

Increases in Human Papillomavirus Vaccination Among Adolescent and Young Adult Males in the United States, 2011–2016

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In the United States, human papillomavirus (HPV) vaccination has been recommended for females since 2006 and males since 2011. We assessed temporal trends in HPV vaccine coverage (defined as receipt of ≥ 1 dose) among 9–26-year-old participants in the 2011–2016 National Health and Nutrition Examination Surveys. While coverage increased overall, from 37.7% to 45.7%, among females (adjusted prevalence difference [aPD], 7.1%; 95% confidence interval [CI], .1%–13.7%), there was no change among female adolescents aged 9–17 years. For males, coverage increased overall, from 7.8% to 27.4% (aPD, 18.8%; 95% CI, 14.1%–23.5%), and among every stratum of age, race/ethnicity, health insurance status, poverty level, and immigration status ($P \leq .05$). The increase in HPV vaccine coverage observed among males is encouraging, but coverage remains below national targets for both males and females.

Keywords. NHANES; human papillomavirus (HPV); sexually transmitted infections (STIs); vaccination; cancer prevention; trends.

Human papillomavirus (HPV) vaccination is a powerful tool for cancer prevention. Three prophylactic HPV vaccines are licensed in the United States (a bivalent formulation [Cervarix], a quadrivalent formulation [Gardasil], and a nonavalent formulation [Gardasil-9]). Each vaccine confers protection against HPV types 16 (HPV-16) and HPV-18, which are responsible for 63% of HPV-associated cancers in the United States [1]. The nonavalent vaccine confers protection against additional oncogenic HPV types (ie, HPV-31, 33, 45, 52, and 58) that cause approximately 10% of HPV-associated cancers [1]. The quadrivalent and nonavalent vaccines also confer protection against HPV-6 and HPV-11, which cause genital warts. HPV vaccination is most effective when initiated

before individuals reach sexual debut, because there is a lower likelihood of prior HPV exposure among recipients [2]. Young adolescents aged 9–14 years have also been shown to mount a stronger immune response to HPV vaccination, compared to older individuals aged 15–26 years [3]. As evidence of HPV vaccine immunogenicity, safety, and effectiveness has rapidly accumulated [4, 5], recommendations for early vaccination have evolved accordingly.

The Advisory Committee on Immunization Practices (ACIP) has, since 2006, recommended routine HPV vaccination for females and, since 2011, for males [6]. Routine HPV vaccination is recommended for individuals aged 11–12 years, but the vaccination schedule can be initiated as early as 9–10 years of age. Catch-up HPV vaccination is recommended for all females aged 13–26 years and all males aged 13–21 years. Additionally, men aged 22–26 years are permissively eligible for catch-up HPV vaccination, particularly if they have an immunocompromising condition or report having sex with men. Adequate HPV vaccination for all ages previously required a 3-dose schedule. However, since October 2016, immunocompetent adolescents who receive the first dose before their 15th birthday only require a 2-dose schedule to be considered adequately vaccinated.

HPV vaccine uptake in the United States has been suboptimal, especially in comparison to uptake of other recommended vaccines [6, 7]. Disparities in HPV vaccination have been noted by sex, race/ethnicity, sexual orientation, and geographic region [6–8]. Nationally, there has only been a modest indirect population-level effect of HPV vaccination (ie, via herd immunity), as assessed among young adults participating in the National Health and Nutrition Examination Survey (NHANES) [9]. Data from the National Immunization Survey (NIS)–Teen suggest that HPV vaccine coverage has recently increased among adolescent males aged 13–17 years [6]. However, it is unclear whether there have been changes in HPV vaccine uptake among other age-eligible members of the general US population, particularly in the era of gender-neutral vaccination.

In this study, we describe sex-specific trends in HPV vaccination during 2011–2016 in a national sample of females and males aged 9–26 years in the United States.

