Area-Level Variation and Human Papillomavirus Vaccination among Adolescents and Young Adults in the United States: A Systematic Review

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ABSTRACT

Understanding how human papillomavirus (HPV) vaccination coverage varies by geography can help to identify areas of need for prevention and control efforts. A systematic review of the literature was conducted using a combination of keywords (HPV vaccination, geography, neighborhoods, and sociodemographic factors) on Medline and Embase databases. Studies had to provide information on HPV vaccination by area-level variables, be conducted in the United States, and be published in English (analyzing data from January 2006 to February 2020). Conference abstracts and opinion pieces were excluded. Of 733 records identified, 25 were included for systematic review. Across studies, the average initiation rate was 40.5% (range, 6.3%–78.0%). The average rate of completion was 23.4% (range, 1.7%–55.2%). Geographic regions and area-level factors were associated with HPV vaccination, including zip code tabulation area-level poverty, urbanicity/rurality, racial/ethnic composition, and health service region characteristics. Only three studies utilized geospatial approaches. None accounted for geospatial–temporal associations. Individual-level and area-level factors and their interactions are important for characterizing HPV vaccination. Results demonstrate the need to move beyond existing multilevel methods and toward the adoption of geospatial approaches that allow for the mapping and detection of geographic areas with low HPV vaccination coverage.

Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection. An estimated 75% of all sexually active people are infected during their lifetime (1). Although most HPV infections clear within a couple years, persistent infections can lead to more serious conditions (2). Certain HPV types are associated with precancerous lesions, genital and anogenital warts, and cancer. Approximately 33,700 new cancer cases are attributed to HPV annually (3). The two most common types of cancer caused by HPV are cervical and oropharynx cancers, as 91% of all cervical cancer cases and 70% of all oropharyngeal cancer cases are linked to HPV (4). The FDA currently recommends the approved nanovalent (9-valent) HPV vaccine to provide additional protection against of HPV (strains 6, 11, 16, 18, 31, 33, 45, 52, 58) and to prevent an additional 4.2% to 18.3% of new cancer cases (5). Recent estimates, however, indicate that only 54.2% of adolescents are up-to-date on HPV vaccination (6).

To better understand why coverage is low, extensive research has focused on identifying individual-level factors associated with HPV vaccination (7–9). A recent systematic review suggested a relationship between awareness and knowledge of HPV and vaccination (1). Other studies identified conflicting associations between individual-level sociodemographic factors (e.g., education level, income) and initiation (10–13). A meta-analysis of observational studies of parents' coverage of HPV vaccines for their children demonstrated that having health insurance coverage, lower out-of-pocket costs, and recommendation by physicians are associated with greater odds of vaccination (14). Healthcare professionals also cite low perceived risk of HPV infection or lack of direct benefit for children among parents as barriers to HPV vaccination (2).

Intervention efforts addressing these factors have helped to improve vaccination initiation (15). However, efforts are often untargeted or limited to geographic areas selected from convenience samples. Further, despite overall increases, HPV vaccination coverage is very heterogeneous over space. Up-to-date HPV vaccination varies across U.S. states, from 77.7% in Rhode Island to 28.8% in Mississippi (16). Geographic disparities in vaccination may contribute to continuing disparities in HPV-related cancers, especially in certain geographic areas within the United States where HPV vaccination prevalence is low (e.g., rural and southern regions; ref. 17). Identifying area-level characteristics (e.g., race/ethnicity, poverty, provider shortage areas, etc.) associated with variation in vaccination will be useful for identifying areas for systems-level intervention efforts.

The most widely used method involving area-level effects in HPV research is multilevel regression analysis. Although the multilevel approach helps to correct for area-level correlation among individual observations, it typically ignores potential between-area correlations due to underlying spatial processes. Using a multilevel approach that does not take into account spatial processes could lead to overstatement of the statistical significance of area-level effects (18–20).

Given the potential limitations of this approach, there is increasing interest in population precision health approaches that leverage

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geospatial technologies, such as geographic information system (GIS) tools, and spatial analysis methods to tailor prevention efforts to areas of high need (21). Spatial regression modeling explicitly models spatial correlations among observations (22, 23) and can be used to improve mapping, detect significant risk areas, and identify potential risk factors at a particular geographic level (24, 25). Further, geospatial methods can also be used to recognize patterns of occurrence, identify priority areas for prevention, and provide more accurate modeling of spatially clustered data (26, 27). Despite the known benefits of using geospatial methods for disease surveillance and data exploration in a spatial context (28), its use in the context of HPV vaccination research is unknown.

As previously mentioned, HPV vaccination coverage varies greatly across U.S. states (16). Yet, few studies have examined area-level variation in HPV vaccination and the factors associated with it. This systematic review will summarize and synthesize findings regarding associations between variation in area-level factors and HPV vaccination coverage. We will also summarize results with respect to how individual-level factors may interact with area-level factors to predict HPV vaccination.

