Prevalence of HPV After Introduction of the Vaccination Program in the United States

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abstract

BACKGROUND: Since mid-2006, human papillomavirus (HPV) vaccination has been recommended for females aged 11 to 12 years and through 26 years if not previously vaccinated.

METHODS: HPV DNA prevalence was analyzed in cervicovaginal specimens from females aged 14 to 34 years in NHANES in the prevaccine era (2003–2006) and 4 years of the vaccine era (2009–2012) according to age group. Prevalence of quadrivalent HPV vaccine (4vHPV) types (HPV-6, -11, -16, and -18) and other HPV type categories were compared between eras. Prevalence among sexually active females aged 14 to 24 years was also analyzed according to vaccination history.

RESULTS: Between the prevacccine and vaccine eras, 4vHPV type prevalence declined from 11.5% to 4.3% (adjusted prevalence ratio [aPR]: 0.36 [95% confidence interval (CI): 0.21–0.61]) among females aged 14 to 19 years and from 18.5% to 12.1% (aPR: 0.66 [95% CI: 0.47–0.93]) among females aged 20 to 24 years. There was no decrease in 4vHPV type prevalence in older age groups. Within the vaccine era, among sexually active females aged 14 to 24 years, 4vHPV type prevalence was lower in vaccinated (≥1 dose) compared with unvaccinated females: 2.1% vs 16.9% (aPR: 0.11 [95% CI: 0.05–0.24]). There were no statistically significant changes in other HPV type categories that indicate cross-protection.

CONCLUSIONS: Within 6 years of vaccine introduction, there was a 64% decrease in 4vHPV type prevalence among females aged 14 to 19 years and a 34% decrease among those aged 20 to 24 years. This finding extends previous observations of population impact in the United States and demonstrates the first national evidence of impact among females in their 20s.

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Dr Markowitz conceptualized and designed the analyses and drafted the manuscript; Ms Liu conducted the data analyses and reviewed and revised the manuscript; Dr Hariri assisted with study design and data analyses and reviewed and revised the manuscript; Dr Steinau supervised laboratory testing and reviewed and revised the manuscript; Dr Dunne assisted with study design and data collection and reviewed and revised the manuscript; and Dr Unger assisted with study design, supervised laboratory testing, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Previous studies have found declines in vaccine type human papillomavirus (HPV) prevalence and genital warts among young females in the United States after introduction of the HPV vaccination program.

WHAT THIS STUDY ADDS: This study extends previous observations of quadrivalent HPV vaccine impact and examines cross-protection. Within 6 years of vaccine introduction, there were decreases in national vaccine type HPV prevalence of 64% and 34% among females aged 14 to 19 years and 20 to 24 years, respectively.

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Three prophylactic human papillomavirus (HPV) vaccines are available, and they have been shown in clinical trials to have high efficacy for prevention of HPV vaccine-type infection and associated disease.[1–3] The bivalent vaccine targets HPV-16 and -18; the quadrivalent vaccine (4vHPV) targets HPV-6, -11, -16, and -18; and the 9-valent vaccine (9vHPV), licensed at the end of 2014, targets HPV-6, -11, -16, and -18 as well as 5 additional HPV types (31, 33, 45, 52, and 58). HPV vaccination has been recommended for females in the United States since mid-2006 and for males since 2011[4]; through 2014, almost all vaccines used were 4vHPV.[5] Routine vaccination is recommended for females and males aged 11 or 12 years and for females through age 26 years and males through age 21 years if not previously vaccinated. Although rates of HPV vaccination have been increasing in the United States, coverage is still low; in 2013, a national survey found that 57% of 13- to 17-year-old females had received at least 1 dose and 38% had received 3 doses.[5] Despite this moderate coverage, data from NHANES exhibited a 56% decrease in 4vHPV type prevalence among females aged 14 to 19 years in the first 4 years of the vaccine era (2007–2010) compared with the prevaccine era.[6]

The present report analyzes data from the 4 most recent years available from NHANES (2009–2012) and compares HPV prevalence with the prevaccine era (2003–2006). In these more recent years, vaccine coverage was higher than in the first 4 years of the vaccine era evaluated previously.[6,7] We also explore vaccine effectiveness, by analyzing HPV prevalence according to report of vaccination, herd effects, and potential cross- protection against non-4vHPV types.