METHODS

Study Design and Population

NHANES is a complex household survey of the noninstitutionalized US civilian population. Details on study design and procedures for each 2-year NHANES cycle have been described elsewhere [2, 5, 10]. This study used data collected during the household interview in the 3 most recent NHANES cycles (2011–2016), which had overall interview response rates of 61.3%–72.6%. Participants aged 9–26 years at the time of the

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interview were eligible for inclusion in this analysis. Oral and written informed consent was obtained from participants aged ≥ 18 years or from the parent/guardian of participants aged < 18 years. The NHANES study protocols were approved by the Research Ethics Board of the National Center for Health Statistics, Centers for Disease Control and Prevention. The present analysis was exempted from review by the Johns Hopkins University School of Medicine Institutional Review Board.

HPV Vaccination History

Data on HPV vaccination have been collected using a computer-assisted personal interview system since 2007 for females and since 2011 for males; participants aged 9–59 years were eligible to complete the questionnaire. Participants aged ≥ 16 years and emancipated minors were interviewed directly. A parent/guardian provided responses for participants aged < 16 years and for participants who could not independently respond. Participants were asked if they ever received a dose of an HPV vaccine (Table S1). Participants who responded “yes” were further queried about the age at which they received their first dose and the number of doses they received. For this analysis, participants who refused to answer, did not know their HPV vaccination status, or had no recorded information regarding their HPV vaccination history were considered to have inadequate HPV vaccination data (Table S2).

Statistical Analysis

Data analysis was conducted in Stata/SE, version 14.2 (StataCorp, College Station, TX). Estimates were weighted to adjust for the unequal probability of selection, nonresponse to the household interview, and noncoverage of the non-institutionalized U.S. civilian population. Weights provided by NCHS were further adjusted to account for the use of three NHANES cycles. Taylor series linearization was used for variance estimation. The primary analysis excluded participants with inadequate HPV vaccination data.

All analyses were stratified by sex. The survey period was the exposure of interest. The primary outcome was the percentage of participants with a history of receiving ≥ 1 dose of any HPV vaccine. Secondary outcomes were the percentage of participants with a history of receiving ≥ 2 doses and 3 doses of any HPV vaccine. Temporal trends in HPV vaccine coverage across the 3 survey periods were assessed by a test for linear trend (P_{trend}). The probability of HPV vaccination was also examined by multivariable logistic regression. The difference in the predicted margins of HPV vaccination in 2015–2016 as compared to 2011–2012 (the reference period) is reported as an adjusted prevalence difference (aPD). Multivariable models included adjustment for potential sociodemographic confounders determined a priori (ie, age group, race/ethnicity, health insurance, poverty status, and immigration status). Subgroup analyses were conducted after stratification by sociodemographic characteristics.

Several sensitivity analyses were performed. First, to assess the potential impact of excluding participants with inadequate HPV vaccination data, a sensitivity analysis was conducted

using multiple imputation with chained equations. Second, we compared sex-specific estimates of HPV vaccination among 13–17-year-old participants in this study versus estimates from the NIS-Teen, which annually collects provider-verified data. Finally, by restricting the analysis to participants aged 9–26 years, we may have excluded older individuals who were vaccinated before the recommended upper age limit. Thus, we performed a sensitivity analysis that eliminated the age-based inclusion criterion and examined sex-specific trends in the proportion of participants aged 9–59 years who reported initiating the HPV vaccine series before their 27th birthday.

RESULTS

Study Population

There were 4033 females and 4007 males aged 9–26 years who participated in the household interview. Adequate HPV vaccination data were ascertained for 3780 females and 3588 males. Prevalence of inadequate HPV vaccination data did not vary significantly by survey period for males or females overall (Table S3). However, upon stratification, there was an increase over time in the percentage of 18–26-year-old males, non-Hispanic Asian males, and Hispanic males with inadequate HPV vaccination data (Table S4).

Temporal Trends in HPV Vaccination Among All Age-Eligible Participants

The percentage of females who received ≥ 1 dose increased overall, from 37.7% in 2011–2012 to 45.7% in 2015–2016 (aPD, 7.1%; $P = .034$; Table 1). In stratified analyses, temporal increases in the percentage of females who received ≥ 1 dose were observed among non-Hispanic black females, Mexican American females, and US-born females ($P_{\text{trend}} \leq .05$; Table 1).