Materials and Methods

Electronic search strategy

A systematic search for published literature was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines using Medline (Ovid) and Embase (Ovid) databases. An initial search was conducted in February 2019, and a subsequent search using the same search strategy was conducted in February 2020 to update the review. The search used a combination of keywords and controlled vocabulary for the following concepts: HPV vaccination, geography, neighborhoods, and sociodemographic factors, adapted to each database (see Supplementary Table S1). Reference lists from journal articles were also used to discover publications not identified in database searches. Study selection process are depicted in **Fig. 1**.

Study selection

Articles were included if they: described HPV vaccination (e.g., initiation, completion, and "missed opportunities" for vaccination) by area-level factors (e.g., region, other neighborhood-level variables), were conducted in the United States, and were published in English. In addition, studies were eligible for inclusion only if they analyzed data from January 2006 (e.g., the year that vaccination programs were first implemented; ref. 7) to February 2020 (e.g., when the updated search was conducted). Initially, 733 articles were identified. All references were uploaded to reference management software and exported into Microsoft Excel for review. Studies that were identified as duplicates ($N = 6$), conducted outside of the United States ($N = 314$), or did not directly analyze HPV vaccine coverage by area-level variables ($N = 344$) were excluded. Following full-text review, systematic reviews ($N = 37$), conference notes ($N = 1$), and conference abstracts with no attached article ($N = 6$) were excluded.

Data collection, extraction, and analysis

Twenty-five articles were included and underwent an assessment of methodological quality, using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies (29). This tool includes component ratings on selection bias, study design, confounders, blinding, data collection methods, withdrawals and dropouts, intervention integrity, and analysis. From component ratings, a global rating is calculated and a qualitative score (e.g., weak, moderate, or strong) is assigned. The EPHPP has been applied to other systematic reviews and demonstrated interrater reliability for individual domains and overall scores (30). The EPHPP was modified for use with cross-sectional studies by examining selection bias (e.g., sample representativeness, participation rate), data collection (e.g., reliability and validity), and study design. Methodological quality assessments were conducted by two reviewers (E.K. Do, B. Rossi, and/or C.A. Miller), working independently. In the case of discrepancy, all reviewers worked to come to consensus. All studies were considered moderate to strong quality, as shown in Supplementary Table S2.

Following assessment of methodological quality, study information was collected using a double-coded, standardized data collection form including: author names, article title, journal, year of publication, study design, dataset/sample population and years data were collected, statistical methodological approach, sample size, age range and mean of sample, sex(es) of sample, measure of area-level variation, vaccination measure, prevalence of HPV vaccination, reported effect size, and potential confounders included in statistical analyses, as seen in Supplementary Table S3.

Results

Study characteristics

Study design

All studies that met inclusion criteria ($N = 25$) utilized a secondary data analysis approach. Studies were conducted on data obtained between 2008 and 2017. A majority of studies obtained data from self-reported surveys [$n = 14$; from the National Immunization Survey (31–44), the National Health Interview Survey (9), Behavioral Risk Factor Surveillance System (17, 45–47)], smaller observational studies conducted in Ohio (48), Texas (49), and Minnesota (50), and immunization registries [$n = 6$; from immunization information systems in Utah (51) and North Carolina (52)]. Other studies obtained data from medical records (48) or insurance claims (53).

Sample populations

Across studies, the unit of analyses was the patient/individual. Sample sizes ranged from 277 (45) to 1,691,223 individuals (53). Of the studies, 11 included males and females (31–34, 36, 37, 42, 46, 50, 52, 53), 10 included only females (9, 17, 35, 38–40, 45, 47, 49, 51), and 2 included only males (41, 48). The range of ages spanned from 9 to 26 years, with most studies (e.g., $n = 18$; 72.0%) focusing on children under the age of 18 (17, 31–42, 47–50, 52). Proportions of race/ethnicity groups varied widely across studies (see Supplementary Table S4).

Geographic scale of analysis

Across studies, there was variation in the geographic scale of analysis for variables explaining vaccination coverage. Most studies focused on U.S. geographic region (9, 17, 31, 34, 35, 38, 39, 46, 53). Across national studies (9, 17, 31–37, 39–41, 46, 47), U.S. geographic region was defined, at minimum as: living in the Northeast, West, or South of the contiguous United States. One study combined North Central and Midwest regions (9), whereas other studies included Midwest (9, 17, 39, 46), North Central (53), and Southwest (17) regions. One study investigated Appalachian regions extending from New York to Mississippi (e.g., Northern, North Central, Central, South Central, and South; ref. 38), whereas another investigated the regions of the Intermountain West, which is comprised of Arizona, Colorado,

