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Research Article

Acceptance of HPV Vaccination in Kidney Transplant Recipients

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Abstract

***Background*:** Human Papilloma virus (HPV) infections are an increasingly concerning etiology for post-transplantation viral-related malignancies. The nonavalent HPV vaccine (Gardasil 9) affords transplant recipients the best opportunity for malignancy prevention, but vaccine

uptake remains low. Not previously reported for solid organ transplant recipients, we studied influential factors for HPV vaccine non-initiation.

***Methods*:** This survey, conducted from May to December 2017, examined influential factors for HPV vaccine non-initiation. Post-survey we provided brief, informal education on the risks and benefits of HPV vaccination.

***Results*:** Of the 164 patients approached for the study, 157 participated and 154 completed the survey resulting in a 95% response rate. Thirty-two percent of patients within the United States Food and Drug Administration (FDA) approved age range had started or completed the HPV vaccine series at survey administration. The most significant reason for HPV vaccine non-initiation among these kidney transplant patients was a reduced physician recommendation. In addition, HPV vaccine series initiation improved from 32% pre-survey to 62% post-survey.

***Conclusions*:** HPV vaccination uptake remains low in kidney transplant patients. Emphasis on physician recommendation of HPV vaccination will reduce vaccine non-initiation rates.

Keywords

Kidney transplantation; human papillomavirus; immunosuppression; malignancy

1. Introduction

Transplantation remains the treatment of choice for patients with end stage kidney disease. While newer and stronger immunosuppression has led to better graft and patient survival, viral infections and viral-related malignancies have increased. Consistent evidence supports a 2-fold higher incidence of malignancies in solid organ transplant recipients [1].

Previous studies in adult transplant recipients have shown virus related cancers are common post-transplantation [2]. Engels et al using data from the U.S. Transplant Cancer Match Study, identified significantly elevated standardized incidence ratios (SIR) for cancers of the oropharynx, anus, vulva, and penis [1]. Molecular evidence attributed these same cancer subsets to human papillomavirus (HPV) [3]. Subsequently, Madeleine et al explored the relationship between immunosuppression and HPV-related cancers. SIRs ranged from three-fold higher for cervical cancers to 20-fold for vulvar and penile cancers [4]. An increased incidence was found for those transplanted at a younger age along with patients who received multiple transplants and therefore a higher cumulative immunosuppression history.

Adult kidney transplant recipients echo 2- to 3-fold cancer incidence rates as compared with the general population [1]. However, cancer risk is less delineated in kidney transplant recipients during childhood. A recent study from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) showed increased incidence of viral-related cancers in these patients. Compared with the general population, childhood kidney transplant recipients had an 8-fold increased risk of nonskin cancers. Importantly, the magnitude of increased risk for cervical cancer in women who received a kidney transplant as a child (SIR 29.4), was substantially higher than adult female transplant recipients (SIR 3). This finding reiterates the cumulative risk of immunosuppression, but also illustrates that women transplanted as a child are more likely to be

immunosuppressed at their first HPV encounter. In their immunosuppressed state, they are less likely to clear the infection, and are more likely to develop cancer [5].

Malignancy is now one of the most common causes of death in kidney transplant recipients [6]. Given that HPV infection and subsequent associated cancers are potentially preventable, the 2013 Infectious Disease Society of America developed clinical practice guidelines for HPV-vaccination of the immunocompromised host. These guidelines provide a strong recommendation to vaccinate 11-26 year old male and female solid organ transplant recipients [7]. The United States Food and Drug Administration (FDA) has approved three HPV vaccines: Gardasil, Cervarix, and Gardasil 9.

Cervarix, a bivalent vaccine approved for females between the ages of 10 and 25 years, provided protection against two high risk HPV serotypes 16 and 18. These serotypes were responsible for approximately 70% of cervical cancer cases. Since late 2016, Gardasil 9 is the only HPV vaccine available in the United States. Gardasil 9 is a FDA approved recombinant 9-valent HPV vaccine licensed for men and women 9-26 years of age. It expands coverage to include 9 HPV strains, which are associated with cervical cancer, anal cancer, and throat cancer, as well as serotypes responsible for most genital warts and HPV associated ano-genital diseases [8].

