

# Vaccine-Type Human Papillomavirus and Evidence of Herd Protection After Vaccine Introduction

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## KEY WORDS

human papillomavirus vaccines, herd protection, adolescent, prevalence

## ABBREVIATIONS

CIN—cervical intraepithelial neoplasia

HPV—human papillomavirus

ICC—invasive cervical cancer

All coauthors have made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data, have either drafted the article or revised it critically for important intellectual content, and have given final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

www.pediatrics.org/cgi/doi/10.1542/peds.2011-3587

doi:10.1542/peds.2011-3587

Accepted for publication Apr 18, 2012

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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**FINANCIAL DISCLOSURE:** Dr Kahn is cochair of 2 human papillomavirus (HPV) vaccine trials in HIV-infected individuals funded by the National Institutes of Health, but for which Merck, Inc, is providing vaccine and immunogenicity testing. She also receives funding from the Society for Adolescent Health and Medicine (SAHM) to chair a grant review committee to evaluate proposals for public health demonstration projects; the funding for the SAHM grant program is from Merck, Inc. Dr Shew is an investigator on HPV vaccine clinical trials for which she receives support from Merck, Inc. Dr Brown serves on the Women's Health Advisory Board at Merck, and his laboratory receives funding from Merck. Indiana University and Merck and Co, Inc have a confidential agreement that pays the University based on certain landmarks of vaccine development. Dr Brown receives a portion of these moneys as income. The other authors have indicated they have no financial relationships relevant to this article to disclose.

**FUNDING:** This study was supported through a grant (R01 073713) from the National Institutes of Health, National Institute of Allergy and Infectious Diseases (Principal Investigator: Jessica Kahn, MD, MPH). Funded by the National Institutes of Health (NIH).



**WHAT'S KNOWN ON THIS SUBJECT:** Clinical trials have demonstrated that prophylactic human papillomavirus (HPV) vaccines are highly effective in preventing HPV infection, but the impact of vaccination on HPV prevalence rates in real-world, community settings is uncertain.



**WHAT THIS STUDY ADDS:** This study provides evidence of a substantial decrease in the prevalence of vaccine-type HPV among young women and evidence of herd protection in a community only 4 years after the quadrivalent HPV vaccine was licensed.

## abstract



**OBJECTIVES:** The aims of this study were to compare prevalence rates of human papillomavirus (HPV) in young women before and after HPV vaccine introduction to determine the following: (1) whether vaccine-type HPV infection decreased, (2) whether there was evidence of herd protection, and (3) whether there was evidence for type-replacement (increased prevalence of nonvaccine-type HPV).

**METHODS:** Young women 13 to 26 years of age who had had sexual contact were recruited from 2 primary care clinics in 2006–2007 for a prevaccination surveillance study ( $N = 368$ , none were vaccinated) and 2009–2010 for a postvaccination surveillance study ( $N = 409$ , 59% were vaccinated). Participants completed a questionnaire and were tested for cervicovaginal HPV DNA. HPV prevalence rates were compared in the pre- versus postsurveillance studies by using  $\chi^2$  tests. Propensity score weighting was used to balance differences in covariates between the 2 surveillance studies.

**RESULTS:** The mean age was ~19 years for both groups of participants and most were African American and non-Hispanic. After propensity score weighting, the prevalence rate for vaccine-type HPV decreased substantially (31.7%–13.4%,  $P < .0001$ ). The decrease in vaccine-type HPV not only occurred among vaccinated (31.8%–9.9%,  $P < .0001$ ) but also among unvaccinated (30.2%–15.4%,  $P < .0001$ ) postsurveillance study participants. Nonvaccine-type HPV increased (60.7%–75.9%,  $P < .0001$ ) for vaccinated postsurveillance study participants.

