Immunogenicity of Human Papillomavirus Recombinant Vaccine in Children with CKD

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Abstract

Background and objectives There is a disproportionate burden of human papillomavirus (HPV) –related genital tract disease in patients with CKD and kidney transplantation; therefore, the potential effect of the quadrivalent HPV vaccine (Gardasil; Merck GmbH, Darmstadt, Germany) is profound. Immune abnormalities associated with CKD and immunosuppression may prevent optimal vaccine response. Our objective was to determine antibody response to the HPV vaccine in adolescent girls with CKD.

Design, setting, participants, & measurements This cohort study conducted from 2008 to 2012 included 57 girls aged 9–21 years old with CKD (n=25), on dialysis (n=9), or with status postkidney transplantation (n=23) who received the standard three–dose vaccine series of the HPV vaccine recruited from two pediatric nephrology clinics. Antibody levels to HPV genotypes 6, 11, 16, and 18 were measured before vaccine dose 1 (baseline), <12 months after vaccine dose 3 (blood draw 2), and ≥12 months after vaccine dose 3 (blood draw 3). Seropositivity was defined as antibody level above an established threshold for each HPV genotype. Not all participants completed three blood draws.

Results Antibody response to all four HPV genotypes was 100% in the CKD and dialysis groups with samples drawn at <12 and ≥12 months after dose 3 of the HPV vaccine. Among patients with transplants, the percentages of patients achieving seropositivity were significantly lower at blood draw 2 for HPV genotypes 6 (63.6%; P=0.003), 11 (63.6%; P=0.003), and 18 (72.7%; P=0.02) and blood draw 3 for HPV genotypes 6 (62.5%; P=0.02), 11 (50%; P=0.001), 16 (75%; P=0.04), and 18 (50%; P=0.001).

Conclusions Antibody response to the quadrivalent recombinant HPV vaccine was robust and sustained in girls and young women with CKD and on dialysis. A less robust response to the vaccine was observed among those with a kidney transplant. Additional study is needed to determine if vaccination before kidney transplantation or an alternative vaccination regimen would benefit transplant recipients.

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Introduction

Cervical cancer is the second most common cancer in women worldwide (1). There were 12,109 new patients and 4902 deaths in 2011 attributed to cervical cancer in the United States. Infection with human papillomavirus (HPV) is the first step in the development of cervical cancer. HPV genotypes 16 and 18 are responsible for 70% of cervical cancers. HPV genotypes 6 and 11 are responsible for 90% of anogenital warts and a significant proportion of precancerous lesions (2,3).

The burden of all types of HPV-related disease is substantially greater in kidney transplant recipients (4,5). Viral warts have been described in ≤85% of kidney transplant recipients 5 years after transplantation (6). In a study examining the rates of malignancies among first–time women kidney transplant recipients from 1995 to 2001 (7), there was a sixfold increase in the likelihood of cervical cancer and a fivefold increase in the likelihood of vulvovaginal cancers by the second year post-transplant compared with in the general population of women . In the same analysis, risk of HPV-related cancers among those with ESRD on the transplant waiting list was compared with transplant recipients with similar results: cervical cancer relative risk, 1.28; 95% confidence interval (95% CI), 0.48 to 3.36 and vulvovaginal cancer relative risk, 2.19; 95% CI, 0.67 to 7.12. The risk of HPV-related cancers is, therefore, increased in both the later stages of CKD and after kidney transplantation.

A noninfectious, recombinant quadrivalent vaccine (Gardasil; Merck GmbH, Whitehouse Station, New Jersey) composed primarily of virus-like particles (VLPs) of the major capsid (L1) protein of HPV types 6, 11, 16, and 18 is licensed for men and women 9–26 years of age (8). Delivered at 0, 2, and 6 months, the HPV vaccine induces a polyclonal antibody response directed against specific conformational and linear epitopes displayed on the VLP. Immunogenicity studies of >4000 healthy girls and women 9–26 years of age have shown >99% seropositivity to the four HPV genotypes included in the HPV vaccine.

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Given the increased burden of HPV-related disease among women and girls with CKD, the potential of the HPV vaccine to prevent genital tract disease is substantial. However, hyporesponsiveness to several vaccines has been described in children with CKD (9–16). In this study, we examine the immunogenicity of the quadrivalent HPV vaccine in girls with CKD, ESRD, or kidney transplants.

