

Reduction in Human Papillomavirus (HPV) Prevalence Among Young Women Following HPV Vaccine Introduction in the United States, National Health and Nutrition Examination Surveys, 2003–2010

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Background. Human papillomavirus (HPV) vaccination was introduced into the routine immunization schedule in the United States in late 2006 for females aged 11 or 12 years, with catch-up vaccination recommended for those aged 13–26 years. In 2010, 3-dose vaccine coverage was only 32% among 13–17 year-olds. Reduction in the prevalence of HPV types targeted by the quadrivalent vaccine (HPV-6, -11, -16, and -18) will be one of the first measures of vaccine impact.

Methods. We analyzed HPV prevalence data from the vaccine era (2007–2010) and the prevaccine era (2003–2006) that were collected during National Health and Nutrition Examination Surveys. HPV prevalence was determined by the Linear Array HPV Assay in cervicovaginal swab samples from females aged 14–59 years; 4150 provided samples in 2003–2006, and 4253 provided samples in 2007–2010.

Results. Among females aged 14–19 years, the vaccine-type HPV prevalence (HPV-6, -11, -16, or -18) decreased from 11.5% (95% confidence interval [CI], 9.2–14.4) in 2003–2006 to 5.1% (95% CI, 3.8–6.6) in 2007–2010, a decline of 56% (95% CI, 38–69). Among other age groups, the prevalence did not differ significantly between the 2 time periods ($P > .05$). The vaccine effectiveness of at least 1 dose was 82% (95% CI, 53–93).

Conclusions. Within 4 years of vaccine introduction, the vaccine-type HPV prevalence decreased among females aged 14–19 years despite low vaccine uptake. The estimated vaccine effectiveness was high.

Keywords. human papillomavirus; vaccine effectiveness; HPV vaccine; vaccine impact; prevalence.

Two prophylactic human papillomavirus (HPV) vaccines are available and have been shown in clinical trials to have high efficacy for prevention of infection and associated disease due to HPV types targeted by the vaccine [1, 2]. The quadrivalent vaccine is directed

against HPV-6, -11, -16, and -18; the bivalent vaccine is directed against HPV-16 and -18. In June 2006, the Advisory Committee on Immunization Practices recommended routine vaccination with 3 doses of quadrivalent HPV vaccine for females aged 11 or 12 years and catch-up vaccination for those aged 13 through 26 years [3]. In October 2009, this recommendation was updated to include either HPV vaccine [4]. In 2011, a recommendation was made for routine vaccination of males [5]. While HPV vaccine coverage is increasing in the United States, a 2010 national survey found that only 49% of females aged 13–17 years had received at least 1 dose and that 32% had received 3 doses [6]. From mid-2006 through 2010, almost all HPV vaccine

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administered in the United States was quadrivalent HPV vaccine (Centers for Disease Control and Prevention, unpublished data).

HPV includes a group of >40 sexually transmitted types that are classified epidemiologically according to oncogenic risk [7]. Oncogenic or high-risk HPV types cause cervical cancers and contribute to a high proportion of other anogenital and oropharyngeal cancers. The high-risk types HPV-16 and -18 are responsible for approximately 70% of cervical cancers [8]. Non-oncogenic (ie, low-risk) HPV types, including HPV-6 and -11, cause anogenital warts and recurrent respiratory papillomatosis [9]. A variety of projects have been established to monitor the impact of HPV vaccine on infection and disease outcomes [10, 11]. Declines in the prevalence of infection due to HPV types targeted by the vaccines (ie, HPV-16 and -18 for bivalent vaccine and HPV-6, -11, -16, and -18 for quadrivalent vaccine) will be one of the earliest measures of their impact.

While the main end points of the HPV vaccine clinical trials were vaccine type-associated disease and infection, efficacy against some nonvaccine HPV types was also evaluated, including those related to HPV-16 (ie, HPV-31, -33, -35, -52, and -58 in the alpha 9 species) and to HPV-18 (ie, HPV-39, -45, -59, and -68 in the alpha 7 species) [12–14]. Postlicensure monitoring evaluations also have the opportunity to evaluate cross-protection against nonvaccine HPV types, as well as possible type replacement.

We initiated monitoring of HPV prevalence in cervicovaginal swabs in the National Health and Nutrition Examination Survey (NHANES) in 2002. Previous reports described HPV type-specific prevalence in the prevaccine era [15, 16]. In this article, we compare national HPV prevalence among females in the prevaccine era (NHANES 2003–2006) and the vaccine era (NHANES 2007–2010) and estimate vaccine effectiveness.

METHODS

Survey Design and Population

NHANES is an ongoing series of cross-sectional surveys conducted by the National Center for Health Statistics (NCHS) of the CDC. The surveys are designed to be nationally representative of the civilian, noninstitutionalized US population. Consenting participants have a household interview followed by a physical examination in a mobile examination center (MEC). To increase the precision of estimates, NHANES oversampled certain subdomains. In NHANES 1999–2006, Mexican Americans, blacks, low income white and others, and adolescents aged 12–19 years were oversampled. In 2007–2010, Hispanics, non-Hispanic blacks, and low income white and others were oversampled. Because adolescents were not oversampled in 2007–2010, there was a reduced number of individuals aged 14–19 years. This survey was approved by the NCHS/CDC Research Ethics Review Board.

