**Distribution Agreement**

Clustering of pertussis cases around immunization exemption clusters in New Mexico

By

Jessie R. Clippard
Master of Public Health

Epidemiology

Dr. Kevin Sullivan
Faculty Thesis Advisor

Meg Adams-Cameron, MPH, Jessica Jungk, M.S., MPH
Thesis Field Advisors

# Clustering of pertussis cases around immunization exemption clusters in New Mexico

By

Jessie R. Clippard

Bachelor of Science
The Pennsylvania State University
2009

Faculty Thesis Advisor: Dr. Kevin Sullivan

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 Public Health
in Epidemiology
2011

## Abstract

Clustering of pertussis cases around immunization exemption clusters in New Mexico
By Jessie R. Clippard

It is important for states to monitor immunization coverage at a level finer than statewide. Pockets of unimmunized children have been found to be associated with clusters of several communicable diseases (e.g., measles, pertussis). However, the relationship between geographically clustered immunization exemptions to preschool and grade school immunization requirements and geographically clustered pertussis cases within a state with a strict and difficult immunization exemption acquisition process has not been previously examined. We analyzed pertussis case data for children less than 18 years of age as well as immunization exemption data from 2006-2009 in New Mexico using a Geographic Information System (GIS). Being located within an exemptions cluster was associated with higher odds of also being located within a cluster of pertussis. With the awareness of these exemption clusters, public health officials and individual communities can be aware of a greater risk for communicable disease outbreaks in these areas. This study demonstrates support for the need for finer examination and reporting of immunization coverage.

Clustering of pertussis cases around immunization exemption clusters in New Mexico

By

Jessie Clippard

Bachelor of Science
The Pennsylvania State University
2009

Faculty Thesis Advisor: Dr. Kevin Sullivan
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 Public Health
in Epidemiology
2011

## Acknowledgments

Many thanks to Dr. Gonzalo Vazquez-Prokopec, Dr. Uriel Kitron, Michael Page, Jessica Jungk, Meg Adams-Cameron, and Dr. Kevin Sullivan for their invaluable assistance with this thesis.

# Table of Contents

# List of Tables & Figures

# Chapter I: Literature Review

*Pertussis Disease*

Pertussis (commonly known as whooping cough) is a vaccine-preventable disease (VPD) caused by the gram-negative bacteria, *Bordetella pertussis (1)*. The Centers for Disease Control and Prevention (CDC) and the Council of State and Territorial Epidemiologists (CSTE) define a case as a cough illness lasting at least two weeks with one of the following: paroxysms of coughing, inspiratory 'whoop,' or posttussive vomiting, and without other apparent cause (as reported by a health-care professional) (2). Humans are the only known reservoir for pertussis (1). Transmission is person-to-person through droplets expelled during coughing of an infected individual (1). Epidemics in the post-vaccine era tend to be cyclic and occur usually every 2-5 years (3).

Death and/or hospitalization due to complications from pertussis is more common among infants than for adolescents and adults (4). Potential complications resulting from pertussis infection include pneumonia, convulsions, apnea, encephalopathy, and death. More than half of infected infants less than one year of age must be hospitalized due to the disease (5). This represents a significant burden to the United States healthcare system, considering that one-half of cases reported to CDC occur in infants less than one year of age

(6). The reported incidence of pertussis among infants less than one has been increasing within the past decade (7).

Though the majority of cases are reported in infants, pertussis infection is common among adolescents and adults, though highly underreported by physicians (7-10). These missed diagnosis opportunities and resulting underreporting of pertussis might mask a potentially large reservoir for *Bordetella pertussis* (11). Complications from infection for adolescents and adults are typically less severe among those vaccinated; very few of those infected are hospitalized. The most common severe complications among adolescents and adults include pneumonia, weight loss, loss of bladder control, fainting, and rib fractures from violent coughing (5).

Historically, pertussis was a major cause of morbidity and mortality in the United States. The average number of reported cases from 1922-1925 (pre-vaccine development) was 147,271 whereas in 1998, provisional morbidity had reduced to 6,279, representing a 95.7% decrease (12). Infant and child mortality due to pertussis has been estimated to be as high as 10% of those reportedly infected (13). In 2009, CDC reported just under 17,000 pertussis cases nationally (4). New Mexico reported 85 cases in 2009 (4 cases per 100,000 person-years) (14).

In 2010, California saw an increase in pertussis cases and even declared a pertussis epidemic in the state (15). Perhaps part of a larger outbreak of pertussis, New Mexico also experienced an increase in reported pertussis cases in 2010. In 2010, New Mexico had a rate of 6.1 cases per 100,000 person-years (PY), which is the highest rate since 2006 when the rate was 7.3 cases per 100,000 PY (14).

*Pertussis Vaccines*

There are currently two vaccines that can aid in the prevention of pertussis infection. One is a whole-cell vaccine known as DTP (diphtheria-tetanus-pertussis), and another is an acellular vaccine, known as DTaP (diphtheria-tetanus-acellular pertussis)(1). Acellular vaccines began being used in Japan as early as 1981 as a result of concerns surrounding the whole-cell vaccine; the primary difference in the two vaccines is that the acellular does not contain an endotoxin component (16). In the United States, there are currently three DTaP vaccines licensed for use: DAPTACEL (Sanofi Pasteur), Tripedia (Sanofic Pasteur), and INFANRIX (GlaxoSmithKline) (17).

Efficacy studies comparing the two vaccines have found that the two vaccines (DTP vs. DTaP) result in similar levels of protection against pertussis (18). In the case of children, it has been shown that three doses of the DTaP vaccine provide protection from disease for five years. Using decay curves as a means of modeling, “reasonable” coverage is provided for ten years following vaccination (16). Use of the acellular vaccine was found to be more cost effective than whole-cell vaccines (19).

Despite the reduction in pertussis cases due to widespread use of the pertussis vaccine, there is evidence that vaccination does not provide life-long immunity to pertussis (10, 20). Current vaccine schedule, as established by the Advisory Committee of Immunization Practices (ACIP), recommends DTaP immunizations for children at two, four, six months, 15-18 months, and 4-6 years of age (21).

The recent increase in incidence of pertussis has been greatest in the population greater than five years of age (18). Cases of pertussis in vaccinated adults has lead many to suggest regular pertussis vaccine boosters for adults (7, 11, 16, 22, 23). Cost-benefit analyses of pertussis vaccination beyond the ACIP recommendations have been conducted; the results of comparing different booster strategies indicated that vaccinating adolescents would be economically efficient (i.e., reducing healthcare costs more than the cost of vaccination), whereas ten-year boosters for all adults would not be cost effective (19).

*Vaccine Exemptions*

Vaccines have been successful due in large part to school (licensed day care facilities are included in many states) immunization requirements (24-26). However, in most states children are allowed exemptions from immunization. There are three types of vaccine exemptions: medical, religious, and philosophical (27). Laws regarding which types of exemptions are permitted as well as due process for exemption varies from state to state. However, all states permit medical exemptions (28). Medical exemptions allow children with medical contraindications to vaccines to attend school without being vaccinated.

Presently in New Mexico, medical, religious, and philosophical exemptions to immunization are allowed (29). While exemptions are legal, the process to obtain a legal exemption has been categorized as "difficult" in New Mexico compared to the processes in many other states (28). In New Mexico, due process stipulates that exemption paperwork be submitted to the Department of Health Immunization Program as well as to the child's school. The certificate must also be notarized to be valid. Additionally, exemption paperwork must be renewed every nine months (i.e., the exemption paperwork is only valid for one school year) (30).

Examination of the decision-making processes of parents and guardians of children with philosophical exemptions has been thorough (31). A common theme is a risk versus benefits concept. Parents decide whether to vaccinate their children based on a perceived weighting of the risks of vaccine side effects versus the benefits of disease prevention. Over time, there can be a societal shift in this perceived balance of risk and benefits.

One explanation for changes in risk perception utilizes a cyclic model. After a vaccine is introduced and coverage increases, the incidence of disease decreases. At a certain point of coverage and time, disease incidence becomes low enough that parents become unfamiliar with the disease (32). At this point, parents might perceive that the potential side effects of the vaccine outweighing the risk of contracting the disease, and vaccine coverage begins to decrease. When a critical mass population of unvaccinated people is reached, the disease can reemerge. Disease reemergence then reasserts the need for the vaccine, and vaccine coverage increases again. For some conditions, if coverage becomes high enough and is sustained for a long enough period of time, disease eradication can be achieved, and vaccinations can cease (e.g., smallpox) (33).