**CONCLUSIONS:** Four years after licensing of the quadrivalent HPV vaccine, there was a substantial decrease in vaccine-type HPV prevalence and evidence of herd protection in this community. The increase in nonvaccine-type HPV in vaccinated participants should be interpreted with caution but warrants further study. *Pediatrics* 2012;130:e249–e256

Clinical trials have revealed that prophylactic human papillomavirus (HPV) vaccines are highly effective in preventing (1) HPV infection; (2) moderate/severe cervical intraepithelial neoplasia (CIN), a precursor to invasive cervical cancer (ICC); and (3) vulvar, vaginal, and anal cancer precursors and cancer.<sup>1–3</sup> The first prophylactic HPV vaccine was licensed for use in the United States in June of 2006, and the US Advisory Committee on Immunization Practices has recommended vaccination of girls and women 11 to 26 years of age.<sup>4,5</sup> Widespread HPV vaccination not only has the potential to reduce rates of HPV infection, CIN, and ICC, but also to decrease existing racial and socioeconomic disparities in HPV infection and cervical cancer.<sup>6,7</sup> In addition, HPV vaccination is expected to provide herd protection; ie, to provide indirect protection to those who have not been vaccinated, due to a reduced prevalence of HPV in communities.<sup>8</sup> Because CIN and ICC take years to develop after initial infection, an early indicator of the public health impact of HPV vaccine introduction will be a decrease in HPV prevalence.<sup>9</sup> It is challenging to predict the impact of vaccination on HPV prevalence rates in a community based on clinical trials data because vaccination rates are difficult to predict and because the trials were conducted in generally healthy women with relatively few sexual partners, most of whom were uninfected with vaccine-type HPV at baseline and compliant with the vaccination series.<sup>1–3</sup> Vaccine effectiveness is expected to be lower among young women in the community who may be at higher risk of HPV infection than those enrolled in clinical trials because vaccination does not prevent type-specific HPV in women infected with those types at the time of vaccination.<sup>10</sup> Surveillance studies are needed to understand the impact of HPV vaccine introduction on the epidemiology of HPV in a community.

Although widespread HPV vaccination has the potential to substantially reduce rates of vaccine-type HPVs, concern has been raised about the potential for type replacement; ie, an increase in the prevalence of HPV genotypes not targeted by the vaccines due to an ecological niche created by a reduction in the prevalence of HPV genotypes targeted by the vaccines. Significant increases in the prevalence of nonvaccine serotypes occurred after introduction of a heptavalent conjugate pneumococcal vaccine and a *Bordetella pertussis* vaccine.<sup>11–17</sup> Type replacement is thought to be unlikely to occur after HPV vaccination.<sup>18</sup> However, only surveillance of type-specific HPV rates after vaccination over a period of years after vaccine introduction will provide the necessary data to determine whether type-replacement is occurring.

To examine the impact of HPV vaccine introduction on the epidemiology of HPV in the community, we conducted 2 HPV surveillance studies in diverse samples of sexually experienced adolescent and young adult women in 2006–2007 and 2009–2010. We enrolled sexually experienced 13- to 26-year-old women for the following reasons: (1) it is more feasible to sample for genital HPV infection in young women >12 years of age, (2) changes in HPV prevalence are likely to be seen earlier in a sexually experienced versus inexperienced population, providing an early indication of the impact of vaccination on HPV prevalence, and (3) the data provide insight into the impact of vaccination in the age group for which “catch-up” vaccination is recommended (as compared with the target age group for vaccination, 11- to 12-year-olds).<sup>4,5</sup> The aims were to compare prevalence rates of HPV before and after HPV vaccine introduction to determine the following: (1) whether overall and vaccine-type HPV infection decreased, (2) whether there was evidence of herd protection (ie, whether

the prevalence of HPV decreased in unvaccinated as well as vaccinated women), and (3) whether there was evidence for type-replacement (ie, an increased prevalence of nonvaccine-type HPVs in vaccinated women).

## METHODS

### Study Population

Young women 13 to 26 years of age who had had sexual contact (genital-oral or genital-genital with a male or female partner) were recruited between October 2006 and May 2007 for the prevaccination surveillance study and between December 2009 and June 2010 for the postvaccination surveillance study, using a sequential sampling strategy. Participants were recruited from a hospital-based adolescent clinic in Cincinnati, Ohio, and a community health center affiliated with the city's health department. Those who enrolled in the prevaccination surveillance study were excluded from participation in the postvaccination surveillance study. The only HPV vaccine administered in these clinical settings during the study period was the quadrivalent (HPV-6, -11, -16, -18) vaccine. The Institutional Review Boards of the hospital and health department approved the study and a waiver of parental consent for those <18 years of age.

