Human Papillomavirus Vaccine Effectiveness and Herd Protection in Young Women

Chelse Spinner,[a] Lili Ding,[b,c] David I. Bernstein,[b,c] Darron R. Brown,[d] Eduardo L. Franco,[e] Courtney Covert,[c] Jessica A. Kahn, MD, MPH[b,c]

abstract

BACKGROUND: Clinical trials of the 4-valent human papillomavirus (HPV) vaccine demonstrate high efficacy, but surveillance studies are essential to examine the long-term impact of vaccine introduction on HPV prevalence in community settings. The aims of this study were to determine during the 11 years after vaccine introduction the prevalence of (1) vaccine-type HPV in adolescent and young adult women who were vaccinated (to assess vaccine effectiveness) and (2) vaccine-type HPV in women who were unvaccinated (to assess herd protection).

METHODS: Young women 13 to 26 years of age were recruited from hospital-based and community health clinics for 4 surveillance studies from 2006 to 2017. We determined the proportion of vaccinated and unvaccinated women who were positive for vaccine-type HPV across the studies, and the odds of positivity for vaccine-type HPV using logistic regression; all analyses were propensity score–adjusted to control for between-wave differences in participant characteristics.

RESULTS: Vaccination rates increased from 0% to 84.3% (97% of study participants received the 4-valent vaccine). Among women who were vaccinated, 4-valent vaccine–type HPV detection decreased from 35% to 6.7% (80.9% decline; odds ratio 0.13, 95% confidence interval 0.08 to 0.22). Among women who were unvaccinated, 4-valent vaccine–type HPV detection decreased from 32.4% to 19.4% (40% decline; odds ratio 0.50, 95% confidence interval 0.26 to 0.97). Estimated vaccine effectiveness was 90.6% in wave 3 and 80.1% in wave 4.

CONCLUSIONS: In this study in which trends in HPV in a US community >10 years after 4-valent HPV vaccine introduction and after 9-valent vaccine introduction were examined, we found evidence of vaccine effectiveness and herd protection. Further research is needed to examine trends in 9-valent vaccine–type HPV after higher rates of vaccination are achieved.

[a]University of Cincinnati, [b]College of Medicine, Cincinnati, Ohio; [c]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; [d]Indiana University, Indianapolis, Indiana; and [e]McGill University, Montreal, Canada

Ms Spinner assisted with the design of the analyses, did the literature search, interpreted the results, and codrafted the initial manuscript; Dr Ding designed and conducted the statistical analyses, interpreted the results, and critically revised the manuscript for intellectual content; Drs Bernstein and Franco assisted with study conceptualization and design, interpreted the results, and critically revised the manuscript for intellectual content; Dr Brown assisted with study conceptualization and design, conducted the human papillomavirus DNA analyses, interpreted the results, and critically revised the manuscript for intellectual content; Ms Covert recruited participants for the study and interpreted the results; Dr Kahn conceptualized and designed the study, obtained funding for the study, interpreted the results, codrafted the initial

WHAT'S KNOWN ON THIS SUBJECT: Researchers in clinical trials of the 4-valent human papillomavirus (HPV) vaccine demonstrate high efficacy, but surveillance studies are essential to examine the long-term impact of vaccine introduction on HPV prevalence in community settings.

WHAT THIS STUDY ADDS: In this study in which trends in HPV in a US community >10 years after 4-valent HPV vaccine introduction and after 9-valent vaccine introduction are examined, we found evidence of vaccine effectiveness and herd protection.

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Infection with human papillomavirus (HPV) may cause genital warts and cancers. In women, HPV infection may cause cervical, vaginal, vulvar, anal, and oropharyngeal cancers, whereas in men, infection may cause anal, penile, and oropharyngeal cancers.[1–3] The first prophylactic HPV vaccine, a 4-valent vaccine that prevents HPV-6, -11, -16, and -18, was licensed in 2006 in the United States.[4] A 2-valent vaccine that prevents HPV-16 and -18 was licensed in 2009,[5] and a 9-valent vaccine that prevents HPV-6, -11, -16, -18, -31, -33, -45, -52, and -58 was licensed in 2014.[6] The 9-valent vaccine, the only vaccine available in the United States as of the end of 2016, prevents 5 additional oncogenic HPV types (-31, -33, -45, -52, and -58) and could prevent ~90% of cervical cancers.[7–10]