METHODS

Survey Design and Population

NHANES is an ongoing series of cross-sectional surveys conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention (CDC). The surveys are designed to be nationally representative of the civilian, noninstitutionalized US population. Surveys are conducted in ~15 counties, which vary each year. Consenting participants undergo a household interview followed by a physical examination in a mobile examination center (MEC). To increase the precision of estimates, NHANES oversampled certain subpopulations. In 1999 to 2006, Mexican-Americans, non-Hispanic blacks, low-income non-Hispanic whites and others, as well as adolescents aged 12 to 19 years, were oversampled. Adolescents were not oversampled after 2006. In 2009 to 2012, all Hispanics were also oversampled and in 2011 to 2012, Asians were also oversampled. Informed consent or assent was obtained from all participants and consent from guardians of minors. This survey was approved by the National Center for Health Statistics/CDC Research Ethics Review Board.

NHANES data from 2003 to 2006 and 2009 to 2012 were analyzed. Because adolescents were not oversampled after 2006, there was a reduced number of 14- to 19-year-olds in the second time period. Years 2003 to 2006 were considered the prevaccine era because vaccination was first recommended in June 2006. Analyses for the present report were limited to participants aged 14 to 34 years with adequate self-collected cervicovaginal samples. In 2003 to 2006, a total of 3325 females aged 14 to 34 years were interviewed; 3210 (96.5%) received an examination in an MEC. Of those, 2649 (82.5%) submitted a self-collected cervicovaginal swab, and 2587 (80.6%) samples were adequate for DNA typing (as discussed in the Specimen Collection and Laboratory Methods section). In 2009 to 2012, a total of 2473 females aged 14 to 34 years were interviewed; 2403 (97.2%) received an examination in an MEC. Of those, 2070 (86.1%) submitted a cervicovaginal swab, and 2061 (85.8%) were adequate for DNA typing. HPV prevalence testing among males was not included in NHANES during this time period.

Demographic, Behavioral, and HPV Vaccination History

Demographic information was ascertained during household interviews. Sexual history information was collected among participants aged 14 to 59 years by using audio computer-assisted self-interviews in an MEC. Respondents who reported ever having sex (described as vaginal, oral, or anal sex) were asked additional questions about their sexual history, including age at first sexual encounter, number of lifetime sex partners, and number of sex partners in the past 12 months. NHANES 2003–2004 did not collect information about partners in the past 12 months from persons aged 14 to 17 years. HPV vaccination history was collected beginning in 2007. Persons aged ≥16 years and emancipated minors were interviewed directly. Parents/guardians were interviewed regarding vaccination history for those aged <16 years.

Specimen Collection and Laboratory Methods

Females aged 14 to 59 years who were examined in an MEC were asked to self-collect a cervicovaginal sample.[8,9] Extractions and testing were performed at the CDC as previously described.[9] Briefly, extracted DNA was tested by using the Research Use Only Linear Array HPV Genotyping Test (Roche Molecular Diagnostics, Indianapolis, IN) with supplementary HPV-52

quantitative polymerase chain reaction, as previously described.[9] This assay uses L1 consensus polymerase chain reaction followed by type-specific hybridization for qualitative detection of 37 HPV types (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, 89, and IS39) and β-globin (control for sample amplification). Samples that tested negative for both HPV and β-globin were considered inadequate.

Data Analysis

The 2 most recent NHANES cycles of the vaccine era (2009–2010 and 2011–2012) were combined to achieve stable estimates. The 5-year age groups included in the present report are those in which an impact of vaccination would first be observed (14–19, 20–24, and 25–29 years) and the next oldest age group (30–34 years). We analyzed report of at least 1 dose and 3-dose vaccination history in 2009–2012 and compared sexual behavior in 2009–2012 versus 2003–2006.

HPV prevalence was compared among females in 2003–2006 and 2009–2012 according to age group. HPV type categories investigated include any of 37 HPV types, 4vHPV types (6, 11, 16, and 18), 4vHPV high-risk types (16 and 18), any non-4vHPV types, non-4vHPV high-risk types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), 3 high-risk types (31, 33, and 45) for which some cross-protection has been suggested[10,11]; and the 5 additional high-risk types in 9vHPV (31, 33, 45, 52, and 58).[3] In analyses limited to sexually active females aged 14 to 24 years, we compared lifetime sex partners and race/ethnicity according to vaccination status in the vaccine era and compared these data with data from the prevaccine era. Vaccine effectiveness was evaluated for prevention of vaccine type HPV detection in 2009–2012; vaccination was defined as report of at least 1 HPV vaccine dose.

