HUMAN VACCINES & IMMUNOTHERAPEUTICS
2019, VOL. 15, NOS. 7–8, 1962–1969
https://doi.org/10.1080/21645515.2018.1564438

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RESEARCH PAPER

Evidence for cross-protection but not type-replacement over the 11 years after human papillomavirus vaccine introduction

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ABSTRACT

Examination of cross-protection and type replacement after human papillomavirus (HPV) vaccine introduction is essential to guide vaccination recommendations and policies. The aims of this study were to examine trends in non-vaccine-type HPV: 1) genetically related to vaccine types (to assess for cross-protection) and 2) genetically unrelated to vaccine types (to assess for type replacement), among young women 13–26 years of age during the 11 years after HPV vaccine introduction. Participants were recruited from a hospital-based teen health center and a community health department for four cross-sectional surveillance studies between 2006 and 2017. Participants completed a survey that assessed sociodemographic characteristics and behaviors, and cervicovaginal swabs were collected and tested for 36 HPV genotypes. We determined changes in proportions of non-vaccine-type HPV prevalence and conducted logistic regression to determine the odds of infection across the surveillance studies, propensity-score adjusted to control for selection bias. Analyses were stratified by vaccination status. Among vaccinated women who received only the 4-valent vaccine (n = 1,540), the adjusted prevalence of HPV types genetically related to HPV16 decreased significantly by 45.8% (adjusted odds ratio [AOR] = 0.48, 95% confidence interval [CI] = 0.31–0.74) from 2006–2017, demonstrating evidence of cross-protection. The adjusted prevalence of HPV types genetically related to HPV18 did not change significantly (14.2% decrease, AOR = 0.83, 95% CI = 0.56–1.21). The adjusted prevalence of HPV types genetically unrelated to vaccine types did not change significantly (4.2% increase, AOR = 1.09, CI = 0.80–1.48), demonstrating no evidence of type replacement. Further studies are needed to monitor for cross-protection and possible type replacement after introduction of the 9-valent HPV vaccine.

ARTICLE HISTORY
Received 4 October 2018
Revised 3 December 2018
Accepted 23 December 2018

KEYWORDS
Cross-protection; type-replacement; human papillomavirus

Introduction

Human papillomavirus (HPV) infection causes cervical cancer, the second most commonly diagnosed cancer in women.[1] In 2012, GLOBOCAN reported 528,000 new cases of cervical cancer globally.[1] HPV infection may cause other anogenital and oropharyngeal cancers in both women and men. It is estimated that 90–93% of anal cancers, 36–40% of penile cancers, 40–64% of vaginal cancers, 40–51% of vulvar cancers, and 12–63% of oropharyngeal cancers are attributable to HPV.[2-4] Three prophylactic HPV vaccines have been licensed: a 2-valent vaccine (2vHPV) that prevents HPV16 and 18; a 4-valent vaccine (4vHPV) that prevents HPV6, 11, 16 and 18; and a 9-valent vaccine (9vHPV) that prevents HPV16, 18, 6, 11, 31, 33, 45, 52, and 58.[5] HPV16, of the *Alphapapillomavirus* 9 species (A9), and HPV18, of the *Alphapapillomavirus* 7 species (A7), are the most carcinogenic HPV types, causing approximately 70% of cervical cancers, and are targeted by all three licensed HPV vaccines.[6] Studies have demonstrated that HPV vaccines not only have high efficacy in clinical trials, but also high effectiveness in real-world settings: we have demonstrated that 4-valent vaccine-type HPV detection decreased from 35%-6.7% (80.9% decline) among vaccinated women, demonstrating vaccine effectiveness, and decreased from 32.4%-19.4% (40% decline) among unvaccinated women, demonstrating herd protection.[7]

Vaccination may also result in cross-protection; that is, protection against HPV types genetically related to vaccine types, because HPV16 is genetically related to other A9 types and HPV18 is genetically related to other A7 types. It has been hypothesized that anti-HPV16 and anti-HPV18 antibodies generated by vaccination may bind to and neutralize HPV virions genetically related to HPV16 or HPV18, given the polyclonal immune response to vaccination.[8] Several HPV vaccine clinical trials have shown evidence of cross-protection; however, less is known about cross-protection outside of the trial setting. Information about cross-protection in real-world settings is important for clinical- and cost-effectiveness assessments and health policy decisions, given that cross-protection could increase vaccine effectiveness. Long-term surveillance is essential given that there is some evidence from clinical trials that cross-protection wanes over time.[9,10]

