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The Association Between School Immunization Non-medical Exemptions and Pertussis Incidence:
A Geographic Clustering and Transmission Model Approach

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Bachelor of Science in Public Health
National Taiwan University
2008

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science in Public Health
in Global Epidemiology
2012

Abstract

The Association Between School Immunization Non-medical Exemptions and Pertussis Incidence: A Geographic Clustering and Transmission Model Approach

By Ching-Yi Chuo

Background

School entrance immunization requirement has been an important strategy in preventing vaccine preventable diseases among school-aged children in the United States. 48 states allow for personal beliefs vaccination exemptions which pose threats of disease transmission in the population. Our research, based on non-medical vaccine exemption and pertussis incidence data from California, attempted to establish association between exemptions and vaccine preventable disease transmission on both temporal and spatial scales.

Method

We received 84,721 geo-coded records from kindergarten on non-medical exemption from 1994 to 2003. 5695 under age 18 pertussis cases information from year 2000 to 2004 were provided by the California Department of Public Health. We accumulated the records into 7049 census tracts as our study individual. Kulldorff's scan statistics were applied for temporal, spatial cluster identifying. Descriptive analysis on demographic factors related to both exemption and pertussis clusters was performed. We applied Poisson regression model for testing the association between exemption clusters and pertussis. We also construct SIR disease transmission model with force of infection accounting for exemption clustering risks. Results of model simulation are compared with observed pertussis on the spatial scale by Geographically Weighted Regression model (SWR).

Result

We identified 56 non-medical vaccine exemption clusters and 8 pertussis incidence clusters. Both exemption and pertussis clusters are associated with higher percentage of white ethnicity, lower under 18 population, and lower poverty percentage (all $P<0.001$). Our Poisson model on exemption clusters to incidence of pertussis controlling for demographics yields RR:1.19, 95% CI (1.04, 1.21). Stimulated results from spatial cluster SIR model are matched with observed pertussis cases ($R^2=0.15$) and pertussis cluster ($R^2=0.21$) by GWR.

Conclusion

Our findings suggested that vaccine exemption clusters are associated with the risk of pertussis outbreaks in California.

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BACKGROUND & LITERATURE REVIEW

Pertussis

1. Global Prospective

A. Epidemiological and Pathogen Characteristics

Ever since the first description of epidemic by Guillaume de Baillou in the late 17th century, Pertussis has been one of the major killers of infants and young children even after the introduction of vaccine in 1940s. Today, it is estimated that there are still 16 million cases around the world, and about 195000 children died from the disease (WHO immunization, 2011). Although 95% of the cases were in developing countries, resurgence of the disease due to waning immunity and anti-vaccine movements still pose threats to the developed world. It is estimated that the incidence in countries where immunization coverage were well maintained is 10 to 100 times lower than in countries where immunization program were disrupted by anti-vaccine moments (Gangarosa EJ et. al. 1998).

Caused by Bordetella Pertussis, gram negative pleomorphic aerobic bacilli, the clinical signs of pertussis generally include paroxysmal cough, inspiratory whoop and vomiting after whooping (Bettiol S et al. 2010). Other documented complications are subconjunctival hemorrhages, rib fractions, hearing lost, carotid artery dissection and pseumonia (Hewlett et al. 2005). Pertussis is highly contagious, it is reported in

studies that its Ro (basic reproduction number) is around 16~18 (Anderson RM et al. 1982), compared to seasonal and pandemic flu's ranged between 1.5 and 3. The transmission means of Pertussis is through respiratory droplets, it is rarely observed by contact transmission. Incubation period for Pertussis is typically 7 to 10 days, and followed by 3 clinical stages: Catarrhal, Paroxysmal and Convalescent. Catarrhal stage lasts for 1~2 weeks with mild respiratory illness, it is also the most infectious stage of Pertussis; followed by paroxysmal, happened when coughing has becoming whooping and last for 1~7 weeks, and convalescent 2~3 weeks (Long SS. Et al. 2000). Clinical manifestation differs from person to person depends on age of the patient, immunization status, infection history and treatment process (Harnden A et al. 2006).

B. Transmission

As stated earlier, the transmission vector for Pertussis is droplets from nose and throat. Transmission of Pertussis is much easier compared to other respiratory infectious diseases, probability of infection rises in crowded conditions where contacts are easily made. It is also notice that the disease spread out often via asymptomatic cases, which most likely being adults, to more symptomatic young children. In a research in California (California Department of Health Report, 2010), 90% of household members believe infected through contacting the disease from a household member.