### Study Procedures

Procedures for the presurveillance study have been described previously<sup>19</sup> and were identical for the post-surveillance study. Briefly, all participants completed a self-administered questionnaire that assessed demographic factors, HPV knowledge, gynecologic history, and behaviors. Cervicovaginal swabs were collected from each participant by using a clinician- or self-collected swab.<sup>19,20</sup> All samples were genotyped by using 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 37 different HPV genotypes (Roche Molecular Systems, Alameda, CA).<sup>21</sup>  $\beta$ -globin controls were positive in 100% of the samples in the prevaccination study and 99.8% of samples in the postvaccination study, indicating adequate DNA for polymerase chain reaction amplification. In this assay, the probe used to detect HPV 52 amplicons also hybridizes to amplicons of HPV types 33, 35, and 58.<sup>22</sup> Thus, reported values for HPV 52 indicate detection of HPV 52 DNA as per the algorithm provided by the manufacturer (that is, HPV 52 only when HPV 33, 35, or 58 were not detected). Because pre and post HPV surveillance samples were evaluated by using the same methods but in 2 different laboratories, we performed a validation analysis comparing results for a random sample of 96 swabs from the prevaccination surveillance study to ensure that results were consistent. Results were highly concordant (98%): the prevalence of any HPV (62.50%) and high-risk HPV (52.08%) were identical in the 2 laboratories.

### Analyses

The participants in the prevaccination surveillance study who had received an HPV vaccine dose were excluded from analyses. We first compared participants in the prevaccination surveillance study to those in the postvaccination surveillance study to determine if there were any differences in demographic characteristics, knowledge about HPV/HPV vaccines, gynecologic history, and sexual history that could be associated with either the outcome variables or with prevaccination versus postvaccination surveillance group status. As there were a number of statistically significant differences, a propensity score analysis based on inverse probability of treatment weighting was performed.<sup>23</sup> The propensity score is the probability that a subject belongs to a naturally

occurring treatment group, based on a set of background characteristics. The propensity score adjusts for selection bias in an observational study, allowing one to analyze an observational study so that it mimics the characteristics of a randomized controlled trial. It provides a one-dimensional summary of multidimensional covariates, X, such that when the propensity scores are balanced across the 2 treatment groups, the distribution of observed baseline covariates is similar between subjects in the 2 groups.

The outcome variables (defined in Table 1) included any HPV infection, vaccine-type HPV, nonvaccine-type HPV, high-risk HPV (as defined in Bouvard et al<sup>24</sup>), high-risk vaccine-type HPV, and high-risk nonvaccine-type HPV. Vaccination status was defined as having received at least 1 HPV vaccine dose before the date of enrollment and was assessed by reviewing documentation of vaccination in the statewide immunization registry, which both clinics used consistently to document vaccination. Vaccination status could be confirmed by using registry data for 354 of 409 participants (87%); for the remainder, self-report of HPV vaccination was used. Descriptive analyses were performed for all outcome variables (ie, HPV prevalence rates) in the pre- and postvaccination surveillance studies. HPV prevalence rates were then compared in the pre- versus postvaccination surveillance studies by using  $\chi^2$  tests. The propensity score was used to balance differences in baseline

covariates between pre- and postvaccination surveillance studies in total and stratified by vaccination status among the postsurveillance study participants.

### RESULTS

For the prevaccination surveillance study, 384 of 392 (98%) participants who were approached agreed to participate, and for the postvaccination surveillance study, 409 of 417 (98%) participants agreed to participate. Approximately one-third were recruited from the Department of Public Health clinic and two-thirds from the adolescent clinic for each surveillance study. Of the 384 participants in the prevaccination surveillance study, 16 (4.0%) had been vaccinated and were excluded from analysis, resulting in a sample size of 368. Of the 409 participants in the postvaccination surveillance study, 242 (59.2%) had received at least 1 HPV vaccine dose before study enrollment (mean: 2.2 years since vaccination; interquartile range: 1.5, 2.8 years).