We analyzed NHANES 2003–2010 data. Years 2003–2006 were considered the prevaccine era because vaccination was first recommended in June 2006; some introduction started at the end of that year, although the recommendations were not published until early 2007. In 2003–2006, 5178 females aged 14–59 years were interviewed; 4990 (96.4%) received an examination in the MEC. Of those, 4233 (85%) submitted a self-collected cervicovaginal swab specimen, and 4150 specimens (83%) were adequate for DNA typing (see “Specimen Collection and Laboratory Methods,” below). In 2007–2010, 4988 females aged 14–59 years were interviewed; 4879 (97.8%) received an examination in the MEC. Of those, 4275 (88%) submitted a swab specimen, and 4253 specimens (87%) were adequate for DNA typing. HPV prevalence testing among males was not included in NHANES during this period.

Demographic, Behavioral, and HPV Vaccination History Data

Demographic information was ascertained during the household interview. Sexual history information was determined by self-report among participants aged 14–59 years, using audio computer-assisted self-interview in the MEC. Respondents who reported ever having sex (described as vaginal, oral, or anal) were asked additional questions about their sexual history, including age at first sex, lifetime number of partners, and number of partners in the past 12 months. NHANES 2003–2004 did not ask persons aged 14–17 years about partners in the past 12 months; this variable was not compared between the 2 time periods for 14–19 year-olds.

HPV vaccination history was collected in 2007–2010. Persons aged ≥ 16 years and emancipated minors were interviewed directly. For those aged <16 years, parents or guardians were interviewed. The question was stated as follows: “Human Papillomavirus (HPV) vaccine is given to prevent cervical cancer in girls and women. It is given in 3 separate doses over 6 months and has been recommended for girls and women since June, 2006. Have you (has xx) ever received one or more doses of the HPV vaccine? (The brand name for the vaccine is Gardasil).” Information on number of doses received was also collected. Persons with missing data or who answered “don’t know” were excluded from analysis of vaccine coverage or associations of prevalence with vaccination history.

Specimen Collection and Laboratory Methods

Females aged 14–59 years who were examined in the MEC were asked to self-collect a cervicovaginal sample [15, 17]. Extractions and testing were performed at the CDC as previously described [15]. Briefly, extracted DNA was tested using the Linear Array HPV Genotyping Assay (Roche Diagnostics, Indianapolis, IN). All samples were hybridized to the typing strip that included probes for 37 HPV types (HPV-6, -11, -16, -18, -26, -31, -33, -35, -39, -40, -42, -45, -51, -XR[52], -53, -54, -55, -56, -58, -59, -61, -62, -64, -66, -67, -68, -69, -70, -71, -72, -73,

-81, -82, -83, -84, -89, and -IS39). The XR probe indicates HPV-52; however, this probe also hybridizes to HPV-33, -35, and -58. Samples positive for XR and one of the cross-reacting types were ambiguous for HPV-52; in this situation, a type-specific quantitative polymerase chain reaction assay was performed. Samples negative for both β -globin and HPV were considered inadequate.

Statistical Analysis

Analyses were limited to subjects aged 14–59 years with adequate self-collected cervicovaginal samples. Data were analyzed using SAS (version 9.3, SAS Institute, Cary, NC) and SAS-callable SUDAAN (version 11.0, RTI, Cary, NC). We estimated HPV prevalence among females aged 14–59 years in NHANES 2003–2006 and 2007–2010 by age group for any HPV, high-risk (HR) nonvaccine type HPV, vaccine type HPV (HPV-6, -11, -16, and -18), and HR vaccine type HPV (HPV-16 and -18). Any HPV included any of 37 types. The HR nonvaccine types included 12 clinically relevant types: HPV-31, -33, -35, -52, and -58 (in the alpha 9 species); HPV-39, -45, -59, and -68 (in the alpha 7 species), and HPV-51, -56, and -66 (in other species). All estimates were weighted as specified by the NCHS, using 2-year weights to account for unequal probabilities of selection and adjustment for nonresponse [18]. Variance estimates were calculated using a Taylor series linearization to account for the complex survey design [19]. Prevalence estimates with a relative standard error (RSE) of >30% or based on ≤ 10 positive cases are noted; these are considered unstable and should be interpreted with caution. When we used logistic regression to determine adjusted prevalence ratios (aPRs), we adjusted for race/ethnicity in addition to lifetime number of sex partners because of the association with prevalence [15]. Sample size limited consideration of other variables for most analyses. The prevalence ratio was the predicted probability calculated from the logistic regression model, using the PREDMARG statement in SUDAAN [20]. Throughout the analyses, *P* values were not adjusted for multiple comparisons.

Prevalence ratios comparing NHANES 2003–2006 with NHANES 2007–2010 were calculated. To assess the comparability of participants in the 2 periods in selected age groups, we compared frequencies of demographic and sexual behavior variables. In NHANES 2007–2010, we calculated the percentage of individuals aged 14–19 years and 20–24 years with a history of vaccination. To compare the individual HPV types among participants 14–19 years old in these 2 periods, we plotted the prevalence of 37 types.

We further evaluated individuals aged 14–19 years and limited our analyses to sexually active females. Population characteristics and HPV prevalence in the prevaccine and vaccine eras were compared, overall and by vaccination history. We used logistic regression to determine aPRs. Among sexually active females aged 14–19 years in NHANES 2007–2010, we

evaluated associations of vaccination history with vaccine-type HPV prevalence. Vaccine effectiveness was calculated as $1 - \text{aPR}$ [21].

