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Predictors Of Patterns In Pediatric Pneumococcal Vaccine Uptake In Connecticut, 2000-2009

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Abstract

Introduction:
Streptococcus pneumoniae is an important human pathogen with more than 92 identified serotypes of varying invasiveness. Asymptomatic colonization of the nasopharynx can later cause diseases such as sinusitis, AOM, or IPD. Children under age five are the major reservoirs of infection. Pediatric conjugate vaccines effectively reduce vaccine-type carriage and disease. Vaccinating children can have indirect effects on adults.

Materials and Methods:
This paper used CIRTS to describe patterns of three- and four-dose PCV uptake throughout Connecticut in 2000 to 2009 birth cohorts. Spatial cluster analysis was used to detect any clusters with higher than expected proportions of unvaccinated children. Log-binomial regression models were used to assess unadjusted and adjusted associations between variables from the 2000 U.S. Census and proportions of unvaccinated children in ZCTAs. These factors describe the racial and socioeconomic composition, age distribution, population density, and housing characteristics of ZCTAs.

Results:
There were 315,628 children across 266 ZCTAs in the registry. Across all cohorts and ZCTAs, 91 percent of children received three doses of PCV and 74 percent received all four doses. Vaccination rates varied across cohorts and by poverty level. Cluster analysis revealed several significant clusters. All selected community-level variables were independently associated with a high proportion of unvaccinated children in ZCTAs. All but three variables comprise a final multivariate model.

Discussion:
Connecticut enjoys a robust uptake of both three and four doses of PCV. Areas near Groton, New Haven, and parts of Windham, Tolland, Hartford, and New London counties would benefit from increased vaccine delivery efforts. Socioeconomic variables were consistently related to risk of ZCTAs having a high proportion of unvaccinated children.

Abbreviations Used:
AIC= Akaike information criterion
APIC=Advisory Committee on Immunization Practices
AOM=acute otitis media
CDC=Centers for Disease Control and Prevention
CIRTS=Connecticut Immunization Registry and Tracking System
HMO=health maintenance organization
IAP=Immunization Action Plan
IPD=invasive pneumococcal disease
NP=nasopharyngeal
PCP=primary care physician
PCV=pneumococcal conjugate vaccine
PCV7=heptavalent pneumococcal vaccine

PCV13=13-valent pneumococcal conjugate vaccine
PPV23=23-valent plain polysaccharide vaccine
RR=relative risk
CHIP=Children's Health Insurance Program
UFFS=unassigned fee-for-service
VFC=Vaccines for Children
VT=vaccine type
ZCTA=zip code tabulation area

Acknowledgments

I would like to thank Ms. Sharova and the Connecticut Department of Health for use of the CIRTS data set, and Drs. Daniel Weinberger and Melinda Pettigrew for continued guidance through the project's inception and completion. As always, to EMM and JIM for constant support and proofreading, and to ARM for inspiring my original interest in human biology and public health.

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Introduction

Streptococcus pneumoniae: Introduction and Epidemiology

Streptococcus pneumoniae is a lancet-shaped, Gram-positive bacterium with more than 92 identified serotypes. Pneumococci are part of the normal flora found in the nasopharynx, although rates of asymptomatic carriage vary with environment, presence of upper respiratory tract infections, and age. In 2000, an estimated 14.5 million children under age five worldwide were affected by severe pneumococcal disease, resulting in about 11 percent of deaths in this age group (Camilli et al., 2013). In 2011, in the United States, more than 36,000 cases of invasive pneumococcal disease (IPD) were diagnosed; more than 90 percent of these cases were in children younger than age two and in adults over age 50 (Drijkoningen & Rohde, 2014). Children under five years old are the major reservoirs of infection. The rate of colonization with the bacteria is usually quite high in the first years of life. Transmission of *S. pneumoniae* occurs through direct person-to-person contact by way of respiratory droplets or via autoinoculation in carriers.

Colonization with *S. pneumoniae* is a necessary precursor to disease development. Serotype invasiveness and host susceptibility (such as age, nutritional and immune status, recent infections, and co-morbidities) are important factors in disease incidence following exposure. Factors found to be associated with carriage include young age, current upper respiratory tract infection, child-care attendance, having younger siblings, lower income, and living in communities with crowded households (Hsu et al., 2013). Crowding and season, particularly winter and spring, also play roles in transmission of the bacteria to susceptible people.

S. pneumoniae causes a range of ailments if it moves from its ecological niche in the nasopharynx (NP) to other sites in the body, such as the sinuses, middle ear cavity, lungs, or bloodstream (Camilli et al., 2013). In these sites, it can manifest as sinusitis, acute otitis media (AOM), or IPD, resulting in pneumonia, bacteremia, and meningitis. IPD is a nationally notifiable disease to the Centers for Disease Control and Prevention via the National Notifiable Diseases Surveillance System or Active Bacterial Core Surveillance (as in Connecticut).

Not all pneumococci are encapsulated, but the antiphagocytic, complex polysaccharide capsule surrounding the pneumococci is the major virulence factor and the basis for serotype classification. Serotype distribution differs by age group and geography, but the more heavily encapsulated serotypes are carried more frequently (Steens, Bergsaker, Aaberge, Ronning, & Verstrheim, 2013; Weinberger, Malley, & Lipsitch 2011). Type-specific antibody to the capsule is protective and some antibodies may cross-react with additional serotypes. Antibodies and the complement system opsonize the bacterium and mark it for phagocytosis and clearance. Serotypes vary in their capacity to evade complement deposition (Weinberger et al., 2011). For example, serotype 19F has an increased antibody requirement for clearance, likely due to its thick polysaccharide capsule and increased resistance to C3 accumulation (Grant et al., 2013).

Pneumococcal Vaccines

In the past, young children have experienced a significant burden of pneumococcal disease prior to routine pediatric vaccination. The first pneumococcal vaccine targeting the polysaccharide capsule was licensed in the United States in 1977, but was replaced by a 23-

valent polysaccharide vaccine (PPV23) in 1983. PPSV23 is currently recommended for adults over 65 years old and for children over 2 years old with certain immunocompromising conditions. The first pneumococcal conjugate vaccine (PCV) was introduced in 2000. The vaccine works by conjugating the capsular polysaccharide to proteins, resulting in antigens that are T-cell dependent immunogens. Children's immune systems are then able to develop an effective response (Shapiro, 2012). In the United States, the conjugate vaccine is given in four doses at months two, four, and six, and between months 12 and 15.

PPSV23 has been reported to be reasonably effective in preventing IPD in adults but does not protect adults from noninvasive *S. pneumonia* infections such as non-bacteremic pneumonia. Additionally, the vaccine is not effective in children under two years old, as polysaccharide antigens induce T-cell independent immunity, resulting in low antibody levels and inadequate immunologic memory (Kellner, Church, MacDonald, Tyrrell, & Scheifele, 2005). It has been shown, however, to significantly reduce mortality due to pneumonia in adults over age 65 (Soneji & Metlay, 2011).

