Research Article

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Geospatial Patterns in Human Papillomavirus Vaccination Uptake: Evidence from Uninsured and Publicly Insured Children in North Carolina

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Abstract

Background: Human papillomavirus (HPV) vaccination coverage is far below the national objective set by Healthy People 2020. This paper explores spatial patterns in HPV vaccination uptake.

Methods: Secondary data for publicly funded HPV vaccinations among age-eligible children from 2008 through 2013 from the North Carolina Immunization Registry (NCIR) were used in 2014 in an ecological analysis at the ZIP code tabulation area (ZCTA) level. We tested for spatial autocorrelation in unadjusted HPV vaccination rates using choropleth maps and Moran's I. We estimated nonspatial and spatial negative binomial models with spatially correlated random effects adjusted for demographic, economic, and healthcare variables drawn from the 2010 U.S. Census Bureau, 2008–2012 American Community Survey, 2010 ZIP Business Patterns, and the 2012–2013 Area Resource File.

Results: The NCIR revealed areas of especially low rates in publicly funded HPV vaccinations among uninsured and means-tested, publicly insured children. For boys, but not girls, ZCTAs tended to have HPV vaccination rates that were similar to their neighbors. This result was partially explained by included ZCTA characteristics, but not wholly.

Conclusions: To the extent that the geospatial clustering of vaccination rates is due to causal influences from one ZCTA to another (e.g., through information networks), targeting interventions to increase HPV vaccination in one area could also lead to increases in neighboring areas.

Impact: Spatial targeting of HPV vaccination, especially in clusters of low vaccination areas, could be an effective strategy to reduce the spread of HPV and related cancers. *Cancer Epidemiol Biomarkers Prev; 24(3); 595–602. ©2015 AACR.*

Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States, causes genital warts, and is associated with cervical, vaginal, vulvar, anal, penile, and throat cancers (1). In June 2006, the FDA approved the use of a quadrivalent HPV vaccine to protect against four types of HPV. In 2007 the U.S. Advisory Committee on Immunization Practices (ACIP) began recommending the three-dose vaccine regimen for all girls ages 11 to 12 years, but the vaccine may be administered as early as age 9, with catch-up vaccination for girls and women ages 13 to 26 years (2). In 2010, the ACIP permitted the use of HPV vaccination for males ages 9 through 26 years, with full recommendation for use in males in the same manner as females in 2011 (3). The vaccination has been shown to be effective, and potentially cost-effective, in protecting against the targeted strains of HPV and related cancers (4–8).

However, HPV vaccination coverage is far below the national objective set for girls (80%) by Healthy People 2020 (no goal was set for boys; ref. 9). In 2012, completion of the three-dose series at ages 13 to 17 years was only 33% for girls and 7% for boys (1, 9). In North Carolina, HPV vaccine initiation (i.e., at least one dose) increased modestly over time for girls ages 11 to 17 years: 2008 = 34%, 2009 = 41%, and 2010 = 44% (10), but remains below the national goal.

Vaccination is of particular importance for under- and uninsured children, who are less likely to be vaccinated (11, 12) and therefore more likely to become infected (13). Several barriers to HPV vaccination exist, including low levels of provider recommendation (14), parental concerns about the vaccine's effect on sexual behavior and perceptions of risk (14), religious affiliation (14), and low access to the health care system (15). Area-level variables associated with lower HPV vaccination rates include poverty (12, 16), rural areas (15), pediatric specialty clinics (17), and distance to the place of vaccination (18).

Previous studies have focused on spatial patterns of HPV-associated cancers (19) and cervical cancer screening, incidence, and mortality (20, 21). For example, Appalachia, which includes western North Carolina, is an area with a high burden of cervical cancer and lower HPV vaccination rates (22). These studies suggest that spatial targeting of HPV vaccination could be an effective strategy to reduce the spread of HPV and related cancers, especially in areas of low cervical cancer screening (19–22).

This study explores geospatial patterns in HPV vaccination uptake over time among age-eligible, uninsured and means-tested, publicly insured children in North Carolina. To our knowledge, this study is one of the first to investigate geospatial

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patterns in HPV vaccination (18). Using vaccination registry data, we conducted an ecological analysis of publicly funded HPV vaccination rates to (i) characterize trends in uptake between 2008 and 2013 and (ii) determine whether vaccination rates tend to cluster geographically. The analysis will test the extent to which HPV vaccination rates cluster geographically due to similar demographic, economic, and health characteristics. Analyzing vaccination clustering provides a more complete picture of HPV-associated cancer occurrence, screening, incidence, and mortality. The results will identify new correlates of low HPV vaccination rates in areas of need. The results can also be used to geographically target areas of low coverage for interventions to increase HPV vaccination.