RESULTS

Comparison of HPV Prevalence, 2003–2006 and 2007–2010

A total of 4150 females in 2003–2006 and 4253 females in 2007–2010 aged 14–59 years were included in the analysis. Among those aged 14–19 years, there were differences in HPV prevalence between the 2 periods (Table 1). In this age group, any HPV, vaccine type, and HR vaccine type prevalences were lower in 2007–2010, compared with 2003–2006 ($P < .01$ for all comparisons). Vaccine type prevalence decreased from 11.5% (95% confidence interval [CI], 9.2–14.4) to 5.1% (95% CI, 3.8–6.6), a decline of 56% (95% CI, 38–69). HR vaccine type prevalence decreased from 7.2% (95% CI, 5.8–8.7) to 3.6% (95% CI, 2.5–5.0), a decline of 50% (95% CI, 26–66). There was a decline in HR nonvaccine type HPV, but this was not statistically significant. Among the other age groups, there were no differences in prevalence between these 2 periods ($P > .05$ for all comparisons).

We further evaluated females aged 14–19 years, since prevalence changes were observed in this group. In 2007–2010, 98% answered the HPV vaccination question. Receipt of at least 1 vaccine dose was reported by 34.1% (95% CI, 28.5–40.2); among these females, 62.5% had a history of all 3 doses. Sexual behavior among females aged 14–19 years overall was similar in the 2 periods. In 2003–2006 and 2007–2010, 53.9% (95% CI, 50.8–56.9) and 50.3% (95% CI, 45.0–55.5), respectively, reported having had sex ($P = .24$). There were only small, nonsignificant differences in lifetime number of partners and race/ethnicity.

While NHANES can be analyzed in 2-year cycles, we used 4 years of data from each period, to increase the sample size for our comparisons. However, among females aged 14–19 years, there was no decline in vaccine type HPV prevalence between 2003–2004 (10.8%; 95% CI, 7.4–15.3) and 2005–2006 (12.3%; 95% CI, 9.3–16.0). In the vaccine era, vaccine type prevalence was 5.5% (95% CI, 4.0–7.5) in 2007–2008 and 4.5% (95% CI, 2.8–7.3) in 2009–2010.

We also evaluated women aged 20–24 years, since vaccination is also recommended for this age group. In 2007–2010, 98% answered the HPV vaccination question. Receipt of at least 1 dose was reported by 17.8% (95% CI, 12.5–24.8); among these females, 53.6% had a history of all 3 doses. Ever having had sex was reported by 91.4% (95% CI, 86.2–94.7) in 2003–2006 and by 91.9% (95% CI, 88.4–94.5) in 2007–2010 ($P = .83$). Among those who were sexually active, 66.4% (95% CI, 60.9–71.5) in 2003–2006 and 78.1% (95% CI, 72.4–82.9) in 2007–2010 had ≥ 3 sex partners in their lifetime ($P = .004$); 25.6% (95% CI, 21.0–30.8) and 38.5% (95% CI, 32.1–45.4), respectively,

Table 1. Prevalence of Human Papillomavirus (HPV) Among Females Aged 14–59 Years, National Health and Nutrition Examination Surveys, 2003–2006 and 2007–2010, by Age Group

Age, HPV Type ^a	Prevalence, %, (95% CI)		Prevalence Ratio (95% CI)
	2003–2006	2007–2010	
Overall	n = 4150	n = 4253	
Any HPV	42.5 (40.4–44.7)	39.8 (37.7–42.0)	...
14–19 y	n = 1363	n = 740	
Any HPV	32.9 (29.5–36.4)	26.1 (22.4–30.2)	0.79 (0.66–0.95)*
HR nonvaccine type HPV	20.7 (17.9–23.9)	16.4 (12.9–20.6)	0.79 (0.60–1.04)
Vaccine type HPV	11.5 (9.2–14.4)	5.1 (3.8–6.6)	0.44 (0.31–0.62)**
HR vaccine type HPV	7.2 (5.8–8.7)	3.6 (2.5–5.0)	0.50 (0.34–0.74)**
20–24 y	n = 432	n = 445	
Any HPV	53.8 (46.0–61.3)	59.8 (54.0–65.3)	1.11 (0.94–1.32)
HR nonvaccine type HPV	32.9 (26.8–39.6)	37.4 (32.5–42.6)	1.14 (0.90–1.44)
Vaccine type HPV	18.5 (14.9–22.7)	19.9 (15.5–25.2)	1.08 (0.78–1.48)
HR vaccine type HPV	15.2 (11.7–19.5)	16.2 (12.2–21.4)	1.07 (0.73–1.56)
25–29 y	n = 403	n = 414	
Any HPV	46.8 (42.9–50.7)	50.8 (46.0–55.6)	1.08 (0.96–1.23)
HR nonvaccine type HPV	24.6 (19.1–31.0)	28.4 (23.3–34.1)	1.15 (0.85–1.57)
Vaccine type HPV	11.8 (8.9–15.5)	13.1 (10.0–17.1)	1.11 (0.76–1.64)
HR vaccine type HPV	8.1 (6.1–10.7)	10.3 (7.5–14.0)	1.27 (0.83–1.94)
30–39 y	n = 702	n = 903	
Any HPV	44.2 (40.6–48.0)	39.1 (35.4–43.0)	0.88 (0.78–1.00)
HR nonvaccine type HPV	20.7 (16.9–25.0)	18.3 (15.5–21.5)	0.88 (0.68–1.14)
Vaccine type HPV	9.2 (7.1–11.9)	6.9 (5.4–8.8)	0.75 (0.52–1.07)
HR vaccine type HPV	6.7 (4.6–9.7)	5.7 (4.4–7.3)	0.85 (0.54–1.34)
40–49 y	n = 705	n = 960	
Any HPV	42.4 (39.1–45.9)	39.6 (36.6–42.6)	0.93 (0.83–1.04)
HR nonvaccine type HPV	18.1 (14.7–22.1)	15.4 (12.5–18.1)	0.85 (0.64–1.14)
Vaccine type HPV	5.2 (3.4–7.7)	5.7 (4.0–8.1)	1.11 (0.65–1.89)
HR vaccine type HPV	3.4 (2.0–5.5)	4.5 (3.1–6.5)	1.34 (0.72–2.49)
50–59 y	n = 545	n = 791	
Any HPV	38.8 (34.0–43.9)	33.7 (28.7–39.1)	0.87 (0.71–1.06)
HR nonvaccine type HPV	16.3 (13.3–19.8)	12.9 (9.5–17.1)	0.79 (0.55–1.13)
Vaccine type HPV	4.7 (3.1–7.1)	3.9 (2.5–5.9)	0.82 (0.46–1.49)
HR vaccine type HPV	2.9 (1.7–4.8)	2.8 (1.8–4.5)	0.98 (0.49–1.94)