After vaccination with a conjugate vaccine, serotype prevalence in the NP is in flux for a few years before it reaches a steady state. Vaccine serotypes are less likely to colonize the NP and transmission is therefore interrupted (Shapiro, 2012; Weinberger et al., 2011). The heptavalent PCV (PCV7) contained serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F: the seven most common causes of disease in children at the time of introduction (Camilli et al., 2013). By 2005, uptake of PCV7 reached approximately 83 percent for a three-dose series (Link-Gelles, Taylor, & Moore, 2013). In 2010, six additional serotypes were added to the collection in PCV7 to make a 13-valent pneumococcal conjugate vaccine (PCV13). Schuck-

Paim and colleagues (2013) explain PCV13 coverage rose rapidly, due in part to existing procedures established for PCV7. They estimate by March 2012, 82 percent of children aged six to 23 months were fully immunized with PCV13 and about 40 percent of toddlers 15 to 59 months old received a catch-up dose by March 2013. Therefore, most benefits from the vaccine for children under five years old will be achieved within four years of introduction, including coverage sufficient to achieve and maintain herd immunity.

Vaccine Effects

Worldwide, PCV7 is highly effective at reducing vaccine-type (VT) carriage and IPD in places where it has been included in infant and childhood immunization programs. However, effectiveness of PCV7 varied by serotype, ranging from 87 percent against 19F to 100 percent against 9V (Grant et al., 2013; Nurhonen and Auranen, 2014). Eight years after the introduction of PCV7, about 60 percent of invasive disease in children under age five was caused by non-vaccine types 1, 3, 5, 6A, 7F, and 19A. Introducing PCV7 opened an ecological niche to be filled by serotypes not included in the vaccine. The non-vaccine serotypes that fill this void, such as 19A, depend on biological properties of the strain (that is, virulence) and antibiotic use (Weinberger et al., 2011). Additionally, community-level variables can impact carriage rates differently (Hsu et al., 2013). VT 19F continues to colonize and occasionally cause invasive disease in Navajo and Apache populations in the United States (Grant et al., 2013). The introduction of PCV7 in 2000 resulted in diminished cases of pediatric AOM and lower respiratory tract infections, as well as a net decline in IPD in children under five years old except in certain populations in Spain, France, and Alaska (Steens et al., 2013; Weinberger et al., 2011). The decline in IPD observed in vaccinated

children was similarly detected in unvaccinated people of all ages. However, because non-PCV7 serotypes replaced PCV7 types as nasopharyngeal colonizers, there was little net change in bacterial carriage prevalence (Weinberger et al., 2011). Antibodies against 19F showed little cross-protection against 19A, and this serotype caused a majority of the increase in disease caused by non-PCV7 serotypes (Grant et al., 2013; Shapiro, 2012). Several studies have also documented heterogeneity in the indirect benefits of vaccinating children, describing no net benefit as a consequence of serotype replacement versus modest replacement (Weinberger et al., 2011).

PCV13 has been shown to generate levels of antibodies commensurate to those induced by PCV7. In a predictive model based on active surveillance data, Link-Gelles et al. (2013) estimate PCV13 will prevent 167,000 to 170,000 IPD cases in the decade from 2010 to 2020. Rates of invasive disease in children under five years old will decrease from 21.9 to 9.3 cases per 100,000 population. Cross-reaction between serotypes 6A and 6C has been demonstrated in vitro, and use of PCV13 resulted in a decrease in serotype 6C in both targeted and non-targeted age groups in Norway (Camilli et al., 2013; Steens et al., 2013). PCV13 is likely to result in additional serotype replacement in the same pattern of carriage and disease replacement as resulted from PCV7 (Steens et al., 2013; Weinberger et al., 2011). For example, incidence of non-PCV13 types, especially 23B and 15A, increased in Norway after the introduction of PCV13 (Steens et al., 2013). Nurhonen and Auranen (2014) predict PCV13 can reduce IPD cases in Finnish children under five years old by 75 percent, but that serotype replacement on the population level is likely to temper this reduction to 20 to 40 percent. The authors describe the currently available vaccines as sub-optimal and introduce an algorithm to discover optimal serotype compositions for future

pneumococcal vaccinations, depending on the age group of interest (Nurhonen & Auranen, 2014).

This Paper

Clearly, PCV uptake is not only important in protecting children from disease, but can impact adults as well. Immunization registries record pediatric vaccinations, which help ensure high coverage, decrease over-immunization, and provide data regarding vaccine safety (Linkins et al., 2006). Unfortunately, despite available resources in the United States for registry development, only about 48 percent of children were enrolled in one in 2004. Funding for registries can be supplied by federal, state, or local governments, private foundations, or managed care organizations. Registries can include mandatory provider reporting or may need explicit parental consent for participation (opt-in). Linkins and colleagues (2006) found most parents in a sample from Colorado, Massachusetts, Missouri, and Washington were unaware of immunization registries in their areas. Parents of vaccinated children were more likely than parents of exempt children to support laws authorizing registries and to support mandatory physician reporting to registries. Therefore, parental support for registries may increase as awareness of their existence increases, in addition to improved knowledge about vaccine preventable diseases, the risks of refusing vaccination, and the safety and utility of childhood vaccines. Registries can be especially useful given the increasingly complex pediatric vaccination recommendations. Additionally, widespread registry participation will improve the usefulness of the registry and help ensure more complete and accurate information for both the individual and the population.

The goal of this paper is to use the Connecticut Immunization Registry and Tracking System (CIRTS) to describe patterns of PCV uptake throughout the state, by zip code, in 2000 to 2009 birth cohorts. The paper assesses which, if any, community-level factors collected in the 2000 United States Census are associated with lower vaccine uptake and how they may describe the patterns in uptake. Spatial cluster analysis identifies parts of Connecticut with higher proportions of unvaccinated children, which provides areas for continued research and possible future interventions. Community-level variables hypothesized to be associated with vaccine coverage are based on previously published reports (Omer et al., 2008). These include variables that describe the racial and socioeconomic composition, age distribution, population density, and housing characteristics of Connecticut zip code tabulation areas (ZCTA).

Materials

Vaccination information come from previously collected CIRTS surveillance data and include the total number of Connecticut children in the registry, the total number vaccinated with three doses of PCV, and the total number vaccinated with four doses of PCV, all aggregated by zip code and birth cohort (2000 to 2009). CIRTS is a statewide pediatric immunization registry introduced in 1998. It helps keep children's vaccinations up-to-date by making such records available to healthcare providers and parents. The registry is an integral part of the Connecticut Immunization Action Plan (IAP). The Centers for Disease Control and Prevention (CDC) funds the IAP to increase and maintain immunization rates of preschool children in an effort to reduce the burden of disease and the spread of vaccine-preventable diseases. The IAP program is maintained by 11 sites in

areas with the highest risk of low immunization rates: Bridgeport, Danbury, health departments of Hartford, New Britain, New Haven, Norwalk, Stamford, Waterbury, and West Haven, and health districts of Naugatuck Valley and Torrington Area (Connecticut Department of Health, 2013).

In addition to tracking immunization rates through CIRTS, the IAP provides education to the pubic regarding the importance of vaccination and conducts assessments in a variety of locations to improve vaccine delivery. Connecticut children born after January 1, 1998, are included in CIRTS via their birth certificate information, although parents can opt-out of the registry. The Connecticut Department of Health sends monthly compliance reports to pediatric practices to collect immunization histories of children who have turned seven to 19 months old, key ages at which immunization status should be confirmed. Connecticut law protects confidentiality of all records.