2. Pertussis in US

Although most of the cases around the world are in developing countries, the burden of Pertussis in the United States is substantial. There were approximately 300,000 cases and 10,000 deaths prior to widespread use of vaccine. Even after the implementation of Pertussis vaccines into children immunization recommendation schedule since 1940s (the DTP), the infection rates of Pertussis have been rising starting at the early 1980s in the United States (MMWR 2002). Possible explanations for the situation are a) decreased vaccine efficacy; b) waning immunity among adolescents and adult vaccination; c) increased vaccination exemption rates in young children; d) increased diagnosis and reporting of cases because of social awareness and improved surveillance tools (MMWR 1997). When looking at incidence trends by different age groups, incidence among adolescents and infants too young for vaccination had an overall increased trend in particular(Cherry JD et. al. 1999; Davis SF et. al. 1992; Guris D et.al. 1996). As for 2010, there were a total of 27,550 reported cases. Pertussis has now become an endemic disease in the United States with a frequency of 3 to 5 years. For the past decade, outbreaks were reported from Washington, Michigan, California and other states.

Vaccination & challenges

1. Pertussis Vaccination

The pathogen for Pertussis—Bordetella Pertussis was first isolated in 1906 by Jules Bordet and Octave Gengou. The development of inactivated whole-cell Pertussis vaccine began soon after the isolation of *B. pertussis*. In 1920, Dr. Louis W. Sauer developed the first vaccine and in 1925, the first massive application of the whole-cell vaccine was conducted for controlling outbreaks in the Faroe Islands in North Sea (baker JP et al. 2004). In 1942, the first combined vaccine of whole-cell Pertussis, Diphtheria and Tetanus (DTwP) was developed by American Scientist Pearl Kendrick. However, DTwP (whole cell Pertussis vaccine) is commonly associated with several local adverse effects such as erythema, swelling and pain at the injection site, fever and other mild symptoms. Other more severe but rare adverse effects such as hypotonic hyporesponsive episodes (one case in 1750 doses administrated) and acute encephalopathy (0~10.5 cases to a million doses administrated) were also observed (National Academy Press, 1994). The introduction of acellular *B. Pertussis* component into combined vaccine (DTaP) was later introduced by Japanese Scientist Yuji Sato in hoping to reduce the side effect of Pertussis vaccine. Since 1991, acellular Pertussis vaccines were licensed in the United States for the fourth and fifth doses for individuals completed 3 doses of DTwP (whole cell Pertussis combined

vaccine) due to uncertainty of effectiveness applying acellular vaccine on infants and young children. Finally in 1996, with sufficient evidences from studies over the world, DTaP vaccines were introduced for primary series (MMWR, 1997). According to the latest recommended immunization schedule for persons aged 0 through 6 by CDC 2011, DTaP is recommended at the 2^{nd} , 4^{th} and 6^{th} month after birth (the primary series) and followed by the 4^{th} dose at around one- and-a-half-year-old and 5^{th} dose around 4 to 6 years old; after 6 years old, a dose of TdaP (with reduced Diphtheria and Tetanus units) at 11 to 12 years-old is recommended and every 10 years of TdaP thereafter. Recommendations for unvaccinated persons by the advisory Committee on Immunization Practices (ACIP) aged 7 and above are primary 3 doses (4 wks and 6 to 12 months after first dose) and booster doses every 10 years (MMWR, 2011).

2. Vaccine efficacy and safety

Vaccine efficacy is defined as the reduction in the incidence of a disease among people who have received vaccination compared to the unvaccinated population in individual level. The efficacy of vaccine is often measured at phase II or III clinical trials. The calculation of vaccine efficacy can be presented as:

$$\text{VE} = \frac{Attack\ rate\ in\ unvaccinated\ population - attack\ rate\ in\ vaccinated\ population}{attack\ rate\ in\ unvaccinated\ population} \times 100\%$$

or VE=(1-relative risk of infection).

Compared to acellular vaccines, whole cell vaccines tend to have relatively

higher reactogenicity since they contain approximately 3,000 antigens/dose from the whole cell of B. Pertussis. The efficacy estimates for DTwP vaccines vary from 37% to 96% (Greco 1996; Gustafsson, 1996; Liese, 1997; Simondon, 1997; Stehr, 1998). Average acellular Pertussis vaccines contain 10 to 30 antigens/dose (Edwards et. al. 2008). From results of several randomized controlled trials in Europe, the efficacy of DTaP vaccines vary from 59% to 85%.

The efficacy of multi-doses (more than 3 doses) of the vaccine is also higher than only one- or two-doses vaccines against typical whooping cough (84%~85% for multi-dose v.s. 59%~78% for one- or two-dose) and mild pertussis disease (71%~78% for muit-dose v.s. 41%~54% for one- or two-dose)(Zhang L et.al., 2012). As for vaccine safety, the superiority of acellular vaccines over whole cell vaccines can be observed in the following prospective. First, acellular vaccines have significantly lower incidence of primary series non-completion due to adverse events than whole cell vaccines. Secondly, acellular vaccines are also less likely to cause febrileconvulsions and hypotonic –hyporesposive episodes during the primary series (Zhang L et. al., 2012). However, the risk of death between the two kinds of vaccines were similar.

