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Non–Vaccine-Type Human Papillomavirus Prevalence After Vaccine Introduction: No Evidence for Type Replacement but Evidence for Cross-Protection

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Abstract

Background—We examined non–vaccine-type human papillomavirus (HPV) prevalence in a community before and during the first 8 years after vaccine introduction, to assess for (1) type replacement with any non–vaccine-type HPV and (2) cross-protection with non–vaccine types genetically related to vaccine-type HPV.

Methods—Sexually experienced 13- to 26-year-old women were recruited for 3 cross-sectional studies from 2006 to 2014 (N = 1180). Outcome variables were as follows: (1) prevalence of at least 1 of 32 anogenital non–vaccine-type HPVs and (2) prevalence of at least 1 HPV type genetically related to HPV-16 and HPV-18. We determined changes in proportions of non–vaccine-type HPV prevalence across the study waves using logistic regression with propensity score inverse probability weighting.

Results—Vaccine initiation rates increased from 0% to 71.3%. Logistic regression demonstrated that from 2006 to 2014, there was no increase in non–vaccine-type HPV among vaccinated women (adjusted odds ratio [AOR], 1.02; 95% confidence interval [CI], 0.73–1.42), but an increase among unvaccinated women (AOR, 1.88; 95% CI, 1.16–3.04). Conversely, there was a decrease in types genetically related to HPV-16 among vaccinated (AOR, 0.57; 95% CI, 0.38–0.88) but not unvaccinated women (AOR, 1.33; 95% CI, 0.81–2.17).

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Conflict of Interest and Sources of Funding

Dr Kahn has co-chaired 2 National Institutes of Health-funded human papillomavirus (HPV) vaccine clinical trials in HIV-infected individuals, for which Merck & Co, Inc, provided vaccine and immunogenicity titers. Dr Franco has served as occasional advisor to companies involved with HPV vaccination (Merck, GSK) and HPV and cervical cancer diagnostics (Roche, BD, Qiagen). His institution has received unconditional funding from Merck for investigator-initiated studies carried out in his unit. Dr Brown has received honoraria and grant support from Merck, and his institution Indiana University and Merck have a confidential agreement that pays the university based on certain landmarks of vaccine development; Dr Brown receives a portion of this money as income. For the remaining authors, no competing financial interests exist.

Conclusions—We did not find evidence of type replacement, but did find evidence of cross-protection against types genetically related to HPV-16. These findings have implications for cost-effectiveness analyses, which may impact vaccine-related policies, and provide information to assess the differential risk for cervical cancer in unvaccinated and vaccinated women, which may influence clinical screening recommendations. The findings also have implications for public health programs, such as health messaging for adolescents, parents, and clinicians about HPV vaccination.

Persistent infection with human papillomavirus (HPV), a common sexually transmitted infection, may cause cancers of the cervix, vagina, vulva, penis, anus, and oropharynx.¹ Approximately 35,000 new HPV-associated cancers are diagnosed yearly in men and women in the United States, and HPV infection is estimated to account for 5% of the worldwide cancer burden.² Three currently licensed HPV vaccines prevent the most common types associated with disease. The 2-valent HPV vaccine prevents HPV-16 and HPV-18 infection; the 4-valent vaccine prevents HPV-6, HPV-11, HPV-16, and HPV-18 infection; and the 9-valent vaccine prevents HPV-6, HPV-11, HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58 infection.

Although there is substantial evidence from clinical trials supporting the high efficacy of HPV vaccines in preventing infection and disease caused by targeted HPV types,^{3–6} post-vaccination surveillance is essential to define the population effectiveness of HPV vaccine introduction, because vaccine effectiveness in community settings may differ substantially from vaccine efficacy in clinical trials. Several studies have demonstrated that introduction of HPV vaccines in real-world settings has led to a dramatic decline in the prevalence of vaccine-type HPV among vaccinated individuals.^{7–9} However, data regarding the impact of vaccination on non-vaccine-types are still emerging.^{10–14}