Materials and Methods

Data

In 2014, we collected and analyzed data for publicly funded HPV vaccinations among age-eligible children from 2008 through 2013 from the North Carolina Immunization Registry (NCIR). The NCIR is a secure, web-based clinical tool to provide official immunization information to the state (23). The registry's primary users are local health departments (100% participate) and private provider offices that receive vaccines from the federally funded Vaccines for Children (VFC) program (over 90% of offices that receive VFC vaccines participate). The VFC provides vaccines at no cost to children who otherwise might not be vaccinated because of inability to pay (24). Health care providers who receive VFC vaccines are required to document administration of those vaccines in the NCIR (approximately 95%) or via an alternative hard copy form (approximately 5% that are not captured in the NCIR). To ensure complete records for patients in the registry, our analysis sample included children receiving publicly funded HPV vaccinations between the ages of 9 years, the youngest age at which the HPV vaccination can be given, and 14 years in 2013. The NCIR contains complete vaccination history for this cohort of children, the oldest of which were 9 years in 2008.

We aggregated the cumulative number of publicly funded HPV doses and the number of children receiving all three HPV doses (i.e., full series) using public funds by patient ZIP code. We then cross-walked to ZIP code tabulation area (ZCTA) using a crosswalk created by a Health Resources and Services Administration-funded project directed by the Robert Graham Center (25). ZCTAs are generalized area representations of ZIP code service areas developed by the U.S. Census Bureau to overcome the difficulties in precisely defining the land area covered by each ZIP code. The crosswalk lists all ZIP codes included in each ZCTA. For our analysis, ZCTAs can be used for mapping and provide sufficient variation across geographic areas while also having data available for area-level characteristics. We collected geographic boundary and demographic characteristics for North Carolina ZCTAs from the U.S. Census Bureau: 2013 TIGER shape files (26), 2010 U.S. Census, 2008–2012 (5-year) American Community Survey (ACS), and 2010 ZIP Business Patterns (ZBP).

We also collected county-level characteristics from the 2012–2013 Area Resource File (ARF). All variables at the county level, which cross ZCTA boundaries, were converted to ZCTAs using weighted averages of the county-level data. For count variables, we used Census calculations of the percentage of the total population of the 2010 county represented by the ZCTA/county overlap for the weights (e.g., a ZCTA that accounted for 10% of the county population received 10% of the county's medical providers). For dichotomous variables, all counties touched by the ZCTA must have a positive indicator for the ZCTA to receive a positive value. For per capita variables, we used Census calculations of the percentage of the total population of the 2010 ZCTA represented by the ZCTA/county overlap for the weights (e.g., a ZCTA with 90% of its population in county A and 10% in county B weighted per capita variables from county A at 90% and per capita variables from county B at 10%).

Variables

The dependent variables in the analysis were (i) the number of publicly funded cumulative doses in the cohort from 2008 through 2013 and (ii) the number of fully vaccinated children (i.e., full series of three publicly funded doses) between the ages of 9 years and 14 years in 2013, by ZCTA and sex. The explanatory variables included the following demographics: the population of age-eligible, uninsured and means-tested, publicly insured children ages 9 to 14 years (logged when used as exposure in count models, ACS); percentage of the total population that is female (Census), Hispanic, black non-Hispanic, or other or multirace/ethnicity (white non-Hispanic omitted; Census); and the percentage of the total population with less than high- school diploma and with at least some college (high school diploma omitted; ACS). We expected ZCTA's with more females and white non-Hispanics to have higher HPV vaccination rates (13 and 14).

We adjusted for indicators of USDA-defined persistent poverty (ARF; The Economic Research Service, U.S. Department of Agriculture defined persistent poverty as having 20% or more of residents below poverty in each of the last four censuses: 1970, 1980, 1990, and 2000) and Health Professional Shortage Area (HPSA) defined by Health Resources and Services Administration (ARF; A ZCTA was designated as having a shortage of primary medical care professionals by the Health Resources and Services Administration if the following three criteria were met: (i) The area is a rational area for the delivery of primary medical services; (ii) One of the following conditions prevails within the area: (a) the area has a population to full-time-equivalent primary care physician ratio of at least 3,500:1 or (b) the area has a population to full-time-equivalent primary care physician ratio of less than 3,500:1 but greater than 3,000:1 and has unusually high needs 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). We hypothesized that higher rates of poverty and HPSA status would be associated with lower HPV vaccination rates due to lower access to the vaccinations. We also adjusted for outpatient visits per capita (ARF) and the number of religious organizations (North American Industry Classification System code 8131) per 1,000 population (ZBP). We used 2010 values for all explanatory variables.

Statistical analysis

We conducted analyses separately for boys and girls and for cumulative doses as well as the number of children fully vaccinated. We tested for spatial autocorrelation in the unadjusted HPV vaccination rates using choropleth maps generated using Stata's user-written command *spmap*, which color code each ZCTA using quintiles for HPV vaccination rates, and Moran's I (27). Values of I greater than (less than) the expected value indicate positive

(negative) spatial autocorrelation; nearby ZCTAs tend to exhibit similar (dissimilar) publicly funded HPV vaccination rates among eligible children. We used two definitions of neighbors. Contiguous neighbors share a common border or a single common point. We also used a weighted average of all ZCTAs with each ZCTA's contribution weighted by the inverse of the Euclidean distance between the centroids of the ZCTA and the other ZCTAs.