The "tragedy of the commons" is an important result of mass exemption. (34). Because vaccines offer the promise of herd immunity if a high percentage of the population is vaccinated, some individuals who do not get vaccinated will be protected from disease. This is particularly beneficial for those with medical contraindications to vaccines (32). However, some parents might choose to not vaccinate their child because of concerns of vaccine side effects under the assumption that the child will also be protected from disease due to herd immunity. A problem with this philosophy arises when a large number of parents adopt the philosophy; herd immunity cannot be maintained, and there is the potential for an increased risk of disease. In the case of vaccines, a small amount of risk associated with vaccines (side effects) must be tolerated to avoid larger risks due to disease outbreaks (35).

In the case of new vaccines, safety plays a large role in the decisions of individuals to get vaccinated (36). For example, one major contemporary safety concern is the unsupported link between vaccines and autism. Even though numerous peer-reviewed studies have not been able to find a statistically significant association between the two, some parents are not convinced that vaccines do not cause autism (37-40). Specific concerns surrounding the pertussis vaccines include sudden infant death syndrome (SIDS) and encephalopathy (3, 41). Other common concerns among parents include the belief that children receive more vaccines than their bodies can handle and that too many vaccinations might harm the immune system (26). Many have proposed that physicians continue to work to educate these concerned individuals and present them with the facts about vaccine safety and about the rarity of adverse events (27, 42).

Several systems exist to track illnesses following vaccinations. In the United States, passive surveillance is conducted by the Vaccine Adverse Event Reporting System (VAERS) (43). Drug manufacturers perform active surveillance as part of Phase IV clinical trials (44). Such safeguards have been successful in identifying rare but serious and potentially fatal adverse events related to vaccines. Intussusception in children following vaccination with a tetravalent rotavirus vaccine was recognized due to the systems put in place to monitor vaccine safety (45). The mere existence and the ease with which one can make reports of vaccine adverse events might help comfort some concerned parents, which is why a strong physician-parent relationship is believed to be beneficial to vaccine acceptance (27).

There have been several court cases examining the constitutionality of compulsory policies in response to claims that mandatory immunization requirements for school enrollment violates civil liberties. The first was a result of a smallpox vaccination campaign. In 1905, in *Jacobson v. Massachusetts*, the Supreme Court ruled in favor of states to be able to pass and enforce immunization (3). Then in 1922, the laws requiring children to be immunized for school entry were challenged in the Supreme Court, and ultimately ruled Constitutional (3). While individual liberties were being restricted, the situation was one where "the safety of the general public" was at risk (46). Achieving balance between public health programs and individual rights and freedoms is necessary, though establishing this balance can be difficult and should continue to be reviewed and assessed (32).

Religious and philosophical exemptions tend to be clustered geographically (41, 47). People with similar characteristics and beliefs tend to live near one another. Those most likely to claim vaccine exemptions typically are highly concerned with vaccine safety, often do not believe their child is at risk for disease, believe that the disease is not very severe, and frequently express distrust in the government (31, 47, 48). Parents who choose exemptions typically have a higher education level and live in a house with a higher income compared to nonexemptors (31, 47).

Examining only statewide immunization coverage can potentially hide pockets of unimmunized individuals where disease outbreaks are more likely to originate. However, measuring a statewide rate is important for comparison across the country. Smith, et al. estimated percentage of unvaccinated children in each state using data from 1995-2001. New Mexico had the 23$^{rd}$ highest estimated percentage of unvaccinated children aged 19 to 35 months of age (41).

*Vaccine Exemptions Consequences*

There can be serious consequences as a result of vaccine exemptions, not only for the individual exemptor, but for the entire community (32, 49). People who claim exemptions are likely susceptible to the vaccine-preventable diseases (32, 49-51). Unvaccinated children are estimated to be 23 times more likely to become infected with pertussis (52). Outbreaks frequently begin with an unvaccinated person or unvaccinated cohort from which the disease can spread (41, 53).

Even if an outbreak begins with an unvaccinated population, those who have been vaccinated can also be affected (23, 24, 54). While vaccines have greatly reduced the morbidity and mortality of many infectious diseases, vaccines are not 100% effective. Some who receive a vaccine might only develop a weak immunity to the organism, for example (55). When large numbers of people refuse vaccination, herd immunity is compromised. Those with medical contraindications are put at risk for disease because they are the population most dependent on herd immunity for protection (49). This population is also more likely to have already-weakened immune systems (e.g. due to chemotherapy) and are most likely to experience the most severe disease complications (47).

# Chapter II: Manuscript

## Clustering of pertussis cases around immunization exemption clusters in New Mexico

**Jessie R. Clippard**


### Abstract

It is important for states to monitor immunization coverage at a level finer than statewide. Pockets of unimmunized children have been found to be associated with clusters of several communicable diseases (e.g., measles, pertussis). However, the relationship between geographically clustered immunization exemptions to preschool and grade school immunization requirements and geographically clustered pertussis cases within a state with a strict and difficult immunization exemption acquisition process has not been previously examined. We analyzed pertussis case data for children less than 18 years of age as well as immunization exemption data from 2006-2009 in New Mexico using a Geographic Information System (GIS). Being located within an exemptions cluster was associated with higher odds of also being located within a cluster of pertussis. With the awareness of these exemption clusters, public health officials and individual communities can be aware of a greater risk for communicable disease outbreaks in these areas. This study demonstrates support for the need for finer examination and reporting of immunization coverage.

## Introduction

In 2010, the United States experienced a dramatic increase in reported pertussis cases, particularly among infants less than one year of age (7). California reported the greatest number of pertussis cases in 65 years: 9,477 cases (15, 56). New Mexico also experienced a large increase in pertussis cases in 2010; the state reported 6.1 cases per 100,000 person-years (146 confirmed and probable cases), which is the highest rate in the state since 2006 (14).

Pertussis can be a serious condition, especially for infants. More than half of infected infants less than one year of age are hospitalized (5). Infant and child mortality among those with pertussis has been estimated to be as high as 10% (13). This represents a significant, and largely preventable, burden to the United States healthcare system, considering that one-half of cases reported annually to the Centers for Disease Control and Prevention (CDC) occur in infants (6).

Vaccines are highly effective in preventing communicable disease transmission (56). From 1922-1925, before the development of the first pertussis vaccine, the average number of reported cases annually was 147,271. By 1998, there were only 6,279 cases, representing a 95.7% decrease in reported cases nationally (12). The current recommended vaccination schedule includes diphtheria-tetanus-acellular pertussis (DTaP) immunizations at two, four, six months, 15-18 months, and 4-6 years of age (21). Adult and adolescent family members are important sources of infection for infants, which emphasizes the importance of vaccination to protect those too young to be vaccinated (11, 57). By ensuring high levels of vaccine coverage among school-aged children, infants can be protected from infection by herd immunity.

School immunization requirements are generally credited as being largely responsible for reducing the number of outbreaks of many communicable diseases (e.g. measles, varicella, and pertussis) (27). For medical, religious, philosophical, or personal belief reasons, some parents choose to lawfully exempt their child from vaccination. Nationally, the three legal types of vaccine exemptions—medical, religious, and philosophical—were drafted to compromise between personal liberties and public health (46).

Presently in New Mexico, all three types of exemptions to immunization are allowed. Compared to the processes in many other states, the process to obtain a legal exemption in New Mexico has been categorized as "difficult" because the paperwork must be notarized, renewed every nine months, and submitted to the state health department (28). States with difficult processes have statistically significant lower rates of pertussis vaccine exemption.

Safety concerns play a large role in the decisions of individuals to get vaccinated, especially in the case of newer vaccines (36). Specific health concerns surrounding the pertussis vaccines include sudden infant death syndrome and encephalopathy (3, 41). Despite studies showing lack of support for these claims, concerns linger among many apprehensive parents. Additionally, as a result of high vaccine coverage, cohorts of younger parents tend to be unfamiliar with how debilitating many vaccine-preventable diseases can be; these parents might believe that the potential side effects of vaccination outweigh the risks of contracting the disease (49).

States annually report the levels of immunization coverage to the CDC. However, examining only a statewide immunization coverage proportion can hide pockets of unimmunized individuals where disease outbreaks are more likely to originate. Immunization exemptions tend to be clustered geographically, which is in accordance with Tobler's first law of geography that states that "Everything is related to everything else, but near things are more related than distant things" (41, 47, 58).