In contrast to cross-protection, type replacement could lead to an increase in non-vaccine-type HPV which could decrease vaccine effectiveness.[11] This may occur if the ecological niche that was occupied by HPV16 and HPV18 becomes vacated due to a decrease in vaccine-type.[11] Currently, there is

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no definitive evidence of type replacement after HPV vaccine introduction.[12,13] This is expected, as HPVs are genetically stable DNA viruses that have co-evolved with their specific vertebrate host, and have a very low rate of mutations, at about one nucleotide every 1,000 years.[13,14] However, it is important to exclude type replacement after HPV vaccine introduction because type replacement has been documented after introduction of other vaccines, including Haemophilus influenza and Streptococcus pneumococcal vaccines,[15-17] and because the evidence regarding type replacement after HPV vaccine introduction is not conclusive. Some studies suggest a possible competitive advantage for non-vaccine types or an increase in non-vaccine-types after vaccine introduction,[18-21] supporting continued monitoring for type replacement. To determine accurately whether emerging type-replacement is occurring, it is important to examine non-vaccine-type HPV that is genetically unrelated to vaccine-type HPV, as cross-protection may decrease the prevalence of types genetically related to those in the vaccines, which could mask an increase in non-vaccine-type HPV.

In order to assess cross-protection and type-replacement in a community setting, we conducted surveillance studies examining the prevalence of non-vaccine-type HPV before and during the 11 years after widespread HPV vaccine introduction. The first aim was to examine trends in the prevalence of HPV types genetically related to those targeted by the 4vHPV vaccine. We hypothesized, based on clinical trials data,[8,9] that there would be a significant decrease in the prevalence of HPV types genetically related to HPV16 (HPV31, 33, 35, 52, 58, 67) and HPV18 (HPV39, 45, 59, 68, 70) among young women who received the 4vHPV vaccine. The second aim was to assess for emerging type replacement by examining trends in the proportion of young women infected with non-vaccine-type HPV. We hypothesized we would not observe an increase in non-vaccine-type HPV genetically unrelated to vaccine-type HPV.

Results

A total of 1,580 participants were enrolled across four surveillance studies, and 1,540 were included in these analyses: 40 (2.5%) were excluded because they had received at least one dose of the 9-valent HPV vaccine. Between 95% and 98% of those approached agreed to participate across the surveillance studies. Participant characteristics across the four surveillance studies are shown in Table 1. The mean age of participants across the four studies was 18.7–19.2 years, 69.9%-76.7% identified as African American or Multiracial, and 52.8%-70.6% reported having Medicaid health insurance. Between 70.1% and 77.8% of all participants reported sexual initiation between 14 and 17 years of age, 78%-87.8% reported having more than one lifetime male partner, and 64.3%-73.9% reported not using a condom at last sexual intercourse. Vaccination rates increased from 0% in study 1 to 59.2% in study 2, 71.5% in study 3, and 82.5% in study 4.

Demographic characteristics, gynecologic history, and sexual behaviors were compared across the four studies (Table 1). Due to several significant differences across studies, variables were balanced using propensity score weighting. After propensity score weighting, there were no significant differences in variables across studies. When we compared the prevalence of baseline variables across the four study waves by vaccination status, before and after propensity score weighting, we found that the only variable that was not balanced was Appalachian background among unvaccinated women. Therefore, Appalachian background was included in the logistic regression model for unvaccinated women only. The β-globin control in the Roche Linear Array test, indicating adequate DNA for PCR amplification, was positive in 98.8% to 100% of all samples across the four studies.

The proportions of women (all, vaccinated, and unvaccinated) who were positive for non-vaccine-type HPV genetically related to HPV16 and HPV18, and positive for types not included and genetically unrelated to those in the vaccine, are shown in Table 2. The propensity score-adjusted proportion of all women with non-vaccine-type HPV genetically related to HPV16 did not change significantly from studies 1 to 4. However, the adjusted proportion of vaccinated women with non-vaccine-type HPV genetically related to HPV16 decreased significantly from 22.7% to 12.3% (45.8% decrease) from studies 1 to 4 while the adjusted proportion of unvaccinated women with non-vaccine-type HPV genetically related to HPV16 increased significantly from 22.3% to 35.3% (58.3% increase) from studies 1 to 4. The adjusted proportion of all women who were positive for non-vaccine-type HPV genetically related to HPV18 did not change significantly for all women or for vaccinated women, but decreased significantly from 20.2% to 6.3% (68.8% decrease) among unvaccinated women. There were no significant changes in non-vaccine-type HPV genetically unrelated to A9 and A7 species among all, vaccinated, and unvaccinated women except for a transient increase from study 1 to study 2.

