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# Patterns of Use of Human Papillomavirus and Other Adolescent Vaccines in the United States



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#### ABSTRACT

**Purpose:** The purpose of the study was to describe the patterns of use of universally recommended adolescent vaccines in the United States.

**Methods:** We identified 11-year-olds using the MarketScan insurance claims database (2009–2014). Human papillomavirus (HPV), tetanus-diphtheria-acellular pertussis (Tdap), and meningococcal (MenACWY) vaccination claims were identified using diagnosis and procedure codes. Generalized linear models estimated vaccination incidence rates and correlates of adolescent vaccination and timely vaccination.

**Results:** Among 1,691,223 adolescents, receipt of Tdap (52.1%) and MenACWY (45.8%) vaccinations exceeded receipt of HPV vaccination (18.4%). While both sexes had similar Tdap and MenACWY vaccination proportions, girls received HPV vaccination more frequently than boys (21.9% vs. 15.1%). Adolescents received HPV vaccination later (mean age: 11.8 years) than Tdap or MenACWY vaccination (mean age: 11.2 years for both). Half of vaccinated adolescents received Tdap and MenACWY vaccination only; however, coadministration with HPV vaccine increased with birth cohort. Western adolescents had the highest incidence rates of HPV vaccination, and Southern adolescents had the lowest. Rural adolescents were less likely than urban adolescents to receive each vaccination except in the Northeast, where they were more likely to receive HPV vaccination (incidence rate ratio: 1.09, 95% confidence interval: 1.2005–1.13). Timely HPV vaccination was associated with female sex, urbanicity, Western residence, and later birth cohort.

**Conclusions:** HPV vaccination occurred later than Tdap or MenACWY vaccination and was less frequent in boys and rural adolescents. Girls, Western and urban residents, and younger birth

# IMPLICATIONS AND CONTRIBUTION

This study assessed vaccine coadministration and the dual influence of geography and urbanicity on adolescent vaccination using insurance claims. Access to and demand for vaccines should improved in rural areas, providers should encourage human papillomavirus vaccination and vaccine coadministration to all eligible adolescents.

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**Conflicts of interest:** M.A.B. serves on a scientific advisory panel for Merck & Co. S.B.-D. is receiving an investigator-initiated research award from Pfizer for an unrelated study. J.S.S. has received research grants, served on paid advisory boards, and/or been a paid speaker for GlaxoSmithKline and Merck & Co., Inc. over the past 5 years. The other authors have no conflicts of interest to disclose.

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cohorts were more likely to receive timely HPV vaccination. Vaccine coadministration increased over time and may encourage timely and complete vaccination coverage.

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The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) recommended routine meningococcal conjugate (MenACWY) and tetanus-diphtheria-acellular pertussis (Tdap) vaccination for adolescents at age 11 years, in 2005 and 2006, respectively [1–3]. ACIP subsequently recommended routine human papillomavirus (HPV) vaccination for females aged 11–12 years on June 29, 2006, and for males aged 11–12 years on October 21, 2009 [4–6]. Phase III clinical trials of the prophylactic quadrivalent (4vHPV) and bivalent (2vHPV) HPV vaccines demonstrated over 90% efficacy against high-grade or greater cervical intraepithelial neoplasia (CIN-2+) associated with high-risk HPV (hrHPV) types 16 and 18 [7,8].

Despite ACIP's recommendations and strong evidence for the safety and efficacy of HPV vaccines, receipt of at least one dose of HPV vaccine (56.1%) among boys and girls aged 13—17 years lags behind receipt of Tdap (86.4%) or MenACWY (81.3%) vaccines in the United States, according to the 2016 nationally representative National Immunization Survey-Teen (NIS-Teen) [9].

In the NIS-Teen surveys, parents report their children's vaccination status and their children's vaccination providers are contacted to confirm vaccination status. However, vaccination status might be misclassified if parents do not accurately recall their children's vaccination providers, or if providers have inaccurate vaccination records [10]. Furthermore, the random digit dialing sampling strategy used for NIS-Teen results in low response rates, and the sample may not be generalizable to the U.S. population. Alternatively, insurance claims provide accurate data on adolescent vaccination for millions of individuals, eliminating the need to review medical records and reducing recall and information biases. Furthermore, insurance claims also allow monitoring of coadministration of vaccines on the same service date and trends over time in uptake of different vaccine combinations, which have only been recently reported in two studies using NIS-Teen data [11,12].

