Patterns and Disparities in Human Papillomavirus (HPV) Vaccine Uptake for Young Female Adolescents among U.S. States: NIS-Teen (2008–2016)

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ABSTRACT

Background: Several studies have reported differential vaccine uptake outcomes that are associated with sociodemographic and socioeconomic characteristics, as well as provider type. However, none has examined a trend over a multiple-year span. In this study, we utilize a longitudinal data-based approach to examine state-level human papillomavirus (HPV) vaccine trends and their influences over time.

Methods: We analyzed National Immunization Survey – Teen data (2008–2016) to estimate HPV vaccine initiation rate in young female adolescent ages 13–17 years old among U.S. States. We identified growth patterns using the latent class growth method and explored state-level characteristics, including socioeconomic and sociodemographic attributes, and health legislation and policy-related programs among patterns.

Results: We identified three growth patterns, which showed gradually increasing vaccination trends but different baseline HPV uptake rates (high, moderate, low). States within Pattern 1 (highest HPV vaccination rates) included the lowest percentage of families with incomes below federal poverty level, the highest percentage of bachelor's degree or higher, and the lowest number of uninsured, while states within Pattern 3 (lowest HPV vaccination rates) included families with socioeconomic attributes along the opposite end of the spectrum.

Conclusions: Latent class growth models are an effective tool to be able to capture health disparities in heterogeneity among states in relation to HPV vaccine uptake trajectories.

Impact: These findings might lead to designing and implementing effective interventions and changes in policies and health care coverage to promote HPV vaccination uptake for states represented under the lowest trajectory pattern.

Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI) in the United States (1). According to the Centers for Disease Control and Prevention (CDC), about 79 million Americans have been exposed to HPV, and 14 million people become newly infected every year (2–5). The term "ubiquitous" has commonly been used to describe this pervasive virus, and nearly all sexually active people will become infected with HPV if they do not prophylactically vaccinate against this virus (6). There are more than 150 HPV strains, including 12 (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) that have the potential to cause cancer and two noncancerous strains (types 6 and 11), which cause the majority of genital warts (6–8). Persistent infection with high-risk HPV strains, largely types 16 and 18 can cause the development of various cancers (9). Specifically, HPV is considered to be the cause of nearly all cervical cancers, approximately 90% of anal, 75% of vaginal, 69% of vulvar, 63% of penile, 70% of oropharyngeal, and 32% of oral cavity cancers (10). However, the majority of these cancers (and noncancerous genital warts) can be prevented by the timely uptake and completion of the HPV vaccine series (10).

The CDC's Advisory Committee on Immunization Practices (ACIP) recommended routinely vaccinating girls against HPV beginning in 2006 (11), and they updated their recommendations to include boys in 2011 (12). Currently, Gardasil 9, a 9-valent HPV vaccine, is commercially available in the United States, and it offers potential protection against types 6 and 11 (the strains which cause genital warts), and seven cancerous strain types (16, 18, 31, 33, 45, 52, and 58). To prevent cancers associated with HPV infections, ACIP recommends a two-dose HPV immunization schedule for all children ages 9 through 14 years, and a three-dose schedule for persons who either initiate the vaccination series between ages 15 through 26 years or for populations who are immunosuppressed (13). Healthy People 2020 aims for 80% of all U.S. adolescents complete the HPV vaccine by age 13–15 years old (14). However, National Immunization Survey – Teen (NIS-Teen) data illuminate the discrepancy between these goals and state-level HPV vaccine completion rates (15, 16). State-level disparities in HPV vaccination rates may be due to differing HPV vaccine-specific (e.g., required HPV vaccination for school entry) and general health care (e.g., allowing pharmacists to administer vaccines to adolescents) policies (17, 18). A recent comparative analysis of state health policies found that using the combination of expanding Medicaid, requiring HPV vaccine for school entry, mandating sexual education in schools, and allowing pharmacists to administer the HPV vaccine led to the highest rates of HPV vaccination (17).

Past research has reported differential vaccine uptake outcomes that are associated with heterogeneity in the sociodemographic and socioeconomic characteristics, as well as provider type that administers the vaccine (19, 20). None, to our knowledge, has examined a trend in U.S. states over a multiple-year span using a longitudinal data-based approach. It is valuable to examine the patterns of HPV vaccination uptake rates since 2006 as this information may help to inform why

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some states have lower or higher HPV vaccination rates, or why some states show a steady increasing trend in HPV vaccination over time compared with others. This study explored whether HPV vaccination rates among U.S. states are associated with sociodemographic and economic disparities, as well as HPV-related funding and education programs, by examining the trends of HPV vaccine uptake among young female adolescents (13–17 years of age) from 2008 through 2016.

Methods

For our research, a multi-year comprehensive database was created using in individual- and state-level variables from publicly available datasets and online sources.

Data sources

All data were obtained from the NIS-Teen, an annual survey conducted by the CDC that monitors vaccination uptake in the United States (21, 22). NIS-Teen has two main sources of data which include: (i) a list-assisted random digit–dialing telephone survey of households and (ii) a mailed survey to teens' immunization providers to monitor teen immunization coverage. It includes a nationally representative stratified sample of boys and girls aged 13 to 17 years in all 50 states and the District of Columbia. Details of NIS-Teen methods, including data collection and weights generation has been described previously (23–26). State-level socioeconomic status (SES) and household data came from the American FactFinder Download system of the US Census Bureau (27), while state-based policies were extracted from multiple literature and online searches (17, 21, 22, 28, 29).

Data manipulation

On the basis of the suggested methods from the Data User's Guide (2016 NIS-Teen Data and User's Guide), we downloaded the nine Public-Use data files of NIS-Teen datasets for 2008 to 2016 and combined the data files using a unique household identifier, "SEQNUM" and a year variable, "YEAR". To avoid duplicate SEQNUM among 9 years, we created a variable "SEQNUMTYR," which concatenated two variables of "SEQNUM" and "YEAR". Several questions related to HPV have different variable names between before 2015 survey and after 2014 survey, so we unified those variables. Similar to past research (Reiter and colleagues 2013), we utilized sampling weights to determine effect estimates, frequencies/proportions, and corresponding 95% confidence intervals (CI) with NIS-Teen data (30). We excluded data about male vaccination rates from the analyses over the span of a decade because boys' data was initiated in 2011, which was 5 years later than girls'.