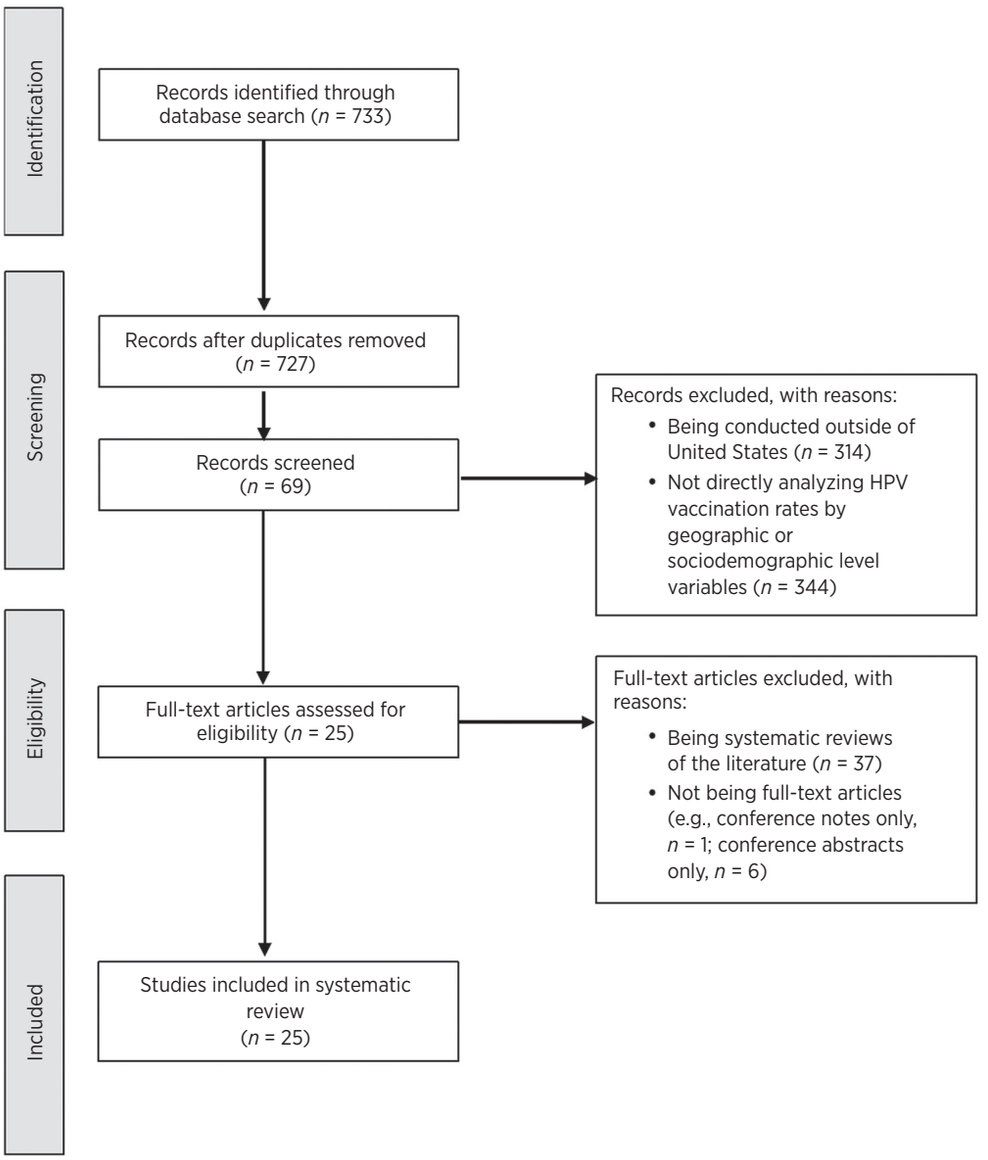

Figure 1.
PRISMA flow diagram of literature search.

Idaho, Montana, Nevada, New Mexico, Utah, and Wyoming (e.g., East, Central, and West; ref. 35). A few studies focused on HPV vaccination coverage across states (37, 42, 43), whereas others used data that were specific to the following states: Minnesota (50), Utah (51), Texas (49), Ohio (48), and North Carolina (52). The remaining studies focused on ZIP Code or ZIP Code tabulation area (ZCTA; refs. 33, 40, 41, 48, 51, 52), metropolitan statistical areas (44, 48), or independent school zones (45).

Measures

HPV vaccination initiation and completion

Most studies reported measures of HPV vaccine initiation ($n = 20$), which was defined as receiving 1 dose (17, 31, 33–48, 50, 53). Eleven studies reported HPV vaccine series completion, or receiving 3 doses within a year (17, 33, 35, 38, 39, 41–43, 46, 48, 50). Other studies reported: cumulative number of doses administered (52), receiving ≥2 doses (49, 50), or "missed opportunities" (i.e., a clinical encounter when at least one adolescent vaccination was received, but not the HPV vaccine; refs. 31, 51).