The results of unadjusted and adjusted logistic regression models, comparing the odds of infection with non-vaccine-type HPV in studies 1, 2 and 3 with study 4, are shown in Table 3. The odds of non-vaccine-type HPV genetically related to HPV16 was significantly lower in study 4 vs. 1 (OR 0.48, 95% CI 0.31–0.74) among vaccinated women, and the odds of non-vaccine-type HPV genetically related to HPV18 was significantly lower in study 4 vs. 1 among unvaccinated women (OR 0.25, 95% CI 0.09–0.75). The odds of infection with non-vaccine-type HPV genetically unrelated to HPV16 and HPV18 did not change significantly from study 1 to 4.

Discussion

In this study, we investigated trends in the prevalence of HPV types genetically related to oncogenic HPV types targeted by 4vHPV (to assess for cross-protection), and the prevalence of HPV types genetically unrelated to 4vHPV (to assess for type-replacement), during the 11 years after HPV vaccine introduction, from 2006–2017. To our knowledge, this is the first U.S. study to assess cross-protection and type replacement more than 10 years after HPV vaccine introduction in a real-world setting, and extends the findings of our previous study[22] which assessed these outcomes from 2006–2014. In separate analyses, we examined trends in vaccine-type HPV to assess effectiveness and herd protection during this time period.[7]

Table 1. Comparison of participant characteristics across all four studies, propensity score unadjusted and adjusted.

Characteristic[a]	Study 1 (N = 371)		Study 2 (N = 409)		Study 3 (N = 400)		Study 4 (N = 360)		P[b], unadjusted	P[b], propensity score adjusted
	N (%)	Mean (SD)	N (%)	Mean (SD)	N (%)	Mean (SD)	N (%)	Mean (SD)		
Enrollment site										
Teen Health Center	239 (64.4)		268 (65.5)		250 (62.5)		271 (75.3)		0.001	0.069
Health Department	132 (35.6)		141 (34.5)		150 (37.5)		89 (24.7)			
Demographic characteristics and medical history										
Age (years)		18.7 (3.0)		18.8 (2.9)		19.1 (2.7)		19.2 (2.7)	0.03	
Race	110 (30.1)		114 (27.9)		108 (27.0)		84 (23.3)		0.22	0.85
White or Asian	255 (69.9)		295 (72.1)		292 (73.0)		376 (76.7)			
African-American or Multiracial										
Appalachian descent	24 (6.7)		16 (3.9)		9 (2.3)		6 (1.7)		0.001	0.32
Hispanic ethnicity	25 (6.9)		24 (5.9)		28 (7.0)		21 (5.8)		0.85	0.47
Marital status	331 (92.7)		391 (95.6)		392 (98.0)		349 (96.9)		0.002	0.58
Never married	26 (7.3)		18 (4.4)		8 (2.0)		11 (3.1)			
Ever married										
Health insurance										
Private	32 (8.6)		63 (15.4)		35 (8.8)		48 (13.3)		<0.0001	0.90
Medicaid	196 (52.8)		217 (53.1)		269 (67.3)		254 (70.6)			
None/Not Sure	143 (38.5)		129 (31.5)		96 (24.0)		58 (16.1)			
History of any STI[c]	170 (46.5)		212 (52.0)		202 (50.5)		192 (53.3)		0.272	0.3722
HPV vaccinated	0 (0)		242 (59.2)		286 (71.5)		297 (82.5)			
Behaviors										
Age of first sexual intercourse	76 (21.5)		85 (20.8)		63 (15.8)		36 (10.1)		0.0003	0.09
≤ 13 years of age	248 (70.1)		294 (72.1)		297 (75.3)		277 (77.8)			
14–17	30 (8.5)		29 (7.1)		40 (10.0)		43 (12.1)			
≥18										
Number of male sexual partners, lifetime:	68 (19.4)		49 (12.2)		71 (17.8)		78 (22.0)		0.0147	0.84
1	171 (48.9)		229 (56.8)		207 (52.0)		184 (51.8)			
2–5	111 (31.7)		125 (31.0)		120 (30.2)		93 (26.2)			
>5										
Number of male sexual partners, past three months:	48 (13.6)		43 (10.5)		40 (10.0)		32 (9.1)		0.279	0.15
0	235 (66.4)		280 (68.5)		282 (70.7)		260 (74.3)			
1	71 (20.1)		86 (21.0)		77 (19.3)		58 (16.6)			
>1										
Main sexual partner male	319 (89.1)		380 (92.9)		361 (90.3)		285 (80.1)		<0.0001	0.64
Had anal sex with a male partner	89 (25.3)		93 (22.7)		81 (20.3)		79 (22.6)		0.4481	0.63
Condom use with main partner, past three months										
Less than every time	298 (80.3)		333 (81.4)		342 (85.5)		320 (88.9)		0.005	0.64
Every time	73 (19.7)		76 (18.6)		58 (14.5)		40 (11.1)			
Condom use, last sexual intercourse	121 (37.5)		146 (38.5)		139 (34.8)		94 (26.1)		0.023	0.69
Smoked at least 100 cigarettes in lifetime	114 (31.8)		117 (29.1)		86 (21.9)		62 (17.4)		<0.0001	0.81

