Published in final edited form as:

Vaccine. 2017 December 19; 35(52): 7217–7221. doi:10.1016/j.vaccine.2017.11.005.

Differences between Vaccinated and Unvaccinated Women Explain Increase in Non-Vaccine-Type Human Papillomavirus in Unvaccinated Women after Vaccine Introduction

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Abstract

The aim of this study was to determine whether an observed increase in non-vaccine-type human papillomavirus (HPV) in unvaccinated women during the first eight years after vaccine introduction may be explained by differences in demographics or sexual behaviors, instead of type replacement. We analyzed data from three cross-sectional surveillance studies of 13–26 year-old women (total N=1180). For women recruited from a health department clinic, older age (OR=1.4, 95% CI: 1.2–1.6) and consistent condom use with main partner in the past 3 months (OR=11.6, 95% CI: 3.4–40) were associated with being unvaccinated. For women recruited from a teen health center African American race (OR=0.2, 95% CI: 0.07–0.7) and having Medicaid health insurance (OR=0.3, 95% CI: 0.1–0.7) were inversely associated with being unvaccinated. The observed increase in non-vaccine-type HPV prevalence in unvaccinated women may be explained by differences between unvaccinated and vaccinated women.

Keywords

human papillomavirus; vaccine; women

Background

Human papillomavirus (HPV) infection is a common sexually transmitted infection that may cause anogenital and oropharyngeal cancers. Surveillance studies after introduction of prophylactic HPV vaccines have demonstrated that vaccine introduction has led to a substantial decline in vaccine-type HPV prevalence in vaccinated individuals [1], supporting

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

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vaccine effectiveness, and a decline in vaccine-type HPV among unvaccinated individuals in regions where vaccination rates are high, supporting herd protection [1, 2].

Studies have also examined trends in non-vaccine-type HPV after vaccine introduction to identify if cross protection or type replacement is occurring. Cross-protection against HPV types genetically related to vaccine-type HPV may lead to a decrease in non-vaccine-type HPV and increase vaccine effectiveness [3–6]. Type-replacement, defined as an increase in non-vaccine-type HPV due to an ecological niche created by a reduction in vaccine-type HPV, could lead to an increase in cancers caused by non-vaccine HPV types, but is thought to be very unlikely given that HPV is a genetically stable virus and competition between HPV types has not been observed [7, 8]. Recent studies have not demonstrated evidence of type replacement [9], but findings are inconsistent [4, 5, 10].

In our ongoing study in which three unique cohorts of young women were recruited before and after HPV vaccine introduction, we found a significant increase in non-vaccine-type HPV prevalence among unvaccinated, but not vaccinated, women [11]. In that study, non-vaccine-type HPV was comprised of types genetically related and unrelated to vaccine-type HPV, and therefore we did not take into account the effects of cross-protection, which could decrease non-vaccine-type HPV prevalence. We hypothesized that a possible mechanism for the increase in non-vaccine-type HPV prevalence might be differences in demographic characteristics or behaviors between unvaccinated and vaccinated women that are associated with the risk of HPV acquisition, such as race, insurance status, and sexual behaviors [12–19]. Therefore, the first aim of this study was to examine changes in non-vaccine-type HPV genetically unrelated to vaccine-type HPV, in order to take into account the possible effects of cross-protection, over first 8 years after vaccine introduction in vaccinated and unvaccinated women. The second aim was to examine whether there were any differences between unvaccinated and vaccinated women; we hypothesized that unvaccinated women would be more likely to have demographic and behavioral characteristics that have been associated with HPV infection in previous studies [12–19].

Methods

We conducted three cross-sectional studies before (2006–2007, n=371) and during the 8 years after (2009–2010, n=409, and 2013–2014, n=400) widespread HPV vaccine introduction [1]. A total of 1180 young women 13–26 years of age were recruited sequentially from a hospital-based teen health center and health department clinic in Cincinnati, Ohio. Participants completed a survey immediately after enrollment which assessed sociodemographic characteristics, gynecological history and behaviors, and vaccination status, defined as having received at least one HPV vaccine dose before enrollment and verified by medical record. The survey was developed and validated in several studies [20]. Cervicovaginal swabs were obtained and were tested for 36 HPV types using the Roche Linear Array test (Roche Molecular Systems, Alameda, CA) [1, 21]. The study was approved by the Institutional Review Boards of the hospital and health department, and written informed consent was obtained from participants.