As shown in **Fig. 2**, HPV vaccination coverage varied across studies. Average percent of initiation across all studies was 40.5% (range, 6.3%–78.0%). Average percent of completion was 23.4% (range, 1.7%–55.2%). Generally, lower HPV vaccination coverage was found among studies conducted earlier in time, whereas more recent studies demonstrated higher coverage of HPV vaccination initiation and completion—suggesting a cohort effect. By sex, the average percent of initiation and completion was 43.7% and 30.8% among females versus 37.3% and 12.6% among males. The highest

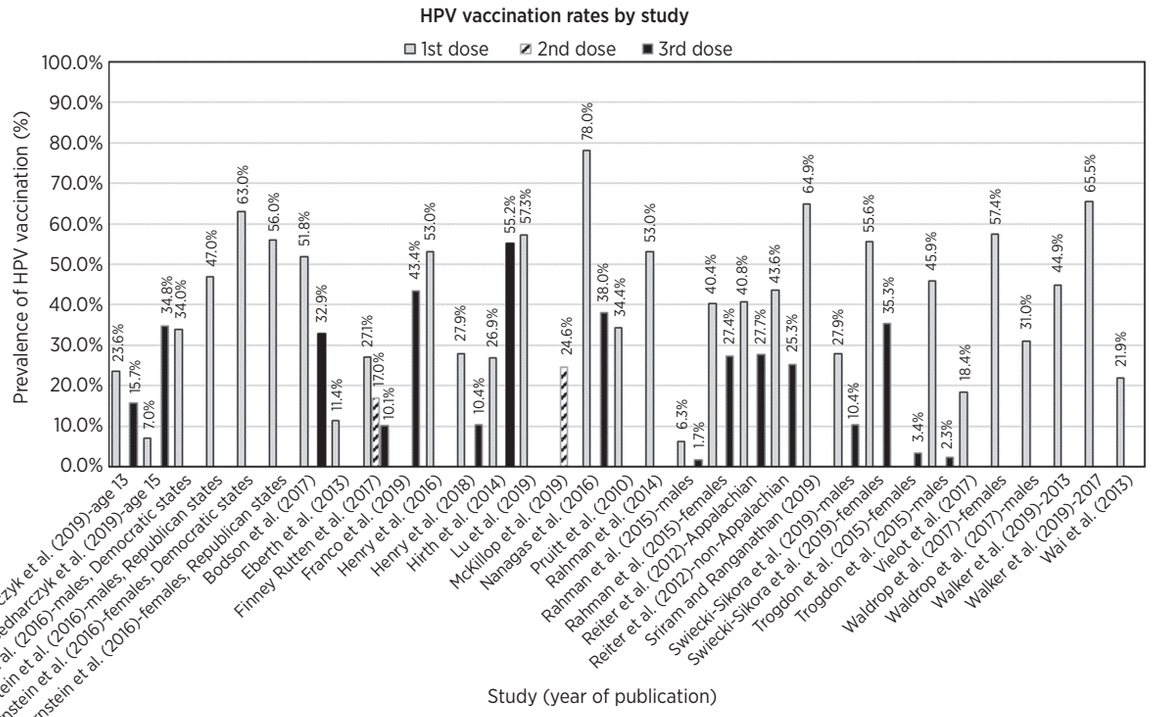

Figure 2.
Rates of HPV vaccination by study. NOTE: The studies by Kepka and colleagues and Williams and colleagues are not shown as their outcome variable is different from rates of HPV vaccination (missed opportunity).

percent reported was found for a prospective medical chart review of male participants enrolled in a cohort study (48).

Potential covariates

Across these studies, covariates were divided into individual-level (n = 24; refs. 9, 17, 31–51, 53) and area-level covariates (n = 8; refs. 36, 40, 43, 45, 47, 50, 52, 53), as shown on Supplementary Table S3. A summary of these domains (sociodemographic characteristics, rurality/urbanicity, family characteristics, healthcare access, health history, substance use, HPV knowledge, and other variables) are provided on Supplementary Table S5. Sociodemographic characteristics were included in studies as either individual-level variables, area-level variables, or a combination of the two, as described below.

Individual-level variables

The most common individual-level covariates included in studies were race/ethnicity (n = 24; refs. 9, 17, 31–52), age (n = 21; refs. 9, 17, 31–33, 35, 36, 38–51), health insurance coverage and type (n = 18; refs. 17, 31, 33–36, 38–41, 44–50, 53), and parent educational status (n = 16; refs. 17, 31–33, 35, 36, 38, 40, 41, 43–48, 50). At the individual level, race/ethnicity was defined by self-report of race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, Asian, and/or Other race/ethnicity). Age was calculated from subtracting the year of birth from the date of HPV vaccination receipt. Health insurance was derived from electronic medical records data (Employer or Union, Medicaid or State Children's Health Insurance Program, military or Indian Health Service, or no insurance). Educational status was often derived from self-report (less than high school, some college or associate's degree, bachelors' degree or higher). Other individual-level covariates included: receipt of other vaccinations (such as Tdap, MCV; refs. 9, 17, 36, 39, 46, 48, 49), information on provider/facility type administering vaccination (32, 33, 35, 36, 40–42, 44), marital status (married/partnered, single-never married, or separated/divorced/widowed; refs. 9, 17, 32, 35, 38, 40, 41, 44, 46, 47), rurality or urbanicity based on home residence (e.g., urban, suburban, rural), poverty status based on self-reported annual household income (below federal poverty line, moderate income or above federal poverty level and earning less than $75,000, high income or above federal poverty level and earning $75,000 or greater; refs. 33, 35, 37, 40–43) or income–poverty ratio (31, 32), and other health behaviors, history, and comorbidities (see Supplementary Table S3).