Epidemiologic shifts in non-vaccine-type HPV after vaccine introduction could be detrimental or beneficial. An increase in non-vaccine HPV types due to type replacement could be detrimental because it could lead to an increase in the incidence of cancers caused by high-risk, non-vaccine types. The proposed mechanism for type replacement is that a decrease in the prevalence of vaccine-type HPV creates an ecological niche that other HPV types could occupy. Type replacement has occurred after introduction of other vaccines.^{15–18} However, given that HPV is a genetically stable virus and HPV types seem to act independently from one another,^{19–23} type replacement is considered very unlikely after HPV vaccine introduction. In contrast, a decrease in non-vaccine-types due to cross-protection against types genetically related to the types targeted by current vaccines could enhance vaccine effectiveness and therefore be beneficial. Clinical trials have demonstrated that HPV vaccines may provide cross-protection,^{6,24,25} and studies of adult women attending cervical cancer screening visits have demonstrated direct evidence of cross-protection against HPV infection in real-world settings.^{11–13} Epidemiologic studies of trends in nonvaccine HPV after vaccine introduction have important implications for cost-effectiveness analyses, clinical screening recommendations, and public policy.

Therefore, we designed this analysis of data from 3 cross-sectional surveillance studies, to examine both type replacement and cross-protection before and during the first 8 years after

HPV vaccine introduction in 2006. We enrolled women aged 13 to 26 years from primary care settings and collected detailed information on risk factors to assess for selection bias across the study periods. The aims were as follows: (1) to investigate type replacement by determining changes in proportions of non-vaccine-type HPV and (2) to evaluate for cross-protection by determining changes in proportions of HPV types genetically related to vaccine-type HPV among vaccinated and unvaccinated young women.

MATERIALS AND METHODS

Study Design

We conducted 3 cross-sectional surveillance studies in 2006 to 2007 (N = 368), 2009 to 2010 (N = 409), and 2013 to 2014 (N = 400). Participants (13- to 26-year-old women with a history of sexual contact) were recruited from a hospital-based teen health center and a community health center providing primary care to adolescent and young adult women. Written informed consent was obtained from participants, and the study was approved by the hospital's institutional review board.

Study Procedures

Study procedures were identical for all 3 surveillance studies and are described in detail in a previous article.²⁶ Participants were recruited using a sequential recruitment strategy. Participants completed a self-administered survey assessing sociodemographic characteristics, behaviors, and sexual history, and then underwent self- or clinician-testing for HPV with a cervicovaginal swab.²⁷ All specimens were tested for 36 different HPV types using the Roche Linear Array test, a PCR amplification technique that uses an L1 consensus primer system and a reverse-line blot detection strip.²⁸ β -Globin controls were positive in 100% of the samples in wave 1, 99.8% in wave 2, and 98.8% in wave 3, indicating adequate DNA for PCR amplification. The only HPV vaccine administered in the clinical settings during the study periods was the quadrivalent (HPV types 6, 11, 16, and 18) vaccine. Vaccination history was verified by accessing the participants' immunization records via the electronic medical record and a statewide vaccine registry.²⁹

Statistical Analyses

Data were analyzed using SAS version 9.3 (SAS Institute, Cary, NC). The overall analytic strategy was to determine changes in proportions of non-vaccine-type HPV prevalence among vaccinated (defined as women who had received at least 1 vaccine dose) and unvaccinated young women across the 3 surveillance studies, similar to the strategy used in another analysis, which determined changes in proportions of vaccine-type HPV prevalence across the studies.⁹ Outcome variables for aim 1 were any non-vaccine-type HPV (HPV other than types 6, 11, 16, and/or 18) and any high-risk non-vaccine-type HPV (high-risk HPV other than types 16 and/or 18). Outcome variables for aim 2 were non-vaccine-type HPVs genetically related to HPV-16 and HPV-18; specifically (a) alphapapillomavirus 9 (A9) species except for HPV-16 (HPV types 31, 33, 35, 52, 58, and 67) and (b) alphapapillomavirus 7 (A7) species except for HPV-18 (HPV types 39, 45, 59, 68, and 70).

