Nonmedical Vaccine Exemptions and Pertussis in California, 2010

WHAT’S KNOWN ON THIS SUBJECT: Previous studies have shown that nonmedical exemptions (NMEs) to immunization cluster geographically and contribute to outbreaks of vaccine-preventable diseases such as pertussis. The 2010 pertussis resurgence in California has been widely attributed to waning immunity from acellular pertussis vaccines.

WHAT THIS STUDY ADDS: This study provides evidence of spatial and temporal clustering of NMEs and clustering of pertussis cases and suggests that geographic areas with high NME rates were also associated with high rates of pertussis in California in 2010.

abstract

BACKGROUND: In 2010, 9,120 cases of pertussis were reported in California, more than any year since 1947. Although this resurgence has been widely attributed to waning immunity of the acellular vaccine, the role of vaccine refusal has not been explored in the published literature. Many factors likely contributed to the outbreak, including the cyclical nature of pertussis, improved diagnosis, and waning immunity; however, it is important to understand if clustering of unvaccinated individuals also played a role.

METHODS: We analyzed nonmedical exemptions (NMEs) for children entering kindergarten from 2005 through 2010 and pertussis cases with onset in 2010 in California to determine if NMEs increased in that period, if children obtaining NMEs clustered spatially, if pertussis cases clustered spatially and temporally, and if there was statistically significant overlap between clusters of NMEs and cases.

RESULTS: Kulldorff’s scan statistics identified 39 statistically significant clusters of high NME rates and 2 statistically significant clusters of pertussis cases in this time period. Census tracts within an exemptions cluster were 2.5 times more likely to be in a pertussis cluster (odds ratio = 2.47, 95% confidence interval: 2.22–2.75). More cases occurred within as compared with outside exemptions clusters (incident rate ratios = 1.20, 95% confidence interval: 1.10–1.30). The association remained significant after adjustment for demographic factors. NMEs clustered spatially and were associated with clusters of pertussis cases.

CONCLUSIONS: Our data suggest clustering of NMEs may have been 1 of several factors in the 2010 California pertussis resurgence. Pediatrics 2013;132:624–630

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KEY WORDS: pertussis, immunization, vaccine refusal, nonmedical vaccine exemptions, California, cluster analysis

ABBREVIATIONS

CDPH—California Department of Public Health
CI—confidence interval
IRR—incident rate ratio
NME—nonmedical exemption
OR—odds ratio

Ms Atwell conceptualized and designed the study, conducted the literature review, cleaned the data, contributed to the data analysis plan and execution and interpretation, drafted the initial manuscript, and reviewed and revised the manuscript; Mr Van Otterloo designed and performed the data analysis plan, the execution and interpretation of the analysis, created the tables and figures, drafted the initial manuscript, and reviewed and revised the manuscript; Dr Zipprich and Ms Winter assisted with project conceptualization and design, contributed to data analysis plan and execution and interpretation, and reviewed and revised the manuscript; Drs Harriman, Salmon, and Halsey assisted with project conceptualization and design, contributed to interpretation of the data, and reviewed and revised the manuscript; Dr Omer supervised the project conceptualization and design, the data analysis plan, execution and interpretation, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2013-0878
doi:10.1542/peds.2013-0878
Accepted for publication Jul 24, 2013
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Before introduction of pertussis-containing vaccines in the 1940s, pertussis was a leading cause of childhood mortality in the United States. In 1934, there were >265,000 cases nationally, compared with a nadir of 1010 cases in 1976. Pertussis is a cyclical disease with peaks in incidence approximately every 2 to 5 years when the number of susceptible people increases sufficiently to sustain transmission; however, a substantial resurgence of pertussis has occurred in recent years. Significant increases in pertussis activity began in 2003 and continued through 2005 in various locations throughout the United States, including California and the Midwest. Although ~5100 to 7800 cases had been seen nationally each year in the late 1990s and early 2000s, >25,000 cases were reported in the United States in both 2004 and 2005. In 2010, California experienced an outbreak of 9120 cases of pertussis and 10 deaths, representing one-third of all cases seen in the country that year. Although a statewide outbreak occurred in California in 2005 as well, the magnitude of cases seen in 2010 was unprecedented, with more cases reported in California in 2010 than in any year since 1947.