All vaccinated women had received the 4-valent vaccine. The four outcome variables were: 1) non-vaccine-type HPV, 2) non-vaccine-type HPV genetically related to HPV16 (HPV31, 33, 35, 52, 58, 67), 3) non-vaccine-type HPV genetically related to HPV18 (HPV39, 45, 59, 68, 70), and 4) non-vaccine-type HPV genetically unrelated to HPV16 or HPV18.

Propensity score analysis as previously described [1] was carried out to balance baseline covariates across the 3 study waves by vaccination status. We previously examined changes in prevalence of the first three outcome variables between waves 1 and 3 in vaccinated and unvaccinated women, not stratified by recruitment site.[11] In this study, we examined changes in prevalence of the fourth outcome variable, and also stratified analyses for all four outcomes by recruitment site. We then determined whether there were any differences in demographics or sexual behaviors between the vaccinated and unvaccinated women between waves 1 and 3, using t-test or Wilcoxon rank-sum test for continuous variables, and Chi-square test or Fisher's exact test for categorical variables. For factors that were different between vaccinated and unvaccinated women in univariable analysis at $p < .10$, multivariable logistic regression analysis with stepwise variable selection was used to determine if any of these factors were independently associated with HPV vaccination status. In addition, univariable logistic regression models were run to examine the associations between those factors that differed significantly by vaccination status ($p < .05$) and non-vaccine-type HPV infection. We stratified all above analyses by recruitment site because the populations recruited from the two sites differed demographically. For example, women recruited from the health department were older, more likely to be Hispanic, more likely to be married, and more likely to be uninsured (vs. having private or public insurance) compared to women recruited from the teen health center. All analyses were done with inverse propensity score weighting. SAS version 9.3 (Cary, NC) was used for all analyses.

Results

We enrolled 1180 young women in the three study waves: none were vaccinated in wave 1 and 71.5% (286/400) were vaccinated in wave 3. Participant sociodemographic characteristics, gynecological history and behaviors were described in previous publications [1]. Table 1 and Figure 1 demonstrate non-vaccine-type HPV prevalence in waves 1 and 3 after inverse propensity score weighting. As previously reported,[11] in vaccinated women, there was no change in all non-vaccine type HPV, no change in non-vaccine-type HPV genetically related to HPV18, and a 36.1% ($p=0.01$) decrease in non-vaccine-type HPV genetically related to HPV16. In these analyses, we also noted a small (3.9%) but nonsignificant increase in non-vaccine-type HPV genetically unrelated to vaccine types. In unvaccinated women, as previously reported,[11] there was a 24.5% ($p=0.01$) increase in all non-vaccine type HPV, a 55.2% ($p=0.022$) increase in non-vaccine-type HPV genetically related to HPV18, and no significant change in non-vaccine-type HPV genetically related to HPV16. In these analyses, we also noted a 24.3% ($p=0.042$) increase in non-vaccine-type HPV genetically unrelated to vaccine-type HPV. In analyses stratified by recruitment site, the direction of the changes in non-vaccine-type HPV were similar except for non-vaccine-type HPV genetically related to HPV16: among unvaccinated women from the health department, prevalence decreased 24.9% ($p > .05$), but among women from the teen health center, prevalence increased by 74.7% ($p=0.012$). The increase in all non-vaccine-type HPV,

non-vaccine-type HPV genetically related to HPV18, and non-vaccine-type HPV genetically unrelated to HPV16 or HPV18 noted among unvaccinated women in analyses that were not stratified by site were also noted in analyses stratified by site, but the increases were not all statistically significant, likely due to smaller sample sizes in stratified analyses.