We then estimated nonspatial count data models for HPV vaccinations at the ZCTA level. These models explore how much of the spatial autocorrelation in HPV vaccination rates is explained by observable ZCTA characteristics. Specification tests revealed evidence of overdispersion in the number of vaccinations per ZCTA, so we estimated negative binomial models that adjusted for the variables discussed above. We tested for spatial autocorrelation of the residuals (expressed as the difference between the actual and predicted values divided by the eligible population) using choropleth maps and Moran's I.

Finally, we estimated negative binomial models with spatially correlated random effects [conditional autoregressive (CAR) models; ref. 28]. The vaccination rate was a function of ZCTA characteristics and two error terms: a standard negative binomial dispersion term and a spatial error term whose mean (conditional on the other ZCTAs) is equal to the average spatial error term among adjacent ZCTAs. We estimated the CAR model in a Bayesian framework using Markov chain Monte Carlo (MCMC) implemented in WinBUGS. We ran 200,000 simulations of the MCMC and report summary statistics from the posterior distribution of the model's parameters using the last 50,000 simulations. See the Supplementary Materials and Methods for details of the model and estimation. We also report choropleth maps showing the quintiles of HPV vaccination rates attributable to the CAR random effects.

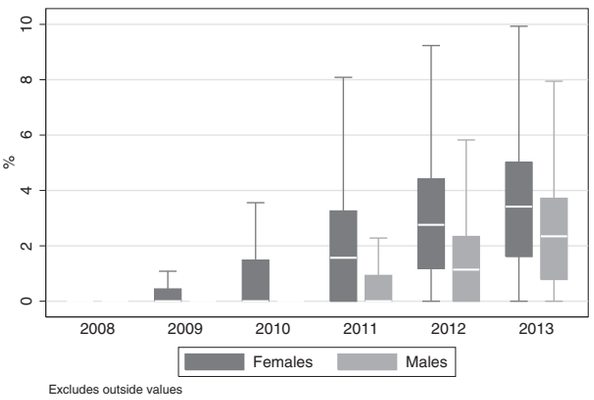

Figure 1.
Box plot of the percentage of uninsured and mean-tested, publicly insured children ages 9 to 14 years vaccinated against HPV (full series) using public funds over time ($N = 751$ ZCTAs).

Results

The percentage of uninsured and mean-tested, publicly insured children ages 9 to 14 years vaccinated against HPV (full series) using public funds has increased over time (Fig. 1). HPV vaccination rates for boys lagged behind those for girls in the 3 years after ACIP recommendation. In 2013, the median percentage that

Table 1. Summary statistics

	Mean	SD	Min.	Max.
ZCTAs used for girls ($N = 751$)				
Cumulative publicly funded doses	50.0	68.4	0.0	482.0
Publicly funded full series	8.9	12.8	0.0	97.0
Eligible population[a]	223.8	265.0	0.5	2,019.6
Female	0.509	0.031	0.157	0.576
Hispanic[b]	0.066	0.059	0.000	0.466
Black, non-Hispanic	0.201	0.195	0.000	0.986
Other race/ethnicity	0.041	0.070	0.000	0.786
Less than high school[c]	0.181	0.083	0.007	0.495
At least some college	0.509	0.144	0.122	0.957
Persistent poverty	0.080	0.271	0.000	1.000
HPSA	0.605	0.489	0.000	1.000
Outpatient visits per capita	1.840	1.283	0.000	7.708
Religious organizations per 1,000 population	1.180	1.460	0.000	17.340
ZCTAs used for boys ($N = 750$)				
Cumulative publicly funded doses	45.9	64.7	0.0	542.0
Publicly funded full series	6.8	10.5	0.0	93.0
Eligible population[a]	234.4	281.2	0.4	1,987.8
Female	0.509	0.029	0.157	0.597
Hispanic[b]	0.066	0.059	0.000	0.466
Black, non-Hispanic	0.196	0.189	0.000	0.865
Other race/ethnicity	0.041	0.070	0.000	0.786
Less than high school[c]	0.179	0.083	0.000	0.459
At least some college	0.511	0.143	0.122	0.957
Persistent poverty	0.075	0.263	0.000	1.000
HPSA	0.596	0.491	0.000	1.000
Outpatient visits per capita	1.847	1.279	0.000	7.708
Religious organizations per 1,000 population	1.150	1.350	0.000	17.340

[a]Uninsured and means-tested, publicly insured children ages 9 to 14 years.
[b]White, non-Hispanic is the reference group.
[c]High school is the reference group.