Materials and Methods

Study Participants

All girls attending the pediatric nephrology clinics at Johns Hopkins and The Children's Healthcare of Atlanta were screened for eligibility from October of 2008 to October of 2010. Inclusion criteria included those ages 9–21 years old with CKD, dialysis dependence, or a history of kidney transplantation. Patients naïve to the vaccine and those who had been previously vaccinated or started the vaccination series with their primary care physician within 2 years before the enrollment period were eligible for inclusion. CKD was classified as stages 1–5 using National Kidney Foundation criteria on the basis of eGFR. GFR was estimated using the bedside Chronic Kidney Disease in Children Equation (17) for those <18 years old and the Chronic Kidney Disease Epidemiology Collaboration Equation (18) for those ≥18 years old. Kidney disease status (CKD, dialysis, or transplant) was assigned on completion of three vaccine series. The underlying diagnoses of CKD were categorized into three groups: (*1*) glomerular, (*2*) nonglomerular, and (*3*) unknown.

Exclusion criteria included children with known hypersensitivity to any components of the vaccine. Participants were not vaccinated within 3 months of kidney transplantation or treatment for a kidney transplant rejection episode per standard of care. Written consent was provided by patients or their caretakers if the participant was a minor. This study was approved by the institutional review boards of both clinical centers and adhered to the Declaration of Helsinki, and the clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

Study Protocol

Each dose of HPV vaccine was delivered as closely as possible to the recommended three–dose schedule at 0, 2, and 6 months. If vaccinations had been previously given at the primary care physician's office, the dates of vaccination were verified. To determine immunogenicity, three blood draws occurred at regularly scheduled clinic visits. The first was obtained immediately before vaccine 1 (blood draw 1), the second (blood draw 2) was obtained 1–12 months after completion of the vaccination series, and the third (blood draw 3) was obtained 12–35 months after completion of the vaccine series (Figure 1). Some patients did not complete all three blood draws because of (*1*) previous vaccination at primary care physician's office, which precluded blood draws 1 and/or 2; (*2*) inconsistent clinic visits, which precluded the second or third blood draw; and/or (*3*) administrative censoring in July of 2012. To be included for analysis, patients had to complete the three–dose vaccine series and have at least one blood draw after vaccination (blood draw 2 or 3). Patient data, including diagnosis, time with CKD, height, weight, creatinine, age, race, immunosuppressant regimen, and interval events, were collected at the time of vaccination and each blood draw. In our analysis, immunosuppressant use was defined on the basis of the medication regimen at the time of vaccine 1. Prednisone exposure was examined as milligrams per kilogram per day. Mycophenolate mofetil exposure was examined as milligrams per body surface area per day. Tacrolimus and sirolimus exposure were examined using troughs nearest to the time of vaccine 1. If the patient was vaccinated before entering the study, patient information nearest to the time of vaccination was extracted from the medical record (<30 days from vaccine 1; median =0 days).

Outcomes

The primary outcome was antibody response to each of four HPV genotypes contained within the HPV vaccine at the time periods specified for the blood draws as outlined above. Antibody levels, measured by Merck GmbH, were initially determined using the competitive Luminex immunoassay (cLIA; Merck GmbH), the assay used in the original licensing studies. Seropositivity was defined as being above thresholds set at 20, 16, 20, and 24 milliMerck units for HPV genotypes 6, 11, 16, and 18, respectively, as determined in phase 2 studies among patients who were immunocompetent (19).

Antibody levels were reanalyzed using the IgG cLIA in stored serum from blood draws 2 and 3. Seropositivity for this assay was defined as being above thresholds set at 15, 15, 7, and 10 milliMerck units for HPV genotypes 6, 11, 16, and 18, respectively.

Secondary analyses evaluated the association of immunosuppressant medication with antibody response and the association of time from initiation of dialysis or time from transplantation with antibody response. Sensitivity analyses included exclusion of patients who took >1 year to complete the vaccine series (n=9).