This outbreak has largely been attributed to waning immunity of acellular pertussis vaccines and other explanations including large birth cohorts of susceptible infants, increased detection of cases, and the possibility of genetic changes in circulating strains have been widely discussed in recent months. Importantly, however, the role that nonmedical exemptions (NMEs) and clustering of unvaccinated individuals may have played in this outbreak has not been investigated. NMEs to immunization have been on the rise in many states in recent years, including California. Correlations between the ease of obtaining NMEs and the rates of NMEs have been demonstrated. California’s NME rates have more than tripled from 0.77% to 2.33%, with some schools reporting NME rates as high as 84% in 2010. Despite recent increases in NMEs, most estimates of statewide immunization coverage remain high. In 2010, 90.7% of the 509,849 students enrolled in reporting kindergartens (including conditional entrants) received all required immunizations, yet statewide coverage estimates can obscure lower community-level immunization rates.

Given what other studies have shown about the geographic clustering of unvaccinated or undervaccinated individuals, increased risk among vaccine refusers, and geographic and temporal clustering of pertussis outbreaks, it is possible that refusal may also play a role in this resurgence. Our aim is to understand if refusal, and specifically geographic clustering of persons with NMEs, were contributing factors to the 2010 resurgence of pertussis in California. To explore these relationships, we evaluated the spatial clustering of NMEs from the 2005–2006 school year through the 2009–2010 school year and the space-time clustering of pertussis cases in 2010.

**METHODS**

**Data Sources and Study Population**

Data on NMEs for kindergarten students, the number of children enrolled in kindergarten (public and private), and pertussis cases were obtained from publically available data reported by the California Department of Public Health (CDPH). NME data were available for all elementary schools in California with 10 students for the school years 2005–2006 to 2009–2010. Parents in California can obtain NMEs if all or some immunizations are contrary to their beliefs, whether those beliefs are religious, philosophical, or related to other unspecified nonmedical reasons. The process of obtaining an NME varies across states; California only requires a signed form from the parent, whereas in other states, the process is more difficult. Although California refers to such nonmedical philosophical or religious exemptions as Personal Belief Exemptions, we use the term NME here to indicate all exemptions for nonmedical reasons.

Pertussis is a reportable disease in California, and our data set included all confirmed, probable, and suspect pertussis cases reported to CDPH with onset dates from January 1, 2010, through December 31, 2010. According to CDPH, the clinical case definition of confirmed and probable pertussis in 2010 was a cough illness lasting ≥2 weeks without other apparent cause (as reported by a health professional) and ≥1 of the following: paroxysms of coughing, inspiratory “whoop,” or posttussive vomiting. CDPH also used a suspect case category defined as an acute cough illness of any duration with detection of Bordetella pertussis–specific nucleic acid by polymerase chain reaction or an acute cough illness of any duration with ≥1 of the following: paroxysms of coughing, inspiratory “whoop,” or posttussive vomiting that is epidemiologically linked directly to a confirmed case.

Data on age, gender, race/ethnicity, date of onset, and outcome were also included for each case. All school addresses were geocoded to their exact point location (latitude and longitude). To protect confidentiality, pertussis data were geocoded and aggregated to the census-tract level by CDPH staff before data were shared with the other investigators. School enrollment and number of NMEs were aggregated to the census tract level.
Temporal Trends in Exemption Rates and Cluster Identification

NME rates for each school year were calculated by dividing the number of children with NMEs by the total number of kindergarten children in each census tract. We used generalized estimating equations to compute incident rate ratios (IRR) and evaluate temporal trends in exemption rates, treating each census tract as a repeated observation. Census-tract-level kindergarten enrollment numbers were used as denominators in models evaluating NME temporal trends.

Kulldorff spatial scan statistics were used to identify spatial and space-time clusters of events.25 Because the investigators considered the buildup of susceptibles to be a long-term phenomenon, and we observed within-school stability of NME rates (despite a temporal trend), we chose a spatial Poisson model for identifying school exemption clusters. Clustering of pertussis cases was considered a relatively short-term occurrence, and a space-time Poisson model was used to identify clusters of monthly pertussis cases. A detailed description of this application of Kulldorff spatial scan statistics and additional notes on the methods used here can be found in the Supplemental Information.

Evaluation of Census Tract Demographic Variables, the Overlap of NME and Pertussis Case Clusters, and the Incidence of Pertussis Within Versus Outside NME Clusters

Simple and multivariate logistic regression models were used to compute odds ratios (ORs) comparing demographic characteristics of census tracts inside versus outside NME clusters and pertussis case clusters. The demographic variables (from 2005–2009 American Community Survey estimates) of proportion of racial and ethnic minorities (proportion of the population identifying as not non-Hispanic white), average family size, population density, percent of the population with a college degree, median household income, and being within a metropolitan area (defined as Rural Urban Commuting Areas code, which characterizes census tracts according to their rural and urban status26) were chosen a priori based on epidemiologic plausibility or evidence in the literature of associations with individual-level vaccine refusal.21,27 Logistic regression models were used to estimate the overlap between NME clusters and pertussis clusters. We estimated the overlap by calculating the ratio of the odds of a census tract within a NME cluster also being within a pertussis cluster compared with the odds of a census tract outside a NME cluster also being in a pertussis cluster.