Figure 2.
Percentage of uninsured and means-tested, publicly insured children ages 9 to 14 years vaccinated against HPV using public funds (full series, unadjusted rates). A, girls; B, boys.

have had a publicly funded full series HPV vaccination was 3.4% for girls [interquartile range (IQR): 1.4%–5.0%] and 2.3% for boys (IQR: 0.6%–3.7%).

On average for ZCTAs, 50 publicly funded HPV doses were given between 2008 and 2013 for girls and 45.9 for boys, with SDs larger than the mean (Table 1). The number of children receiving publicly funded full doses was much lower on average: 8.9 per ZCTA for girls and 6.8 per ZCTA for boys. ZCTAs had 224 eligible girls and 235 eligible boys on average, ranging from 1 to approximately 2,000. On average, ZCTAs were evenly divided between males and females, 20% black, non-Hispanic, 6.6% Hispanic, and had over 50% of the population with at least some college. Approximately 8% of ZCTA's were in counties with persistent poverty and 60% were HPSA.

Choropleth graphs show pockets of high- and low-HPV vaccination rate ZCTAs (Fig. 2). Moran's I indicates significant positive clustering of HPV vaccination rates by ZCTA for boys using both definitions of neighboring ZCTAs (Table 2). This indicates that ZCTAs have vaccination rates for boys similar to their neighbors. Conversely, for girls, there was no statistically significant spatial autocorrelation for cumulative doses or full series rates.

The following variables were associated with higher levels of publicly funded HPV vaccination among girls in the negative binomial count data models [Table 3, maximum likelihood estimation (MLE) columns): share of the population that was Hispanic, black non-Hispanic, and other race/ethnicity for cumulative doses (relative to white, non-Hispanic); outpatient visits per capita; religious organizations per 1,000 population; and the number of uninsured and means-tested, publicly insured children ages 9 to 14 years. Conversely, the following variables were associated with lower levels of publicly funded HPV vaccination among girls: the share of the population with less than high-school education (relative to high school) and HPSA. Results for HPV vaccination among boys were similar in sign and statistical significance to girls except that the associations with other race/ethnicity, HPSA, and religious organizations per 1,000 population were less significant. The estimates of α were statistically significantly different from zero, indicating overdispersion in the data.

Conditional on the explanatory variables, there is still significant geospatial clustering of HPV vaccination rate residuals for boys. Moran's I values are much lower once we adjust for the covariates, but the *P* values indicate statistically

Table 2. Global test of spatial autocorrelation in publicly funded HPV vaccination rates: Moran's I[a]

	Girls				Boys			
	Cumulative doses		Full series		Cumulative doses		Full series	
	Unadjusted	Negative binomial residuals	Unadjusted	Negative binomial residuals	Unadjusted	Negative binomial residuals	Unadjusted	Negative binomial residuals
Contiguity neighbors								
I	0.018	0.009	0.011	0.010	0.068	0.030	0.065	0.037
P	0.198	0.314	0.283	0.300	**0.001**	**0.031**	**0.001**	**0.011**
Inverse-distance								
I	0.003	0.002	0.000	−0.000	0.008	0.002	0.008	0.004
P	0.057	0.107	0.286	0.315	**0.000**	**0.020**	**0.000**	**0.001**

NOTE: Bold *P* values indicate significance at the 95% confidence level.
[a]The expected value of Moran's I for 751 ZCTAs is −0.001.

Table 3. Publicly funded HPV immunizations among girls: negative binomial models

	Cumulative doses		Full series	
	MLE	CAR	MLE	CAR
Female	0.709	1.093[a]	0.030	0.204
	(−0.849 to 2.267)	(−0.150 to 2.342)	(−1.902 to 1.961)	(−1.873 to 2.331)
Hispanic[c]	1.961[b]	2.069[b]	1.842[b]	1.887[b]
	(1.339–2.583)	(1.398–2.738)	(0.960–2.724)	(0.997–2.783)
Black, non-Hispanic	0.492[b]	0.612[b]	0.233[a]	0.430[b]
	(0.295–0.688)	(0.345–0.874)	(−0.016 to 0.482)	(0.077–0.791)
Other race/ethnicity	0.422[b]	0.352	0.126	0.091
	(0.035–0.809)	(−0.175 to 0.890)	(−0.373 to 0.625)	(−0.600 to 0.781)
Less than high school[d]	−0.184[b]	−0.030	−0.200[b]	−0.157
	(−0.343 to −0.025)	(−0.931 to 0.908)	(−0.399 to −0.002)	(−1.513 to 1.227)
At least some college	−0.372	0.141	−0.241	0.206
	(−1.440–0.695)	(−0.389 to 0.676)	(−1.613 to 1.131)	(−0.570 to 0.990)
Persistent poverty	−0.046	0.004	0.012	−0.063
	(−0.634–0.543)	(−0.183 to 0.198)	(−0.765 to 0.788)	(−0.320 to 0.201)
HPSA	−0.100[b]	−0.073[a]	−0.111[b]	−0.081
	(−0.166 to −0.035)	(−0.155 to 0.008)	(−0.204 to 0.018)	(−0.191 to 0.030)
Outpatient visits per capita	0.035[b]	0.032[a]	0.045[b]	0.046[b]
	(0.009–0.061)	(−0.001 to 0.064)	(0.014–0.075)	(0.003–0.088)
Religious organizations per 1,000 population	0.082[b]	0.078[b]	0.108[b]	0.118[b]
	(0.030–0.135)	(0.042–0.114)	(0.038–0.178)	(0.052–0.179)
ln (eligible population)[e]	0.936[b]	0.935[b]	1.004[b]	1.011[b]
	(0.891–0.981)	(0.902–0.969)	(0.952–1.057)	(0.959–1.062)
Constant	3.116[b]	3.075[b]	1.352[b]	1.243[b]
	(3.071–3.160)	(3.044–3.107)	(1.288–1.416)	(1.126–1.333)
α (over dispersion)	0.126[b]	0.072[b]	0.130[b]	0.085[b]
	(0.103–0.155)	(0.054–0.093)	(0.098–0.171)	(0.059–0.117)
σ^2_u (variance of spatial error term)		0.185[b]		0.184[b]
		(0.114–0.267)		(0.092–0.291)
Observations	751	751	751	751