Characteristics of the study samples are shown in Table 2. The mean age for both groups of participants was ~19 years of age, participants were predominantly African American and non-Hispanic, and the majority had Medicaid or no health insurance. Participants in the pre- and postvaccination surveillance studies differed significantly in terms of health insurance coverage, health insurance plan, HPV knowledge scale score, history of *Trichomonas vaginalis*, history

**TABLE 1** Outcome Variables: HPV Prevalence and Definitions

Variable	Definition
Any HPV	Positive for $\geq 1$ of the following HPV types: 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, IS39, and CP-610
High-risk HPV	Positive for $\geq 1$ of the following HPV types: 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 67, 68, 70, 73, 82, and IS39
Vaccine-type HPV	Positive for $\geq 1$ of the following HPV types: 6, 11, 16, and/or 18
High-risk, vaccine-type HPV	Positive for HPV 16 and/or 18
Nonvaccine-type HPV	Positive for $\geq 1$ HPV type other than 6, 11, 16, and/or 18
High-risk, nonvaccine-type HPV	Positive for $\geq 1$ high-risk, nonvaccine-type HPV (ie, all high-risk types other than 16 and 18)

of an abnormal Pap test, history of sexual intercourse, and whether the participant's main sexual partner was male. After balancing by using the propensity score, these differences were not significant between pre- and

postvaccination surveillance studies in total (Table 2) and stratified by vaccination status among the postsurveillance study participants (data not shown).

A comparison of HPV prevalence rates in the prevaccination and postvaccination

surveillance studies is shown in Table 3. Overall, HPV prevalence rates, adjusted for the propensity score, increased 8.5% (68.3%–76.8%,  $P = .0003$ ) in a comparison of all prevaccination and all postvaccination surveillance study participants, and 9.0% (68.1%–77.1%,  $P = .001$ ) in a comparison of all prevaccination participants to the subset of postvaccination surveillance study participants who had been vaccinated. The prevalence of vaccine-type HPV decreased 18.3% (31.7%–13.4%,  $P < .0001$ ) for all participants: the decrease was greater (21.9%) for vaccinated participants (31.8%–9.9%,  $P < .0001$ ) than unvaccinated participants, but the decrease was also substantial (14.8%) for unvaccinated participants (30.2%–15.4%,  $P < .0001$ ). Similar changes in HPV prevalence rates were noted for high-risk, vaccine-type HPV (HPV-16 and/or HPV-18). In contrast, the prevalence of nonvaccine-type HPV increased 14.0% (60.8%–74.8%,  $P < .0001$ ) for all participants: the increase was also significant (15.2%,  $P < .0001$ ) for vaccinated but not for unvaccinated participants. Similarly, the prevalence of high-risk, nonvaccine-type HPV increased 7.6% (48.6%–56.2%,  $P = .0038$ ) for all participants, and the increase was significant (13.6%,  $P < .0001$ ) for vaccinated but not for unvaccinated participants.

## DISCUSSION

We conducted surveillance studies of HPV prevalence before and after widespread vaccination in a diverse sample of sexually experienced adolescent and young adult women, to examine the short-term impact of HPV vaccination on HPV prevalence in a real-world setting and to explore the potential for herd protection and HPV type replacement after widespread vaccination. Because the study sample primarily comprised minority, low-income young women, the results provide insight into the impact of vaccination in a group of young women

**TABLE 2** Comparison of Participants' Demographic Characteristics, Knowledge, Gynecologic History, and Behaviors in the Pre- Versus Postvaccination Surveillance Studies