All estimates were weighted by using sample weights to account for unequal probabilities of selection and adjustment for nonresponse.[12] Variance estimates were calculated by using a Taylor series linearization to account for the complex survey design.[13] Logit confidence intervals (CIs) were calculated for prevalence estimates, with an α of .05. Prevalence estimates with a relative SE (RSE) >30% or based on <10 cases are noted; these are considered unstable and should be interpreted with caution. We calculated prevalence ratios, adjusted prevalence ratios (aPRs), and their 95% CIs, adjusted for race/ethnicity (non-Hispanic black, non-Hispanic white, Mexican American, and other), and lifetime and past year number of sex partners. Because data on past year sex partners were not available for 14- to 17-year-olds in 2003 to 2004, this variable was not included in some models. The prevalence ratio was the predicted probability calculated from the logistic regression model by using the PREDMARG statement in SAS-Callable SUDAAN.[14] Vaccine effectiveness was calculated as 100 × (1 – aPR). Throughout the analyses, *P* values were not adjusted for multiple comparisons. Statistical analyses were conducted in SAS version 9.3 (SAS Institute, Inc, Cary, NC) and SUDAAN version 11.0 (Research Triangle Institute, Research Triangle Park, NC).

RESULTS

HPV Prevalence Among All Females Aged 14 to 34 Years According to Age Group

In NHANES 2009–2012, receipt of at least 1 HPV vaccine dose was reported by 51.4% of females aged 14 to 19 years, 32.6% aged 20 to 24 years, 14.7% aged 25 to 29 years, and 3.3% aged 30 to 34 years (Table 1). Between 2003–2006 and 2009–2012, there were no significant changes in the percentage of females who reported having had sex or in past year or lifetime sexual partners in any age group except 20- to 24-year-olds. In this age group, a higher percentage of participants in 2009–2012 than in 2003–2006 reported having ≥2 sex partners in the past year and ≥3 lifetime sex partners.

Among females aged 14 to 19 years, there were statistically significant declines in 4vHPV type prevalence, from 11.5% to 4.3% (aPR: 0.36 [95% CI: 0.21–0.61]), as well as prevalence of HPV-16, -18, from 7.1% to 2.8% between the prevaccine and vaccine eras (Table 2). There were no significant differences in prevalence of HPV-31, -33, -45 in the prevaccine (4.3%) and vaccine (2.6%, RSE >30%) eras or the 5 additional 9vHPV types (8.4% in the prevacccine era and 6.2% in the vaccine era). Among females aged 20 to 24 years, there were statistically significant declines in 4vHPV type prevalence, from 18.5% to 12.1% (aPR: 0.66 [95% CI: 0.47–0.93]), and prevalence of HPV-16, -18, from 15.2% to 10.5%. No statistically significant changes were observed in 4vHPV type prevalence among females aged 25 to 29 years or 30 to 34 years. For individual types examined in the 2 youngest age groups, significant differences between the prevaccine and vaccine eras were observed for HPV-6, -16, and -56 among females aged 14 to 19 years and for HPV-51 among those 20 to 24 years (Supplemental Fig 1, Supplemental Tables 5 and 6).

HPV Prevalence Among Sexually Active Females Aged 14 to 24 Years, Overall and According to Vaccination History

Analyses according to vaccination history were limited to sexually active females aged 14 to 24 years, combining the 2 age groups (14–19 years and 20–24 years)

TABLE 1 Selected Sexual Behavior and Reported Vaccination History in Females Aged 14 to 34 Years, According to Age Group, NHANES 2003–2006 and 2009–2012