By identifying these "high risk" areas with large numbers of exemptors within a state, health officials, as well as the communities themselves, can carefully monitor vaccine-preventable disease activity in these areas. While this analysis examines pertussis vaccination exemptions only, high pockets of pertussis vaccinations might indicate higher levels of objections to other vaccines as well. As such, outbreaks of any vaccine-preventable disease in these areas could serve as the "canary in the coal mine" for other areas in the state or southwestern U.S..

## Methods

*Data and study population description*

Cases of pertussis included all probable and confirmed cases reported in New Mexican residents from 2006-2009 in children eighteen years of age and younger. Data were obtained from the New Mexico Department of Health. Vaccination exemption data included all preschool and school pertussis vaccine exemptions (both number of schools with exemptions as well as number of children with exemptions) from 2006-2009 and were obtained from the New Mexico Department of Health Immunization Registry. Those who were home schooled were not included in this study. Disease onset was defined as the last day of the MMWR week the case was reported as well as the MMWR year.

Probable cases were defined by the Centers for Disease Control and Prevention (CDC) criteria: as cough for a minimum of 14 days, with at least one of the following: paroxysms, whoop, or post-tussive vomiting. A case is considered confirmed if the patient is coughing and is culture-positive or when the clinical case definition has been met and there has been polymerase chain reaction (PCR) confirmation or direct contact with a patient with PCR or culture confirmation(2).

The primary source of spatial data was the New Mexico Geographic Information Systems Clearinghouse that is maintained by the University of New Mexico. Additional data were obtained using 2000 U.S. Census data because 2010 data were not yet available at the time of analysis. U.S. Census tracts were used as the primary geographic unit. Census tracts were used because they represent "small, relatively permanent subdivisions of a county…to provide a stable set of geographic units for the presentation of decennial census data" (59). There were 456 census tracts in New Mexico.

*Cluster identification*

Cases and schools reporting exemptions were geocoded to the street level and aggregated by census tract. Exemption rates were calculated as the number of documented exemptions divided by the total number of school-years of exemption data. Incidence of pertussis among children less than 18 years of age was calculated as the number of reported confirmed and probable cases residing in this census tract of this age group divided by the population of children less than 18 years of age in that census tract.

Kulldorff's scan statistic was used to identify spatial clustering of the pertussis cases and immunization exemptions. All clusters selected for further analysis had a P-value of 0.001. Temporal clustering of pertussis cases was not considered because the rates of infection were relatively stable over the study period. Temporal clustering of exemptions was not considered, despite differences in exemptions over time, as documented in prior studies (24). Census tract centroids were used for point analysis.

*Model selection*

Bivariate and multivariate logistic models were fit to the data to assess the relationship between pertussis clusters and exemptions clusters. The primary outcome was whether a census tract was located within a cluster of cases. The primary exposure was defined as a census tract being located in an exemptions cluster. Covariates considered included percentage of the population less than 5 years of age, proportion of the population that was not White, proportion of the population that identified as Hispanic, proportion of the population with no more than a high school diploma, proportion of the population below the poverty level, population density of the census tract, and proportion of non-U.S. citizens in the population within each tract.

To establish a "gold standard" model, all first-order interaction terms were first assessed for significance. If any terms had been statistically significant, they would have been considered part of the gold standard model along with all covariates for further assessment. Terms were dropped using backward elimination. Confounders were assessed using a 10 percent change in the gold standard estimate rule.

*Analytical tools*

Geocoding and mapping of cases was completed using ArcGIS 9.3.1 (ESRI, Redlands, California). Identification of clusters was done using ClusterSeer 2.3.20

(TerraSeer, Inc.). All statistical analyses were done using SAS 9.2 (SAS Institute, Inc., Cary, North Carolina).

*Ethical Clearance*

This study was approved through an expedited review by the Emory University Institutional Review Board.

**Results**

Of the 1035 schools for which exemption data were reported, 931 unique schools (90%) were able to be geocoded to the street level. Of the 175 cases of pertussis in children less than 18 years of age with some address information reported from 2006-2009, 140 case addresses (80%) were able to be geocoded to the street level. The addresses that were not able to be geocoded included some rural addresses, post office boxes, or otherwise incomplete or unclear address data. Of the geocoded cases, 55 (39%) were female, 103 (74%) were White, and 61 (44%) were Hispanic. Of the geocoded pertussis cases, 83 (60%) were confirmed, and the remaining cases were probable (Table 1).

The annual rates of pertussis in New Mexico for the study period (2006-2009) varied from 3.6 per 100,000 person-years (PY) in 2007 to as high as 7.3 per 100,000 PY in 2006. Rates were highest among infants (less than 1 year) in each year examined during the study period (14). The annual rates of pertussis immunization-exempted children varied from 4.90 per 1,000 in 2006 and 2007 to as high as 5.86 exemptions per 1,000 PY in 2009 (Table 2).

In the bivariate analysis, the likelihood of a census tract being located within an exemptions cluster was associated with the proportion of the population with a high school diploma or less as well as the proportion of the population that was not White (Table 4).

From 2006-2009, there were twelve statistically significant (*P*-value < 0.05) clusters of immunization exemptions in New Mexico (Figure 1). For this same time period, three statistically significant clusters of pertussis were identified (Figure 1). Fifty-five census tracts were located within both a pertussis case tract as well as an immunization exemptions tract (Table 3). In the bivariate analysis of exemptions clusters predicting clusters of pertussis cases, census tracts of pertussis clusters were four times as likely to be located in an exemptions cluster compared to non-pertussis cluster tracts (OR: 12.45, 95% CI: 5.23, 29.64) (Table 5).

A multivariate logistic model was constructed to predict whether a tract would be in a pertussis case cluster. Being located in an exemptions cluster remained a statistically significant predictor of being within a pertussis cluster when controlling for the proportion of the population that were not U.S. citizens, the proportion of the population below the poverty level, the population density of the census tract, the proportion of the population that was not White, and the proportion of the population that reported being Hispanic (OR: 14.67, 95% CI: 5.06, 42.48) (Table 6). There were no statistically significant interaction terms.

## Discussion

Children less than 18 years of age residing in a cluster of pertussis immunization exemptions were about fifteen times more likely to also be in a cluster of pertussis cases. Being in a pertussis disease cluster was associated with the proportion of the population that were not U.S. citizens, the proportion of the population that was note White, the population density of the census tract, the proportion of the population that identified as Hispanic, and the proportion of the population that was at or below the poverty level.

Factors associated with higher odds of being located within a pertussis cluster were higher population density of the census tract, higher proportions of non-Whites and higher proportions of Hispanics within a population, though the latter two were nearly statistically insignificant at the 0.05 level (Table 6). Given New Mexico's proximity to Mexico and one of the largest border-crossing areas in the country (El Paso, Texas), a higher proportion of the population that are not U.S. citizens is understandable. However, the largest city near this border crossing (Las Cruces) was found to be the location of neither clusters of pertussis cases nor clusters of immunization exemptions. The results of this study are in close agreement with previous studies examining similar outcomes and exposures.

*Public Health Implications*

While this study only examined cases of pertussis in children less than 18 years of age, pertussis can and does infect adolescents and adults, though cases in adults and adolescents are thought to be highly underreported and frequently misdiagnosed (9). Clustering of cases among children could indicate higher levels of pertussis-related morbidity among adolescents and adults in the area as well. With the knowledge of whether they practice within a cluster of immunization exemptions among children, physicians could be more aware of the potential for pertussis cases among their adolescent and adult patients.

The ease with which immunization exemptions are obtained in each state has been characterized (28). The process in New Mexico has been described as “hard” because the paperwork must be renewed every nine months, must be notarized, and must be returned to the New Mexico Department of Immunization Registry as opposed to only the school the child attends. In spite of these stricter requirements, exemptions were still clustered (in accordance with Tobler’s first law of geography) and still contributed to clusters of pertussis disease.

By identifying areas prone to clustering of immunization exemptions, public health entities as well as the communities themselves can be aware of increased risk for outbreaks of vaccine-preventable diseases. These areas might also serve as sentinel sites for the entire state; if outbreaks of vaccine-preventable diseases occur, it can be expected that they will occur here first within a state where the susceptible population is highest.

Parents who choose religious or philosophical immunization exemptions not only put their own child at risk for contracting disease, but also increase risk for others within the community (32). This effect of greater risk of contracting pertussis as a result of exemptions is most dangerous for those with contraindications to vaccination and infants, who account for the greatest incidence as well as the greatest likelihood for complications from disease (49).