[a]Missing data are not reported in this table, as there were no or few missing data associated with each variable (<5% of data for each variable).
[b]P value calculated using the following tests: Chi-square, Fisher's exact, Kruskal Wallis, or Analysis of Variance.
[c]STI = sexually transmitted infection.

Table 2. Change in proportions of all, vaccinated and unvaccinated women positive for non-vaccine-type HPV, positive for ≥ 1 A9 species except HPV16, and positive for ≥A7 species except HPV18, across the 4 studies, propensity score adjusted.

	Prevalence of HPV types across studies, propensity score adjusted: %				Between-wave changes in HPV prevalence, propensity score adjusted: % (95% confidence interval) [% decline/increase]			
Vaccination status[a]	Study 1 (N = 371)	Study 2 (N = 409)	Study 3 (N = 400)	Study 4 (N = 360)	Study 1 to 2	Study 2 to 3	Study 3 to 4	Study 1 to 4
A9 species except HPV16[b]								
All	23.3	28.0	16.9	17.6	4.7 (−1.4,+10.8) [+20.2]	**−11.0 (−16.7,-5.3) [−39.6]**	0.7 (−4.8,+6.1) [+4.1]	−5.7 (−11.6,+0.2) [−24.5]
Vaccinated	22.7	28.9	15.5	12.3	6.2 (−0.9,+13.3) [+27.3]	**−13.4 (−20.5,-6.3) [−46.4]**	−3.1 (−8.8,+2.6) [−20.6]	**−10.4 (−16.1,-4.6) [−45.8]**
Unvaccinated	22.3	29.1	27.7	35.3	+6.8 (−1.4,+14.9) [+30.5]	−1.4 (−12.3,+9.4) [−4.8]	+7.6 (−7.1,+22.4) [+27.4]	**+13.0 (+0.1,+25.9) [58.3]**
A7 species except HPV18[c]								
All	22.1	31.8	25.0	17.3	**+9.7 (+3.5,+15.9) [+43.9]**	**−6.9 (−13.0,-0.7) [−21.4]**	**−7.7 (−13.5,-1.8) [−30.8]**	−4.8 (−10.6,+1.0) [−21.7]
Vaccinated	23.3	36.9	23.3	20.0	**+13.6 (+6.1,+21.0) [+58.4]**	**−13.6 (−21.4,-5.7) [−36.9]**	−3.3 (−10.1,+3.5) [−14.2]	−3.3 (−9.6,+3.1) [−14.2]
Unvaccinated	20.2	23.8	28.6	6.3	+3.6 (−4.1,+11.3) [+17.8]	+4.8 (−5.8,+15.5) [+20.2]	**−22.3 (−32.8,-11.9) [−78.0]**	**−13.9 (−21.3,-6.4) [−68.8]**
Non-vaccine-type HPV genetically unrelated to A7 and A9 species[d]								
All	48.2	59.7	53.4	54.5	**+11.5 (+4.6,+18.5) [+23.9]**	−6.4 (−13.2,+0.4) [−10.6]	+1.2 (−6.0,+8.4) [+2.1]	+6.3 (−1.0,+13.6) [+13.1]
Vaccinated	49.6	60.5	52.5	51.7	**+10.9 (+2.9,+18.9) [+22.0]**	−8.0 (−16.6,+0.5) [−13.2]	−0.8 (−9.1,+7.5) [−1.5]	+2.1 (−5.7,+9.8) [+4.2]
Unvaccinated	46.0	56.0	57.6	59.0	**+10.1 (+0.9,+19.2) [+21.7]**	+1.6 (−10.3,+13.5) [+2.9]	+1.3 (−14.2,+16.9) [+2.4]	+13.0 (−0.5,+26.5) [+28.3]