Measures and characteristics

HPV vaccination uptake was examined (at least one dose of HPV vaccine) among female adolescents as the primary outcome variable. The outcome variable is dichotomous given the value "1" for one or more HPV doses and "0" for no doses. The HPV vaccination uptake rates were generated through the merged dataset to analyze the trajectories of longitudinal series of adoption rates over 9 years for all U.S. states and the District of Columbia (DC). We studied individual-level variables from the survey including age in years, race/ethnicity [non-Hispanic (NH) white, NH black, NH other, and Hispanic)], mothers' age (≤34, 35–44, and ≥45), mothers' education level [less than high school, high school, post–high school education (non-college degree), college graduate], poverty status (below poverty, above poverty and below $75,000, over $75,000), mother's marital status (married, never married, divorced, widowed), the number of children under 18 years in household, the number of people in household, census region (Northeast, Midwest, South, and West), facility (all public facilities, all hospital facilities, all private facilities, all others, and mixed), and provider recommendation to receive HPV shots (yes, no), as analyzed in previous research related to HPV vaccination using NIS-Teen data (30, 31). SAS V.9.4 statistics program was used to import and merge the 9 years of NIS-Teen datasets, and to produce the proportions and corresponding 95% CIs and P values from Wald χ^2 statistics to compare the distributions of three different HPV vaccination uptake levels (≥1, ≥2, and ≥3) for each of the individual-level variables.

Statistical analysis

State-level longitudinal trajectories of HPV vaccine uptake rates over the 9-year span may be heterogeneous due to various socioeconomic, developmental, and health attributes, and such heterogeneities might lead into several distinct trajectory patterns with homogeneous trajectories within patterns, but heterogeneous between patterns. In the longitudinal view, we hypothesize that heterogeneity or clustering of individual trajectories may be characterized into distinct patterns of trajectories based on their patterns of growth. Because trajectories (or growth) patterns within the states over the 9-year span were unmeasured (or latent), they were identified using latent class growth models (LCGM). For executing latent class growth models, we created a dataset in HPV vaccine uptake rates by state and year from NIS-Teen datasets. State-level longitudinal trajectories of HPV vaccine uptake rates over the 9-year span may be heterogeneous due to various socioeconomic, developmental, and health attributes, and such heterogeneities might lead to several distinct trajectory patterns with homogeneous trajectories within patterns but heterogeneous between patterns. In the longitudinal view, we hypothesized that heterogeneity or clustering of state-level longitudinal trajectories may be characterized into distinct patterns of trajectories based on their patterns of growth. Because trajectories (or growth) patterns within the states over the 9-year span were unmeasured (or latent), they were identified using latent class growth models (LCGM), which is the same as the growth mixture model with no within-class variation (GMM-NW). In addition to LCGM, growth mixture model with class-invariant variation (GMM-CI) was also used to confirm the results from LCGM and GMM-NW (32–40). Then the identified patterns were examined by the characteristics including sociodemographic attributes and HPV vaccination legislation and policy. First, we estimated a traditional latent growth curve analysis (LGCA) to determine whether individuals have uniform variation with a common growth function using model fit indices [e.g., root mean square error of approximation (RMSEA), comparative fit index (CFI), and χ^2 statistic] and variances of growth factors. If the model fit statistics were poor and variances of growth factors were significant, we moved to LCGMs to allow heterogeneities in longitudinal changes of HPV vaccine uptake rates. LCGMs find distinct clusters with homogeneous growth pattern within class and heterogeneous growth pattern between classes, and allow for estimation of a prespecified number of latent classes of trajectories. For model fit for each cluster, we calculated log-likelihood values, Bayesian Information Criterion (BIC), Sample-size adjusted Bayesian Information Criteria (SSABIC), and Entropy. We used adjusted Lo-Mendell-Rubin Likelihood Ratio Test (LMRLRT) and Bootstrapped Likelihood Ratio Test (BLRT) to determine the number of growth patterns by testing for the null hypothesis (n-1 classes) versus the alternative hypothesis (n classes). We had considered additional criterion of 5% of the sample as minimum sample size of the smallest cluster and interpretability of each cluster trajectory for model selection (41, 42). Latent class growth analyses were analyzed using M-Plus V.7. Because local maxima problems result in incorrect class solutions, we investigated whether the best log-likelihood value was replicated with multiple random sets of starting values. In addition to latent growth modeling, a K-means clustering analysis was executed to see how another approach produced the number of clusters and the members within each cluster (43).

Once the distinct patterns were identified using LCGM, we explored the characteristics of sociodemographic and socioeconomic attributes and HPV vaccination legislation and policy. To compare the characteristics of different trajectory patterns based on the longitudinal series of HPV vaccination uptake from 2008 to 2016, we calculated percentages of sociodemographic and socioeconomic attributes, providers and facilities, and health legislation and policy-related programs as follows: mother age, race and ethnicity of teen, marital status of mother, education of mother, number of children, census region, poverty status, provider recommendation, facilities from individual-level NIS-Teen data and number of health insurance, families with income below family poverty level (FPL), mother's education level (high school graduate or higher), provider and government-level information such as doctor's recommendation (had or has doctor or other health care professional ever recommended that teen receive HPV shots?) from NIS-Teen data, and HPV vaccine policy and legislation (laws for HPV prevention and control, Pap and/or HPV tests).