The percentage of males who received ≥ 1 dose increased overall, from 7.8% in 2011–2012 to 27.4% in 2015–2016 (aPD, 18.8%; $P < .001$; Table 1). There was an increase in the percentage of males who received ≥ 1 dose for each stratum of race/ethnicity, health insurance, poverty status, and immigration status ($P_{\text{trend}} \leq .05$; Table 1).

Temporal Trends in HPV Vaccination by Age Group

Age-specific temporal trends in HPV vaccination are shown for females in Figure 1A and for males in Figure 1B. The percentage of females who received ≥ 1 dose remained stable between 2011–2016 among the groups aged 9–10, 11–12, and 13–17 years (Figure 1A). Although there was a significant increasing trend in the percentage of females that received ≥ 1 dose among the cohorts aged 18–21 and 22–26 years ($P_{\text{trend}} \leq .05$; Figure 1A), the absolute increase between 2011–2012 and 2015–2016 was only statistically significant for the group aged 22–26 years in multivariable analysis (aPD, 19.4%; $P = .002$; Table S5). In contrast, there was a statistically significant increase between 2011–2012 and 2015–2016 in the percentage of males who received ≥ 1 dose among all age groups (9–10 years: aPD, 5.5% [$P = .050$]; 11–12 years: aPD, 16.9% [$P = .005$]; 13–17 years: aPD, 30.3% [$P < .001$]; 18–21 years: aPD, 22.1% [$P < .001$]; and 22–26 years: aPD, 10.7% [$P = .005$]; Table S5). Similar age-specific

Table 1. Temporal Trends in Human Papillomavirus (HPV) Vaccine Coverage (≥1 Dose) Among Females and Males Aged 9–26 Years, 2011–2016 National Health and Nutrition Examination Surveys (NHANES)