Area-level variables

Studies used area-level sociodemographic variables such as urbanicity/rurality (31–33, 38, 40, 41, 48, 50, 51, 53), poverty level (33, 40, 41, 47, 50, 52), racial/ethnic composition (40, 41, 50, 52), and health service region characteristics (45, 52) to explain variation in HPV vaccination coverage. Urban/rurality was measured using census block-area level estimates for population density (50) or Rural-Urban Commuting Area (RUCA) codes, which classifies U.S. census tracts using measures of population density, urbanization, and daily commuting (33, 51). Studies included ZIP Code level rurality of residence, as classified as urban, large rural, small rural, and isolated rural (31–33, 41, 45, 51), or a combination of these classifications (e.g., urban, suburban, rural; ref. 48). Measures of area-level poverty included the following: USDA-defined persistent poverty, having 20% or more of residents living below poverty in the last four censuses (52);

≥20% of residents living below poverty (40, 41); or percent (33, 47) or quartile living in poverty (47); or a composite factor measuring low socioeconomic status, including measures of low median income, high percent unemployment, high percent noncollege education, high Medicaid insurance, and high poverty (50). Racial/ethnic composition at the area-level was defined as the proportion of non-White populations (e.g., Hispanic, Asian/Pacific Islander, Black, or Other, including American Indian/Native Alaskan; refs. 40, 41, 50, 52). Measures of health service region characteristics included the percentage of uninsured at the county and public health region level (45) and health professional shortage areas (HPSA). HPSAs were defined as (i) the rational area for the delivery of primary medical services, where (ii) there the ratio of population to full-time–equivalent primary care physicians is 3,500:1 or a ratio less than 3,500:1 but greater than 3,000:1 and has a unusually high need for primary care services or insufficient capacity of existing primary care providers, and (iii) primary medical care professionals in contiguous areas are over utilized, excessively distant, or inaccessible to the population of the area under consideration, according to the Health Resources and Services Administration (52). One study included state-level variables, such as public health department type (decentral, central, mixed, or shared), Centers for Disease Control and Prevention funding per capita, HPV vaccination mandates, sex education policy, political ideology, and religiosity (43).

Statistical approaches

Assessing geographic differences in HPV vaccination

Studies used a range of statistical methodological approaches to assess geographic differences in HPV vaccination. The most common approaches were regression-based modeling techniques, such as generalized linear mixed effects modeling (51), Poisson regression (35, 53), linear regression (31), logistic regression, hierarchical linear modeling (39, 42), or Bayesian hierarchical regression (48, 52). Most often, such analyses employ a binary dichotomous outcome (initiated or completed, coded as yes/no) in a logistic model. Then, different individual- or higher-level (county, state) covariates are used as predictors of the binary outcome. The outcome can also be modeled as continuous, as when vaccination rate per geographic unit is analyzed, and employ linear regression, or as count data, which is then analyzed with Poisson regression modeling. Because many of the studies used large public datasets, they typically adjusted for complex sample design (clustering and stratification) and oftentimes used sample weights to make the results representative of the studied population. Several studies used a multilevel model accounting for the nesting of individuals in geographic units (e.g., individuals in counties and higher levels). Such model can then include covariates estimated at different levels of the model, as well as the interactions across levels. Some studies geocoded individual patient data and spatially linked it to American Community survey data at the census block group level (48, 50) or ZCTA level (41, 52).

Testing for spatial heterogeneity in area-level effects on HPV vaccination

Three studies tested for spatial heterogeneity to determine if area-level effects on individual-level HPV vaccination varied by space (17, 39, 53). These studies utilized a common approach, which involved fitting models with main effects for region and area-level measures [e.g., ZCTA-level race/ethnicity, income (39), urban/rural (53), provider characteristics (17)] and interaction terms. Where significant interactions were found, models were stratified and reported by region.

Geospatial modeling of HPV vaccination coverage

Only three studies utilized geospatial approaches that account for spatial correlation when modeling HPV vaccination coverage (49, 50, 52). Finney Rutten and colleagues assessed spatial variation using a multilevel spatial logistic regression model consisting of random effects with Bayesian inference using Integrated Nested Laplace Approximation and modeled the outcome as a binomial response (50). The other two studies tested for the presence of spatial autocorrelation in HPV vaccination for outcome measures using Moran's I (49, 52). Although McKillop and colleagues utilized a spatial autoregressive probit model to assess the relationship between neighborhood vaccination coverage within a 0.5 mile of the individual and individual vaccination decisions among a sample of low-income adolescent females residing in Dallas, Texas, from 2011 to 2012 (49), Trogdon and Ahn estimated negative binomial models with spatially correlated random effects (referred to as "conditional autoregressive models"), adjusted for demographic, economic, and healthcare variables using data from the North Carolina Immunization Registry (2014), U.S. Census Bureau (2010), American Community Survey (2008–2012), and Zip Business Patterns (2010; ref. 52).