Routine HPV vaccination is recommended at ages 11 or 12 years as optimal efficacy occurs if it is given prior to infection. Kidney transplant recipients should receive the 3-dose series (0, 1-2, and 6 months) [9]. Patients not completing the series prior to transplant may receive additional doses beginning three to six months following transplantation; however, preliminary studies suggest poor immunogenicity 12 months post vaccination if given after transplant [10]. In lieu of these recommendations, only a small number of patients at our institution had completed the vaccine series prior to referral for transplant evaluation. Physician recommendation, parent-child communication, history of childhood immunizations, perceptions of peer and significant other beliefs are cited factors negatively influencing HPV vaccination in immunocompetent patients and in cancer survivors [11]. We studied the influential factors for HPV vaccine non-initiation which has not previously been reported in solid organ transplant recipients.

2. Materials and Methods

2.1 Survey Design

Surveys on HPV vaccine non-initiation in immunocompetent patients have identified influential factors to serve as the focus for future interventions (physician recommendation, parental attitudes, and adolescent attitudes) [11]. Faced with a relative paucity of literature on vaccine non-initiation in immunocompromised patients, we developed a survey to examine influential factors in our regional transplant population.

A literature search identified existing items from published studies of HPV knowledge in immunocompetent patients. We discussed the following themes for our survey development: 1) kidney transplant status; 2) demographic characteristics; 3) HPV awareness; 4) causes, risk factors, and transmission; 5) prevention with vaccination. We evaluated the survey for face validity, and then administered a pilot study to three patients for completeness and usability. This step allowed us to modify survey answer choices per patient feedback. As we have a predominant Hispanic population with limited English proficiency, we translated the survey into a Spanish version. Our study took place over an 8-month period from May - December 2017. After survey completion,

the surveyors provided an informal educational session. Patients, parents, and caregivers were then invited to discuss concerns of HPV vaccine initiation. Following this session, the patients were provided the opportunity to initiate the HPV vaccine series during that clinic visit.

Ethical approval was provided by the Institutional Review Board for the Protection of Human Subjects at the McGovern Medical School at University of Texas Health at Houston. Notice of approval to begin research was granted on March 16, 2017 with outcome letter for submission #147802.

2.2 Patient Recruitment

Pediatric and adult patients from the Memorial Hermann Hospital- Texas Medical Center and Children's Memorial Hermann Hospital- Texas Medical Center Abdominal Transplant Clinic were eligible for inclusion. Study participants were comprised of kidney, combined kidney and liver, and combined kidney and pancreas recipients both prior to and after transplant. They were recruited for participation during routine clinic visits. Medical staff administering the survey recorded survey completion date in the patient's electronic medical record to avoid data duplication.

2.3 Consent

To provide informed consent, all surveys began with a brief paragraph regarding the intent of the research study. We required electronic consent before proceeding with the survey questions. Adult patients consented individually, while parents or caregivers consented for pediatric transplant patients. Interested pediatric patients provided assent if they desired to complete the survey individually. Though, parental or caregiver consent was still required for participation. Withdrawal of a patient's consent terminated the interview set.

2.4 Data Collection

Nephrology fellows from the McGovern Medical School at University of Texas Health at Houston approached prospective eligible patients for their interest in participation. They gave agreeable patients a Health Insurance Portability and Accountability Act compliant electronic tablet and allowed to choose their preferred language, English or Spanish. Utilizing the Qualtrics offline app, patients would typically complete the survey in 10 minutes. Patients completed the survey anonymously. Qualtrics software encrypted all data. To ensure optimal security, we entered the survey on only password protected electronic tablets and granted access to the principal investigator and specific collaborators. We confirmed vaccination initiation with chart review.

2.5 Data Analysis

Survey data was collected with electronic tablets utilizing the web-based software, Qualtrics. Categorical variables were reported as counts (percentages) and tested with Chi-Square and Fisher exact statistics. Continuous variables were reported as means, medians, and standard deviations. Qualtrics and Stata 13 SE software was used to analyze the data and two-sided p-value of 0.05 was considered statistically significant.

3. Results

Of the 164 patients approached for the study, 157 agreed to participate and 154 completed the survey, resulting in a 95% response rate (Figure 1). Two patients were excluded because they did not provide adequate information on age. One isolated liver transplant recipient was excluded due to not having a kidney transplant. The study sample included 154 adult and pediatric pre-and post-transplant patients (114 adult and 40 pediatric patients). Patient demographics are provided in Table 1.