Through evidence from clinical trials, researchers have demonstrated that all 3 HPV vaccines have high efficacy in preventing infection and disease caused by the specific HPV types targeted by the vaccines.[7,11–14] However, vaccine effectiveness in community settings may be lower; women in the community may have been infected with vaccine-type HPV before vaccination and may have lower compliance with the vaccination series or be less healthy than those in the clinical trials. Researchers in studies have demonstrated that after introduction of the 2-valent and 4-valent vaccines, there is a substantial reduction in the prevalence of vaccine-type HPV as well as precancers in real-world settings among women who are vaccinated, indicating vaccine effectiveness.[15–19] Studies are also emerging in which researchers demonstrate a reduction in vaccine-type HPV among women who are unvaccinated, suggesting herd protection,[15,16,18] but findings are not consistent.[17,20,21] Longer-term surveillance is essential to establish trends in vaccine-type HPV prevalence after vaccine introduction among women who are vaccinated and women who are unvaccinated, to examine HPV prevalence among younger women who are in the target age group for vaccination, and to examine the impact of 9-valent vaccine introduction on these trends. Assessments of vaccine effectiveness and herd protection are essential to guide public health messaging, clinical counseling, vaccination recommendations, and cervical cancer screening recommendations.

To evaluate effectiveness and herd protection after 4-valent and 9-valent HPV vaccine introduction in a community over the 11 years after vaccine introduction, we designed a study to extend our previous findings[15,22] with the following primary specific aims: (1) to determine trends in vaccine-type HPV (types targeted by the 4-valent and 9-valent HPV vaccines) among young women who are vaccinated to examine vaccine effectiveness and (2) to determine trends in vaccine-type HPV among young women who are unvaccinated to assess for evidence of herd protection. We hypothesized that (1) the prevalence of 4-valent vaccine–type HPV would decrease significantly from 2006 to 2017 among women who were vaccinated, which would indicate vaccine effectiveness, and that (2) the prevalence of 4-valent vaccine–type HPV would decrease significantly in women who were unvaccinated, which would suggest herd protection. As an exploratory specific aim, we examined trends in the prevalence of the 5 additional types in the 9-valent vaccine (HPV-31, -33, -45, -52, and -58). Decreases in the prevalence of the 5 additional types in the 9-valent vaccine may be driven either by direct protection after vaccination with the 9-valent vaccine or crossprotection after vaccination with the 4-valent vaccine, given that these 5 types are genetically related to HPV-16 and HPV-18.

METHODS

The study population comprised young women recruited from a university-affiliated, hospital-based primary care clinic (Cincinnati Children's Hospital Teen Health Center) and the Cincinnati Health Department (obstetrics and gynecology clinic and a sexually transmitted disease clinic). The study was approved by the hospital's and health department's institutional review boards, and participants provided written informed consent. Parental consent was waived for participants <18 years of age to protect patient confidentiality because history of sexual contact was an inclusion criterion. To participate, individuals had to be 13 to 26 years of age and sexually experienced, which was defined as having had sexual contact (oral-genital or genital-genital, with a male or female partner).[22] Individuals were not eligible if they had participated in previous surveillance studies. Participants were enrolled by using a sequential recruitment strategy; 95% to 98% of those approached in each study agreed to participate. We collected the following 4 waves of data: wave 1 (2006–2007, $N = 371$), wave 2 (2009–2010, $N = 409$), wave 3 (2013–2014, $N = 400$), and wave 4 (2016–2017, $N = 400$). A survey instrument was used to collect data on sociodemographic and behavioral variables that may be risk factors for type-specific HPV infection; details about survey development and validity are described in previous articles.[15,22] Cervicovaginal swabs were collected by self-swab or clinician swab from each female participant, and samples were genotyped for HPV by using a 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 HPV genotypes.[23] In previous studies, researchers have demonstrated

TABLE 1 Comparison of Participant Characteristics Across All 4 Study Waves, Unadjusted and Adjusted for Propensity Score