Statistical Analyses

Data were analyzed using STATA v13.1 (Statacorp., College Station, TX) (20). Covariates of interest included age (as a continuous variable and a dichotomous variable of <16 or ≥16 years old), race (white, black, or other), CKD status (CKD, dialysis, or transplant), CKD stage, three–vaccine immunization series completed within 1 year (yes or no), time from transplant (>1 or <1 year), CKD diagnosis (glomerular, nonglomerular, or unknown), and both number and dose of immunosuppressant medications. Fisher exact test and chi-squared test were used to compare categorical variables for descriptive statistics. Univariate and multivariate logistic regressions were performed to assess the influence of covariates on IgG antibody response at both blood draws 2 and 3. IgG antibody titers were logarithmically transformed and represented graphically with boxplots. Boxplots show differences in antibody response between patients with CKD, on dialysis, and with transplants at both blood draws 2 and 3, and comparisons were made using the Wilcoxon rank sum (Mann–Whitney) test. Geometric mean titer (GMT) was calculated using cLIA antibody levels. If an antibody level

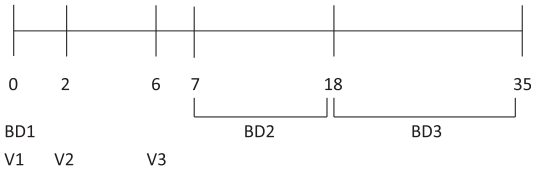

Figure 1. | Study protocol timeline (months). BD, blood draw; V, vaccine.

was below the lower limit of detection, the median between zero and the lower limit of detection was substituted; 9%–18% of antibody titers fell below the level of detection depending on genotype and blood draw. The Wilcoxon rank sum (Mann–Whitney) test was also used to compare GMTs of the CKD, dialysis, and transplant groups with the healthy population from licensing data that were used the cLIA (8).

Univariate and multivariate linear regressions were used to examine the relationship between tacrolimus trough, mycophenolate mofetil dose, prednisone dose, and IgG antibody response. Chi-squared and Fisher exact tests were used to compare IgG antibody response between patients with CKD, on dialysis, and with transplants.

Results

Of 67 patients enrolled, 57 patients completed the three-vaccine series and had at least one blood draw after vaccination (Figure 2). Baseline patient characteristics are shown in Table 1.

Among 44 patients with a prevaccine blood draw, 41 were seronegative to all four HPV genotypes contained in the vaccine. Three patients (two patients with CKD and one patient with a transplant) were seropositive to one of the HPV genotypes included in the vaccine, indicating previous exposure to the virus genotype.

Blood draw 2 occurred at a median of 3.6 months after vaccination (n=49). Seropositivity to all four HPV genotypes was observed in all participants with CKD or on dialysis using the IgG assay. Among patients with transplants (n=22), 63.6% were seropositive for HPV 6, 63.7% were seropositive for HPV 11, 100% were seropositive for HPV 16, and 72.7% were seropositive for HPV 18. Blood draw 3 occurred at a median of 20.7 months (n=32). The percentage of patients achieving seropositivity using the IgG assay was 100% for all genotypes in patients with CKD and patients on dialysis; however, patients with transplants (n=8) showed a less robust antibody response, with antibody response as follows: HPV 6, 62.5%; HPV 11, 50%; HPV 16, 75%; and HPV 18, 50%. Race, CKD stage, time from transplant, and number of immunosuppressant medications were not associated with achievement of seropositivity among patients with a transplant at blood draw 2 (n=22) or blood draw 3 (n=8; all P values >0.25). Previous studies have shown higher GMTs in adolescent patients (10–15 years old) compared with young women (16–23 years old) (21); Table 2, therefore, includes the results stratified by age. The analysis was limited by the small sample size, but there was not a statistically significant difference between patient's ages 9–15 and 16–21 years old at the time of first vaccination.

The distribution of IgG antibody levels at blood draws 2 and 3 by vaccine genotype and CKD status are shown in Figure 3. There were no significant differences in antibody titers between patients with CKD and patients on dialysis at blood draw 2, with the exception of lower titers in dialysis patients compared with CKD for HPV genotype 6 (P=0.05). IgG antibody titers were significantly lower in patients with transplants compared with patients with CKD for HPV genotypes 6 (CKD: median =277; interquartile range [IQR], 109–1154; transplant: median =117; IQR, 5.5–511; $P<0.01$), 11 (CKD: median =673; IQR, 473–1140; transplant: median =167; IQR, 15–809; P=0.01), 16 (CKD: median =2696; IQR, 1230–3922; transplant: median =627; IQR, 5.5–1977; $P<0.01$), and 18 (CKD: median =348; IQR, 167–856; transplant: median =30; IQR, 5–344; P=0.004) and compared with patients on dialysis for HPV genotypes 6 (dialysis: median =272; IQR, 151–1647; transplant: median =117; IQR, 5.5–511; P=0.02), 11 (dialysis: median =638; IQR, 278–1745; transplant: median =167; IQR, 15–809; P=0.04), 16 (dialysis: median =2637; IQR, 1412–5882; transplant: median =627; IQR, 5.5–1977; P=0.03), and 18 (dialysis: median =348; IQR, 167–856; transplant: median =30; IQR, 5–344; $P<0.01$) at blood draw 2. Analysis at blood draw 3 showed significantly lower antibody titers in patients on dialysis versus patients with CKD for all HPV genotypes ($P\leq0.05$) and patients with CKD versus patients with transplants for HPV 18 (P=0.05); however, given the small sample size, these results should be interpreted with caution.