Bold indicates $p < 0.05$.

[a]No women were vaccinated in study 1, 242 (59.2%) were vaccinated in study 2, 286 (71.5%) were vaccinated in study 3, and 297 (82.5%) were vaccinated in study 4.

[b]Positive for ≥ 1 HPV type of the following: 31, 33, 35, 52, 58 and/or 67.

[c]Positive for ≥ 1 HPV type of the following: 39, 45, 59, 68 and/or 70.

[d]Positive for ≥ 1 HPV type other than 6, 11, 16, 18, 31, 33, 35, 39, 45, 52, 58, 59, 67, 68, and/or 70.

Table 3. Comparisons of the proportions of women positive for ≥ 1 non-vaccine HPV type, ≥ 1 A9 species except HPV16, and ≥ 1 A7 species except HPV18, across the four surveillance studies, stratified by vaccination status: results of logistic regression analyses unadjusted and adjusted for propensity scores.[a,b].

	Study 4 vs.1		Study 4 vs. 2		Study 4 vs. 3	
	Unadjusted OR[c,d] (95% CI[e])	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
A9 species except HPV16[f]						
All	0.58 (0.40–0.84)	0.70 (0.49–1.02)	0.45 (0.31–0.64)	**0.55 (0.39–0.78)**	0.93 (0.64–1.38)	1.05 (0.72–1.53)
Vaccinated	0.54 (0.36–0.80)	**0.48 (0.31–0.74)**	0.39 (0.26–0.60)	**0.35 (0.22–0.54)**	0.98 (0.62–1.55)	0.77 (0.48–1.25)
Unvaccinated	0.80 (0.42–1.54)	1.78 (0.99–3.21)	0.66 (0.33–1.33)	1.31 (0.70–2.47)	0.97 (0.46–2.08)	1.41 (0.71–2.76)
A7 species except HPV18[g]						
All	0.83 (0.58–1.20)	0.74 (0.51–1.07)	0.54 (0.39–0.76)	**0.45 (0.32–0.63)**	0.77 (0.54–1.09)	**0.63 (0.44–0.90)**
Vaccinated	0.98 (0.68–1.42)	0.83 (0.56–1.21)	0.53 (0.36–0.77)	**0.43 (0.29–0.64)**	0.90 (0.61–1.32)	0.82 (0.55–1.23)
Unvaccinated	0.24 (0.09–0.69)	**0.25 (0.09–0.75)**	0.22 (0.07–0.63)	**0.21 (0.07–0.65)**	0.23 (0.08–0.69)	**0.17 (0.05–0.51)**
Non-vaccine-type HPV genetically unrelated to A7 and A9 species[h]						
All	1.15 (0.86–1.55)	1.29 (0.96–1.73)	0.67 (0.50–0.90)	0.81 (0.60–1.08)	1.00 (0.75–1.33)	1.05 (0.78–1.40)
Vaccinated	1.14 (0.84–1.54)	1.09 (0.80–1.48)	0.58 (0.41–0.83)	**0.70 (0.49–0.99)**	0.96 (0.69–1.33)	0.97 (0.69–1.35)
Unvaccinated	1.25 (0.73–2.13)	1.66 (0.95–2.90)	0.87 (0.48–1.55)	1.14 (0.62–2.07)	1.13 (0.61–2.10)	1.06 (0.56–2.02)

[a]Variables included in the propensity score analysis included: enrollment site, age, race, Hispanic ethnicity, health insurance plan, male partners in the past three months, whether one's main partner is male, history of anal sex, condom use with main partner, condom use at last sexual intercourse, and history of cigarette smoking. Appalachian descent was used as an additional covariate in unvaccinated women after propensity score adjustment. The odds ratio for Appalachian descent for A9 species was 0.5 (CI = 0.21–1.38), for A7 species was 0.77 (CI = 0.32–1.87), and for non-vaccine-type unrelated to A7 and A9 species was 1.34 (CI = 0.67–2.66).