Data are for all females, including those who did not report having had sex.

Abbreviation: CI, confidence interval.

^a High-risk (HR) nonvaccine types consist of HPV-31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, and -68. Vaccine types consist of HPV-6, -11, -16, and -18. HR vaccine types consist of HPV-16 and -18.

* $P = .01$; ** $P < .001$, by the F statistic, from the Wald χ^2 test.

had ≥ 2 partners in the past 12 months ($P = .004$). After adjustment for sexual behavior and race/ethnicity, there was still no change in vaccine type prevalence between the 2 periods in this age group (aPR = 1.07%; 95% CI, .76–1.52).

HPV type-specific prevalence among females aged 14–19 years is shown in Figure 1 and Supplementary Table 1. While there were increases or decreases in prevalence of individual types between the periods, differences were statistically significant only for HPV-16 (6.0% vs 3.0%; $P < .05$) and HPV-6 (5.4% vs 1.6%; $P < .05$). Prevalence estimates for many individual

types were unstable, and differences were not tested for statistical significance.

Changes in HPV Prevalence Among Sexually Active Females Aged 14–19 Years, by Vaccination History

Further analyses were limited to sexually active females aged 14–19 years. Overall, demographic and sexual risk behavior characteristics did not differ between the 2 periods (Table 2). However, compared with the prevaccine era, in 2007–2010 a greater percentage of vaccinated females (57.6% vs 47.6%;

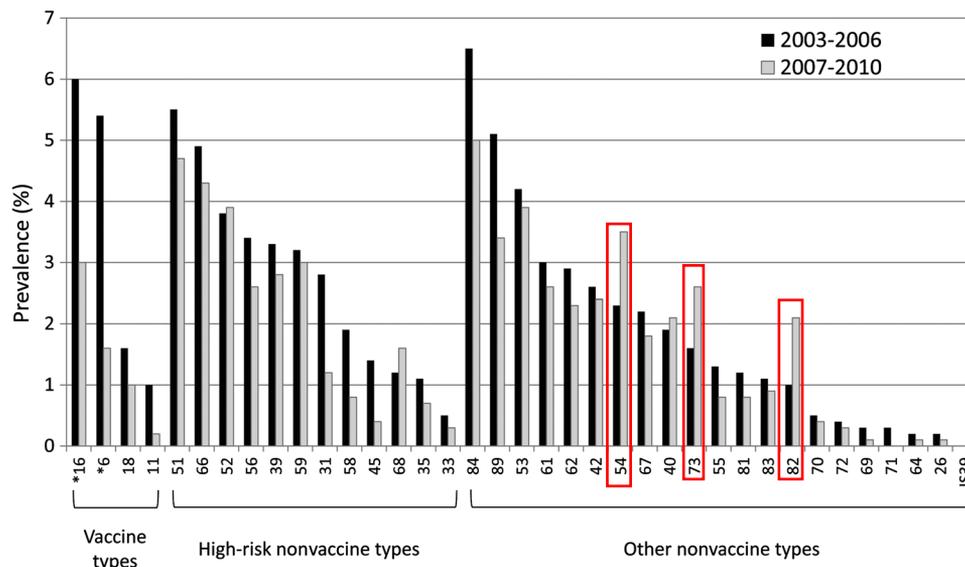


Figure 1. Prevalence of individual human papillomavirus (HPV) types among females aged 14–19 years, 2003–2006 and 2007–2010. Data are for all females aged 14–19 years, including those who did not report having had sex. HPV types ordered from highest to lowest prevalence in the prevaccine era within each HPV type category. Estimates with a relative standard error (RSE) of >30% or <10 observations: 2003–2006, HPV-11, -26, -33, -64, -69, -71, -72, -82 and -IS39; 2007–2010, HPV-11, -18, -21, -26, -31, -33, -35, -45, -55, -56, -58, -64, -69 -70, -72, and -81 (Supplementary Table 1 provides further detail). * $P < .05$.

$P = .06$) and a smaller percentage of unvaccinated females (37.9% vs 47.6%; $P = .03$) had ≥ 3 partners in their lifetime. Non-Hispanic blacks composed 16.5% of the prevaccine era population and, in the vaccine era, 8.4% of the vaccinated and 20.3% of the unvaccinated populations. There were no statistically significant differences in overall distribution of race/ethnicity among the vaccinated ($P = .08$) or unvaccinated ($P = .49$) participants, compared with the prevaccine era.

