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Impact of state legislation of human papillomavirus vaccination on vaccine uptake among adolescents in the United States

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Abstract

Purpose: We assessed the impact of state legislation on adolescent human papillomavirus (HPV) vaccination rates in states that legislated information dissemination or administration of HPV vaccination.

Methods: Using insurance claims, we calculated monthly HPV vaccination rates (November 2009 – December 2017) among adolescents in states that passed HPV vaccination legislation during that period: Missouri (July 2010), Kentucky (February 2012), Indiana (March 2013), Oregon (June 2013). We used segmented regression to estimate levels and trends of HPV vaccination rates, comparing pre-legislation to post-legislation segments, adjusting for seasonal vaccination patterns and changes to the vaccination recommendation among males during the study period. States with significant post-legislation changes in HPV vaccination rates were compared to control states without HPV vaccination legislation.

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Results: Indiana's legislation allowed pharmacists to administer HPV vaccination; legislation in Kentucky, Missouri, and Oregon included provisions HPV and cervical cancer education. No statistically significant increases in HPV vaccination levels or trends were observed in the post-legislation segments among adolescents overall; however, a significant post-legislation increase in vaccination trends was observed among boys in Missouri (β=0.16, p=0.03).

Conclusions: Evidence for a positive impact of legislation on HPV vaccination rates is limited. The scarcity of policies that directly facilitate or promote HPV vaccination, and the breadth of exemptions to school vaccination requirements, may limit the effectiveness of these policies. Continuing efforts to introduce and pass legislation that directly facilitates HPV vaccination, combined with promoting existing evidence-based interventions, can provide opportunities to identify the most effective strategies to increase adolescent HPV vaccination rates.

Keywords

human papillomavirus; vaccination; adolescents; legislation; policy; time series analysis; segmented regression

Introduction

Human papillomavirus (HPV) vaccines are universally recommended by the United States Advisory Committee on Immunization Practices (ACIP) for adolescents at age 11–12, along with tetanus-diphtheria-acellular pertussis (Tdap) and meningococcal conjugate (MenACWY) vaccination [1]. Even though HPV vaccination rates in the United States (U.S.) have gradually increased since their introduction in 2006, uptake of HPV vaccination remains lower than the uptake of Tdap and MenACWY [2]. In 2017, the national coverage of HPV vaccination initiation (i.e. receipt of the first dose of HPV vaccine) was only 66%, which falls short of the Healthy People 2020 target goal of 80% for receipt of two or three doses as recommended [2, 3]. Disparities also exist in vaccine uptake, as HPV vaccination rates are lower among boys and adolescents living in rural areas of the U.S., compared to girls and urban adolescents [4].

As of 2018, 49 states and the District of Columbia (D.C.) require Tdap vaccination and 28 states and D.C. require MenACWY vaccination for middle school entry [5, 6]. However, only Rhode Island, Virginia, and D.C. require HPV vaccination for middle school entry, and the latter two allow broad philosophical and religious exemptions to HPV vaccination [7, 8]. These factors may contribute to reduced uptake of HPV vaccination compared to Tdap and MenACWY.

While school requirements for HPV vaccination are uncommon, some states have enacted legislation relating to HPV vaccination in other ways. These laws include education requirements in schools about cervical cancer and HPV vaccination in schools, requiring insurance coverage of HPV vaccination, and allowing pharmacists to administer HPV vaccination [9, 10]. However, there is limited evidence that such legislation has contributed to increased rates of HPV vaccination among adolescents living in those states [11–13]. To better understand the association of passage of state legislation on HPV vaccination rates, we used employer-sponsored insurance claims data to assess temporal trends in HPV vaccination rates, changes in levels and trends in HPV vaccination following the passage of HPV vaccination legislation, and differences in HPV vaccination rates by sex and urbanicity in selected U.S. states.

Methods

Data sources

The IBM® MarketScan Research Database® ("MarketScan") captures the insurance claims of over 200 million employer-sponsored insurance beneficiaries in the U.S. and territories since 1995. MarketScan includes basic demographic details of enrollees, diagnosis codes, and procedure codes pertaining to healthcare encounters, and unique enrollee identification numbers allow linkages between enrollment details and insurance claim details. We accessed MarketScan insurance claims between 2009 and 2017, as described previously [4].