We first compared participant characteristics using univariable methods (χ^2 , Fisher exact, analysis of variance, or Kruskal-Wallis) to determine whether participants across 3 waves were comparable in terms of sociodemographic characteristics, gynecologic history, sexual history, and enrollment site by study wave (Table 1 footnote). Because there were statistically significant differences between waves for some of these variables across waves, we conducted a propensity score analysis based on inverse probability of treatment weighting.^{30,31s} Propensity score analysis adjusts for selection bias, thus simulating the characteristics of a randomized controlled trial.^{32s} The purpose of the propensity score analysis was to assess whether any differences in non-vaccine-type HPV prevalence across the 3 waves were driven by HPV vaccine introduction, instead of confounding factors. We then checked for adequacy of the propensity score to ensure that the distribution of observed baseline covariates was similar between subjects in different waves.^{30,31s} For detailed information on the covariates and propensity score analysis, please see the Table 1 footnote and previously published articles.^{26,33s}

We then compared the prevalence of baseline variables and non-vaccine-type HPV across the 3 study waves by vaccination status (among all women, vaccinated women, and unvaccinated women) before and after propensity weighting. The comparison of all women was defined as non-vaccine-type HPV among all women across waves 1, 2, and 3 (all women in wave 1 were unvaccinated; women in waves 2 and 3 were either vaccinated or unvaccinated); the comparison of vaccinated women was defined as non-vaccine-type HPV among all women in wave 1 (all of whom were unvaccinated) and vaccinated women in waves 2 and 3; and the comparison of unvaccinated women was defined as non-vaccine-type HPV among all women in wave 1 (all of whom were unvaccinated) and unvaccinated women in waves 2 and 3. Using logistic regression, we compared the proportions of women infected with non-vaccine-type HPV across the 3 waves before and after propensity weighting. In these models, the dependent variables were non-vaccine-type HPV prevalence, and the independent variable was study wave. Logistic regression models were performed for all, vaccinated, and unvaccinated women.

RESULTS

Across the 3 waves, 1180 participants were enrolled, 95.2% to 97.6% of those who were approached to participate were eligible, and greater than 98% of those eligible agreed to participate. Vaccination across the 3 waves increased from 0 (wave 1) to 59.2% (wave 2) to 71.3% (wave 3). Participant characteristics for the 3 waves have been described in detail in a previous article,⁹ but briefly, the mean age was 18.7 to 19.1 years across the 3 waves, most (69.9%–73.0%) identified as black or multiracial, and most (52.8%–67.3%) had Medicaid (public) insurance, that is, were low income. Between 15.8% and 21.5% reported sexual initiation before age 14 years, 80.6% to 87.8% reported at least 2 lifetime sexual partners and 30.2% to 31.0% reported more than 5 lifetime sexual partners. Approximately one third (32.6%–35.7%) had used a condom at last sexual intercourse and between 21.9% and 31.8% had smoked at least 100 cigarettes in her lifetime.

Demographic characteristics, gynecologic history, and sexual behaviors were compared across the 3 study waves.⁹ Several differed significantly across study waves, but after

propensity score weighting, all baseline variables were balanced; that is, there were no longer significant differences across study waves. Three comparisons of baseline data and 3 propensity score analyses were performed: for all, vaccinated, and unvaccinated women. For these 3 comparisons, all baseline variables were also balanced after propensity score weighting. The proportions of women (all, vaccinated, and unvaccinated) who were positive for non-vaccine-type HPV, high-risk non-vaccine-type HPV, and non-vaccine-type HPVs genetically related to HPV-16 and HPV-18, before and after propensity weighting, are shown in Table 1. The proportions of vaccinated and unvaccinated women with non-vaccine-type HPV, as well as the proportions of vaccinated and unvaccinated women with types genetically related to HPV-16 (A9) and HPV-18 (A7), propensity score adjusted, are shown in Figure 1. The adjusted proportion of all and vaccinated women with non-vaccine-type HPV did not increase significantly from waves 1 to 3, but the adjusted proportion of unvaccinated women with non-vaccine-type HPV increased significantly (by 24.5%) from waves 1 to 3. The adjusted proportions of all, vaccinated, and unvaccinated women with high-risk non-vaccine-type HPV did not increase significantly from waves 1 to 3. The adjusted proportion with non-vaccine-type HPV genetically related to the A9 species significantly decreased from waves 1 to 3 among all (by 31.4%) and among vaccinated women (by 36.1%). The adjusted proportion of unvaccinated women with non-vaccine-type HPV related to the A9 species increased, but not significantly. No significant changes in the adjusted proportion of all and vaccinated women with non-vaccine-type HPV genetically related to the A7 species were noted, but the proportion of unvaccinated women positive for these types increased significantly (by 55.2%) from waves 1 to 3.