Compared with the prevaccine era, the prevalence of any HPV was lower in 2007–2010 overall (aPR = 0.82; 95% CI, .69–.98) and among unvaccinated females (aPR = 0.77; 95% CI, .64–.93; Table 3). Vaccine type prevalence was lower in 2007–2010, with an adjusted decline of 53% overall (aPR = 0.47; 95% CI, .33–.67) and an adjusted decline of 88% among vaccinated females (aPR = 0.12; 95% CI, .05–.29). Although the differences did not reach statistical significance, vaccine type prevalence was also lower among unvaccinated females in 2007–2010, compared with the prevaccine era (aPR = 0.72; 95% CI, .50–1.02). Compared with the prevaccine era, HR nonvaccine type prevalence in 2007–2010 did not differ significantly overall, among vaccinated females or unvaccinated females.

Vaccine Effectiveness in 2007–2010

In NHANES 2007–2010, race/ethnicity, lifetime number of partners, and history of vaccination were associated with vaccine type prevalence among sexually active females aged 14–19 years (Table 4). Vaccine type prevalence was 3.1% among vaccinated females (RSE > 30%) and 12.6% among those who

were unvaccinated (PR = 0.24; 95% CI, .10–.58). Vaccinated females had a greater lifetime number of sex partners (Table 2). In multivariate analysis, after adjustment for lifetime number of sex partners and race/ethnicity, the association between vaccination history and HPV prevalence was stronger (aPR = 0.18; 95% CI, .07–.47). The estimated vaccine effectiveness of at least 1 dose was 82% (95% CI, 53–93).

DISCUSSION

We found a decrease in vaccine type HPV prevalence among a nationally representative sample of females 14–19 years old in the vaccine era (2007–2010) compared with the prevaccine era (2003–2006). No decreases were observed in other age groups. Our point estimate of a 56% decrease in prevalence is greater than expected, considering vaccination history in our data and vaccine coverage estimates from national immunization surveys [6]. In NHANES 2007–2010, only 34% of females in this age group reported receipt of at least 1 HPV vaccine dose. National immunization surveys found that coverage by at least 1 dose among females aged 13–17 years increased from 25% in 2007 to 49% in 2010 [6].

We investigated factors that could have accounted for the decrease in vaccine type HPV prevalence. There were no differences in sexual behavior that we measured or in race/ethnicity between the 2 periods. We also found no downward trend in vaccine type HPV prevalence in the two 2-year NHANES cycles prior to vaccine introduction. Furthermore, there was no

Table 2. Characteristics of Sexually Active Females Aged 14–19 Years, Overall and by Vaccination History, National Health and Nutrition Examination Surveys, 2003–2006 and 2007–2010

Characteristic	Females, % (95% CI)			
	2003–2006		2007–2010	
	Overall (n = 736)	Overall ^a (n = 358)	Vaccinated ^b (n = 111)	Unvaccinated (n = 239)
Race/ethnicity				
White, non-Hispanic	63.5 (55.2–71.2)	61.1 (54.3–67.8)	71.1 (60.2–80.0)	56.0 (46.3–65.3)
Black, non-Hispanic	16.5 (11.6–22.9)	15.7 (11.6–21.0)	8.4 (5.0–13.7)	20.3 (14.2–28.2)
Other	19.9 (15.4–25.5)	23.1 (18.3–28.7)	20.6 (13.9–29.3)	23.7 (17.1–31.8)
Poverty index				
Below poverty level	33.5 (27.5–40.0)	32.9 (26.1–40.5)	28.1 (20.2–37.6)	34.6 (27.0–43.0)
At or above level	66.5 (60.0–72.5)	67.1 (59.5–73.9)	71.9 (62.2–79.8)	65.4 (57.0–73.0)
Lifetime sex partners, no.				
1–2	52.4 (47.1–57.7)	55.0 (50.2–59.6)	42.5 (33.5–52.0)	62.2 (55.4–68.5)
≥3	47.6 (42.3–52.9)	45.1 (40.4–49.8)	57.6 (48.0–66.5)	37.9 (31.5–44.6)
Age at first sex, y				
<14	15.3 (11.5–20.1)	14.1 (10.5–18.6)	11.5 (6.3–20.0)	15.7 (10.5–22.9)
≥14	84.7 (80.0–88.5)	85.9 (81.4–89.5)	88.6 (80.0–93.7)	84.3 (77.1–89.6)

Abbreviation: CI, confidence interval.

^a Eight females who had no information on vaccination status are included in the overall value.

^b History of receipt of at least 1 HPV vaccine dose.

* $P < .05$ compared with 2003–2006, by the F statistic from the Wald χ^2 .

change in herpes simplex virus type 2 seroprevalence among females in this age group between the periods (CDC, unpublished data). While other factors that we did not measure could have contributed to the decrease in prevalence in 2007–2010, our findings suggest an early impact of HPV vaccination. Early vaccine impact in the United States has also been suggested by investigation of genital warts trends [22].