Age Group/Characteristic	Prevaccine Era 2003–2006	Vaccine Era 2009–2012
	% (95% CI)	% (95% CI)
14–19 y	*n* = 1363	*n* = 736
HPV vaccination history		
≥1 dose	NA	51.4 (47.3–55.3)
3 doses	NA	34.6 (30.3–39.2)
Sexual behavior		
Ever had sex	53.8 (50.6–56.9)	50.4 (45.0–55.8)
≥2 sex partners in past year	40.4 (35.1–46.0)[a]	42.3 (36.8–48.1)
≥3 lifetime sex partners	47.6 (42.3–52.9)	52.2 (45.6–58.8)
20–24 y	*n* = 432	*n* = 470
HPV vaccination history		
≥1 dose	NA	32.6 (26.5–39.3)
3 doses	NA	18.1 (13.0–24.6)
Sexual behavior		
Ever had sex	91.3 (86.1–94.7)	90.8 (85.9–94.1)
≥2 sex partners in past year*	25.6 (21.0–30.7)	34.6 (29.4–40.3)
≥3 lifetime sex partners*	66.4 (60.8–71.5)	77.4 (72.8–81.4)
25–29 y	*n* = 403	*n* = 424
HPV vaccination history		
≥1 dose	NA	14.7 (10.9–19.5)
3 doses	NA	8.8 (5.2–14.4)
Sexual behavior		
Ever had sex	95.0 (91.8–97.0)	94.6 (91.1–96.7)
≥2 sex partners in past year	22.6 (18.5–27.4)	20.6 (15.5–27.0)
≥3 lifetime sex partners	77.0 (69.8–83.0)	76.1 (70.1–81.3)
30–34 y	*n* = 389	*n* = 428
HPV vaccination history		
≥1 dose	NA	3.3[b] (1.5–6.9)
3 doses	NA	1.2[b] (0.3–5.9)
Sexual behavior		
Ever had sex	97.6 (95.0–98.9)	99.2 (98.1–99.6)
≥2 sex partners in past year	12.8 (9.5–17.1)	11.9 (8.5–16.4)
≥3 lifetime sex partners	74.8 (69.9–79.1)	74.1 (67.8–79.5)

Number of past year and lifetime partners among those who reported ever having sex. HPV vaccination history is according to self-report or parent report. NA, not applicable.

[a] Data limited to 2005 to 2006.

[b] RSE >30% or <10 cases.

* $P < .05$ from the Wald χ^2 test.

in which declines in 4vHPV type prevalence were observed between the prevaccine and vaccine eras. Compared with the prevaccine era (58.4%), in the vaccine era, a larger percentage of females aged 14 to 24 years overall (67.7%) and those unvaccinated (70.0%) reported ≥3 lifetime sex partners (Table 3). There were no statistically significant differences in race/ethnicity (percent non-Hispanic white shown in Table 3).

Any HPV type prevalence was similar in the prevaccine era (54.4%) and the vaccine era (58.1%) (Table 4). Compared with the prevaccine era, 4vHPV type prevalence was significantly lower overall in the vaccine era (18.6% vs 10.8%; aPR: 0.53 [95% CI: 0.40–0.71]) and among those vaccinated (18.6% vs 2.1%; aPR: 0.09 [95% CI: 0.05–0.18]). The 4vHPV type prevalence among those unvaccinated in the vaccine era was not significantly different from the prevaccine era (18.6% vs 16.9%). Overall or according to vaccination history, there were no statistically significant differences in the vaccine era compared with the prevaccine era in the prevalence of non-4vHPV high-risk types; HPV-31, -33, -45; or the 5 additional 9vHPV types.

Within the vaccine era, there was no difference in the percentages of sexually active females reporting ≥3 lifetime sex partners in vaccinated compared with those unvaccinated (Table 3). A larger percentage of vaccinated was non-Hispanic white. The 4vHPV type prevalence was lower among vaccinated compared with unvaccinated females (2.1% vs 16.9%; aPR: 0.11 [95% CI: 0.05–0.24]), corresponding to a vaccine effectiveness of 89% (Table 4). There were no statistically significant differences between vaccinated and unvaccinated females in the prevalence of any HPV; non-4vHPV high-risk types; HPV-31, -33, -45; or the 5 additional 9vHPV types.

DISCUSSION

In this study of HPV prevalence in cervicovaginal specimens from a nationally representative sample of females in the United States, we extend our previous findings of vaccine impact with 2 additional years of data from NHANES.[6] Our analysis using the 4 most recent years of data from the vaccine era (2009–2012) showed that among all females aged 14 to 19 years and 20 to 24 years, 4vHPV type prevalence decreased 64% and 34%, respectively, compared with the prevaccine era. There was no statistically significant change in prevalence of any HPV or other categories of HPV types in these age groups and no decline in 4vHPV type prevalence among females aged 24 to 29 years or 30 to 34 years.