Here, we present data from employer-sponsored insurance claims to describe patterns of use of HPV, Tdap, and MenACWY vaccination among vaccine-eligible girls and boys in the United States. Results from this study will identify gaps in vaccination coverage and can inform targeted adolescent vaccination promotion strategies.

#### Methods

# Study population

The MarketScan Commercial Claims and Encounters database captures patient-level medical claims provided by over 300 large employers in all 50 states, the District of Columbia, and Puerto Rico, including over 170 million unique enrollees since 1995 [13]. MarketScan provides patient demographic data, type and duration of health plan enrollment, claims for medical diagnoses and procedures using International Classification of Diseases—Ninth Revision (ICD-9) and Current Procedural Terminology (CPT) codes, respectively, and dates of medical services. We obtained Market-Scan data between 2000 and 2014 from Truven Health Analytics.

The study period began in October 21, 2009—when ACIP supported HPV vaccination for boys—marking the first opportunity for all eligible adolescents to receive all three recommended vaccines. We included girls and boys who (1) turned 11 years of age between 2009 and 2014; (2) had no prior history of adolescent vaccination; and (3) had at least 1 year of continuous insurance plan enrollment before the start of follow-up.

# Data analysis

We began observing adolescents from their 11th birthdays, when they became eligible for adolescent vaccination according to the ACIP recommendations. Because date of birth is protected health information, we searched monthly insurance enrollment files to identify the month in which the adolescent's age changed and then set the date of birth to the last day of that month. We followed adolescents from their estimated 11th birthdays (time 0) until vaccination, disenrollment, or the end of the study period on December 31, 2014.

We searched outpatient records for the first billed claim for 2vHPV (CPT code 90650) or 4vHPV (CPT code 90649), Tdap (CPT code 90715, ICD-9 code 9939), and MenACWY (CPT code 90734). We excluded Tdap claims related to injuries or accidents (ICD-9 codes 037.X, 87X–91X, V01–V02, all E codes) or receipt of antenatal care (ICD-9 codes V22.X–V39.X). While the HPV vaccination series includes multiple doses and MenACWY vaccine requires a booster, we only identified the first dose of each vaccine, as limited follow-up might prevent us from observing subsequent doses. Descriptive statistics summarized service-related characteristics at the time of vaccination, and the combinations of vaccines received by adolescents, including coadministered vaccines.

For each vaccine, we estimated time to vaccination as the difference between time 0 and the date of the first vaccination claim. We estimated total follow-up time as the difference between time 0 and the date of service for adolescents who received vaccination; or the difference between time 0 and the date of disenrollment or the end of the study period for adolescents who did not receive vaccination. We used generalized estimating equations with a Poisson distribution and a robust variance estimator to estimate vaccination incidence rates (IRs) per 10,000 person-months of observation, incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for correlates of vaccination, and IRs of vaccine coadministration over time. IRs and cumulative incidence were stratified by covariates of interest, including sex; region (Northeast, North Central, South, West, per the U.S. Census Bureau [14]); urbanicity, as defined by urban residence (metropolitan statistical area with population >50,000) or rural residence (micropolitan statistical area with population <50,000); receipt of primary care in the year before observation; and insurance plan type. We also plotted the cumulative incidence of receiving the first dose of HPV vaccine at age 11 or 12 years (i.e., timely HPV vaccination), stratified by sex, urbanicity, region, and birth cohort.

As many as 18 states had offered at least one adolescent vaccine free of charge, regardless of income level, since 2006

**Table 1** Incidence of HPV, Tdap, and MenACWY vaccination among adolescents in the MarketScan database, 2009–2014<sup>a</sup>

Incidence of vaccination	Overall (n = 1,691,223)	Girls (n = 822,554)	Boys (n = 868,669)
Median duration (IQR) of follow-up, months	16.1 (7.1-31.2)	16.1 (7.1-31.2)	16.1 (7.1–31.2)
Cumulative incidence (incidence proportion) of adolescent vaccination			
Any vaccination	948,995 (56.1%)	467,355 (56.8%)	481,640 (55.5%)
HPV vaccination	311,110 (18.4%)	180,373 (21.9%)	130,737 (15.1%)
Tdap vaccination	880,586 (52.1%)	431,814 (52.5%)	448,772 (51.7%)
MenACWY vaccination	774,132 (45.8%)	378,377 (46.0%)	395,755 (45.6%)
	Overall (n = 948,995)	Girls (n = 467,355)	Boys (n = 481,640)
Mean age (SD) at first adolescent vaccination	11.5 (.8)	11.5 (.8)	11.5 (.8)
HPV vaccination (n = 311,110)	11.8 (1.0)	11.7 (1.0)	12.0 (1.1)
Tdap vaccination ( $n = 880,586$ )	11.2 (.5)	11.2 (.5)	11.3 (.5)
MenACWY vaccination (n = 774,132)	11.2 (.6)	11.3 (.6)	11.3 (.6)

IQR = interquartile range; HPV = human papillomavirus vaccine; MenACWY = meningococcal conjugate vaccine; Tdap = tetanus-diphtheria-acellular pertussis vaccine; SD = standard deviation.

