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Original Contribution

Geographic Clustering of Nonmedical Exemptions to School Immunization Requirements and Associations With Geographic Clustering of Pertussis

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School immunization requirements are important in controlling vaccine-preventable diseases in the United States. Forty-eight states offer nonmedical exemptions to school immunization requirements. Children with exemptions are at increased risk of contracting and transmitting vaccine-preventable diseases. The clustering of nonmedical exemptions can affect community risk of vaccine-preventable diseases. The authors evaluated spatial clustering of nonmedical exemptions in Michigan and geographic overlap between exemptions clusters and clusters of reported pertussis cases. Kulldorf's scan statistic identified 23 statistically significant census tract clusters for exemption rates and 6 significant census tract clusters for reported pertussis cases between 1993 and 2004. The time frames for significant space-time pertussis clusters were August 1993–September 1993, August 1994–February 1995, May 1998–June 1998, April 2002, May 2003–July 2003, and June 2004–November 2004. Census tracts in exemptions clusters were more likely to be in pertussis clusters (odds ratio = 3.0, 95% confidence interval: 2.5, 3.6). The overlap of exemptions clusters and pertussis clusters remained significant after adjustment for population density, proportion of racial/ethnic minorities, proportion of children aged 5 years or younger, percentage of persons below the poverty level, and average family size (odds ratio = 2.7, 95% confidence interval: 2.2, 3.3). Geographic pockets of vaccine exemptors pose a risk to the whole community. In addition to monitoring state-level exemption rates, health authorities should be mindful of within-state heterogeneity.

cluster analysis; geographic information systems; immunization; space-time clustering; vaccines; whooping cough

Abbreviations: CI, confidence interval; IQR, interquartile range; OR, odds ratio.

School immunization requirements have played an important role in controlling vaccine-preventable diseases in the United States (1–3). All states require receipt of vaccines at the time of school entry. Medical exemptions to school immunization requirements are offered in all states, and 48 states offer nonmedical exemptions. There are differences between states in administrative requirements for obtaining exemptions. Between 1991 and 2004, rates of nonmedical exemptions increased in states with relatively easier administrative procedures for obtaining nonmedical exemptions, and from 1986 to 2004, the incidence of pertussis was almost 50% higher in states that easily granted nonmedical exemptions (4).

Moreover, pockets of high exemption rates occur within states (5, 6). These pockets could produce the critical mass of susceptible persons required to maintain transmission of vaccine-preventable diseases, even when overall state-level vaccination coverage is high (5, 6). In a Colorado study (7), the incidence of measles and pertussis among vaccinated children in a county was associated with the frequency of exemptions in that county. In addition, at least 11% of nonexempt children who acquired measles were infected through contact with an exempt child with measles. School-based outbreaks have been associated with high exemption rates, and in a recent survey of schools, substantial intrastate variability in implementation of exemptions was reported (7, 8).

We evaluated the spatial clustering of nonmedical exemptions in Michigan and tested the hypothesis that there is a higher likelihood of pertussis cases' occurring in areas

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with high rates of nonmedical exemptions, as measured by geographic overlap between exemptions clusters and clusters of reported pertussis cases.

MATERIALS AND METHODS

Data sources and study population

We used the number of children with nonmedical exemptions from immunization requirements and the number of children attending kindergarten by school address in Michigan for the years 1991–2004. This information is systematically and routinely collected by the Michigan Department of Community Health. These data did not include information for homeschooled children. We chose Michigan because it has had relatively high overall exemption rates and has easy administrative requirements for obtaining exemptions in comparison with other states (9). According to the Michigan Department of Education, there were 4,500 schools in the state in the fall of 2005. The Michigan Department of Education has not retained records for previous years. In recent years, the number of schools reporting exemption information has been very close to the number of schools on record with the Michigan Department of Education, giving us confidence that the school-level exemption data used for this analysis were reasonably complete.

