates against Tdap, PCV13, and RZV were found to be low (Table 2). Only 9 (11%) of 82 patients ≥50 y had received 2 doses of RZV. Four additional patients ≥50 y had received a single dose of RZV. Seven (18%) of 38 patients ≥60 y (recommended vaccine age group for live zoster vaccine) had received live zoster vaccine. Three additional patients <60 y had also received live zoster vaccine. None of these 10 of 150 patients had received RZV. Twenty-four

(16%) had received any zoster vaccine (live zoster vaccine or a dose of RZV) among the cohort of 150 patients. Among 82 vaccine-eligible patients (≥50 y old for RZV and ≥60 y old for live zoster vaccine), a total of 16 (20%) had received either a live zoster vaccine or full RZV vaccine.

PPSV23 immunization rate was 67%. Among 100 patients who had been immunized against PPSV23, 60 patients had received the vaccine within 5 y or after 65 y old, 14 had received it between 5 and 10 y, and 1 had received it 10 y before evaluation in the TID clinic. Twenty-four patients had an unknown date of PPSV23.

Forty-four (30%) of 149 patients had a positive HepAIgG. It could not be determined whether these patients had a natural infection or had been vaccinated. Among 105 HepAIgG negative cases, at least 10 had received 1 dose of hepatitis A vaccine, 1 was a nonresponder (had received 2 doses), but a complete vaccination history was not available for the majority of patients. Ninety-nine (66%) patients had a positive HepBsAb, and 10 (10%) of these had a positive hepatitis B core antibody (including 1 with an active infection), implying a past infection. Among 51 patients with negative HepBsAb, 30 (59%) had received at least 1 dose of hepatitis B vaccine (including 7 who had completed 3 dose series and 5 nonresponders); 2 had declining antibody titer to a negative level (including 1 with positive core antibody); 2 had chronic hepatitis B infection; 1 was core antibody positive; and 1 had completed 3-dose series; however, HepBsAb was done before the completion of the 3-dose vaccine series. Most patients had positive MMR or varicella IgG, the lowest being 78% for mumps virus and highest 96% for varicella virus. Only 95 (67%) of 141 patients had a positive IgG against MMR viruses. Information on past immunization was not routinely available, and hence, whether the serologic immunity was due to vaccination or natural infection could not be determined.

Seven (5%) of 150 patients who underwent pretransplant evaluation in TID clinic had previously completed immunization against Tdap, PCV13, PPSV23, and RZV (latter among ≥50) and had positive HepAIgG, HepBsAb, MMR, and varicella IgG (or had history of complete vaccination or contraindications to vaccination in case of negative MMR and varicella serology). Of these 7 patients, 1 had a negative rubella IgG but had MMR vaccination a month earlier. Another patient <50 y old had a negative varicella IgG but was on mycophenolate for granulomatosis with polyangiitis thus precluding varicella administration. The remaining 143 patients were eligible for at least 1 vaccination. All vaccine-eligible patients were offered recommended vaccines except 4 patients with unknown Tdap status and 10 patients with negative HepAIgG who were not offered Tdap and hepatitis A vaccines, respectively. These patients, however, were offered other indicated vaccines. Five (3%) of 143 vaccine-eligible patients declined vaccination (Table 3). Out of 138 patients who agreed to get vaccinated, only 12 (9%) agreed for partial vaccination (Table 3). The reason for vaccine declination was not stated in most of the cases.

One hundred twenty-six (91%) of 138 patients (who accepted vaccination) received at least 1 dose of recommended vaccine in the TID clinic on the day of visit. Depending on the patients' preference, the remaining vaccination was either scheduled in the TID clinic at a future date or the patients were advised to get the vaccines through their primary care provider. Twelve (9%) vaccine-eligible patients did not get vaccination in the TID clinic but agreed to get them through their primary care provider. Out of these, 5 had already scheduled vaccination with their primary care provider, and 2 were getting transplanted soon and vaccination was deferred at the time of evaluation, but the patients agreed to get vaccinated through their primary care provider after transplantation.

Vaccination eligibility and acceptance against individual vaccines are summarized below:

1. Tdap: Among 95 Tdap-unvaccinated patients, 94 were eligible for vaccination (1 had contraindication). Ninety-two of them agreed to get vaccinated, and 2 declined. Four other patients who did not have information on prior Tdap vaccination were not offered Tdap but were offered other indicated vaccines.
2. PCV13: All 68 unvaccinated patients were eligible for PCV13 vaccination, and all except 1 agreed for vaccination.
3. PPSV23: All 50 unvaccinated were eligible for vaccination and all except 1 agreed for vaccination. In addition, 2 patients ≥65 who had received PPSV23 > 5 y prior were eligible and agreed for vaccination.
4. RZV: Seventy-three patients ≥50 y old were eligible. One of them was negative for varicella IgG and received varicella instead of RZV. Two declined vaccination.
5. Hepatitis A: Out of 105 with negative HepAIgG, 104 were considered eligible (1 had received full 2 doses vaccination). Ten of these patients were not offered hepatitis A vaccination but were offered other indicated vaccines. Fifteen (16%) of 94 patients who were eligible declined to get vaccinated. None of the simultaneous kidney-liver transplant candidates refused hepatitis A vaccination.
6. Hepatitis B: Fifty-one were HepBsAb negative. Eight were deemed ineligible for vaccination (5 nonresponders, 2 active infection, 1 had antibody test done before completion of hepatitis B series). All 43 eligible patients agreed for vaccination.
7. MMR: Fifty-two were negative for either measles, mumps, or rubella IgG. Twenty-one of them were ineligible for vaccination (8 were immunocompromised, 2 had impending transplant, 4 had a negative rubella serology but were of nonchildbearing age and deemed to be low risk and vaccination not offered, 7 had documented recent vaccination, or had a follow-up positive serology following 1 dose of MMR). Thirty-one patients were eligible, and 2 declined vaccination.
8. Varicella: Six had negative serology. Three of them were deemed ineligible (2 were immunocompromised, and 1 had a repeat serology that was positive). The remaining 3 eligible patients accepted vaccination.

DISCUSSION

This retrospective single-center study demonstrated low baseline rates of immunization and/or serological immunity against vaccine-preventable infections (tetanus, diphtheria, pertussis, *S. pneumoniae*, herpes zoster, hepatitis A, hepatitis B, and mumps) except measles, rubella, and varicella in a group of patients undergoing evaluation for KT. The disappointing low rate of RZV immunization is concerning, especially since the incidence of zoster in transplant patients is significantly higher compared with healthy adults.[15] In addition, varicella seropositivity was 96%, thus even bolstering the need for RZV to prevent reactivation. Zoster immunization (using live zoster vaccine or full-dose RZV) among all candidates irrespective of age was higher compared with 1

TABLE 3.

Vaccine refusal among eligible candidates

Patient	Recommended vaccines	Vaccines declined	Reason for declination
1	Hepatitis A	Hepatitis A	None
2	Tdap, PCV13, PPSV23, RZV, hepatitis A	Tdap, PCV13, PPSV23, RZV, hepatitis A	None
3	RZV	RZV	None
4	Hepatitis A	Hepatitis A	Wanted to think about it
5	Tdap, hepatitis A	Tdap, hepatitis A	Wanted to think about it
6	PCV13, PPSV23, Tdap, RZV, hepatitis A	Hepatitis A	None
7	Remaining hepatitis B series, hepatitis A, PCV13, RZV	Hepatitis A	None
8	Tdap, PCV13, PPSV23, hepatitis A	Hepatitis A	None
9	PPSV23, hepatitis A	Hepatitis A	None
10	Tdap, MMR, hepatitis A	Hepatitis A	None
11	Tdap, hepatitis A	Hepatitis A	None
12	Tdap, hepatitis A	Hepatitis A	None
13	Hepatitis A, varicella	Hepatitis A	None
14	MMR, Tdap, RZV	MMR	None
15	Tdap, hepatitis A, RZV	Hepatitis A	None
16	PCV13, MMR, hepatitis A, RZV, PPSV23	Hepatitis A	None
17	Tdap, remaining hepatitis B, hepatitis A, RZV, MMR	Hepatitis A, MMR	None

MMR, measles, mumps and rubella vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; RZV, recombinant zoster vaccine; Tdap, tetanus, diphtheria, and pertussis.

study (13% versus 7%) but was similar among vaccine recommended age groups when compared with a study done by Kasper et al (20% versus 24%).[11,12] Even PPSV23 immunization and HepBsAb seropositivity rates were only a meager 67% and 66%, respectively. Rates of Td without pertussis and or Tdap, PCV13, and PPSV23 immunization in our study were higher compared with that of most recent studies, whereas HepBsAb, measles, and varicella seropositivity rates were similar.[11-13,16] In a Brazilian study, the Td vaccination rate was 37% among 101 waitlisted KT candidates which is similar to our study.[17] However, in their study, only about 18%–66% of patients had a positive MMR, varicella serology, and/or vaccination.

It is important to note that HepBsAb was used as a marker of hepatitis B immunity, but some patients with positive HepBsAb likely had natural infection (especially those with positive hepatitis B core antibody) and are at risk for reactivation posttransplant. Conversely, patients who had initiated hepatitis B vaccination likely had negative HepBsAb, and a few patients despite completing vaccination series were nonresponders. Similarly, adequately vaccinated patients with negative MMR IgG could still have serological and T-cell immunity since commercial assays lack sensitivity in detecting all seroconversions. Although patients born before 1957 and 1980 could be considered immune against MMR and varicella, we required proof of prior vaccination or positive serology. This is in accordance with the American Society of Transplantation guidelines where MMR and varicella vaccination is recommended (unless contraindicated) in adult seronegative pretransplant candidates irrespective of their age.[8]

