Trends in Human Papillomavirus Vaccination in Commercially Insured Children in the United States

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OBJECTIVES: The human papillomavirus (HPV) vaccine was recommended in 2006 for girls and in 2011 for boys. The Healthy People 2020 goal for 2-dose HPV vaccination coverage is 80% by age 15 for girls and boys. We used nationwide population-based data to describe trends in HPV vaccination in children.

abstract

METHODS: We conducted a cohort study nested within the MarketScan health care database between January 2003 and December 2017. Children were followed from the year they turned 9 until HPV vaccination, insurance disenrollment, or the end of the year when they turned 17, whichever came first. We estimated the cumulative incidence of at least 1- and 2-dose HPV vaccination, stratified by birth year, sex, and state. In secondary analyses, we evaluated the association between state-level vaccination policies and HPV vaccination coverage.

RESULTS: This study included 7 837 480 children and 19.8 million person-years. The proportion of 15-year-old girls and boys with at least a 1-dose HPV vaccination increased from 38% and 5% in 2011 to 57% and 51% in 2017, respectively; the proportion with at least a 2-dose vaccination went from 30% and 2% in 2011 to 46% and 39% in 2017, respectively. By 2017, 2-dose HPV vaccination coverage varied from 80% in Washington, District of Columbia, among girls to 15% in Mississippi among boys and was positively correlated with legislation for HPV vaccine education and pediatrician availability.

CONCLUSIONS: Despite the increasing trends in uptake, HPV vaccine coverage among commercially insured children in the United States remains behind target levels, with substantial disparities by state.





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WHAT'S KNOWN ON THIS SUBJECT: The human papillomavirus (HPV) vaccine has been recommended for girls since 2006 and for boys since 2011. The Healthy People 2020 goal for HPV vaccination coverage is 80% by age 15. There is a lack of nationwide population-based data on HPV vaccination.

WHAT THIS STUDY ADDS: This study revealed that by 2017, the HPV vaccine coverage by age 15 in commercially insured children was still lower than the Healthy People 2020 goal and that the substantial variability in coverage across states correlated with state-level vaccination policies.

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Human papillomavirus (HPV) infection with oncogenic types causes various cancers, including cervical, vaginal, and oropharyngeal cancers in women and anal, penile, and oropharyngeal cancers in men. 1 HPV vaccination reduces the prevalence of targeted-type HPV infection in populations² and prevents HPVrelated cancer precursors.3 The public health objective of extensive HPV vaccination is to achieve herd immunity and prevent HPV-related cancers as well as genital warts.4 No serious safety concerns have arisen to date, except for anaphylaxis, which rarely occurs.^{5,6} The US Food and Drug Administration approved HPV vaccines for girls in 2006 and for boys in 2009. Since 2011, the Advisory Committee on Immunization Practices and the Centers for Disease Control and Prevention recommend that girls and boys be vaccinated at age 11 to 12 to achieve the greatest effectiveness^{7–9} and before sexual exposure because the cancer protection by the HPV vaccine results from the prevention of infection rather than the prevention of progression after infection.¹⁰ Models based on population-level effectiveness, including herd immunity effects, of HPV vaccination predicted that the vaccine-specific HPV types may be eliminated with a sustained 80% coverage with complete vaccination in girls and boys.4 Thus, the Healthy People 2020 goal for at least 2-dose HPV vaccination coverage was set at 80% by 15 years of age. 11

Despite the safety and efficacy evidence, state-level HPV vaccination policies vary from school-mandated vaccination and vaccine education to exemptions based on family preferences. ^{12,13} Available data suggest that HPV vaccination coverage in the United States remains low relative to other infant and adolescent vaccines. ^{14,15} The uptake of at least 1 and 2 doses of the HPV vaccine among children aged 13 to 17

was 65.5% and 48.6%, respectively, in 2017 according to the National Immunization Survey-Teen (NIS-Teen).¹⁵ However, the low response and completion rates (~7.5% of those contacted completed the survey) raised concerns regarding the representativeness of the sample. Other immunization registry studies with more representative samples reported lower local HPV vaccination coverages within several states. 16-23 There are no nationwide populationbased reports to provide national HPV vaccination estimates and comparable state-level estimates. Moreover, the cross-sectional nature of surveys does not allow for projection of vaccination coverage over time to assess how far the United States is from attaining the Healthy People 2020 goal.¹¹

Understanding regional and temporal variations in HPV vaccination coverage may help improve HPV vaccination uptake by informing public health policy. Our primary objective was to describe the trends of 1- and 2-dose HPV vaccination coverage by using a large longitudinal health care database of commercial insurance beneficiaries during the decade after approval of the HPV vaccine.