Differences in demographics and sexual behaviors between unvaccinated and vaccinated women in wave 3 are shown in Table 2. Among women recruited from the health department, unvaccinated vs. vaccinated women were more likely to lack health insurance; to use condoms consistently with one's main male partner over the past 3 months; and to be older. In multivariable analyses, older age (OR=1.4, 95% CI: 1.2–1.6) and consistent condom use with main partner in the past 3 months (OR=11.6, 95% CI: 3.4–40) were associated with being unvaccinated. Among women recruited from the teen health center, unvaccinated women were less likely to be African-American; less likely to have Medicaid; more likely to have at least one new sexual partner in past 3 months; and less likely to have had anal sexual intercourse. In multivariable analysis, African American race (OR=0.2, 95% CI: 0.07–0.7) and having Medicaid health insurance (OR=0.3, 95% CI: 0.1–0.7) were inversely associated with being unvaccinated.

Logistic regression analysis examining the association between the variables that differed significantly by vaccination status and non-vaccine-type HPV infection, by recruitment site, demonstrated the following. Among women recruited from the health department, lack of health insurance was associated with overall non-vaccine-type HPV infection (OR=2.3, 95% CI: 1.1–4.8) and non-vaccine-type HPV genetically unrelated to HPV 16 or 18 (OR=2.3, 95% CI: 1.2–4.6); and consistent condom use with main partner in the past 3 months was associated with non-vaccine-type HPV types that are genetically related to HPV 18 (OR=4.7, 95% CI: 2.0–10.9). Among women recruited from the teen health center, one or more new male sexual partners in past 3 months was associated with overall non-vaccine-type HPV infection (OR=2.4, 95% CI: 1.3–4.2), non-vaccine-type HPV types genetically unrelated to HPV 16 or 18 (OR=2.7, 95% CI: 1.5–4.7), and non-vaccine-type HPV types genetically related to HPV 16 (OR=2.4, 95% CI: 1.2–4.8).

Discussion

In this study, we examined mechanisms for observed increases in non-vaccine type HPV infections among unvaccinated women after HPV vaccine introduction. We previously reported an increase in all non-vaccine-type HPV and non-vaccine-type HPV genetically related to HPV18,[11] and in this study found an increase in non-vaccine types genetically unrelated to HPV16 and HPV18, indicating that the increase in non-vaccine-type HPV was present even after accounting for the non-vaccine types that might be expected to decrease in prevalence due to cross-protection.

We compared participant characteristics and behaviors by vaccination status in order to explore whether differences between vaccinated and unvaccinated women could explain the observed increase in non-vaccine-type HPV in unvaccinated women, hypothesizing that unvaccinated women may be more likely to have characteristics that would increase risk for HPV infection. Among women recruited from the health department, unvaccinated vs.

vaccinated women were more likely to lack health insurance, use condoms consistently, and be older in univariable analyses; consistent condom use and older age remained significant in the multivariable analysis. A lack of health insurance may indicate poverty or poor access to health care, which have been associated with HPV in previous studies [12, 15, 18] and which we also demonstrated in this study. As a number of women from the health department were married, condom use may reflect not being in a stable, monogamous relationship which could increase the risk of HPV [12, 14, 15] which we also demonstrated in this study. The finding that unvaccinated women were older than vaccinated women (21.5 vs. 19.4 years) also aligns with our hypothesis, as previous studies have demonstrated that women in the 20–24 year-old age range are at the highest risk for HPV infection [12, 22].