Study results

Geospatial clustering of HPV vaccination

Significant geospatial clustering was identified in two studies (49, 52). McKillop and colleagues found positive spatial autocorrelation for completing ≥2 HPV vaccination doses among females in Texas, suggesting that individuals were more likely to become vaccinated when others living within 0.5 miles were also vaccinated (49). Meanwhile, Trogdon and colleagues found significant geospatial clustering of HPV vaccination initiation and completion for males, but not for females in North Carolina.

Variation in HPV vaccination by U.S. geographic region

Variation in HPV vaccination coverage was identified across the U.S. geographic region (i.e., South, West, etc.; refs. 9, 17, 39, 46) and between geographic subregions (36, 38). Lower HPV vaccination coverage was found in Southern regions (17, 39, 46). However, other generalizations about HPV vaccination based on U.S. geographic region are complicated by inconsistent region definitions and results. For example, one study found that girls living in the Western region were less likely to initiate HPV vaccination compared with girls living in the Northeast (46), whereas another found those living in the West were more likely to initiate compared with girls living in the Northeast (39). A study comparing the Appalachia and non-Appalachian subregions of 13 states revealed higher but not statistically significant vaccination completion among initiated girls living in Appalachia (compared with non-Appalachian regions; ref. 38).

State-level political affiliation, religiosity, and vaccination mandates and HPV vaccination

Differences in coverage among boys and girls based on the presidential election results of states were identified, with higher initiation among girls and boys in "blue" (Democratic) states relative to "red" (Republican) states (36). States with mandates requiring sex education and vaccination had higher completion rates, whereas states with a larger percentage of highly religious adults had significantly lower completion rates (43). Variables that were associated with higher levels of cumulative HPV vaccination among girls and boys included the share of the population that was Hispanic and Non-Hispanic Black

relative to Non-Hispanic White, outpatient visits per capita, religious organizations per 1,000 population, and the number of uninsured and publicly insured children ages 9 to 14 years (52).

Urbanicity/rurality and HPV vaccination

The overall effects of urbanicity and rurality were mixed. One study using ZCTA-level urban/rurality based on RUCAs found that females living in a rural area had higher odds of HPV initiation (40), whereas another using ZIP Code-level RUCA codes found that females living in rural areas were more likely to have a missed opportunity to receive the HPV vaccine (51). A more consistent trend was observed among males. Males living in urban, higher population density communities had higher initiation (41, 44, 48) and completion (41), when compared with nonurban, less densely populated areas [at the ZCTA level (41), or metropolitan statistical area or MSA level (44, 48)]. Among both male and females, one study found rural adolescents at the MSA level were less likely to vaccinate, when compared with urban adolescents, with the exception of those living in the Northeast region who were more likely to vaccinate (53). Another study of southern Minnesota found census-block rural residency was associated with increased odds of initiation (50).

Poverty and HPV vaccination

Across studies, poverty was measured at the household level (31, 35, 37, 38, 40, 43, 47), ZCTA level (40, 41, 52), census-block level (50), county level (47), and state level (36). ZCTA-level poverty was associated with greater odds of HPV vaccine series completion in males [OR = 1.22; 95% confidence interval (CI), 1.01–1.48; ref. 41] and initiation in females (OR = 1.18; 95% CI, 1.04–1.33; ref. 40). When including both county-level and state-level poverty in models for HPV vaccination coverage, higher county-level poverty was associated with greater odds of vaccination (OR = 1.64; 95% CI, 1.13–2.37). However, increasing state-level poverty associated with lower odds of vaccination (OR = 0.91; 95% CI, 0.84–0.98; ref. 47). In contrast, lower census block group-level SES scores were associated with decreased odds of initiation and subsequent doses among males and females in southern Minnesota (OR = 0.96; 95% CI, 0.92–0.99; ref. 50).

Racial and ethnic composition and HPV vaccination

Higher HPV vaccination coverage was found among communities with a greater proportion of non-white individuals at the census block group level (50) and among adolescents living in mostly Hispanic communities at the ZCTA level (40, 41, 52). However, mixed associations were found for girls living in mostly Non-Hispanic Black communities at the ZCTA level, as shown on Supplementary Table S4. One study showed an increased likelihood of HPV vaccination rate (40), whereas others showed either a decrease in likelihood (52) or no statistically significant difference (41). This study also found that African American adolescent females were less likely to complete the series when compared with Hispanics, and older girls were less likely to complete compared with the youngest age group (49).

Health insurance and provider shortages and HPV vaccination

Results suggest associations between HPV vaccination and area-level health insurance and provider shortages. Higher percentages of uninsured at county and health services region levels were associated with lower odds of initiation among Texan females (45). HPV vaccination coverage was lower in areas of North Carolina with ZCTA-level provider shortages, even among those qualifying for publicly funded vaccination (52).

Spatial heterogeneity in area-level effects on HPV vaccination

Three studies tested for spatial heterogeneity of area-level effects on individual-level HPV vaccination (17, 39, 53). Hirth and colleagues reported that not having a primary care doctor was associated with lower odds of initiation within the Northeast/Midwest/Western region (OR = 0.53; 95% CI, 0.32–0.87) and Hispanic girls were more likely to have initiated vaccination in the South/Southwest (OR = 1.57; 95% CI, 1.13–2.18; ref. 17). Rahman and colleagues tested for statistical interactions between region and area-level variables for race/ethnicity, and income, but none significantly influenced individual-level HPV vaccination intake (39). Meanwhile, Vielot and colleagues found that rural adolescents had higher incidence ratios of HPV vaccination compared with urban adolescents in the Northeast, suggesting that region size and barriers to vaccination might be influencing associations between geographical area and vaccination rate (53).