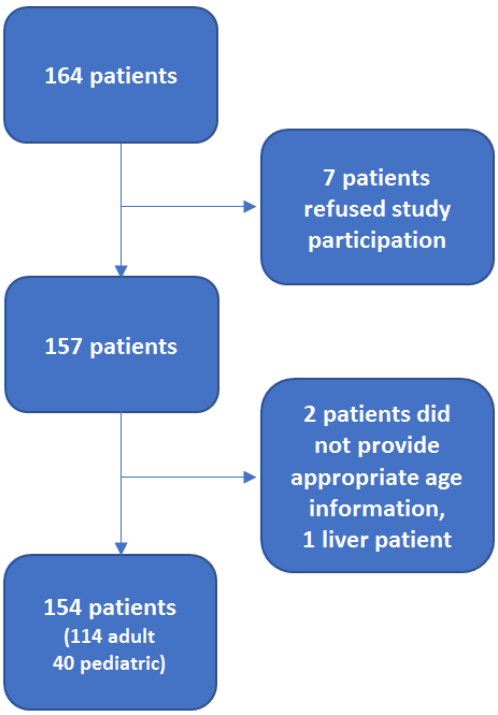

Figure 1 Survey profile

Patients were defined as within the United States FDA approved age range for HPV vaccine initiation if their age at survey was between 9 and 26 years old. Thirty-four patients were within this approved age range for HPV vaccine initiation. Pre-survey, eleven patients (32 %) had started the vaccine series. Of those eleven, only four had completed the three-dose series.

Findings from this survey demonstrated poor physician recommendation, gaps in knowledge that immunosuppression increases HPV disease risk, and concern over potential vaccine adverse reactions were important factors for vaccine non-initiation. Importantly, physician recommendation was critical for decreasing HPV vaccination non-initiation. Seventy-two percent of patients within the FDA approved age range for HPV vaccination acknowledged dialogue with a physician prior to the survey. Patients and their parents/caregivers were more likely to start the HPV vaccine series if a physician not only discussed the vaccine with them, but also recommended vaccination. For those who did not initiate the vaccine series, physician recommendation occurred in 64% in contrast to 100% of those starting the vaccine series.

Poor insight into the immunosuppressive contribution to HPV-related disease also impacted vaccine non-initiation. Ninety-eight (64%) of the 154 surveyed patients were aware of HPV prior to the survey, and 85% of patients with pre-survey HPV knowledge understood that HPV-related

disease was preventable with vaccination (Table 2). Unfortunately, the translation of this knowledge into a transplant patient's heightened personal risk, was only 46%.

Table 1 Baseline Characteristics (Categorical data with number of patients followed by percentages)

Gender	
Male	95 (61.7 %)
Female	59 (38.3 %)
Categories	
Adult	114 (74 %)
Pediatric	40 (26 %)
Within FDA approved age range for vaccination	
Yes	34 (22 %)
No	120 (78 %)
Transplant Status	
Pre-Transplant	30 (19.5 %)
Post-Transplant	124 (80.5 %)
Type of Organ Transplanted	
Kidney	115 (92.7 %)
Combined Kidney Pancreas	7 (5.7 %)
Combined Kidney Liver	2 (1.6 %)
Primary Language	
English	113 (73.4 %)
Spanish	38 (24.7 %)
Other	3 (1.9 %)
Race/Ethnicity	
Hispanic	75 (47.2 %)
African American	42 (26.4 %)
Caucasian	26 (16.3 %)
Asian	8 (5 %)
American Indian	3 (1.9 %)
Native Hawaiian/ Pacific Islander	3 (1.9 %)
Other	2 (1.3 %)

Table 2 Patient Human papillomavirus (HPV) knowledge (Categorical data with number of patients followed by percentages)

	Yes	No
Have you ever heard of HPV ?	98 (64 %)	56 (36 %)
Are you aware that HPV related disease is preventable by vaccine ? *	82 (85 %)	15 (15 %)
Do you think patients' HPV risk is increased after transplant ? **	45 (46 %)	52 (54 %)

* Among patients responding yes to "have you ever heard of HPV"

** Among patients responding yes to "HPV related disease preventable by vaccine"

Lack of information was cited as the primary reason for vaccine non-initiation, where most patients expressed the need for more nonspecific vaccine information before they would consider initiating the series (Table 3). The second most common concern leading to non-initiation differed between the pediatric and the adult patients. While adult patients noted anxiety over fear of organ rejection after vaccination, parents of pediatric patients were more concerned with the publicized vaccine adverse reaction syncope and other potential side effects. Promotion of sexual promiscuity is an often-quoted public concern, but it was the fifth of seven reasons parents cited for vaccine non-initiation.