In our study, despite low rates of vaccination, vaccine uptake was strikingly high. It looks like most patients accept vaccination if offered. In contrast to the study by Schneider et al,[14] even live vaccine acceptance rates among eligible patients were high in our study (94% and 100% versus 7% and O for MMR and varicella, respectively). Almost all patients who accepted vaccination received at least 1 dose of the vaccine in the TID clinic on the day of visit. Since these patients were not followed up routinely, it is not clear whether they completed all remaining recommended vaccines. The value of Infectious Disease consultation or structured programs for screening and catch-up immunization in improving vaccination rates among KT candidates have been demonstrated in other studies, and this was further strengthened by our study.[12,13,18-20] Vaccine acceptance rate was as high as 99% in 1 study, whereas in others, despite ID consultation or structured catch-up immunization programs, there was only a modest increase in immunization rates.[12,13,18,20] We did not have data on reasons for refusal except for a few patients. It is noteworthy that hepatitis A vaccine refusal was common (refused by 15/17 patients who refused vaccination). Coincidentally, hepatitis A vaccine was also not recommended to 10 patents who were eligible for it. This might be due to low priority of hepatitis A vaccination compared with other vaccines. It should be noted that hepatitis A outbreaks can and have occurred in the United States, leading to declarations of public health emergency and transplant patients without immunity can be vulnerable to it.[21]

Barriers in immunization remain among KT candidates. Many studies have cited multifactorial causes of barriers to vaccination in solid organ transplants, including financial coverage for vaccination, fear of allograft rejection and other adverse effects, lack of knowledge and access to healthcare, vaccine unavailability, lack of coordination between transplant teams, low priority for vaccination, and late evaluation for vaccination (precluding use of live vaccines in those who are likely to get transplant soon).[16,17,22,23] Based on our study, intentional consultation of pre-KT recipients offers an opportunity to address potential barriers and maximize opportunity for immunization against vaccine preventable illnesses in a vulnerable population. Access to immunization in transplant specific clinics is another way of increasing immunization rates.[23] Digital health tools, including mobile apps, can also be used to serve as reminders or alerts for vaccination.[23,24]

There have also been a few significant changes in immunization recommendation in the United States since the study was conducted. At the time of the study, RZV was recommend to patients ≥50 y. In early 2022, Centers for Disease Control and Prevention expanded the indication to all adults ≥19 y who are immunocompromised or going to be immunocompromised.[10] Around the same time, 2 new pneumococcal conjugate vaccines (PCV15 and PCV20) were approved and recommended.[25] PCV20 is a single 1-time vaccine (without the need for PPSV23), and this might be more convenient to administer. The generalizability of RZV and convenience of PCV20 will likely increase overall vaccine uptake. We have already incorporated PCV20 and expanded use of RZV at our center.

Although this is a single-center study with some limitations as outlined below, one of the strengths of this study is that all potential KT recipients were evaluated in the TID clinic before transplantation at our center. This avoids bias in vaccine recommendation and uptake, which could have occurred if only selective patients had been referred to TID clinic. Nevertheless, a number of factors could have impacted the immunization and seropositivity rates in our study. The study was conducted during the early phase of COVID-19 pandemic when many health services, including immunization, were interrupted, and this could have lowered immunization rates.[26,27] However, previous studies also showed low immunization rates, and the rates of Tdap (or Td), PCV13, and PPSV23 immunization were higher in our study.[11-13,16] Moreover, most KT candidates have had kidney disease for several months to years providing a wider window of opportunity for immunization. Thus, the overall impact of COVID-19 pandemic on immunization was probably low, but without a comparative study with prepandemic immunization rates, this cannot be answered with certainty. RZV is a relatively new vaccine (approved in 2017 in the United States), and there was a shortage of the vaccine in the market around 2018, and this could have potentially impacted the vaccination rate. Our study looked at both live and inactive zoster vaccines and found low rates of immunization for both. Prior studies also showed low rates of previously available live zoster vaccination (RZV was not available at that time).[11,12] Patients could have had difficulty remembering which vaccines they had received, and medical records may not have complete information on prior vaccination. This can erroneously result in low vaccination rates. We did not require written documentation of prior vaccination except for MMR and varicella. In 1 study of solid organ transplant candidates, vaccine serology was found to be more reliable than vaccine history as illustrated by 88% transplant candidates who had a protective tetanus antibody compared with only 24% who recalled having a prior tetanus vaccine.[18] We also did not have access to childhood vaccination records (especially of MMR and varicella), and our electronic medical records carried information since 2010 only. Another limitation of the study was unavailability of outcome data on vaccinated versus unvaccinated KT candidates who eventually got transplanted.

In summary, KT candidates have low rates of immunization against recommended vaccines or are seronegative and thus, remain vulnerable to vaccine preventable diseases. On a positive note, we observed higher immunization rates, although still below a desirable level against Td or Tdap, PCV13, and PPSV23 compared with recent studies. Measles, rubella, and varicella seropositivity remains high, and positive HepBsAb rate appears similar to other studies. Importantly, vaccine uptake among eligible KT candidates was high except for hepatitis A vaccine (likely due to low prioritization of hepatitis A vaccination). Routine pretransplant evaluation of KT candidates at TID clinic provides a needed opportunity to improve vaccination and protection against preventable disease among those undergoing renal transplantation.

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