*Limitations*

There were several limitations of this study that were unavoidable. The main limitation was the inclusion of exemptions that might have been for medical reasons. The nature of the procedure for obtaining a legal immunization exemption in New Mexico does not vary by immunization exemption type; this data is not recorded by the state. By potentially including medical exemptions in this analysis, bias was introduced because medical exemptions are not expected to be clustered. However, including these exemptions would bias the results towards the null because we expect that the medical exemptions will be located randomly.

Another source of bias was that the exemption data only specified which vaccines a child was exempt from after May 2009; before May 2009, the paperwork filed was non-vaccine specific. We expect that including exemptions that were for other vaccines would also bias the clustering towards the null and decrease the likelihood of overlap between pertussis clusters and exemption clusters because non-pertussis exemptions would add noise or "false positives" during the identification of clusters. It is not likely that non-pertussis exemptions would not be associated with increased cases of pertussis.

We assume that children attend a school or preschool within their own census tract or a neighboring census tract. This assumption might not hold true in the more urban areas (e.g., Albuquerque and Santa Fe). This was one challenge of working with data from New Mexico where the size of census tracts varies widely, where there are both rural and urban areas, and where Native American tribal lands are numerous. The New Mexico Department of Health maintains exemptions data for schools on tribal lands, though these exemptions are uncommon.

Additionally, the data available for this analysis only included the MMWR week and MMWR year that each case was reported. Therefore, the precision of the onset of disease was within one week. The date of onset was arbitrarily set as the last day of the MMWR week for consistency, though this date is not clinically significant. Though pertussis is a nationally notifiable condition, it is to be expected that some cases of pertussis were misdiagnosed or otherwise not reported to the state health department; due to the relative lack of cases and unfamiliarity with the disease, even cases of pediatric pertussis are sometimes unrecognized by physicians (8, 60).

# TABLES

**Table 1.** Characteristics of all cases and successfully geocoded reported pertussis cases in children less than 18 years of age in New Mexico, 2006-2009.

| **Characteristic** | **All Cases N (%)** 231 (100) | **Geocoded Cases N (%)** 140 (100) |
|---|---|---|
| **Case gender** | | |
| Female | 106 (46) | 55 (39) |
| **Race** | | |
| White | 163 (71) | 103 (74) |
| Black | 1 (0.4) | 1 (1) |
| Other | 20 (8) | 5 (4) |
| Missing | 47 (20) | 31 (22) |
| **Ethnicity** | | |
| Hispanic | 85 (37) | 61 (44) |
| Missing | 49 (21) | 26 (19) |
| **Year** | | |
| 2006 | 76 (33) | 49 (35) |
| 2007 | 40 (17) | 21 (15) |
| 2008 | 66 (29) | 43 (31) |
| 2009 | 49 (21) | 26 (19) |
| **Age (Years)** | | |
| 0 | 67 (29) | 43 (31) |
| 1-5 | 65 (28) | 36 (26) |
| 6-10 | 47 (20) | 28 (20) |
| 11-15 | 32 (14) | 18 (13) |
| 16-18 | 19 (8) | 14 (10) |
| **Case Status** | | |
| Confirmed | 141 (61) | 81 (58) |

**Table 2.** Children with pertussis exemptions on file with the New Mexico Department of Health Immunization Registry from 2006-2009.

| Year | Children with Exemptions (N) | Schools Reporting Exemptions (N)[1] | State-wide Exemption Rate (per 1,000 PY) |
|---|---|---|---|
| 2006 | 2485 | 606 | 4.90 |
| 2007 | 2487 | 627 | 4.90 |
| 2008 | 2764 | 632 | 5.45 |
| 2009 | 2972 | 720 | 5.86 |

[1]There were 1035 unique schools statewide over the entire study period from which 931 were able to be geocoded to the street level.

**Table 3.** Summary and description of New Mexico immunization clusters and pertussis case clusters, 2006-2009.

| | **Tracts not in exemptions cluster** | **Tracts in exemptions cluster** |
|---|---|---|
| **Tracts not in case cluster** | 216 | 6 |
| **Tracts in case cluster** | 159 | 55 |

**Table 4**. Bivariate analysis of location within an immunization exemptions cluster with various predictors.

| **Parameter**[1] | **Odds Ratio** | **95% Confidence Interval** | **P-value** |
|---|---|---|---|
| Educ_leHS | 0.94* | 0.92, 0.96 | < 0.0001 |
| Nativeborn | 1.00 | 0.96, 1.03 | 0.84 |
| Perbelowpov | 0.98 | 0.95, 1.00 | 0.09 |
| Lnpopdens | 1.51* | 1.27, 1.78 | <0.0001 |
| Race2 | 0.97* | 0.95, 0.99 | 0.005 |
| Per_hisp | 1.00 | 0.99, 1.01 | 0.67 |
| Lncit | 1.19 | 0.92, 1.53 | 0.18 |

[1]Parameter descriptions:

1. educ_leHS: prop. of population with high school education or less
2. nativeborn: prop. of population born in the U.S.
3. perbelowpov: prop. of population below the poverty level
4. lnpopdens: log transformed population density of census tract
5. race2: prop. of population that is not White (i.e., racial minority)
6. per_hisp: prop. of population that identifies as Hispanic
7. lncit: log transformed prop. of population that is not a U.S. citizen

*Indicates significance when $\alpha = 0.05$

**Table 5.** Bivariate and multivariate logistic regression results where main outcome is location within a pertussis case cluster and the main exposure is location within an immunization exemption cluster.

| | Odds Ratio (OR) | 95% Confidence Interval (CI) |
|---|---|---|
| Tracts within exemptions cluster (bivariate) | 12.45 | 5.23, 29.64 |
| Tract within exemptions cluster (multivariate) | 14.67 | 5.06, 42.48 |

**Table 6.** Odds ratio estimates for multivariate regression where the outcome is location within a pertussis cluster and the main exposure is location within an immunization exemptions cluster.

| Effect | Odds Ratio | 95% Wald Confidence Limits | |
|---|---|---|---|
| Exemption | 14.67 | 5.06 | 42.48 |
| Nativeborn | 0.97 | 0.93 | 1.01 |
| Perbelowpov | 0.83 | 0.80 | 0.87 |
| Lnpopdens | 1.59 | 1.40 | 1.81 |
| Race2 | 1.05 | 1.02 | 1.07 |
| Per_hisp | 1.02 | 1.01 | 1.04 |