METHODS

Data Source and Study Design

We conducted a cohort study using the IBM MarketScan health care commercial insurance claims database, which contained 192 million subjects between January 2003 and December 2017. Because the HPV vaccine is approved only for children aged 9 or older, follow-up started when children turned 9 to avoid missing vaccination before enrollment (Supplemental Fig 3). Only children with full benefits that included prescriptions who were enrolled before the end of the ninth year after birth were included. The first birth cohort included was born

in 1994 and turned 9 in 2003 because these children were within the recommended vaccination age by 2006, when vaccination began. All eligible children were followed until the event of interest (ie, first or second HPV vaccination), full benefits insurance plan disenrollment, December 2017, or the end of the year when they turned 17, whichever came first. Given the years of data available and given that some families changed insurance companies and discontinued enrollment in MarketScan, not all children had 9 years of follow-up. Because the HPV vaccine was recommended for girls in 2006 and for boys in 2011, all analyses were stratified by birth year (from 1994 to 2008) and sex to understand the sex disparity. The use of this database for research was approved by the Institutional Review Board at Brigham and Women's Hospital.

Outcome Measures

The primary outcomes of interest were the cumulative incidence of at least 1 dose and at least 2 doses of the HPV vaccination. We included any of the 3 types of HPV vaccines identified by *Current Procedural Terminology* codes 90649 for quadrivalent, 90650 for bivalent, and 90651 for nonavalent HPV vaccines.

Statistical Analysis

We used Kaplan-Meier survival analysis to estimate the cumulative incidence of the HPV vaccinations from age 9 to 17, while accounting for censoring. The cumulative incidence was estimated as

 $\left(1-\Pi_i\left[1-\frac{N\ \text{children\ receiving\ vaccination}}{N\ \text{children\ eligible\ for\ vaccination}}
ight]\right),$ with i representing the monthly interval. We used segmented regression to project the HPV vaccine coverage for at least 1 and 2 doses beyond 2017 based on the annual trends trajectories in vaccination rates observed for previous age cohorts. For example, for children

born in 2005, who were 12 by the end of follow-up, the model estimated the cumulative incidence of HPV vaccination from age 13 to age 17. Log-rank tests and Wilcoxon rank tests were used to compare survival curves between girls and boys of the same birth year. A generalized linear regression model was used to compare the cumulative incidence of HPV vaccination by age 17 between girls and boys and between years.

The cumulative incidence of HPV vaccination (at least 1 or 2 doses) among children of the same birth year was mapped geographically by state (including Washington, DC). Because the Healthy People 2020 HPV vaccination coverage goals targeted age 15, we focused on the cumulative incidences for children aged 15 years in 2016–2017, the 2 most recent years available in our data (combined to obtain more stable estimates).

In a secondary analysis, we evaluated the association between state-level policies and HPV vaccination coverage by age 15 in girls and boys using generalized linear regression models. Five state-level factors, which are common factors or policies that have been widely discussed, 12,19,24-28 were selected as independent variables: (1) law enactment of school requirement of HPV vaccination (binary variable), (2) allowance of personal beliefs exemption of HPV vaccination (binary variable), (3) legislation to improve HPV vaccination education (binary variable), (4) state-purchased HPV vaccination policy (binary variable), and (5) the number of pediatric generalists per 10 000 children (numerical variable). In addition, we included population characteristics that might affect both vaccine policies and vaccination coverage, including the total population and the proportion of urbanized population in the state.

HPV vaccine-related legislation information for each state occurring before 2016 was obtained from the National Conference of State Legislatures organization. ²⁹ Information on the number of children per pediatric generalist in a state was obtained from the 2015–2016 workforce report from the American Board of Pediatrics. ³⁰ Information on urbanization status and the state population was obtained from the US 2010 Decennial Census data. ³¹

Sensitivity Analyses

We conducted a sensitivity analysis using the subset of children with continuous enrollment until the end of age 17 to confirm that censoring was noninformative (ie, that it was not associated with the likelihood of vaccination, and thus there were similar vaccination patterns among those with continuous enrollment). The cumulative incidence of HPV vaccination among children with continuous enrollment was calculated as the total number of children vaccinated between ages 9 and 17 divided by the size of the cohort and stratified by year of birth and sex. Within this subcohort, we estimated the proportion of children who received a second dose after the first HPV vaccination.