We used repeated-measures negative binomial regression models to compare the likelihood of being a pertussis case inside versus outside census tracts belonging to a NME cluster. Census-tract-level population values were used as denominators in models evaluating population dynamics. In addition to simple regression models for overlap and incidence, we used multivariate regression models adjusting for proportion of racial and ethnic minorities, average family size, median age, percent of the population with a college degree, median household income, and being within a metropolitan area.

Analytical Tools and Statistical Significance

School addresses were geocoded using ArcGIS (ESRI, Redlands, CA). Pertussis cases were geocoded at CDPH by using the California Environmental Health Tracking Program’s geocoding tool on a secure server. Geographic cluster analysis was performed by using SatScan version 8.0 (Information Management Services Inc, Boston, MA). All regression and other statistical analyses were performed with SAS v9.3 (SAS Institute, Inc, Cary, NC). Results were considered significant at α = .05.

Ethical Review

The Institutional Review Boards of CDPH, Johns Hopkins School of Public Health, and Emory Rollins School of Public Health deemed this project nonhuman subjects research. Non-CDPH staff members were not allowed to access disaggregated case data or personal identifying information.

RESULTS

Data on NME rates were obtained from 8360 schools during the 2005–2006 to 2009–2010 school years, producing 36,447 school years of NME rate data. One hundred percent of schools in the 2008–2009 and 2009–2010 school years were successfully geocoded. Of schools in the 2005–2006, 2006–2007, and 2007–2008 school years, 575 (7.80%), 386 (5.24%), and 326 (4.46%), respectively, could not be geocoded because of missing or incomplete addresses and were excluded from the analysis. In 2010, 9143 confirmed, probable, and suspect pertussis cases were reported. Of these, 622 (7.15%) cases could not be geocoded because of missing or incomplete addresses and were excluded from this analysis. Analyses comparing gender, age, ethnicity, race, and mortality between the entire data set and geocoded cases did not differ by >1% in any category; therefore, the subset of cases geocoded is likely to be representative of all cases.

The mean census-tract-level NME rate increased from 1.6% in the 2005–2006 school year to 2.4% in the 2009–2010 school year (yearly IRR = 1.11, 95% confidence interval [CI]: 1.10–1.12). During the study period, 39 statistically
significant clusters of high NME rates were identified (Tables 1 and 2, Fig 1), ranging from large geographic areas to single census tracts. Results from bivariate analysis with demographic variables are shown in Table 3.

Reported pertussis cases varied by month from <100 in January 2010 to a peak of >1000 in August 2010. Two statistically significant clusters of pertussis cases were identified spanning from May 2010 to October 2010 and from July 2010 to November 2010 (Tables 1 and 2, Fig 1). Significant demographic characteristics associated with pertussis clusters are shown in Table 3.

Census tracts within a NME cluster were more likely to be in a pertussis case cluster than census tracts outside of a NME cluster (OR = 2.47, 95% CI: 2.22–2.75). The association between the overlap remained significant after adjustment for demographic factors (IRR = 1.12, 95% CI: 1.02–1.23).

**DISCUSSION**

Our findings suggest that geographic areas with high rates of NMEs are associated with high rates of pertussis. The contribution of NMEs to the changing epidemiology of pertussis should be acknowledged and explored.

### TABLE 1 Personal Beliefs Exemption Spatial Clusters From 2005–2010

<table>
<thead>
<tr>
<th>Exemptions Cluster</th>
<th>Cluster Centroid</th>
<th>Observed Exemptions</th>
<th>Expected Exemptions</th>
<th>Relative Risk</th>
<th>P</th>
<th>Description</th>
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<td>10 020</td>
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<td>Greater Escondido area</td>
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<td>1178</td>
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<td>0.019</td>
<td>&gt;100</td>
<td>.02</td>
<td>Woodcrest Area</td>
</tr>
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</table>
in future studies along with other contributing factors, such as waning immunity of acellular vaccines.

In California, both NME and pertussis clusters were associated with factors characteristic of high socioeconomic status such as lower population density; lower average family size; lower percentage of racial or ethnic minorities; higher percentage of high school, college, or graduate school graduates; higher median household income; and lower percentage of families in poverty.