We abstracted a comprehensive list of state bills related to HPV vaccination between 2009 and 2017 from LexisNexis, the National Conference of State Legislatures website, and state legislative websites using search criteria to yield results pertaining to cervical cancer and/or HPV: (("cerv!" w/3 cancer w/3 vaccin!) OR "human papillomavirus" OR "human papilloma virus" OR "HPV) [14, 15]. Each bill was reviewed and the details of proposed HPV vaccination legislation were summarized (e.g. inclusion of a school entry requirement for HPV vaccination; provisions for cervical cancer and/or HPV vaccination education in school and in healthcare settings; and payment mechanisms for HPV vaccination). Seven states introduced, and five states passed, bills during the study period between November 2009 and December 2017: Indiana, Kentucky, Missouri, Oregon, and Hawaii. Due to the small sample size of Hawaiian adolescents in MarketScan, small number of insurance claims for HPV vaccination, and only eight months of post-legislation follow-up in Hawaii [15], we excluded this intervention state from analysis. Primary analyses were restricted to the remaining four states (hereafter referred to as intervention states).

Study design and study population

We conducted a retrospective cohort study of HPV vaccination among adolescents in the intervention states, calculating monthly HPV vaccination rates after ACIP recommended HPV vaccination for boys and girls in October 2009. Observation began November 1, 2009 and ended December 31, 2017. We identified adolescents with an estimated 11th birthday during this period and followed them from the month of the 11th birthday until the month of their first insurance claim for bivalent (2vHPV), quadrivalent (4vHPV), or nine-valent (9vHPV) HPV vaccination (Current Procedural Terminology codes 90650, 90649, and 90651, respectively). Adolescents who did not receive HPV vaccination during the study period were administratively censored at the end of the study period. Our final analytic cohort included 11-year-old boys and girls who had not received HPV vaccination by the 11th birthday; who had at least one year of continuous enrollment in their insurance plans prior to the 11th birthday; and who lived in the same intervention state for their entire enrollment period. We derived urban or rural residence based on the metropolitan statistical area (MSA) of residence indicated for each adolescent.

Data analysis

We calculated monthly HPV vaccination rates as the number of HPV vaccinations administered in a given month, divided by the number of adolescents enrolled in that month who had not yet received HPV vaccination. We plotted monthly rates stratified by sex (girls versus boys) and urbanicity (urban versus rural). Urban residence was defined by an MSA with population ≥50,000 and rural residence was defined by an MSA with population <50,000.

Next, we used a segmented linear regression model to estimate trends in HPV vaccination rates relative to the passage of HPV vaccination legislation. Briefly, segmented linear regression estimates changes in the level and trend of HPV vaccination, comparing the periods before and after the passage of legislation (i.e. segments) [16]. We estimated a multivariable model for each intervention state with monthly HPV vaccination rate as the outcome, and month of observation (1–98), time segment (pre- or post-legislation), and time since passage of the legislation (in months) as model predictors. First, we estimated the overall trend in HPV vaccination rates over the study period, November 2009 – December 2017 (β_1). To estimate changes in the level of HPV vaccination (i.e. a sudden increase or decrease in the rates from the pre- to post-legislation segment, β_2), we categorized each month of observation into the pre- or post-legislation segment; the month in which the legislation was passed was considered pre-legislation. To estimate changes in the trend of HPV vaccination rates (i.e. the slope of the rates in the post-legislation segment, β_3), we created a continuous variable to represent time in months since passage of the legislation; months in the pre-legislation segment were coded as 0. The final models were adjusted for seasonal trends in HPV vaccination using transformed sine and cosine functions of the vaccination rates [16], and for the change in the CDC recommendation from “permissive” to “routine” vaccination of males in December 2011 [17]. The recommendation change was modeled as an additional intervention using the methods described above and by Wagner and colleagues [18]. We used the Wald chi-squared test to determine the statistical significance of each covariate at α=0.05.

Analysis of de-identified existing data was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill, and a MarketScan data use agreement was approved by the Cecil G. Sheps Center for Health Services Research. All analyses were conducted in SAS 9.3 (SAS Institute, Cary, North Carolina).

Results

Monthly adolescent vaccination rates among adolescents in all states and territories increased significantly from November 2009 to December 2017 (Figure 1). During this period, the Missouri, Kentucky, Indiana, and Oregon state legislatures passed legislation regarding HPV vaccination and had sufficient data in MarketScan for analysis (Table 1). Indiana’s HB 1464 allowed pharmacists to administer HPV vaccination, whereas Missouri’s HB 1375 and Oregon’s SB 722 included provisions for increasing awareness of HPV infection and HPV-associated cancers, and awareness of the CDC’s recommendation for HPV vaccination (Table 1). Kentucky’s HR 80 was a resolution urging HPV vaccination for age-eligible individuals but defined no specific policy measures. None of the bills required HPV vaccination for school entry

