Title

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Journal

Journal of Pediatric and Adolescent Gynecology, 31(2)

ISSN

1083-3188

Authors

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Publication Date

2018-04-01

DOI

10.1016/j.jpag.2017.09.008

Peer reviewed

HHS Public Access

Author manuscript

J Pediatr Adolesc Gynecol. Author manuscript; available in PMC 2019 April 01.

Published in final edited form as:

J Pediatr Adolesc Gynecol. 2018 April ; 31(2): 89–93. doi:10.1016/j.jpag.2017.09.008.

Who's not protected in the herd? Factors associated with vaccine-type HPV in unvaccinated women

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Abstract

Study Objective—Evidence suggests that vaccine-type human papillomavirus (HPV) prevalence may decrease in unvaccinated women after HPV vaccine introduction, indicating herd protection. The aim of this study was to determine factors associated with vaccine-type HPV (i.e. absence of herd protection) after vaccine introduction.

Design—We conducted three cross-sectional studies from 2006-2014 (n=1180): wave 1 (2006-2007), wave 2 (2009-2010), and wave 3 (2013-2014).

Setting—Participants were recruited from a hospital-based teen health center and a community health department.

Participants—We recruited 13-26 year-old young women; those included in this analysis had not received an HPV vaccine.

Main Outcome Measures—The outcome measure was infection with at least one vaccine-type HPV (HPV6, 11, 16, 18).

Results—Multivariable logistic regression demonstrated that in wave 1 (before vaccine introduction), history of anal intercourse (OR=1.8, 95% CI=1.1-3.0), age 18-21 vs. 13-17 years (OR=2.1, CI=1.2-3.6), and Black/multiracial vs. White race (OR=1.8, CI=1.1-3.0) were associated with vaccine-type HPV in unvaccinated women. In wave 2, no variables were associated with HPV. In wave 3, sexually transmitted infection history (OR=3.6, CI=1.3-9.7) was associated with HPV.

Conclusions—We did not identify a consistent set of modifiable risk factors associated with vaccine-type HPV after vaccine introduction across the three study waves, underscoring the

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Potential Conflicts of Interest. For the remaining authors, no competing financial interests exist.

urgency of vaccination for primary HPV prevention and the limitations of relying on herd protection.

Keywords

human papillomavirus; herd protection; vaccine; women

Introduction

Human papillomavirus (HPV) infection may cause cervical, vulvar, vaginal, penile, anal, and oropharyngeal cancers.(1) Infection with HPV was estimated to be responsible for almost 5% of global cancers in 2008.(2) Three highly effective prophylactic HPV vaccines have been licensed. These include 2-valent, 4-valent, and 9-valent HPV vaccines: each prevents infection with HPV16 and HPV18, which cause approximately 70% of cervical cancers globally.(3) Studies have demonstrated that HPV vaccine introduction has resulted in a rapid and substantial decrease in the prevalence of vaccine-type HPV in vaccinated young women, supporting vaccine effectiveness.(4-6) A recently published study examined the early effects of HPV vaccination in young women younger than 30 years of age attending cervical cancer screening in Belgium from 2010-2014. The study demonstrated that HPV vaccination was protective against infection with HPV16, HPV18, and high-risk HPV, and was also protective against cytological abnormalities associated with HPV16/18. Vaccine effectiveness decreased with age; no protection was observed against abnormal cytology in 25-29 year-old young women.(7, 8)

Several recent studies have also demonstrated a decrease in vaccine-type HPV in unvaccinated women (and in men after vaccine introduction in women), indicating herd protection.(4, 9-11) Herd protection is an indirect benefit of vaccination for those who are unvaccinated, driven by the smaller pool of individuals capable of transmitting a pathogen.(12) Evidence for herd protection has been strongest in regions with high female vaccination coverage. Herd protection effects may be manifest through a decline in vaccine-type HPV in unvaccinated women or men, or a decrease in cervical precancers in women or in anogenital warts in women or men.(11) A recent study in Australia demonstrated a substantial reduction in the prevalence of vaccine-type HPV among unvaccinated men, providing early evidence that female vaccination has resulted in herd protection in men.(11) Although one population-based U.S. study did not demonstrate evidence of herd protection as evidenced by a decrease in vaccine-type HPV in unvaccinated women,(13) another U.S. study that we conducted in young women with relatively high vaccination coverage did demonstrate herd protection.(5)