Community-level demographic information was drawn from the U.S. Census Bureau's American FactFinder, which makes information from various censuses and surveys available to the public. Variables were drawn from several matrices in summary files one and three of the 2000 U.S. Census, and, as described above, were chosen for this study based on previously published reports (Omer, 2008). These variables are: (1) average household size (total households, including family and non-family households); (2) family size (total households; related by birth, marriage, etc.); (3) total population (both sexes); (4) total population under five years old (both sexes); (5) percent of population under five years old (both sexes); (6) percent of population identified as black (alone or in combination with other races); (7) income per capita (U.S. dollars, in 1999); (8) median household income (U.S. dollars, in 1999); and (9) percent of the population below the U.S.

Census poverty threshold (all individuals for whom status is determined; $17,029 for a family of four in 1999). Percent below the poverty threshold was also made into a four-level categorical variable (0.0-4.9 percent, 5.0-9.9 percent, 10.0-19.9 percent, and greater than or equal to 20.0 percent) based on published work by Kreiger, Chen, Waterman, Rehkopf, and Subramanian (2003, 2005) on using a priori cut-points for area-based socioeconomic measures in studying public health disparities. Area information (in square miles) was also obtained and was used to calculate population density variables for the total population and population less than five years old.

Because CIRTS data is aggregated at the zip code level, it was necessary to obtain U.S. Census information at the ZCTA level. ZCTAs are statistical entities used by the U.S. Census Bureau to tabulate summary statistics. They were first used in the 2000 U.S. Census and are comprised of census blocks. ZCTAs may represent a few city blocks or many square miles, as they reflect the size of the census blocks in the area. All addresses (residential and non-residential) in each census block were examined for United States Postal Service zip codes (available in the U.S. Census Bureau's MAF/TIGER database), and the most frequently occurring zip code was assigned to the block. Blocks were then aggregated by zip code to create larger areas. Blocks without a single most frequently occurring zip code were assigned to the ZCTA with the longest shared boundary. Individual businesses or organizations with their own zip codes may not have a ZCTA, and zip codes representing very few addresses are not assigned a ZCTA. In most cases, the ZCTA code matches the zip code for an area. CIRTS data sets were merged with FactFinder sets and restricted to those observations with census-defined ZCTAs.

Methods

Vaccination rates for three and four doses of PCV were calculated from the CIRTS data. Univariate analysis was conducted on the demographic and geographic variables to better understand their distributions across Connecticut.

SaTScan version 9.2 was used for spatial cluster detection, again, for three and four doses of PCV. The analysis was purely spatial and used a Bernoulli model to scan Connecticut ZCTAs for high rates of unvaccinated children, based on ZCTA centroids and a circular window shape with a maximum spatial cluster size of 50 percent of the population at risk. SaTScan handles sparse data well due to its continuously moving window design (Kulldorff & Nagarwalla, 1995). The program runs a number of simulations to generate random replications of the data set under the null hypothesis of complete spatial randomness. If the maximum likelihood ratio calculated for the most likely cluster in the data set is high compared to the maximum likelihood ratio calculated for the most likely cluster in the randomly generated data sets, there is evidence against the null and for the presence of clusters. P-values were calculated with the default option, which is a combination of standard and sequential Monte Carlo methods and the Gumbel approximation, and included 999 Monte Carlo replications. P-values are adjusted for multiple testing. No geographic overlap was chosen for reporting of secondary clusters, which is the default setting, but more importantly, the most restrictive option. Setting no restrictions on secondary clusters would result in reporting the most likely cluster for each grid point, including clusters with p=1.0. Clusters were also based on the Gini index, which is a measure of spatial dispersion. SaTScan selects the group of non-overlapping clusters

that maximizes this index, engendering large differences in rates between the cluster and non-cluster areas.

SAS version 9.3 (SAS Institute, Inc., Cary, N.C.) was used for all statistical analyses and mapping. Bivariate analysis examined the unadjusted associations between the study variables and the proportion of unvaccinated children in the registry across ZCTAs. These analyses were carried out for both three and four doses of PCV. This analysis was accomplished using log-binomial regression, which is an appropriate method to estimate relative risk (RR) when the outcome of a cohort study is common. In such scenarios, the odds ratios become increasing different from relative risks and tend to overestimate the true effect of an exposure variable on the risk of the outcome (McNutt, Wu, Xue, & Hafner, 2003; Robbins, Chao & Fonseca, 2002). Three variables were log-transformed because they were highly positively skewed (population under five years old, population density, and population density under five years old). Analyses were also restricted to 2006 to 2009 birth cohorts, as vaccination uptake rates were relatively stable in these cohorts, as compared with the 2000 to 2005 cohorts.

Multivariate analysis on the restricted data sets was conducted to understand the adjusted associations between study variables and the proportion of unvaccinated children across ZCTAs. These analyses were again performed with both the three- and four-PCV dose data sets. The same log-transformed variables were included. Backwards selection sequentially dropped the least-significant predictor variables (p-value greater than 0.05), and Akaike information criterion (AIC) was used to determine the best fit.

Results

Demographic Information

Table 1 describes the median and range of the selected demographic and geographic variables. The variability in size and population represented inherent in ZCTAs as entities for the U.S. Census is apparent, compared to, for example, census tracts.

Table 1. Selected demographic and geographic variables of Connecticut ZCTAs (n=266).

Variable	Median	Range
Household Size	2.57	1.54 - 3.21
Family Size	3.05	2.38 - 4.00
Total Population	8,696.00	42.00 - 60,153.00
Population Under 5 Years Old	553.00	2.00 - 4,086.00
Percent of Population Under 5 Years Old	6.30	0.20 - 23.50
Percent Black Residents	1.53	0.00 - 90.19
Area[a]	20.11	0.01 - 112.55
Population Density[b]	458.84	22.91 - 9,449.42
Population Density Under 5 Years Old[c]	27.43	1.03 - 994.31
Percent Poverty	4.10	0.00 - 44.80
Income per Capita[d]	27,750.00	3,042.00 - 97,111.00
Median Household Income[d]	68,901.00	18,760.00 - 175,083.00

[a]Square miles.
[b]People per square mile.
[c]Children under 5 years old per square mile.
[d]U.S. dollars, in 1999.

For instance, total population of ZCTAs in 2000 ranged from 42 to 60,153 people. The median area of ZCTAs was approximately 20 square miles, although it ranged from 0.01 to more than 112 square miles. Median population density in ZCTAs was approximately 460 people per square mile. Population under five years old and population density of this group was similarly variable. Discrepancies in the racial and socioeconomic composition of

ZCTAs are also clear: the median percent of black residents ranged from zero to more than 90 percent and percent of residents below the poverty threshold was as low as zero and as high as 45 percent in some ZCTAs.