The results of unadjusted and adjusted logistic regression models comparing the proportions of women (all, vaccinated, and unvaccinated) with non-vaccine-type HPV across the waves are shown in Table 2. There was no significant change in the adjusted proportion of non-vaccine-type HPV from waves 1 to 3 among all and among vaccinated women, but there was a significant increase among unvaccinated women (adjusted odds ratio [AOR], 1.88). There was no significant change in the adjusted proportion of high-risk non-vaccine-type HPV among all, vaccinated, and unvaccinated women. There was a significant decrease in non-vaccine-type HPV genetically related to HPV-16 (A9 species) from waves 1 to 3 among all women (AOR, 0.62) and among vaccinated women (AOR, 0.57), but no change among unvaccinated women. In contrast, there were no significant changes among all or among vaccinated women in non-vaccine-type HPV genetically related to HPV-18 (A7 species), but there was a significant increase among unvaccinated women (AOR, 1.83).

DISCUSSION

Clinical trials have established the efficacy of HPV vaccination in preventing vaccine-type HPV infection and precancers, and studies have confirmed vaccine effectiveness in community settings.⁷ Several recent studies assessing the effect of vaccine introduction on rates of non-vaccine-type HPV in community settings have demonstrated evidence of cross-protection,^{11–14} but results are not consistent.⁸ This study is novel in that we recruited women across a broad age range (13–26 years), enrolled women attending primary care visits in contrast to cervical cancer screening visits, examined HPV prevalence over an extended period before and after vaccine introduction, and collected detailed information on

risk factors for HPV, which allowed us to adjust for selection bias across the study periods using propensity score analysis.

We found no evidence of type replacement in this population, that is, no significant change in non-vaccine-type HPV from waves 1 to 3 among all and vaccinated women, and no significant change in high-risk non-vaccine-type HPV among all and vaccinated women. Concerns have been raised about type replacement, that is, 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.^{34s} Type replacement has occurred after introduction of other vaccines,^{15–18} and although current understanding of HPV evolution and epidemiology suggests that type replacement would not occur,^{19–23} early studies after HPV vaccination have been inconclusive. Mesher et al.¹⁴ reported increased prevalence of HPV-39, HPV-52, HPV-53, and HPV-73, but results were inconsistent between age groups and vaccines received, and there were alternative explanations for these increases so the authors concluded that the data provided no definite evidence for type replacement. Söderlund-Strand et al.¹⁰ reported an increase in HPV-52 and HPV-56 in young women after vaccine introduction. Kavanagh et al.¹¹ and Oliver et al.^{35s} did not find evidence of type replacement after vaccine introduction. Continued surveillance of type-specific HPV after vaccine introduction will be necessary to determine if type replacement is occurring.

We found an unexpected increase in the prevalence of non-vaccine-type HPV from waves 1 to 3 in unvaccinated women, and a similar increase (only from waves 1 to 2) in vaccinated women. Given that non-vaccine-type HPV did not increase from waves 1 to 3 in vaccinated women, this finding is unlikely to represent type replacement. One possible explanation for this increases noted in unvaccinated women and vaccinated women is that it represents “unmasking,” a diagnostic artifact from the PCR assay used for HPV detection, which has been noted to perform with reduced sensitivity in cases of multiple infection and low viral load.^{36s,37s} If a sample contains many HPV types, there is competition among the HPV genome targets in the amplification mixture. Because HPV-16 has a relatively high viral load, it tends to lead to false-negative results for the other HPV types. After reduction in HPV-16, the assay has the ability to detect other HPV types that were previously present but undetectable. Further monitoring would be needed to confirm unmasking; if it were true, we would expect that there would be no change in the prevalence of non-vaccine-type HPV for this group from waves 3 to 4 (data collection is ongoing). Another possible explanation for this finding is that the unvaccinated group of women may be engaging in riskier behaviors than vaccinated women, putting them at higher risk for HPV acquisition: vaccination tends to be associated with other preventive health behaviors.^{38s} The propensity score analysis does not account for differences between unvaccinated and vaccinated women.