Michigan requires students entering school to be immunized against pertussis and other vaccine-preventable diseases. However, students' families have been allowed to waive immunization for medical, religious, or other reasons since 1978 (10). There is no standard statewide process for granting exemptions from immunization. In most cases, simply providing a signed statement by a parent is sufficient to obtain an exemption, although a few counties have stricter requirements. Schools must annually report the number of kindergarten students and the number of exemptions to the health department (10).

We received pertussis case records from the Michigan Department of Community Health for the years 1993–2004. Pertussis cases were reported to the Michigan Department of Community Health by local health departments in the course of pertussis surveillance. Our analysis included all patients with reported confirmed or probable cases of pertussis who were aged 18 years or younger at disease onset. According to the criteria of the Centers for Disease Control and Prevention, a probable case is defined as cough for a minimum of 14 days, with at least 1 of the following: paroxysms, whoop, or posttussive vomiting (11). A case is categorized as confirmed if 1) the patient is coughing and culture-positive and 2) the clinical case definition has been met and there has been polymerase chain reaction confirmation or direct contact with a patient with a polymerase chain reaction-confirmed or culture-confirmed case (11, 12).

Immunization information for 6% of cases was supplemented by information obtained from the Michigan Care Improvement Registry. The locations of pertussis cases were identified through geocoding of the case addresses collected by the Michigan Department of Community Health as part of their case database.

US Census tract was used as the primary unit of geographic aggregation for pertussis case data. School locations (i.e., geocoded addresses) were used for the exemptions data in identifying exemptions clusters; once an exemptions cluster was identified, census tracts included in the cluster were used for subsequent geographic analysis. Census tracts are reasonably stable geographic units delineated by local participants as part of the US Census Bureau's Participant Statistical Areas Program (13). The Census Bureau delineates the census tracts where there are no local participants or where a local or tribal government refused to participate. Their relatively small size and internal homogeneity and the local involvement in delineation make census tracts uniquely suitable for geographic analyses.

Secular trends in exemption rates

We used a population-averaged (generalized estimating equations) Poisson model to estimate annual changes in census-tract-level nonmedical exemption rates over the study period. The census-tract-level rate of nonmedical exemptions in each year was computed by totaling the number of nonmedical exemptions in all schools in a particular census tract and dividing it by the number of children attending kindergarten during that year in that census tract.

Cluster identification

Kulldorff's scan statistics were used to identify spatial and space-time clusters (14). This approach is useful in identifying localized, statistically significant geographic clusters of events. With this method, random data sets of events (exemptions or pertussis cases) are generated under a known null hypothesis (999 simulations in our study). The data sets follow the relevant probability distribution (e.g., Poisson distribution for count data with a constant or known population denominator). Candidate spatial clusters of events are identified—for both simulated and observed data sets—by varying the size of a moving circular window around each grid point (in this case, school location for exemptions clusters and census tract centroids for pertussis clusters) on a spatial plane, such that the contrast between the density of events inside the window versus outside the window is maximized. For identification of space-time clusters, a cylindrical window is used, where the height of the cylinder represents the time period of data included in the cluster. The test statistic, derived as a likelihood ratio, is calculated for each candidate cluster (14, 15). The values of the test statistic for candidate clusters of observed events are compared for statistical significance against a distribution of values computed for the simulated data sets. We used Kulldorff's scan statistics because they permitted evaluation of the statistical significance of geographically grounded clusters (i.e., identification of actual locations of clusters in contrast to general tests of clustering) and because they do not assume an a priori fixed cluster size in terms of either number of events or geographic dimensions.