Characteristic, by Sex	2011–2012 NHANES		2013–2014 NHANES		2015–2016 NHANES		<i>P</i> _{trend} ^a	2011–2012 NHANES vs 2015–2016 NHANES, aPD (95% CI) ^b
	Participants, No.	Coverage, % (95% CI)	Participants, No.	Coverage, % (95% CI)	Participants, No.	Coverage, % (95% CI)		
<i>Female</i>								
Overall	1233	37.7 (33.8–41.7)	1331	38.7 (33.1–44.6)	1216	45.7 (41.3–50.1)	.010	7.1 (0.1, 13.7)
Race/ethnicity ^c								
Non-Hispanic white	307	41.5 (34.1–49.4)	376	39.8 (31.3–48.9)	359	48.4 (42.1–54.7)	.180	5.2 (–6.2, 16.5)
Non-Hispanic black	377	34.1 (29.5–39.0)	325	39.4 (31.4–47.9)	249	49.2 (44.7–53.7)	<.001	16.4 (9.8, 22.9)
Non-Hispanic Asian	153	34.8 (25.6–45.3)	136	33.1 (20.4–49.0)	109	39.6 (28.0–52.4)	.548	7.2 (–7.7, 22.2)
Mexican American	188	30.8 (22.8–40.2)	287	39.8 (33.2–46.7)	263	42.4 (37.1–47.8)	.034	9.2 (0.7, 17.6)
Other Hispanic	141	34.5 (24.8–45.8)	132	36.9 (28.6–46.1)	164	42.6 (34.5–51.1)	.238	11.2 (–2.0, 24.4)
Health insurance								
Yes, private	529	37.4 (32.0–43.2)	582	39.4 (30.7–48.8)	491	46.0 (40.0–52.1)	.045	7.8 (–0.6, 16.2)
Yes, Medicaid	324	41.2 (30.4–52.9)	382	44.1 (36.7–51.7)	382	46.1 (41.0–51.3)	.426	3.7 (–7.8, 15.2)
Yes, other	177	44.9 (33.6–56.8)	152	33.6 (24.6–43.8)	194	47.3 (38.1–56.6)	.734	4.4 (–8.0, 16.8)
No health insurance	200	29.8 (20.2–41.6)	214	33.0 (25.3–41.7)	148	41.8 (31.1–53.3)	.149	12.2 (–3.6, 28.0)
Poverty status								
At or above poverty level	718	38.5 (34.1–43.1)	791	39.3 (32.8–46.2)	804	46.6 (41.6–51.8)	.019	6.9 (–0.3, 14.1)
Below poverty level	431	38.3 (33.0–44.0)	446	38.5 (31.7–45.8)	312	41.8 (34.5–49.5)	.481	6.6 (–3.4, 16.6)
Immigration status								
US born	1046	38.3 (34.0–42.8)	1176	39.9 (33.9–46.2)	1059	46.8 (42.4–51.4)	.009	7.2 (0.1, 14.3)
Foreign born	187	32.7 (22.5–44.8)	155	25.7 (17.2–36.6)	156	33.6 (23.9–45.0)	.959	8.7 (–5.2, 22.5)
<i>Male</i>								
Overall	1214	7.8 (6.0–10.2)	1248	19.7 (17.5–22.3)	1126	27.4 (23.3–31.9)	<.001	18.8 (14.1, 23.5)
Race/ethnicity ^c								
Non-Hispanic white	315	6.4 (4.3–9.2)	379	19.7 (15.9–24.2)	338	27.8 (21.7–34.9)	<.001	21.5 (14.4, 28.5)
Non-Hispanic black	345	11.9 (9.1–15.2)	313	20.8 (16.5–25.9)	257	28.1 (23.0–33.9)	<.001	16.9 (9.9, 23.9)
Non-Hispanic Asian	166	7.7 (3.4–16.7) ^d	113	16.5 (12.0–22.2)	124	26.4 (19.7–34.6)	<.001	19.5 (9.0, 29.9)
Mexican American	205	7.3 (3.2–15.8) ^d	252	20.5 (15.6–26.5)	218	28.0 (23.8–32.7)	<.001	19.6 (11.8, 27.4)
Other Hispanic	121	8.5 (5.0–14.0)	119	24.9 (16.2–36.1)	125	27.8 (19.9–37.3)	<.001	12.8 (3.7, 21.9)
Health insurance								
Yes, private	516	7.5 (4.6–11.8)	555	20.7 (17.4–24.3)	468	29.8 (22.9–37.8)	<.001	23.9 (14.8, 33.0)
Yes, Medicaid	290	13.1 (8.2–20.3)	351	25.6 (20.0–32.1)	321	30.7 (22.8–39.8)	.002	20.8 (10.4, 31.2)
Yes, other	163	9.9 (4.9–19.0) ^d	123	19.5 (11.5–30.9)	188	26.7 (18.9–36.4)	.004	17.4 (4.8, 30.1)
No health insurance	241	3.5 (1.6–7.8) ^d	218	10.4 (7.2–14.6)	146	13.7 (9.6–19.2)	<.001	11.5 (4.6, 18.4)
Poverty status								
At or above poverty level	713	6.7 (4.6–9.7)	759	19.7 (16.3–23.6)	756	27.3 (22.7–32.4)	<.001	23.1 (16.3, 29.8)
Below poverty level	398	9.2 (5.4–15.5)	397	20.4 (14.8–27.6)	268	23.9 (16.4–33.4)	.002	13.5 (5.6, 21.3)
Immigration status								
US born	1018	7.9 (5.9–10.5)	1122	20.7 (18.3–23.3)	988	28.4 (23.9–33.3)	<.001	22.0 (16.0, 27.9)
Foreign born	196	7.1 (4.3–11.5)	126	8.4 (5.1–13.6)	138	17.7 (11.4–26.6)	.012	10.1 (2.9, 17.3)

Abbreviation: CI, confidence interval.

^aBy the test for linear trend across the 3 survey periods. Values of $\leq .05$ denote statistically significant differences.