3. Adolescent and Adult Infection & Vaccination

Although incidence of Pertussis is highest among infants and young school aged children, evidences of increasing reports of cases among adolescents and adults population are observed worldwide (CDC 2005; Cherry 2006; Dworkin 2005). There are two main reasons that infections in adults and adolescents are important. First, Since the estimated force of infection of Pertussis is still considerably high among persons older than the age of 15 (estimated 0.1, compared to 0.12 of infants)(Hethcote, 1997),there is possibility that the epidemic of Pertussis among adults and adolescents are underestimated since symptoms of Pertussis are milder and more atypical among them (Edwards, 2005). It is estimated that the true case number is likely to be 5-6 times more than reported (Shaikh R, 1998; Sutter RW, 1992).

4. Vaccine Exemption

School vaccination requirements, which can be dated back to 1855, is considered one of the major policies controlling vaccine preventable diseases in the United States (MMWR, 2009). However, there are two situations allowing for vaccination requirement exemptions: Medical exemptions, which are offered in all states in the U.S. and non-medical exemptions due to personal philosophical (offered in 20 states) or religional reasons (offered in 48 states). For pertussis, literature indicated that easier granting of exemptions (incidence rate ratio=1.53; 95% confidence interval,

1.1~2.14) and availability of personal belief exemptions (incidence rate ratio=1.48; 95% confidence interval, 1.03~2.13) were associated with increased pertussis incidence (Omer et. al. 2006).

INTRODUCTION

Since its first introduction in 1855, school immunization requirements have been an important strategy in preventing vaccine preventable diseases among school-aged children in the United States [1, 2]. All states require proof of vaccination for entering schools; however, exemptions are offered for medical reasons (in all states) and other religious or personal beliefs reasons (in 48 states). Since non-medical exemptions (e.g. personal beliefs) are easily granted in some situations, our research of interest is whether non-medical exemptions can be a risk factor of higher pertussis incidence. Previous research showed that from 1991- 2004, the rates of nonmedical exemptions increased in states which are more easily granting non-medical exemptions; furthermore, the incidence of pertussis was almost 50% higher in states with easy procedures for granting exemptions [3]. At the state level, areas with higher exemption rates can still pose a threat of state wide epidemic by providing susceptible population [4-6]. A study in Colorado showed that the incidence of vaccine preventable disease such as measles and pertussis was associated with county-level exemption rates [7]. Even in schools, vaccine exemptions can cause threats. In a study, at least 11% of non-exemption children who acquired measles had contacts with measles infected children who had obtained vaccine exemptions [8].

In this study, we identified both exemption and pertussis clusters in California,

characterized their traits, and determined the association between high non-medical exemption rates and pertussis clusters.

METHODS

Data Source and Study Population

According to the Centers for Disease Control and Prevention's (CDC) recommendation on Childhood immunization schedule, children need five doses of DTaP (combined vaccines with diphtheria, tetanus toxoids and acellular pertussis components) by kindergarten (age 4-6). Under the California School Immunization Law[9], all children are required to receive certain vaccinations in order to attend and public or private schools, children care centers and nurseries. However, students are allowed to obtain exemptions for medical and belief reasons.[9] In California, religious, philosophical and other belief-based exemptions are all termed "Personal Beliefs Exemptions" (PBE). We acquired non-medical exemptions records of immunization requirements from 1994 to 2003 kindergarten assessment from the California Department of Health Services. There were 84,721 records containing school's geographical identifiers, year of assessment and number of kindergartener's with personal beliefs exemptions. These records did not contain homeschooled children; however, the data should be very representative of exemption status for California school children.

We received pertussis cases information by census track from the California Department of Public Health for years 2000-2004. Pertussis case records were derived

from a state wide surveillance system which gathered information directly from local health department. In our study, we include all the cases under the age of 18 at disease onset. A reportable probable case, based on the recommendation of the CDC, is defined as cough illness lasting at least 2 weeks with at least 1 of the following: paroxysms of coughing, inspiratory “whoop”, or post-tissue vomiting, without other apparent cause[10]. A case was defined as confirmed if 1) the patient had acute cough illness with isolation of *B. pertussis* antigen by immunohistochemistry (IHC) methods, 2) a case that met clinical case definition and was confirmed by positive PCR, or 3) clinical case definition was met and was epidemiological linked with other confirmed cases[10, 11]. The geographical identification of cases was geocoded by California Department of Health Services.

We used census tracts as our primary unit of geographic aggregation for pertussis cases. As for exemption data, school locations (i.e. geocoded addresses) were used for primary identification. The school locations then are accumulated into census tracts level for further analysis. Census tracts are relatively stable geographical units delineated by local participants as part of the US Census bureau’s Participant Statistical Area Program[12]. Their unique characteristics such as relatively small size, internal homogeneity and local participation in delineation make census tracts ideal for geographic analysis.