cLIA GMTs of participants in this study were compared with GMTs of healthy girls and women from the vaccine licensing studies (cLIA) (Table 3) (8). Data are shown for two age groups, 9–15 and ≥16 years old, consistent with the original licensing study of healthy girls and women. Compared with healthy patients, GMTs were lower in all groups, but this only achieved statistical significance in patients with transplants at blood draw 2 (P=0.02 for both 9- to 15-year-old and 16- to 26-year-old girls and women). The lack of a statistically significant difference in the GMTs at blood draw 3 compared with the healthy population may be because of the small sample size.

Patients who completed both blood draws 2 and 3 (n=24) were examined to assess persistence of IgG antibody response. The mean length of time between blood draws 2 and 3 was 15.8 months. Of 14 patients with CKD and three patients on dialysis, all maintained antibody levels above the established threshold for seropositivity. Of seven kidney transplant recipients, one lost antibody response.

Immunosuppression, defined as medications at vaccine 1 (prednisone, tacrolimus, sirolimus, cyclosporin, mycophenolate mofetil, abatacept, or leflunomide), is shown in Table 1. One patient with a transplant and post–transplant lymphoproliferative disorder was not on immunosuppression. Of three patients on sirolimus, all had antibody levels above the established threshold for seropositivity. One patient who received abatacept was seronegative for all HPV genotypes at both blood draws 2 and 3. One patient with a transplant on cyclosporin had antibody response at blood draw 2 and did not complete blood draw 3. Of 20 patients who were on tacrolimus at vaccine 1, troughs within 1 month of vaccination were available for 18 patients (15 patients with transplants, two patients on dialysis, and