In our preliminary analysis of the exemptions data, we observed overall within-school stability of exemption rates over time despite clear secular trends (detailed analysis available on request). We therefore treated *clustering* of exemptions as a relatively long-term phenomenon and chose

a purely spatial Poisson model for identifying clusters of school-level exemption rates. Clustering of pertussis cases, on the other hand, was treated as a relatively short-term phenomenon, and a space-time Poisson model was used to identify clusters of monthly counts of pertussis cases. Logarithms of the number of children in kindergarten for each school and the number of persons aged 18 years or younger in a census tract were used as offset terms (denominators) for the exemption and pertussis Poisson models, respectively. The exemptions clusters and pertussis clusters were assumed to have no geographic overlap with the other exemptions and pertussis clusters, respectively (i.e., if a census tract was included in an exemptions or pertussis cluster, it could not be included in an adjacent cluster of the same type). Assuming the clusters to be nonoverlapping is a conservative approach that increases the specificity of the cluster identification technique.

Census tracts were categorized as being inside or outside a cluster on the basis of the geographic location of their centroids (geographic centers). If the centroid of a census tract was located within the boundaries of a spatial or space-time cluster, it was categorized as being inside that cluster.

Evaluation of census-tract-level demographic variables

Simple and multiple logistic regression were used to explore the association between a census tract's being (geographically) located inside an exemptions cluster and the census-tract-level demographic variables: population density (modeled as a continuous variable in hundreds of persons per square mile), proportion of racial/ethnic minorities in a census tract, proportion of children aged 5 years or younger, percentage of persons below the poverty level in a census tract, and mean family size. The demographic variables (based on 2000 US Census data) included in the a priori model either were shown to be associated with vaccine coverage in previous studies (proportion of racial/ethnic minorities (16)) or were epidemiologically plausible indicators of accumulation of susceptible persons (population density, proportion of children aged $\leq$5 years, percentage of persons below the poverty level, and mean family size). We included population density, proportion of children aged $\leq$5 years, and mean family size in our model because population density and distribution of contacts in a population are associated with rate of disease spread after introduction of an infection in the population (17).

Assessment of overlap between exemptions clusters and pertussis clusters

Logistic regression was used to estimate the overlap between exemptions clusters and pertussis clusters. We estimated the overlap by calculating the ratio of the odds of a census tract in an exemptions cluster also being in a pertussis cluster and the odds of a census tract outside an exemptions cluster also being in a pertussis cluster. In addition to bivariate analysis of the overlap between exemption and pertussis clusters, we included the census-tract-level demographic variables population density (in hundreds of persons per square mile), proportion of racial/ethnic minorities in a census tract, proportion of children aged $\leq$5 years, percentage of persons below the poverty level in a census tract, and mean family size in the multivariate models.

For demographic and epidemiologic variables with data for at least 50% of cases, the distribution inside the pertussis clusters versus outside was analyzed using multiple logistic regression. The variables included gender, hospitalization, laboratory testing, laboratory confirmation, race/ethnicity, use of antibiotics, being vaccinated, having an up-to-date vaccination status (receipt of at least 3, 4, and 5 doses of a pertussis-containing vaccine by children at least 6, 18, and 72 months of age, respectively), and occurrence of seizures.

Analytical tools and statistical °significance

We used ArcGIS, version 9.1 (ESRI, Redlands, California), for geocoding and for creating geographic analysis layers. The reference data set used for geocoding was the Michigan Geographic Framework, version 4b, street, county, city, and civil division data set (available from the Michigan Geographic Data Library (18)). SatScan, version 7 (Information Management Services, Inc., Boston, Massachusetts), was used to perform cluster analysis. Other statistical analyses were performed using Stata, versions 7 and 8 (Stata Corporation, College Station, Texas). Identified clusters and associations were considered statistically significant with reference to $\alpha = 0.05$.

Ethical clearance

The study was declared exempt from review by the Johns Hopkins Bloomberg School of Public Health Committee on Human Research and by the Michigan Department of Community Health Institutional Review Board.

RESULTS

Data on exemption rates were obtained from 4,495 schools for the years 1991–2004, producing 34,362 school-years of exemption rate data. For the years 1993–2004, 1,111 confirmed and probable pertussis cases were reported among persons aged 18 years or younger. Approximately 5% of cases could not be geocoded to the street level, so their census tract assignment was estimated on the basis of city or township centroid. Two cases could not be reliably geocoded. Therefore, the analysis set included 1,109 cases. Among the pertussis cases, 750 (67.6%) were categorized as confirmed cases (11).