Exemption Rate Estimation

Census-tract-level personal beliefs exemption rates were computed as the sum of all exemptions in all schools of a particular census tract divided by the total number of children attending kindergarten during the year. We applied population-averaged Poisson models in estimating annual changes.

Cluster Identification

All spatial and space-time cluster identification including exemption and pertussis case clusters were done by using Kulldorff's scan statistics[13]. With this method, random sets of events (exemptions or pertussis cases) were permutated under null hypothesis under known distribution as expected values (999 simulations under Poisson distribution). Identification of spatial clusters was done by moving various sized circular windows around spatial grid points in order to maximize the contrast of event density inside and outside the windows (in our study, exemption numbers and pertussis cases). For identifying space-time clusters, cylinders were used instead, where the height of the cylinders representing time period. A test statistic, derived as likelihood ratio, was calculated as comparing observed values with expected values we permutated with p-value following chi-square distribution. The specialty of Kulldorff's scan statistics is that there's no pre-assumption of distance and neighboring relationship for identifying clusters.

Since we observed an overall stability of within-school exemption rate and pertussis incidence overtime, we treated both clusters as long term phenomenon and used a purely spatial Poisson model for identifying clusters.

Census tract level characteristics and cluster Poisson model

There are two disease related measurements: pertussis incidence at census tract level and pertussis clusters; and one vaccine related measurement—exemption clusters in our study. Other basic demographic information of each census tract such as population size, population density, age structure, gender and race distribution, male female percentage and other demographic measurements were derived from census data. To explore the characteristics of both exemption and pertussis clusters, we performed chi-square statistics as well as odds ratio with 95% confidence interval for categorical variables [14] and two-sample-t-test for continuous variables.

Studies showed that the incidence of pertussis is related to immunization status and other demographic factors [3, 4]; Poisson regression was applied to conduct the analysis.

Transmission Model considering Cluster effect

Infectious disease transmission models have been applied to study the trends of disease spreading, to predict future course of an outbreak and to evaluate disease control strategies as well as risk factors in favor of better control of epidemics[15].

Our approach in this research is to incorporate exemption cluster risks from Kulldorff's scan statistics into a basic SIR transmission model in an attempt to model the effect of exemption clustering on pertussis transmission.

The SIR model (susceptible, infectious and Recovery model) is the very basic form of epidemic modeling illustrating the transmission of disease (flow from susceptible to infectious), and the recovery of the infected persons. The flow from susceptible to infectious (pertussis cases) is determined by the product of susceptible and force of infection (λ); and the recovery flow from infectious to recovered is determined by Υ, which is the inverse of average infection period of the disease. Previous literature [16-19] demonstrated the use of age-structure model in pertussis, which featured different force of infections for different age groups and contact structures between age groups; our structure (figure 1) incorporated force of infections from different age groups by weighting population size of age groups. Furthermore, we incorporated the scale of exemption cluster risks into the force of infection to stimulate the effect of geographical clusters on disease transmission.

To determine the predictiveness our estimated pertussis cases to true case number and pertussis clusters, we performed Geographically Weighted Regression (GWR), a regression model that is widely used in Public Health studies [20-22] for spatial relationships which takes into account the spatial neighboring effect.

Analytical tools and statistical significance

We used SAS, version 9.2 (SAS Institute Inc, Cary, North Carolina) for descriptive analysis as well as Poisson regression model. Clusters of Pertussis cases and exemptions were identified by SatScan, version 9.1.1 (Information Management service, Inc., Boston, Massachusetts). Geocoding and geographical analysis were performed by ArcGIS, version 10 (ESRI, Redlands, California) and Open GeoDa version 0.9.9.10 (GeoDa center for Geospatial Analysis and Computation and Arizona Board of Regents). R, version 2.14.1 (The R Foundation for Statistical Computing) was used for SIR model construction. All statistical tests including the identifying of clusters and association were considered significant with $\alpha=0.05$.

RESULTS

Exemption data were used from 14,811 schools for year 1994 -2003 yielding a total of 118,488 school-year for exemption rates. There were 5,720 pertussis cases reported under the age of 18 for the years 2000-2004. All cases were accumulated into each census tract for case incidence and cluster identification; there were total 3096 census tracts that had at least 1 case.

Basic Demographic characteristics of the 7,049 California census tracts were as follows: population density, median 6135 persons per square mile (interquartile range (IDR) 2403.3-10516.7); median age 34 years (IQR 29.3-38.7); median percentage of male 49.3% (IQR 48.2%-50.6%); percentage population under poverty status 12% (IQR 5.9%-24.8%), and percentage white 50% (IQR 27.9%-71.3%).