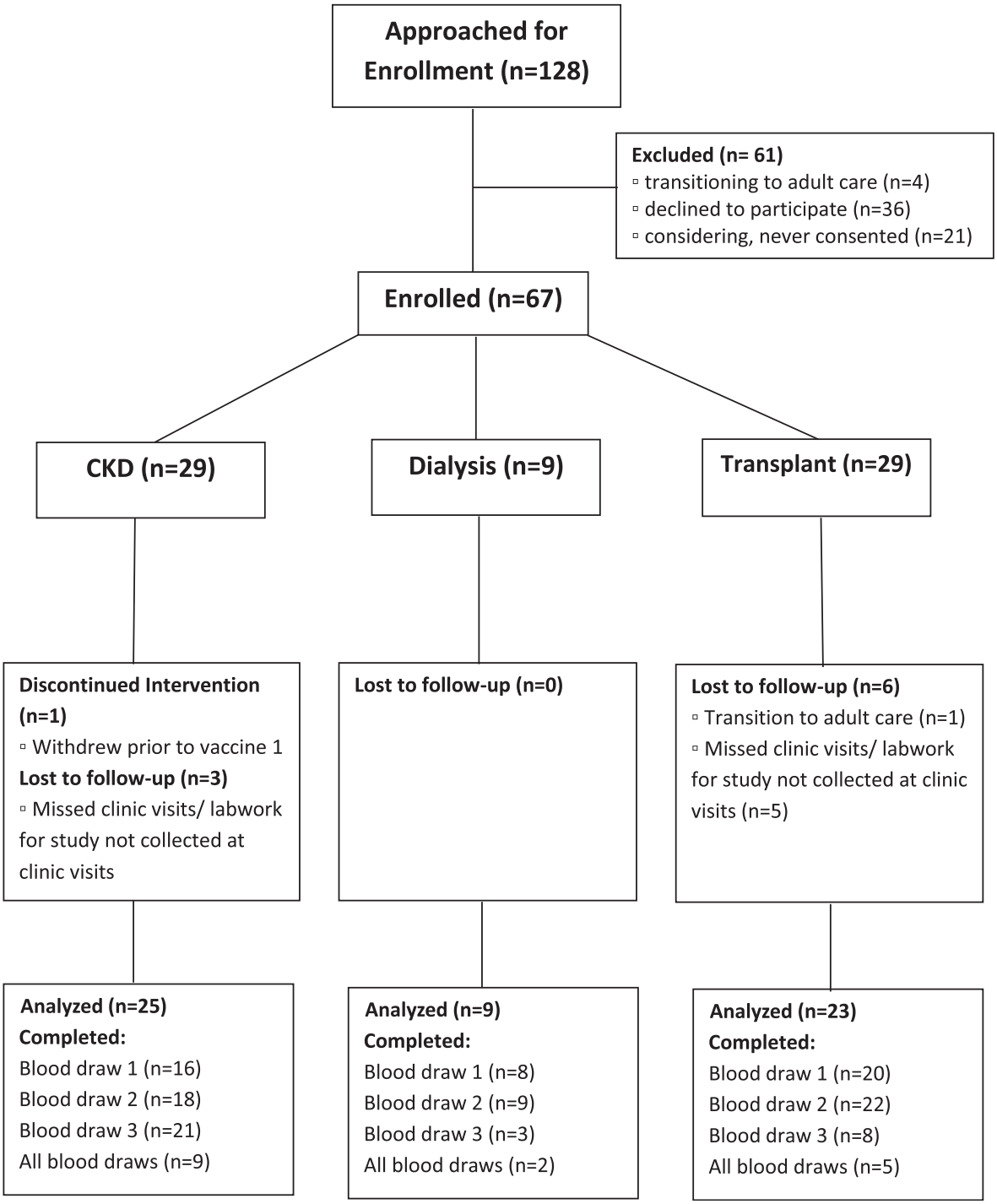

Figure 2. | **Study flowchart.**

one patient with CKD) at blood draw 2 and five patients (four patients with transplants and one patient with CKD) at blood draw 3. Among patients on tacrolimus during vaccination, at blood draw 2 (n=18), seropositive patients had tacrolimus troughs, on average, 1.3 mg/dl lower than those in seronegative patients (P=0.30; 95% CI, −4.0 to 1.3), and at blood draw 3 (n=5), seropositive patients had troughs, on average, 2.3 mg/dl lower than those in seronegative patients (P=0.05; 95% CI, −4.5 to <0.01). There was no change in inference when patients with transplants were examined as a separate group or after adjusting for time from transplant. No association was seen between baseline prednisone dose (milligrams per kilogram per day) or mycophenolate mofetil dose (milligrams per body surface area) and seropositivity at blood draws 2 or 3.

Nine patients completed the vaccine series over >12 months, one of whom did not have an IgG antibody level

Table 1. Baseline characteristics

Characteristic	CKD, *n*=25	Dialysis, *n*=9	Transplant, *n*=23
Mean age (range), yr	15.2 (11–21)	15.3 (12–18)	16.8 (11–21)
Race			
White	12 (48%)	2 (22%)	14 (61%)
Black	10 (40%)	4 (44%)	6 (26%)
Other	3 (12%)	3 (33%)	3 (13%)
CKD stage[a]			
1	8 (32%)	N/A	5 (22%)
2	5 (20%	N/A	9 (39%)
3	10 (40%)	N/A	7 (30%)
4	2 (8%)	N/A	1 (4%)
5	0	9 (100%)	1 (4%)
Dialysis			
Hemodialysis	N/A	4 (44%)	N/A
Peritoneal dialysis	N/A	5 (56%)	N/A
Baseline immunosuppression[b]	6 (24%)	4 (44%)	22 (96%)
Average no. of medications	0.24	0.9	2.5
Prednisone	1 (4%)	4 (44%)	19 (83%)
Tacrolimus	1 (4%)	2 (22%)	17 (74%)
Rapamycin	0	1 (11%)	3 (13%)
Cyclosporin	2 (8%)	0	1 (4%)
Mycophenolate mofetil	2 (8%)	1 (11%)	15 (65%)
Abatacept	0	0	1 (4%)
Leflunomide	0	0	1 (4%)
Diagnosis			
Glomerular	15 (60%)	3 (33%)	8 (35%)
Nonglomerular	10 (40%)	3 (33%)	13 (56%)
Unknown	0	3 (33%)	2 (9%)
Time from transplant/dialysis, mo			
Median	N/A	8	29
Range		0–60	0–163
≤12		5 (56%)	6 (26%)