The median demographic characteristics of the 2,757 Michigan census tracts delineated in the 2000 US Census were as follows: population density, 1,843.7 persons per square mile (interquartile range (IQR), 215.4–4,596.4); age, 36.3 years (IQR, 32.7–39.6); mean family size, 3.1 (IQR, 2.9–3.2); and percentage white, 90.8% (IQR, 73.1–95.2).

The mean census-tract-level exemption rate increased from 1.9% (IQR, 0–2.23) in 1991 to 5.2% (IQR, 1.23–6.90) in 2004 (incidence rate ratio = 1.14, 95% confidence interval (CI): 1.13, 1.15). During the study period, 23 statistically significant clusters of high exemption rates were identified,

TABLE 1. Characteristics of Statistically Significant Clusters of High Rates of School Immunization Exemptions, by Significance Level, Michigan, 1993–2004

Cluster	Cluster Centroid		*P* Value[a]	Observed No. of Exempted Children	Expected No. of Exempted Children	Relative Risk[b]	Cluster Description
	Latitude, °N	Longitude, °W					
1	42.2899	−83.7749	≤0.001	24,387	19,627.76	1.48	Southeastern Michigan
2	42.3733	−85.63	≤0.001	87	3.44	25.36	Cooper Township
3	43.6316	−84.4089	≤0.001	874	421.28	2.09	Midland County
4	42.9808	−85.63	≤0.001	122	12.65	9.67	Northeastern Grand Rapids
5	43.233	−85.7119	≤0.001	104	9.56	10.9	Tyrone Township
6	44.7673	−85.6304	≤0.001	1,115	673.27	1.67	Northwestern Lower Peninsula
7	43.4067	−83.9447	≤0.001	101	17.18	5.89	Saginaw
8	43.5693	−85.4017	≤0.001	29	0.96	30.29	Starwood and Morley area
9	42.1125	−85.9778	≤0.001	120	32.14	3.74	Decatur area
10	43.3661	−85.2353	≤0.001	26	0.69	37.56	Northwestern Montcalm County
11	42.7291	−84.6071	≤0.001	100	34.63	2.89	Delta and Lansing townships
12	42.8633	−84.9034	≤0.001	115	45.84	2.51	Portland area
13	42.7161	−84.5561	≤0.001	50	11.5	4.35	Lansing
14	42.3148	−85.6677	≤0.001	29	3.65	7.95	Northwestern Kalamazoo
15	42.2478	−85.5806	≤0.001	22	2.58	8.52	Kalamazoo/Portage
16	42.0145	−86.5268	≤0.001	34	8.07	4.21	Stevensville area
17	42.8845	−85.7196	≤0.001	22	4.56	4.83	Wyoming area
18	43.0869	−85.629	0.002	50	20.14	2.48	Plainfield Township
19	42.8884	−85.6065	0.003	40	14.6	2.74	Southeastern Grand Rapids
20	44.0309	−86.3405	0.007	27	8.33	3.24	Victory Township area
21	42.8534	−85.5279	0.009	87	48.15	1.81	Caledonia and Gaines townships
22	43.2706	−85.2323	0.048	5	0.21	23.49	Northwestern Montcalm County
23	42.0457	−84.7536	0.049	169	115.24	1.47	Litchfield area

[a] Two-sided test of significance using scan statistics.
[b] Relative risk of exemptions inside the cluster versus outside the cluster. For example, a relative risk of 1.48 implies that the mean exemption rate was 48% higher inside the cluster than outside the cluster.

