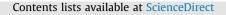
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Statewide analysis of missed opportunities for human papillomavirus vaccination using vaccine registry data



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ABSTRACT

Background: Human papillomavirus (HPV) vaccine 3-dose completion rates among adolescent females in the US are low. Missed opportunities impede HPV vaccination coverage.

Methods: A population-based secondary data analysis of de-identified vaccination and demographic data from the Utah Statewide Immunization Information System (USIIS) was conducted. Records were included from 25,866 females ages 11–26 years at any time during 2008–2012 who received at least one of the following adolescent vaccinations documented in the USIIS: Tdap (Tetanus, Diphtheria, Pertussis), meningococcal, and/or influenza. A missed opportunity for HPV vaccination was defined as a clinical encounter where the patient received at least one adolescent vaccination, but not a HPV vaccine.

Results: Of 47,665 eligible visits, there were 20,911 missed opportunities (43.87%). Age group, race/ ethnicity, and rurality were significantly associated with missed opportunity (p < 0.0001). In a multivariable mixed-effects logistic regression model that included ethnicity, location and age, as fixed effects and subject as a random effect, Hispanics were less likely to have a missed opportunity than whites OR 0.59 (95% CI: 0.52–0.66), small rural more likely to have a missed opportunity than urban youth OR 1.8 (95% CI: 1.5–2.2), and preteens more likely than teens OR 2.4 (95% CI: 2.2–2.7).

Conclusion: Missed clinical opportunities are a significant barrier to HPV vaccination among female adolescents. Interventions targeted at providers who serve patient groups with the highest missed opportunities are needed to achieve adequate protection from HPV-associated illnesses.

Impact: This is one of the first studies to utilize state immunization information system data to assess missed opportunities for HPV vaccination.

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1. Introduction

In 2006, the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommended that girls ages 11 and 12 years receive a routine 3-dose human papillomavirus (HPV) vaccine to protect against cervical and other HPV-associated cancers and genital warts [1]. Compared to older adolescents, girls at ages 11–12 years exhibit a stronger immune response to the vaccine and are less likely to have initiated sexual activity; however, the HPV vaccine is also

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effective in older adolescents. Additionally, ACIP has also recommended it as a catch-up vaccination for teens and young women at ages 13–26 years [1].

Despite these recommendations, HPV vaccine coverage in the United States (US) is poor, with national completion of the 3-dose vaccine series among adolescent females at 39% [2]. In 2014, Utah's was among the lowest completion rates among female adolescents nationwide with only 26% of adolescent teens completing the 3-dose series [2]. These HPV vaccine completion rates are problematic because despite the availability of a cancer prevention vaccine, adequate protection from HPV-related illnesses is not being realized. The 2013 President's Cancer Panel Report emphasized the urgency to improve HPV vaccine coverage in the US, and reach the CDC's Healthy People 2020 goal of HPV vaccine completion at 80% among female adolescents [3,4].

Nationally, although HPV vaccination rates are low, other adolescent vaccination rates are relatively high. In 2014,

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meningococcal vaccine coverage among adolescents was 79%, and Tetanus, Diphtheria, and Pertussis (Tdap) vaccine coverage among adolescents was 87% [2]. In Utah, other adolescent vaccination rates are similarly higher than HPV vaccination rates, with 66% and 84% of adolescents having received meningococcal and Tdap, respectively [2]. One reason for this discrepancy in vaccination rates may be that health care providers are not strongly recommending the HPV vaccine when providing other recommended immunizations [5]. Therefore, missed opportunities, when an eligible patient receives another recommended vaccine but not the HPV vaccine, are a barrier to adequate HPV vaccine coverage, as well as an opportunity for intervention and improvement [3,6,7]. Reducing missed opportunities to recommend and administer HPV vaccines is the first goal of the 2012–2013 President's Cancer Panel Report for accelerating HPV vaccine uptake in the US [3].

To identify viable intervention opportunities for improving HPV vaccination, it is critical to quantify missed opportunities and to identify the demographic factors associated with missed opportunities for HPV vaccination. More research is needed in states with low HPV vaccine completion rates such as Utah. This study is among the first in the US and the first in Utah to use state level vaccine registry data to assess missed opportunities for HPV vaccination and to determine which patient demographic factors are related to these missed opportunities among eligible females using the Utah Immunization Information System (USIIS) data. These data may guide clinic-based interventions for HPV vaccination to promote strong and consistent recommendations for the HPV vaccine when providing other recommended immunizations.