In each intervention state, we identified the following numbers of unvaccinated adolescents from November 2009 to December 2017: Missouri=53,635; Kentucky=42,592; Indiana=80,648; Oregon=28,481. The numbers of eligible adolescents enrolled in each state, by year and by analytic segment, are shown in the Appendix. The post-legislation follow-up time (in months) for each state was: Missouri=89; Kentucky=70; Indiana=57; Oregon=54. In the four intervention states analyzed, we observed a seasonal trend in HPV vaccination rates, with peaks occurring in July or August of each year (Figures 2 and 3). We did not observe any sudden changes in vaccination rates in the months following passage of legislation in the intervention states, aside from seasonal peaks (Figures 2 and 3).

Stratifying by sex, we observed higher HPV vaccination rates among girls than boys, particularly in the first half of the study period (Figure 2). However, in all intervention states we observed an increase in HPV vaccination rates among boys, with all states achieving comparable rates for both sexes by the end of the study period (Figure 2). Stratifying by urbanicity, we observed that urban and rural adolescents had comparable HPV vaccination rates in Indiana and Kentucky, but urban adolescents appeared to have higher HPV vaccination rates than rural adolescents in Missouri and Oregon (Figure 3).

For each intervention state, segmented regression coefficients are displayed in Table 2. From November 2009 to December 2017, all intervention states showed positive changes in the trends in HPV vaccination rates between the pre- and post-legislation segments (β_3), but these were not statistically significant. We observed a significant positive change in the HPV vaccination trends among boys in Missouri in the post-legislation segment, after adjustment for seasonality and the change in the CDC’s recommendation for vaccination in males ($p=0.03$) (Table 2). No significant changes were observed among girls, nor among the subsets of urban or rural adolescents.

Discussion

From November 2009 to December 2017, we observed an increasing trend in HPV vaccination rates at the national level. Missouri, Kentucky, Indiana, and Oregon had passed legislation pertaining to HPV vaccination during the study period, though only Indiana implemented a policy that directly impacted vaccine delivery (i.e. allowing pharmacists to administer HPV vaccination). Rural adolescents had comparable or lower HPV vaccination rates than urban adolescents in all intervention states from November 2009 to December 2017. Girls generally had higher rates of HPV vaccination than boys, although we observed a significant increase in vaccination trends following the passage of legislation among boys in Missouri. Among adolescents overall, however, we identified no positive trends in HPV vaccination rates in any of the intervention states that were associated with the passage of HPV vaccination legislation. Our findings suggest that observed trends in HPV vaccination rates may be influenced by other factors.

The National Immunization Survey-Teen (NIS-Teen) has shown positive trends in annual HPV vaccination coverage (receipt of ≥1 doses of HPV vaccine) among adolescents ages 13–17 from 2009 to 2017. NIS-Teen also corroborates our findings that and urban adolescents tend to have higher uptake than rural adolescents, and, while girls tend to have higher vaccination uptake than boys, vaccine uptake among boys is trending upward [2]. NIS-Teen showed annual increases in HPV vaccination coverage in each of the intervention states, with some fluctuations between years, and with Oregon having higher coverage than the other states [19]. Our monthly vaccination rates are not directly comparable to coverage estimates, as they are contingent on insurance enrollment, and while we observed a nationwide increase in HPV vaccination rates over the study period, not all intervention states followed this trend. This could be a result of lapses in insurance enrollment, after which study participants were censored and insurance claims for HPV vaccination may not have been observed.

All intervention states experienced seasonal peaks in vaccination rates in the late summer months, suggesting that adolescents are more likely to receive HPV vaccination when Tdap and MenACWY vaccinations are due for middle school entry. Requirements for Tdap and MenACWY vaccination provide an opportunity for HPV vaccination if is also offered during those clinic encounters; simultaneous administration of all three adolescent vaccines is recommended by ACIP and reduces the burden of clinic visits for adolescent vaccination [1, 20]. Missed opportunities for HPV vaccination can also be reduced through clinic-based interventions that promote tracking of HPV vaccination rates, providing more convenient vaccination services, and making strong recommendations for HPV vaccination [21]. Providers can also help to increase HPV vaccination rates during the non-summer months by scheduling vaccination appointments well in advance of the school entry deadline. Prior research has shown that a high burden of vaccination appointments during the summer months makes it difficult to schedule appointments for all eligible adolescents [22].