We explored whether the larger-than-expected decrease in vaccine type HPV prevalence among females aged 14–19 years might be a reflection of herd immunity. Among the sexually active participants, there was a decrease (88%) in vaccine type HPV prevalence among those vaccinated in the vaccine era, compared with the prevaccine era. While not statistically significant, there was also a decrease (28%) among those who were unvaccinated. Interpretation of these findings was complicated by the differences in characteristics of vaccinated and unvaccinated females. The demographic and sexual risk behavior characteristics we analyzed were similar in the 2 periods. However, when we stratified by vaccination history, we found that unvaccinated females in the vaccine era had fewer lifetime partners, compared with the prevaccine era population. Furthermore, the lower prevalence of any HPV type among those who were unvaccinated indicates a lower overall risk of HPV infection. We adjusted for race/ethnicity and sexual behavior in our analysis; however, our findings suggest that some of the decrease in vaccine type HPV prevalence among the unvaccinated females was due to differences in risk behaviors or other factors we were not able to control

for in our analysis. Although we cannot conclude that our data provide evidence for herd immunity, herd immunity has been suggested by other evaluations of HPV prevalence or genital warts [23–25]. In Australia, where high 3-dose HPV vaccine coverage among females has been achieved, dramatic decreases in genital warts among young adult females were observed within the first few years of the vaccine introduction. Decreases were also observed among males, although they were not included in the vaccination program [25].

In clinical trials, 3 doses of quadrivalent HPV vaccine had >96% efficacy against vaccine type infection and associated disease in the per protocol populations [2, 26]. Our estimate of vaccine effectiveness, 82%, is encouraging since several factors could have decreased our estimate. We likely included in our analysis persons infected before vaccination, evaluated prevalent infection (not incident persistent infection, as in the trials [26]), and considered females who had a history of 1, 2, or 3 vaccine doses. We could not evaluate effectiveness separately on the basis of the number of doses, because of a small sample size. Other data suggest that vaccination with <3 doses might be efficacious [27, 28]. The current recommendation in the United States is for a complete 3-dose series [3].

To investigate either cross protection against HR nonvaccine type or type replacement, we evaluated changes in type-specific prevalence between the 2 periods. There was no change in HR nonvaccine type prevalence among females aged 14–19 years overall. Because vaccine coverage was low and only about 50%

Table 3. Human Papillomavirus (HPV) Prevalence Among Sexually Active Females Aged 14–19 Years, Overall and by Vaccination History, National Health and Nutrition Examination Surveys, 2003–2006 and 2007–2010

HPV Type ^a / Vaccination History	Prevalence, % (95% CI)		aPR ^c (95% CI)
	2003–2006 (n = 736)	2007–2010 (n = 358 ^b)	
Any HPV			
Overall	53.1 (48.9, 57.2)	42.9 (36.2–49.9)	0.82 (0.69–0.98)*
Vaccinated	NA	50.0 (38.3–61.6)	0.90 (0.72–1.16)
Unvaccinated	NA	38.6 (30.8–47.2)	0.77 (0.64–0.93)**
Vaccine type			
Overall	19.4 (15.7, 23.8)	9.0 (6.5–12.2)	0.47 (0.33–0.67)***
Vaccinated	NA	3.1 ^d (1.4–6.6)	0.12 (0.05–0.29)***
Unvaccinated	NA	12.6 (9.1–17.3)	0.72 (0.50–1.02)
HR nonvaccine type			
Overall	33.5 (29.6, 37.6)	29.1 (23.0–36.0)	0.90 (0.71–1.13)
Vaccinated	NA	35.2 (24.6–47.4)	1.02 (0.72–1.43)
Unvaccinated	NA	25.3 (19.6–32.1)	0.81 (0.64–1.02)
Alpha-9 species			
Overall	12.9 (9.7, 17.1)	12.0 (8.6–16.6)	0.97 (0.64–1.47)
Vaccinated	NA	17.8 (10.2–29.2)	1.30 (0.74–2.29)
Unvaccinated	NA	8.4 (5.2–13.5)	0.72 (0.42–1.24)
Alpha-7 species			
Overall	12.4 (9.8, 15.6)	11.1 (9.7–14.3)	0.92 (0.62–1.38)
Vaccinated	NA	15.0 (9.0–24.0)	1.22 (0.72–2.07)
Unvaccinated	NA	8.9 (6.0–13.0)	0.74 (0.48–1.15)

Abbreviations: CI, confidence interval; aPR, adjusted prevalence ratio; NA, not applicable; HR, high risk.

^a Vaccine types consist of HPV-6, -11, -16, and -18. High-risk (HR) nonvaccine types consist of HPV-31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, and -68. Nonvaccine type alpha 9 species consist of HPV-31, -33, -35, -52, and -58. Nonvaccine type alpha 7 species consist of HPV-39, -45, -59, and -68.

^b A total of 111 females were vaccinated (defined as a history of receipt of ≥ 1 vaccine dose), and 239 were unvaccinated. Data for 8 females who had no information on vaccination status are included in the overall group.

^c Prevalence during 2007–2010 compared with prevalence during 2003–2006, adjusted for race/ethnicity and lifetime no. of sex partners.

^d Relative standard error >30%.

* $P < .05$; ** $P < .01$; *** $P < .001$, all by the F statistic, from the Wald χ^2 test.

of females in this age group were sexually active, we might not observe cross-protection or type replacement, if either occurs, at this time. In our analysis restricted to sexually active females, we also found no difference in the prevalence of HR nonvaccine HPV, alpha 7 species, or alpha 9 species among vaccinated females, compared with the prevaccine era.

Replacement by HPV types not targeted by vaccine has been considered unlikely [29, 30]. Studies have evaluated the potential for type replacement and found no tendency for vaccine types to cluster with other types, positively or negatively [31–35]. In the vaccine trials, efficacy against incident persistent infection and disease end points was evaluated for types related to HPV-16 and -18 [12, 13]. In quadrivalent vaccine trials, some efficacy against HPV-31 and HPV-59 persistent infections was reported [13]. In a bivalent vaccine trial, efficacy against persistent infection and some disease end points was reported for HPV-31, -33, -45, and -51. Negative efficacy was observed for some HPV-52 and -58 disease end points, although findings were

inconsistent across end points [14]. A postlicensure evaluation reported an increase in HR nonvaccine types among vaccinated females; differences in some demographic characteristics with respect to vaccination status could have impacted findings [24].