Figure 1 (panels a through d) illustrates a few of these demographic variables. Panel (a) shows population density across Connecticut ZCTAs. As expected the most densely

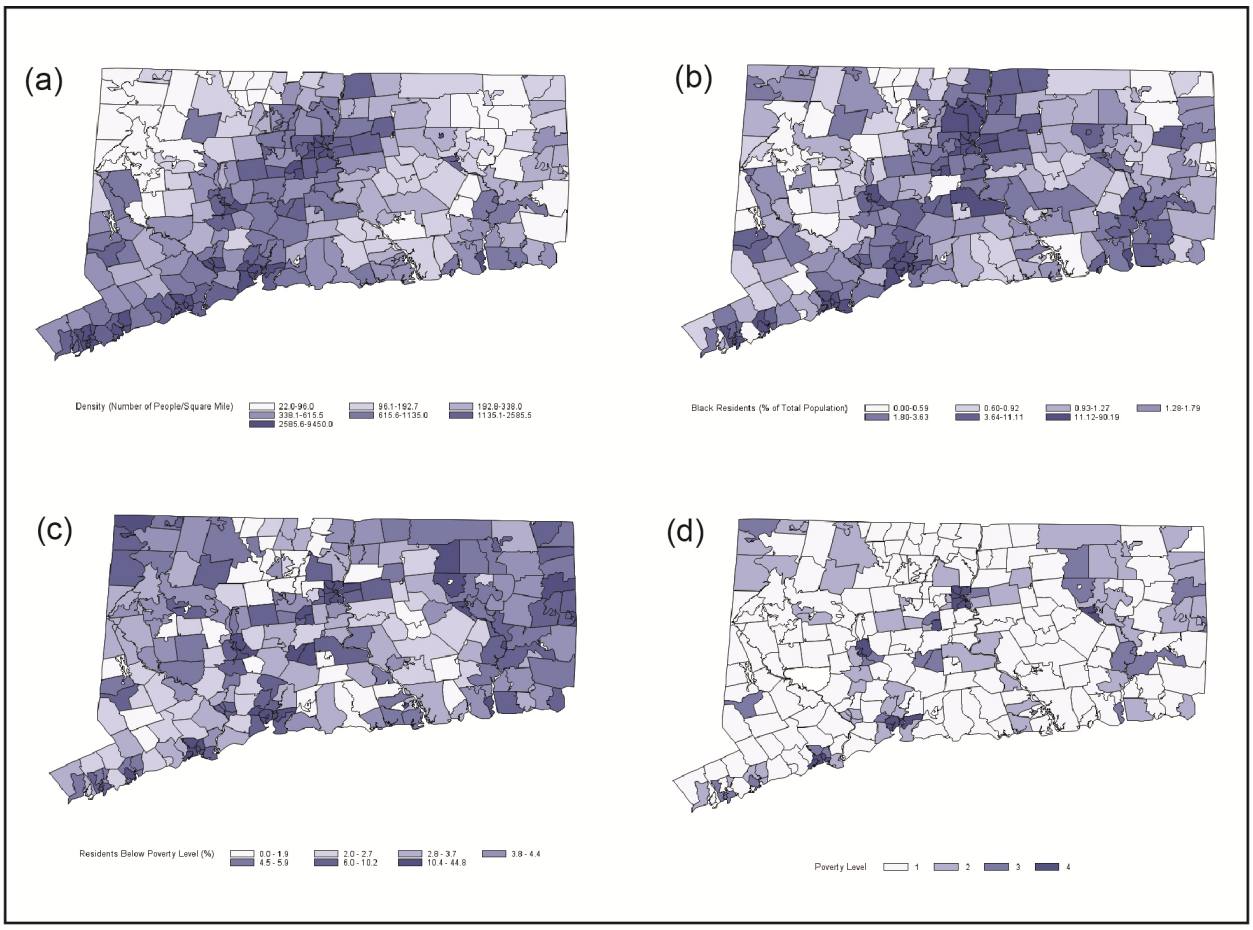

Figure 1. Selected demographic variables in Connecticut ZCTAs (n=266): (a) population density; (b) black residents as percent of total population; (c) percent of ZCTA residents below the U.S. Census poverty threshold, determined in 1999; (d) ZCTA poverty level [Level 1: 0.0-4.9%; Level 2: 5.0-9.9%; Level 3: 10.0-19.9%; Level 4: ≥20.0%].

populated areas are along the Atlantic coast, parts of the New York metropolitan area, and around Hartford, the capital. The state is generally more densely populated west of the Connecticut River. Population is less dense in the northeastern and northwestern corners

of the state. The highest percentages of black residents (see panel [b]) are concentrated in large, densely populated urban areas like Hartford, Bridgeport, New Haven, Stamford, and Groton and New London. In general, these larger cities also have higher percentages of the population below the U.S. Census poverty threshold (see panel [c]). Poverty levels are also higher in some of the less densely populated parts of the northeastern, northwestern, and southeastern corners (see panels [c] and [d]).

PCV Uptake

There were 315,628 children across 266 Connecticut ZCTAs in the CIRTS registry in the 2000 to 2009 birth cohorts. Across all cohorts and ZCTAs combined, 90.6 percent of children in the registry received three doses of PCV, and 74.3 percent received all four recommended doses (data not shown). Figure 2 shows the total percent of children vaccinated with three (blue line) and four doses (green line) of PCV across all birth cohorts. The 2000 cohort started with roughly 80 percent uptake of the initial three vaccine doses and steadily increased through 2009, as compared to the 51 percent vaccination rate for four doses in the 2000 cohort. There was some variability in uptake of four doses from the 2000 to 2003 cohorts; uptake did not exceed 80 percent until the 2004 cohort. Figure 3 shows the same data but graphed by poverty level. Panel (a) shows the trends in uptake of three doses of PCV. ZCTAs with the lowest poverty level (0.0-4.9 percent) maintained the highest vaccination rates across birth cohorts, while those ZCTAs with at least 20 percent of residents below the poverty threshold increased uptake of three doses slowly but had the second highest vaccination rates in the 2009 cohort. Panel (b) illustrates trends with four doses of PCV. ZCTAs with the lowest poverty levels were again always more highly