During the study period (1994-2003) there were 54 statistically significant exemption clusters identified, the likelihood of a census tract being in an exemption cluster was associated with slightly lower male percentage (OR (odds ratio) 0.99, 95% CI (0.88,0.99)), higher percentage of white ethnicity (OR 2.65, 95% CI (2.64,2.65)),slightly lower under 18 population (OR 0.91, 95% CI(0.91,0.91)), lower poverty percentage (OR 0.77, 95% CI(0.76,0.77)) (table 2.) and lower population density (Average 3,566 persons per square mile (SQMI) inside exemption clusters. vs 9,064 SQMI, $P<0.001$)

Eight pertussis clusters were identified during the period 2000-2004. Compared with census tracts outside pertussis clusters, census tracts inside pertussis cluster were more likely to have slightly higher male percentage (OR 1.005, 95% CI (1.003, 1.006)), higher white ethnicity percentage (OR 1.35, 95% CI (1.348, 1.351)), lower under 18 population (OR 0.7782, 95% CI (0.777,0.7794)), and lower poverty percentage (OR 0.771, 95% CI (0.7695, 0.7726))(TABLE 2). Pertussis clusters are also associated with higher population density (Average 9565.7 SQMI in pertussis clusters and 7360.5 SQMI outside pertussis clusters, P<0.001)

We also conducted Poisson regression model for pertussis incidence by census tracts. In the bivariate regression analysis, the incidence of pertussis was 21% higher in census tracts in exemption clusters compared to census tracts outside exemption clusters (IRR=1.2; 95% CI: 1.13, 1.31); after controlling for male percentage, white ethnicity percentage, age distribution under age 18, percentage under poor economic status and population density, the incidence rate ratio for pertussis incidence inside vs. outside exemptions clusters was 1.19, 95% CI (1.04, 1.21).

We conducted SIR simulation for each census track. The Susceptible (S) in our model were unvaccinated school aged children estimated from vaccine coverage rate. Our force of infection (λ) estimation was calculated based on historic estimate of age-structure models [16, 23, 24]. Our estimated force of infection incorporating age

factors was around 0.3158. Since the estimated relative risk for pertussis clusters ranged from 1.87 to 163.173 (not accounting for those outside pertussis cluster and have 0 risk), some transformation was required. Our approach was to log transform the cluster relative risk and incorporate it into our estimate of force of infection. Since the main goal of our estimation was to see the trend of geographical distribution rather than the exact case number permutated, we still allowed for 18 census tracts having a force infection value greater than 1. As for the census tracts having 0 risk, we inputted a very small non-zero value. Our estimated recovery rate was calculated as 1/21. The smallest non-zero value for Ro (basic reproduction number, calculated as λ/Υ) was 4.12, while the largest was 33.33. The temporal trend of our simulation is shown in FIGURE 2. Case number ("I" in the figure) reached the peak on the second year of simulation. Since there was no demographic component in the model, the trend of simulation was considered stable; we took the simulated case number of year 2 (I2) to regress with precalcuated pertussis cluster risks (FIGURE 3) and observed case numbers (FIGURE 4) to test the predictiveness of our model in spatial contents.

Our result of fitting adaptive weighted Geographically Weighted Model of our permutated case number on pertussis cluster risks yielded an adjusted R^2 of 0.15, poor fitted area are mainly urban areas such as Los Angeles and San Jose. As for the model for pertussis cases, the corresponding adjusted R^2 for the model was 0.21.

DISCUSSION

We demonstrated that high exemption rates was associated with pertussis incidence in California by several approaches, the Poisson model accounting for exemption clusters and also the simulation and geographical fitting model in cooperating exemption cluster risks. Our Poisson model showed that census tracts in exemption clusters have 1.19 times higher incidence rate than in census tracts outside exemption clusters when controlling for gender, race, age, and population density. Our results from SIR simulation considering exemption cluster risks and unvaccinated population presented the concept of "spatial Ro" defining a spatial relationship between exemptions and pertussis cases when both the susceptible boosting effect and increased transmission risk due to vaccine exemption were considered in school aged population. The models showed fair strength in predicting spatial locations of both pertussis incidences (adjusted R^2=0.15) and clusters (adjusted R^2=0.21).

Exemption clusters and pertussis clusters shared several traits; both types of clusters were associated with higher proportion white ethnicity, lower percentage of under 18 population, and lower percentage of population under economical poverty status. In multivariate analysis, these factors were still significantly associated with the outcome variables (exemption clusters, and pertussis clusters). These results showed that both the pertussis incidence and exemption rates were associated with

places that have higher socio economic status [25].

The introduction of DTwP, DTaP vaccinations did very much lower the incidence rate of pertussis in developed world; it is estimated that vaccination reduced 90% of pertussis incidence and mortality [26]. However, since the early 1980s, reported pertussis incidence has increased periodically with a cycle of 3-4 years[27]. Possible explanations are: decreased vaccine efficacy, waning immunity among adolescents and adults, increased reporting rate and increased rate of immunization exemptions[28].