The mechanisms of herd protection after HPV vaccine introduction are not well-understood. Herd protection is influenced by a number of factors including transmission potential of the infection and vaccine effectiveness, coverage, and distribution.(12) Herd protection also assumes homogeneous mixing across relevant population groups and across different seasons. In reality, however, this is not always observed, especially in the case of a sexually transmitted virus, which may follow patterns of assortative mixing.(14) Studies of herd protection after HPV vaccination have not examined the specific factors associated with herd

protection – or lack of herd protection – and whether these factors change over time after vaccine introduction. Examination of these factors is important in that different assumptions about herd protection have key implications for cost-effectiveness analyses, cervical cancer screening recommendations, and public health messaging. Therefore, the aims of this study were to determine the factors associated with lack of herd protection, defined as vaccine-type HPV in unvaccinated young women, and to examine whether these factors change before and over the first eight years after HPV vaccine introduction.

Materials and Methods

Three cross-sectional studies of diverse, unvaccinated and vaccinated adolescent and adult women 13-26 years of age were conducted in 2006-2007 (wave 1, N=371), 2009-2010 (wave 2, N=409) and 2013-2014 (wave 3, N=400). Adolescent girls and young women were recruited from a hospital-based adolescent clinic and a public health department clinic. At the time of the study, all vaccinated women were receiving the 4-valent vaccine, a three-dose schedule was recommended, and vaccination was recommended at 11-12 years of age, with catch-up vaccination of those women 13-26 years of age. Those who had participated in a previous study wave were excluded from each sequential wave. Inclusion criteria were having had sexual contact with a male or female partner. Participants underwent cervicovaginal HPV DNA testing and completed a paper-and-pencil questionnaire. The procedures for HPV testing were identical in all three waves and are described in previous manuscripts.(5, 15) Samples were genotyped with the Roche Linear Array test, a polymerase chain reaction amplification technique that uses an L1 consensus primer system and a reverse-line blot detection strip to identify 36 different HPV genotypes (Roche Molecular Systems, Alameda, CA).(16) Surveys assessed demographic factors, HPV knowledge, gynecological history, and behaviors. The study was approved by the Institutional Review Boards of the hospital and health department with a granted waiver of parental consent for participants younger than 18 years of age.

Analyses were conducted among unvaccinated young women, defined as having received no vaccine doses, which was determined by a review of both an electronic medical record and a state-wide immunization registry. The outcome variable was positivity for at least one of the HPV types targeted by the vaccine (HPV6, 11, 16, 18). We determined whether demographic and behavioral variables were associated with vaccine-type HPV among unvaccinated women across the three waves, using inverse propensity score-weighted univariable and multivariable logistic regression to account for participant differences across waves, as described in a previous manuscript.(5) Of note, a few variables used in the propensity score analysis were categorized differently in this compared to the previous analyses, leading to slightly different results for vaccine-type HPV prevalence.

Variables associated with vaccine-type HPV at $p < 0.10$ were entered into separate multivariable logistic regression models for each wave, and variables associated with vaccine-type HPV in the multivariable models at $p < .05$ were retained in the final models. All analyses were performed using SAS version 9.3.

Results

Participant recruitment site, demographic characteristics, HPV knowledge, health history, substance use, sexual behaviors, and partner characteristics across the three waves are shown in Table 1. Mean age ranged from 18.7-21.1 years, 45.5%-60.8% described their race as Black, mean number of lifetime male sexual partners ranged from 5.4-6.0, and approximately 25% reported a history of anal intercourse. Some of the differences in participant characteristics across the waves were significant (e.g. age). The proportion of participants who were unvaccinated was: 371/371 (100%) in wave 1, 167/409 (40.8%) in wave 2, and 114/400 (28.5%) in wave 3. Vaccine-type HPV was detected in 31.9% of unvaccinated women in wave 1, 19.1% in wave 2 (vs. 10% among vaccinated women), and 18.8% in wave 3 (vs. 3.2% among vaccinated women).