Table 3 Vaccine non-initiation etiology among patients and parents.

	Patient	Parent
Need more information prior to initiating vaccine series	47.70%	36.70%
Fear of organ rejection after vaccine	20.30%	11.70%
Concern about potential adverse reactions	17%	21.60%
Patient is too young	3.90%	11.70%
Concern that it promotes sexual promiscuity	3.90%	8.30%
Cost	6.50%	5%
Patient has already received too many vaccines	0.70%	5%

Patients or parents cited perceived barriers to HPV vaccine initiation; multiple selections permitted during survey completion; categorical data presented as percentages.

At survey completion, the surveyor provided a brief, informal education on the benefits and risks of HPV vaccination. This post survey period presented the optimal opportunity to intervene by addressing knowledge gaps and answering patient centric questions to alleviate potential concerns. Consequently, ten more patients within the FDA approved age range initiated the vaccine, translating to an increase from 32% pre-survey to 62% post-survey and educational intervention.

4. Discussion

In our study, we identified a low uptake of HPV vaccine among our kidney transplant patients who were within the FDA approved age range. Previous U.S. based studies have identified HPV vaccine uptake in females ranging from 11% to 58%, with the lowest odds of vaccine receipt in the geographic South region [12]. Our low HPV vaccine uptake of 32% agrees with these studies. This survey examined current perceptions of HPV vaccine non-initiation in a single center patient population.

The most frequently cited reason for parents not vaccinating their adolescent children is lacking the physician's recommendation for HPV vaccine initiation [13]. Consistent with literature summarizing HPV vaccine uptake in both immunocompetent and immunocompromised adolescents with systemic inflammatory disease, our adolescent and young adult responses similarly highlight the importance of receiving this physician recommendation.

Although our patients acknowledged HPV vaccine discussion, it was their perception of physician recommendation that led to HPV vaccine initiation. This may seem surprising as many health care professionals believe they offer and support adolescent and young adult HPV vaccination. However, a recurring theme in HPV vaccine literature is health care professionals tend to offer vaccine recommendation based on perceived risk [13]. In qualitative studies, health care professionals reported using a risk-based approach to the perceived level of the patient's sexual activity or household characteristics. They expressed a preference for vaccinating older than younger adolescents and more girls than boys [14, 15].

Many factors contribute to poor physician recommendation. Primary care physicians may be hesitant to provide vaccinations to immunocompromised adolescents and young adults due to concern for inadequate response. Furthermore, as subspecialists increasingly provide primary care services, patients may not follow up with their primary care physicians. Consequently, subspecialty physicians may not recommend HPV vaccination if the vaccine is not stored in their clinics [12]. Identifying physician type as primary care or subspecialty was beyond the scope of our survey, yet, we believe both types may benefit from guidance on communicating HPV vaccine recommendations to patients and their parents/caregivers. Interestingly, data from the 2011 National Immunization Survey (NIS)-Teen indicate that African American and Hispanic girls may be less likely to receive a recommendation for HPV vaccination from their health care professional [16]. This finding may partially explain the perceived poor physician recommendation in our diverse patient population (Table 1).

The participants in our survey demonstrated an awareness of HPV but lacked understanding of the immunosuppressive impact on HPV-related disease. Additionally, our patients and parents/caregivers reported needing more nonspecific information as the most common reason for vaccine non-initiation. Prior studies of immunocompetent patients within the FDA approved age range for HPV vaccination confirm this barrier experienced by parents/caregivers [17]. As physicians educate patients and parents/caregivers on HPV infection sources, vaccine safety, and potential adverse effects, they must emphasize the increased risks of HPV-related disease after kidney transplantation.