Rural adolescents had lower HPV vaccination rates than urban adolescents in Missouri and Oregon, and they also had stagnant rates in Indiana, Kentucky, and Missouri. Prior work suggests that a provider’s recommendation for HPV vaccination is among the strongest predictors of receiving HPV vaccination [23]. However, health care in rural areas is provided primarily by family physicians rather than pediatricians, potentially reducing the frequency of provider recommendations for adolescent vaccines [24, 25]. Other vaccination barriers in rural areas may include religious beliefs, costs to stock the vaccine in low-resource clinics, and reduced access to clinics providing HPV vaccination [26–28]. Ongoing research is investigating barriers to HPV vaccination in rural regions of the U.S., and testing the efficacy of provider-focused interventions to increase HPV vaccination uptake in rural adolescents [29, 30].

The legislation that was passed in intervention states directly facilitated vaccine uptake only in Indiana, where pharmacists gained privileges to administer HPV vaccination. These results suggest that promoting HPV vaccination and cervical cancer prevention via advocacy and education may be insufficient to measurably increase adolescent HPV vaccination rates. The Guide to Community Preventive Services suggests that vaccination requirements for child care, primary/middle school, and college entry are an evidence-based intervention to increase vaccination rates [31]. The enactment of school requirements for HPV vaccination, however, remains challenging. School vaccination requirements are decided mostly by state legislature, with some granting regulatory agencies (e.g. health departments) having the power to require vaccines, but actions remain tied to availability of state funds. Some legislators who support availability of HPV vaccination do not support school requirements, citing concerns about cost, safety, and parents' right to refuse. Moral objections also exist for a vaccine requirement related to a sexually transmitted infection [32]. Where HPV vaccination requirements do exist, the breadth of personal exemptions for HPV vaccination, allowing parents to refuse HPV vaccination for their children for any reason, may encourage non-compliance [32].

As our results show, individual policies may be insufficient to increase adolescent HPV vaccination rates on a large scale. Rather, combinations of legislative actions that increase availability (e.g. allowing pharmacists to administer HPV vaccination), affordability (e.g. expanding Medicaid access to uninsured or underinsured children), and awareness (e.g. requirements for sex education in schools and parental education on HPV vaccination), in addition to HPV vaccination requirements for school entry, have been associated with increased HPV vaccination rates [33]. However, bills related to HPV vaccination have been introduced at far lower levels in recent years compared to the first two years following the introduction of HPV vaccination, and only one bill, allowing pharmacists in Hawaii to administer HPV vaccination, has been passed since 2015 [15]. Limited resources should be devoted to advocacy for state legislation that directly encourages and facilitates HPV vaccination, including in schools and at the health systems level, the impacts of which subsequent research efforts can assess.

Limitations of this work include the use of aggregate population data and the inability to control for individual-level factors that influence vaccine uptake in our regression models. However, by stratifying on sex and urbanicity we were able to observe differences between subgroups in HPV vaccination rates over time. Further, the use of employer-sponsored insurance claims data likely underestimates true vaccination uptake, as uninsured and underinsured adolescents may have received subsidized or free vaccinations through government programs, and Medicaid recipients are not included. As a result, the levels and trends we estimated may not be generalizable to those in the total vaccine-eligible population. Finally, the dearth of state legislation of HPV vaccination resulted in a sample size of only four states for this study, limiting the scope of our conclusions. However, prior research has evaluated the impact of the school vaccine requirement in a single state, Rhode Island, which is the only state to enact a requirement free of broad philosophical and religious exemptions [34]. Strengths of this study include large sample sizes from each state included in the analysis, and long post-intervention segments that permit the measurement of legislative impact. Both factors maximize statistical power to detect changes in HPV vaccination rates over time [35].

Despite overwhelming evidence for vaccine efficacy and safety, many adolescents remain under-vaccinated and at risk of HPV infection and HPV-associated cancers. While overall HPV vaccination rates are increasing across the country, including among boys and rural adolescents, disparities between states indicate that state legislation has not surmounted barriers to vaccination. Comprehensive promotion of HPV vaccination at the clinic and provider level, in addition to the state level, should continue. Continuing efforts to introduce and pass legislation that directly facilitates HPV vaccination can provide research opportunities to identify and promote effective HPV vaccination policies.

Acknowledgments:

Preliminary results from this study were presented orally at the EUROGIN 2018 International Multidisciplinary HPV Congress in Lisbon, Portugal, December 2–5, 2018.