Individual-level and area-level variable interactions and HPV vaccination

Among identified studies, only one reported statistical interactions between individual-level characteristics and area-level variables (41). Henry and colleagues tested for interactions between individual-level race/ethnicity and ZIP Code-level poverty and individual-level race/ethnicity and ZIP Code-level racial–ethnic composition. The authors noted that both interactions were statistically significant, such that Hispanics living in high poverty ZIP codes had higher odds of HPV vaccination initiation, compared with Hispanics living in lower poverty ZIP codes. Similar associations were found for other/multiple races living in high poverty versus low poverty ZIP codes (41).

Discussion

To our knowledge, this is the first systematic review of area-level variation in HPV vaccination among U.S. adolescents and young adults. Generally, those residing in Southern regions were less likely to initiate or complete HPV vaccination, relative to the North or Northeastern regions. Included studies also demonstrate that HPV vaccination varies by ZCTA-level urbanicity/rurality, poverty, racial/ethnic composition, and health services. It seems to be the case that area-level attributes are more important for explaining variation in HPV vaccination coverage than random area-level effects. However, the strength of these associations is difficult to quantify from existing studies. Generally, higher area-level poverty (e.g., at the ZCTA-level, county-level) was associated with higher coverage of initiation. HPV vaccination initiation decreased with higher uninsured and lower provider shortages at the county level. Communities where at least 50% of the population was Hispanic generally had higher coverage of HPV vaccination, relative to communities where at least 50% of the population was Non-Hispanic White. Mixed associations were found when comparing majority Non-Hispanic Black communities with majority Non-Hispanic White communities. Effects of urbanicity/rurality were mixed, potentially due to differing definitions of urbanicity and rurality across studies. Few studies investigated interactions between individual-level factors and area-level factors.

Current gaps and challenges

With the exception of two studies examining "missed opportunities" (31, 51), all studies examined initiation and/or completion, using similar definitions (e.g., receiving 1 and 3 doses of the vaccine within a year, respectively). This suggests that the operational definition used for the outcome of interest (HPV vaccination) is consistent across studies. A majority of studies utilized a multilevel

approach that ignores potential between-area correlations, which potentially violates the independent errors model assumption. If errors are not independent, due to spatial correlation, then spatially correlated random effects can be used to overcome the violation. This is standard practice with Bayesian hierarchal modeling, an approach used by three studies that also modeled spatial correlations in vaccination coverage (49, 50, 52). No studies incorporated geospatial–temporal effects into their statistical models.

Furthermore, there were inconsistencies in the operational definitions of variables included in analyses across studies. Definitions for area-level variables varied greatly by study (e.g., different combinations of U.S. regions such as Northern, Southern, Eastern, Central, West, Midwest, Southwest, etc. were used across studies to define geographic region). Similar issues arose for variables measuring urbanicity/rurality at different geographical units. Definitions included U.S. Census Bureau definitions of urban (based on population density and ZIP Code; e.g., urban, suburban, and rural; small rural town, large rural town, and urban focused), qualitative descriptors of residence based on ZIP Code (e.g., urban, suburban, and rural), and/or ZCTA-population density by quartile (e.g., based on population by square mile). More consistency in definition was found for variables measuring racial/ethnic composition (based upon ZCTA-level percentage of population of Hispanic, Non-Hispanic Black, Non-Hispanic White, or mixed/other race/ethnicity) and poverty (based upon percentage of the population below poverty at ZCTA, county, or state level). A couple of studies investigated health service variables, but measures were inconsistent (ZCTA-level HPSAs vs. percent uninsured adults at the county and health service region level). Inconsistencies in operational definitions and geographic unit of measurements hinder the ability to make study comparisons. In addition, it seems to be the case that studies examining geopolitical variation in HPV vaccination coverage are not reporting findings across states prior to aggregating these states into regions, which may influence the associations that are found—especially if certain states are receiving more resources relative to others within the same geographic region.

Another issue for consideration is that a majority of the studies focused on examining individual-level factors by location, neglecting to take into consideration potential statistical interactions between variables across space and/or time. Few studies accounted for any type of statistical interaction between area-level and individual-level variables. Even fewer reported on statistically significant interactions showing variation between area-level variables such as ZCTA-level urbanicity/rurality and poverty. Cross-level interactions are important for assessing potential ecological fallacies, or false inferences of the association of individual-level variables on the basis of the observed association of parallel ecological variables (54).