Data shown as *n* (%), unless otherwise indicated. N/A, not applicable.
[a]CKD stage by the National Kidney Foundation definition of eGFR: stage 1, ≥90 ml/min per 1.73 m^2; stage 2, 60–89 ml/min per 1.73 m^2; stage 3, 30–59 ml/min per 1.73 m^2; stage 4, 15–29 ml/min per 1.73 m^2; and stage 5, <15 ml/min per 1.73 m^2.
[b]Immunosuppression is defined by the immunosuppressant medication at vaccine 1: prednisone, tacrolimus, cyclosporin, mycophenolate mofetil, or rapamycin.

above the threshold for HPV 6 genotype at blood draw 2 (transplant). Sensitivity analyses excluding these nine patients did not change our results.

Adverse reactions included pain (*n*=8) and bruising (*n*=1) at the injection site and headache postinjection (*n*=2). One patient with a transplant developed acute rejection while receiving the vaccine series (between vaccines 2 and 3) at 10 months post-transplantation. Another patient with a transplant developed rejection 1 month after completion of vaccination (at 4 months post-transplantation). This rejection rate of 8.6% (2 of 23 transplant recipients) is similar to nationally reported North American Pediatric Renal Trials and Collaborative Studies data (2011) (22) and suggests no increased risk of rejection in this cohort.

Discussion

Given the disproportionate burden of HPV–related genital tract disease in patients with advanced CKD or kidney transplantation, the potential effect of an effective HPV vaccine in this vulnerable population is profound. In this study, all of those with CKD or on dialysis achieved seropositivity to all four genotypes of the vaccine, and this response was sustained >12 months from completion of the vaccine series. In contrast, patients with kidney transplants showed lower GMTs, and a lower percentage of patients with transplants was seropositive. Immunosuppressive medications likely contribute to decreased antibody response. This hypothesis is supported by the observation that patients with transplants and antibody response had lower tacrolimus troughs; this achieved statistical significance at blood draw 3, which was >12 months after vaccination.

The HPV vaccine was first licensed for use in 2006 and is currently recommended for girls, women, boys, and men ages 9–26 years old to prevent disease associated with HPV genotypes 6, 11, 16, and 18 (8). Studies in healthy individuals show a robust antibody response, with >99% of girls becoming seropositive to each genotype after vaccination (19). Efficacy trials have also shown excellent results. A phase 3 randomized, controlled trial (the

Table 2. Percentage of patients achieving seropositivity (IgG assay) at blood draws 2 and 3

HPV Genotype	CKD		Dialysis		Transplant[a]		*P* Value[b]	
	9–15 yr	16–21 yr	9–15 yr	16–21 yr	9–15 yr	16–21 yr	9–15 yr	16–21 yr
BD2								
HPV 6								
n	10/10	8/8	6/6	3/3	7/8	7/14	0.35	0.02
Percentage (95% CI)	100 (69 to 100)	100 (63 to 100)	100 (54 to 100)	100 (29 to 100)	88 (47 to 100)	50 (23 to 77)		
HPV 11								
n	10/10	8/8	6/6	3/3	6/8	8/14	0.11	0.05
Percentage (95% CI)	100 (69 to 100)	100 (63 to 100)	100 (54 to 100)	100 (29 to 100)	75 (35 to 97)	57 (29 to 82)		
HPV 16								
n	10/10	8/8	6/6	3/3	8/8	14/14	N/A	N/A
Percentage (95% CI)	100 (69 to 100)	100 (63 to 100)	100 (54 to 100)	100 (29 to 100)	100 (63 to 100)	100 (77 to 100)		
HPV 18								
n	10/10	8/8	6/6	3/3	7/8	9/14	0.35	0.09
Percentage (95% CI)	100 (69 to 100)	100 (63 to 100)	100 (54 to 100)	100 (29 to 100)	88 (47 to 100)	64 (35 to 87)		
Median (IQR) time to BD2, mo	4.5 (2.6–7.4)		1.3 (1.1–2.7)		3.2 (2.5–4.4)			
BD3								
HPV 6								
n	11/11	10/10	2/2	1/1	3/5	2/3	0.05	0.14
Percentage (95% CI)	100 (72 to 100)	100 (69 to 100)	100 (16 to 100)	100 (3 to 100)	60 (15 to 95)	67 (9 to 99)		
HPV 11								
n	11/11	10/10	2/2	1/1	3/5	1/3	0.05	0.01
Percentage (95% CI)	100 (72 to 100)	100 (69 to 100)	100 (16 to 100)	100 (3 to 100)	60 (15 to 95)	33 (1 to 91)		
HPV 16								
n	11/11	10/10	2/2	1/1	4/5	2/3	0.25	0.14
Percentage (95% CI)	100 (72 to 100)	100 (69 to 100)	100 (16 to 100)	100 (3 to 100)	80 (28 to 99)	67 (9 to 99)		
HPV 18								
n	11/11	10/10	2/2	1/1	3/5	1/3	0.05	0.01
Percentage (95% CI)	100 (72 to 100)	100 (69 to 100)	100 (16 to 100)	100 (3 to 100)	60 (15 to 95)	33 (1 to 91)		
Median (IQR) time to BD3, mo	22 (17.8–23)		18.3 (17.4–22.6)		19.5 (18.6–21.2)			