Univariable analyses in waves 1, 2 and 3 (Table 2) demonstrated that the following variables were associated with vaccine-type HPV across the three waves ($p < .10$). In wave 1, age (18-21 vs. 13-17 years of age, OR=1.9), race (Black/multiracial vs. White, OR=1.6), lifetime number of male sexual partners (OR=1.0), and history of anal sexual intercourse (OR=1.6) were associated with HPV. In wave 2, no variables were associated with HPV. In wave 3, type of insurance (none vs. private, OR=0.2) and self-reported history of a sexually transmitted infection or STI (OR=3.4) were associated with HPV. Multivariable analyses in waves 1, 2, and 3 (Table 2) demonstrated that the following variables were associated with vaccine-type HPV across the three waves ($p < .05$): in wave 1, history of anal intercourse (OR=1.8), age 18-21 vs. 13-17 years (OR=2.1), and race (Black/multiracial vs. White, OR=1.8); and in wave 3, self-reported history of an STI (OR=3.6).

Discussion

In this study, we determined the factors associated with vaccine-type HPV in unvaccinated women; that is, lack of herd protection, before and over the first eight years after HPV vaccine introduction. Vaccine-type HPV prevalence decreased over this time period as previously reported, suggesting herd protection effects.(5) In contrast, in a nationally representative U.S. sample of 14 to 24 year-old women, there was no decrease noted in vaccine-type HPV prevalence from the pre-vaccination (2003-2006) to the post-vaccination period (2009-2012) among unvaccinated women.(13) Vaccination rates were substantially higher in our sample compared to the national sample, which may explain the difference in findings, as higher rates of HPV vaccination have been associated with a greater degree of herd protection.(4)

We found that in wave 1, before widespread vaccine introduction, factors associated with vaccine-type HPV in unvaccinated women were sexual risk behaviors, age, and race, as expected based on previous literature examining risk factors for any type of HPV.(17-21) No variables were associated with HPV in wave 2, and only history of an STI was associated with HPV in wave 3. Few studies have examined risk factors for HPV in the post-vaccination era, but history of an STI similarly was associated with vaccine-type HPV in a study by Schlecht et al.(22) The finding that factors associated with vaccine-type HPV differed markedly across the three waves of data collection suggests that risk factors for

vaccine-type HPV are changing in the post-vaccination era among unvaccinated women in this community. This may be a result of the decrease in vaccine-type HPV in the community, or because unvaccinated women differ in terms of the behaviors that would put them at risk for acquiring HPV. Further research may provide insights into the mechanisms driving this change in risk factors for HPV over time, including an examination of sexual networking behaviors that may be influencing patterns of herd immunity.

Limitations of this study were that sexual behaviors and history of an STI were self-reported, which may affect their validity, and that the number of unvaccinated women with HPV was relatively small, limiting the power to detect associations. In addition, the power to detect associations between predictor variables (such as age) and HPV infection in the regression models decreases over the three study waves, due to the decreasing number of unvaccinated women. Strengths of the study are its longitudinal design, availability of validated data regarding vaccination status, and detailed assessment of participant characteristics, medical history and behaviors.

In conclusion, examining factors associated with vaccine-type HPV in unvaccinated women after vaccine introduction has implications for practice and public health. The finding that a consistent set of modifiable risk factors associated with vaccine-type HPV after vaccine introduction was not identified across the three study waves, as well as the finding that unvaccinated women in wave 3 were approximately six times more likely than vaccinated women to be infected with vaccine-type HPV, underscore the urgency of public health efforts to promote vaccination for primary HPV prevention and the limitations of relying on herd protection.

Acknowledgments

We gratefully acknowledge the Clinical Research Coordinators (Lisa Higgins RPh, Charlene Morrow RN MSN, and Rachel Thomas MS) and staff of the Teen Health Center and Cincinnati Health Department for their assistance with this research study.

Sources of funding. This work was supported by grants from the U.S. National Institutes of Health, National Institute of Allergy and Infectious Diseases [R01 AI073713 and R01 AI104709].

Dr. Kahn has co-chaired two NIH-funded HPV vaccine clinical trials in HIV-infected individuals, for which Merck & Co., Inc., provided vaccine and immunogenicity titers. Dr. Franco has served as occasional advisor to companies involved with HPV vaccination (Merck, GSK) and HPV and cervical cancer diagnostics (Roche, BD, Qiagen). His institution has received unconditional funding from Merck for investigator-initiated studies carried out in his unit.