NOTE: Point estimates (MLE) and posterior means (CAR) reported. 95% confidence intervals (MLE) and 95% credible intervals (CAR) in parentheses.
[a]$P < 0.10$.
[b]$P < 0.05$.
[c]White, non-Hispanic is the reference group.
[d]High school is the reference group.
[e]Uninsured and means-tested, publicly insured children ages 9 to 14 years.

significant positive clustering in the residuals (Table 2). There is no evidence of spatial autocorrelation in the residuals for girls.

Compared with the maximum likelihood estimates that do not account for spatial autocorrelation, the coefficients (point estimates for MLE and posterior means for CAR) for other race/ethnicity, less than high school, HPSA (except girls cumulative doses), and outpatient visits per capita (boys) are no longer significant in the CAR model (i.e., the posterior 95% credible interval includes zero; Tables 3 and 4). In addition, for boys the coefficients for percentage of the population that is female (positive) and persistent poverty (negative) are statistically significant in the CAR model for the full HPV series. The coefficients for Hispanic, black non-Hispanic, outpatient visits per capita (girls), and religious organizations per 1,000 population (girls) are very similar in the CAR models. The CAR model's estimate of α still indicates significant overdispersion in vaccination rates, supporting the negative binomial specification over Poisson, but the estimates are much smaller than MLE; the CAR model attributes a larger portion of the over dispersion to spatial correlation in the error terms.

We calculated the incidence rate ratio from the full series CAR estimates. A 1% point increase in the share of the population that was Hispanic was associated with a 2% increase in the publicly funded HPV vaccination rate for girls [IRR = 1.02 = exp (1.887/100)] and a 3% increase for boys, holding the other covariates constant. (The coefficient was scaled to express the variable as a percentage instead of a fraction.) A 1% point increase in the share of the population that was black non-Hispanic was associated with a 0.4% increase in the vaccination rate for girls and a 1% increase for boys. Each additional religious organization per 1,000 population in the ZCTA was associated with a 12% increase in the vaccination rate for girls. Persistent poverty status was associated with a 30% lower vaccination rate among eligible boys (IRR = 0.70).

Figure 3 shows quintile choropleth maps of HPV vaccination rates attributable to the CAR random effects in the CAR model. Under the assumptions of the CAR model, these values represent spatial heterogeneity conditional on population size and the covariates included in the model. Clustering of HPV vaccination rates is evident, with areas of relatively low rates concentrated in the northeast, south, and west-central portions of the state.

Discussion

Registry data from North Carolina revealed areas of especially low rates in publicly funded HPV vaccinations among uninsured and means-tested, publicly insured children. The spatial analysis revealed spatial autocorrelation of HPV vaccination rates among boys—ZCTAs tended to have HPV vaccination rates that were similar to their neighbors. This result was partially explained by