Characteristic	Wave 1, *N* = 371		Wave 2, *N* = 409		Wave 3, *N* = 400		Wave 4, *N* = 400		*P*,[a] Unadjusted	*P*,[a] 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)	—	307 (76.8)	—	<.0001	.55
Health department	132 (35.6)	—	141 (34.5)	—	150 (37.5)	—	93 (23.3)	—	—	—
Demographic characteristics and medical history										
Age, y	—	18.7 (3.0)	—	18.8 (2.9)	—	19.1 (2.8)	—	19.1 (2.6)	.18	.5
Race and/or ethnicity										
White or Asian American	110 (30.1)	—	114 (27.9)	—	108 (27.0)	—	91 (22.8)	—	.13	.78
African American or multiracial	255 (69.9)	—	295 (72.1)	—	292 (73.0)	—	309 (77.3)	—	—	—
Appalachian descent	24 (6.7)	—	16 (3.9)	—	9 (2.3)	—	6 (1.5)	—	.0006	.22
Hispanic ethnicity	25 (6.9)	—	24 (5.9)	—	28 (7.0)	—	21 (5.3)	—	.69	.53
Health insurance plan										
Private	32 (8.6)	—	63 (15.4)	—	35 (8.8)	—	52 (13)	—	<.0001	.69
Medicaid	196 (52.8)	—	217 (53.1)	—	269 (67.3)	—	284 (71)	—	—	—
None or not sure	143 (38.5)	—	129 (31.5)	—	96 (24.0)	—	64 (16)	—	—	—
History of any STI	170 (46.5)	—	212 (52.0)	—	202 (50.5)	—	215 (53.8)	—	.22	.29
Behaviors										
Age of first sexual intercourse ≤13 y of age	76 (21.5)	—	85 (20.8)	—	63 (15.8)	—	44 (11.1)	—	.0014	.07
No. male sexual partners in lifetime ≥2	282 (80.6)	—	354 (87.8)	—	327 (82.2)	—	311 (78.7)	—	.02	.29
No. male sexual partners in the past 3 mo ≥2	71 (20.1)	—	86 (21.0)	—	77 (19.3)	—	68 (17.4)	—	.48	.15
Main sexual partner male	319 (89.1)	—	380 (92.9)	—	361 (90.3)	—	314 (79.3)	—	<.0001	.97
Ever had anal sex with a male partner	89 (25.3)	—	93 (22.7)	—	81 (20.3)	—	83 (21.3)	—	.39	.50
Condom use with main partner in the past 3 mo										
Less than every time	298 (80.3)	—	333 (81.4)	—	342 (85.5)	—	353 (88.3)	—	.01	.45
Every time	73 (19.7)	—	76 (18.6)	—	58 (14.5)	—	47 (11.8)	—	—	—
Condom use at last sexual intercourse	121 (37.5)	—	146 (38.5)	—	139 (34.8)	—	105 (26.3)	—	.02	.42
Smoked at least 100 cigarettes in lifetime	114 (31.8)	—	117 (29.1)	—	86 (21.9)	—	67 (16.9)	—	<.0001	.58

—, not applicable.

[a] *P* value calculated by using χ^2 test, Fisher's exact test, Kruskal-Wallis test, or analysis of variance.

TABLE 2 Prevalence of Vaccine-Type HPV and Between-Wave Changes by Vaccination Status Adjusted for Propensity Score

Vaccination Status	Prevalence of HPV Types Across Waves, Propensity Score Adjusted, %				Between-Wave Changes in HPV Prevalence, Propensity Score Adjusted, % (95% CI) [% Decline or Increase]			
	Wave 1, *N* = 371	Wave 2, *N* = 409	Wave 3, *N* = 400	Wave 4, *N* = 400	Wave 1–2	Wave 2–3	Wave 3–4	Wave 1–4
Types in the 9-valent vaccine[a]								
All	46.1	33.8	22.3	17.6	−12.3 (−19.2 to −5.5) [−26.7][b]	−11.5 (−17.6 to −5.4) [−34][b]	−4.7 (−10.2 to 0.8) [−21.1]	−28.5 (−34.8 to −22.2) [−61.8][b]
Vaccinated	46.6	32.6	16.7	13.5	−14 (−21.8 to −6.2) [−30][b]	−15.9 (−23.2 to −8.5) [−48.8][b]	−3.2 (−8.9 to 2.5) [−19.2]	−33.1 (−39.4 to −26.8) [−71][b]
Unvaccinated	43.4	35.0	45.5	42.1	−8.3 (−17.3 to 0.6) [−19.4]	+10.5 (−1.3 to 22.2) [30]	−3.4 (−18.5 to 11.7) [−7.5]	−1.3 (−14.3 to 11.8) [−3.0]
Types in the 4-valent vaccine[c]								
All	34.6	13.5	8.2	8.6	−21.1 (−27.0 to −15.3) [−61][b]	−5.3 (−9.6 to −1.0) [−39.3][b]	+0.5 (−3.4 to 4.3) [4.9]	−26.0 (−31.6 to −20.4) [−75.1][b]
Vaccinated	35.0	9.9	3.3	6.7	−25.1 (−31.2 to −18.9) [−71.7][b]	−6.6 (−10.9 to −2.3) [−66.7][b]	+3.5 (+0.05 to 6.9) [103][b]	−28.2 (−33.8 to −22.7) [−80.9][b]
Unvaccinated	32.4	17	22.3	19.4	−15.4 (−22.9 to −7.9) [−47.5][b]	+5.3 (−4.3 to 14.9) [31.2]	−2.9 (−15.2 to 9.4) [−13]	−13 (−23.8 to −2.2) [−40.1][b]
Types in the 9-valent but not 4-valent vaccine[d]								
All	23.9	24.8	16.8	12.1	+1.0 (−5.1 to +7.0) [3.8]	−8.1 (−13.6 to −2.5) [−32.3][b]	−4.7 (−9.6 to 0.2) [−28]	−11.8 (−17.2 to −6.4) [−48.1][b]
Vaccinated	23.4	26.6	14.1	7.3	+3.1 (−3.9 to +10.2) [13.7]	−12.4 (−19.3 to −5.5) [−47][b]	−6.8 (−11.8 to −1.9) [−48.2][b]	−16.1 (−21.3 to −11.0) [−68.8][b]
Unvaccinated	22.9	24	30.4	36.1	+1.1 (−6.7 to +9.0) [4.8]	+6.4 (−4.4 to 17.1) [26.7]	+5.8 (−8.7 to 20.2) [18.8]	+13.2 (−0.8 to +25.7) [57.6]

CI, confidence interval.