Results

Survey data for 86,705 respondents were analyzed. **Table 1** presents sociodemographic information of these respondents and HPV vaccine uptake among female adolescents between ages 13 to 17 years old. Distributions were relatively even across years and ages of adolescent participants. The demographic data showed the majority of participants were non-Hispanic white (56.0%), mothers aged 35 and older (90.6%), married mothers (66.3%), had two or three children under 18 years (55.4%), and spoke English as their primary language (88.8%). A little more than a third of mothers had college degrees (35.2%), while only 13.7% of mothers had less than a high school education. Most families were above poverty level (73.6%; 35.8% for ≥$75,000 and 37.8% for ≤75,000), while only 21.2% of families were below poverty level. Most adolescent participants (by census regions) came from the South (37.2%), followed by the West (23.9%), Midwest (21.8%), and Northeast (17.1%). Sixty-one percent of families reported having received HPV doses based on recommendations by providers. The health care facilities offering the vaccine were private (50.8%) followed by mixed (17.6%) and public (15.6%).

The average HPV vaccine uptake percentages (2008–2016) for HPV vaccine doses one, two, and three were 53.6%, 48.7%, and 37.5%, and these rates increased to 65.1% (dose 1 only), 55.0% (dose 2), and 43.0% (dose 3) in 2016, respectively. Characteristics of adolescents' mothers were associated with HPV vaccine initiation rates. For example, mothers were more likely to have their age-eligible children vaccinated against HPV if they were ≤34 years old (59.9%), had less than a high school degree (62.2%), and whose marital status was single, widowed, divorced, or separated (61.3%). Families living below poverty also demonstrated the highest HPV uptake rates (62.8%). With respect to race and ethnicity, Hispanics had the highest (61.8%) rate of HPV vaccine initiation (at least one dose) and non-Hispanic whites were the least likely to initiate the vaccine series (49.8%). Families whose preferred language was Spanish had the highest HPV vaccine uptake rate (67.5%). Families who received a provider's recommendation to immunize for HPV showed twice greater likelihood of HPV vaccine uptake compared with families without a recommendation (65.7% vs. 32.3%).

In **Table 2**, we show the model fit statistics for the different growth models. We performed both GMM-NW (LCGM) and GMM-CI for two-, three-, and four-cluster models. We selected GMM-NW models over GMM-CI models because the former showed better model fit statistics of entropy (0.873 vs. 0.844 for 3-cluster models) and LMRLRT showed clear discrimination between cluster models in GMM-NW rather than GMM-CI. Among different cluster models within LCGM (GMM-NW), both three- and four-class models clearly showed smaller values in model fit statistics like log-likelihood (LL) and SSABIC compared with the two-class model, and a higher value in Entropy. Thus, the two-class model was eliminated from the analysis. Even though the four-class model had a slightly higher value than the three-class model for Entropy (0.885 vs. 0.873), and slightly lower in LL and SSABIC values, the three-class model was chosen because: (i) LMRLRT showed a significant P value (0.0101) for three-cluster model, but insignificant P value (0.2126) for four-cluster model, which implied that the three-cluster model should be selected over the four-cluster model; (ii) the smallest cluster of four-class models was less than 5% of the sample (only 1 state of the 51 states); and (iii) the three-cluster model looked more interpretable. Two growth parameters of intercepts and slopes were examined among three classes. The slopes were very similar to each other (6.1, 6.6, and 6.3, respectively) but intercepts were very distinct each other (53.2, 43.6, and 33.3, respectively). The identified three classes had different baseline HPV vaccine uptake (high, moderate, and low uptake) and showed a gradually increasing pattern: (i) a gradually increasing pattern with the highest baseline HPV vaccine uptake (6 states), (ii) a gradually increasing pattern with moderate baseline rate of vaccine uptake (23 states), and (iii) a gradually increasing pattern with lowest baseline vaccine uptake rate (22 states). **Figure 1** is a plot of estimated means and observed individual values. The x-axis represents years from 2008 through 2016 in increments of 2 years, and the y-axis is the percentage of at least one HPV vaccination dose. Each line represents the patterns of percentages over time for each of the U.S. states. As seen in **Table 2**, three clusters of patterns were identified. We also performed sensitivity analyses with a couple of datasets that exclude some states (NC, SD) with steep fluctuation over time. The results did not change with slightly changed model fit statistics under our linear growth modeling. **Table 3** shows characteristics of socioeconomic status and state legislation based on identified patterns by growth mixture modeling. There is heterogeneity in the socioeconomic characteristics that are highly associated with growth patterns in trajectories of HPV vaccination rates. States within Pattern 1 (highest HPV vaccination rates) had the lowest percentage of families with income below FPL, the highest percentage of mothers with a bachelor's degree or higher, and the lowest percentage of uninsured population, while states within Pattern 3 represent the opposite of these trends. Three jurisdictions (RI, DC, and VA) require HPV vaccine for school attendance, though gender requirements and number of doses required vary among them. Among these jurisdictions, RI and the DC belong to Pattern 1 and VA belong to Pattern 3. There were six states that do not have any HPV vaccine legislation, of which four states (AK, ID, MT, and WY) belonged to Pattern 3.

Table 1. Sociodemographic characteristics of HPV vaccine uptake (at least one, two, and three HPV doses) among female adolescents aged 13 to 17 and their family: NIS–Teen, 2008–2016.