2. Material and methods

In this study, we investigated missed opportunities for HPV vaccination among females ages 11–26 years that occurred between 2008 and 2012 using data from the Utah Statewide Immunization Information System (USIIS). This study took place between July 2013 and July 2015. Approval was obtained from the University of Utah Institutional Review Board and the Utah Department of Health.

2.1. Data source

The USIIS program at the Utah Department of Health maintains a secure and confidential system that collects and consolidates immunization records for Utah residents of all ages. USIIS includes a web-based application that is designed to track immunization records and provide clinical decision support for patient care for clinicians. USIIS complies with state law and CDC functional standards to protect patient privacy and is populated with birth records of Utah born children as well as immunization records from 100% of public health care providers and more than 78% of private providers. The research team applied for and obtained access to de-identified USIIS patient immunization and demographic data for this analysis.

2.2. Outcome

Missed HPV vaccination opportunities were counted using unique patient visits at which one or more adolescent vaccines were administered. We limited clinical encounters to when vaccines were administered because USIIS only captures encounters when a vaccine is given. A missed opportunity for the HPV vaccine was defined as a unique visit in which an eligible individual received an age-appropriate adolescent vaccine, i.e., who received at least one of the following adolescent vaccinations documented in the USIIS: Tdap (Tetanus, Diphtheria, Pertussis), meningococcal, and/or influenza. Individuals who had previously completed three doses of the HPV vaccine were not considered eligible for a missed opportunity. To account for delays in data entry a vaccine could have been administered within the following 7 days to be counted as being administered during a visit.

2.3. Patients

There were N=48,673 unique individuals in the original USIIS dataset, who received any immunization between 2008 and 2012. For this analysis we included females who were ages 11–26 years at a visit that occurred at any time between 2008 and 2012. Due to the different timing of HPV vaccination recommendations by the Advisory Committee on Immunization Practices (ACIP) for females and males, males were excluded from this investigation. Vaccinations that were administered to an individual who was outside the recommended age range for HPV vaccination by the ACIP (ages 11–26) at the time of the visit were excluded. We did not extend our analysis to those younger than age 11 because we were interested in understanding factors related to missed opportunities for those who were receiving on-time vaccination at ages 11–12, and late vaccination ages 13-26. These ages were selected according to the ACIP HPV vaccination recommendations. There was a small proportion of records with an HPV vaccine administered before age 11 (0.21%) that were excluded. Additionally, immunizations and demographic records of individuals who did not have a Utah ZIP code were excluded as were individuals who had already completed the 3-dose HPV vaccine series. After exclusions, there were N=25,866 unique females. For those females, N=47,665 unique visits were identified.

2.4. Measures

Individual's age, race/ethnicity, and rurality of residence were obtained from the patient demographic data for missed opportunities by unique individuals and visits (N=47,665 visits). Patient age was classified into three age groups: pre-teen (11-12 years), teen (13-18 years), or young adult (19-26 years). Race/ethnicity, as determined by the provider, included White, American Indian/ Alaskan Native, Black/African American, Asian/Pacific Islander, Hispanic, Other, and Not given. Approximately 40% of females did not have adequate race/ethnicity data. Rurality of residence was classified according to the 4-level Rural Urban Area Commuting code using patient ZIP codes, which were determined by the provider, from the vaccination record [8]. RUCA codes utilize commuting information and census-track coding definitions from the Bureau of Census Urbanized Area and Urban Cluster to assign urban, large rural, small rural, and isolated rural status to zip codes. Two recently formed ZIP codes were classified by the authors based on population density.

2.5. Statistical analysis

All analyses were performed using SASTM version 9.4. Summary statistics were calculated for patient characteristics and to describe visits and clinics. SAS TM PROC GLIMMIX was used to implement a Generalized Linear Mixed Effects model with assumed binomial responses and a logit link. Significance and confidence intervals are at the p=0.05 level of significance, values are post hoc, and there is no adjustment for multiplicity. Age-Group, Race and Rural Status were chosen as fixed effects and subject was taken as a random effect. Completion of the 3 vaccine series conditional on 0, 1 and 2 inoculations already given was described by summary statistics.

Table 1

Female vaccination visits among those who were eligible for HPV vaccination at the time of visit by age group (N visits=47,665).