	Prevaccination Surveillance Study (N = 368)		Postvaccination Surveillance Study (N = 409)		P <sup>a</sup>	P, Adjusted <sup>b</sup>
	N (%)	Mean (SD)	N (%)	Mean (SD)		
<b>Enrollment site</b>						
Teen health center	247 (67.1)	—	268 (65.5)	—	.64	.79
Health department	121 (32.9)	—	141 (34.5)	—	—	—
<b>Demographic characteristics</b>						
Age	—	18.7 (3.0)	—	18.8 (2.9)	.44	.66
Race	—	—	—	—	.46	.33
White or Asian	109 (30.3)	—	114 (27.9)	—	—	—
African American or multiracial	251 (69.7)	—	295 (72.1)	—	—	—
Appalachian descent	24 (6.7)	—	16 (3.9)	—	.080	.98
Hispanic ethnicity	25 (7.0)	—	24 (5.9)	—	.51	.41
Health insurance coverage	250 (70.4)	—	329 (80.4)	—	.0013	.97
Health insurance plan	—	—	—	—	.015	.82
Private	31 (8.7)	—	63 (15.4)	—	—	—
Medicaid	194 (54.7)	—	217 (53.1)	—	—	—
None/not sure	130 (36.6)	—	129 (31.5)	—	—	—
Knowledge about HPV vaccines, mean scale score	—	4.7 (2.6)	—	6.1 (2.3)	<.0001	.55
<b>Gynecologic history</b>						
Number of times pregnant	—	0.78 (1.1)	—	0.79 (1.1)	.88	.36
History of <i>Chlamydia</i>	145 (40.1)	—	161 (39.5)	—	.84	.96
History of gonorrhea	67 (18.6)	—	81 (19.9)	—	.65	.41
History of <i>Trichomonas vaginalis</i>	77 (21.3)	—	115 (28.2)	—	.028	.29
History of genital warts	19 (5.3)	—	12 (2.9)	—	.10	.82
History of abnormal Pap test	111 (31.0)	—	95 (23.2)	—	.0057	.86
<b>Behaviors</b>						
History of sexual intercourse	342 (97.4)	—	409 (100.0)	—	.0011	.17
Age of first sexual intercourse, y	—	14.9 (2.4)	—	14.9 (1.8)	.97	.94
Number male sexual partners, lifetime	—	5.4 (5.9)	—	5.7 (6.6)	.45	.85
Number male sexual partners, past 3 mo	—	1.2 (1.1)	—	1.2 (0.8)	.67	.98
Main sexual partner is male	309 (88.0)	—	380 (92.9)	—	.0052	.32
Ever had anal sex with male partner	88 (25.4)	—	93 (22.7)	—	.40	.58
Condom use with main partner, past 3 mo	—	—	—	—	.29	.84
Never	114 (32.5)	—	143 (35.0)	—	—	—
Every once in a while	71 (20.2)	—	94 (23.0)	—	—	—
Most of the time	54 (15.4)	—	67 (16.4)	—	—	—
Every time	73 (20.8)	—	76 (18.6)	—	—	—
Condom use, last sexual intercourse	122 (34.5)	—	146 (35.8)	—	.17	.48
Smoked at least 100 cigarettes in lifetime	114 (31.9)	—	117 (28.6)	—	.32	.88
Smoked in the past 30 d	121 (33.8)	—	114 (27.9)	—	.076	.58

<sup>a</sup> P value derived from either a  $\chi^2$  test comparing the proportion of participants with specific characteristics or a 2-sample  $t$  test comparing means of continuous variables in the prevaccination versus the postvaccination surveillance studies.

<sup>b</sup> Adjusted by using a propensity score.



**TABLE 3** Comparison of Proportion of Participants in the Pre- Versus the Postvaccination Surveillance Studies With Specific HPV Types: Total and Stratified by Vaccination Status

HPV	Prevaccination Surveillance Study (N = 368)		Postvaccination Surveillance Study (N = 409)		P	P, Adjusted for Propensity Score	Change Pre- to Postvaccination	
	Unadjusted, N (%)	% Adjusted for Propensity Score <sup>a</sup>	Unadjusted, N (%)	% Adjusted for Propensity Score				% Adjusted for propensity score (95% CI)
Any type	All	242 (66.5)	313 (76.7)	76.8	.0016	.0003	+8.5 (3.8, 13.2) <sup>b</sup>	
	—	—	Vaccinated	191 (79.3)	77.1	.0007	.0010	+9.0 (3.4, 14.3)
High-risk type	—	—	Unvaccinated	122 (73.1)	68.5	.13	.57	+1.8 (-4.4, 8.0)
	All	203 (55.8)	All	249 (61.0)	59.4	.14	.66	+1.1 (-4.0, 6.4)
Vaccine-type	—	—	Vaccinated	160 (66.4)	61.2	.009	.083	+5.2 (-0.9, 11.1) <sup>b</sup>
	All	115 (31.6)	Unvaccinated	89 (53.3)	50.3	.59	.022	-7.5 (-14.0, -0.9) <sup>b</sup>
High-risk, vaccine-type	—	—	All	57 (14.0)	13.4	<.0001	<.0001	-18.3 (-22.5, -13.9) <sup>b</sup>
	All	88 (24.2)	Vaccinated	26 (10.8)	9.9	<.0001	<.0001	-21.9 (-26.7, -17.1) <sup>b</sup>
Nonvaccine-type	—	—	Unvaccinated	31 (18.6)	15.4	.0018	<.0001	-14.8 (-20.0, -9.2) <sup>b</sup>
	All	216 (59.3)	All	45 (11.0)	10.6	<.0001	<.0001	-14.2 (-18.2, -10.2) <sup>b</sup>
High-risk, nonvaccine-type	—	—	Vaccinated	19 (7.9)	8.0	<.0001	<.0001	-17.6 (-22.0, -13.0)
	All	173 (47.5)	Unvaccinated	26 (15.6)	11.6	.025	<.0001	-12.0 (-17.0, -7.1) <sup>b</sup>
Any type	—	—	All	304 (74.5)	74.8	<.0001	<.0001	+14.0 (9.0, 18.8) <sup>b</sup>
	All	216 (59.3)	Vaccinated	187 (77.6)	75.9	<.0001	<.0001	+15.2 (9.7, 20.9) <sup>b</sup>
High-risk, nonvaccine-type	—	—	Unvaccinated	117 (70.1)	65.6	.018	.064	+5.9 (-0.5, 12.2) <sup>b</sup>
	All	173 (47.5)	All	236 (57.8)	56.2	.0041	.0038	+7.6 (2.3, 12.8) <sup>b</sup>
Any type	—	—	Vaccinated	157 (65.2)	60.5	<.0001	<.0001	+13.6 (7.4, 19.4) <sup>b</sup>
	All	242 (66.5)	Unvaccinated	79 (47.3)	46.3	.96	.41	-2.7 (-3.9, 9.3)