In this study sample, we found evidence of cross-protection against HPV types genetically related to HPV-16. The prevalence of non-vaccine HPV types genetically related to HPV-16 decreased significantly among vaccinated, but not unvaccinated, women, suggesting cross-protection. Clinical trials demonstrated cross-protective effects to HPV types genetically related to HPV-16, especially HPV-31 and HPV-33.^{24,25,39s,40s} In real-world settings, however, evidence for cross-protection is more limited. Studies conducted after HPV vaccine introduction in several countries found decreases in HPV-31 and/or HPV-33,^{11–14} whereas

studies in the United States demonstrated no evidence of cross-protection.^{8,35s} The differences in findings between studies may be due in part to the prevalence of vaccine types genetically related to HPV-16: in our study, prevalence was relatively high, increasing statistical power to detect changes over time. The differences may also be related to prevalence of vaccination: in the studies demonstrating cross-protection, vaccination rates tended to be higher. Finally, differences by country may be due to the fact that the bivalent vaccine was the primary vaccine introduced in some countries (e.g., the United Kingdom), in contrast to the quadrivalent vaccine in other countries (e.g., Australia and the United States). In clinical trials, differences have been noted in cross-protection by vaccine type; i.e. the bivalent vaccine may provide a higher degree of cross-protection than the quadrivalent vaccine.^{41s}

Our study did not show cross-protective effects against non-vaccine HPV types genetically related to HPV-18, in contrast to studies of the bivalent and quadrivalent vaccines demonstrating cross-protection against HPV-45 that were clinical trials^{24,25,39s,40s,42s,43s} or conducted in communities.^{11,12} This may be explained by data demonstrating differences in the immune response to HPV-18 in the bivalent versus quadrivalent vaccines and a more robust immune response to HPV-16 vs. HPV-18 with the quadrivalent vaccine, although some of these differences may be a function of the assays used to determine immune response.^{44s} The clinical significance of cross-protection is not yet clear, although some studies demonstrate protection against precancers associated with cross-protective types.²⁵ Future research should continue to monitor cross-protection, because effects may wane over time.^{40s}

One of the limitations of this study was the clinic-based recruitment strategy, which could reduce generalizability and lead to selection bias. However, the racial and ethnic distributions of patients, as well as the geographic catchment areas of the clinics, have remained stable in recent years. Furthermore, although the propensity score analysis is a well-established method to control for selection bias, it is possible that there were unmeasured differences in participant demographics or behaviors that could be associated with HPV prevalence. We attempted to prevent unmeasured confounding in the study design phase by measuring all demographic and behavioral factors that may be associated with HPV prevalence, recruiting a stable population, recruiting a sequential sample, ensuring that participation rates were high, and recruiting boys and girls across sites using identical methods. In addition, the number of participants enrolled may be too low for detecting type replacement. Finally, we were unable to assess the effect of unmasking.

In summary, we found no evidence for type replacement but evidence for cross-protection against HPV types genetically related to HPV-16 in this population. These data, combined with the results of a previous analysis of these data that demonstrated a substantial decrease in vaccine-type HPV in vaccinated young women as well as evidence of herd protection,⁹ have significant implications for clinical practice and public policy. The results may be used to inform cervical cancer screening recommendations, cost-effectiveness analyses, educational messaging, and public health policy. The suboptimal rates of HPV vaccine uptake in many countries, representing a missed opportunity to prevent cervical cancer and

other HPV-associated cancers, underscore the importance of evidence-based educational strategies and policies to promote HPV vaccination.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Proportions and 95% confidence intervals of vaccinated and unvaccinated women with non-vaccine-type HPV, as well as proportions of vaccinated and unvaccinated women with types genetically related to HPV-16 (A9 species) and HPV-18 (A7 species), adjusted for propensity scores, across the 3 study waves (2006–2014).

TABLE 1.