# FIGURES

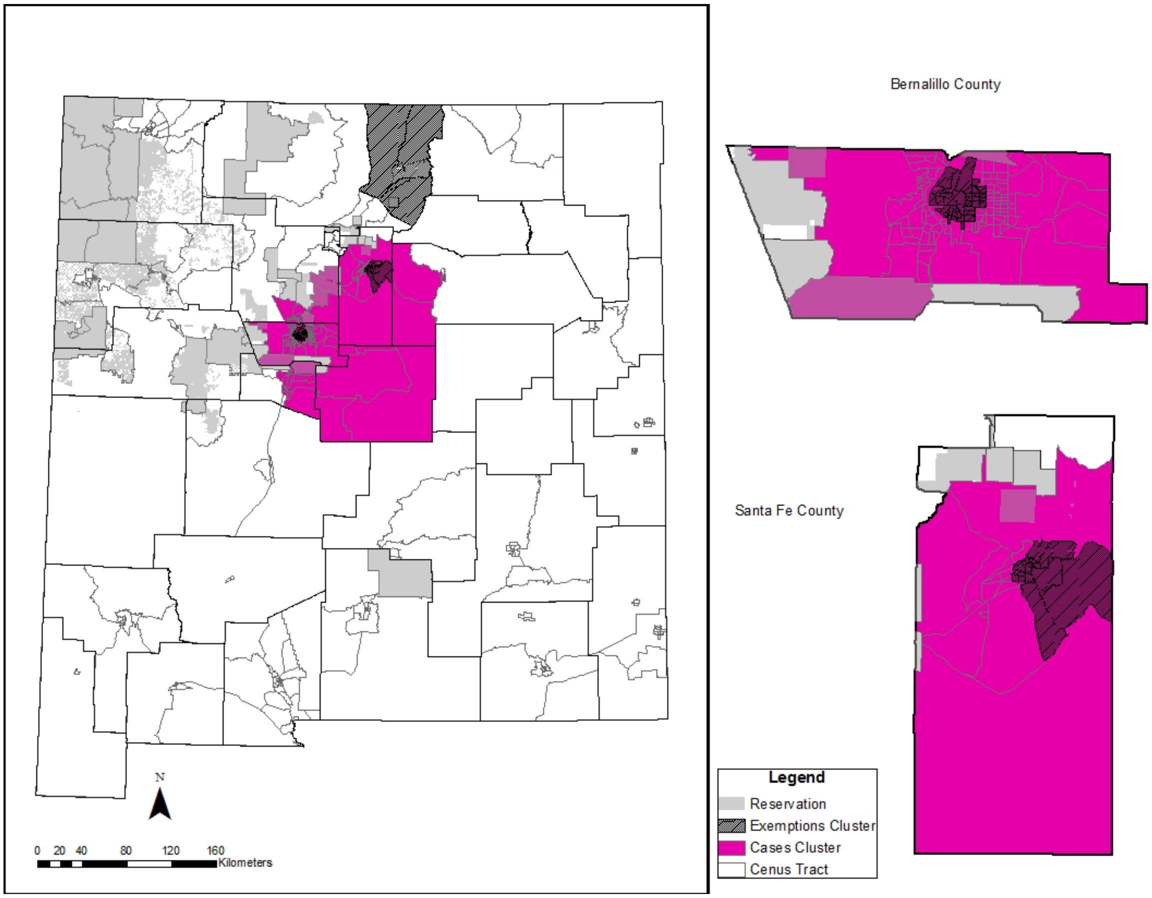



**Figure 1.** Locations of reported pertussis case and exemption clusters by census tract (2006-2009) in New Mexico. Insets include data from Bernalillo and Santa Fe counties.

**References**


1. *Control of Communicable Diseases Manual*. 19th ed. Washington, DC: American Public Health Association; 2008.

2. Centers for Disease Control. CDC and Council of State and Territorial Epidemiologists (CSTE) Pertussis Case Defintion. *Morbidity and Mortality Weekly Report* 2006(55(RR17)).

3. Plotkin S, Orenstein W, Offit P. *Vaccines*. 5th ed.: Saunders Elsevier; 2008.

4. Centers for Disease Control. Pertussis (Whooping Cough). 2010. (http://www.cdc.gov/pertussis/). (Accessed January 9 2011).

5. Centers for Disease Control. Pertussis Complications. 2010. (http://www.cdc.gov/pertussis/about/complications.html). (Accessed January 9 2011).

6. Mink CM, Cherry JD, Christenson P, et al. A search for Bordetella pertussis infection in university students. *Clin Infect Dis* 1992;14(2):464-71.

7. Cortese MM, Baughman AL, Brown K, et al. A "new age" in pertussis prevention new opportunities through adult vaccination. *Am J Prev Med* 2007;32(3):177-85.

8. Deeks S, De Serres G, Boulianne N, et al. Failure of physicians to consider the diagnosis of pertussis in children. *Clin Infect Dis* 1999;28(4):840-6.

9. Cromer BA, Goydos J, Hackell J, et al. Unrecognized pertussis infection in adolescents. *Am J Dis Child* 1993;147(5):575-7.

10. Cherry JD. The epidemiology of pertussis: a comparison of the epidemiology of the disease pertussis with the epidemiology of Bordetella pertussis infection. *Pediatrics* 2005;115:1422-7.

11. Nelson JD. The changing epidemiology of pertussis in young infants. The role of adults as reservoirs of infection. *Am J Dis Child* 1978;132(4):371-3.

12. Centers for Disease Control and Prevention. Ten Great Public Health Achievements --United States, 1900-1999. *Morbidity and Mortality Weekly Report* 1999;48(12):241-8.

13. Jamison DT, Breman JG, Measham AR, et al. *Disease Control Priorities in Developing Countries*. 2nd ed.: World Bank Publications; 2006.

14. Infectious Disease Epidemiology Bureau. New Mexico Electronic Disease Surveillance System (NM-EDSS). New Mexico Department of Health.

15. Landau E. Vaccination role unclear in whooping cough outbreak. 2010. (http://articles.cnn.com/2010-06-28/health/california.whooping.cough_1_whooping-cough-pertussis-vaccines-and-autism/2?_s=PM:HEALTH). (Accessed December 19 2010).

16. Cherry JD. How can we eradicate pertussis. *Adv Exp Med Biol* 2009;634:41-51.

17. Centers for Disease Control. Diphtheria, Tetanus, and Acellular Pertussis (DTaP) Vaccine. 2010. (http://www.cdc.gov/vaccinesafety/Vaccines/dtap/dtapindex.html). (Accessed December 22 2010).

18. Casey JR, Pichichero ME. Acellular pertussis vaccine safety and efficacy in children, adolescents and adults. *Drugs* 2005;65(10):1367-89.

19. Caro JJ, Getsios D, Payne K, et al. Economic burden of pertussis and the impact of immunization. *Pediatr Infect Dis J* 2005;24(5 Suppl):S48-54.

20. Christie CD, Marx ML, Marchant CD, et al. The 1993 epidemic of pertussis in Cincinnati. Resurgence of disease in a highly immunized population of children. *N Engl J Med* 1994;331(1):16-21.

21. Centers for Disease Control. Pertussis: Summary of Vaccine Recommendations. 2010. (http://www.cdc.gov/vaccines/vpd-vac/pertussis/recs-summary.htm). (Accessed January 9 2011).

22. Forsyth KD, Campins-Marti M, Caro J, et al. New pertussis vaccination strategies beyond infancy: recommendations by the global pertussis initiative. *Clin Infect Dis* 2004;39(12):1802-9.

23. Halperin SA, Bortolussi R, MacLean D, et al. Persistence of pertussis in an immunized population: results of the Nova Scotia Enhanced Pertussis Surveillance Program. *J Pediatr* 1989;115(5 Pt 1):686-93.

24. Omer SB, Enger KS, Moulton LH, et al. Geographic clustering of nonmedical exemptions to school immunization requirements and associations with geographic clustering of pertussis. *Am J Epidemiol* 2008;168(12):1389-96.

25. Robbins KB, Brandling-Bennett D, Hinman AR. Low measles incidence: association with enforcement of school immunization laws. *Am J Public Health* 1981;71(3):270-4.

26. Colgrove J, Bayer R. Could it happen here? Vaccine risk controversies and the specter of derailment. *Health Affairs* 2005;24(3):729-39.

27. Diekema DS. Responding to parental refusals of immunization of children. *Pediatrics* 2005;115(5):1428-31.

28. Omer SB, Pan WK, Halsey NA, et al. Nonmedical exemptions to school immunization requirements: secular trends and association of state policies with pertussis incidence. *JAMA* 2006;296(14):1757-63.

29. Centers for Disease Control. Childcare and school immunization requirements. In: Singleton JA, ed, 2006.

30. New Mexico Department of Health. Certificate of exemption from school/daycare immunization requirements. 2009,

31. Salmon DA, Moulton LH, Omer SB, et al. Factors associated with refusal of childhood vaccines among parents of school-aged children: a case-control study. *Arch Pediatr Adolesc Med* 2005;159(5):470-6.

32. Salmon DA, Haber M, Gangarosa EJ, et al. Health consequences of religious and philosophical exemptions from immunization laws: individual and societal risk of measles. *JAMA* 1999;282(1):47-53.

33. Chen RT. Vaccine risks: real, perceived and unknown. *Vaccine* 1999;17 Suppl 3:S41-6.

34. Hardin G. The Tragedy of the Commons. *Science* 1968;162(5364):1243-8.

35. Epstein RA. It did happen here: fear and loathing on the vaccine trail. *Health Aff (Millwood)* 2005;24(3):740-3.

36. Hopfer S, Clippard JR. College Women's HPV Vaccine Decision Narratives. *Qualitative Health Research* 2011;21(2):262-77.

37. DeStefano F. Vaccines and autism: evidence does not support a causal association. *Clin Pharmacol Ther* 2007;82(6):756-9.

38. Schechter R, Grether JK. Continuing increases in autism reported to California's developmental services system: mercury in retrograde. *Arch Gen Psychiatry* 2008;65(1):19-24.

39. Uchiyama T, Kurosawa M, Inaba Y. MMR-vaccine and regression in autism spectrum disorders: negative results presented from Japan. *J Autism Dev Disord* 2007;37(2):210-7.

40. Freed GL, Clark SJ, Butchart AT, et al. Parental Vaccine Safety Concerns in 2009. *Pediatrics* 2010;125(4):654-9.

41. Smith PJ, Chu SY, Barker LE. Children who have received no vaccines: who are they and where do they live? *Pediatrics* 2004;114(1):187-95.