The greatest decline in 4vHPV type prevalence observed in 14- to 19-year-olds is consistent with the highest reported vaccine coverage in this age group. Of note, the percentage of females aged 14 to 19 years who reported having received at least 1 vaccine dose in NHANES 2009–2012 (51%) is similar to data from national coverage surveys. Among females aged 13 to 17 years

TABLE 2 HPV Prevalence Among Females Aged 14 to 34 Years, According to Age Group, NHANES 2003–2006 and 2009–2012

Age Group/HPV Types	Prevaccine Era 2003–2006 % (95% CI)	Vaccine Era 2009–2012 % (95% CI)	Comparison of Vaccine Era With Prevaccine Era	
			PR (95% CI)	aPR (95% CI)
14–19 y	*n* = 1363	*n* = 736		
Any HPV	32.9 (29.5–36.4)	29.0 (24.5–33.9)	0.88 (0.73–1.07)	0.93 (0.79–1.09)
Non-4vHPV	31.2 (28.0–34.7)	28.4 (24.0–33.2)	0.91 (0.75–1.11)	0.96 (0.82–1.14)
Non-4vHPV HR	20.7 (17.9–23.9)	18.6 (14.7–23.4)	0.90 (0.68–1.18)	0.99 (0.79–1.26)
HPV-31, -33, -45	4.3 (3.1–6.1)	2.6[a] (1.2–5.5)	0.59 (0.25–1.38)	0.66 (0.27–1.59)
HPV-31, -33, -45, -52, -58	8.4 (6.7–10.5)	6.2 (4.1–9.3)	0.74 (0.46–1.19)	0.82 (0.53–1.28)
4vHPV	11.5 (9.2–14.4)	4.3 (2.7–6.8)	0.37 (0.22–0.63)**	0.36 (0.21–0.61)**
HPV-16, -18	7.1 (5.8–8.7)	2.8 (1.6–4.7)	0.39 (0.22–0.68)**	0.37 (0.20–0.67)**
20–24 y	*n* = 432	*n* = 470		
Any HPV	53.7 (46.0–61.3)	57.9 (52.5–63.2)	1.08 (0.91–1.28)	1.02 (0.88–1.18)
Non-4vHPV	50.7 (43.6–57.9)	56.1 (50.4–61.6)	1.10 (0.93–1.32)	1.05 (0.90–1.23)
Non-4vHPV HR	32.9 (26.8–39.6)	36.8 (30.8–43.3)	1.12 (0.87–1.45)	1.11 (0.85–1.44)
HPV-31, -33, -45	7.8 (5.0–12.0)	5.4 (3.6–8.2)	0.70 (0.38–1.27)	0.85 (0.48–1.50)
HPV-31, -33, -45, -52, -58	16.5 (11.4–23.2)	12.7 (8.6–18.2)	0.77 (0.46–1.29)	0.85 (0.51–1.41)
4vHPV	18.5 (14.9–22.7)	12.1 (9.1–16.0)	0.66 (0.46–0.93)*	0.66 (0.47–0.93)*
HPV-16, -18	15.2 (11.7–19.5)	10.5 (7.7–14.2)	0.69 (0.47–1.03)	0.66 (0.45–0.97)*
25–29 y	*n* = 403	*n* = 424		
Any HPV	46.8 (42.9–50.7)	49.1 (43.8–54.5)	1.05 (0.92–1.20)	1.06 (0.90–1.24)
Non-4vHPV	43.8 (39.0–48.8)	47.5 (42.1–53.0)	1.08 (0.92–1.27)	1.09 (0.91–1.31)
Non-4vHPV HR	24.6 (19.1–31.0)	28.1 (23.9–32.9)	1.14 (0.86–1.53)	1.09 (0.79–1.50)
HPV-31, -33, -45	5.8 (3.7–9.0)	6.2 (3.7–10.0)	1.07 (0.55–2.08)	1.27 (0.68–2.38)
HPV-31, -33, -45, -52, -58	10.8 (7.3–15.6)	13.4 (10.1–17.6)	1.25 (0.78–1.99)	1.34 (0.81–2.21)
4vHPV	11.8 (8.8–15.5)	11.7 (8.7–15.4)	0.99 (0.66–1.48)	1.04 (0.72–1.50)
HPV-16, -18	8.1 (6.1–10.7)	9.9 (7.3–13.3)	1.22 (0.81–1.85)	1.17 (0.79–1.73)
30–34 y	*n* = 389	*n* = 428		
Any HPV	47.9 (42.4–53.4)	40.3 (34.7–46.1)	0.84 (0.70–1.01)	0.80 (0.66–0.98)*
Non-4vHPV	44.5 (39.2–50.0)	37.9 (32.1–44.1)	0.85 (0.70–1.04)	0.83 (0.67–1.02)
Non-4vHPV HR	21.0 (15.6–27.6)	21.6 (17.6–26.3)	1.03 (0.73–1.46)	0.98 (0.67–1.42)
HPV-31, -33, -45	4.1[a] (2.2–7.5)	4.2 (2.8–6.2)	1.02 (0.48–2.14)	0.85 (0.40–1.80)
HPV-31, -33, -45, -52, -58	9.8 (7.1–13.4)	7.5 (5.5–10.1)	0.76 (0.49–1.18)	0.58 (0.35–0.97)*
4vHPV	9.5 (6.8–13.1)	8.0 (5.8–10.9)	0.84 (0.53–1.32)	0.77 (0.48–1.24)
HPV-16, -18	7.6 (5.0–11.2)	6.6 (4.5–9.5)	0.87 (0.50–1.50)	0.78 (0.45–1.36)