Appendix.: Enrolled adolescents* by year and analytic segment, November 2019 – December 2017

Study Year	Indiana	Kentucky	Missouri	Oregon
2009	1,214	543	1,048	304
2010	7,871	3,246	7,757	3,233
2011	20,695	8,731	14,908	6,186
2012	34,027	14,024	20,046	9,031
2013	35,238	14,443	21,496	10,066
2014	40,374	16,180	22,328	11,172
2015	15,505	11,577	18,806	10,773
2016	16,947	14,330	20,097	9,862
2017	13,558	10,672	16,693	8,673
Pre-legislation segment	43,536	11,014	5,047	12,849
Post-legislation segment	61,407	39,435	53,077	22,637

*Adolescents may be enrolled in multiple study years, depending on the duration of their insurance coverage.

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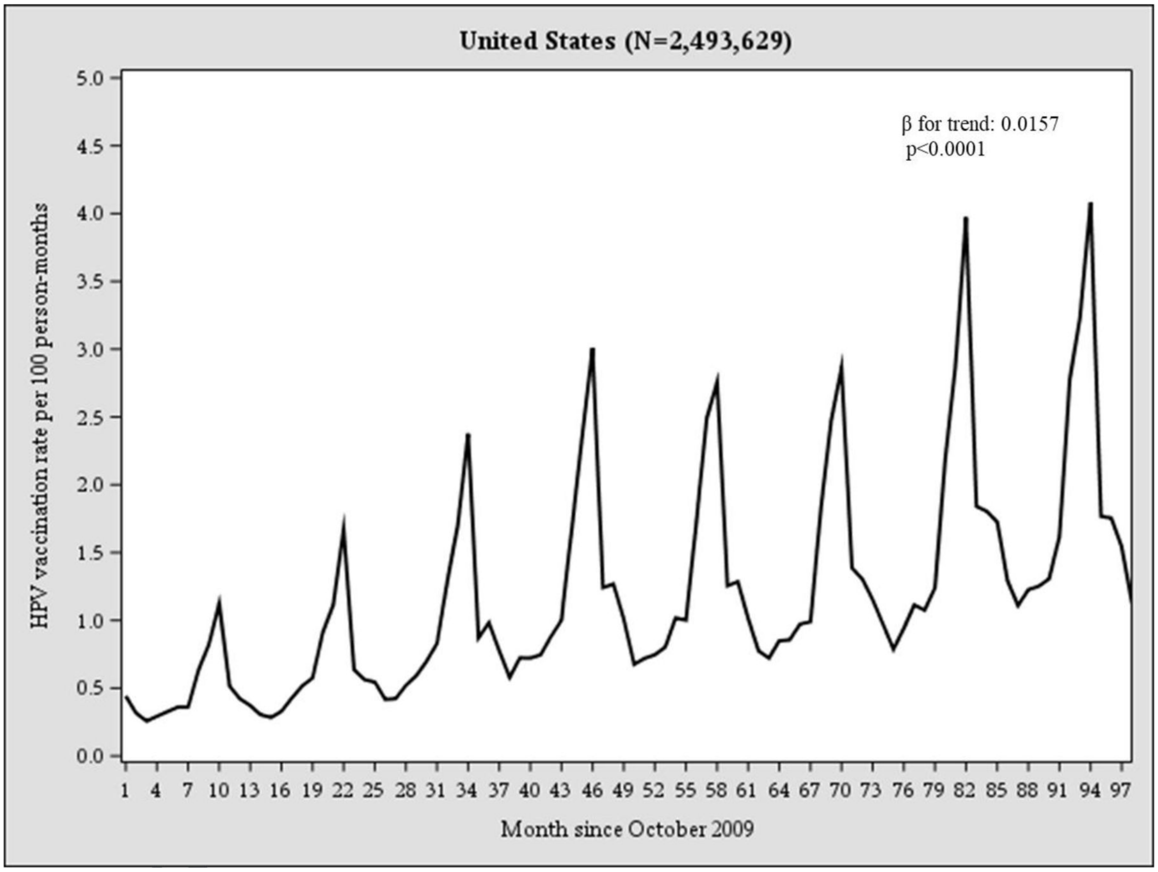

Figure 1.