42. Freed GL, Katz SL, Clark SJ. Safety of vaccinations. Miss America, the media, and public health. *JAMA* 1996;276(23):1869-72.

43. Varricchio F, Iskander J, Destefano F, et al. Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. *Pediatr Infect Dis J* 2004;23(4):287-94.

44. Orenstein WA, Douglas RG, Rodewald LE, et al. Immunizations in the United States: success, structure, and stress. *Health Aff (Millwood)* 2005;24(3):599-610.

45. Murphy TV, Gargiullo PM, Massoudi MS, et al. Intussusception among infants given an oral rotavirus vaccine. *New England Journal of Medicine* 2001;344(8):564-72.

46. Mariner WK, Annas GJ, Glantz LH. *Jacobson v Massachusetts*: It's not your great-great grandfather's public health law. *American Journal of Public Health* 2005;95(4):581-90.

47. Omer SB, Salmon DA, Orenstein WA, et al. Vaccine refusal, mandatory immunization, and the risks of vaccine-preventable diseases. *N Engl J Med* 2009;360(19):1981-8.

48. Meszaros JR, Asch DA, Baron J, et al. Cognitive processes and the decisions of some parents to forego pertussis vaccination for their children. *J Clin Epidemiol* 1996;49(6):697-703.

49. Feikin DR, Lezotte DC, Hamman RF, et al. Individual and community risks of measles and pertussis associated with personal exemptions to immunization. *JAMA* 2000;284(24):3145-50.

50. Novotny T, Jennings CE, Doran M, et al. Measles outbreaks in religious groups exempt from immunization laws. *Public Health Rep* 1988;103(1):49-54.

51. Salmon DA, Sotir MJ, Pan WK, et al. Parental vaccine refusal in Wisconsin: a case-control study. *WMJ* 2009;108(1):17-23.

52. Wallace A. An epidemic of fear: how panicked parents skipping shots endangers us all. *Wired*, 2009.

53. Etkind P, Lett SM, Macdonald PD, et al. Pertussis outbreaks in groups claiming religious exemptions to vaccinations. *Am J Dis Child* 1992;146(2):173-6.

54. Long SS, Lischner HW, Deforest A, et al. Serologic evidence of subclinical pertussis in immunized children. *Pediatr Infect Dis J* 1990;9(10):700-5.

55. Luman ET, Shaw KM, Stokley SK. Compliance with vaccination recommendations for U.S. children. *Am J Prev Med* 2008;34(6):463-70.

56. Centers for Disease Control. Pertussis: Outbreaks. 2010. (http://www.cdc.gov/pertussis/outbreaks.html). (Accessed February 9 2011).

57. Long SS, Welkon CJ, Clark JL. Widespread silent transmission of pertussis in families: antibody correlates of infection and symptomatology. *J Infect Dis* 1990;161(3):480-6.

58. Tobler WR. A computer movie simulating urban growth in the Detroit region. *Economic Geography* 1970;46:234-40.

59. U.S. Census Bureau. Cartographic Boundary Files. 2001. (http://www.census.gov/geo/www/cob/tr_metadata.html). (Accessed March 19, 2011 2011).

60. Centers for Disease Control. Nationally Notifiable Conditions. 2011. (http://www.cdc.gov/osels/ph_surveillance/nndss/phs/infdis.htm#top). (Accessed April 9 2011).

# APPENDIX A: MODEL SELECTION DETAILS

| **Model** | **Odds Ratio** | **95% Confidence Interval** |
|---|---|---|
| GOLD STANDARD[1] | | |
| Exemption, nativeborn, educ_leHS, perbelowpov, lnpopdens, race2, per_hisp lncit | 15.89 | 5.11, 49.47 |
| MODEL 1 (drop education level) | | |
| Exemption, nativeborn, perbelowpov, lnpopdens, race2, per_hisp, lncit | 15.41 | 5.23, 45.42 |
| MODEL 2 (drop lncit) | | |
| Exemption, nativeborn, perbelowpov, lnpopdens, race2, per_hisp | 14.67 | 5.06, 42.48 |
| MODEL 3 (drop nativeborn) | | |
| Exemption, perbelowpov, lnpopdens, race2, per_hisp | 13.61[2] | 4.81, 38.51 |
| FINAL MODEL | | |
| Exemption, nativeborn, perbelowpov, lnpopdens, race2, per_hisp | 14.67 | 5.06, 42.48 |

[1]Description of variables:

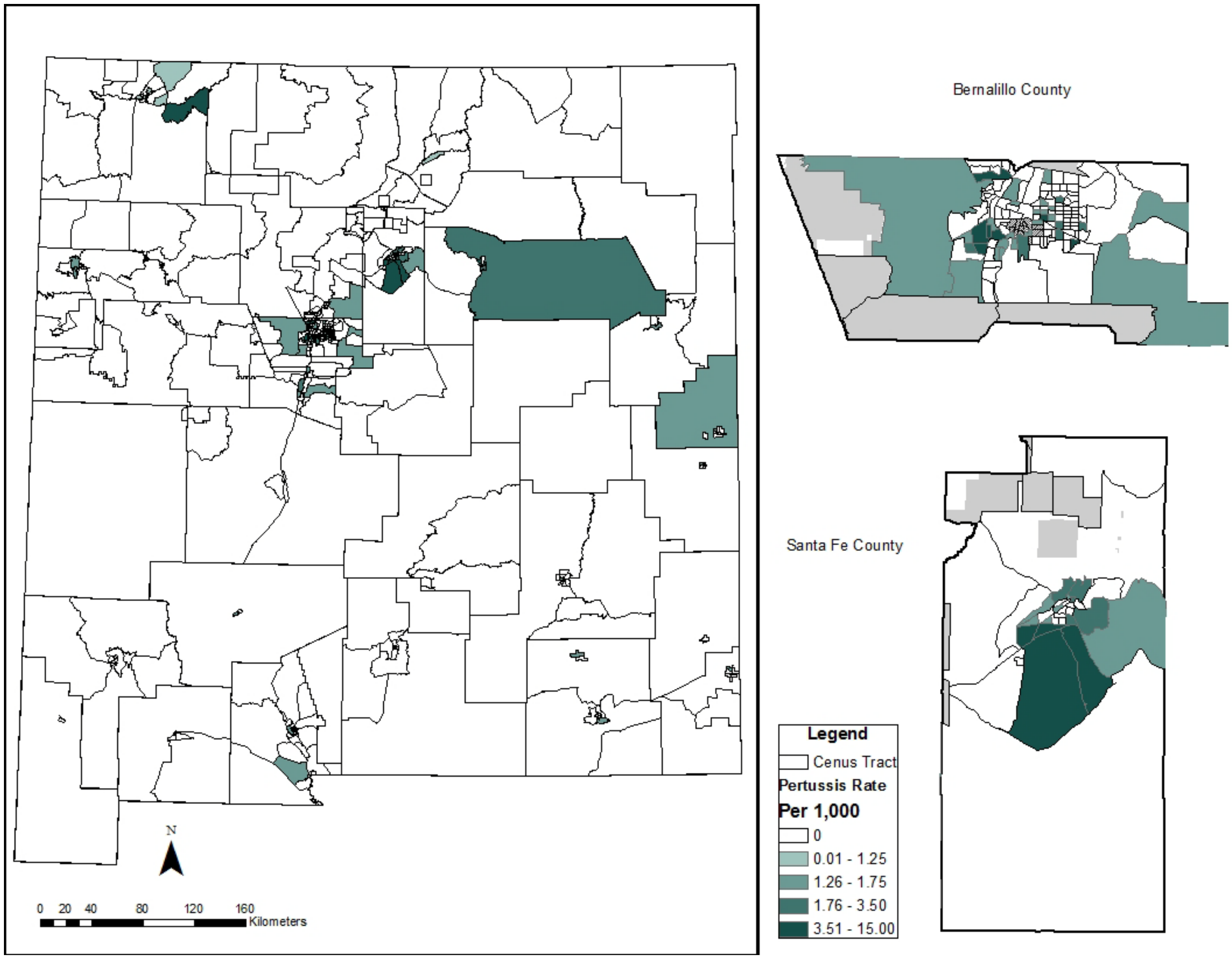
1. educ_leHS: prop. of population with high school education or less
2. nativeborn: prop. of population born in the U.S.
3. perbelowpov: prop. of population below the poverty level
4. lnpopdens: log transformed population density of census tract
5. race2: prop. of population that is not White (i.e., racial minority)
6. per_hisp: prop. of population that identifies as Hispanic
7. lncit: log transformed prop. of population that is not a U.S. citizen