[a] HPV-6, -11, -16, -18, -31, -33, -45, -52, and -58.

[b] $P < .05$.

[c] HPV-6, -11, -16, and -18.

[d] HPV-31, -33, -45, -52, and -58.

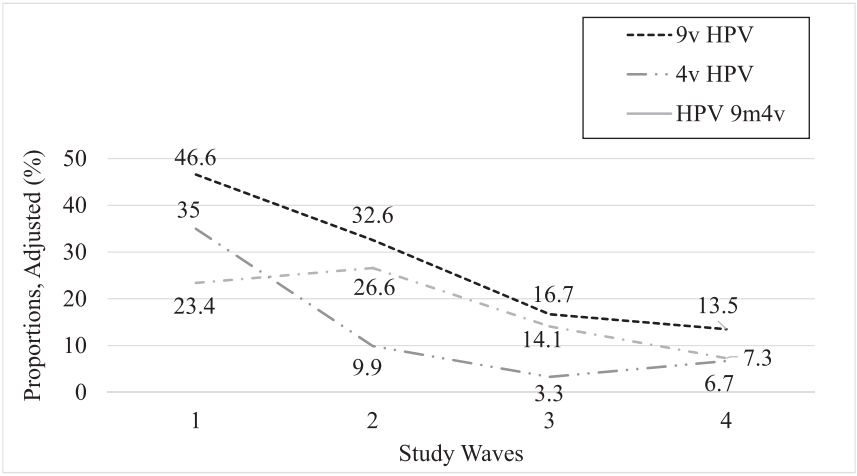

FIGURE 1
Proportions of women who were vaccinated across the 4 study waves infected with any vaccine-type HPV, adjusted for propensity scores. HPV 9m4v, 5 additional HPV types only in 9-valent vaccine (HPV-31, -33, -45, -52, and -58); 4v HPV, 4-valent vaccine–type human papillomavirus; 9v HPV, 9-valent vaccine–type human papillomavirus.

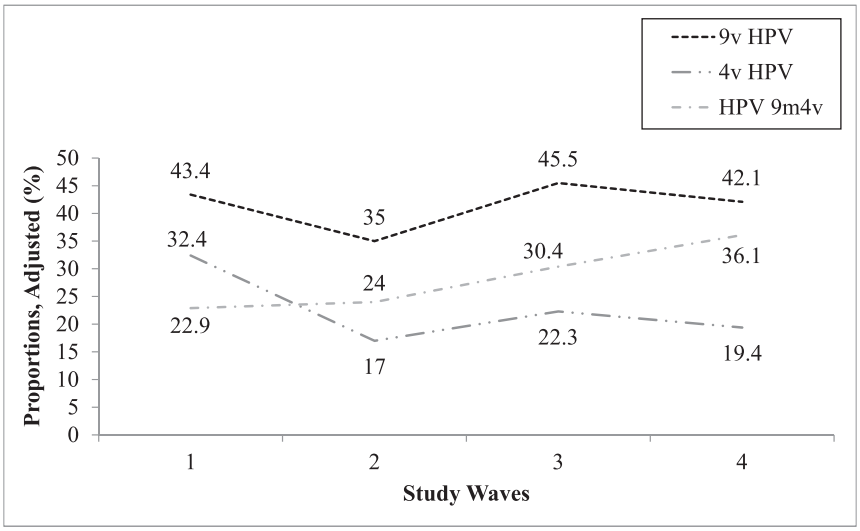

FIGURE 2
Proportions of women who were unvaccinated across the 4 study waves infected with any vaccine-type HPV, adjusted for propensity scores. HPV 9m4v, 5 additional HPV types only in 9-valent vaccine (HPV-31, -33, -45, -52, and -58); 4v HPV, 4-valent vaccine–type human papillomavirus; 9v HPV, 9-valent vaccine–type human papillomavirus.

that the results of self- and clinician testing for vaginal HPV in women are highly concordant.[24–26] Vaccination status was defined as having received at least 1 HPV vaccine dose before enrollment, and it was assessed by using the Ohio statewide immunization registry and the electronic health record, both systems with high reliability.[27] Documentation in at least 1 of these systems was available for 98% of the participants who were vaccinated. Vaccination status was determined by a positive record in either or both databases and, in the small number of cases in which no information was available, by self-report.