^bAdjusted prevalence differences (aPDs) represent the change in prevalence of HPV vaccination (≥1 dose) between the 2011–2012 period (reference) and the 2015–2016 period (ie, an absolute measure of the effect of time) for a given subgroup. Each multivariable model included the survey period, age group, race/ethnicity, health insurance, poverty status, and immigration status.

^cData for the "other/multiracial" group, as categorized by NCHS, are not shown because of insufficient sample sizes. However, these participants are included in all other estimates.

^dRelative standard error, 30%–40%.

temporal trends were observed in the percentage of females and males who received ≥2 or 3 HPV vaccine doses between 2011 and 2016 (Figure 1).

Sensitivity Analyses

Sex-specific estimates of HPV vaccine coverage (≥1 dose) in the primary analysis were similar to estimates calculated using

imputed vaccination data (Table S6). Sex-specific estimates of HPV vaccine coverage (≥1 dose) among 13–17-year-old participants were comparable but slightly lower than estimates among 13–17-year-old participants in the NIS-Teen (Figure S1). Among participants aged 9–59 years, the proportion who reported initiating the HPV vaccine series prior to their 27th birthday increased over time for both females and males (Table S7).

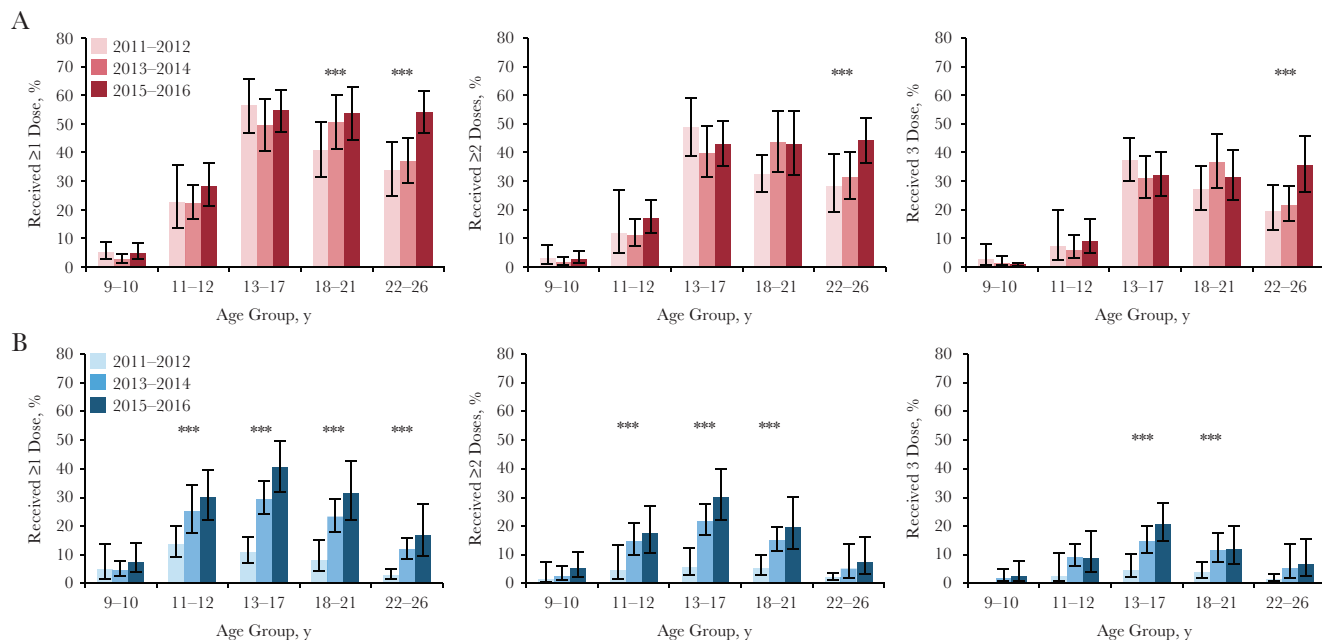


Figure 1. Age-specific temporal trends in human papillomavirus virus (HPV) vaccine coverage among females and males aged 9–26 years, National Health and Nutrition Examination Surveys, 2011–2016. *A* and *B*, Data for female (*A*) and male (*B*) participants. The percentages of females and males who reported previously receiving ≥ 1 , ≥ 2 , and 3 HPV vaccine doses are shown by age group and survey period. *** $P < .05$ for linear trend across the 3 survey periods.