In addition, to test the robustness of the study design, we used a control vaccine: the pneumococcal conjugate vaccine (PCV), identified by Current Procedural Terminology codes 90669 for the 7-valent PCV and 90670 for the 13-valent PCV. The infant PCV was chosen because of its known steady high vaccine coverage in past years.¹⁴ The approach was identical to that used for the HPV vaccine, except that infants who received the PCV were followed from birth until vaccination, disenrollment from the insurance plan, or the end of the year when they turned 3, whichever came first.

All analyses were performed by using the Aetion platform, R (version 3.1.2.5; R Foundation for Statistical Computing, Vienna, Austria), and SAS software (version 9.4; SAS Institute, Inc, Cary, NC). Epi Info 7 software was used to map HPV vaccination rates geographically.³²

RESULTS

This study population included 7 837 480 children at age 9 and a total of 19 843 737 person-years between January 1, 2003, and December 31, 2017. A total of 11.7% of those born in 1994–2000 had continuous enrollment from age 9 to 17. Among all enrollees, 48.9% were girls.

For girls, the cumulative incidence of HPV vaccination increased significantly over time (Fig 1 A and B; number at risk provided in Supplemental Tables 2). The proportion of girls vaccinated with at least 1 dose of the HPV vaccine by age 15 was 2% (95% confidence interval [CI], 2.0% to 2.2%) in 2006, the first year the vaccine was recommended for girls; 38% (95% CI, 37.3% to 38.2%) in 2011, the first year the vaccine was recommended for boys; and 57% (95% CI, 56.3% to 57.0%) in 2017, the last year of data available for this study. The proportion of girls vaccinated with at least 2 doses of the HPV vaccine by age 15 was 30% (95% CI, 29.9% to 30.7%) in 2011 and 46% (95% CI, 45.2% to 46.0%) in 2017. In boys, HPV vaccination uptake followed similar patterns as in girls (Fig 1 C and D; number at risk provided in Supplemental Table 3). The proportion of boys vaccinated with at least 1 dose by age 15 was 5% (95% CI, 4.5% to 5.0%) in 2011 and 51% (95% CI, 50.4% to 51.1%) in 2017. The proportion of boys vaccinated with at least 2 doses by age 15 was 2% (95% CI, 2.2% to 2.5%) in 2011 and 39% (95% CI, 38.8% to 39.5%) in 2017. Therefore,

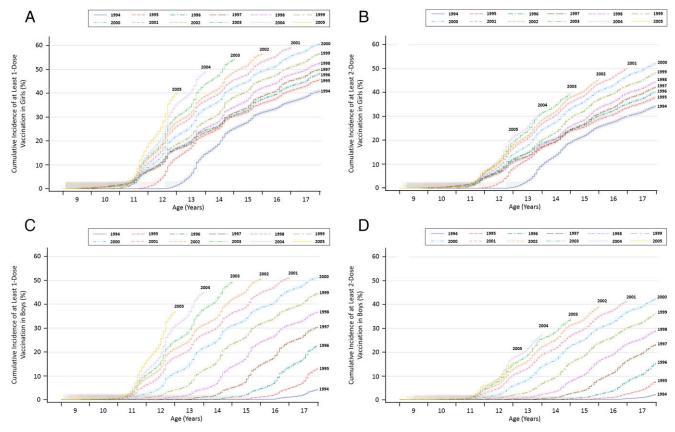


FIGURE 1
Cumulative incidence of at least 1- and 2-dose HPV vaccination for commercially insured girls and boys by birth year cohort. A, Girls, 1 dose. B, Girls, 2 doses. C, Boys, 1 dose. D, Boys, 2 doses. Data were obtained from IBM MarketScan 2003–2017. Light shadows refer to 95% Cls.

although boys at age 17 started at a lower 2-dose HPV vaccination coverage than girls in 2011 (2.2% vs 34.4%), coverage increased 3 times faster in boys than in girls so that the difference between them narrowed by 4.0% (95% CI, 3.6% to 4.5%) per year, decreasing from 32.2% in 2011 to 9.9% in 2017 (Supplemental Tables 4 and 5). Overall, although the majority of girls and boys were vaccinated at ages 11 to 13, some received their first HPV vaccination later. We projected the HPV vaccine coverage (with at least 1 and 2 doses) for girls and boys born in 2005 to approach 70% (1 dose) and 45% (2 doses) by age 15 in 2020 and 80% (1 dose) and 55% (2 doses) by age 17 in 2022 (Supplemental Fig 4).