We first examined participant characteristics and behaviors using descriptive statistical methods. We then determined if there were differences by study wave in participant characteristics using univariable methods (eg, χ^2 test, Fisher's exact test, Kruskal-Wallis test, or analysis of variance). Because there were between-wave differences for some variables, we conducted a propensity score analysis adjusted by inverse probability of treatment weighting. This adjusts for selection bias, ensuring that any differences noted in HPV prevalence across the study waves were due to HPV vaccine introduction instead of differences in measured participant factors, which may have been confounders. These factors included sociodemographic characteristics, gynecologic history, sexual history, and enrollment site (see Table 1 for all factors included). We then determined HPV prevalence for all women in the study, women who were vaccinated, and women who were unvaccinated across the 4 study waves; these results were unadjusted and adjusted for the propensity score. Methodologic details are described in previous articles.[15,22] Total vaccine effectiveness (the relative infection risk in individuals who were vaccinated versus the infection risk in individuals who were unvaccinated before the introduction of a vaccine) was assessed by comparing vaccine-type HPV prevalence in women who were vaccinated in waves 2, 3, and 4 with women in wave 1, all of whom were unvaccinated.[28]

Finally, we conducted logistic regression analyses to determine the odds of HPV prevalence across the study waves, unadjusted and adjusted for the propensity score. The independent variables were study waves (eg, wave 4 versus wave 1), and the dependent variables were prevalence of at least 1 of the HPV types included in the 9-valent vaccine (HPV-6, -11, -16, -18, -31, -33, -45, -52, and -58), at least 1 of the HPV types included in the 4-valent vaccine (HPV-6, -11, -16, and -18), or at least 1 of the 5 HPV types in the 9-valent but not the 4-valent vaccine (-31, -33,

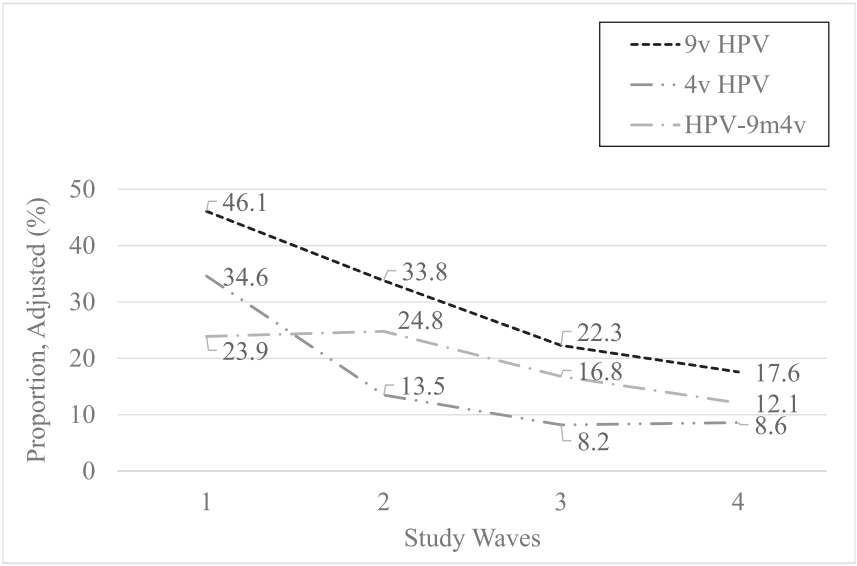

FIGURE 3
Proportions of all women across the 4 study waves infected with any vaccine-type HPV, adjusted for propensity scores. HPV 9m4v, 5 additional HPV types only in 9-valent vaccine (HPV-31, -33, -45, -52, and -58); 4v HPV, 4-valent vaccine–type human papillomavirus; 9v HPV, 9-valent vaccine–type human papillomavirus.

-45, -52, and -58). Separate models were estimated for all women in the study, those who were unvaccinated, and those who were vaccinated. Data were analyzed by using SAS software version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

A total of 1580 participants were enrolled across the 4 studies. Participant characteristics are shown in Table 1. The range of mean ages across all waves was 18.7 to 19.1 years. Between 62.5% and 76.8% of participants were recruited from the Teen Health Center and 23.3% to 37.5% were recruited from the health department. The majority of participants (69.9%–77.3%) identified as African American or multiracial, 48.9% to 56.8% reported at least 2 male lifetime sexual partners, 26.3% to 38.5% used condoms during their last sexual intercourse, and 16.9% to 31.8% had smoked at least 100 cigarettes in their lifetime. The rate of HPV vaccination (defined as receipt of at least 1 dose) increased from 0% in wave 1 to 59.2% in wave 2, 71.5% in wave 3, and 84.3% in wave 4. Virtually all participants in waves 1 to 3 received the 4-valent vaccine; in wave 4, 88% received the 4-valent and 12% the 9-valent vaccine. Overall, 97% of participants received the 4-valent vaccine.