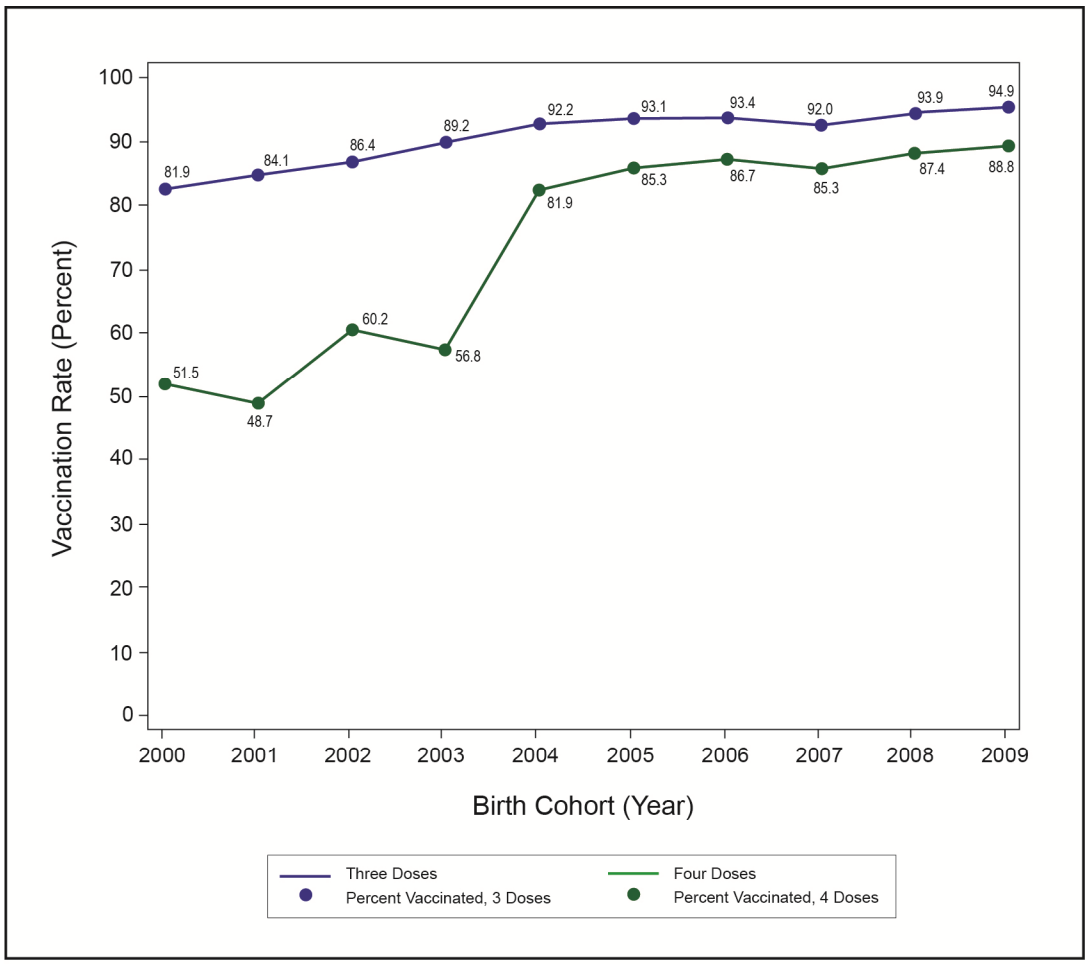

Figure 2. Total percent of Connecticut children vaccinated with three and four doses of PCV, 2000 to 2009 birth cohorts.

vaccinated than the other levels. All ZCTAs experienced the variability in vaccination rates in the 2000 to 2003 cohorts, but rates were generally higher in ZCTAs with lower poverty levels. It is clear from both panels (a and b) that vaccination rates were generally stable beginning with the 2006 cohort.

Figure 4 illustrates these more stable trends across ZCTAs. The majority of ZCTAs had at least 92 percent of children vaccinated with three doses of PCV (panel [a]). West of the Connecticut River is a more highly vaccinated area (and more densely populated in general). Large parts of New London, Windam, Tolland, and Litchfield counties and areas

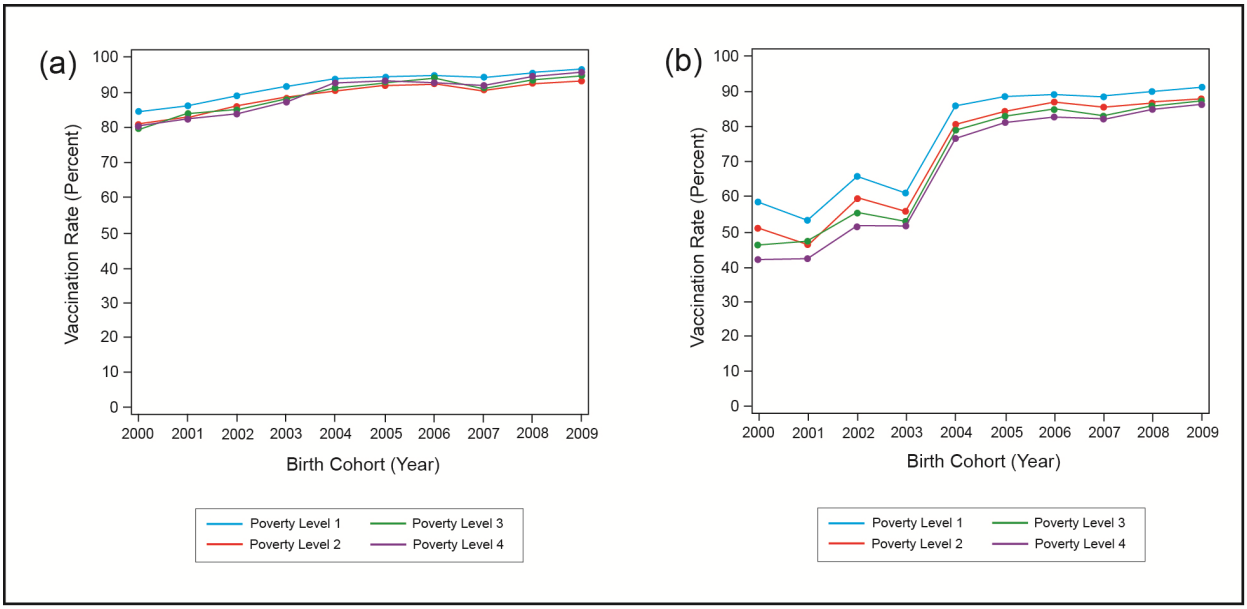

Figure 3. Total percent of Connecticut children vaccinated with three and four doses of PCV, by ZCTA poverty level, 2000 to 2009 birth cohorts: (a) three doses of PCV; (b) four doses of PCV. [Poverty levels are as follows: Level 1: 0.0-4.9%; Level 2: 5.0-9.9%; Level 3: 10.0-19.9%; Level 4: ≥20.0%.]

near some urban areas (East Haven, Hartford, Fairfield, for example) stand out with between zero and 91 percent of children vaccinated. Panel (b) makes clear which towns in these counties had less than 80 percent of children vaccinated with three doses in the 2006 to 2009 cohorts. The majority of ZCTAs had vaccinated had least 83 percent of children with four doses (panel [c]). Very few had vaccination rates above 94 percent. The same northwestern, northeastern, and southeastern corners again stand out with less than 80 percent of children vaccinated (panel [d]).

Spatial Cluster Analysis

The results of the spatial cluster analysis are shown in Figure 5. Three clusters of ZCTAs are significant at the $p<0.0001$ level, indicating significantly higher proportions of