The cumulative incidence of HPV vaccination varied substantially

across states (Fig 2, Supplemental Fig 5). For girls and boys aged 15 years in 2016–2017, there were 33 and 46 states with vaccination coverage (at least 2 doses) <50%, respectively. The states (or district) ranked in the top 3 for vaccination coverage were Washington, District of Columbia (80%); North Dakota (68%); and Rhode Island (67%) for girls and Rhode Island (66%), North Dakota (63%), and South Dakota (52%) for boys.

The states with more HPV vaccine interventions tended to have a higher coverage (Supplemental Figs 6 and 7). The strongest association was observed for legislation to improve vaccination education, with an 8.8% (95% CI, 3.3% to 14.2%) increase in coverage for girls and an 8.7% (95% CI, 3.2% to 14.2%) increase for boys (Table 1). Rhode Island and

Washington, District of Columbia, were the only state and district with both a school requirement and no personal beliefs exemptions for HPV vaccination, and both had high vaccination coverage. State-level pediatrician density was also associated with HPV coverage for girls, with a 1.1% (95% CI, 0.1% to 2.0%) estimated increase in coverage with every additional pediatrician per 10 000 children (Table 1).

The cumulative incidence of HPV vaccination curves among continuous enrollees were almost identical to those in the primary analysis (Supplemental Fig 8), which supports the assumption of noninformative losses to follow-up. After the initial HPV vaccination, 87% of girls and 82% of boys received a second dose by age 17 in the most recent cohorts.

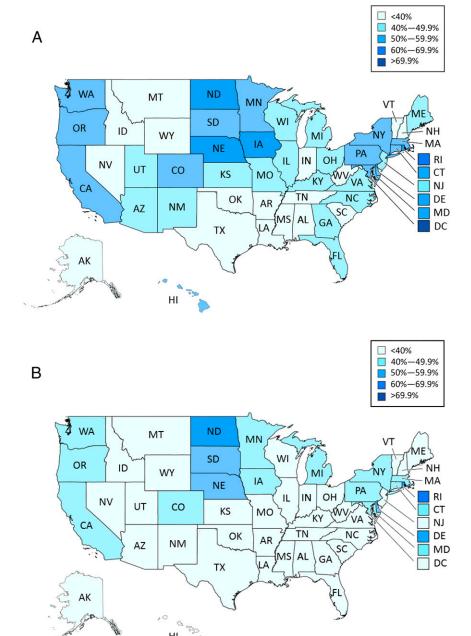


FIGURE 2A and B, Cumulative incidence of at least a 2-dose HPV vaccination by age 15 for commercially insured girls and boys in 2016–2017 by state. Data were obtained from IBM MarketScan 2003–2017.

For the most recent birth cohorts with follow-up through age 3 in our data (born in 2009–2015), the cumulative incidence of PCV vaccination by the end of age 3 was steady over time, ranging between 96.9% and 99.0%, with no significant variation by state (Supplemental Fig 9); this is consistent with

surveillance reports from the same years¹⁴ and therefore supports the sensitivity of our approach to identify vaccine coverage.

DISCUSSION

In this study, we used a large health care use database that is

representative of US commercial insurance beneficiaries³³ to estimate the HPV vaccination uptake in a nationwide longitudinal cohort. Overall, HPV vaccine coverage improved between 2006 and 2017. Although HPV vaccination uptake increased faster in boys, because the recommendation for boys lagged 5 calendar years behind that for girls, vaccination coverage remained lower in boys than in girls of the same age over the study period. In 2017, the proportion of children vaccinated with at least 2 doses was still below the 80% target for both girls and boys by age 15 (46% and 39%, respectively) and even by age 17 (52% and 42%, respectively).