Among women recruited from the teen health center, unvaccinated vs. vaccinated women were less likely to be African-American, less likely to have Medicaid (public) health insurance, more likely to have at least one new sexual partner in the past 3 months, and less likely to have had anal sexual intercourse in univariable analyses; not reporting African-American race and lack of Medicaid insurance remained significant in the multivariable analysis. Although several previous studies have identified an association between African-American race and HPV infection [18, 19], African-American women in this clinic may have been more likely to be offered or accept HPV vaccination. The finding that unvaccinated women were less likely to have Medicaid insurance is expected, given that it covers the cost of HPV vaccines and is associated with vaccination status [13] and improved health outcomes [17]. The finding that unvaccinated women were more likely to have a new recent sexual partner is consistent with our hypothesis, as number of recent sexual partners is consistently associated with HPV infection [16, 19, 22], which was also demonstrated in the current study. Although the finding that unvaccinated women were less likely to have had anal sexual intercourse would be unexpected given our hypothesis, this finding is difficult to interpret as only 4 women reported anal sex.

The primary limitation of this study was that it was a cross-sectional study with local geographic distribution of participants, which may limit generalizability of the study findings. However, the findings suggest that unvaccinated vs. vaccinated women may have poorer access to health care and engage in behaviors that increase their risk of acquiring non-vaccine-type HPV infection. Surveillance studies that examine changes in non-vaccine type HPV prevalence after vaccine introduction should take into account demographic and behavioral differences between unvaccinated and vaccinated women, and exercise caution in attributing any increase in non-vaccine-type HPV to type replacement.

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.

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].

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Figure 1.

Prevalence of non-vaccine HPV types in waves 1 and 3, inverse propensity score weighted. Data in the figure are proportions and 95% confidence intervals of vaccinated and unvaccinated women, all and stratified by recruitment site, with all non-vaccine-type HPV, non-vaccine-HPV types genetically related to HPV16 (A9 species) and HPV18 (A7 species), and non-vaccine-HPV types genetically unrelated to HPV16 or 18. Note: some of the data in the left panel of the figure were previously published.[11]

Table 1

Prevalence of non-vaccine HPV types in waves 1 and 3, inverse propensity score weighted

	All non-vaccine types % (95% CI) ¹	Genetically related to HPV18 (A7) % (95% CI)	Genetically related to HPV16 (A9) % (95% CI)	Genetically unrelated to HPV 16 or 18 % (95% CI)
All women²				
Unvaccinated women in wave 1 and vaccinated women in wave 3				
Wave 1³ (n=371)	60.7(55.4 ,65.8)	23.3(19.1 ,28.1)	24.1(19.8 ,29)	50.7(45.3 ,56)
Wave 3 (n=277)	61.1(55 ,66.9)	24(19.2 ,29.7)	15.4(11.5 ,20.4) ⁴	52.7(46.6 ,58.7)
Unvaccinated women in wave 1 and unvaccinated women in wave 3				
Wave 1³ (n=371)	57.9(52.5 ,63.1)	21(16.9 ,25.7)	24.1(19.8 ,29)	47.3(42 ,52.7)
Wave 3 (n=112)	72.1(62.7 ,79.9) ⁴	32.6(24.3 ,42.2) ⁴	29.7(21.7 ,39.2)	58.8(49.1 ,67.9) ⁴
Women recruited from the health department				
Unvaccinated women in wave 1 and vaccinated women in wave 3				
Wave 1³ (n=132)	51.5(41.1, 61.9)	16.5(10.0, 26.0)	21.9(14.3, 31.9)	43.1(33.1, 53.7)
Wave 3 (n=62)	63.7(51.7 ,74.2)	22.8(14.3, 34.3)	14.6(8.0, 25.1)	54.7(42.8, 66.0)
Unvaccinated women in wave 1 and unvaccinated women in wave 3				
Wave 1³ (n=132)	52.1(44.4, 59.7)	19.6(14.1, 26.5)	22.5(16.6, 29.6)	43.1(35.7, 50.9)
Wave 3 (n=81)	65.0(51.7, 76.2)	30.8(20.1, 44.0)	16.9(9.2, 29.0)	53.5(40.5, 66.0)
Women recruited from the teen health center				
Unvaccinated women in wave 1 and vaccinated women in wave 3				
Wave 1³ (n=239)	63.9(57.8, 69.6)	25.6(20.6, 31.4)	24.9(19.9, 30.6)	53.3(47.1, 59.4)
Wave 3 (n=215)	60.1(53.0, 66.9)	24.4(18.8, 31.1)	15.7(11.2, 21.7) ⁴	52.0 (44.9, 59.0)
Unvaccinated women in wave 1 and unvaccinated women in wave 3				
Wave 1³ (n=239)	63.4(55.9, 70.2)	22.3(16.7, 29.1)	25.7(19.7, 32.8)	51.3(43.8, 58.7)
Wave 3 (n=31)	80.6(66.9, 89.5) ⁴	34.8(22.7, 49.3)	44.9(31.5, 59.1) ⁴	65.2(50.7, 77.3)