Data are for all females, including those who did not report having had sex. aPR was adjusted for race/ethnicity and lifetime and past year sex partners (14- to 19-year-old age group not adjusted for past year partners). Non-4vHPV high-risk (HR) includes types -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, and -68. 4vHPV includes types -6, -11, -16, and -18. PR, prevalence ratio. *$P < .05$; **$P < .01$ obtained by using the logistic regression model.

[a] RSE >30%.

with provider-verified records in the National Immunization Survey–Teen receipt of at least 1 dose ranged from 44.3% to 53.8% between 2009 and 2012.[7] Although provider-verified vaccine history is not available from national surveys for persons aged ≥18 years, the 2012 National Health Interview Survey

TABLE 3 Characteristics of Sexually Active Females Aged 14 to 24 Years, Overall and According to Vaccination History, NHANES 2003–2006 and 2009–2012

Variable	% (95% CI)		Prevalence Ratio (95% CI)	
	Prevaccine Era 2003–2006 (*n* = 1092)	Vaccine Era 2009–2012 (*n* = 753[a])	Comparison of Vaccine Era With Prevaccine Era[b]	Comparison Within Vaccine Era[c]
≥3 lifetime sex partners				
Overall	58.4 (54.9–61.7)	67.7 (64.1–71.1)	1.16 (1.07–1.25)	NA
Vaccinated	NA	64.9 (56.7–72.3)	1.11 (0.98–1.27)	0.93 (0.78–1.11)
Unvaccinated	NA	70.0 (63.9–75.4)	1.20 (1.09–1.32)	Ref
Non-Hispanic white				
Overall	64.0 (56.7–70.7)	56.8 (49.1–64.2)	0.89 (0.75–1.05)	NA
Vaccinated	NA	63.9 (54.0–72.8)	1.00 (0.83–1.20)	1.19 (1.01–1.40)
Unvaccinated	NA	53.7 (45.4–61.7)	0.84 (0.70–1.01)	Ref

NA, not applicable.

[a] A total of 287 sexually active females were vaccinated (defined as a history of receipt of ≥1 vaccine dose), and 439 were unvaccinated. Data for 27 sexually active females who had no information on vaccination status are included in the overall group.

[b] Overall, vaccinated, and unvaccinated in 2009–2012 compared with overall in 2003–2006.

[c] Vaccinated compared with unvaccinated in 2009–2012.