	Received HPV vaccine (n=26,754)	Missed oopportunity for the HPV vaccine (n=20,911)	P-value ¹
	No. (%) ²	No. (%) ²	
			< 0.0001
Pre-teens at ages 11– 12 years (n=9,263)	4,890 (52.79)	4,373 (47.21)	
Teens at ages 13–18 years (n=30,113)	19,127 (63.52)	10,986 (36.48)	
Young adults at ages 19–26 years (n=8,289)	2,737 (33.02)	5,552 (66.98)	

p-value calculated using Chi-Square test.

² Percentages calculated based on row totals.

3. Results

3.1. Missed opportunities for the HPV vaccine by visits for females ages 11-26 years

Mean age of eligible patients was 16.1 years (Standard Deviation (SD): 3.15 years, range: 11.0–25.9 years). For all patients, we identified 47,665 visits (Table 1). Although not a majority, there was a high number of missed opportunity visits for the HPV vaccine (n=20,911, 43.9%). Given the high proportion of records with missing race/ethnicity data, we conducted a sensitivity analysis comparing the reporting of race in our data compared to the U.S. Census data for Utah and found that the number of those supplying race among the larger ethnic groups was the same. As shown in Table 1, age at the time of the visit was significantly associated with the outcome of the visit (e.g., whether the visit was a missed opportunity for the HPV vaccine or not) (p < 0.0001). Two-thirds of visits among young adult women were missed opportunity visits for the HPV vaccine (n=5.552, 66.98%), while nearly half of the pre-teen visits were missed opportunity visits for the HPV vaccine (n=4,373, 47.21%). Though the proportion of missed opportunity visits for the HPV vaccine among female teens was lower than other age groups (36.48%), these visits translate into a large number of missed opportunities (n=10,986). In

Table 2

Missed opportunity visits for HPV vaccination among pre-teens ages 11-12 years.

	Got HPV vaccine (n=4,890)	· · · · · · · · · · · · · · · · · · ·	
	No. (%) ²	No. (%) ²	
Racial/ethnic group			< 0.0001
American Indian/Alas- kan Native (n=35)	17 (48.57)	18 (51.43)	
Asian or Pacific Islander (n=99)	35 (35.35)	64 (64.65)	
Black or African Amer- ican (n=50)	29 (58.00)	21 (42.00)	
Hispanic $(n=647)$	370 (57.19)	277 (42.81)	
White (n=3,768)	1,784 (47.35)	1,984 (52.65)	
Other $(n=320)$	158 (49.38)	162 (50.63)	
Not Given (n=4,344)	2,497 (57.48)	1,847 (42.52)	
Rurality of residence			< 0.0001
Urban (n=8,265)	4,496 (54.40)	3,769 (45.60)	
Large Rural (n=256)	101 (39.45)	155 (60.55)	
Small Rural (n=424)	162 (38.21)	262 (61.79)	
Isolated $(n=188)$	70 (37.23)	118 (62.77)	
Not given (n=130)	61 (46.92)	69 (53.08)	

¹ p-value calculated using Chi-Square test.

² Percentages calculated based on row totals.

Table 3

Multivariable regression of demographic factors and having a missed opportunity for the HPV vaccine among females ages 11–18 years.

Racial/ethnic group	OR	95% CI	p-Value
White	Ref.		
American Indian/Alaskan Native	0.72	0.48-1.06	0.10
Asian or Pacific Islander	1.23	0.95-1.60	0.12
Black or African American	0.89	0.62-1.30	0.56
Hispanic	0.59	0.53-0.66	< 0.001
Rurality of Patient's Residence			
Urban	Ref.		
Large Rural	1.61	1.19-2.18	< 0.01
Small Rural	1.83	1.49-2.24	< 0.001
Isolated	1.08	0.79-1.48	0.62
Age			
Preteen	2.44	2.22-2.68	< 0.001
Teen	Ref.		