Although statewide immunization coverage in California is high among children entering kindergarten, in many communities within the state, coverage is far lower. Our findings are consistent with a previous study in which NMEs were associated with pertussis clusters.\(^{21}\) Several studies have previously demonstrated the increased risk of vaccine-preventable diseases among those who refuse vaccines.\(^{15,16,21,27–29}\)

Other studies have shown increased community level-risk of vaccine-preventable diseases for persons living in areas with high NME rates.\(^{21,28}\) With diseases like pertussis and measles, which have the highest known infectious disease reproduction numbers,\(^{30}\) it is estimated that >95% of the population must be immune to prevent outbreaks and suppress sustained transmission.\(^{30,31}\) Herd immunity must be maintained to reduce the risk of disease for those too young to be vaccinated or unable to receive vaccines.

This analysis is subject to several limitations. NME data from California do not contain specific data on which vaccine(s) or dose(s) were not received by a child with a NME, and it is possible that some children with a NME were completely vaccinated against pertussis. Future studies should attempt to analyze varying rates of vaccine avoidance for specific antigens to determine the magnitude of impact within populations with high NMEs. Furthermore, NME data from kindergarten entry are a 1-time measurement and only a proxy for community-level vaccination coverage and immunity. Immunization status of cases was not available for a large enough proportion of the pertussis cases to include this variable in our analysis. Also, underreporting of pertussis is known to occur, particularly in adults.\(^{32,33}\) California implemented the “suspect” case definition to capture cases with positive polymerase chain reaction test results but for whom complete clinical information was not available. Analyses of subgroups by various combinations of case definition were not possible with this data set but should be incorporated into future analyses.

### TABLE 2 Pertussis Case Spatial-Temporal Clusters in 2010 in California

<table>
<thead>
<tr>
<th>Pertussis Cluster</th>
<th>Cluster Centroid Latitude °N</th>
<th>Longitude °W</th>
<th>Start Date</th>
<th>End Date</th>
<th>Observed Cases</th>
<th>Expected Cases</th>
<th>Relative Risk</th>
<th>P</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36.201</td>
<td>121.153</td>
<td>May 2010</td>
<td>Oct 2010</td>
<td>3783</td>
<td>1835.53</td>
<td>2.91</td>
<td>&lt;.001</td>
<td>Central California</td>
</tr>
<tr>
<td>2</td>
<td>33.231</td>
<td>117.097</td>
<td>July 2010</td>
<td>Nov 2010</td>
<td>980</td>
<td>390.52</td>
<td>2.71</td>
<td>&lt;.001</td>
<td>San Diego County</td>
</tr>
</tbody>
</table>

### FIGURE 1

Relative locations of pertussis space-time clusters and personal beliefs exemption (PBE) clusters from 2005–2006 to 2009–2010. The inset in the top right corner shows the relative locations of pertussis space-time clusters and PBE spatial clusters in San Diego County.
Schools with <10 students were not included in the data set provided by CDPH for this analysis because the CDPH expects that these schools are likely to be individual family home schools. Although the number of homeschooled children in the state is unknown, the US Department of Education estimates that ~1% of the school-age population nationally is homeschooled.34 Exclusion of homeschooled children could affect the results of this analysis if homeschooled children are more or less likely to be immunized compared with children who are not homeschooled or if homeschooled children cluster geographically. Additionally, analysis of immunization coverage among homeschooled children should be explored.

We used census tracts as the unit of analysis to maintain compatibility with available demographic data and retain confidentiality of precise case location. It is possible that students did not attend schools within the census tract where they resided, but our clustering analysis identified geographically adjacent areas that most likely captured the residences of most children attending a given school. Additionally, size and location of clusters are influenced by underlying state characteristics such as geography, demographics, and population density. This complicates comparisons of such analyses from different states or geographic regions. Finally, small area problems could be an issue here, but this concern is not unique to analyses such as these.35 Our results are still significant despite the small number of exemptions in some clusters and would remain essentially the same if such clusters were removed from the analysis.

**CONCLUSIONS**

Other studies have shown evidence to support several factors that have likely contributed to the increase in pertussis cases in recent years. Our findings suggest that communities with large numbers of intentionally unvaccinated or undervaccinated persons can lead to pertussis outbreaks. In the presence of limited vaccine effectiveness and waning immunity, sustained community-level transmission can occur, putting those who are most susceptible to communicable diseases, such as young infants, at increased risk.

**ACKNOWLEDGMENTS**

We acknowledge Teresa Lee from the CDPH for provision of the NME data, Tina Proveaux for her editorial assistance with the article, and Will Probert and the Special Pathogens and Molecular Diagnostics Units of the Microbial Diseases Laboratory at the CDPH for mentorship of Jessica Atwell and their contributions to pertussis case detection for the state of California.

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DOI: 10.1542/peds.2013-0878

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