Proportions of Women (All, Vaccinated, and Unvaccinated) Positive for 1 Non-Vaccine Type, 1 High-Risk Non-Vaccine-Type HPV, 1 A9 Species Except HPV-16, and 1 A7 Species Except HPV-18, Unadjusted and Adjusted for Propensity Scores, Across the 3 Study Waves

Wave 1 (N = 371)			Wave 2 (N = 409)			Wave 3 (N = 400)			Change in Proportions, Adjusted for Propensity Score		
	Proportion, Unadjusted % (n) [SE]	Proportion, Adjusted for Propensity Score % [SE]	Proportion, Unadjusted % (n) [SE]	Proportion, Adjusted for Propensity Score % [SE]	Proportion, Unadjusted % (n) [SE]	Proportion, Adjusted for Propensity Score % [SE]	Waves 1-2, % (95% CI) [Decline/Increase]	Waves 2-3, % (95% CI) [Decline/Increase]	Waves 1-3, % (95% CI) [Decline/Increase]		
Non-vaccine-type HPV											
All	59.3 (220) [0.03]	59.5 [0.03]	All	74.3 (304) [0.02]	74.5 [0.02]	62.0 (248) [0.02]	63.3 [0.03]	+15.0 (8.2, 21.8) [+25.2]	-11.3 (-17.8 to -4.7) [-15.0]	+3.7 (-3.4 to 10.9) [+6.4]	
—	—	60.7 [0.03]	Vaccinated	77.3 (187) [0.03]	75.4 [0.03]	61.2 (175) [0.03]	61.1 [0.03]	+14.7 (7.0 to 22.3) [+24.2]	-14.3 (-22.5 to -6.1) [-19.0]	+0.4 (-7.6 to 8.3) [+0.7]	
—	—	57.9 [0.03]	Unvaccinated	70.1 (117) [0.04]	67.9 [0.04]	64.0 (73) [0.05]	72.1 [0.04]	+10.0 (0.8 to 19.2) [+17.3]	+4.3 (-7.2 to 15.7) [+6.2]	+14.2 (4.1 to 24.4) [+24.5]	
High-risk non-vaccine-type HPV											
All	48.8 (179) [0.03]	48.6 [0.03]	All	57.6 (235) [0.03]	58.2 [0.03]	43.5 (172) [0.03]	45.1 [0.03]	+9.6 (2.4 to 16.9) [+19.8]	-13.1 (-20.2 to -6.0) [-22.5]	-3.5 (-10.8 to 3.8) [-7.2]	
—	—	49.3 [0.03]	Vaccinated	64.7 (156) [0.03]	63.9 [0.03]	43.1 (121) [0.03]	41.8 [0.03]	+14.6 (6.4 to 22.9) [+29.6]	-22.1 (-30.8 to -13.3) [-34.6]	-7.5 (-15.6 to 0.6) [-15.2]	
—	—	48.2 [0.03]	Unvaccinated	47.3 (79) [0.04]	47.9 [0.04]	44.7 (51) [0.05]	56.7 [0.05]	-0.3 (-10.0 to 9.4) [-0.6]	+8.8 (-3.7 to 21.3) [+18.4]	+8.6 (-2.4 to 19.5) [+17.6]	
A9 species except HPV-16											
All	24.8 (91) [0.03]	24.5 [0.02]	All	29.7 (121) [0.05]	29.5 [0.02]	17.0 (67) [0.02]	16.8 [0.02]	+5.0 (-1.5 to 11.5) [+20.4]	-12.8 (-18.7 to -6.8) [-43.1]	-7.7 (-13.7 to -1.8) [-31.4]	
—	—	24.1 [0.02]	Vaccinated	30.7 (74) [0.03]	29.9 [0.03]	15.3 (43) [0.02]	15.4 [0.02]	+5.8 (-1.8 to 13.3) [+24.1]	-14.5 (-21.9 to -7.0) [-48.5]	-8.7 (-15.1 to -2.3) [-36.1]	
—	—	24.1 [0.02]	Unvaccinated	28.1 (47) [0.04]	28.9 [0.04]	21.1 (24) [0.04]	29.7 [0.02]	+4.8 (-3.9 to 13.4) [+19.9]	+0.8 (-10.7 to 12.2) [+2.8]	+5.5 (-4.4 to 15.5) [+23.2]	
A7 species except HPV-18											
All	22.1 (81) [0.02]	22.0 [0.02]	All	30.2 (123) [0.02]	30.5 [0.02]	23.5 (93) [0.02]	26.2 [0.02]	+8.5 (2.1 to 14.9) [+38.6]	-4.3 (-10.7 to 2.1) [-14.1]	+4.2 (-2.1 to 10.5) [+19.1]	
—	—	23.3 [0.02]	Vaccinated	34.4 (83) [0.03]	34.9 [0.03]	23.8 (67) [0.03]	24.0 [0.03]	+11.6 (3.9 to 19.3) [+49.8]	-10.9 (-19.1 to -2.8) [-31.2]	+0.7 (-6.2 to 7.6) [+3.0]	
—	—	21.0 [0.02]	Unvaccinated	24.0 (40) [0.03]	24.4 [0.04]	22.8 (26) [0.04]	32.6 [0.05]	+3.4 (-4.8 to 11.6) [+16.2]	+8.2 (-3.2 to 19.6) [+33.6]	+11.7 (1.6 to 21.7) [+55.2]	