with *P* values ranging from 0.001 to 0.049 (Table 1 and Figure 1). In bivariate analysis, the likelihood of a census tract's being in an exemptions cluster was associated with higher population density (in hundreds of persons per square mile; odds ratio (OR) = 1.02, 95% CI: 1.01, 1.02), higher percentage of racial/ethnic minorities in a census tract (OR = 1.01, 95% CI: 1.01, 1.02), higher percentage of children aged ≤5 years (OR = 1.10, 95% CI: 1.05, 1.16), and larger mean family size (OR = 3.9, 95% CI: 2.8, 5.5). The likelihood of a census tract's being in an exemptions cluster was not associated with percentage of persons below the poverty level in that census tract (OR = 1.0, 95% CI: 1.0, 1.01). Population density (OR = 1.02, 95% CI: 1.01, 1.02) and mean family size (OR = 2.8, 95% CI: 1.8, 4.4) remained significantly associated in multivariate analysis.

The annual number of reported pertussis cases in the 2,757 census tracts varied over time, from 89 cases in 1993 to 59 cases in 1999. However, there were 114 cases reported in 2000, and the number of reported cases increased to 222 in 2004. The absolute number of cases increased in all age groups. Infants contributed the highest percentage of pertussis cases in all years. However, during the study period, the relative contribution of children aged 11–18 years increased (from 7.9% to 21.2%) and the relative contribution of infants decreased (from 73.0% to 48.6%).

Among the 1,108 cases with gender data, 559 (50.4%) were female. Of the 689 cases with information on race/ethnicity, 578 (83.9%) were Caucasian and 87 (12.6%) were African-American. The remaining 24 (3.5%) cases occurred in persons of other races/ethnicities. Of the 1,081 cases with hospitalization information, 460 (42.5%) were hospitalized, for a mean of 6.9 days (standard deviation, 8.0).

Six statistically significant clusters of pertussis cases were identified (Table 2 and Figure 1). The 6 clusters spanned the following time frames: August 1993–September 1993, August 1994–February 1995, May 1998–June 1998, April 2002, May 2003–July 2003, and June 2004–November 2004.

Census tracts in exemptions clusters were 3 times more likely to also be in a pertussis cluster than were census tracts outside any exemptions cluster (OR = 3.02, 95% CI: 2.52,