Monthly rates of initiation of human papillomavirus vaccination based on employer-sponsored insurance claims among adolescents in the United States: November 2009 – December 2017

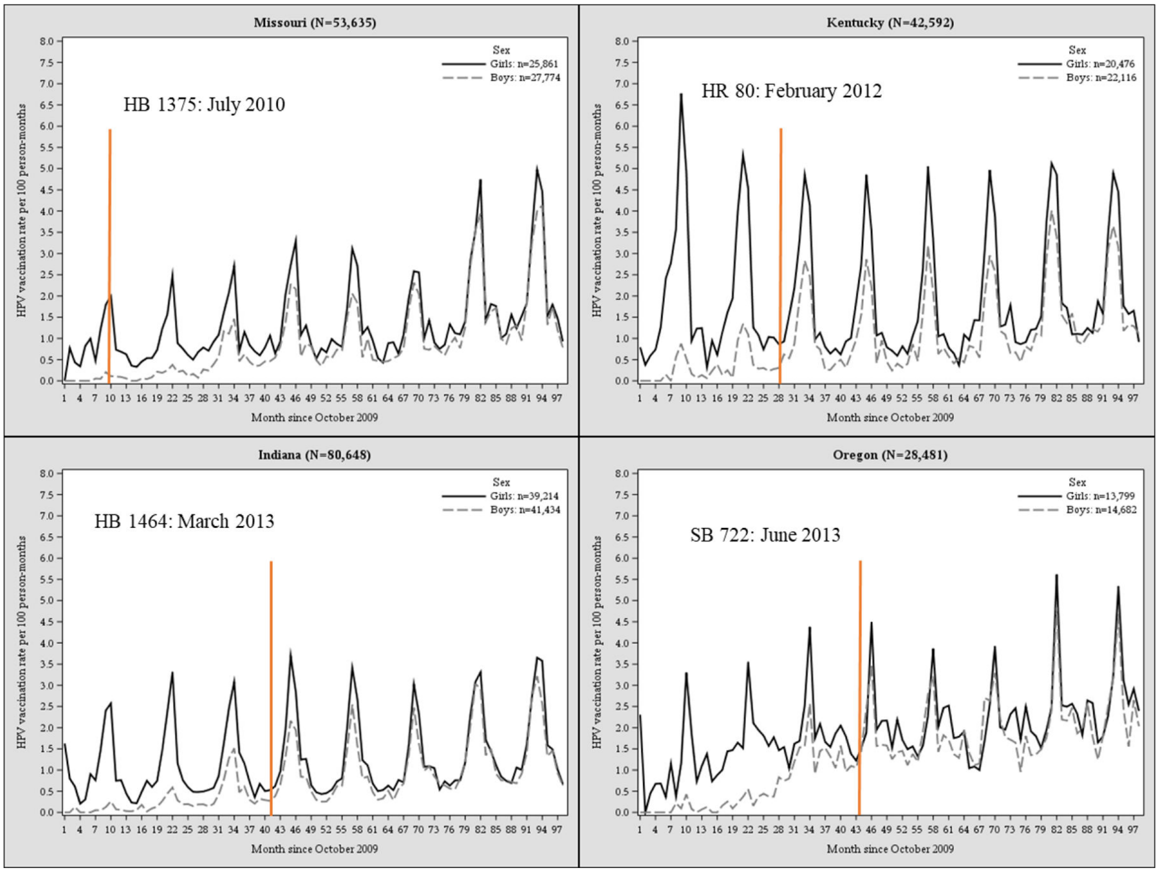

Figure 2.

Monthly rates of initiation of human papillomavirus vaccination based on employer-sponsored insurance claims among adolescents in four states, stratified by sex: November 2009 – December 2017. The rate of HPV vaccination is plotted for each month of the study period, per 100 person-months. The red bar indicates the month of the study period in which legislation was passed.