Table 4. Publicly funded HPV immunizations among boys: negative binomial models

	Cumulative doses		Full series	
	MLE	**CAR**	**MLE**	**CAR**
Female	1.522[a]	1.231	1.783	2.163[a]
	(−0.046 to 3.089)	(−0.256 to 2.715)	(−1.899 to 5.465)	(−0.302 to 4.777)
Hispanic[c]	2.933[b]	2.856[b]	2.804[b]	2.721[b]
	(2.113–3.753)	(2.065–3.614)	(1.603–4.004)	(1.677–3.785)
Black, non-Hispanic	0.578[b]	0.671[b]	0.644[b]	0.871[b]
	(0.329–0.827)	(0.367–0.979)	(0.289–0.999)	(0.461–1.284)
Other race/ethnicity	0.435[a]	0.098	0.216	0.070
	(−0.046–0.916)	(−0.580 to 0.759)	(−0.527 to 0.960)	(−0.784 to 0.904)
Less than high school[d]	−0.232[b]	−0.526	−0.507[b]	−0.638
	(−0.430 to 0.034)	(−1.481 to 0.487)	(−0.778 to 0.235)	(−2.229 to 0.950)
At least some college	−0.425	0.160	−0.388	0.181
	(−1.762–0.911)	(−0.404 to 0.746)	(−2.087 to 1.312)	(−0.724 to 1.086)
Persistent poverty	0.179	−0.026	0.063	−0.360[b]
	(−0.553–0.911)	(−0.242 to 0.196)	(−0.842 to 0.968)	(−0.685 to 0.033)
HPSA	−0.076[a]	−0.025	−0.054	−0.031
	(−0.156–0.003)	(−0.121 to 0.072)	(−0.165 to 0.058)	(−0.164 to 0.102)
Outpatient visits per capita	0.028[a]	0.027	0.034[a]	0.043
	(−0.004–0.059)	(−0.010 to 0.066)	(−0.004 to 0.071)	(−0.008 to 0.094)
Religious organizations per 1,000 population	0.053	0.059[b]	0.055	0.060
	(−0.017–0.123)	(0.014–0.104)	(−0.037 to 0.148)	(−0.020 to 0.136)
ln (eligible population)[e]	0.875[b]	0.896[b]	0.910[b]	0.916[b]
	(0.819–0.930)	(0.860–0.932)	(0.842–0.978)	(0.860–0.973)
Constant	3.040[b]	2.967[b]	1.096[b]	0.996[b]
	(2.988–3.093)	(2.934–3.000)	(1.015–1.177)	(0.929–1.063)
α (over dispersion)	0.196[b]	0.071[b]	0.203[b]	0.094[b]
	(0.160–0.239)	(0.051–0.096)	(0.147–0.283)	(0.064–0.134)
σ^2_u (variance of spatial error term)		0.389[b]		0.359[b]
		(0.284–0.506)		(0.226–0.519)
Observations	750	750	750	750

NOTE: Point estimates (MLE) and posterior means (CAR) reported. 95% confidence intervals (MLE) and 95% credible intervals (CAR) in parentheses.
[a]$P < 0.10$.
[b]$P < 0.05$.
[c]White, non-Hispanic is the reference group.
[d]High school is the reference group.
[e]Uninsured and means-tested, publicly insured children ages 9 to 14 years.

demographic, economic, and healthcare characteristics of the ZCTAs, but not wholly. HPV vaccination rates for girls were higher than for boys, but still well below Healthy People 2020 targets. We did not detect any significant geographic clustering of publicly funded HPV vaccinations among eligible girls. Our finding of significant clustering for boys and not girls could be because the diffusion process is less advanced for boys, who display areas with early adopters.

The results of this study could be useful in helping to target areas to increase HPV vaccinations and reduce the spread of HPV within the state. Previous studies of HPV and cervical cancer burden have suggested geospatial targeting as an effective strategy (19–22). To the extent that the geospatial clustering of vaccination rates is due to causal influences from one ZCTA to another (e.g., through information networks), targeting interventions to increase HPV vaccination among eligible children in one area could also lead to increases in neighboring areas.

Several federal and state policies have attempted to increase access to HPV vaccinations by reducing out-of-pocket costs of the vaccine, including the VFC program and the inclusion of the vaccine in preventive services mandated by the Affordable Care Act. However, our results indicate that even among children qualifying for publicly funded vaccination, rates were lower in areas of persistent poverty and shortages of providers. Therefore, access to the vaccine entails more than just lower out-of-pocket costs, including access to providers.

This study has limitations that are important for the interpretation and application of the results. Our analysis did not include privately funded vaccines, vaccinations given by pharmacies during this period, or doses given to children who might have moved out of state. We also focused on younger ages than earlier studies (10). Thus, the vaccination rates reported in Fig. 1 are lower than in other data sources. For example, based on data from the 2012 NIS-Teen survey, the rate of full vaccination (i.e., three or more doses) by the age of 13 years was 6.8% nationally and 6.6% for North Carolina. We focused on publicly funded vaccinations, for which reporting to the NCIR was required, to minimize the extent of under-reporting for our analysis sample. The benefit of registry data is that it avoids recall and self-reporting bias present in surveys (29, 30).

The unexpected results for the number of religious organizations could result from unmeasured differences in denominational attitudes. ZCTAs and ZIP codes were not created as geographic markers and their use in spatial analysis may lead to representational errors (31). There are alternative Bayesian specifications for spatial effects, which could generate different clusters (32, 33).