Characteristics	Teen participants *N* (weighted %)	≥1 HPV vaccine shot % (95% CI)	≥2 HPV vaccine shots % (95% CI)	≥3 HPV vaccine shots % (95% CI)	*P*
Total teens	86,705	53.6 (52.9–54.2)	48.7 (48.0–49.5)	37.5 (36.8–38.2)	
Year					<0.0001
2008	8,607 (11.3)	37.2 (35.1–39.3)	—[a]	—	
2009	9,621 (11.1)	44.3 (42.1–46.1)	—	—	
2010	9,220 (11.0)	48.7 (46.9–50.5)	—	32.0 (30.3–33.6)	
2011	11,236 (11.1)	53.0 (51.4–54.7)	43.9 (42.3–45.6)	34.8 (33.2–36.4)	
2012	9,058 (11.1)	53.8 (52.0–55.7)	43.4 (41.5–45.2)	33.4 (31.7–35.2)	
2013	8,710 (11.1)	57.3 (55.4–59.2)	47.7 (45.7–49.6)	37.6 (35.7–39.6)	
2014	10,084 (11.1)	60.0 (58.1–61.8)	50.3 (48.4–52.2)	39.7 (37.8–41.5)	
2015	10,508 (11.1)	62.8 (61.0–64.6)	52.2 (50.3–54.0)	41.9 (40.1–43.7)	
2016	9,661 (11.1)	65.1 (63.3–66.8)	55.0 (53.1–56.8)	43.0 (41.1–44.8)	
Age of teens					<0.0001
13	17,558 (19.7)	45.9 (44.6–47.3)	37.9 (36.3–39.5)	25.2 (23.9–26.5)	
14	17,928 (19.7)	50.3 (48.9–51.7)	43.8 (42.2–45.5)	33.1 (31.7–34.6)	
15	17,616 (21.1)	55.6 (54.2–57.0)	50.6 (48.9–52.3)	39.0 (37.5–40.6)	
16	17,693 (20.7)	56.3 (54.9–57.7)	52.8 (51.1–54.5)	42.5 (41.0–44.0)	
17	15,910 (18.8)	59.6 (58.2–61.1)	58.8 (57.0–60.5)	47.8 (46.2–49.5)	
Race/ethnicity					<0.0001
Hispanic	12,781 (20.8)	61.8 (60.1–63.5)	56.4 (54.3–58.5)	41.9 (40.0–43.8)	
NH white	57,013 (56.0)	49.8 (49.1–50.5)	45.5 (44.7–46.4)	35.8 (35.1–36.6)	
NH black	8,793 (14.5)	54.7 (52.9–56.4)	48.1 (46.0–50.2)	35.4 (33.6–37.3)	
NH other	8,118 (8.7)	56.0 (53.8–58.2)	50.0 (47.5–52.5)	40.3 (38.0–42.6)	
Age of mothers					<0.0001
≤34	6,725 (9.4)	59.9 (57.9–62.0)	50.9 (48.4–53.5)	35.7 (33.3–38.1)	
35–44	36,064 (44.8)	52.5 (51.5–53.5)	47.4 (46.2–48.6)	36.0 (34.9–37.0)	
≥45	43,916 (45.8)	53.3 (52.4–54.2)	49.6 (48.5–50.6)	39.3 (38.4–40.3)	
Education of mothers					<0.0001
Less than high school	9,041 (13.7)	62.2 (60.2–64.1)	56.5 (54.1–58.9)	40.5 (38.3–42.7)	
High school	15,906 (24.7)	53.4 (52.0–54.7)	49.2 (47.5–50.9)	36.7 (35.2–38.2)	
Non–college graduate	24,337 (26.4)	50.7 (49.5–51.9)	45.2 (43.7–46.6)	34.9 (33.6–36.2)	
College graduate	37,421 (35.2)	52.5 (51.6–53.4)	48.1 (47.0–49.2)	38.8 (37.8–39.8)	
Marital status of mothers					<0.0001
Married	56,916 (66.3)	52.7 (52.0–53.5)	47.1 (46.2–48.0)	36.8 (36.0–37.6)	
Never/widowed/divorced/separated	21,182 (33.7)	61.3 (60.1–62.5)	51.6 (50.3–53.0)	38.8 (37.6–40.1)	
Number of children under 18 years					0.0379
One	33,246 (31.9)	52.5 (51.6–53.5)	49.0 (47.7–50.2)	39.1 (38.0–40.2)	
Two or three	44,538 (55.4)	54.3 (53.4–55.2)	49.4 (48.3–50.4)	37.9 (37.0–38.9)	
Four or more	8,921 (12.7)	52.8 (50.8–54.8)	45.4 (43.1–47.7)	31.6 (29.6–33.6)	
Poverty status					<0.0001
Above poverty, >$75K	37,912 (35.8)	52.9 (51.9–53.8)	48.8 (47.6–49.9)	38.9 (37.9–39.9)	
Above poverty, ≤$75K	31,919 (37.8)	49.2 (48.1–50.2)	44.3 (43.0–45.5)	34.6 (33.4–35.7)	
Below poverty	13,856 (21.2)	62.8 (61.3–64.2)	55.8 (54.1–57.6)	40.4 (38.8–42.0)	
Unknown	3,018 (5.2)	52.7 (49.5–55.9)	48.3 (44.3–52.3)	35.9 (32.5–39.3)	
Census region					<0.0001
Northeast	16,790 (17.1)	58.1 (56.9–59.3)	54.2 (52.7–55.6)	43.7 (42.3–45.0)	
Midwest	19,346 (21.8)	50.8 (49.7–51.8)	46.9 (45.6–48.2)	35.9 (34.8–37.1)	
South	31,163 (37.2)	49.3 (48.4–50.3)	44.2 (43.1–45.3)	33.7 (32.7–34.7)	
West	19,406 (23.9)	59.5 (57.8–61.2)	53.7 (51.6–55.8)	40.5 (38.6–42.4)	
Interview language					<0.0001
English	80,629 (88.8)	52.0 (51.3–52.6)	46.9 (46.1–47.7)	36.4 (35.7–37.1)	
Spanish	5,056 (9.5)	67.5 (64.9–70.1)	63.6 (60.6–66.6)	46.3 (43.3–49.2)	
Other	1,020 (1.7)	59.1 (54.0–64.3)	54.3 (47.8–60.7)	40.7 (34.6–46.8)	
Facility					<0.0001
All public facilities	12,732 (15.6)	47.7 (46.0–48.4)	75.2 (72.4–78.0)	55.3 (52.4–58.2)	
All hospital facilities	7,490 (7.6)	60.6 (58.5–62.7)	83.6 (80.5–86.6)	66.1 (62.8–69.4)	
All private facilities	39,772 (50.8)	54.8 (53.9–55.7)	85.7 (84.7–86.7)	69.3 (68.0–70.5)	
All STD/school/teen clinic/other	2,423 (2.8)	44.4 (40.6–48.2)	81.1 (76.2–86.1)	64.7 (59.0–70.3)	
Mixed	16,534 (17.6)	55.9 (54.4–57.4)	82.3 (80.5–84.0)	64.2 (62.2–66.2)	
Unknown	4,402 (5.4)	52.5 (49.7–55.4)	81.4 (78.0–84.8)	60.5 (56.4–64.5)	