¹ CI: Confidence interval² Some of the data on all women were previously published.[11]

³ The change in non-vaccine-type HPV in vaccinated women was defined as change in non-vaccine-type HPV prevalence among all women in wave 1 (all of whom were unvaccinated) and vaccinated women in wave 3. The change in non-vaccine-type HPV in unvaccinated women was defined as change in HPV prevalence among all women in wave 1 (all of whom were unvaccinated) and unvaccinated women in wave 3. In each analysis (changes in non-vaccine type HPV in vaccinated women and changes in non-vaccine type HPV in unvaccinated women) baseline covariates across the 3 study waves were balanced using propensity score analysis. Propensity score analyses were carried out for analysis of vaccinated women and for unvaccinated women, which resulted in two different sets of propensity scores for the participants in study wave 1. This accounts for the different numbers for non-vaccine-type HPV prevalence for vaccinated and unvaccinated for study wave 1 after inverse propensity score weighting.

⁴ Statistically significant different from wave 1 (p<0.05)

Table 2
Differences in demographics or sexual behaviors between the unvaccinated and vaccinated women in wave 3 by recruitment site.

	All women			Health department			Teen health center		
	Unvaccinated (n=112 ^I)	Vaccinated (n=277 ^I)	N (% adjusted)	Unvaccinated (n=81 ^I)	Vaccinated (n=62 ^I)	p-value ² PS Adjusted	Unvaccinated (n=31 ^I)	Vaccinated (n=215 ^I)	p-value ² PS adjusted
				N (% adjusted)			N (% adjusted)		
Demographic characteristics									
Age, years, mean (SD), adjusted	19.8 (3.3)	18.2 (2.1)		21.5 (3.0)	19.4 (2.8)	<0.0001	17.7 (2.0)	17.8 (1.7)	0.5826
Race						0.7580			0.0297
White/Asian, Pacific Islander/Native American	56 (42.2)	50 (22.5)		50(64.2)	37(66.8)		6(16.2)	13(6.4)	
African American/Multiracial/other	56 (57.8)	227 (77.5)		31(35.8)	25(33.2)		25(83.8)	202(93.6)	
Appalachian descent	4 (5.3)	5 (4.9)		4(9.7)	4(15.3)	0.3529	0(0)	1(1.1)	0.4591
Hispanic ethnicity	19 (8.0)	7 (3.2)		16(12.1)	5(10)	0.7174	3(3.3)	2(0.7)	0.1548
Insurance status						0.0370			0.2081
Not insured/not sure/missing	33 (35.3)	40 (17.5)		31(47.8)	15(29.6)		2(20.4)	25(13.2)	
Insured	79 (64.7)	237 (82.5)		50(52.2)	47(70.4)		29(79.6)	190(86.8)	
Health insurance plan						0.0834			0.0407
Private	9 (9.6)	25 (11.7)		1(0.7)	5(8.6)		8(20.2)	20(12.9)	
Medicaid	66 (48.1)	197 (62.7)		48(50)	38(54.1)		18(45.8)	159(65.8)	
Others/none/not sure/missing	37 (42.3)	55 (25.5)		32(49.3)	19(37.3)		5(34)	36(21.3)	
Marital status of ever married	6 (6.5)	2 (2.0)		6(11.9)	1(5.3)	0.1813	0(0)	1(0.8)	0.5417
Gynecologic history									
Any pregnancy	74 (50.6)	90 (37.0)		67(79.4)	40(69)	0.1857	7(16.3)	50(25.4)	0.1885
Any STI (other than warts)	43 (47.6)	152 (54.2)		27(37.1)	21(34.9)	0.7970	16(60)	131(61.3)	0.8716
Behaviors									
Age at first sexual intercourse						0.6929			0.2533
13 and younger	7 (17.6)	54 (19.9)		6(17.5)	9(16.4)		1(17.8)	45(21.1)	
14–17	76 (69.3)	212 (74.9)		51(64.4)	47(70.6)		25(75)	165(76.4)	
18 and older	29 (13.1)	11 (5.2)		24(18.1)	6(12.9)		5(7.2)	5(2.4)	
Lifetime male sexual partners						0.3746			0.7044