Table 2, we see the bivariate associations between race and rurality and missed opportunity for the HPV vaccine among 11 and 12 year olds. A Generalized Linear Model was used to estimate the effect of age group, race and rural status on the probability of missed HPV inoculation opportunity, all effects were highly significant as was the overall model (p < 0.001). As shown in Table 3, within race, Hispanic patients were less likely to miss an opportunity than non-Hispanic patients (p < 0.0001), OR=0.59, (95% CI: 0.52-.66). Pre-Teen patients were more likely to miss an opportunity (p < 0.0001), OR = 2.44 (95% CI: 2.2-2.7) and Large Rural and Small Rural patients were more likely to miss an opportunity (p=0.0019, < 0.0001 and OR=1.61 and 1.83 respectively). Table 4 shows the total number of HPV immunization doses for patients in our study. 11,320 patients (44%) received no HPV immunizations, and only 4506 (17%) completed the three dose HPV vaccination series. If a patient completed 1 or more HPV doses (n = 14,546), they had an increased probability of completing the series (4506/ 14546 or 31%). In a secondary analysis, analyzing time as both continuous and categorical variable, we identified a significant increase in the percentage of mixed opportunities from 2008 to 2012. For the model with categorical time, an odds ratio of 8.42 (p < 0.0001) was observed for 2012 vs. 2008.

4. Discussion

Despite the opportunity for cancer prevention, the HPV vaccine has been largely underused. Almost ten years after its recommendation, national HPV vaccination rates among adolescent females are below target, with some of the lowest vaccination rates in the United States occurring in Utah [2]. Past research has identified several possible explanations for low HPV vaccine coverage, including lack of parental knowledge about HPV and the HPV vaccine, lack of health care provider recommendations for the vaccine, lack of reminder system for follow-up doses, religious and cultural factors, inadequate health insurance coverage, vaccine

Number of doses of the HPV vaccine received among females ages 11-26.

Number of HPV vaccine doses	Number of females	Percent	Cumulative frequency
0	11,320	43.76	43.76
1	6,229	24.08	67.85
2	3,811	14.73	82.58
3	4,346	16.80	99.38
4	139	0.54	99.92
5	20	0.08	100
6	1	0	100

costs, and beliefs that vaccinating pre-teens against a sexually transmitted infection is unnecessary and/or may promote sexual activity [9]. Many of these factors may attribute to the high level of missed opportunities for HPV vaccination, a clear barrier to adequate HPV vaccine coverage [3,6,7].

This study is among the first to use data from a state immunization information system to investigate statewide missed opportunities for HPV vaccination and the demographic factors related to these missed opportunities. Our findings may inform interventions to promote the receipt of this preventive cancer vaccine among eligible females by limiting the number of missed opportunities for HPV vaccination.

Of the visits that met our inclusion criteria, excluding those who had already completed the HPV vaccine series, a high number (nearly 21,000 or 43.87%) were missed opportunities for HPV vaccination. These visits—across all age, racial/ethnic, and residence groups—signal that missed opportunities for HPV vaccination represent a serious barrier to HPV vaccine coverage and protection from HPV-associated illnesses. This finding adds detail to comparisons between HPV and other adolescent vaccination rates by quantifying the number of visits in which a HPV vaccine could have been administered, but was not.

Similar to previous findings of age associations with HPV vaccine initiation and completion [10], age was significantly associated with missed opportunity. In our sample, young adult women, those ages 19–26 years, had the highest proportion of missed opportunity visits of any age group. Potential reasons for this finding may be attributed to feelings that young adults are lowerpriority candidates for the HPV vaccine or that patients at this age are responsible for their own vaccination status. Furthermore, this age cohort is not covered by the Vaccines for Children (VFC) Program and has high rates of being uninsured and/or underinsured [11]. Furthermore, lack of uncertainty about their relationship status and sexual activity may cause more young adults to feel as though the vaccine is not useful for them [12,13].

On the other hand, girls ages 11–12 years whose parents are responsible for the vaccination decision also had a high proportion (almost half) of missed opportunity visits. This finding is particularly unsettling because of the vaccine's superior efficacy for this age group and the ACIP guidelines prioritizing immunization at ages 11 and 12 years [1]. This result may reflect provider or parental discomfort with vaccinating early adolescents against a sexually transmitted infection [9]. Like many rural and frontier states in the United States, Utah is a highly religious state. Utah has a high density of members of the Church of Jesus Christ of Latter Day Saints [14], a religious denomination with strong positions against sexual activities of youth, which may affect provider and parental decisions about vaccinating adolescents at ages 11–12 [9,15].

Many studies of HPV vaccination focus on adolescents (i.e., the National Immunization Survey-Teen studies adolescents age 13–17), thus this study contributes invaluably to the existing literature by focusing on missed opportunities for HPV vaccination among pre-teens (age 11–12) and young adult women (age 19–26). This study fills the gaps on missed opportunities among these age groups in Utah and suggests that the vaccination behavior of individuals in these age groups is significantly different compared to that of teens (ages 13–18).