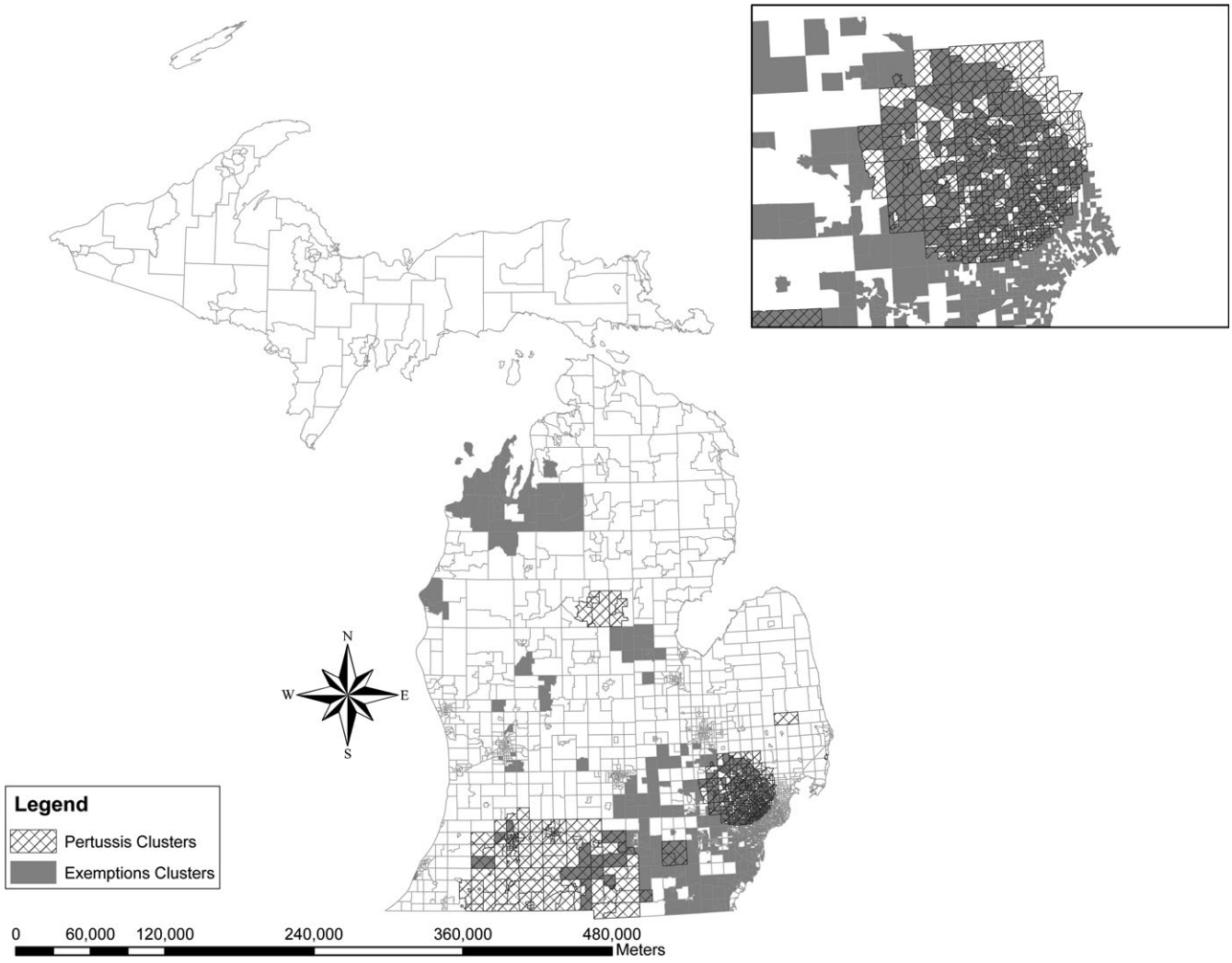

FIGURE 1. Relative locations of pertussis space-time clusters (1993–2004) and exemptions spatial clusters (1991–2004) in Michigan. The inset in the top right corner shows relative locations of pertussis space-time clusters and exemptions spatial clusters in the Detroit metropolitan area.

3.61) (Table 3). The overlap of exemptions clusters and pertussis clusters remained significant after adjustment for population density, proportion of racial/ethnic minorities, proportion of children aged ≤5 years, percentage of persons below the poverty level, and average family size (OR = 2.73, 95% CI: 2.25, 3.31).

TABLE 2. Characteristics of Statistically Significant Pertussis Clusters, by Significance Level, Michigan, 1993–2004

Cluster	Cluster Centroid		Starting Date	Ending Date	*P* Value[a]	Observed No. of Cases	Expected No. of Cases	Relative Risk[b]	Cluster Description
	Latitude, °N	Longitude, °W							
1	43.9332	−84.6832	August 1, 1994	February 28, 1995	≤0.001	86	0.16	598.56	Clare and Gladwin counties
2	41.8227	−85.2061	June 1, 2004	November 30, 2004	≤0.001	53	2.89	19.19	Southern Michigan
3	42.117	−84.0712	May 1, 2003	July 31, 2003	≤0.001	10	0.02	483.5	Manchester area
4	42.6199	−83.3718	August 1, 1993	September 30, 1993	≤0.001	23	2.68	8.75	Oakland County
5	43.1139	−82.8754	May 1, 1998	June 30, 1998	≤0.001	5	0.01	549.24	Lynn and Brockway townships
6	42.8246	−82.4957	April 1, 2002	April 30, 2002	0.045	3	0	659.52	St. Clair

[a] Two-sided test of significance using scan statistics.
[b] Relative risk of pertussis cases being inside the cluster versus outside the cluster.