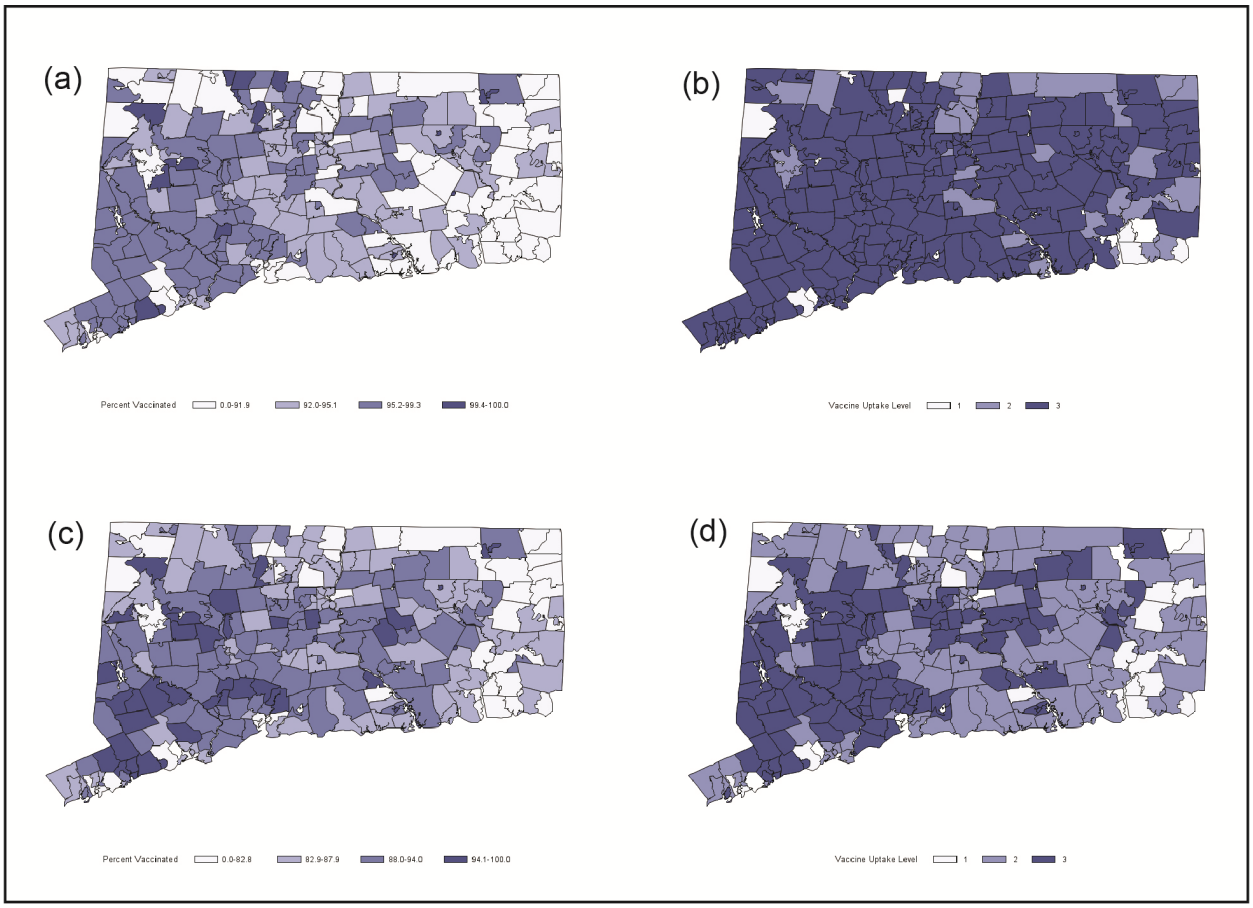

Figure 4. PCV vaccination rates and uptake levels in Connecticut ZCTAs (n=266), 2006 to 2009 birth cohorts: (a) percent of children vaccinated with three doses of PCV; (b) uptake levels of three doses of PCV [Level 1: ≤80%; Level 2: 81-90%; Level 3: ≥91%]; (c) percent of children vaccinated with four doses of PCV; (d) uptake levels of four doses of PCV [Level 1: ≤ 80%; Level 2: 81-90%; Level 3: ≥91%].

unvaccinated children than would be expected (panel [a]). The most likely cluster (red) is near Groton. The second cluster is comprised of almost entire portions of Windham, Tolland, New London, Hartford, and New Haven counties. A third cluster is found around New Haven and Branford towns. Panel (b) presents the seven significant clusters of ZCTAs with higher proportions of children not vaccinated with four doses of PCV than expected. The most likely cluster is again around Groton. Parts of Windham, Tolland, and New London counties are again significant clusters. ZCTAs near Stamford, Bridgeport, and New

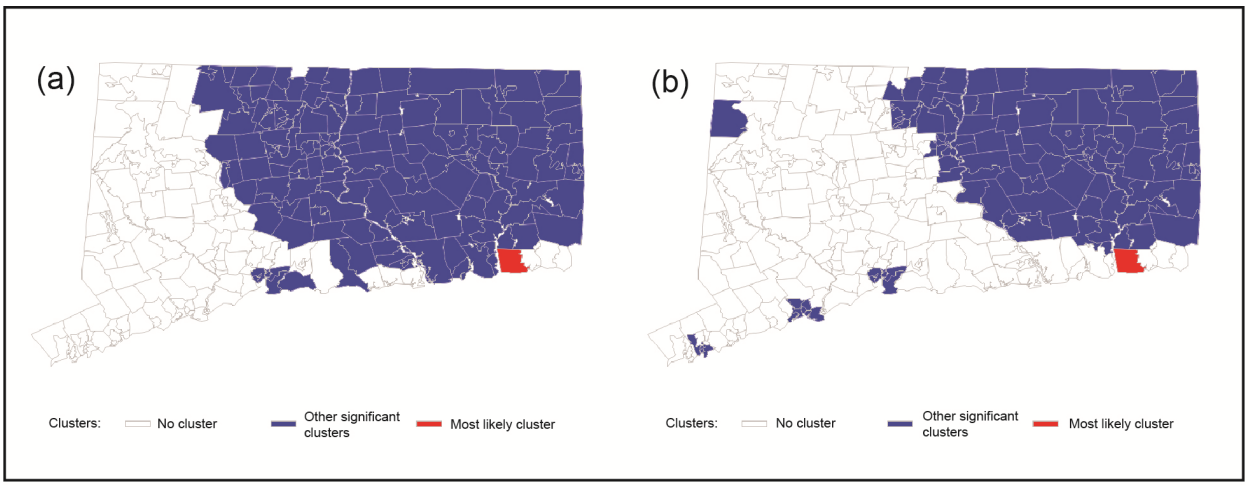

Figure 5. Significant spatial clusters of unvaccinated Connecticut children: (a) three doses of PCV [clusters significant at p<0.0001]; (b) four doses of PCV [clusters significant at p<0.0005].

Haven are clusters, as is a ZCTA near the town of Sharon in the northwestern corner of the state.

Associations between Study Variables and ZCTA Unvaccinated Status

Tables 2 and 3 present the results of the log-binomial regression on the proportion of unvaccinated children (three and four doses, respectively). All study variables were independently associated with the proportion of unvaccinated children in ZCTAs and statistically significant at p<0.05. Household and family size, as well as income per capita and median household income, were protective against being unvaccinated—for example, the risk of being unvaccinated with three doses was about 0.38 times more likely (about 60 percent less likely) when the family size increased by one person. Similarly, the unadjusted relative risk for median household income was 0.663 for each $50,000 increase in household income. Total population had the opposite effect: for every 100,000 person

increase in total population, the risk of being unvaccinated increased by 1.255. Higher poverty levels also increased the risk of

Table 2. Unadjusted associations between study variables and the proportion of unvaccinated children in ZCTAs, three doses of PCV.

Variable	Parameter Estimate[a]	95% Confidence Interval	Relative Risk[a]	95% Confidence Interval
Household Size	-0.943*	-1.045, -0.840	0.390*	0.352, 0.432
Family Size	0.966*	-1.114, 0.817	0.381*	0.328, 0.442
Total Population	0.227**	0.087, 0.367	1.255**	1.091, 1.443
Population Under 5 Years Old†	0.054*	0.027, 0.082	1.056*	1.027, 1.085
Percent of Population Under 5 Years Old	0.092*	0.075, 0.110	1.097*	1.078, 1.116
Percent Black Residents	0.005*	0.004, 0.006	1.005*	1.004, 1.006
Area[b]	0.006*	0.004, 0.007	1.006*	1.004, 1.007
Population Density[c]†	-0.041*	-0.059, -0.023	0.960*	0.943, 0.977
Population Density Under 5 Years Old[d]†	-0.026***	-0.043, -0.009	0.975***	0.958, 0.991
Percent Poverty	0.007*	0.005, 0.010	1.007*	1.005, 1.010
Poverty Level				
0.0-4.9%	—	—, —	Reference	—, —
5.0-9.9%	0.404*	0.350, 0.458	2.243*	2.013, 2.499
10.0-19.9%	0.253*	0.192, 0.314	3.359*	2.856, 3.950
≥20%	0.251*	0.189, 0.312	5.030*	4.052, 6.244
Income per Capita[e]	-0.659*	-0.764, -0.553	0.518*	0.466, 0.575
Median Household Income[e]	-0.411*	-0.459, -0.363	0.663*	0.632, 0.695

[a]P-values: *p < 0.0001; **p = 0.0015; ***p = 0.0025.
[b]Square miles.
[c]People per square mile.
[d]Children under 5 years old per square mile.
[e]U.S. dollars, in 1999.
†Log-transformed variable.