There are likely unmeasured factors that would explain the observed geospatial patterns in HPV vaccination rates and the differences between boys and girls. These include parental and provider attitudes, concerns about effects on sexual behavior, low perceived risk of HPV infection, and social influences (14). We

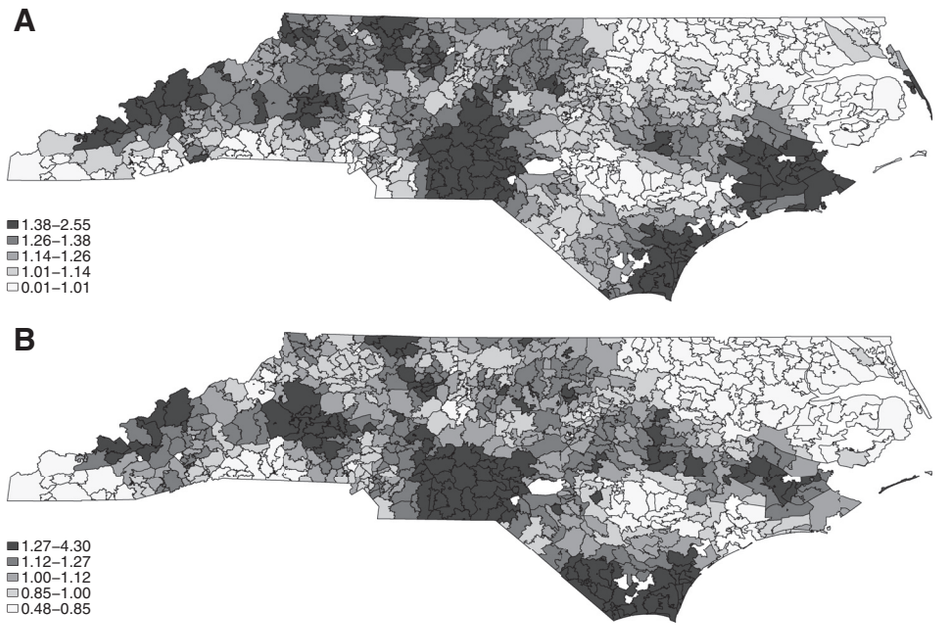

Figure 3.
Publicly funded HPV vaccination rates (full series) attributable to CAR random effects. A, girls; B, boys.

believe that the results motivate further analysis of clusters to find out what is driving the higher- (lower-) than expected use of HPV vaccination. This could include investigating the potential role of network effects through information transmission about HPV vaccination (positive and negative; ref. 34) and potential free-rider problems caused by perceived herd immunity (i.e., relying on others to vaccinate to protect your child from exposure; ref. 35).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J.G. Trogdon
Development of methodology: J.G. Trogdon
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.G. Trogdon
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.G. Trogdon, T. Ahn
Writing, review, and/or revision of the manuscript: J.G. Trogdon, T. Ahn
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.G. Trogdon

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References

1. Centers for Disease Control and Prevention. Human papillomavirus vaccination coverage among adolescent girls, 2007–2012, and postlicensure vaccine safety monitoring, 2006–2013 - United States. MMWR Morb Mortal Wkly Rep 2013;62:591–5.
2. Markowitz LE, Dunne EF, Saraiya M, Lawson HW, Chesson H, Unger ER, et al. Quadrivalent Human Papillomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2007;56:1–24.
3. Centers for Disease Control and Prevention. Recommendations on the use of quadrivalent human papillomavirus vaccine in males–Advisory Committee on Immunization Practices (ACIP), 2011. MMWR Morb Mortal Wkly Rep 2011;60:1705–8.
4. Markowitz LE, Hariri S, Lin C, Dunne EF, Steinau M, McQuillan G, et al. Reduction in human papillomavirus (HPV) prevalence among young women following HPV vaccine introduction in the United States, National Health and Nutrition Examination Surveys, 2003–2010. J Infect Dis 2013;208:385–93.
5. Goldie SJ, Kohli M, Grima D, Weinstein MC, Wright TC, Bosch FX, et al. Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. J Natl Cancer Inst 2004;96:604–15.
6. Goldhaber-Fiebert JD, Stout NK, Salomon JA, Kuntz KM, Goldie SJ. Cost-effectiveness of cervical cancer screening with human papillomavirus DNA testing and HPV-16,18 vaccination. J Natl Cancer Inst 2008;100:308–20.
7. Armstrong EP. Prophylaxis of cervical cancer and related cervical disease: a review of the cost-effectiveness of vaccination against oncogenic HPV types. J Manage Care Pharm 2010;16:217–30.
8. Chesson HW, Ekwueme DU, Saraiya M, Dunne EF, Markowitz LE. The cost-effectiveness of male HPV vaccination in the United States. Vaccine 2011;29:8443–50.
9. Centers for Disease Control and Prevention. National and state vaccination coverage among adolescents aged 13–17 years–United States, 2012. MMWR Morb Mortal Wrkly Rep 2013;62:685–93.
10. Moss JL, Gilkey MB, Reiter PL, Brewer NT. Trends in HPV vaccine initiation among adolescent females in North Carolina, 2008–2010. Cancer Epidemiol Biomarkers Prev 2012;21:1913–22.
11. Fisher H, Trotter CL, Audrey S, MacDonald-Wallis K, Hickman M. Inequalities in the uptake of human papillomavirus vaccination: a systematic review and meta-analysis. Int J Epidemiol 2013;42:896–908.