TABLE 3. Odds Ratios for Overlap Between Exemptions Clusters and Pertussis Clusters and Comparison of Pertussis Cases Inside Pertussis Clusters With Those Outside Pertussis Clusters, Michigan, 1993–2004

	Outside Pertussis Cluster[a]		Inside Pertussis Cluster			
	No. of Census Tracts or Persons	%	No. of Census Tracts or Persons	%	Odds Ratio	95% Confidence Interval
Census tract location						
Inside exemptions cluster (bivariate model) (n = 2,757)	614	30.0	377	56.4	3.02*	2.52, 3.61
Inside exemptions cluster (multivariate model)[b] (n = 2,757)	614	30.0	377	56.4	2.73*	2.25, 3.31
Pertussis case characteristic						
Male gender (n = 1,108)	347	47.0	202	54.6	1.35*	1.05, 1.74
White race/ethnicity (n = 689)	431	82.6	147	88.0	1.55	0.92, 2.61
Hospitalized (n = 1,081)	366	51.0	94	25.9	0.34*	0.25, 0.44
Use of antibiotics (n = 1,052)	658	93.7	326	93.1	0.91	0.54, 1.52
Vaccinated against pertussis (n = 1,082)	283	39.1	137	38.1	0.96	0.74, 1.25
Up-to-date vaccination status[c] (n = 1,109)	248	33.6	125	33.7	1.00	0.77, 1.31
Laboratory testing performed (n = 712)	429	80.9	126	69.2	0.53*	0.36, 0.78
Linked to a laboratory-confirmed case	128	21.0	179	59.1	5.41*	4.01, 7.31
Seizures (n = 1,048)	10	1.4	3	0.9	0.60	0.16, 2.18

* $P < 0.05$.

[a] Reference category (odds ratio = 1).

[b] Adjusted for census-tract-level population density, proportion of racial/ethnic minorities, proportion of children aged 5 years or younger, percentage of persons below the poverty level, and average family size.

[c] Receipt of at least 3, 4, and 5 doses of a pertussis-containing vaccine by children at least 6, 18, and 72 months of age, respectively.

Compared with cases outside the pertussis clusters, cases inside the clusters were more likely to be male (OR = 1.35, 95% CI: 1.05, 1.74), less likely to be hospitalized (OR = 0.34, 95% CI: 0.25, 0.44), less likely to have had laboratory testing performed (OR = 0.53, 95% CI: 0.36, 0.78), and more likely to be linked to a laboratory-confirmed case (OR = 5.41, 95% CI: 4.01, 7.31) (Table 3). The associations between pertussis clusters and race/ethnicity, use of antibiotics, being vaccinated, having an up-to-date vaccination status (receipt of at least 3, 4, and 5 doses of a pertussis-containing vaccine by children at least 6, 18, and 72 months of age, respectively), and occurrence of seizures were not statistically significant.

DISCUSSION

We found evidence of an increase in exemption rates, spatial clustering of nonmedical exemptions, and space-time clustering of pertussis in Michigan. There was considerable overlap between the clusters of exemptions and the clusters of pertussis cases. The likelihood of a census tract's being in an exemptions cluster was associated with high population density, proportion of racial/ethnic minorities in a census tract, proportion of children aged ≤5 years, and mean family size. In multivariate analysis, population density and mean family size remained independently associated with the likelihood of a census tract's being in an exemptions cluster.

There is substantial evidence for an increased risk of vaccine-preventable diseases among vaccine refusers (7, 19–21). Our study demonstrates that in addition to the risk to individuals, the community-level risk of outbreaks is also increased in the presence of geographic clusters of exemptors.

In a recent study exploring associations between school exemption policies and nonmedical immunization exemptions, substantial intrastate variability in implementation of exemption requirements was observed (22). We show that in Michigan, pockets of high exemption rates exist despite overall high state-level vaccination coverage (2003–2004 coverage for 3 or more doses of diphtheria-tetanus-pertussis vaccine: 93.7%) (23). States report exemption rates to

the Centers for Disease Control and Prevention every year. However, state-level data may obscure refusal rates that are much higher in individual communities (e.g., 15–18% in Ashland, Oregon, and Vashon, Washington), making them high-risk for outbreaks of vaccine-preventable diseases (5, 6).