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Table 1

Participant Characteristics, Waves 1-3

	Wave 1 (2006-2007)			Wave 2 (2009-2010)			Wave 3 (2013-2014)		
Participant characteristic	**N (%)[a]**	**Mean (SD)**	**Median (range)**	**N (%)[a]**	**Mean (SD)**	**Median (range)**	**N (%)[a]**	**Mean (SD)**	**Median (range)**
Recruitment site									
Teen Health Center	239 (64.4)			58 (34.7)			31 (27.2)		
Health Department Clinic	132 (35.6)			109 (65.3)			83 (72.8)		
Age (years)		18.7 (3.0)	18 (13-26)		20.6 (3.2)	20 (13-26)		21.1 (3.3)	21 (14-26)
13-17	155 (42.6)			33 (19.8)			20 (17.5)		
18-21	140 (38.5)			71 (42.5)			42 (36.8)		
22-26	69 (19.0)			63 (37.7)			52 (45.6)		
Race									
White	107 (29.3)			75 (44.9)			51 (44.7)		
Black	222 (60.8)			76 (45.5)			54 (47.4)		
Multiracial	15 (4.1)			9 (5.4)			7 (6.1)		
Other	21 (5.8)			7 (4.2)			2 (1.8)		
Appalachian background									
Yes	24 (6.7)			6 (3.6)			4 (3.5)		
No	336 (93.3)			161 (96.4)			110 (96.5)		
Hispanic/Latina									
Yes	25 (6.9)			20 (12.0)			20 (17.5)		
No	335 (93.1)			147 (88.0)			94 (82.5)		
Marital status									
Never married	331 (92.7)			155 (92.8)			108 (94.7)		
Divorced, widowed, or separated	12 (3.4)			3 (1.8)			2 (1.8)		
Married now	14 (3.9)			9 (5.4)			4 (3.5)		
Heath insurance status									
Health insurance	249 (67.1)			112 (67.1)			81 (73.6)		

	Wave 1 (2006-2007)			Wave 2 (2009-2010)			Wave 3 (2013-2014)		
Participant characteristic	**N (%)[a]**	**Mean (SD)**	**Median (range)**	**N (%)[a]**	**Mean (SD)**	**Median (range)**	**N (%)[a]**	**Mean (SD)**	**Median (range)**
No health insurance	122 (32.9)			55 (32.9)			29 (26.4)		
Insurance plan									
Private	32 (8.6)			15 (9.0)			9 (7.9)		
Medicaid	196 (52.8)			79 (47.3)			68 (59.7)		
None/other	143 (38.5)			73 (43.7)			37 (32.5)		
HPV knowledge (scale score, out of 12)		7.3 (1.9)	7 (0-12)		6.0 (2.5)	6 (0-12)		4.7 (2.4)	5 (0-10)
Sexually transmitted infection history									
Any STI[b]	175 (47.8)			75 (44.9)			43 (37.7)		
Chlamydia	146 (39.9)			59 (35.3)			28 (24.6)		
Gonorrhea	64 (17.5)			26 (15.6)			16 (14.0)		
Trichomonas	74 (20.2)			33 (19.8)			20 (17.5)		
Herpes	10 (2.7)			6 (3.6)			6 (5.3)		
Abnormal Pap test history	110 (34.2)			51 (32.7)			19 (18.5)		
Smoked at least 100 cigarettes (lifetime)	114 (31.8)			64 (39.0)			39 (34.8)		
Number of days smoked, past 30 days									
0	259 (71.2)			113 (67.7)			78 (68.4)		
1-29	41 (11.3)			21 (12.6)			12 (10.5)		
30	64 (17.6)			33 (19.8)			24 (21.1)		
Sexual history									
Age of first sexual intercourse		15.0 (2.0)	15 (2-23)		15.3 (2.2)	15 (6-23)		16.4 (2.5)	16 (9-25)
≤15 years	224 (63.3)			89 (53.3)			43 (37.7)		
>15 years	130 (36.7)			78 (46.7)			71 (62.3)		
Number of male partners, lifetime		5.9 (8.4)	4 (0-100)		6.0 (7.0)	4 (1-65)		5.4 (6.4)	3.5 (1-50)
1	64 (18.3)			17 (10.3)			25 (21.9)		