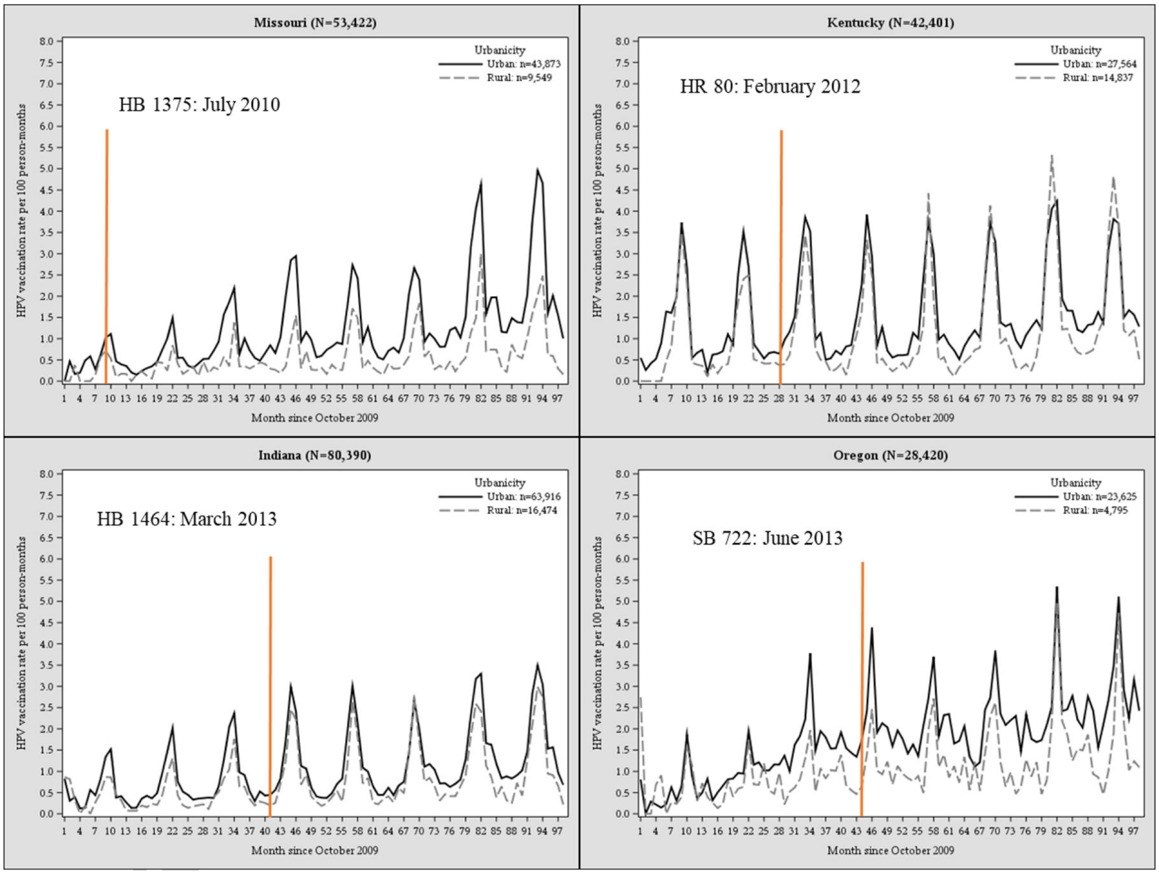

Figure 3.

Monthly rates of initiation of human papillomavirus vaccination based on employer-sponsored insurance claims among adolescents in four states, stratified by residence in urban or rural areas: November 2009 – December 2017. The rate of HPV vaccination is plotted for each month of the study period, per 100 person-months. The red bar indicates the month of the study period in which legislation was passed.

Table 1.

Description of legislation passed in state legislatures related to HPV vaccination during the study period, November 2009 – December 2017

State	Date Passed	Bill Number	Description of Bill Provisions
Missouri	July 3, 2010	HB 1375	• Introduced by W. Cooper, Sater, Jones, Kirkton, Storch (Bipartisan; female/male representation) • Requires Department of Health and Human Services to develop an informational electronic brochure regarding the connection between HPV and cervical cancer and availability of a vaccine. Public school districts must be notified of brochure availability on department website and print material to be provided directly to parents "as the school district deems appropriate." Brochure must include: (1) risk factors for developing cervical cancer, symptoms of HPV, how it's diagnosed, and consequences of not treating; (2) connection between HPV and cervical cancer, how it is transmitted, how to prevent (including encouraging abstinence only as best way to prevent STDs), and risk of contracting for students; (3) latest scientific evidence on HPV vaccine and its effectiveness; (4) that Pap smear is still critical; and (5) statement to see health care provider for questions.
Kentucky	February 21, 2012	HR 80	• Introduced by Watkins, Burch, Palumbo, and Steele (Democratic; female/male representation) • Reports statistics about HPV infections in United States, HPV-related cancer statistics nationwide and in Kentucky, statements about vaccine efficacy, and recommendations from the CDC. • The amended resolution urges "parents to have their daughters ages nine and older and their sons ages 11 and older vaccinated with the HPV vaccination, adult females and males through age 26 to have the HPV vaccination, and all citizens of the Commonwealth of Kentucky to become more knowledgeable of the benefits of HPV vaccination."
Indiana	March 26, 2013	HB 1464	• Introduced by Davisson, Kubacki, Austin, and Frizzell (Bipartisan; female/male representation) • Amends Indiana Code 25–26-13–31.2 to permit a pharmacist to administer immunizations for a number of additional vaccines, including HPV, with a prescription. • Adds additional requirements for record keeping and allowing pharmacist students/interns to administer under supervision.
Oregon	June 6, 2013	SB 722	• Introduced by Ferd Girod, Steiner, Hayward, Keny-Guyer (Bipartisan; female/male representation) • Requires that the Health Authority to create a control plan for HPV related cancers as an addendum to the Oregon Comprehensive cancer plan. • Plan must include existing disease prevention or surveillance policies and programs, existing disease prevention or surveillance measures, public and health care provider awareness, gaps in knowledge related to HPV and related cancers, and opportunities to improve disease prevention and surveillance policies, programs, and measures. • Plan requite to address, at a minimum, cervical, anogenital, oral cavity, and pharyngeal cancers. Plan must be submitted, along with any legislation recommendations, by September 1, 2014. Plan declares the aforementioned cancers an emergency.
Hawaii	April 5, 2017	SB 514	• Introduced by Baker, Kidani, Harimoto, Inouye, Kim, Shimabukuro (Democratic; female/male representation) • Allows pharmacists to administer recommended vaccines, including HPV vaccine, to adolescents 11–17 years of age who present with a valid prescription from a physician. Pharmacists must complete a training program approved by the Accreditation Council of Pharmacy Education (ACPE), and must provide documentation of successful completion of training to the ACPE board.