In addition to age differences, we found significant racial/ethnic differences in missed opportunities that have been reflected in the existing body of literature detailing HPV vaccine use among individuals of different races/ethnicities [10,16]. We found a large number of missed opportunities for White pre-teens. This finding may reflect the demographic homogeneity of Utah being primarily White (91.6%) [17]. However, we also found a high percentage of missed opportunity visits for pre-teen American Indians/Alaskan

Natives, Asians/Pacific Islanders, and other races. This finding may be attributed to the recently emerging and rapidly growing minority and immigrant populations in Utah who may lack access to well-established health care support systems [17]. In contrast, we estimated a lower percentage of missed opportunity visits for Hispanics, which could be due to the increased strength of Hispanic community organizations in Utah, the support that Hispanic communities demonstrate for childhood vaccinations, as well as a developing sensitivity of health institutions to the needs of the growing Hispanic population. This finding suggests that HPV vaccination strategies that have been successfully applied in the Hispanic population may be efficacious in other racial/ethnic groups.

Finally, we found rurality of residence to be significantly associated with missed opportunities, which mirrors research detailing the differential and oftentimes lower access to cancer prevention and treatment services available to individuals living in rural areas [18–21]. Of the visits with 11–12 year olds, a majority of those with rural (i.e., large-rural, small-rural, isolated rural) patients were missed opportunities for HPV vaccination. This result could reflect the difficulty some rural facilities face in stocking adequate supplies of the HPV vaccine [22], or the difficulty of rural families to schedule 3 visits to receive all doses of the vaccine [9]. It could also be attributed to the opposition to the vaccine that is strongest in less metropolitan and more rural areas of Utah [23].

4.1. Limitations

We utilized de-identified patient immunization and demographic data from USIIS for this analysis. There are some limitations to consider in the interpretation of these results. Approximately 40% of females did not have adequate race/ethnicity data, limiting the interpretation of race/ethnicity on missed opportunities for HPV vaccination. Additionally, the majority of females were urban. While this is indicative of Utah's overall population [17], more research is needed to understand risk factors for missed opportunities among female adolescents in rural locations. A small portion of providers in Utah (less than 25%) do not participate in USIIS. This study may have underestimated the number of missed opportunities for the HPV vaccine in this statewide analysis because it only captured patient visits when any vaccine was administered. We did not investigate possible opportunities for HPV vaccine at all clinical encounters, such as other primary and acute care visits. Alternatively, patients may have been counted multiple times because data is by visit and not by individual. Due to the limited nature of USIIS, we were unable to obtain information about reasons for vaccine refusal (e.g., allergy to vaccine ingredients, costs) and dose validity logic (e.g., interval timing for doses). Additionally, it is possible that HPV vaccinations were given during a visit and not recorded in the USIIS system, thus potentially overestimating missed opportunities. Furthermore, estimates provided by USIIS to the CDC indicate that in 2014, approximately 61% of adolescents ages 11-17 in Utah with two or more immunizations participate in USIIS [24], which is equal to national participation in immunization information systems, also at 61%. However, 80% of providers in Utah participate in the USIIS registry. Estimates may be low due to the numbers of adolescents who only receive one immunization in Utah. Lastly, provider type and insurance status have been previously identified as predictors of HPV vaccination, however this data is not available in the USIIS data and thus was not accounted for in our analyses.

5. Conclusions

Missed opportunities for HPV vaccination represent a major barrier to reaching the CDC's Healthy People 2020 objective of 80% coverage among adolescent females and to realizing adequate protection against HPV-associated illnesses. Future interventions that consider certain demographic factors which are associated with increased risk of missed opportunity for HPV vaccination, namely age, race/ethnicity, and rurality of residence are needed. Strategies that have been successful in Latino populations may provide important insight into the development of opportunities for other groups that portray a high level of missed opportunities for HPV vaccination, including other developing minority and immigrant populations in Utah that may have difficulty accessing health information and resources and those living in rural areas. Public health efforts that heighten receipt of the HPV vaccine among adolescents at ages 11–12 years by emphasizing the rationale for vaccinating children at the earlier ages and being sensitive to parental reluctance to vaccinate early adolescents are needed. Reducing missed opportunities for HPV vaccination is a key objective to improving vaccination rates and reaching the CDC's Healthy People 2020 goal of 80% vaccination among adolescent females.

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Conflict of interest disclosures

None reported.

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