[2]Greater than 10% change from the gold standard model

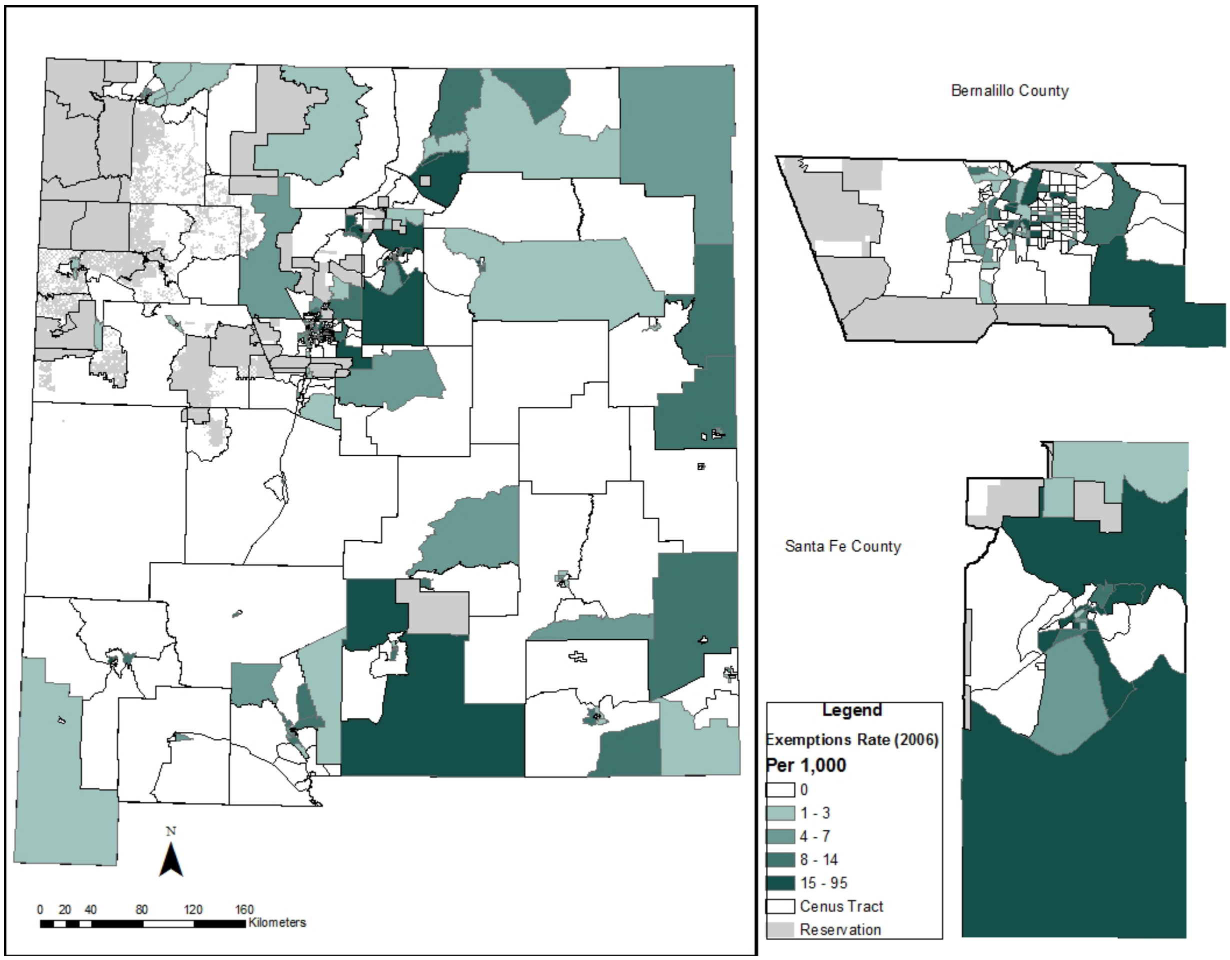
## APPENDIX B: REGRESSSION COEFFICIENT ESTIMATES

| **Parameter** | **DF** | **Coefficient Estimate** | **Standard Error** | **Wald $\chi^2$** | **Pr > $\chi^2$** |
|---|---|---|---|---|---|
| Intercept | 1 | 7.80 | 2.28 | 11.66 | 0.0006 |
| Exemption | 1 | 2.68 | 0.54 | 24.46 | < 0.0001 |
| Nativeborn | 1 | -0.03 | 0.02 | 2.01 | 0.1565 |
| Perbelopov | 1 | -0.18 | 0.02 | 64.20 | < 0.0001 |
| Lnpopdens | 1 | 0.47 | 0.06 | 52.37 | < 0.0001 |
| Race2 | 1 | 0.04 | 0.01 | 16.70 | < 0.0001 |
| Per_hisp | 1 | 0.02 | 0.01 | 8.76 | 0.0031 |

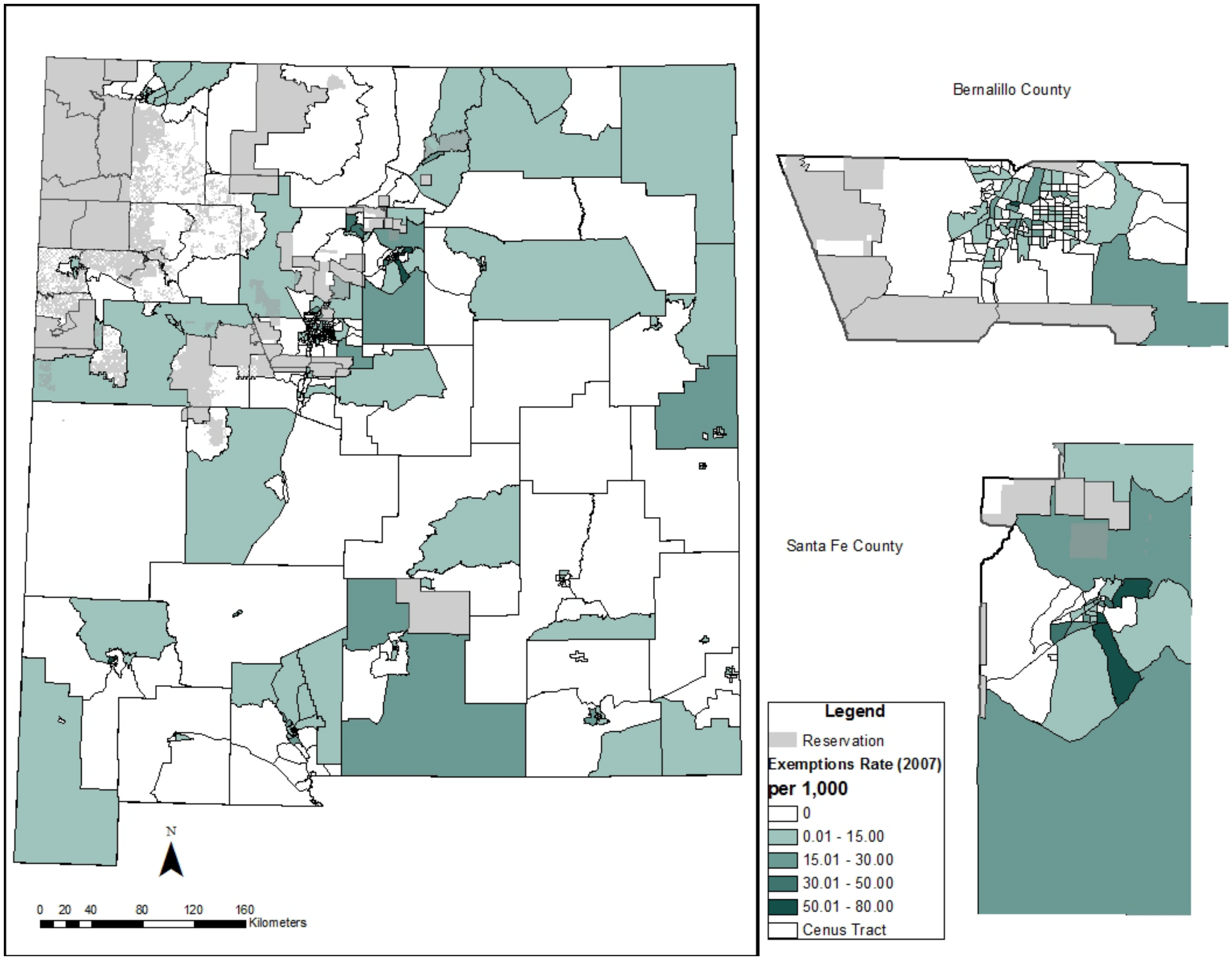
# APPENDIX C: CASE RATES BY CENSUS TRACT (2006-2009)