Table 2.

Segmented regression coefficients representing levels and trends of HPV vaccination rates, stratified by sex and urbanicity, 2009–2017

	Indiana Coefficient (SE)	Kentucky Coefficient (SE)	Missouri Coefficient (SE)	Oregon Coefficient (SE)
Overall				
Baseline level (β0)	0.73 (0.17) **	1.25 (0.25) **	1.03 (0.40) *	0.54 (0.22) *
Monthly trend over time (β1)	−0.0094 (0.011)	−0.0068 (0.016)	−0.10 (0.071)	0.013 (0.014)
Change in level following legislation (β2)	−0.1039 (0.23)	−0.53 (0.64)	0.31 (0.43)	0.057 (0.29)
Change in trend following legislation (β3)	0.0012 (0.025)	0.23 (0.87)	0.11 (0.076)	0.0106 (0.025)
Stratified by Sex				
Girls				
Baseline level (β0)	1.26 (0.20) **	2.28 (0.34) **	1.21 (0.45) *	0.91 (0.27) *
Monthly trend over time (β1)	−0.014 (0.013)	−0.0133 (0.022)	−0.056 (0.080)	0.032 (0.018)
Change in level following legislation (β2)	−0.19 (0.28)	−0.78 (0.88)	0.13 (0.48)	−0.026 (0.35)
Change in trend following legislation (β3)	−0.00010 (0.030)	0.42 (1.20)	0.060 (0.085)	0.030 (0.031)
Boys				
Baseline level (β0)	0.19 (0.16)	0.30 (0.22)	0.88 (0.38) *	0.13 (0.21)
Monthly trend over time (β1)	−0.0023 (0.010)	0.0041 (0.0141)	−0.15 (0.069) *	0.0024 (0.013)
Change in level following legislation (β2)	−0.026 (0.22)	−0.32 (0.55)	0.48 (0.41)	0.12 (0.27)
Change in trend following legislation (β3)	0.0018 (0.024)	0.075 (0.75)	0.16 (0.073) *	−0.0050 (0.024)
Stratified by Urbanicity				
Urban				
Baseline level (β0)	0.74 (0.17) **	1.41 (0.25) **	1.18 (0.44) *	0.46 (0.22) *
Monthly trend over time (β1)	−0.0069 (0.011)	−0.0085 (0.016)	−0.12 (0.078)	0.021 (0.0146)
Change in level following legislation (β2)	−0.12 (0.24)	−0.41 (0.63)	0.38 (0.47)	0.033 (0.29)
Change in trend following legislation (β3)	0.0011 (0.025)	0.21 (0.86)	0.13 (0.83)	0.0091 (0.026)
Rural				
Baseline level (β0)	0.67 (0.18)	0.89 (0.29) *	0.41 (0.28)	0.081 (0.25) *
Monthly trend over time (β1)	−0.019 (0.011)	−0.0006 (0.019)	−0.025 (0.05)	−0.011 (0.016)
Change in level following legislation (β2)	0.027 (0.24)	−0.75 (0.73)	−0.0115 (0.30)	0.089 (0.32)
Change in trend following legislation (β3)	−0.0017 (0.026)	0.26 (0.99)	0.034 (0.053)	0.0091 (0.028)

Abbreviations: SE=standard error

Models adjusted for transformed sine and cosine functions to control for seasonality of vaccination rates, and for the change to the CDC recommendation from “permissive” to “routine” vaccination for males in December 2011.

* $p<0.05$

** $p<0.0001$