Increased risk of vaccine-preventable diseases among vaccine refusers has been demonstrated in several studies [22, 29-31]. The uniqueness of our study was to incorporate spatial factors into our analysis.

Identifying exemption and pertussis clusters is important from public health prospective. Establishment of the association between non-medical exemptions and disease incidence at the state level helps scientific in supporting immunization policies and promote vaccination programs. Meanwhile, our simulation model incorporating the concept of spatial Ro can be further applied into public health surveillance system for identifying potential outbreak sites of vaccine preventable diseases. Moreover, by identifying clusters of exemption and pertussis cases, we could help state and local health department identify hot spots for intervention. Our

research could also serve as a “call to action” for local communities. Our results on demographic factors related to both exemptions and pertussis clusters might inspire further studies into the issues.

This study has several limitations. Our pertussis data was from reporting records of the state government, which might be subjective to underdiagnosed and underreported information biases. Our data on personal beliefs exemptions only include school-educated children; conclusions drawn from our analysis might be biased if the distribution among homeschooled children was different. As for our SIR model accounting for spatial clustering risk, we only included limited assumptions and factors which might not reflect the real situation. However, our models did have around 40% of correlation with the observed location of disease incidence.

Our findings suggested that vaccine exemption clusters were associated with the risk of pertussis outbreaks in California. Health authorities should monitor immunization exemption rates at different administrative levels and try to identify the factors associated with exemptions for further implementation.

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TABLES AND FIGURES

Total exemption clusters(n=54)	outside exemption cluster[a]		inside exemption cluster		Odds ratio	95% confidence interval
	No. of Persons	%	No. of Persons	%		
Male Gender (n=33,871,648)	14483665	49.8%	2391227	49.7%	0.9945*	0.9926, 0.9964
White race/ethnicity (n=44,838,204)	16430991	42.0%	3739068	65.7%	2.651*	2.646, 2.656
Under 18 population (n=33,871,648)	8007435	27.6%	1242394	25.8%	0.9153*	0.9133, 0.9173
Population under poverty status (n=33,100,044)	4156228	14.6%	549902	11.7%	0.7706*	0.7683, 0.7729

* P<0.05

[a] reference category (odds ratio=1)

TABLE 1. Basic characteristics of identified exemption clusters

	outside Pertussis cluster[a]		inside Pertussis cluster		Odds ratio	95% confidence interval
	No. of Persons	%	No. of Persons	%		
Male Gender (n=33,871,648)	9662132	49.8%	7212760	49.9%	1.005*	1.003, 1.006
White race/ethnicity (n=44,838,204)	11191977	42.0%	8978082	49.4%	1.35*	1.348, 1.351
Under 18 population (n=33,871,648)	5709603	29.4%	3540226	24.5%	0.7782*	0.777, 0.7794
Population under poverty status (n=33,100,044)	2947876	15.6%	1758254	12.4%	0.771*	0.7695, 0.7726

* P<0.05

[a] reference category (odds ratio=1)