CI, confidence interval. P values derived from a  $\chi^2$  test assessing differences in proportion of those who were HPV positive in the prevaccination and postvaccination studies, unadjusted and adjusted for propensity score.

<sup>a</sup> The percentages in this column represent the percentages of all participants in the prevaccination surveillance study (all were unvaccinated), adjusted for the propensity score for each comparison with the postvaccination surveillance study participants (who were stratified by vaccination status).

<sup>b</sup>  $P < .05$ .

who are at increased risk for HPV infection, CIN, and ICC compared with the general population. The data also provide insight into the potential health impact of vaccination in young women in the catch-up age group for vaccination, who are currently being vaccinated at higher rates than 11- to 12-year-old girls, the age group targeted for vaccination.<sup>25,26</sup>

The prevalence of HPV in this study was extremely high, as has been shown in previous studies of young women with similar demographic characteristics.<sup>27,28</sup> Among participants in the prevaccination surveillance study, who were unvaccinated, 24% were already positive for at least 1 high-risk, vaccine-type HPV (HPV-16 and/or -18). Vaccination is not effective in clearing vaccine-type HPV or in preventing CIN caused by vaccine-type HPV in women who are infected with those types at the time of vaccination,<sup>10</sup> pointing to the importance of public health policies and educational campaigns that promote targeting of 11- to 12-year-old children for vaccination. It is concerning that in the United States, rates of HPV vaccination are consistently higher in young women >13 years of age compared with those 11 to 12 years of age,<sup>25,26</sup> and effective health messages are urgently needed for both clinicians and parents that provide a clear and compelling rationale for the recommendation to vaccinate younger children.

These data demonstrate that there was a decrease in the prevalence of vaccine-type HPV during the first 4 years after vaccine introduction, suggesting that HPV vaccination may have had an early and significant impact on the prevalence of vaccine-type HPV among young women in this community. Although overall HPV prevalence did not decrease, but in fact increased modestly, both vaccine-type HPV and high-risk vaccine-type HPV decreased by ~60% when participants in the prevaccination study were compared with all participants in the postvaccination

study. Vaccine-type and high-risk vaccine-type HPV decreased by ~70% when participants in the prevaccination study were compared with vaccinated women in the postvaccination study. This change is especially remarkable given that participants were sexually experienced, a substantial proportion were exposed to vaccine-type HPV before vaccination, and only 1 HPV vaccine dose was required to be considered “vaccinated” in this analysis. As the high-risk vaccine-type HPVs, HPV-16 and -18, are responsible for most cases of moderate/severe CIN in young women<sup>29</sup> and cause ~70% of ICC cases,<sup>30</sup> the results are promising in terms of their implications for declining rates of CIN, and ultimately ICC, in this community in the future. In young women such as these, who have high rates of HPV and in whom Pap screening is generally initiated at 21 years of age, the impact of vaccination on CIN prevalence could occur relatively soon. The decrease in HPV-16 and -18 is also promising in terms of its potential impact on rates of anal cancer because the majority of anal cancers are caused by 1 of these types.<sup>31</sup> The decrease in the prevalence of vaccine-type HPV among unvaccinated women provides early evidence for herd protection in this population. Vaccine-type HPV decreased by 49%, and high-risk vaccine-type HPV by 51%, among unvaccinated women, whereas overall rates of HPV among unvaccinated women did not decrease. The magnitude of this decrease in vaccine-type HPV in unvaccinated women was unexpected and could be explained in part by the patterns of sexual networks in this community; eg, assortative mixing between participants with relatively high numbers of sexual partners.<sup>32</sup> These data also imply that HPV prevalence rates among participants’ male sexual partners had substantially decreased in the community well