[b]No women were vaccinated in study 1, 242 (59.2%) were vaccinated in study 2, 286 (71.5%) were vaccinated in study 3, and 297 (82.5%) were vaccinated in study 4.

[c]OR = odds ratio.

[d]Bold indicates $p < 0.05$.

[e]CI = confidence interval.

[f]Positive for ≥ 1 HPV type of the following: 31, 33, 35, 52, 58 and/or 67.

[g]Positive for ≥ 1 HPV type of the following: 39, 45, 59, 68 and/or 70.

[h]Positive for ≥ 1 HPV type other than 6, 11, 16, 18, 31, 33, 35, 39, 45, 52, 58, 59, 67, 68, and/or 70.

Our findings demonstrated evidence of cross-protection against non-vaccine-type HPV genetically related to HPV16: vaccinated women in study 4 vs. study 1 had 0.48 times the odds of infection with a genetically related type. We did not find a similar reduction in non-vaccine-type HPV genetically related to HPV18 among vaccinated women. Although we found a significant decrease in HPV types genetically related to HPV18 in unvaccinated women, these data should not be considered conclusive as the number of unvaccinated women with these HPV types was very low (only 4 unvaccinated women were positive for an HPV type genetically related to HPV18). Cross-protection has been demonstrated in clinical trials, though efficacy against non-vaccine types is lower than among vaccine types, and wanes over time.[9] Malagon et al. conducted a meta-analysis of 2-valent and 4-valent HPV vaccine clinical trials to examine cross-protection against persistent HPV31, 33 and 45 infections and precancers associated with these types.[9] The authors found that the 4-valent vaccine was efficacious against outcomes associated with HPV31, and the 2-valent vaccine against outcomes associated with HPV31, 33, and 45. Efficacy against persistent infections with HPV31 and 45 decreased over time, suggesting waning cross-protection. A 2015 meta-analysis demonstrated an overall decrease in HPV31 and 33 (genetically related to HPV16) and 45 (genetically related to HPV18), among 13–19 year-old girls in real-world settings; however, these reductions were not associated with vaccination status,[23] and similar reductions were not observed among 20–24 year-old women. A 2016 meta-analysis similarly demonstrated evidence for cross-protection against HPV31 among young women <20 years of age.[20] In our study, we observed evidence of cross-protection against HPV16 but not HPV18. One explanation may be lower neutralizing antibodies against the A7 types other than HPV18 vs. the A9 types other than HPV16. In a study of 13–14 year-old girls who had received the 2-valent HPV vaccine series, Draper et al. found that fewer samples were positive for neutralizing antibodies against non-vaccine HPV types from the A7 than the A9 species group.[24]

In this study population, we did not find evidence of type replacement: there was no significant increase in types not included and genetically unrelated to those in the vaccine in all women, vaccinated women, or unvaccinated women. We have recently observed a significant increase in the five additional HPV types included in the 9-valent vaccine but not in the 4-valent vaccine in unvaccinated women (unpublished data). These types included HPV types genetically related to HPV16 and HPV18, thus reinforcing the importance of considering genetically related types when exploring type replacement. Other studies have similarly found no conclusive evidence of type replacement in real-world settings, but some have identified signals that confirm the importance of continued surveillance.[18-21,25,26] Yang et al. examined concurrence of multiple HPV infections in 47,617 women undergoing cervical cancer screening, and found a negative interaction between HPV16 and other HPV types among women with abnormal cytology, but not among those with normal cytology, suggesting that type replacement in vaccinated women is unlikely in the general population.[21] Tota et al. compared acquisition and clearance of 30 HPV types, using data from three studies involving 3200 women. Vaccine-type HPVs did not appear to compete with other types, suggesting that HPV type replacement was unlikely.[26] Carozzi et al. found no statistically significant differences in non-vaccine-type HPV in unvaccinated vs. vaccinated women after vaccine introduction in Italy, suggesting no evidence of type replacement.[25] In contrast, among a sample of 3,183 Finnish women, Merikukka et al. demonstrated a possible competitive advantage for HPV33 over other genital HPV types in the unvaccinated population, and suggested that HPV33 should be monitored for type replacement after widespread HPV vaccination.[19]