The suboptimal HPV vaccination coverage has been recognized as an important public health issue in the United States.^{24,34} In the annual NIS-Teen, 15,35 it was reported that 49.2% of children 13 to 17 years old had received at least 2 HPV vaccine doses by 2016 and 48.6% by 2017, whereas the corresponding estimates from our study were 37.4% and 40.4%, respectively. The NIS-Teen is conducted by random-digit dial sampling, with an ~30% response rate and only 25% of responders completing the survey. 15,35-38 Such self-selection of participants raises concerns regarding representativeness and potential substantial overestimation of HPV vaccination coverage.³⁹ For example, families with healthier behaviors may be more likely to both follow vaccination guidelines and participate in vaccination surveys. 40 In 2016, 64 immunization programs across the United States were assessed in the **Immunization Information Systems** Annual Report, and it was found that 28% of girls and 22% of boys aged 13-17 years had received all the recommended HPV vaccine doses^{23,34}; the corresponding proportions reported in the 2016 NIS-Teen were 43% and 32%,

TABLE 1 Generalized Linear Regression Models in Girls and Boys Regarding the Association Between State-Level Interventions and at Least 2-Dose HPV Vaccination Coverage by Age 15 in 2016–2017 Across 50 States

State-Level Interventions	Girls			Boys		
	β Estimate, %	95% CI, %	Р	β Estimate, %	95% CI, %	Р
Law enactment of school requirement ^a						
Yes versus no	3.0	-10.4 to 16.3	.6573	3.6	-9.8 to 17.0	.5952
Not allowing personal beliefs exemptions ^a						
Yes versus no	-0.2	-5.6 to 5.3	.9481	0.1	-5.4 to 5.5	.9833
Legislation to improve vaccination education ^a						
Yes versus no	8.8	3.3 to 14.2	.0024	8.7	3.2 to 14.2	.0028
State-purchased vaccines ^a						
Yes versus no	0.7	-5.0 to 6.5	.7954	5.4	-0.4 to 11.2	.0671
No. pediatric generalists ^b						
One more physician per 10 000 children	1.1	0.1 to 2.0	.0261	0.2	-0.8 to 1.1	.6984
Urbanization status ^c						
Per 10% increase in urbanized population	2.6	0.5 to 4.7	.0181	1.8	-0.3 to 3.9	.0908
Population size ^d						
Per 1 million increase in population	-0.2	-0.6 to 0.3	.4690	0.1	-0.3 to 0.5	.7104

Vaccination coverage data were obtained from IBM MarketScan 2003-2017.

respectively.¹⁵ For the other 7 infant vaccines evaluated, coverages lower than the corresponding National Immunization Survey-Child estimates were also reported in the **Immunization Information Systems** Annual Report.²³ Similarly, the census data from the Washington State Immunization Information System revealed a >10% lower coverage of girls with 3 HPV vaccine doses than the NIS-Teen estimates.²² These reports support the suspected overestimation of vaccination coverage in the NIS-Teen. That said, all sources are consistent with a suboptimal coverage.

Our data only included commercially insured children, accounting for ~54% of the US population <18 years of age (39% are insured through Medicaid, 2% are insured through other public insurance, and 5% are uninsured). In the 2015 NIS-Teen, 3-dose HPV vaccine coverages among commercially insured, Medicaid-insured, and uninsured children were 42%, 44%, and 25% for girls and 27%, 31%, and

23% for boys,⁴² suggesting that compared with commercially insured children, Medicaid-insured children had slightly higher coverage and uninsured children had a lower coverage.

The lack of routine clinical encounters in children between 11 and 17 years limits the opportunities to administer vaccines by health care providers. That might be particularly true in states with fewer pediatricians relative to the number of children, 25,34 as suggested by our results. In our results, we also found that states with a more urbanized population tended to have higher HPV vaccination coverage. Similarly, studies analyzing NIS-Teen data revealed that girls and boys from urban towns had higher HPV vaccination rates than rural children.26 Thus, measures beyond recommending routine vaccination at annual check-ups might be necessary to attain sufficient HPV vaccine coverage, and the optimal strategy may differ by state characteristics.