	All women			Health department			Teen health center		
	Unvaccinated (n=112 ^f)		Vaccinated (n=277 ^f)	Unvaccinated (n=81 ^f)		Vaccinated (n=62 ^f)	Unvaccinated (n=31 ^f)		Vaccinated (n=215 ^f)
	N (%) adjusted			N (%) adjusted			N (%) adjusted		
1	25 (17.5)	45 (17.0)	18(16.4)	16(25.1)			7(18.8)	29(14)	
2-5	52 (47.1)	149 (52.4)	34(41.8)	26(43.2)			18(53.3)	123(55.7)	
>=6	35 (35.4)	83 (30.7)	29(41.8)	20(31.8)			6(27.9)	63(30.3)	
Male sexual partners in past 3 months						0.5580			0.2449
0	9 (7.5)	31 (13.1)	6(8.7)	5(11.1)			3(6.2)	26(13.8)	
1	85 (68.2)	189 (64.9)	67(76.7)	51(80.2)			18(58.1)	138(59.3)	
2	18 (24.2)	57 (22.1)	8(14.6)	6(8.7)			10(35.7)	51(26.9)	
New male sexual partners in past 3 months						0.3849			0.0035
0	86 (58.6)	196 (67.1)	69(75.8)	54(82.2)			17(38.1)	142(61.6)	
1	26 (41.4)	81 (32.9)	12(24.2)	8(17.8)			14(61.9)	73(38.4)	
Main sexual partner male						0.7324			0.3866
No	3 (2.1)	10 (3.3)	2(2.5)	2(1.9)			1(1.6)	8(3.8)	
Yes	105 (93.8)	246 (89.2)	77(93.9)	59(96.5)			28(93.8)	187(86.5)	
Don't have a main sexual partner	4 (4.1)	21 (7.5)	2(3.6)	1(1.5)			2(4.6)	20(9.7)	
Any history of anal sex with male partner	28 (22.9)	51 (21.4)	24(35.1)	12(21.3)		0.0858	4(8.5)	39(21.5)	0.0409
Condom use with main partner in past 3 months						0.0067			0.2936
Less than every time	94 (73.0)	237 (81.6)	69(75.3)	57(92.8)			25(70.3)	180(77.6)	
Every time	18 (27.0)	40 (18.4)	12(24.7)	5(7.2)			6(29.7)	35(22.4)	
Condom use at last sexual intercourse with main male partner	33 (41.9)	105 (37.8)	20(35.2)	16(25.5)		0.2347	13(49.8)	89(42.2)	0.3492
Any other male sexual partners						0.3353			0.3207
No	16 (15.8)	28 (12.6)	11(18.1)	8(12.6)			5(13.1)	20(12.5)	
Yes	22 (30.0)	100 (30.6)	8(12.9)	6(7.1)			14(50.3)	94(39.1)	
Don't have any other male partners	74 (54.2)	149 (56.8)	62(69)	48(80.2)			12(36.6)	101(48.3)	
Condom use with other male partners, past 3 months						0.9749			0.1194
Less than every time	104 (85.9)	241 (86.6)	79(96.9)	60(97)			25(72.9)	181(82.8)	
Every time	8 (14.1)	36 (13.4)	2(3.1)	2(3)			6(27.1)	34(17.2)	