A propensity score analysis was performed to adjust for between-wave differences in participant characteristics (Table 1). The *P* values after propensity score adjustment were all >.05, and the standardized differences for most of the variables were <20%, indicating that variables were successfully balanced.

The proportions of women across the 4 study waves who were positive for 9-valent HPV types, 4-valent HPV types, and the 5 HPV types included in the 9-valent but not the 4-valent vaccine are shown adjusted for propensity score in Table 2 and in Figs 1–3. Among women who were vaccinated, the proportion infected with ≥1 9-valent vaccine–type HPV decreased from waves 1 to 4 from 46.6% to 13.5% (71% decline), the proportion infected with ≥1 4-valent vaccine–type HPV decreased from 35.0% to 6.7% (80.9% decline), and the proportion infected with ≥1 of the 5 types in the 9-valent but not the 4-valent vaccine decreased from 23.4% to 7.3% (68.8% decline); all were statistically significant. Among women who were unvaccinated, the proportion of women infected with ≥1 9-valent vaccine–type HPV decreased from 43.4% to 42.1% (3.0% decline; nonsignificant) from waves 1 to 4, the proportion infected with ≥1 4-valent vaccine–type HPV decreased from 32.4% to 19.4% (40.1% decline; significant), and the proportion infected with ≥1 of the 5 types in the 9-valent but not the 4-valent vaccine increased from 22.9% to 36.1% (57.6% increase; nonsignificant). Vaccine effectiveness was 71.7% in wave 2 versus wave 1, 90.6% in wave 3 versus wave 1, and 80.1% in wave 4 versus wave 1.

The logistic regression model results are shown in Table 3. In these models, we demonstrate the odds of infection (in waves 4 vs 1, 4 vs 2, and 4 vs 3) with 9-valent vaccine–type HPV, 4-valent vaccine–type HPV, and the 5 additional types in the 9-valent vaccine by vaccination status. Among women who were vaccinated, the odds of infection decreased significantly from wave 1 to wave 4 for 9-valent vaccine–type HPV (adjusted odds ratio [aOR] 0.18), 4-valent vaccine–type HPV (aOR 0.13), and the 5 additional HPV types included only in the 9-valent vaccine (aOR 0.26). Among women who were unvaccinated, the odds of infection did not change significantly from wave 1 to wave 4 for 9-valent vaccine–type HPV; it decreased significantly from wave 1 to wave 4 for 4-valent vaccine–type HPV (aOR 0.50) and increased significantly for the 5 additional HPV types only in the 9-valent vaccine (aOR 1.90).

TABLE 3 Comparisons of the Proportions of Women Who Are Positive for 9-Valent HPV Types, 4-Valent HPV Types, and the 5 HPV Types Included in the 9-Valent But Not the 4-Valent Vaccine Across the 4 Study Waves by Vaccination Status: Results of Unadjusted and Adjusted Logistic Regression Analyses

Vaccination Status	Wave 1–4		Wave 2–4		Wave 3–4	
	Unadjusted OR (95% CI)	aOR (95% CI)	Unadjusted OR (95% CI)	aOR (95% CI)	Unadjusted OR (95% CI)	aOR (95% CI)
9-valent vaccine–type HPV[a]						
All	0.24 (0.17 to 0.34)[b]	0.25 (0.18 to 0.35)[b]	0.35 (0.25 to 0.49)[b]	0.42 (0.30 to 0.58)[b]	0.66 (0.46 to 0.94)[b]	0.74 (0.52 to 1.05)
Vaccinated	0.20 (0.14 to 0.29)[b]	0.18 (0.12 to 0.26)[b]	0.30 (0.20 to 0.46)[b]	0.32 (0.21 to 0.49)[b]	0.77 (0.50 to 1.19)	0.77 (0.50 to 1.21)
Unvaccinated	0.46 (0.26 to 0.84)[b]	0.95 (0.56 to 1.62)	0.66 (0.35 to 1.25)	1.35 (0.75 to 2.43)	0.68 (0.35 to 1.35)	0.87 (0.47 to 1.61)
4-valent vaccine–type HPV[c]						
All	0.12 (0.08 to 0.20)[b]	0.18 (0.12 to 0.27)[b]	0.36 (0.22 to 0.60)[b]	0.61 (0.39 to 0.95)[b]	0.66 (0.38 to 1.16)	1.06 (0.64 to 1.75)
Vaccinated	0.10 (0.06 to 0.17)[b]	0.13 (0.08 to 0.22)[b]	0.39 (0.20 to 0.75)[b]	0.66 (0.36 to 1.20)	1.15 (0.52 to 2.54)	2.13 (0.97 to 4.69)
Unvaccinated	0.26 (0.12 to 0.60)[b]	0.50 (0.26 to 0.97)[b]	0.55 (0.23 to 1.32)	1.17 (0.56 to 2.46)	0.55 (0.22 to 1.39)	0.84 (0.39 to 1.79)
5 HPV types in the 9-valent but not the 4-valent vaccine[d]						
All	0.43 (0.29 to 0.63)[b]	0.44 (0.30 to 0.64)[b]	0.38 (0.26 to 0.55)[b]	0.42 (0.29 to 0.60)[b]	0.69 (0.46 to 1.04)	0.68 (0.46 to 1.02)
Vaccinated	0.37 (0.24 to 0.57)[b]	0.26 (0.16 to 0.42)[b]	0.30 (0.19 to 0.47)[b]	0.22 (0.13 to 0.36)[b]	0.68 (0.42 to 1.10)	0.48 (0.28 to 0.82)[b]
Unvaccinated	0.76 (0.39 to 1.49)	1.90 (1.09 to 3.34)[b]	0.77 (0.37 to 1.59)	1.79 (0.96 to 3.33)	0.93 (0.43 to 2.02)	1.30 (0.68 to 2.48)