There are several limitations to our data. First, data on vaccination history are from self-reports, and there could have been overreporting or underreporting. The vaccine coverage estimate for females aged 14–19 years is consistent with National Immunization Survey (NIS)-Teen findings [6]. By using provider-verified records, NIS-Teen found that coverage by at least 1 dose among females aged 13–17 years was 49% in 2010. A history of at least 1 dose among females aged 14–19 years in NHANES 2009–2010 was reported by 46% (data not shown). A previous study compared self-report of HPV vaccination with provider records in NIS-Teen [36]. While correlation for HPV vaccine was higher than for other vaccines, parent report of at least 1 dose of HPV vaccine had a false-positive value of 7.8% and a false-negative value of 16.6%. It is likely that there was some

Table 4. Association of Race/Ethnicity, Sexual Behavior, and Human Papillomavirus (HPV) Vaccination History With the Prevalence of HPV-6, -11, -16, or -18 Among Sexually Active Females Aged 14–19 Years, National Health and Nutrition Examination Surveys, 2007–2010

Characteristic ^a	Females, No.	Prevalence % (95% CI)	PR (95% CI)	aPR (95% CI)
Overall	350	9.1 (6.6–12.3)
Race/ethnicity				
White, non-Hispanic	118	5.3 (2.5–10.8)	Reference	Reference
Black, non-Hispanic	89	21.8 (16.1–28.6)	4.15 (2.00–8.64)	3.14 (1.57–6.26)
Other ^b	143	10.6 (5.5–19.2)	2.00 (0.65–6.24)	1.77 (0.67–4.67)
Lifetime sex partners, no.				
1–2	190	3.5 (1.8–6.8)	Reference	Reference
≥3	159	15.4 (10.8–21.5)	4.35 (2.08–9.08)	5.53 (2.80–10.90)
Sex partners in past 12 mo, no.				
0–1	232	8.3 (5.7–12.1)	Reference	...
≥2	117	9.8 (5.7–16.4)	1.18 (0.62–2.24)	...
Vaccinated (at least 1 dose)				
No	239	12.6 (9.1–17.3)	Reference	Reference
Yes	111	3.1 ^c (1.4–6.6)	0.24 (0.10–0.58)	0.18 (0.07–0.47)

Abbreviations: CI, confidence interval; PR, prevalence ratio; aPR, adjusted prevalence ratio.

Data are limited to females who reported ever having had sex.

^a Race/ethnicity, sexual history, and vaccination history data are from self-report. The analysis limited to persons with information on vaccination history.

^b Other race/ethnicity includes all persons who were neither white, non-Hispanic nor black, non-Hispanic.

^c Relative standard error >30%.

misclassification of vaccine status in NHANES, which would have biased our analyses and estimate of vaccine effectiveness. Second, vaccine coverage varies by state. In 2010, coverage by ≥1 dose ranged from 29% to 73% [6]. NHANES does not allow state-specific prevalence estimates but is designed to include a representative sample of the US population. Third, starting in 2007, a new sampling methodology was implemented in NHANES, and adolescents were not oversampled. This decreased the number of females aged 14–19 years who were surveyed in 2007–2010. Some of our analyses were limited by small sample sizes, and some prevalence estimates were unstable.

Our data suggest an early impact of HPV vaccination on vaccine type prevalence among females in the United States and a high vaccine effectiveness against vaccine type infection. The decline in vaccine type prevalence is higher than expected and could be due to herd immunity from vaccination, vaccine effectiveness of a series involving <3 doses, and/or changes in sexual behavior that we did not measure. This decline is encouraging, given the substantial health and economic burden of HPV-associated disease [37]. Ongoing analyses of NHANES will allow monitoring of the impact of HPV vaccine on HPV prevalence, vaccine effectiveness for different numbers of doses, possible cross-protection or type replacement, and duration of protection. NHANES, as well as other monitoring systems in the United States, will add to the accumulating data on the population impact of HPV vaccines.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (<http://jid.oxfordjournals.org/>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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References