(Alaska, Connecticut, Hawaii, Idaho, Massachusetts, Maine, Nevada, New Hampshire, New Mexico, North Carolina, North Dakota, Oregon, Rhode Island, South Dakota, Vermont, Washington, Wisconsin, and Wyoming) [15]. Adolescents from these states may have received vaccination without filing insurance claims, and thus, their vaccination status would not be ascertained from MarketScan data. We conducted a sensitivity analysis excluding these states to assess potential bias due to underascertainment of vaccination status.

Analyses were performed in SAS 9.3 (Cary, NC). Proportional Venn diagrams were created using the eulerAPE application (Canterbury, UK) [16]. The University of North Carolina Office of Human Research Ethics approved this study.

# Results

The analytic cohort included 1,691,223 adolescents: 822,544 girls and 868,669 boys. The median duration of follow-up was 16 months (interquartile range, 7–31 months) (Table 1). We observed at least one adolescent vaccination for 948,995 adolescents (56.1%) during the observation period. Of the 922,137 adolescents who were enrolled until the end of the study period on December 31, 2014, 66.7% of them received any adolescent vaccination; of the 769,086 adolescents who disenrolled during follow-up, 43.4% of them received any adolescent vaccination. Similar percentages of girls and boys received Tdap and Men-ACWY; however, the proportion of adolescents receiving HPV vaccination was higher in girls than boys (21.9% vs. 15.1%; Table 1). Mean age at receipt of the first dose of HPV vaccine (11.8 years) was higher than that for Tdap and MenACWY (11.2 years for both), and girls received HPV vaccination relatively earlier than boys (mean age 11.7 years vs. 12.0 years). Among adolescents who received any vaccination, over 96% received Tdap or MenACWY vaccination within the ACIP-recommended age range. In contrast, 81% of girls and 72% of boys received HPV vaccination within the ACIP-recommended age range (Table A1).

One quarter of adolescents who received any vaccination received all three recommended vaccines; 50.6% received Tdap and MenACWY only (Figure 1). For adolescents who received Tdap and MenACWY vaccination only, 92.3% received both concomitantly at their initial adolescent vaccination visit. However, only 24.1% of adolescents who received all three vaccinations received them concomitantly at the initial vaccination visit. Coadministration IRs of Tdap + MenACWY were higher than

those for HPV + Tdap + MenACWY in each birth cohort, although IRs of both coadministration combinations increased steadily with each successive birth cohort (Figure A1).

The IRs of HPV, Tdap, and MenACWY vaccination were lower in rural adolescents than urban adolescents (Table 2). The highest HPV vaccination IRs were observed in the West (117.2, 95% CI: 116.3—118.0), and the lowest HPV vaccination IRs were observed in the South (91.3, 95% CI: 90.8—91.9). The West region had the lowest IRs of Tdap (IR: 404.7, 95% CI: 404.2—407.1) and MenACWY (IR: 299.7, 95% CI: 297.8—301.5) vaccination. The IRs of all vaccinations were lowest among adolescents with comprehensive insurance plans, and adolescents who had received any primary care in the year before the start of observation had higher IRs of all vaccinations than those without a primary care visit (Table 2).

Overall, rural adolescents had lower IRs than urban adolescents of HPV (IRR: .76, 95% CI: .75—.77), Tdap (IRR: .58, 95% CI: .57—.58), and MenACWY vaccination (IRR: .53, 95% CI: .53—.54) (Table 3). Rural adolescents in the North Central, South, and West regions were less likely than urban adolescents to receive HPV vaccination, whereas adolescents in the Northeast were more likely to receive HPV vaccination (IRR: 1.09, 95% CI: 1.05—1.13) (Table 3).