The clustering of exemptions found in our study may have resulted from variation in school-level implementation of exemptions. Alternatively, the clustering of exemptions may have been due to social or cultural characteristics of particular communities. Compared with census tracts outside exemptions clusters, census tracts included in exemptions clusters were likely to have a higher population density, a higher percentage of racial/ethnic minorities, a higher percentage of children aged $\leq$5 years, and a larger mean family size. However, all associations except mean family size were of low magnitude. Further study is needed to determine the factors that contribute to the clustering of exemptions.

Countries with persistently high vaccination coverage have been successful in dramatically reducing rates of infectious diseases, which can result in decreased public perception of susceptibility to and severity of infectious diseases (24). On the other hand, the prominence of real or perceived vaccine safety concerns often increases (24, 25). For example, in a case-control study comparing parents of exempt children with parents of vaccinated children, parents of exempt children reported lower estimates of perceived vaccine safety and efficacy, a lower level of trust in the government, and low perceived susceptibility to and severity of vaccine-preventable diseases (26).

Similarly, in a survey of parents and caregivers regarding the acceptability of routine influenza vaccinations for infants and toddlers, Humiston et al. (27) found that vaccine safety was a concern for almost half of the respondents. In a substudy of the National Immunization Survey, Allred et al. (28) found that vaccine safety concerns were inversely associated with up-to-date vaccine coverage.

Identifying clusters of exemptions and establishing an association between clustering of exemptions and societal risk of pertussis informs immunization policy at the state level and serves as a ''proof of concept'' for identifying high-risk geographic areas for public health intervention. Results from a geographically grounded and locally relevant analysis could help engage and galvanize local communities and could serve as a call to action for local and state-level stakeholders, including community opinion leaders, schools and school boards, health-care providers, public health officials, and the general public.

As with any type of geographic aggregation of data, there is a potential for falsely assigning information of interest to adjacent or nearby geographic areas. For example, exemption rates geocoded to school locations may not represent the locations of residence of children attending these schools, particularly in the case of private schools. On the other hand, pertussis cases were enumerated by the location and census tract of residence. This limitation is mitigated by the fact that our clustering analysis identified groups of adjacent census tracts within each cluster that probably included the places of residence of most children.

Since the exemption data we received did not include information on homeschooled children, our results might be biased if the exemption rates among homeschooled children were different from rates among children who attended school outside the home and/or if there was geographic clustering of homeschooled children. However, based on the number of reported homeschooled kindergarten children (29) in 2004 and previous estimates of underreporting in Michigan (30), we estimated that fewer than 0.5% of children were homeschooled. Therefore, non-inclusion of homeschooled children is unlikely to have had a qualitative impact on our main findings.

We did not have data for exemptions against specific antigens. However, modeling antigen-nonspecific data is likely to decrease the magnitude of association between exemption rates and disease—hence producing conservative values for measures of association.

Pertussis is underdiagnosed and underreported, particularly among adolescents and adults. There is no obvious reason to believe that underreporting of pertussis would be differential in terms of exemptions clusters (i.e., a higher or lower proportion of cases reported in census tracts included in exemptions clusters versus census tracts outside the clusters); therefore, we suspect that the odds ratios for the overlap would be biased towards the null—making our estimates of odd ratios conservative. However, the possibility of selection bias exists if underreporting of pertussis was differential vis-à-vis exemptions clusters. Even in situations where underreporting is nondifferential, the ability to generalize our findings may be undermined by underreporting.

Our findings suggest that geographic pockets of vaccine refusal are associated with the risk of pertussis outbreaks in the whole community. In addition to monitoring state-level exemption rates, state and local health authorities should be mindful of within-state heterogeneity in exemption rates and should actively follow trends in sub-state-level exemption rates.

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