1. Paavonen J, Naud P, Salmeron J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final

- analysis of a double-blind, randomised study in young women. *Lancet* **2009**; 374:301–14.
2. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* **2007**; 356:1915–27.
 3. Markowitz LE, Dunne EF, Saraiya M, Lawson HW, Chesson H, Unger ER. Quadrivalent Human papillomavirus vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* **2007**; 56:1–24.
 4. CDC. FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). *MMWR* **2010**; 59:626–9.
 5. CDC. Recommendations on the use of quadrivalent human papillomavirus vaccine in males—Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR* **2011**; 60:1705–8.
 6. CDC. National and state vaccination coverage among adolescents aged 13 through 17— United States, 2010. *MMWR* **2011**; 60:1117–23.
 7. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens—part B: biological agents. *Lancet Oncol* **2009**; 10:321–2.
 8. de Sanjose S, Quint WG, Alemany L, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. *Lancet Oncol* **2010**; 11:1048–56.
 9. Lacey CJN, Lowndes CM, Shah KV. Burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease. *Vaccine* **2006**; 24(Suppl 3):S335–41.
 10. Markowitz LE, Hariri S, Unger ER, Saraiya M, Datta SD, Dunne EF. Post-licensure monitoring of HPV vaccine in the United States. *Vaccine* **2010**; 28:4731–7.
 11. Bonanni P, Cohet C, Kjaer SK, et al. A summary of the post-licensure surveillance initiatives for GARDASIL/SILGARD. *Vaccine* **2010**; 28:4719–30.
 12. Brown DR, Kjaer SK, Sigurdsson K, et al. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in generally HPV-naïve women aged 16–26 years. *J Infect Dis* **2009**; 199:926–35.
 13. Wheeler CM, Kjaer SK, Sigurdsson K, et al. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in sexually active women aged 16–26 years. *J Infect Dis* **2009**; 199:936–44.
 14. Wheeler CM, Castellsague X, Garland SM, et al. Cross-protective efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. *Lancet Oncol* **2012**; 13:100–10.
 15. Hariri S, Unger ER, Sternberg M, et al. Prevalence of genital human papillomavirus among females in the United States, the National Health And Nutrition Examination Survey, 2003–2006. *J Infect Dis* **2011**; 204:566–73.
 16. Dunne EF, Sternberg M, Markowitz LE, et al. Human papillomavirus (HPV) 6, 11, 16, and 18 prevalence among females in the United States—National Health And Nutrition Examination Survey, 2003–2006: opportunity to measure HPV vaccine impact? *J Infect Dis* **2011**; 204:562–5.
 17. Dunne EF, Unger ER, Sternberg M, et al. Prevalence of HPV infection among females in the United States. *JAMA* **2007**; 297:813–9.
 18. Design and estimation for the National Health Interview Survey, 1995–2004. *Vital Health Stat 2* **2000**:1–31.
 19. Korn EL, Graubard BI. Epidemiologic studies utilizing surveys: accounting for the sampling design. *Am J Public Health* **1991**; 81:1166–73.
 20. Bieler GS, Brown GG, Williams RL, Brogan DJ. Estimating model-adjusted risks, risk differences, and risk ratios from complex survey data. *Am J Epidemiol* **2010**; 171:618–23.
 21. Orenstein WA, Bernier RH, Hinman AR. Assessing vaccine efficacy in the field. Further observations. *Epidemiol Rev* **1988**; 10:212–41.
 22. Flagg E, Schwartz R, Weinstock H. Prevalence of anogenital warts among participants in private health plans in the United States, 2003–2010: Potential impact of human papillomavirus vaccination. *Am J Public Health* **2013**. In press.
 23. Tabrizi SN, Brotherton JM, Kaldor JM, et al. Fall in human papillomavirus prevalence following a national vaccination program. *J Infect Dis* **2012**; 206:1645–51.
 24. Kahn JA, Brown DR, Ding L, et al. Vaccine-type human papillomavirus and evidence of herd protection after vaccine introduction. *Pediatrics* **2012**; 130:1–8.
 25. Read TR, Hocking JS, Chen MY, Donovan B, Bradshaw CS, Fairley CK. The near disappearance of genital warts in young women 4 years after commencing a national human papillomavirus (HPV) vaccination programme. *Sex Transm Infect* **2011**; 87:544–7.
 26. Villa LL, Costa RL, Petta CA, et al. High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. *Br J Cancer* **2006**; 95:1459–66.
 27. Kreimer AR, Rodriguez AC, Hildesheim A, et al. Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine. *J Natl Cancer Inst* **2011**; 103:1444–51.
 28. Dobson SR, McNeil S, Dionne M, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. *JAMA* **2013**; 309:1793–802.
 29. Stanley M, Lowy DR, Frazer I. Prophylactic HPV vaccines: underlying mechanisms. *Vaccine* **2006**; 24:106–13.
 30. Bernard H. Phylogeny and typing of papillomaviruses. In: Garcia R, DiMaio D, eds. *The papillomaviruses*. New York, NY: Springer, **2007**: 29–44.
 31. Vaccarella S, Plummer M, Franceschi S, et al. Clustering of human papillomavirus (HPV) types in the male genital tract: the HPV in men (HIM) study. *J Infect Dis* **2011**; 204:1500–4.
 32. Chaturvedi AK, Katki HA, Hildesheim A, et al. Human papillomavirus infection with multiple types: pattern of coinfection and risk of cervical disease. *J Infect Dis* **2011**; 203:910–20.
 33. Carozzi F, Ronco G, Gillio-Tos A, et al. Concurrent infections with multiple human papillomavirus (HPV) types in the New Technologies for Cervical Cancer (NTCC) screening study. *Eur J Cancer* **2012**; 48:1633–7.
 34. Vaccarella S, Franceschi S, Herrero R, et al. Clustering of multiple human papillomavirus infections in women from a population-based study in Guanacaste, Costa Rica. *J Infect Dis* **2011**; 204:385–90.
 35. Chaturvedi AK, Myers L, Hammons AF, et al. Prevalence and clustering patterns of human papillomavirus genotypes in multiple infections. *Cancer Epidemiol Biomarkers Prev* **2005**; 14:2439–45.
 36. Dorell CG, Jain N, Yankey D. Validity of parent-reported vaccination status for adolescents aged 13–17 years: National Immunization Survey-Teen, 2008. *Public Health Rep* **2011**; 126 (Suppl 2):60–9.
 37. Chesson HW, Ekwueme DU, Saraiya M, Watson M, Lowy DR, Markowitz LE. Estimates of the annual direct medical costs of the prevention and treatment of disease associated with human papillomavirus in the United States. *Vaccine* **2012**; 30:6016–9.