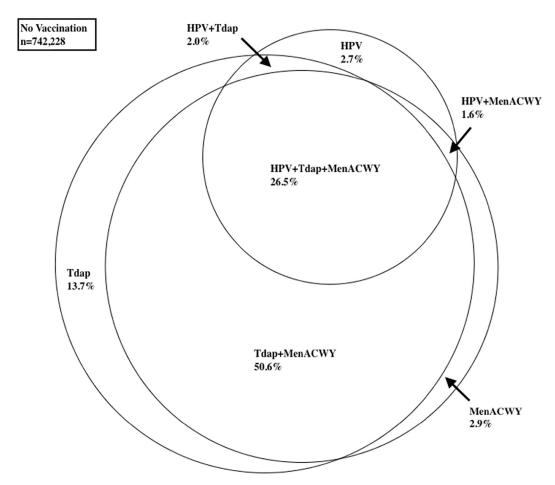
The cumulative incidence of timely HPV vaccination differed across subgroups (Figure 2). Timely HPV vaccination was more frequent in girls versus boys, regardless of the time since start of follow-up. Adolescents residing in urban areas had a higher incidence of timely vaccination than adolescents residing in rural areas, and adolescents in the West had higher incidence of timely HPV vaccination than adolescents in the Northeast, North Central, or South regions. With more recent birth cohort, the cumulative incidence of timely HPV vaccination increased incrementally (Figure 2).

After repeating these analyses excluding the 18 states that offered free universal adolescent vaccine coverage, we observed comparable vaccination proportions, vaccination combinations, and stratified IRs of vaccination. None of the interpretations of our findings were changed.

#### Discussion

Among 1.7 million vaccine-eligible adolescents with employer-sponsored insurance in the United States, we observed relatively lower IRs of HPV vaccination than Tdap or MenACWY

<sup>&</sup>lt;sup>a</sup> Eligible 11-year-olds are those who are continuously enrolled in an insurance plan as of the midpoint of their 11th year and had not previously received HPV/Tdap/MenACWY vaccines. The Advisory Committee on Immunization Practices recommends all three vaccines beginning at age 11 years.



**Figure 1.** Incidence proportions of HPV, Tdap, and MenACWY combinations received (n = 948,995). Combinations of vaccinations received among adolescents who received any vaccination during follow-up. The combinations represent all vaccinations received during follow-up, regardless of receipt in the same or separate clinic visits.

vaccination in girls and boys. Furthermore, HPV vaccination was more often delayed beyond the 11- to 12-year age range universally recommended by ACIP compared with Tdap and Men-ACWY vaccination. For all three recommended vaccines, rural adolescent residents were consistently less likely to be vaccinated than their urban counterparts in all geographical regions (South, Northeast, and West) except in the Northeast. Our data also suggest birth cohort effects for coadministration of all three recommended vaccines, suggesting increased use of coadministration over time and increased integration of HPV into the adolescent vaccination package over time.

Similar to other studies, our data indicate that adolescents have frequent missed opportunities for HPV vaccination, namely clinic visits in which Tdap and/or MenACWY vaccines were administered [17]. In our sample, although over half of adolescents had initiated adolescent vaccination, most adolescents had not received HPV vaccination by the end of follow-up. Of those who did, 23% received HPV vaccination outside of the ACIP-recommended age range (Table A1). The National Health and Nutrition Examination Survey found that 43% of adolescents initiated HPV vaccination after or in the same year as sexual debut, increasing their risk for prevaccination HPV exposure [18]. While ACIP recommends catch-up vaccination for adolescents older than 12 years, HPV vaccine effectiveness is highest before sexual debut [19]. Among 1,139 inner-city adolescent women in

New York City, receiving HPV vaccination after age 15 years was associated with an increased hazard of high-grade cervical lesions relative to receiving vaccination before age 15 years [20]. Thus, it is critical that providers recommend HPV vaccination in boys and girls at the earliest opportunity, including sick visits and visits for other adolescent vaccinations.

Our study found that rural adolescents in the Northeast had higher IRs of HPV vaccination than their urban counterparts, although rural adolescents overall had lower IRs of vaccination with all three adolescent vaccines. The increase in HPV vaccination that we observed in rural, Northeastern adolescents could simply be a function of the smaller size of this region and fewer access barriers to vaccination for rural adolescents. Future research should identify specific barriers to vaccination in rural areas, besides economic factors, and differences in these factors by region. Provider factors in rural areas may influence whether they recommend HPV vaccination for their adolescent patients [21]. A study comparing HPV vaccination recommendation behavior among 334 pediatricians in Appalachian and non-Appalachian counties of Kentucky and West Virginia found that Appalachian pediatricians were less likely to recommend HPV vaccination to their adolescent patients [22]. Furthermore, rural adolescents are more likely to receive care from a family physician rather than a pediatrician and thus may be less likely to receive recommendations for HPV vaccination [23]. All provider