BD2, blood draw 2; HPV, human papillomavirus; 95% CI, 95% confidence interval; N/A, not applicable; IQR, interquartile range; BD3, blood draw 3.

[a]No significant difference in achievement of seropositivity between age groups for any HPV genotype.

[b]*P* value for difference in percentage response between CKD, dialysis, and transplant by HPV genotype.

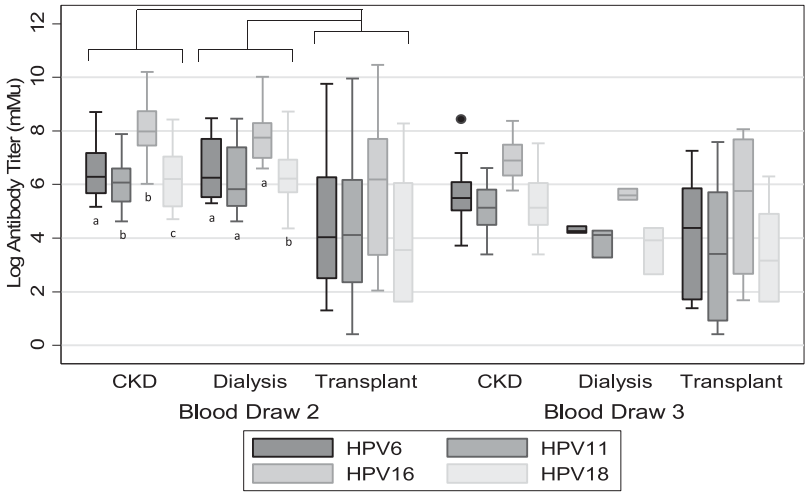

Figure 3. | **Boxplot of logarithmically transformed IgG antibody titers by CKD status at blood draws 2 and 3.** Whiskers represent the 25th and 75th percentiles + (1.5× interquartile range). Antibody levels in patients with transplants are compared with those in patients with CKD and patients on dialysis for human papillomavirus (HPV) genotypes 6, 11, 16, and 18. There was no statistically significant difference between patients with CKD and patients on dialysis, with the exception of lower levels in patients on dialysis compared with in patients with CKD for HPV genotype 6 (P=0.05). Letters indicate P values compared with patients with transplants. [a]$P \leq 0.05$; [b]$P \leq 0.01$; [c]$P < 0.01$.