Discussion

In this nationally representative study, there were substantial increases in HPV vaccine coverage between 2011–2012 and 2015–2016 among age-eligible males. This finding overall is promising. However, it should be noted that increases in HPV vaccine coverage were lowest among males without health insurance, males below the poverty level, and males born outside the United States. These populations may have less exposure to primary healthcare settings, making them more likely to miss the opportunity to be vaccinated. Although this could not be assessed directly, the observed increase in HPV vaccination among males is likely attributable to the introduction of gender-neutral recommendations for HPV vaccination in 2011. In addition to increases in the frequency of visits during which providers recommend HPV vaccination to their patients, changing attitudes about the vaccine during the study period likely also played a role [11]. While the sex disparity in HPV vaccination is closing, HPV vaccine coverage remains lower among males as compared to females. This delay in scaling HPV vaccination among males should be considered when assessing sex-based differences in age-specific patterns of vaccine-associated HPV infections.

During the study period, a modest increase in HPV vaccine coverage (≥ 1 dose) was observed overall among females aged 9–26 years. The prevalence of HPV vaccination was stable over time among adolescent females, even in the age group (ie, 11–12 years) for which there is a routine recommendation from the ACIP. It is concerning that a previous NHANES study also observed no change in HPV vaccination prevalence between

2007–2010 and 2011–2014 among females aged 11–12 years [2]. Possible reasons for the stagnating trends in HPV vaccination among adolescent females may include parental vaccine hesitancy, lack of strong provider recommendations, and limited exposure to healthcare providers. It was recently shown that delayed initiation of the HPV vaccination series among female participants in NIS-Teen 2013 was linked to a lack of well-child/check-up visits between ages 11 and 12 years [12].

This study has strengths and limitations. Here, we present the most up-to-date national data on HPV vaccination. To the best of our knowledge, NHANES is the only nationally representative database that has consistently collected data on HPV vaccination for all age-eligible populations. This particular study examined trends in HPV vaccination among populations for whom data are limited (ie, 9–12-year-old individuals and non-Hispanic Asians). A limitation of all NHANES studies, however, is the inability to monitor trends by geographic region. The primary limitation of the present study is that HPV vaccination data were ascertained by self-report or parent/guardian report and may be subject to reporting biases. In a previous analysis of 13–17-year-old female participants in NIS-Teen conducted during 2008–2013, parent report of HPV vaccine coverage (≥ 1 dose) had 78% sensitivity and 90% specificity as compared to provider-verified data [13]. Estimates for HPV vaccination among 13–17-year-old participants in this study were comparable but consistently lower than estimates from the NIS-Teen. We speculate that this could be due to potential underreporting of HPV vaccination in this study, but it may also be reflective of limitations of the NIS-Teen, such as poor household response

rates (ie, 33%–35% in 2015–2016) and incomplete data linkage with providers [6]. Finally, since the interval between doses was unknown, the prevalence of “adequate” HPV vaccination, as it is currently defined by ACIP, could not be estimated.

The increases in HPV vaccine coverage documented among male adolescents and young adults in this study are indeed encouraging. However, HPV vaccine coverage among males and females in the general US population clearly remains well below national targets, including the Healthy People 2020 goal to achieve up-to-date coverage among >80% of adolescents aged 13–15 years [14]. To maximize individual-level and population-level benefits, there is a critical need to develop and implement evidence-based strategies to overcome residual barriers to early HPV vaccination. Coupled with interventions at the systems level, clinicians should desexualize the HPV vaccine and strongly advocate early HPV vaccination for cancer prevention when educating patients and their parents [15]. Continuing to monitor trends in HPV vaccination is needed to guide effective policy on vaccine implementation and to estimate the projected burden of vaccine-associated HPV infections and incidence of HPV-related cancers.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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