**Table 2** Incidence rates per 10,000 person-months of HPV, Tdap, and MenACWY vaccination among adolescents by selected characteristics, 2009–2014 (n = 1,691,223)

	<u> </u>	<u> </u>	
	HPV	Tdap	MenACWY
	IR (95% CI)	IR (95% CI)	IR (95% CI)
Metropolitan statistical area			
Urban ( $n = 1,423,989$ )	103.9 (103.5-104.2)	527.5 (526.0-528.9)	414.9 (413.7-416.1)
Rural $(n = 231,792)$	78.8 (77.9–79.6)	304.5 (302.3-306.8)	221.8 (220.0-223.6)
Missing (n = 35,442)			
Region of residence			
Northeast $(n = 247,991)$	104.3 (103.4-105.2)	685.3 (680.3-690.3)	526.8 (532.1-530.6)
North Central ( $n = 426,605$ )	99.3 (98.7-100.0)	542.8 (540.1-545.4)	417.2 (415.0-419.3)
South $(n = 637,009)$	91.3 (90.8-91.8)	446.9 (445.1-448.7)	364.1 (362.5-365.7)
West (n = 343,161)	117.2 (116.3–118.0)	404.7 (402.4-407.1)	299.7 (297.8-301.5)
Missing $(n = 36,457)$			
Insurance plan type			
Preferred provider plan ( $n = 1,043,991$ )	96.8 (96.4-97.3)	484.5 (482.9-486.1)	373.4 (372.2-374.7)
Comprehensive ( $n = 18,649$ )	81.5 (78.9-84.3)	423.4 (412.5-434.6)	330.5 (321.8-339.4)
Managed care plan $(n = 332,193)$	109.5 (108.8-110.3)	458.8 (456.1-461.5)	364.6 (362.4-366.8)
High deductible plan ( $n = 244,662$ )	105.5 (104.6-106.3)	575.2 (571.5-579.0)	454.0 (451.0-457.0)
Missing (n = 51,728)			
Received primary care in the past year			
No (n = 1,493,373)	98.4 (98.1-98.8)	472.6 (471.4-473.9)	368.0 (366.9-369.0)
Yes (n = 197,850)	119.8 (118.7–120.9)	676.3 (671.4–681.2)	533.9 (530.0-537.9)

CI = confidence interval; HPV = human papillomavirus vaccine; IR = incidence rate; MenACWY = meningococcal conjugate vaccine; Tdap = tetanus-diphtheria-acellular pertussis vaccine.

types who treat adolescents are encouraged to use messages developed by the Centers for Disease Control and Prevention to recommend HPV vaccination to eligible adolescents. In a national sample, Centers for Disease Control and Prevention messages pertaining to the high prevalence of HPV infection, the importance of HPV vaccination for cancer prevention, and the efficacy of HPV vaccination were acceptable to caregivers who were reticent to vaccinate their adolescents [24].

Studies of caregivers' attitudes toward HPV vaccination reveal concerns about vaccine safety and effectiveness, low perception of risk for HPV infection, and unwillingness to vaccinate adolescents who presumably are not sexually active against a sexually transmitted infection [25–27]. Adolescent health care providers should actively communicate the evidence-based vaccination benefits to caregivers, particularly in regions that have low HPV vaccination coverage. In addition, enhancing health care practices to facilitate vaccination can effectively increase HPV vaccination initiation. In a cluster randomized trial in Pennsylvania pediatric

and family medicine practices, the 4 Pillars Practice Transformation Program, which promotes strategies such as patient notification for vaccination and establishing HPV vaccination champions in practices, was associated with greater increases in HPV vaccination initiation compared with control practices [28].

Our primary limitation is the short follow-up time (median 16 months) to observe vaccination receipt, preventing us from observing vaccination events that occurred after the end of follow-up. As a result, our longitudinal study yielded smaller vaccination incidence proportions than the vaccination coverage rates reported by NIS-Teen, which used cross-sectional methods. We were also limited to reporting only the first instance of HPV and MenACWY vaccination to avoid drawing invalid conclusions about the completion of these vaccination series. Second, there is a chance of misclassification of vaccination status due to the use of incorrect or alternate CPT or ICD-9 codes. We attempted to use all relevant vaccination codes to minimize underascertainment of vaccination receipt. However, MarketScan is not able to track all