CI, confidence interval; OR, odds ratio.

[a] HPV-6, -11, -16, -18, -31, -33, -45, -52, and -58.

[b] $P < .05$.

[c] HPV-6, -11, -16, and -18.

[d] HPV-31, -33, -45, -52, and -58.

DISCUSSION

To our knowledge, this is the first study in which trends in 4-valent and 9-valent vaccine–type HPV among women who are vaccinated and women who are unvaccinated in the United States >10 years after HPV vaccine introduction are examined, and it is the first in which trends after 9-valent HPV vaccine introduction are examined. Consistent with our hypotheses, we found that from 2006 to 2017, the prevalence of 4-valent vaccine–type HPV and 9-valent vaccine–type HPV decreased significantly among women who were vaccinated, and the prevalence of 4-valent vaccine–type HPV decreased significantly among women who were unvaccinated. In exploratory analyses, we demonstrated a significant decrease in the 5 additional types targeted by the 9-valent vaccine among women who were vaccinated and, unexpectedly, a significant increase in the 5 additional types targeted by the 9-valent vaccine among women who were unvaccinated.

The significant decline (81%) in 4-valent vaccine–type HPV in women who were vaccinated and the high degree of vaccine effectiveness when comparing women who were vaccinated with women who were unvaccinated (90.6% in wave 3 versus wave 1 and 80.1% in wave 4 versus wave 1) provide evidence of direct protection by the 4-valent vaccine among the women who were vaccinated in this community, and it suggests high vaccine effectiveness in a real-world setting. This degree of effectiveness is remarkable given the fact that vaccination was defined as having received ≥1 dose (ie, was not defined as having completed the vaccination series) and that women in this study were likely at a substantially higher risk for preexisting HPV infection than those in the HPV vaccine clinical trials because of their reported sexual behaviors. The high efficacy of the

licensed HPV vaccines and high rates of vaccination in this study sample likely contributed to this substantial decrease in HPV infection, even in young women at a high risk for sexually transmitted infections (STIs). Our findings of a decrease in vaccine-type HPV among women who were vaccinated extend the findings of those studies conducted over different time frames and in different populations and settings,[16–19,21,29] and they support the real-world effectiveness of the 4-valent vaccine, especially in younger age groups and countries with high vaccination coverage.[16,21] This decline in HPV prevalence is expected to result in a significant decrease in cervical precancers and cancers in the future. Of note, the findings should not be interpreted as suggesting that current recommendations for a 2- or 3-dose series and vaccinating before sexual initiation are not necessary. In additional exploratory analyses, we have demonstrated that receipt of 1 vs 3 doses was associated with 3.2 times the adjusted odds of vaccine-type HPV infection ($P = .04$) and that young women who did versus did not have sex before vaccination were more likely to be positive for vaccine-type HPV (8.8% vs 3.8%, $P = .0021$).