Though not as significant as anticipated, some parents and caregivers reported concern that initiating the HPV vaccine series may be interpreted as condoning sexual promiscuity. Multiple studies have confirmed that HPV vaccination neither modifies young women's sexual behavior,

nor results in increased sexually transmitted infections [18, 19]. On the other hand, beliefs that only sexually active adolescents need the vaccine may lead parents to decline or delay HPV vaccination. Vaccination at 11 or 12 years old targets adolescents at an age when most are not yet sexually active and when the immune response to vaccination is greater than it is at older ages [20].

An unintended outcome of administering this survey was a near doubling of our patients initiating the HPV vaccine series over 8 months. We originally developed the survey to collect influential factors yet became surprised with its immediate educational impact. Post-survey, HPV vaccination came to the forefront of our clinic discussions. Patients and parents/caregivers discussed their concerns and sought clarity on common misconceptions. Following the post-survey educational sessions, we found patients and their parents/caregivers generally accepting of the vaccine. Continued physician targeted efforts to prioritize HPV education as in our study are needed to optimize HPV vaccine uptake. Although not performed in our study, many clinics may benefit from standardized physician education to provide a streamlined approach to complex, multi-faceted transplant care.

A major strength of this study is our generalizable patient population. Located in Houston, TX, we provide care for an ethnically diverse population with wide ranging social backgrounds. We also expanded the participant age to include patients beyond the age approved for vaccine initiation. In doing this, we identified differing concerns among adult and pediatric patients for HPV vaccine non-initiation. Physicians may find increasing vaccine initiation success with addressing age specific concerns.

A limitation was the survey served as a convenience sample within patients evaluated in our transplant clinics. Despite the convenience sample, we reached approximately 65% of the transplant clinic patient population during the survey period. Another potential limitation of this study includes lack of standardized education by the medical staff post-survey. The medical staff would adapt their post-survey education to not disrupt the clinic flow or prolong patient visits. As the post-survey education was not standardized nor statistically analyzed, it is difficult to delineate the survey from the educational session impact on improving vaccine initiation. A third limitation is that our survey did not collect information regarding school-based or clinic-based vaccination programs. A systematic review examined interventions to improve HPV vaccine uptake. Among national and international interventions, they found environmental interventions such as school-based vaccination programs consistently reached the greatest number of participants and achieved the highest vaccination rates [21].

Areas of interest in reducing HPV-related disease post kidney transplant favor a role of HPV vaccination in both males and females outside the age-based indication. Studies in immunocompetent patients found acceptability for the HPV vaccine in women over 26 years, with potential barriers being insurance coverage and cost to patient [22]. Recently published, vaccinated immunocompetent females aged 15-55 years at series initiation showed sustained immunogenicity with an acceptable safety profile of HPV 16/18 vaccine at ten years [23]. Similar trials in the immunocompromised and male populations are lacking. With expanding HPV coverage and elevated risk of HPV disease on our transplant patients, future research is needed to evaluate the clinical efficacy of HPV vaccination in transplant recipients, even extending beyond the age-based indication. Importantly, vaccine series initiation does not equate adherence and completion of the three-dose series. As prediction of HPV vaccine completion was beyond the

scope of this survey, future research is needed to identify these predictors in immunocompromised patients.

5. Conclusions

HPV infection, one of the most common sexually transmitted infections worldwide, has significantly increased the risk of malignancy among solid organ transplant recipients. Improvements in post-transplant care have afforded recipients longer graft survival. However, compounding the duration and intensity of immunosuppression is countered with potential rising HPV disease burden. Met with advances in screening and treatment of HPV-related disease in immunocompetent patients, studies are lacking in transplant recipients. Primary prevention with the HPV vaccine has the potential to revolutionize our approach to HPV-related diseases. Despite endorsement from national advisory groups, HPV vaccination uptake remains low. Emphasis on identifying vaccine non-initiation factors met with physician dialogue addressing these concerns can help improve vaccine uptake in both males and females. Future vaccine studies are needed urgently in transplant recipients and candidates. The optimal timing (pre- vs post-transplant) of vaccine completion and efficacy of vaccination outside age-based indications remain to be determined.

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SH performed the literature review, administered the survey, and wrote the manuscript. AD was the primary investigator of the study, assisted in developing the survey, and drafting the manuscript. SB and KV assisted in developing and translating the survey. CB analyzed survey results. RS assisted in developing the survey and drafting the manuscript.

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Competing Interests

The authors declare that they have no competing interests.

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