**Table 3** Incidence rate ratios for the association of urbanicity with HPV, Tdap, and MenACWY vaccination among eligible adolescents, stratified by region, 2009–2014

	HPV	Tdap	Men
	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
All Regions (n = 1,655,781) <sup>a</sup>			
Urban	1.0 (ref)	1.0 (ref)	1.0 (ref)
Rural	.76 (.75–.77)	.58 (.5758)	.53 (.5354)
Northeast $(n = 247,991)$			
Urban	1.0 (ref)	1.0 (ref)	1.0 (ref)
Rural	1.09 (1.05-1.13)	.86 (.8488)	.79 (.7782)
North Central $(n = 426,605)$			
Urban	1.0 (ref)	1.0 (ref)	1.0 (ref)
Rural	.76 (.74–.77)	.50 (.4950)	.46 (.4647)
South $(n = 637,009)$			
Urban	1.0 (ref)	1.0 (ref)	1.0 (ref)
Rural	.77 (.75–.78)	.60 (.5960)	.55 (.5456)
West $(n = 343,161)$			
Urban	1.0 (ref)	1.0 (ref)	1.0 (ref)
Rural	.68 (.66–.71)	.55 (.54–.57)	.46 (.45–.47)

CI = confidence interval; HPV = human papillomavirus vaccine; IRR = incidence rate ratio; MenACWY = meningococcal conjugate vaccine; Tdap = tetanus-diphtheria-acellular pertussis vaccine.

<sup>&</sup>lt;sup>a</sup> 35,442 observations missing region status.

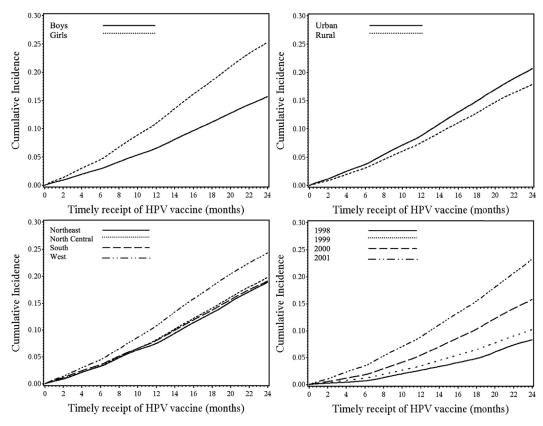


Figure 2. Cumulative incidence of timely HPV vaccination at age 11-12 years, by selected characteristics (n = 1,691,223). Cumulative incidence curves for HPV vaccination within the ACIP-recommended age range, showing differences in timely HPV vaccination, stratified by sex, urbanicity, region, and birth cohort.

enrollees who switch between insurance plans, and thus, historical vaccination data for adolescents who changed insurance might not be recognized. Third, because MarketScan represents employer-sponsored insurance claims, our results may not be generalizable to Medicaid and uninsured populations. We also are unaware of how many MarketScan enrollees are Medicaid eligible and might receive vaccination through channels that bill Medicaid. However, we observed comparable vaccination proportions and IRs after excluding states that offer free adolescent vaccination, indicating that vaccination patterns are similar between adolescents with access to free vaccination and those without. These analyses should be replicated in Medicaid data to identify any disparities in vaccination patterns by insurance source. The Affordable Care Act of 2010 guarantees that immunizations are covered under all insurance plans [29]. Deductible and other payment factors or provider selection factors, however, may influence vaccination decisions. Future research should assess the impacts of insurance coverage on adolescent vaccination. Finally, MarketScan lacks data on race and ethnicity, and we cannot know the degree to which regional differences are influenced by racial or ethnic variation in vaccination patterns.

The strengths of this analysis include a large sample of adolescents in the United States and minimally biased documentation of vaccine receipt. In identifying nearly one million vaccinated adolescents, we had sufficient power to identify correlates of vaccination status with precision. Using procedure and diagnosis codes from a large insurance claims database, we estimated vaccination IRs beginning at the age recommended by ACIP, allowing us to assess vaccination timeliness. We also made

robust estimates of vaccination incidence using methods that account for differential follow-up times and censoring.