Mesher et al. examined type-replacement in a meta-analysis of 9 real-world studies including data for 13,886 girls and women ≤19 years of age and 23,340 women 20–24 years of age.[20] The analyses demonstrated slight increases in two non-vaccine high-risk HPV types, HPV39 and HPV52.[20] Finally, Gray et al. explored whether type-replacement occurred in a community-randomized trial of the 2-valent HPV vaccine, and identified a possible signal indicated by clustering between HPV39 and HPV16 or HPV18/45, and between HPV51 and HPV16 or HPV18/45, suggesting that the prevalence of HPV39 and HPV51 should be monitored after vaccine introduction.[18]

This study has several strengths, including collection of epidemiological data on HPV prevalence before and during the 11 years after HPV vaccine introduction, and collection of detailed participant behavioral data, allowing us to adjust for differences across studies using propensity score weighting. This study also has several limitations, including the fact that participants were recruited from clinical settings and most reported their race as underrepresented minority. Therefore, the findings cannot be generalized to the U.S. population; however, the findings do provide important information about a population at elevated risk for morbidity and mortality due to HPV-related cancers. In addition, inadequate statistical power may have contributed to negative findings for some outcomes. The parent study was designed to power for vaccine-type HPV outcomes, while non-vaccine type HPV was a secondary outcome. We did find statistically significant results for A9 species except HPV16, indicating that the sample size was sufficient to determine whether there was a statistically significant change from study 1 to 4, but not for A7 species except for HPV18 and for non-vaccine-type HPV genetically unrelated to A7 and A9 species. A post-hoc power analysis demonstrated that the study had 80% power to detect a decrease of 8.6% for A7 species except HPV18 from study 1 to 4, and an increase of 10.8% for non-vaccine-type HPV genetically unrelated to A7 and A9 species from study 1 to 4. Therefore, the study was not adequately powered for the observed small differences for A7 species except HPV18 (−3.3%) and non-vaccine-type HPV genetically unrelated to A7 and A9 species (+2.1%), but was powered adequately to detect larger and more clinically meaningful differences. Another limitation of this study is that although the propensity score analysis adjusts for differences in measured characteristics related to HPV infection, it may not adjust for unmeasured characteristics. Finally, only a small proportion of women in this study had received the 9-valent HPV vaccine, precluding an examination of cross-protection and type-replacement after widespread uptake of the 9-valent vaccine. It will be important to assess effectiveness, cross-protection and type-replacement after more robust uptake of the 9-valent vaccine.

In summary, we found evidence for cross-protection against non-vaccine-type HPV genetically related to HPV16, but no evidence for type-replacement, during the 11 years after 4-valent vaccine introduction in a community. Given that cross-protection appears to wane in HPV vaccine clinical trials, continued surveillance for cross-protection as well as research examining whether cross-protection differs by age, vaccine type, and other factors will be important to guide clinical- and cost-effectiveness analyses and related public health and policy decisions. Although there has been no conclusive evidence to date of type replacement after HPV vaccine introduction, the possible signals of an increase in non-vaccine-type HPV after vaccine introduction and the fact that type replacement has occurred after introduction of other vaccines[15-17] suggest that type replacement should continue to be monitored in future surveillance studies, especially after more widespread uptake of the 9-valent HPV vaccine.

Materials and methods

Study design

We enrolled young women 13–26 years of age in four cross-sectional surveillance studies: 2006–2007 (N = 371), 2009–2010 (N-409), 2013–2014 (N = 400), and 2016–2017 (N = 400). Participants were recruited from a hospital-based Teen Health Center and the Cincinnati Health Department, using a sequential recruitment strategy. Adolescent and young adult women between 13 and 26 years of age with a history of sexual contact were eligible to participate. Women who participated in a previous study were ineligible for re-enrollment. The study was approved by the hospital and Health Department Institutional Review Boards and written informed consent from each participant was obtained. Only individuals who received the 4vHPV vaccine or did not receive any HPV vaccine were included in this analysis, because the 9vHPV vaccine was only available to participants in the fourth study and only 40 (2.5%) of participants received the 9vHPV vaccine.