TABLE 2. Basic characteristics of identified pertussis case clusters

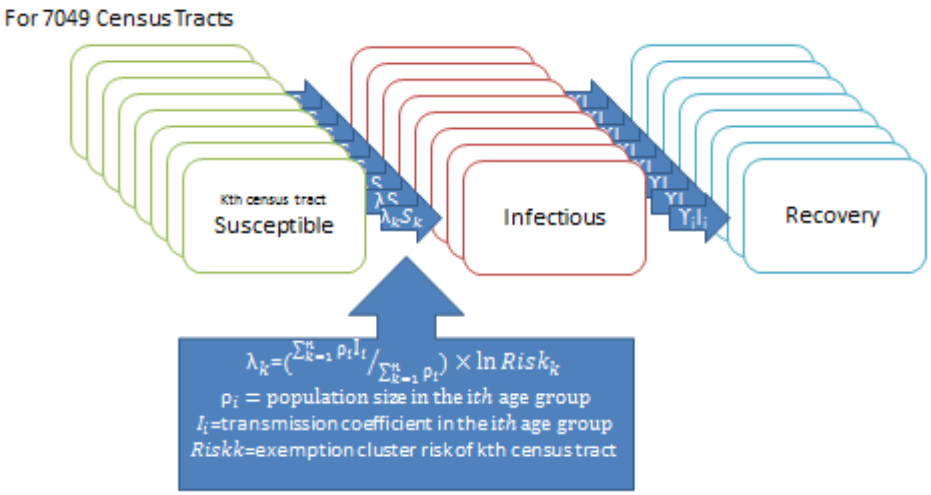

FIGURE 1. Schematic representation of transmission model

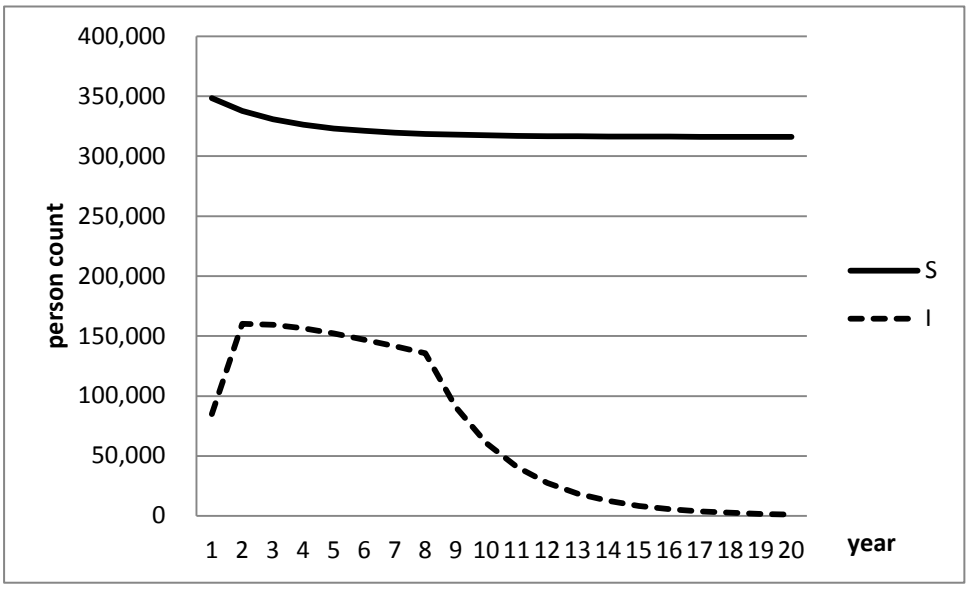

FIGURE 2. Stimulated result of spatial weighted SIR model