Recent changes to HPV vaccine availability and recommendations may improve the uptake and impact of this vaccine. A nine-valent vaccine (9vHPV) preventing the seven hrHPV types most highly associated with CIN-2+ was approved by the U.S. Food and Drug Administration in December 2014 and recommended by ACIP for 11- and 12-year-olds in March 2015 [30,31]. This broad-coverage prophylactic vaccine promises to prevent even more cases of CIN-2+ attributed to hrHPV types when administered in a timely fashion. Future research can use MarketScan to monitor patterns of use of 9vHPV relative to 4vHPV and 2vHPV, and its concomitant use with Tdap and MenACWY. In addition, following a review of immunogenicity and effectiveness data, ACIP recommended in December 2016 that the HPV vaccination series be reduced to two doses from three for adolescents who vaccinate before age 15 years [32]. This new recommendation may increase the acceptability of HPV vaccination due to a lower burden of clinic visits; reduce safety concerns associated with multiple doses of HPV vaccination; and simplify medical record keeping and vaccination status monitoring.

Offering HPV, Tdap, and MenACWY as a comprehensive adolescent vaccination package could increase HPV vaccination to the same levels as Tdap and MenACWY. Safety and immunogenicity research supports coadministration of HPV, Tdap, and MenACWY, and ACIP recommends coadministration of all three vaccines at age 11 or 12 years [33,34]. HPV vaccination trends are encouraging, as indicated by more timely HPV vaccination and coadministration of all three recommended adolescent vaccines

among adolescents born more recently. However, adherence to ACIP recommendations for HPV vaccination timing and HPV vaccination in boys remains particularly suboptimal. Providers can educate caregivers about the benefits of vaccination, including information about recent disease outbreaks due to poor vaccine coverage. Providers should also avoid creating exceptions for HPV vaccination, stressing that all adolescent vaccines are safe, effective, and appropriate for 11- and 12-year-old girls and boys, unless contraindicated. Demand for and access to HPV vaccination for adolescents in rural areas must be improved, and early and concomitant vaccination can reduce the burden of adolescent preventive care in harder-to-reach areas.

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# **Supplementary Data**

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jadohealth.2017.05.016.

# References

- [1] Bilukha O, Rosenstein N. Prevention and control of meningococcal disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Morb Mortal Wkly Rep 2005;54(RR07):1–21.
- [2] Broder K, Cortese M, Iskander J, et al. Preventing tetanus, diphtheria, and pertussis among adolescents: Use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Morb Mortal Wkly Rep 2006;55(RR03):1—34.
- [3] U.S. Centers for Disease Control and Prevention. Recommended immunization schedules for persons aged 0 through 18 years, United States, 2017. Atlanta, GA. Available at: http://www.cdc.gov/vaccines/hcp/acip-Recs/index.html www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html. Accessed September 19, 2016.
- [4] Markowitz LE, Dunne EF, Saraiya M, et al. Quadrivalent human papillomavirus vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Morb Mortal Wkly Rep 2007;56(RR-2):1–24.
- [5] Centers for Disease Control and Prevention (CDC). FDA licensure of quadrivalent human papillomavirus vaccine (HPV4, gardasil) for use in males and guidance from the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2010;59:630—2.
- [6] Dunne EF, Markowitz LE, Chesson H, et al. Recommendations on the use of quadrivalent human papillomavirus vaccine in males — Advisory Committee on Immunization Practices (ACIP), 2011. MMWR Morb Mortal Wkly Rep 2011;60:1705–8.
- [7] Harper DM, Franco EL, Wheeler C, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: A randomised controlled trial. Lancet 2004;364:1757–65.
- [8] The FUTURE II Study Group. Prophylactic efficacy of a quadrivalent human papillomavirus (HPV) vaccine in women with virological evidence of HPV infection. J Infect Dis 2007;196:1438–46.