We also demonstrated a significant decline among women who were vaccinated in the prevalence of 9-valent vaccine–type HPV (71%), as hypothesized, and in the prevalence of the 5 additional HPV types included in the 9-valent vaccine (68.8%). All 5 additional types in the 9-valent vaccine are genetically related to HPV-16 (HPV-31, -33, -52, and -58) and HPV-18 (HPV-45). In clinical trials, researchers have demonstrated evidence of crossprotection against HPV types genetically related to HPV-16 and -18,[14,30–32] and in studies conducted in clinical and community settings, researchers have also demonstrated evidence of crossprotection against HPV types genetically related to the 2-valent or 4-valent HPV vaccines[33–35]; however, it is not well established whether crossprotection occurs among younger women recruited from broader settings or after introduction of the 9-valent HPV vaccine. In this study, only 12% of women in wave 4 received at least 1 dose of the 9-valent vaccine; therefore, it is unlikely that these findings were due only to direct protection against the types in the 9-valent vaccine among women who were vaccinated. Instead, the decreases noted in 9-valent vaccine–type HPV and the 5 additional types in the 9-valent vaccine may represent evidence of crossprotection against genetically related types (-31, -33, -45, -52, and -58). In a separate analysis, we are examining trends in nonvaccine-type HPV in more depth by exploring the prevalence of nonvaccine-type HPV genetically related to HPV-16 and HPV-18 among women who received the 4-valent vaccine to examine for crossprotection and by exploring non–vaccine-type HPV genetically unrelated to vaccine-type HPV to examine for type replacement (C.S., L.D., D.B., et al, unpublished observations).

There was a significant decline of 40.1% in the prevalence of 4-valent vaccine–type HPV among women who were unvaccinated, suggesting herd protection. Evidence of herd protection was found in our previous study during the first 3 waves of data collection.[15] In addition, evidence of herd protection was found in 2 studies conducted in Scotland among adult women attending cervical cancer screening,[33,35] in studies in Australia among adult women attending cervical cancer screening[19] and recruited through a social networking site,[18] and in the United States before 9-valent vaccine introduction.[29,36] As noted in a recent review,[37] evidence about herd protection will be a key component of cost-effectiveness analysis evaluating cervical cancer screening strategies.

We unexpectedly found a significant increase from 2006 to 2017 in the prevalence of the 5 additional types in the 9-valent vaccine among women who were unvaccinated. A theoretical explanation could be type replacement, which would be an increase in non–4-valent vaccine–type HPV created by an ecological niche after the 4-valent vaccine was introduced. However, this phenomenon is thought to be unlikely given the genetic stability of HPV and that HPV types do not seem to compete for trophic epithelial niches.[38] A more likely explanation is differences between women who are unvaccinated and women who are vaccinated. For example, if women who are unvaccinated versus women who are vaccinated are more likely to practice riskier behaviors that would increase their risk of acquiring HPV, they would be more likely to acquire non–vaccine-type HPV. In a previous analysis of the first 3 waves of data from this study, we found that women who were unvaccinated did differ significantly from women who were vaccinated in ways that could increase their risk for HPV acquisition, supporting this explanation.[39] For example, women who were unvaccinated versus women who were vaccinated were more likely to lack health insurance and to have had at least 1 new sexual partner in the past 3 months. Continued community-level research is needed to determine if this trend reverses and if the prevalence of the 5 additional types included in the 9-valent vaccine begin to decline once a higher proportion of young women have received the 9-valent vaccine. In addition, the findings of differences between women who are unvaccinated and women who are vaccinated underscore the importance of understanding predictors of nonvaccination and designing clinical interventions

to reach those youth who are unvaccinated and who may be at an elevated risk for HPV.

A limitation of this study was the small proportion of women who received the 9-valent vaccine in wave 4, which limited our ability to examine the trends in HPV prevalence due to the effects of the 9-valent vaccine. Also, the clinic-based recruitment strategy could limit generalizability to all young women in this age group in the United States. Instead, the sample could be viewed as generalizable to a group of adolescent and young adult women at a relatively high risk for HPV and other STIs and with a fairly high vaccination rate. Finally, risk behaviors were assessed by self-report, which may limit validity.

CONCLUSIONS

Eleven years after the introduction of the HPV vaccine, we noted significant decreases in 4-valent vaccine–type HPV, 9-valent vaccine–type HPV, and the 5 additional HPV types included only in 9-valent vaccine among women who were vaccinated, suggesting 4-valent vaccine effectiveness in a real-world setting and possible crossprotection against genetically related HPV types. The significant decrease in 4-valent HPV types among women who were unvaccinated suggests herd protection. Although these findings are important for clinical care and public health policy, continued surveillance will be important to assess for waning vaccine effectiveness, herd protection, and the impact of 9-valent vaccine introduction.

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ABBREVIATIONS

aOR: adjusted odds ratio
HPV: human papillomavirus
STI: sexually transmitted infection

manuscript, and revised the final manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Ms Spinner was an undergraduate at the University of Cincinnati when this research was conducted; she is currently an entering graduate student at the University of South Florida.

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Address correspondence to Jessica A. Kahn, MD, MPH, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, Cincinnati, OH 45229. E-mail: jessica.kahn@cchmc.org

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