	Wave 1 (2006-2007)			Wave 2 (2009-2010)			Wave 3 (2013-2014)		
Participant characteristic	**N (%)[a]**	**Mean (SD)**	**Median (range)**	**N (%)[a]**	**Mean (SD)**	**Median (range)**	**N (%)[a]**	**Mean (SD)**	**Median (range)**
2-4	144 (41.1)			68 (41.2)			43 (37.7)		
5-9	88 (25.1)			54 (32.7)			24 (21.1)		
10+	50 (14.3)			26 (15.8)			22 (19.3)		
Number of male partners, past 3 months		1.2 (1.2)	1 (0-10)		1.2 (0.6)	1 (0-4)		1.1 (0.7)	1 (0-5)
0	48 (13.6)			12 (7.1)			9 (7.9)		
1	235 (66.4)			126 (75.5)			87 (76.3)		
2+	71 (20.1)			29 (17.4)			18 (15.8)		
Number of new male partners, past 3 months		0.5 (0.8)	0 (0-6)		0.3 (0.6)	0 (0-3)		0.3 (.5)	0 (0-3)
0	215 (60.9)			119 (71.3)			88 (77.2)		
1+	138 (39.1)			48 (28.7)			26 (22.8)		
Anal intercourse, lifetime	89 (25.3)			43 (25.8)			29 (25.4)		
Frequency of condom use, past 3 months, main partner									
Never	115 (35.9)			82 (51.6)			54 (50.5)		
Sometimes	132 (41.3)			56 (35.2)			35 (32.7)		
Always	73 (22.8)			21 (13.2)			18 (16.8)		
Used condom at last intercourse, main partner									
Yes	121 (32.6)			44 (26.4)			33 (30.8)		
No	250 (67.4)			123 (73.7)			74 (69.2)		

[a] Some percentages do not add up to 100% because of missing values.

[b] Any STI was defined as history of gonorrhea, chlamydia, trichomonas, pubic lice, syphilis, herpes simplex virus, and/or human immunodeficiency virus

Table 2

Variables associated with vaccine-type HPV in unvaccinated women: results of inverse propensity score-weighted univariable and multivariable logistic regression models across 3 waves[a]

		Vaccine-type HPV					
		Wave 1 (2006-2007)		Wave 2 (2009-2010)		Wave 3 (2013-2014)	
Variables	**Categories**	**OR[b] (95% CI)**	**AOR[c] (95% CI)**	**OR (95% CI)**	**AOR (95% CI)**	**OR (95% CI)**	**AOR (95% CI)**
Age (years)	22-26 vs. 13-17	1.2 (0.6-2.1)		1.8 (0.6-5.9)		1.1 (0.4-3.0)	
	18-21 vs. 13-17	**1.9 (1.1-3.3)**	**2.1 (1.2-3.6)**	2.0 (0.7-5.9)		0.4 (0.1-1.3)	
Race	Black/mulitracial[d] vs. White	**1.6 (1.0-2.5)**	**1.8 (1.1-3.0)**	0.5 (0.2-1.1)		1.7 (0.7-4.2)	
Lifetime anal intercourse	Yes vs. no	**1.6 (1.0-2.6)**	**1.8 (1.1-3.0)**	1.5 (0.6-3.4)		1.7 (0.6-4.5)	
Lifetime male partners	Continuous	**1.0 (1.0-1.1)[e]**		1.1 (1.0-1.2)		1.1 (1.0-1.1)	
Type of insurance	Medicaid vs. private	1.3 (0.6-2.8)		0.8 (0.2-3.3)		0.4 (0.1-1.3)	
	None vs. private	1.2 (0.5-2.8)		0.8 (0.2-3.6)		**0.2 (0.1-0.8)**	
History of an STI[f]	Yes vs. no	1.3 (0.8-2.0)		1.4 (0.6-3.1)		**3.4 (1.3-9.0)**	**3.6 (1.3-9.7)**

[a] Shown in the Table are all variables associated with the outcome variable in unadjusted models at $p < .10$, in any of the three waves

[b] Unadjusted odds ratio; those variables associated with the outcome variable in unadjusted models at $p < .10$ are bolded

[c] Adjusted odds ratio; those variables associated with the outcome variable in adjusted models at $p < .05$ are bolded

[d] Black and multiracial were combined for analyses due to the small number of multiracial participants; univariable analyses conducted with these categories separate were unchanged

[e] Odds ratios (OR) and 95% confidence intervals (CI) were rounded in this table. The actual numbers for this variable were as follows: wave 1 (OR 1.042, 95% CI 1.001-1.084), wave 2 (OR 1.062, 95% CI 0.976-1.156), wave 3 (OR 1.06, 95% CI 0.977-1.149). If the 95% CI did not include 1.0 we considered it to be significant (as was the case in wave 1; in addition, the p value was < .05). If the 95% CI included 1.0 we considered it to be non-significant (as was the case in waves 2 and 3; in addition, the p value was > .05 for both).

[f] Self-reported history of a sexually transmitted infection