TABLE 4 HPV Prevalence Among Sexually Active Females Aged 14 to 24 Years, Overall and According to Vaccination History, NHANES 2003–2006 and 2009–2012

HPV Types/Vaccination History	Prevalence, % (95% CI)		aPR (95% CI)	
	Prevaccine Era 2003–2006 (n = 1092)	Vaccine Era 2009–2012 (n = 753[a])	Comparison of Vaccine Era With Prevaccine Era[b]	Comparison Within Vaccine Era[c]
Any HPV				
Overall	54.4 (49.5–59.2)	58.1 (52.9–63.1)	1.00 (0.90–1.11)	NA
Vaccinated	NA	56.7 (50.6–62.6)	1.01 (0.89–1.14)	0.99 (0.85–1.15)
Unvaccinated	NA	59.5 (52.3–66.4)	1.00 (0.87–1.16)	Ref
Non-4vHPV HR				
Overall	32.8 (28.9–37.0)	38.0 (32.8–43.4)	1.09 (0.93–1.28)	NA
Vaccinated	NA	37.2 (31.1–43.7)	1.11 (0.91–1.34)	0.98 (0.75–1.27)
Unvaccinated	NA	39.1 (31.6–47.1)	1.10 (0.88–1.36)	Ref
HPV-31, -33, and -45				
Overall	6.6 (4.7–9.2)	5.3 (3.7–7.6)	0.76 (0.48–1.20)	NA
Vaccinated	NA	4.9 (2.9–8.1)	0.74 (0.41–1.34)	0.95 (0.50–1.83)
Unvaccinated	NA	5.8 (3.6–9.1)	0.80 (0.46–1.37)	Ref
HPV-31, -33, -45, -52, and -58				
Overall	14.7 (11.8–18.1)	13.1 (10.2–16.7)	0.83 (0.60–1.15)	NA
Vaccinated	NA	14.3 (10.1–19.9)	0.95 (0.64–1.42)	1.22 (0.81–1.84)
Unvaccinated	NA	12.5 (9.2–16.8)	0.76 (0.53–1.10)	Ref
4vHPV				
Overall	18.6 (16.1–21.3)	10.8 (8.2–14.2)	0.53 (0.40–0.71)	NA
Vaccinated	NA	2.1 (1.1–3.7)	0.09 (0.05–0.18)	0.11 (0.05–0.24)
Unvaccinated	NA	16.9 (12.3–22.6)	0.83 (0.61–1.12)	Ref

Non-4vHPV high-risk (HR) includes types -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, and -68. 4vHPV includes types -6, -11, -16, and -18. Vaccinated assessment was made by self-report or parent-reported receipt of at least 1 HPV vaccine dose. NA, not applicable.

[a] A total of 287 sexually active females were vaccinated (defined as a history of receipt of ≥1 vaccine dose), and 439 were unvaccinated. Data for 27 sexually active females who had no information on vaccination status are included in the overall group.

[b] Prevalence overall, among vaccinated and among unvaccinated in 2009–2012 compared with overall in 2003–2006, adjusted for race/ethnicity and number of lifetime sexual partners.

[c] Prevalence in vaccinated compared with unvaccinated in 2009–2012, adjusted for race/ethnicity and number of lifetime sexual partners.

found that 44% of women aged 19 to 21 years and 28% aged 22 to 26 years reported receipt of at least 1 dose of HPV vaccine.[15] In NHANES 2009–2012, 33% of women aged 20 to 24 years reported receipt of at least 1 dose.

In addition to our analysis of prevalence overall in the prevaccine and vaccine eras, we estimated vaccine effectiveness and explored herd effects and potential cross-protection among sexually active 14- to 24-year-olds. High vaccine effectiveness was found for prevention of 4vHPV types within the vaccine era (89%) and there was a large decline in prevalence among those vaccinated compared with the overall prevalence in the prevaccine era (18.6% to 2.1%). Among those unvaccinated, 4vHPV type prevalence was 18.6% in the prevaccine era and 16.9% in the vaccine era; any HPV prevalence remained stable. In our previous analysis, using data from the first 4 years of the vaccine era, it was difficult to assess herd effects because there were differences in sexual behavior and lower prevalence of any HPV type among those unvaccinated compared with the prevaccine era.[6] In the present analysis, a similar percentage of vaccinated and unvaccinated females reported >3 lifetime lifetime sex partners as well as prevalence of any HPV type. Although we cannot claim evidence of herd effects in this analysis, herd effects have been observed for both genital warts and 4vHPV type prevalence in countries in which higher vaccination coverage has been achieved.[16,17]