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Table 1. Sociodemographic characteristics of HPV vaccine uptake (at least one, two, and three HPV doses) among female adolescents aged 13 to 17 and their family: NIS–Teen, 2008–2016. (Cont'd)

Characteristics	Teen participants *N* (weighted %)	≥1 HPV vaccine shot % (95% CI)	≥2 HPV vaccine shots % (95% CI)	≥3 HPV vaccine shots % (95% CI)	*P*
Provider recommendation to receive HPV shots?					<0.0001
Yes	53,734 (61.5)	65.7 (65.0–66.5)	85.0 (84.2–85.8)	67.9 (66.9–68.9)	
No	25,675 (33.7)	32.3 (31.2–33.5)	76.5 (74.2–78.8)	57.4 (55.0–59.9)	
Don't know	3,335 (4.8)	53.3 (50.0–56.7)	78.8 (74.3–83.5)	60.6 (55.8–65.5)	

Abbreviation: STD, sexually transmitted disease.
[a]Missing values due to no survey data for those years.

In addition, HPV vaccine uptake rates (at least one dose) among female adolescents for characteristics of socioeconomic status and providers' information were examined for the three trajectory patterns (**Table 4**). Overall, the HPV vaccine uptake of Pattern 1 showed the highest rates (45.9%), followed by Patterns 2 (40.0%) and 3 (34.0%). Regarding whether the adolescent ever received a provider's recommendation to vaccinate for HPV, Pattern 1 had the highest HPV vaccine uptake (71.3%), followed by Pattern 2 (67.6%) and 3 (62.0%). White female teens had the lowest uptake rates (59.2%, 53.0%, and 45.8% for each of the 3 patterns, respectively), compared with black female adolescents (70.6%), other female adolescents (68.0%), and Hispanic female adolescents (67.0%) within Pattern 1. For Patterns 2 and 3, Hispanic adolescent women had the highest uptake rates (64.8% and 55.6%, respectively) compared with NH black women (60.2% and 49.1%). Higher HPV vaccine uptake was associated with younger mother (≤34, 77.6%), less educated mothers (<12 years, 71.4%), single

Table 2. Model fit statistics for growth mixture models (GMM) and latent class growth models (LCGM).

Fit statistics	2 Classes	3 Classes	4 Classes
LCGM and GMM-NW			
LL, number of parameters	−875.799 (10)	−862.729 (13)	−858.468 (16)
BIC	1,790.916	1,776.572	1,779.845
SSABIC	1,759.520	1,735.757	1,729.612
Entropy	0.861	0.873	0.885
LMR-LRT, *P*	0.0267	0.0101	0.2126
BLRT, *P*	<0.0001	0.0157	0.1408
Group size, *n* (%)			
C1	24 (47.1%)	6 (11.8%)	1 (2.0%)
C2	27 (52.9%)	23 (45.1%)	6 (11.8%)
C3	—	22 (43.1%)	22 (43.1%)
C4	—	—	22 (43.1%)
Growth factors, intercept/slope			
C1	48.5/2.7	53.2/6.1	25.5/10.8
C2	33.8/3.6	43.6/6.3	55.2/3.3
C3	—	33.3/6.6	33.5/7.3
C4	—	—	44.0/5.6
Equality test, means	—	40.608 (<0.0001)	—
Variances	—	0.306 (0.8582)	—
GMM-CI			
LL	−857.087 (13)	−853.322 (16)	−850.970 (19)
BIC	1,773.151	1,769.554	1,776.645
SSABIC	1,726.142	1,719.320	1,716.993
Entropy	0.824	0.844	0.865
LMR-LRT, *P*	0.5188	0.1998	0.1400
BLRT, *P*	0.6000	0.3750	0.5000
Group size, *n* (%)			
C1	6 (11.8%)	3 (5.9%)	4 (7.8%)
C2	45 (88.2%)	8 (15.7%)	8 (15.7%)
C3	—	40 (78.4%)	16 (31.4%)
C4	—	—	23 (45.1%)
Equality test, means	—	32.599 (<0.0001)	—
Variances	—	112.815 (<0.0001)	—

Note: The model includes five time points (2008, 2010, 2012, 2014, 2016) and linear growth factor models.
Abbreviations: BIC, Bayesian Information Criteria; BLRT, Bootstrap likelihood ratio test; GMM-NW, growth mixture model with no within-class variation (i.e., latent class growth model); GMM-CI, growth mixture model with class-invariant variance and covariances; GMM-CV, growth mixture model with class-varying variances; LL, Log-likelihood value; SSABIC, sample-size adjusted BIC.