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In wave 1, 371 participants (100%) were unvaccinated; in wave 2, 242 (59.2%) were vaccinated and 167 (40.8%) were unvaccinated; and in wave 3, 285 (71.3%) were vaccinated and 115 (28.7%) were unvaccinated. Vaccinated is defined as women who had received at least 1 vaccine dose. Variables included in the propensity score analysis included enrollment site, age, race, Appalachian descent, Hispanic ethnicity, health insurance plan, marital status, history of pregnancy, history of any sexually transmitted infection, age of first sexual intercourse, number of lifetime male partners, number of male partners in the past 3 months, whether one's main sexual partner is male, history of anal sex, condom use with main partner, condom use at last sexual intercourse, and history of cigarette smoking.

CI indicates confidence interval.

TABLE 2.

Comparisons of the Proportions of Women Positive for 1 Non-Vaccine Type, 1 High-Risk Non-Vaccine-Type HPV, 1 A9 Species Except HPV-16, and 1 A7 Species Except HPV-18, Unadjusted and Adjusted for Propensity Scores, Across the 3 Study Waves: Results of Logistic Regression Analyses

	Wave 2 vs. Wave 1		Wave 3 vs. Wave 1	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Non-vaccine-type HPV				
All	1.99 (1.47–2.69)	1.99 (1.45–2.73)	1.12 (0.84–1.50)	1.17 (0.87–1.58)
Vaccinated	2.33 (1.62–3.36)	1.98 (1.36–2.88)	1.08 (0.79–1.48)	1.02 (0.73–1.42)
Unvaccinated	1.61 (1.09–2.37)	1.54 (1.02–2.31)	1.22 (0.79–1.89)	1.88 (1.16–3.04)
High-risk non-vaccine-type HPV				
All	1.43 (1.07–1.90)	1.47 (1.10–1.98)	0.81 (0.61–1.08)	0.87 (0.65–1.17)
Vaccinated	1.93 (1.38–2.69)	1.82 (1.29–2.58)	0.79 (0.58–1.09)	0.74 (0.53–1.03)
Unvaccinated	0.94 (0.65–1.36)	0.99 (0.67–1.46)	0.85 (0.56–1.30)	1.41 (0.90–2.20)
A9 species except HPV-16				
All	1.28 (0.93–1.76)	1.29 (0.93–1.80)	0.62 (0.44–0.88)	0.62 (0.43–0.90)
Vaccinated	1.34 (0.94–1.93)	1.34 (0.92–1.96)	0.55 (0.37–0.82)	0.57 (0.38–0.88)
Unvaccinated	1.19 (0.79–1.79)	1.28 (0.83–1.98)	0.81 (0.49–1.35)	1.33 (0.81–2.17)
A7 species except HPV-18				
All	1.52 (1.10–2.11)	1.55 (1.11–2.18)	1.09 (0.78–1.53)	1.26 (0.89–1.78)
Vaccinated	1.86 (1.29–2.67)	1.77 (1.22–2.57)	1.11 (0.76–1.60)	1.04 (0.71–1.53)
Unvaccinated	1.11 (0.72–1.71)	1.22 (0.77–1.93)	1.04 (0.63–1.72)	1.83 (1.12–2.98)

Bolded numbers represent $P < 0.05$.

CI indicates confidence interval; OR, odds ratio.