Although many states enacted legislations for HPV vaccine education, little is known about the impact of this state-level policy. Statelevel mandated education for HPV vaccination enforces health care professionals to convey education toward teenagers and their parents and provides parents comprehensive information. Strong recommendation for HPV vaccination from clinicians remains a key element to overcome vaccination barriers.²⁷ In the NIS-Teen, the HPV vaccination coverage was 68.8% in adolescents who had received a provider recommendation versus 35.4% in those without it.²⁸ The authors of one recent study reported a positive correlation between state-level sex education policy and HPV vaccination completion. 12 The National Vaccine Advisory Committee also suggested that system-level interventions have greater effectiveness on HPV vaccination coverage than individuallevel ones.³⁴ Our results support the effectiveness of state-level policy for

a Information was obtained from the The National Conference of State Legislatures organization. Available at: http://www.ncsl.org/research/health/hpv-vaccine-state-legislation-and-statutes.aspx. Accessed March 10, 2019.

b Information was obtained from the 2015–2016 workforce report from the American Board of Pediatrics. Available at: https://www.abp.org/sites/abp/files/pdf/workforcedata2015-2016. pdf. Acessed August 10, 2020.

^c Urbanization status was defined as the percentage of the population in urbanized areas by state. Data were obtained from the 2010 Decennial Census, The United States Census Bureau. Available at: https://www.census.gov/programs-surveys/decennial-census/decade.html. Accessed January 19, 2020.

d Information of the state population in 2010 was obtained from the 2010 Decennial Census, The United States Census Bureau. Available at: https://www.census.gov/programs-surveys/decennial-census/decade.html. Accessed January 19, 2020.

HPV vaccination education of families on vaccine coverage.

At present, only 2 states (Virginia and Rhode Island) and Washington, District of Columbia, have adopted law enactment of HPV vaccination for school-entry requirement.⁴³ However, Virginia has exemptions for personal beliefs that could reduce HPV vaccine coverage, 44 in contrast to Washington, District of Columbia, and Rhode Island, which have no personal beliefs exemptions and had the highest vaccination coverages in our data by 2017. In Washington, District of Columbia, other explanations for high vaccination coverage might be the launch of an HPV initiative in 2013⁴⁵ and new regulations in 2014 requiring parents to submit vaccine exemption claims annually.46 Although Rhode Island initiated the law enactment in 2015, this state provided a school-located vaccination program (Vaccine Before You Graduate program) in 2001 and state-purchased vaccines from 2006 onward, which resulted in a high vaccination rate since 2007.47

State-purchased HPV vaccine programs might have a substantial impact in vaccination coverage for Medicaid beneficiaries. ⁴⁷ Although there has been no law enactment of HPV immunization in North Dakota, the state with the third highest HPV vaccination coverage, the North Dakota Comprehensive Cancer

Control Program successfully implemented school-located clinics to improve HPV immunization in adolescents. We did not observe a clear impact of state-purchased vaccine programs in commercially insured children (Table 1). However, our finding might also be explained by incomplete records of state-purchased vaccines in claims databases, unless the procedure itself was charged to the insurance company.

The nationwide population-based sample used in our study provides an alternative to the traditional approaches to estimate vaccination coverage among commercially insured children in the United States as well as to assess regional differences. Moreover, by using longitudinal data, it is possible to follow-up vaccination uptake over time within each birth cohort to monitor annual changes, project trends, and evaluate policies. In addition, use of health care databases may be more cost-effective in both time and money than ad hoc data collection.

However, this approach has limitations. First, if vaccines are received outside the insurance, they would be missed, which would result in an underestimation of vaccine coverage. Although, unlike HPV, there are no school-based programs, the fact that our infant PCV uptake estimate was ~97% suggests that our data accurately

detect vaccine administrations billed to insurance. Second, our results in commercially insured children may not be representative of the vaccine uptake in uninsured children and in children with Medicaid insurance. Results from the NIS-Teen suggest similar coverage rates among commercially and publicly insured children, whereas the rates are lower among the small proportion of uninsured children.

CONCLUSIONS

In 2017, despite the increasing trends in uptake, HPV vaccine coverage remained behind the Healthy People 2020 goal of 80% by 15 years of age. HPV vaccine coverage differed by state and correlated with vaccination policies. The initially pronounced sex disparities due to the delayed introduction of the vaccine for boys have diminished over time. Most states will not achieve the Healthy People 2020 goal of 80% coverage with at least 2 HPV vaccine doses by 2020.

ABBREVIATIONS

CI: confidence interval HPV: human papillomavirus NIS-Teen: National Immunization Survey-Teen

PCV: pneumococcal conjugate vaccine

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