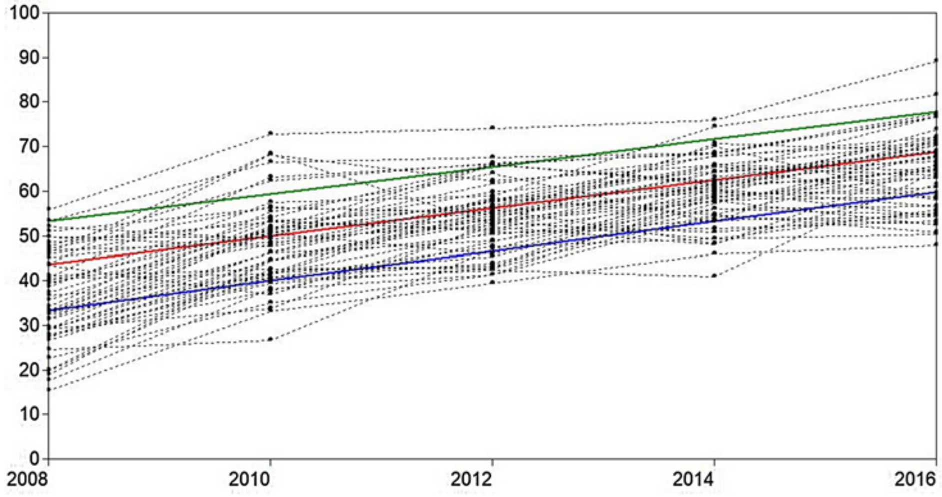

Figure 1.
Plot of estimated means and observed individual values in at-least-one-HPV-vaccination rates for each U.S. state during 9 years. The *y*-axis represents HPV vaccine uptake rates, and the *x*-axis shows five time points (2008, 2010, 2012, 2014, and 2016) of years. The top line shows Pattern 1, the middle line shows Pattern 2, and the bottom line represents Pattern 3.

mothers (never married/widowed/divorced/separated, 69.7%), and lower-income families (below poverty, 73.2%).

Discussion

This analysis revealed that HPV vaccine uptake rates among 13- to 17-year-old females (2008–2016) were highest among groups with the following sociodemographic characteristics: racial/ethnic minorities (non-Hispanic black and Hispanic, younger), low income (below poverty), residing in the Northeast United States, and whose mothers were less educated and single. This is consistent with previous findings that rates of vaccination exemption are commonly associated with regions with a greater percentage of wealth indicators and a lower percentage of minorities (44, 45). Similarly, past research has described disparities in HPV vaccine completion (as opposed to initiation) rates among Hispanic and black adolescent females and among adolescents living in households below the federal poverty level (46). Past research has also identified the correlation between mother's education (less education) and marital status (single, divorced, widowed) and increased rate of HPV vaccine initiation (47, 48). Another study found higher rates of HPV vaccination of younger adolescents (ages 11–12 and 13–14) residing in the West, but higher rates of HPV vaccination among individuals between ages 15–26 among adolescents living in the Northeast (49). Future research could explore the potential rationale (e.g., increased funding for vaccines) for these trends in HPV vaccine initiation by age (and catch-up vaccination) and by region.

Families who received a provider's recommendation to immunize for HPV showed twice greater likelihood of HPV vaccine uptake compared with families without a recommendation (65.7% vs. 32.3%). This finding that there is increased uptake by adolescents reporting a provider's recommendation to vaccinate is consistent with other literature (20, 50, 51). Gilkey and colleagues (2016) found that 48%

Table 3. Characteristics of socioeconomic status and state policy-based funding and education programs based on three trajectory patterns identified by latent growth curve modeling.

Overall vaccination acceptance rates	Trajectory pattern 1 High	Trajectory pattern 2 Moderate	Trajectory pattern 3 Low
Growth factors:			
Intercept (95% CI)	53.2 (47.4–59.1)	43.6 (40.3–46.9)	33.3 (30.2–36.4)
Slope (95% CI)	6.1 (3.8–8.3)	6.3 (5.5–7.1)	6.6 (5.5–7.8)
List of states	6 states: RI, MA, CA, DE, DC, WA	23 states: AZ, CO, CT, GA, HI, IA, LA, ME, MI, MN, NE, NV, NH, NM, NY, NC, ND, OK, OR, PA, SD, VT, WI	22 states: AL, AK, AR, FL, ID, IL, IN, KS, KY, MD, MS, MO, MT, NJ, OH, SC, TN, TX, UT, VA, WV, WY
% Household income below FPL (1 year)	9.2%	11.8%	14.1%
% Bachelor's degree or higher	36.2%	31.7%	24.6%
% Uninsured	6.5%	11.3%	16.5%
State legislative action[a]	DC, RI, WA	CO, IA, LA, ME, MI, MN, NV, NM, NY, NC, ND, O, SD, WI	IL, IN, MD, MO, TX, UT, VA
Three jurisdictions requiring HPV vaccines for school attendance[a]	DC, RI	N/A	VA
No HPV vaccine legislation[a]	DE	NH	AK, ID, MT, WY

[a]Source: National Conference of State Legislatures, 2018.

Table 4. HPV vaccine uptake rates (at least one HPV shot) on characteristics of sociodemographic and socioeconomic status and provider information by three trajectory patterns identified by latent growth curve modeling.