Table 3. Unadjusted associations between study variables and the proportion of unvaccinated children in ZCTAs, four doses of PCV.

Variable	Parameter Estimate	95% Confidence Interval[a]	Relative Risk	95% Confidence Interval[a]
Household Size	-0.375*	-0.446, -0.304	0.687*	0.640, 0.738
Family Size	0.163**	0.068, 0.258	1.177**	1.071, 1.294
Total Population	0.359*	0.264, 0.454	1.432*	1.302, 1.575
Population Under 5 Years Old†	0.087*	0.068, 0.107	1.091*	1.070, 1.112
Percent of Population Under 5 Years Old	0.117*	0.105, 0.129	1.124*	1.111, 1.137
Percent Black Residents	0.009*	0.008, 0.010	1.009*	1.008, 1.010
Area[b]	-0.003*	-0.004, -0.002	0.997*	0.997, 0.998
Population Density[c]†	0.075*	0.062, 0.088	1.078*	1.065, 1.091
Population Density Under 5 Years Old[d]†	0.080*	0.068, 0.092	1.083	1.071, 1.096
Percent Poverty	0.016*	0.014, 0.017	1.016*	1.014, 1.017
Poverty Level				
0.0-4.9%	—	—, —	Reference	—, —
5.0-9.9%	0.252*	0.213, 0.291	1.656*	1.532, 1.790
10.0-19.9%	0.369*	0.328, 0.409	2.130*	1.895, 2.394
≥20%	0.435*	0.395, 0.475	2.741*	2.345, 3.203
Income per Capita[e]	-0.594*	-0.666, -0.522	0.553*	0.514, 0.594
Median Household Income[e]	-0.384*	-0.416, -0.351	0.682*	0.660, 0.704

[a]P-values: *p < 0.0001; **p = 0.0007.
[b]Square miles.
[c]People per square mile.
[d]Children under 5 years old per square mile.
[e]U.S. dollars, in 1999.
†Log-transformed variable.

being unvaccinated. Those ZCTAs with at least 20 percent of residents below the poverty threshold were more than five times more likely to be unvaccinated with three doses than those with the lowest poverty.

The RRs, in general, are similar in the four-dose analysis. However, family size had the opposite effect; that is, being unvaccinated with four doses of PCV is about 1.18 times more likely when family size increases by one person. Poverty levels still have an effect on risk of being unvaccinated with four doses, but it is not as large as in the three dose analysis (5.0-9.9% RR=1.66, 10.0-19.9% RR=2.13, ±20.0% RR=2.74).

Results of the multivariate analysis on the association between study variables and the proportion of unvaccinated children in ZCTAs are presented in Tables 4 and 5 (three and four doses, respectively), as are the final models resulting from model selection. In both models, family size, total population, and area variables were removed. In the model predicting proportion unvaccinated with three doses, household size remains protective against risk of being vaccinated (adjusted RR=0.201). The percent of the population under five years old, income per capita, and log-transformed population density have substantial impacts on the risk of being unvaccinated (adjusted RRs=3.316, 199.554, 6.432, respectively). Poverty levels are now protective against the risk of being unvaccinated, after controlling for the other variables in the model (5.0-9.9% RR=0.844, 10.0-19.9% RR=0.857, ±20.0% RR=0.561). Similar results, although somewhat tempered, are seen in Table 5.

Table 4. Multivariate regression model of factors associated with the proportion of unvaccinated children in ZCTAs, three doses of PCV.

Variable	Parameter Estimate	Standard Error	Relative Risk	95% Confidence Interval[a]
Household Size	-1.605*	0.085	0.201*	0.170, 0.237
Population Under 5 Years Old†	0.205*	0.022	1.228*	1.176, 1.282
Percent of Population Under 5 Years Old	1.199*	0.078	3.316*	2.845, 3.866
Percent Black Residents	0.009*	0.001	1.009*	1.007, 1.011
Population Density[c]†	5.296*	0.527	199.554*	71.061, 560.394
Population Density Under 5 Years Old[d]†	-5.686*	0.527	0.003*	0.001, 0.010
Percent Poverty	-0.027*	0.004	0.937*	0.965, 0.982
Poverty Level				
0.0-4.9%	—	—, —	Reference	—, —
5.0-9.9%	-0.170*	0.041	0.844*	0.778, 0.914
10.0-19.9%	-0.154**	0.057	0.857*	0.766, 0.958
≥20%	-0.579*	0.103	0.561*	0.458, 0.686
Income per Capita[e]	1.860*	0.181	6.423*	4.507, 9.152
Median Household Income[e]	-1.826*	0.113	0.161*	0.129, 0.201

[a]P-values: *p < 0.0001; **p = 0.0068.
[b]Square miles.
[c]People per square mile.
[d]Children under 5 years old per square mile.
[e]U.S. dollars, in 1999.
†Log-transformed variable.

Discussion

This paper described patterns in uptake of three and four doses of PCV in CIRTS birth cohorts across Connecticut and has attempted to identify selected community-level variables associated with higher proportions of unvaccinated children in Connecticut ZCTAs. Although Connecticut is largely a wealthy state, substantial disparities persist

Table 5. Multivariate regression model of factors associated with the proportion of unvaccinated children in ZCTAs, four doses of PCV.

Variable	Parameter Estimate	Standard Error	Relative Risk	95% Confidence Interval[a]
Household Size	-0.870*	0.060	0.419*	0.372, 0.471
Total Population	0.581*	0.072	1.788*	1.553, 2.059
Percent of Population Under 5 Years Old	0.922*	0.059	2.515*	2.242, 2.820
Percent Black Residents	0.009*	0.001	1.009*	1.007, 1.011
Population Density[c]†	4.283*	0.388	72.486*	33.897, 155.006
Population Density Under 5 Years Old[d]†	-4.473*	0.387	0.011*	0.005, 0.024
Percent Poverty	-0.018*	0.003	0.982*	0.976, 0.988
Poverty Level				
0.0-4.9%	—	—, —	Reference	—, —
5.0-9.9%	-0.062****	0.031	0.940*	0.885, 0.999
10.0-19.9%	0.092***	0.042	1.096*	1.010, 1.190
≥20%	-0.167**	0.075	0.846*	0.731, 0.980
Income per Capita[e]	1.397*	0.128	4.044*	3.145, 5.200
Median Household Income[e]	-1.144*	0.079	0.319*	0.273, 0.372

[a]P-values: *p < 0.0001; **p = 0.0259; ***p = 0.0281; ****p = 0.047.
[b]Square miles.
[c]People per square mile.
[d]Children under 5 years old per square mile.
[e]U.S. dollars, in 1999.
†Log-transformed variable.

across ZCTAs of heterogeneous size and population density, age-structure, and racial and socioeconomic compositions. Perhaps unsurprisingly, population density is concentrated near major north-south (I-91) and east-west interstates (I-95) and within the New York metropolitan area. These areas also have higher percentages of residents living below the

U.S. Census poverty threshold. Higher poverty levels are found in less densely populated parts of the northwestern, southeastern, and northeastern corners of the state as well.