before the Advisory Committee on Immunization Practices recommendation that boys and men receive the quadrivalent vaccine.<sup>33</sup>

Although vaccine-type HPV prevalence decreased in both vaccinated and unvaccinated women, the prevalence of nonvaccine-type HPV increased overall by 23%. The prevalence of nonvaccine-type HPV and high-risk, nonvaccine-type HPV increased significantly among all women and among vaccinated women but not among unvaccinated women, a finding that could be consistent with type-replacement. Type-replacement after vaccination is thought to be unlikely<sup>18,34</sup> because (1) papillomaviruses have been genetically stable for thousands of years and are therefore unlikely to rapidly mutate,<sup>35</sup> and (2) when an individual is infected with more than 1 HPV type, these types behave as if they are independent of each other,<sup>36,37</sup> suggesting that HPV types will not compete with each other for a biological niche.<sup>18</sup> A possible explanation for the finding that nonvaccine-type HPV prevalence increased in vaccinated but not in unvaccinated young women is that their risk for HPV may differ. Vaccinated versus unvaccinated girls did not differ in number of recent and lifetime sexual partners; however, they were more likely to be African American (84% vs 54%,  $P < .0001$ ) and reported, on average, an earlier age of first sexual intercourse (mean = 14.6 vs 15.3 years,  $P = .0007$ ), both of which have been associated with higher rates of HPV infection. Only serial surveillance studies in this population, as well as regional or national surveillance studies with larger study samples over longer periods of time, will definitively address the issue of type replacement after vaccination.<sup>9</sup> Even if future studies demonstrate some degree of type replacement, the public health impact is not likely to be substantial, given that the high-risk types not targeted by the vaccines have a lower risk of

progression to cancer and there may be cross-protection against nonvaccine types.<sup>38</sup>

The findings of this study should be interpreted in light of several limitations. First, the study samples for the pre- and postsurveillance studies differed in terms of a number of characteristics that could be related to the outcome variables, HPV prevalence. We used propensity scoring to balance the groups and demonstrated that it was effective in eliminating differences between groups. However, differences in HPV prevalence may have been attributable to factors other than those measured. Second, there may have been errors in the assessment of vaccination status because information may have been missing from the statewide immunization registry, and we used self-report for those participants who had no information recorded in the registry. Third, it is possible that there were errors in determination of HPV DNA status or issues with reproducibility, though the assay used is highly sensitive and specific,<sup>39</sup> and the type-specific reproducibility of the assay has been shown to be excellent.<sup>40</sup> In a validation analysis using a large subset of the pre-vaccination surveillance samples, the prevalence of any HPV and high-risk HPV were identical in the 2 laboratories that performed the HPV test. Finally, this was a convenience sample and relatively small: conclusions about the impact of HPV vaccination on type-replacement would be premature. Larger studies with more representative samples are needed to definitively address this issue.<sup>9</sup>

## CONCLUSIONS

We demonstrated that in this sample of sexually experienced 13- to 26-year-old young women, overall HPV prevalence was extremely high and had not decreased 4 years after the quadrivalent

vaccine was licensed, pointing to the importance of vaccinating girls before 13 years of age. We found evidence of a substantial decrease in vaccine-type HPV prevalence in the community, as well as

evidence of herd protection, only 4 years after the quadrivalent HPV vaccine was introduced; this is expected to translate into a decrease in CIN and ultimately cervical cancer in the community.

## ACKNOWLEDGMENTS

The authors thank the efforts of the directors and staff of the Cincinnati Health Department and the Teen Health Center at Cincinnati Children's Hospital Medical Center.

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