For example, the association between higher ZCTA-level poverty and higher HPV vaccination coverage may signal the success of publicly funded vaccination efforts targeting underserved areas, as eligibility is often based on income (47). However, the relationship between poverty and HPV vaccination coverage may be more complicated and potentially influenced by individual-level indicators of socioeconomic status, including race/ethnicity, education, and household income. The addition of cross-level interactions allows for the opportunity to explore whether area-level effects are different across individual-level socioeconomic status. For example, children from families with lower household incomes living in high socioeconomic neighborhoods may benefit from the collective resources in their neighborhoods (55–57). This information can then be used to inform programmatic efforts to address potential disparities related to HPV vaccination coverage through the quantitative and qualitative evaluation of targeted messaging and campaigns aimed at increasing HPV vaccination among specific populations across different geographic regions.

Limitations and strengths

Our results should be considered within the context of study limitations. Heterogeneity in sample populations and geographic locations across studies made it difficult to compare results. Although most of the studies included information from surveys, the same constructs were typically coded or assessed differently. Further, the majority of studies focused on females, which further limits our ability to characterize HPV vaccination in U.S. adolescents and young adults. Across studies, consideration of state mandates (36, 43), school entry requirements (58, 59), and provider-level factors (31, 33–36, 38, 40, 41, 43, 44) is limited and requires additional investigation. Further, current studies did not account for potential correlation between variables, occurring within the same geographical boundaries, with one exception (52). To balance these weaknesses, future research should report both descriptive and multivariate findings.

Despite these limitations, this study is the first, to our knowledge, to summarize how area-level factors influence HPV vaccination. Studies included in this systematic review focus predominantly on associations between specific area-level factors and HPV vaccination. In addition, this study describes how area-level factors interact with individual-level factors to influence the initiation and completion of HPV vaccination. Results emphasize the importance of considering individual-level and area-level factors in analyses examining HPV vaccination. Results also suggest that multidisciplinary teams with a variety of expertise are needed to incorporate existing geospatial methods that account for significant interaction that variables have within a geographical space in shaping HPV vaccination.

Recommendations and future considerations

Although existing literature incorporates variables measuring area-level characteristics into research on HPV vaccination, there is a paucity of spatial regression modeling approaches in this research. Only three studies incorporated spatial autocorrelation in statistical models (49, 50, 52), and neither of the studies incorporated a geospatial–temporal approach. This reduces the ability of the field to identify geographic areas of need, regarding prevention and control of HPV-related incidence and morbidity. To overcome this challenge, we propose the following five recommendations and future considerations:

1. **Foster interdisciplinary collaborations and research.** Interdisciplinary collaboration, such as that demonstrated by the field of spatial epidemiology, is needed to answer multifaceted problems (60), such as explaining the patterns and variation in HPV vaccination coverage using individual and area-level variables. Spatial epidemiology represents an intersection of statistics, biostatistics, epidemiology, geography, and geospatial information science. Methods and investigators from spatial econometrics and regional science may also be helpful for this problem. Fostering interdisciplinary collaborations encourages researchers to develop and link new data sets assembled from administrative claims, immunization information systems, and other existing sources to support more detailed analyses of geographic disparities in HPV vaccination coverage (61).
2. **Standardize procedures for immunization reporting systems.** As reported elsewhere, technologies for data cataloguing

and transfer of Immunization Information Systems (IIS) information are not standard across states, which makes it difficult to link IIS data to other data resources (62), such as area-level variables (e.g., racial/ethnic composition, poverty level available from the Census and the American Community Survey, and health professionals shortage areas from the Health Resources and Services Administration).

3. **Standardize variable definitions in research on HPV vaccination coverage.** Although a majority of the studies utilized state-level surveys of immunization (e.g., BRFSS or NIS-Teen) and area-level variables obtained from the Census and the American Community Survey, definitions differed by study.
4. **Incorporate spatial regression modeling approaches.** To date, the use of spatial regression methods to studies of HPV vaccination is limited to three studies (49, 50, 52). GIS and spatial analytic approaches can help to identify where HPV-related burdens are elevated and prevention and intervention efforts are needed (63). These methods can be used to account for spatial correlation in HPV vaccination coverage, not explained by individual-level and area-level covariates. Other methods such as spatial lag models and spatial error models could also be applied to HPV vaccination registry data to further characterize spatial patterns in coverage. Bayesian regression models could also be used to model vaccination coverage over space and time (i.e., spatiotemporally), which was not explored in the current literature.
5. **Obtain data on HPV prevalence in smaller geographic areas.** Although the National Immunization Survey is considered the gold standard for establishing national, regional, and state vaccination coverage, it offers limited power to characterize vaccination at smaller geographic levels (e.g., ZIP Code/ZCTA; ref. 61). In order to improve spatial modeling strategies, the use of smaller geographic units may allow for a more detailed description (64) of HPV vaccination coverage and may reveal hidden disparities, especially in areas where population density is smaller.

Conclusions

Given the effect that HPV vaccination has had on cancer prevention, it is important to identify factors influencing HPV vaccination coverage. Results demonstrate that area-level factors and their interactions with individual-level and community-level variables are important for characterizing HPV vaccination coverage. Further research is needed to examine how variation in area-level variables influences HPV vaccination, by either incorporating area-level effects in statistical models or utilizing geospatial approaches that account for spatial correlation.

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