Connecticut generally enjoys a robust uptake of both three and four doses of PCV. By the 2009 birth cohort, almost 95 percent of children in the registry had received three doses, while 89 percent were fully vaccinated with four doses. However, the percent of children receiving four doses did not reach 80 percent until the 2004 birth cohort, illustrating a dramatic increase in uptake compared with the previous cohorts (in which about 50 to 60 percent were fully vaccinated). A shortage of the vaccine from 2001 to 2003 may partially explain these patterns, a time during which receiving a third dose of PCV likely took priority over a fourth dose (N. Sharova, personal communication, March 31, 2014). Pockets of the state with fewer than 80 percent of children vaccinated with either three or four doses of PCV (see Figure 4, panels [b] and [d]) were predominately confirmed by spatial cluster analysis (Figure 5, both panels).

These significant clusters varied in density from large urban areas to some of the most sparsely populated ZCTAs, but were consistent in having higher poverty levels. The ZCTA around Groton was identified as the most likely cluster of a higher proportion of children unvaccinated with three or four doses of PCV. ZCTAs in the New Haven and Hartford areas, in addition to Bridgeport and Stamford, were significant clusters and had higher levels of poverty. Groton, Sharon, and the majority of the eastern part of the state are not covered by Connecticut's IAP area.

Poverty levels had a greater effect on uptake of four doses of the vaccine, and there was a clear gradient across the four levels, especially in the earlier cohorts. Continuous and categorical variables indicate poverty and socioeconomic status in ZCTAs had similar,

significant associations with unvaccinated status in bivariate analysis for both three and four vaccine doses. Increasing poverty was a risk factor for a ZCTA being home to a larger proportion of unvaccinated children, while increases in income per capita and median household income were protective. Surprisingly, however, this pattern was not observed again in multivariate analysis; rather, income per capita became a risk factor, while increasing poverty and median household income were protective factors. It is not clear what caused these patterns. Log-transformed total population densities in both multivariate analyses were associated with considerable increased risk of a ZCTA having a large proportion of unvaccinated children.

The patterns described above could indicate a deficiency of resources in these areas. Urban areas with high poverty may have more residents without insurance or who lack consistent access to preventive care. Less densely populated parts of Connecticut may have a dearth of primary care physicians or options for fulfilling the pediatric immunization schedule. Additionally, poorer Connecticut residents are more likely to delay the fourth vaccination until after 24 months. It is more difficult to encourage families to return for a fourth PCV dose after children have turned two years old, especially because they should have completed almost all other pediatric vaccinations by that point, or would not need additional doses of other vaccines until about age four (N. Sharova, personal communication, March31, 2014). Out-of-pocket costs have been found to be negatively correlated with up-to-date vaccination status, and families below 250 percent of the federal poverty line had the lowest immunization coverage in Georgia (Molinari, Kolasa, Messonnier, & Schieber, 2007). Similarly, children in Colorado who were shifted from a health management organization (HMO) to unassigned fee-for-service (UFFS) program

(under which they were not required to have a primary care physician [PCP]), had fewer primary care and preventive service visits and lower vaccination rates of recommended pediatric immunizations than children not in the UFFS program (Berman, Armon, & Todd, 2005).

PCV adoption by physicians is necessary for overall success of the vaccination in the population. Physicians who had not adopted PCV7 within one year of its introduction in a sample from 24 states were concerned about the purchasing cost of the vaccine and lack of insurance reimbursement, and instead, sent families to health departments for routine pediatric immunizations (Davis, Ndiaye, Freed, & Clark, 2003a). Therefore, state financing of vaccine programs may affect whether physicians vaccinate children without insurance covering PCV. The Vaccines for Children program (VFC), Medicaid, and Children's Health Insurance Program (CHIP) can decrease or eliminate most costs for the poor and reduce burdens on local health departments (Molinari et al., 2007; Davis et al, 2003a), although the type or combination of financing is important. For example, Davis, Ndiaye, Freed, Kim, and Clark (2003b) found physicians practicing in states with only the VFC purchase strategy were less likely to give PCV7 to children without coverage, versus those practicing in states with a universal purchase strategy or an enhanced VFC strategy covering VFC-eligible children and other children seen at private practices without insurance covering all Advisory Committee on Immunization Practices (ACIP)-recommended vaccines.

This paper has a range of limitations in the data and methods. It is important to remember CIRTS aggregated data by zip codes, while the U.S. Census uses ZCTAs for data collection (because zip codes are defined and changed by the U.S. Postal Service). Although the ZCTA code matches the zip code in most instances, a zip code will not be represented

within the ZCTA sphere if the zip code was never the most frequently occurring zip code during the ZCTA creation process. Therefore, some zip codes in CIRTS may not correspond directly with the ZCTA with the same number.

Krieger et al. (2005) explain measuring poverty levels (for example, "percent below the poverty line") consistently detects expected socioeconomic gradients in health across many outcomes, and further, that area-based measures of socioeconomic status are able to capture a mix of individual-level and area-based socioeconomic effects. Using a priori versus data-dependent cut-points for percent below the poverty line enables more meaningful comparisons across place and time. Although there is no consensus on which area-based measure is best, census tracts were found to be more consistent than census block groups or zip codes (Krieger et al., 2003). This is likely due to the homogenous nature of census tracts with respect to population characteristics. Zip codes and ZCTAs represent more heterogeneous populations, and therefore, may not be the most meaningful area-based measure of socioeconomic status.

It would be interesting to know how many parents opt-out of the registry, and to relate data in this paper to pneumococcal disease rates in children and adults. The results of this analysis cannot be assumed to hold for those children who are not in the registry. Analyzing temporal clusters could also provide important insight to the study questions. Future studies with these data should adjust cluster analyses for covariates. Clusters found after adjustment can be understood to be explained by the covariates. For example, the clusters in Figure 5 may be explained by population density of children under age five. Additional analyses should also control for collinearity among the selected predictor variables in the log-binomial regression models. Principal component analysis is sensitive

to the original scaling of variables and could be used to create adjusted variables for use in the regression models in place of the original variables. Further, other community-level variables may be missing from the analyses that have an effect on ZCTAs having a high proportion of children unvaccinated for PCV. For example, the proportion of the population who are immigrants may have an effect (Pavlopoulou, Michail, Samoli, Tsiftis, & Tsoumakas, 2013). Finally, results from this paper should not be understood as an individual child's risk of being under vaccinated; ecological associations may not be present at the individual level.

In conclusion, this paper made use of previously collected surveillance data from CIRTS to describe PCV uptake patterns with three and four doses across Connecticut. Vaccination levels in CIRTS-registered children generally increased from the 2000 to 2009 birth cohorts and varied by poverty level. Spatial cluster analysis revealed several significant clusters of ZCTAs with higher than expected proportions of children unvaccinated with three or four doses of PCV. Areas near Groton, New Haven, and parts of Windham, Tolland, Hartford, and New London counties would benefit from increased vaccine advocacy and delivery efforts, especially given that some of these areas are not covered by Connecticut's IAP. Community-level variables from the 2000 U.S. Census that describe the racial and socioeconomic composition, age distribution, population density, and housing characteristics of Connecticut ZCTAs were independently associated with a high proportion of unvaccinated children in ZCTAs and comprise final multivariate models.

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