- [9] Reagan-Steiner S, Yankey D, Jeyarajah J, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13–17 years — United States, 2015. MMWR Morb Mortal Wkly Rep 2016;65:850–8.
- [10] Elam-Evans L, Yankey D, Jeyarajah J, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13–17 years United States, 2013. Morb Mortal Wkly Rep 2014;63:625–33.
- [11] Moss JL, Reiter PL, Brewer NT. Concomitant adolescent vaccination in the U.S., 2007–2012. Am J Prev Med 2016;51:693–705.
- [12] Moss JL, Reiter PL, Rimer BK, et al. Summer peaks in uptake of human papillomavirus (HPV) and other adolescent vaccines in the United States. Cancer Epidemiol Biomarkers Prev 2016;25:274–81.
- [13] Quint J. Health Research Data for the Real World: The MarketScan(R) Databases. Ann Arbor, MI: Truven Health Analytics; 2015.
- [14] U.S. Census Bureau. Geographic Terms and Concepts Census Divisions and Census Regions. Available at: https://www.census.gov/geo/reference/gtc/ gtc\_census\_divreg.html. Published 2015. Accessed April 26, 2017.
- [15] Centers for Disease Control and Prevention (CDC). VFC childhood vaccine supply Policy 2006. Available at: http://www.cdc.gov/vaccines/programs/vfc/ about/vac-supply-policy/. Published 2007. Accessed September 19, 2016.
- [16] Micallef L, Rodgers P. eulerAPE: Drawing Area-Proportional Euler and Venn Diagrams using Ellipses. Available at: http://www.eulerdiagrams.org/ eulerAPE/. Published 2014. Accessed January 24, 2017.
- [17] Dunne EF, Stokley S, Chen W, Zhou F. Human papillomavirus vaccination of females in a large health claims database in the United States, 2006–2012. J Adolesc Health 2015;56:408–13.
- [18] Petrosky EY, Liu G, Hariri S, Markowitz LE. Human papillomavirus vaccination and age at first sexual activity, National Health and Nutrition Examination Survey. Clin Pediatr (Phila) 2017;56:363—70.
- [19] Markowitz LE, Dunne EF, Saraiya M, et al. Human papillomavirus vaccination recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2014;63:1–30.
- [20] Schlecht NF, Diaz A, Shankar V, et al. Risk of delayed HPV vaccination in inner-city adolescent women. J Infect Dis 2016;214:1952—60.
- [21] Rural Health Research & Policy Centers. Challenges for improving health care access in rural America: A compendium of research and policy analysis studies of rural health research and policy analysis centers. 2010. Available at: https://www.ruralhealthinfo.org/pdf/research\_compendium .pdf. Accessed September 19, 2016.
- [22] Krieger J, Katz M, Kam J, Roberto A. Appalachian and non-appalachian pediatricians' encouragement of the human papillomavirus vaccine: Implications for health disparities. Women's Heal Issues 2012;22:e19–26.
- [23] Mohammed KA, Geneus CJ, Osazuwa-Peters N, et al. Disparities in provider recommendation of human papillomavirus vaccination for U.S. adolescents. I Adolesc Health 2016;59:592—8.
- [24] Malo TL, Gilkey MB, Hall ME, et al. Messages to motivate human papillomavirus vaccination: National studies of parents and physicians. Cancer Epidemiology, Biomarkers Prev 2016;25:1383–91.
- [25] Chan ZCY, Chan TS, Ng KK, Wong ML. A systematic review of literature about women's knowledge and attitudes toward human papillomavirus (HPV) vaccination. Public Health Nurs 2012;29:481—9.
- [26] Trim K, Nagji N, Elit L, Roy K. Parental knowledge, attitudes, and behaviours towards human papillomavirus vaccination for their children: A systematic review from 2001 to 2011. Obstet Gynecol Int 2012;2012:921236.
- [27] Holman DM, Benard V, Roland KB, et al. Barriers to human papillomavirus vaccination among US adolescents: A systematic review of the literature. JAMA Pediatr 2014;168:76–82.
- [28] Zimmerman RK, Moehling KK, Lin CJ, et al. Improving adolescent HPV vaccination in a randomized controlled cluster trial using the 4 Pillars practice Transformation Program. Vaccine 2017;35:109–17.
- [29] U.S. Department of Health and Human Services. Affordable Care Act. Available at: http://www.hhs.gov/healthcare/about-the-law/read-the-law/. Published 2015. Accessed September 19, 2016.
- [30] U.S. Food and Drug Administration. Gardasil 9. Available at: http://www .fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm426445 .htm. Published 2016. Accessed September 19, 2016.
- [31] Petrosky E, Bocchini JA, Hariri S, et al. Use of 9-valent human papillomavirus (HPV) vaccine: Updated HPV vaccination recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep 2015;64:300–4.
- [32] Meites D, Kempe A, Markowitz L. Use of a 2-dose schedule for human papillomavirus vaccination — updated recommendations of the Advisory Committee on Immunization Practices. Morb Mortal Wkly Rep 2016;65: 1405—8.
- [33] Reisinger KS, Block SL, Collins-Ogle M, et al. Safety, tolerability, and immunogenicity of gardasil given concomitantly with Menactra and Adacel. Pediatrics 2010;125:1142–51.
- [34] Wheeler CM, Harvey BM, Pichichero ME, et al. Immunogenicity and safety of human papillomavirus-16/18 ASO4-adjuvanted vaccine coadministered with tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine and/or meningococcal conjugate vaccine to healthy girls 11 to 18 years of age: R. Pediatr Infect Dis J 2011;30:e225–34.