12. Tsui J, Gee GC, Rodriguez HP, Kominski GF, Glenn BA, Singhal R, et al. Exploring the role of neighborhood socio-demographic factors on HPV vaccine initiation among low-income, ethnic minority girls. J Immigr Minor Health 2013;15:732–40.
13. Kahn JA, Lan D, Kahn RS. Sociodemographic factors associated with high-risk human papillomavirus infection. Obstet Gynecol 2007;110:87–95.
14. Holman DM, Benard V, Roland KB, Watson M, Liddon N, Stokley S. Barriers to human papillomavirus vaccination among US adolescents: a systematic review of the literature. JAMA Pediatr 2014;168:76–82.
15. Reiter PL, Cates JR, McRee AL, Gottlieb SL, Shafer A, Smith JS, et al. Statewide HPV vaccine initiation among adolescent females in North Carolina. Sex Transm Dis 2010;37:549–56.
16. Pruitt SL, Schootman M. Geographic disparity, area poverty, and human papillomavirus vaccination. Am J Prev Med 2010;38:525–33.
17. Moss JL, Gilkey MB, Griffith T, Bowling JM, Dayton AM, Grimshaw AH, et al. Organizational correlates of adolescent immunization: findings of a state-wide study of primary care clinics in North Carolina. Vaccine 2013;31:4436–41.
18. Rondy M, van Lier A, vande Kassteele J, Rust L, de Melker H. Determinants for HPV vaccine uptake in the Netherlands: A multilevel study. Vaccine 2010;28:2070–5.
19. Nelson EJ, Hughes J, Kulasingam SL. Spatial patterns of human papillomavirus-associated cancers within the state of Minnesota, 1998–2007. Spat Spatiotemporal Epidemiol 2014;9:13–21.
20. Horner MJ, Altekruse SF, Zou Z, Wideroff L, Katki HA, Stinchcomb DG. U.S. geographic distribution of prevaccine era cervical cancer screening, incidence, stage, and mortality. Cancer Epidemiol Biomarkers Prev 2011;20:591–9.
21. Tsui J, Rodriguez HP, Gee GC, Escobedo LA, Kominski GF, Bastani R. Are HPV vaccination services accessible to high-risk communities? A spatial analysis of HPV-associated cancer and Chlamydia rates and safety-net clinics. Cancer Causes Control 2013;24:2089–98.
22. Reiter PL, Katz ML, Paskett ED. HPV vaccination among adolescent females from Appalachia: implications for cervical cancer disparities. Cancer Epidemiol Biomarkers Prev 2012;21:2220–30.
23. Dayton A. Improving quality of health care using the North Carolina Immunization Registry. North Carolina Med J 2014;75:198–203.
24. Centers for Disease Control and Prevention. Vaccines for Children Program (VFC) [updated April 24, 2014]. Available from: http://www.cdc.gov/vaccines/programs/vfc/index.html.
25. HealthLandscape. ZIP Code to ZCTA Crosswalk [updated May 16, 2014]. Available from: www.udsmapper.org/zcta-crosswalk.cfm.
26. U.S. Census Bureau. TIGER Products [updated May 16, 2014]. Available from: https://www.census.gov/geo/maps-data/data/tiger.html.
27. Moran PAP. Notes on Continuous Stochastic Phenomena. Biometrika 1950;37:17–23.
28. Neyens T, Faes C, Molenberghs G. A generalized Poisson-gamma model for spatially overdispersed data. Spat Spatiotemporal Epidemiol 2012;3:185–94.
29. Brien S, Kwong JC, Charland KM, Verma AD, Brownstein JS, Buckeridge DL. Neighborhood determinants of 2009 pandemic A/H1N1 influenza vaccination in Montreal, Quebec, Canada. Am J Epidemiol 2012;176:897–908.
30. Centers for Disease Control and Prevention. Interim results: state-specific seasonal influenza vaccination coverage - United States, August 2009-January 2010. MMWR Morb Mortal Wrkly Rep 2010;59:477–84.
31. Grubesic TH, Matisziw TC. On the use of ZIP codes and ZIP code tabulation areas (ZCTAs) for the spatial analysis of epidemiological data. Int J Health Geogr 2006;5:58.
32. Best N, Richardson S, Thomson A. A comparison of Bayesian spatial models for disease mapping. Stat Methods Med Res 2005;14:35–59.
33. Wakefield J. Disease mapping and spatial regression with count data. Biostatistics 2007;8:158–83.
34. Freed GL, Clark SJ, Butchart AT, Singer DC, Davis MM. Sources and perceived credibility of vaccine-safety information for parents. Pediatrics 2011;127:S107–12.
35. Wu B, Fu F, Wang L. Imperfect vaccine aggravates the long-standing dilemma of voluntary vaccination. PLoS ONE 2011;6:e20577.