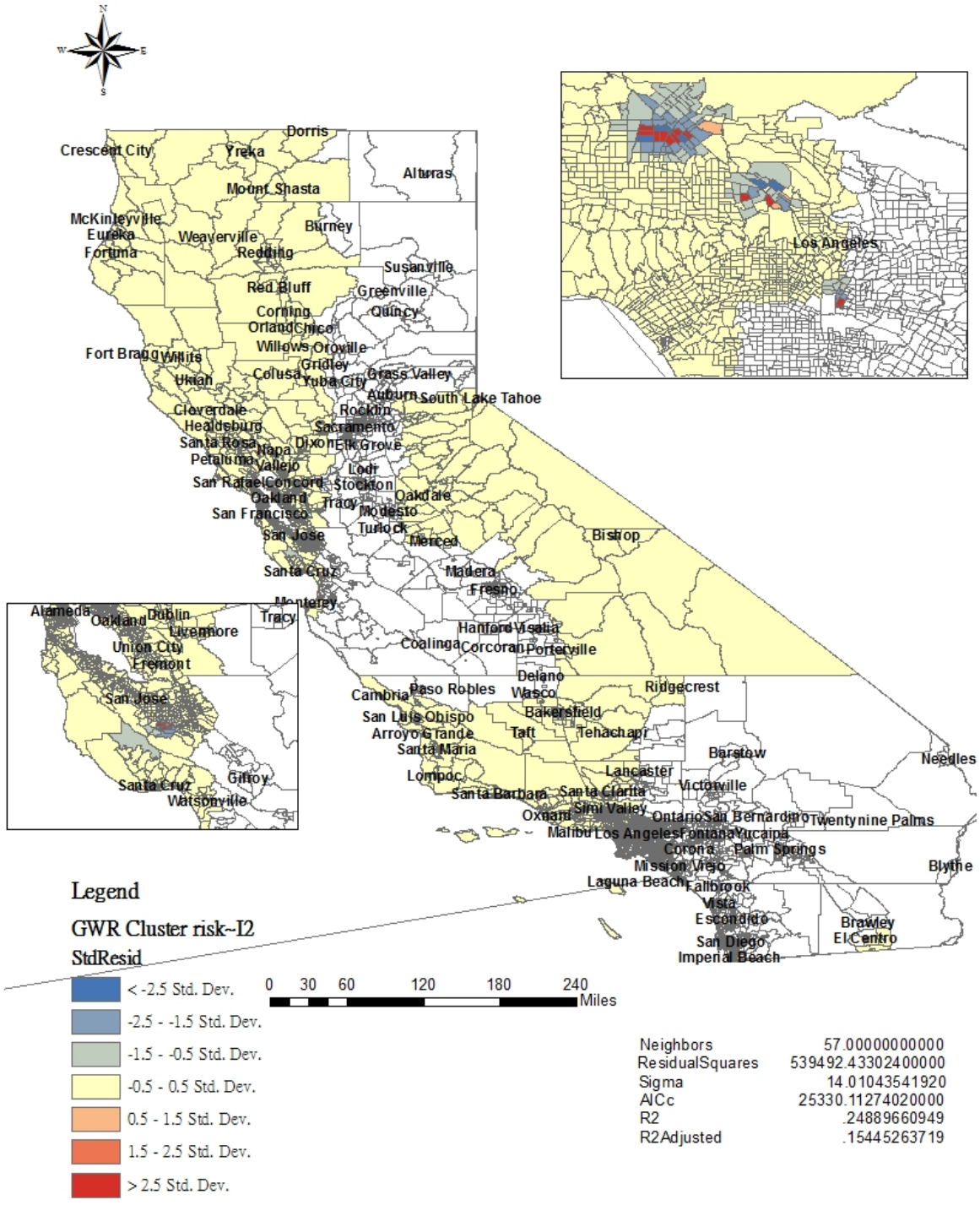

FIGURE 3. Geographically Weighted Regression (Pertussis cluster risk~ permutated cases at year 2)

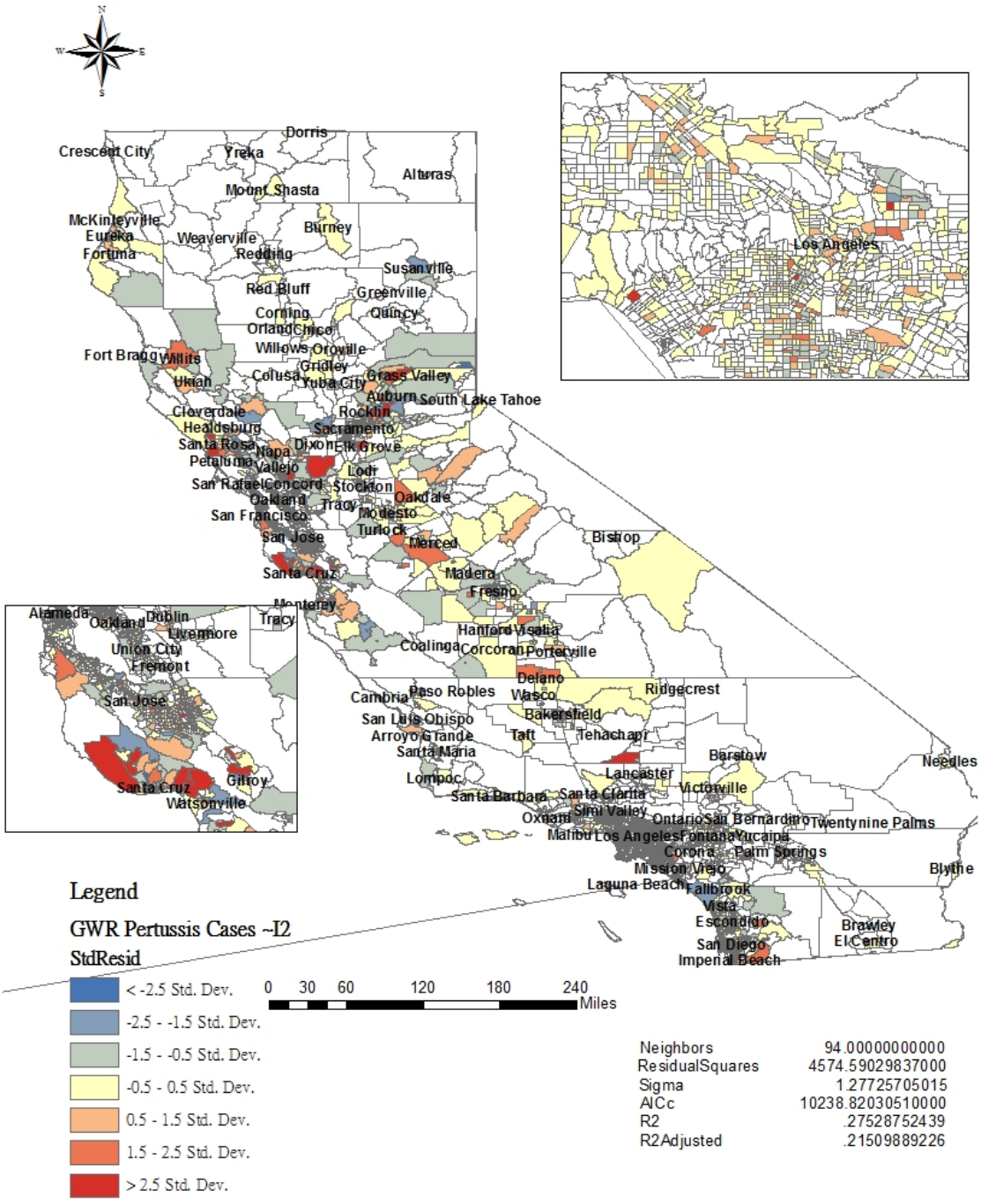

FIGURE 4. Geographically Weighted Regression (Pertussis cases~ permutated cases at year 2)