We also examined the prevalence of 3 HPV types for which there has been some evidence of cross-protection.[10,11] The prevalence estimate for any HPV-31, -33, -45 in the vaccine era among all female subjects aged 14 to 19 years was unstable; there was no statistically significant decline compared with the prevaccine era. We also found no vaccine effectiveness against these 3 types among females aged 14 to 24 years in the vaccine era. Prelicensure clinical trials of both quadrivalent and bivalent vaccines investigated cross-protection against persistent infection and cervical intraepithelial neoplasia due to nonvaccine high-risk types.[10,18–20] Trials of bivalent HPV vaccine found more evidence of cross-protection than did trials of 4vHPV. Other postlicensure prevalence evaluations have investigated cross-protection.[16,21,22] In England and Scotland, where the bivalent HPV vaccine was introduced, decreases were observed in HPV-16, -18, as well as related types, in the vaccine era.[21,22] In Australia, where 4vHPV was introduced, HPV-6, -11, -16, 18 prevalence among women aged 18 to 24 years decreased from 37.6% to 6.5%.[16] For HPV-31, -33, -45, there was no statistically significant change

between the prevaccine and vaccine eras; within the vaccine era, however, a significant 58% effectiveness was observed. Further analyses of NHANES data will assess changes in HPV prevalence in the United States as HPV vaccine coverage increases. However, introduction of 9vHPV will make it more difficult to evaluate changes due to potential 4vHPV cross-protection for these 3 types beyond 2015.[23]

Finally, we also examined prevalence of the 5 additional 9vHPV types to provide a baseline before potential introduction of this vaccine. In the prevaccine era, the prevalence of any 5 additional types in 9vHPV was 8.4% and 16.5% in females aged 14 to 19 years and 20 to 24 years, respectively, similar to the prevalence of HPV-16 and -18 in those age groups. Of note, these 5 types cause substantially less HPV-associated cancer than HPV-16, -18 because they are less likely to progress to cancer.[24] In the United States, it is estimated that 66% of cervical cancers are attributable to HPV-16 and -18 compared with 15% attributable to the 5 additional 9vHPV types.[25,26] There was no statistically significant difference in prevalence of the 5 additional 9vHPV types in the prevaccine/vaccine era comparison or in the comparison of vaccinated and unvaccinated sexually active females aged 14 to 24 years within the vaccine era. Although there were some statistically significant differences in prevalence of individual non-4vHPV types between the prevaccine and vaccine eras, these unadjusted comparisons should be interpreted with caution. Prevalence of individual types will continue to be evaluated in future cycles of NHANES.

Limitations of NHANES data have been described.[6] First, vaccination history is by self-report in NHANES, and overreporting or underreporting could have occurred.[27,28] In the United States, there is wide variation of HPV vaccine coverage by state, with coverage of ≥1 dose ranging from 29% to 73% in 2012.[29] NHANES design does not allow state-specific prevalence estimates; each cycle is designed to include a representative sample of the US population. Third, starting in 2007, adolescents were not oversampled. Some of our analyses were limited by small sample size, and some prevalence estimates were unstable. Although we adjusted the analyses for race/ethnicity and some sexual behaviors, we cannot exclude the possibility of changes or differences in sexual behaviors that were not measured by NHANES.

Ongoing analyses of NHANES will allow monitoring of HPV vaccine impact on HPV prevalence, duration of protection, possible cross-protection, or type replacement. To date, there is no clear indication that type replacement is occurring. Given the low contribution of vaccine types to the overall prevalence of HPV in the population and because co-infections occur, a decrease in any HPV prevalence due to the declines in vaccine type HPV might not be observed, particularly if there is any increase in sexual risk behavior in the population (as we found in women aged 20–24 years).

Our data confirm previous findings of an early impact of HPV vaccination in the United States among females aged 14 to 19 years and extend the findings to females in their early 20s. The decline in vaccine type prevalence after introduction of HPV vaccination is greater than expected based on current 3-dose coverage. This outcome could be due to herd protection or effectiveness of less than a complete 3-dose series, for which there is accumulating evidence.[30,31] There are now data on population impact of HPV vaccines from many countries[32]; most reports of declines in HPV vaccine type prevalence are from countries with higher coverage than the United States.[16,21,22] Data from NHANES contribute to the increasing body of evidence on HPV vaccine impact and will continue to provide important information as coverage increases and vaccine policy changes in the United States.[23]

ABBREVIATIONS

4vHPV: quadrivalent HPV vaccine
9vHPV: 9-valent HPV vaccine
aPR: adjusted prevalence ratio
CDC: Centers for Disease Control and Prevention
CI: confidence interval
HPV: human papillomavirus
MEC: mobile examination center

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