Study procedures

We implemented identical study procedures across all four waves. Participants completed a survey instrument that assessed sociodemographic characteristics (i.e. race, ethnicity, socioeconomic status, etc.), behaviors (substance use, sexual behaviors), reproductive health history, and participant knowledge about HPV and HPV vaccines. Cervicovaginal swabs were collected from each participant. Either the clinician or the participant collected the sample, using a standard procedure. Each sample was evaluated using the Roche Linear Array test. The Linear Array test is a qualitative test that uses biotinylated primer sets PGM09/PGMY11 and PC04/GH20 for simultaneous amplification of fragments of the HPV L1 gene and human beta-globin gene, respectively. After PCR amplification, genotyping is performed using a strip coated with HPV type-specific and beta-globin-specific oligonucleotide probes, to identify 36 HPV genotypes.[27,28] We verified participants' vaccination history using an electronic medical record database and a statewide vaccine registry; validity of vaccination history assessment is described in a previous manuscript.[29]

Statistical analyses

We used SAS version 9.3 (SAS Institute, Cary, NC) to analyze data. Similarly to a previous analysis,[22] our analytic strategy was

to determine changes in proportions of non-vaccine-type HPV prevalence among vaccinated (women who had received at least one vaccine dose) and unvaccinated women across four surveillance studies. Outcome variables for Aim 1 were any A9 HPV types genetically related to HPV16 but not targeted by the 4vHPV vaccine (HPV31, 33, 35, 52, 58, 67) and any A7 HPV types genetically related to HPV18 but not targeted by the 4vHPV vaccine (HPV39, 45, 59, 68, 70). The outcome variable for Aim 2 was any HPV types that were not genetically related to those in the vaccine (i.e. positive for ≥ 1 HPV type other than 6, 11, 16, 18, 31, 33, 35, 39, 45, 52, 58, 59, 67, 68, and/or 70). Only HPV types genetically unrelated to those included in the vaccine were assessed, because cross-protection may decrease the prevalence of genetically related non-vaccine-type HPV, obscuring an increase in non-vaccine-type HPV. Prevalence of HPV types was based on the above groupings, i.e., as composite outcome variables.

We compared participant characteristics across the four surveillance studies using univariable methods (chi-square, Fisher's exact, ANOVA or Kruskal Wallis), to determine if sociodemographic characteristics, behaviors, and reproductive health history differed across these studies. The results of these analyses demonstrated statistically significant differences between studies for some of the variables; therefore, we conducted a propensity score analysis based on inverse probability of treatment weighting[30,31] as we have done in previous studies.[22,32,33] A propensity score analysis adjusts for selection bias, simulating the characteristics of a randomized controlled trial[34] which allows one to assess whether differences in non-vaccine-type HPV prevalence across the studies were due to vaccine introduction, in contrast to confounding variables.

The prevalence of non-vaccine-type HPV was compared across the four studies, stratified by vaccination status, before and after propensity weighting. Vaccination status was defined as follows: 1) all women across the four studies, 2) vaccinated women (all women in study 1, who were all unvaccinated, and vaccinated women in studies 2, 3, and 4), and 3) unvaccinated women across the four studies. Logistic regression models were performed for all, vaccinated, and unvaccinated women in order to determine the odds of infection with non-vaccine-type HPV across the four studies, before and after propensity weighting.

Acknowledgements

We gratefully acknowledge the support provided by Charlene Morrow, RN, Susan Glynn BA, Rachel Thomas, BS, and Lisa Higgins, RPh, as well as the support of the Cincinnati Children's Hospital Teen Health Center and Cincinnati Health Department staff.

Disclosure of Potential Conflicts of Interest

Dr. Brown has received an investigator initiated studies program award from Merck entitled "Cervical cancer prevention in Kenya". Dr. Franco has occasionally served as consultant to companies involved with HPV diagnostics (Roche, BD, Abbott) and HPV vaccines (Merck and GSK). Dr. Kahn served as Co-chair of a study of HPV vaccines in HIV-infected men; the study was funded by NIH but Merck provided vaccine and serology testing. The other authors have no conflicts of interest relevant to this article to disclose.

All authors attest they meet the ICMJE criteria for authorship.

Financial Disclosure Statement

Dr. Brown owns stock in shares of Merck and Co., Inc. The other authors have indicated they have no financial relationships relevant to this article to disclose.

Funding

This work was supported by the National Institutes of Health, National Institute of Allergy and Infectious Diseases [R01 AI073713 and R01 AI104709] and the National Institutes of Health, National Center for Advancing Translational Sciences [UL1 TR001425].

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