	Trajectory 1	Trajectory 2	Trajectory 3	*P*
Provider recommendation to receive HPV shots?				<0.0001
Yes	71.3% (1.47)	67.6% (0.50)	62.0% (0.57)	
No	49.6% (2.58)	33.5% (0.78)	26.2% (0.71)	
Facilities				<0.0001
All public facilities	71.8% (3.67)	51.5% (1.22)	37.0% (1.07)	
All hospital facilities	70.3% (4.04)	64.0% (1.38)	56.0% (1.98)	
All private facilities	62.3% (1.63)	56.4% (0.61)	51.3% (0.65)	
All STD/teen clinics/other	47.0% (8.77)	50.6% (2.82)	37.3% (2.92)	
facilities mixed	65.4% (3.34)	58.2% (0.96)	51.8% (0.97)	
Race/ethnicity of teen				<0.0001
Non-Hispanic white	59.2% (1.63)	53.0% (0.53)	45.8% (0.55)	
Non-Hispanic black	70.6% (5.13)	60.2% (1.42)	49.1% (1.33)	
Non-Hispanic other	68.0% (3.43)	60.4% (1.42)	49.4% (1.63)	
Hispanic	67.0% (2.49)	64.8% (1.17)	55.6% (1.27)	
Age of mothers				<0.0001
≤34	77.6% (3.95)	63.3% (1.55)	53.1% (1.63)	
35–44	62.8% (2.21)	55.7% (0.70)	47.8% (0.71)	
≥45	62.7% (1.71)	55.8% (0.61)	47.8% (0.66)	
Education of mothers				<0.0001
Less than high school	71.4% (3.12)	64.6% (1.42)	54.1% (1.47)	
High school	64.8% (3.16)	56.2% (1.02)	47.7% (1.04)	
Non–college graduate	61.3% (2.68)	54.3% (0.82)	46.2% (0.86)	
College graduate	60.8% (1.90)	55.8% (0.65)	48.5% (0.70)	
Marital status of mothers				0.0283
Married	64.3% (1.59)	54.9% (0.54)	47.6% (0.56)	
Never/widowed/divorced/separated	69.7% (2.53)	65.7% (0.85)	55.6% (0.89)	
Poverty status				<0.0001
Above poverty, >$75,000	62.1% (1.83)	55.4% (0.64)	48.4% (0.69)	
Above poverty, ≤$75,000	59.3% (2.25)	52.2% (0.72)	43.4% (0.75)	
Below poverty	73.2% (2.86)	66.7% (1.04)	57.2% (1.07)	
Number of children				0.0106
One	60.7% (2.14)	55.6% (0.72)	47.6% (0.75)	
Two or three	65.5% (1.76)	56.9% (0.61)	49.0% (0.64)	
Four or more	64.7% (4.21)	56.4% (1.38)	47.5% (1.48)	
Census region				N/A
Northeast	67.4% (1.38)	59.2% (0.82)	51.6% (1.72)	
Midwest	N/A[a]	55.5% (0.88)	47.7% (0.79)	
South	64.1% (1.29)	53.2% (0.95)	48.5% (0.65)	
West	63.2% (1.57)	57.1% (0.82)	46.5% (0.96)	

Note: Pattern (Trajectory) 1 has highest HPV uptake, Pattern 2 shows moderate level, and Pattern 3 is on the lowest HPV uptake rate.
Abbreviation: STD, sexually transmitted disease.
[a]The missing value (N/A) exists due to no NW states on Trajectory 1.

of their sample had not received a recommendation from a provider (52). Interestingly, half of teens in Pattern 1 who initiated the HPV vaccine series did not report provider recommendation. Other factors such as state's political ideology, religiosity, and stances towards sexual health education may also impact HPV vaccine uptake (24). However, these factors are not as easily modified as provider recommendation.

Vaccine hesitancy, the reluctance or refusal to vaccinate despite the availability of vaccination services, was recently identified by the World Health Organization as one of the top threats to global health (53). Vaccine hesitancy is complex—it varies by time, place, and vaccine, and addressing it requires a tailored approach, centered on evidence-based communication between providers and patients (54, 55). Challenges with vaccine acceptance arise, largely, due to parents' concerns about vaccine safety (56) and lack of strong provider recommendation to vaccinate (57). This is consistent with findings from a recent systematic review and meta-analysis of 79 international studies which included 840,838 parents, which indicated that increasing a physician's strong recommendation followed by addressing parents' concerns about the safety of the HPV vaccine had the most influence on HPV vaccine uptake (20). Thus, the best ways to increase HPV vaccine uptake include the following: ensure that patients' have sufficient evidence-based information about the vaccine, use a presumptive (as opposed to shared decision-making) communication style (58), recommend that patients adhere to the vaccine schedule, and ensure that health care providers have the tools they need to follow-up if a patient's schedule becomes delayed. In terms of HPV vaccine policy, mandates for HPV vaccination that impact school may increase vaccination. However, mandating HPV vaccination has been controversial, and interest in this approach has waned since the vaccine was first introduced (29). Currently, only Rhode Island, Virginia, and the District of Columbia require the HPV vaccine for school entry (28). Whereas Rhode Island and District of Columbia