Table 3. Geometric mean titers (competitive Luminex immunoassay in milliMerck units) at blood draws 2 and 3 in study participants compared with the healthy cohort

HPV Genotype	9–15 yr				16–26 yr			
	CKD	Dialysis	Transplant[a]	Healthy	CKD	Dialysis	Transplant[a]	Healthy
HPV 6								
BD2	236 (n=10)	877 (n=6)	154 (n=8)	929 (n=917)	452 (n=8)	103 (n=3)	52 (n=13)	545 (n=3329)
BD3	323 (n=11)	44 (n=2)	79 (n=5)	156 (n=214)	495 (n=10)	48 (n=1)	56 (n=3)	109 (n=2788)
HPV 11								
BD2	572	1226	222	1304	1000	337	72	749
BD3	355	75	107	218	204	56	46	137
HPV 16								
BD2	2093	5916	409	4918	2871	1340	137	2409
BD3	1759	417	156	944	1104	352	133	442
HPV 18								
BD2	317	1032	61	1043	429	199	36	475
BD3	193	34	38	138	71	5	25	51

Competitive Luminex immunoassay used as general population (healthy) data from the licensing study was done using the competitive Luminex immunoassay (8). HPV, human papillomavirus; BD2, blood draw 2; BD3, blood draw 3.
[a]Wilcoxon rank sum test of differences in geometric mean titers: P=0.02 for patients with transplants versus healthy patients at BD2 for both 9- to 15-year-old and 16- to 26-year-old patients, P=0.06 for patients with transplants versus healthy patients at BD3 for 9- to 15-year-old patients, and P=0.15 patients with transplants versus healthy patients at BD3 for 16- to 26-year-old patients.

Future I Trial) (23) following >5000 women (>2000 vaccinated) for an average of 3 years found no vulvar, vaginal, or cervical HPV–associated lesions. Another paper analyzed the results of two large randomized, controlled trials for efficacy against low–grade cervical, vaginal, and vulvar neoplasia (24) and found 94%–100% efficacy at 42 months of follow-up.

Studies have shown defects in neutrophil function, antigen processing, antibody formation, and cell–mediated immune responses in patients with CKD (25–27), and hyporesponsiveness to several vaccines have been described in children with CKD (9–16). However, other vaccines in patients with CKD, such as varicella (28,29), have shown responses similar to those in the general population.

Two prior studies examining antibody response to the HPV vaccine in kidney transplant recipients showed mixed results. In 2014, a study initiated vaccination in 14 kidney transplant adolescents. Of the seven who completed the

vaccine series all showed antibody response (30). However, six of 14 enrolled developed acute rejection after initiation of the vaccine series; this unexpectedly high rejection rate led to early termination of the study. In our study, only two of 23 patients with transplants developed acute rejection. In a study of 50 adult patients with transplants (60% kidney transplants) (31), seropositivity values to HPV genotypes 6, 11, 16, and 18 were 63.2%, 68.4%, 63.2%, and 52.6%, respectively, similar to rates of antibody response observed in our study.

We used the results of the cLIAs when comparing our data with the previously published healthy population data, whereas the IgG assay was used for the remainder of our analyses. The cLIA is an mAb that measures neutralizing antibodies against a single neutralizing epitope (32). The major disadvantage of cLIA is that it measures only the subset of neutralizing antibodies that competes with the cLIA mAb for VLP surface binding. A potentially protective immunogenic response dominated by VLP binding antibodies that do not compete with the cLIA mAb would not be detected (2,33,34). The IgG Luminex immunoassay (Merck GmbH) is an alternative assay to detect antibodies to immunodominant epitopes not recognized by the mAb, thereby increasing the ability to capture patients with antibody response.

Limitations of this study include small sample size and missing blood draws in some participants. Nevertheless, this is the largest study to date to examine antibody response to HPV vaccination among a population of adolescents with CKD. Lack of baseline antibody levels for some patients is also a limitation; however, a very low prevalence of prevaccination HPV exposure to HPV genotypes 6, 11, 16, and 18 was observed in those patients with baseline data. It is also important to note that patients with transplants who have responded to the quadrivalent HPV vaccine may continue to have higher risk of HPV-related morbidity because of complications from HPV strains not included in the vaccine (35) and β-HPVs (36).

In conclusion, the antibody response to the quadrivalent recombinant HPV vaccine among girls and young women with CKD or on dialysis was robust and sustained after vaccination. Among those with kidney transplants, the response was less robust, with only two thirds of participants who were transplanted developing an antibody level above the threshold for seropositivity to vaccine genotypes 6, 11, and 18 (100% to HPV 16 at blood draw 2). Our findings suggest that girls and women with kidney transplants may require an alternative vaccine regimen to achieve effective protection from infection with HPV genotypes 6, 11, 16, and 18. Larger trials and efficacy studies in this at-risk population are warranted, including studies to determine if vaccination before transplantation confers better protection.

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Disclosures

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