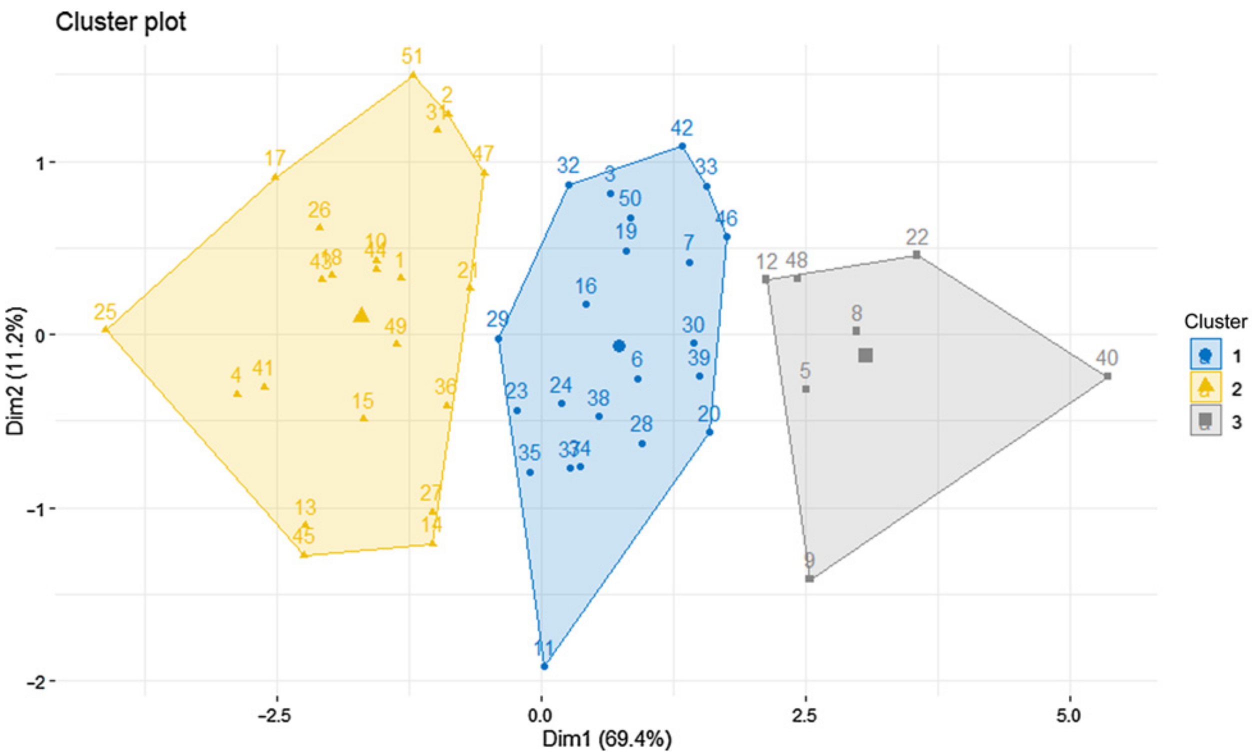

Figure 2.
K-means clustering plot in at-least-one-HPV-vaccination rates for each U.S. state during 9-year span. The cluster 3 (7 states) matches with Pattern 1, the cluster 1 (22 states) with Pattern 2, and the cluster 2 (22 states) with Pattern 3. The cluster 1 includes six states from GMM analysis (CA, DC, DE, MA, RI, and WA) plus HI.

have high levels of HPV vaccine uptake, it is important to note that the mandate to vaccinate for school entry has not led to increased HPV vaccine rates (as compared with states without such mandates). Lower vaccine uptake in Virginia has been attributed to the mandate's liberal vaccine opt-out language as well as focusing on vaccinating girls only (59).

We tested a hypothesis from LCGMs that all trajectory patterns come from homogeneous populations. χ^2 statistic, RMSEA, and CFI were calculated as the model fit statistics with examination of the variances of growth parameters of intercepts and slopes. Poor model fit indices and statistically significant variances of growth factors suggested the existence of heterogeneous or clustered patterns with distinct trajectories. LCGMs successively identified three distinct trajectory patterns among state-level longitudinal trajectories over the 9-year span of HPV vaccine uptake rates. This showed growth mixture models could be an effective tool to identify disparities in the longitudinal trajectories of HPV vaccine uptake in states. The LCGMs assume a normal probability distribution and the number of latent classes identified may be incorrect due to the data nature of multivariate skewness and nonnormality. However, we did not find any evidence of such skewness and nonnormality. Local maxima problems result in incorrect class solution because the iterative optimization process could stop prematurely and return a suboptimal set of parameter values. To ensure the global solution, we checked whether the highest log-likelihood value is replicated and the highest log-likelihood value is also replicated with top two seeds. The LCGM successively replicated the highest log-likelihood value, and the output would include the information of successful replicate of the highest log-likelihood value (34). Monte Carlo simulation studies were performed to decide on sample size and determine the power in the design of the studies (37). The growth model without a covariate and missing data needs a sample size of 50 to satisfy at least 80% of power to reject the hypothesis that the mean of the slope growth factor is zero. There also exist several other techniques like K-means clustering or model-based clustering method to identify potential heterogeneity in longitudinal growth trajectories. To compare LCGM's clustering results with the results from other methods, we executed a popularly used K-means clustering analysis using the R packages “cluster” and “factoextra” to our vaccine uptake data. Our data was scaled/standardized using the R function “scale” in order for the clustering algorithm not to depend on an arbitrary variable unit. **Figure 2** showed that K-means method produced following member distributions (the number of clusters are 7, 22, and 22, respectively) from three clusters, which were very similar results as those of LCGM (6, 23, and 22, respectively). The only difference was the state of Hawaii, which was categorized into Pattern 1 with RI, CA, DE, DC, MA, and WA, while the state was clustered into Pattern 2 in LCGM. The recent simulation study (Martin and colleagues, 2015) showed that LCGMs or GMMs consistently outperform other methods even with small sample sizes (60).

Study strengths include the use of sophisticated statistical techniques to analyze a complex, national longitudinal dataset. Our survey sample was representative of national demographics, similar in educational attainment yet also overrepresenting households that fall below the federal poverty line, according to U.S. census data (61). This study also has limitations. First, a total of 50 states and DC might not be a desired sample size even though research showed that simulated powers are 0.94 with a sample of 50 to select the true 3-class latent class growth model using adjusted Bayesian Information Criteria (62, 63), and all patterns show uniform increases over the last decade. We also assessed HPV vaccine uptake based on one dose. Future studies may wish to test homogeneity of populations among patterns, which assess up-to-date vaccination status among U.S. states, to provide additional information related to completion of the HPV vaccine series. This study might have some limitation because our analysis assumed the linear growth model, not the nonlinear growth model. In addition, we excluded data about male vaccination rates from the analyses because the purpose was to examine the socio-demographic and socioeconomic trends related to HPV vaccine uptake over the span of a decade. Future studies should include data available for both males and females to assess the overall and gender stratified trends of vaccination uptake rates.

Even though HPV vaccine uptake rates have uniformly increased for the last decade, the rates are at a lower rate than necessary to reach herd immunity (80% vaccination rate). Reaching herd immunity could reduce HPV-related cancers, particularly cervical cancer, to near elimination (four per 100,000; ref. 56). This study demonstrates that while disparities in HPV vaccine rates still exist, there is evidence to support policy- and practice-level HPV interventions. Implementing various HPV vaccine policies (e.g. combined Medicaid expansion, allowance for pharmacists to administer HPV vaccines to adolescents, making the HPV vaccine a required immunization for school entry) and working with health care providers to increase their behavior of strongly recommending the HPV vaccine could increase HPV vaccine levels to reach the levels necessary to vastly reduce preventable HPV-related cancers.

Disclosure of Potential Conflicts of Interest

W.K. Huh reports receiving a commercial research grant from Merck. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: W. Yoo, D. Helitzer
Development of methodology: W. Yoo
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): W. Yoo
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): W. Yoo, A. Koskan, W.K. Huh, D. Helitzer
Writing, review, and/or revision of the manuscript: W. Yoo, A. Koskan, M. Scotch, H. Pottinger, W.K. Huh, D. Helitzer
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): W. Yoo
Study supervision: W. Yoo

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