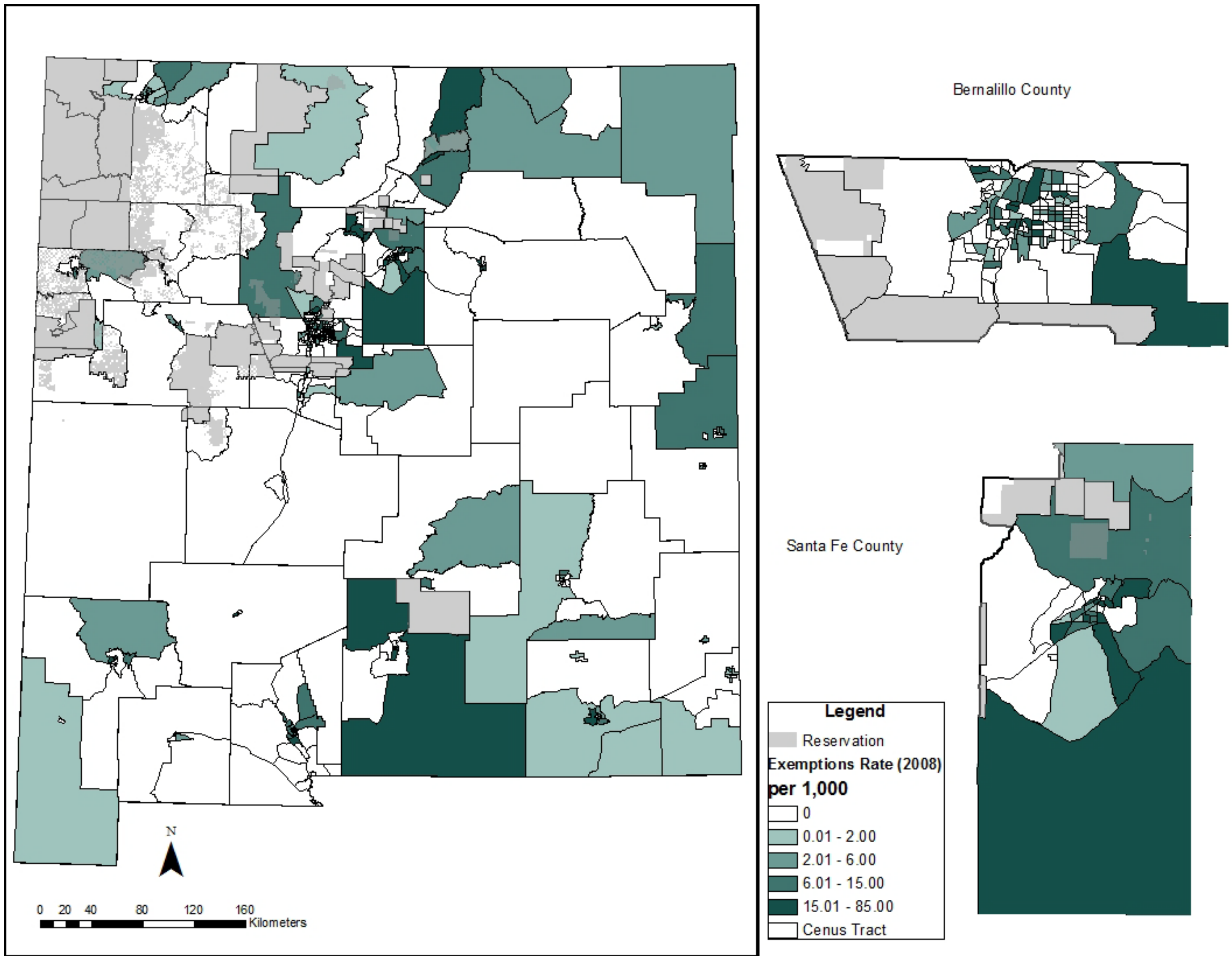
## APPENDIX D: EXEMPTION RATES BY CENSUS TRACT—2006



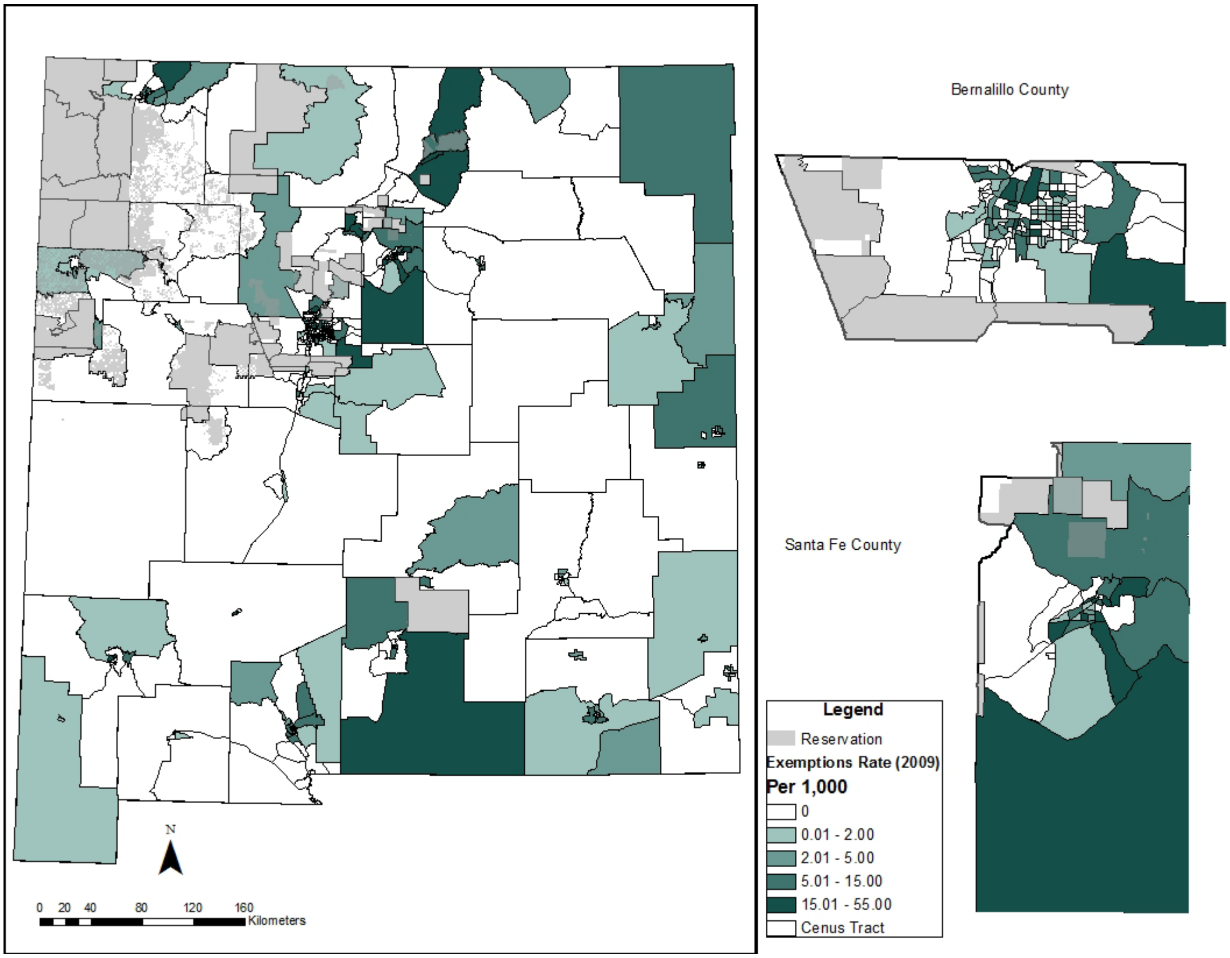
## APPENDIX E: EXEMPTION RATES PER CENSUS TRACT—2007



## APPENDIX F: EXEMPTION RATES BY CENSUS TRACT—2008



# APPENDIX G: EXEMPTION RATE PER CENSUS TRACT—2009



# APPENDIX H: NEW MEXICO EXEMPTION FORM

NEW MEXICO DEPARTMENT OF HEALTH

## CERTIFICATE OF EXEMPTION FROM SCHOOL/DAYCARE IMMUNIZATION REQUIREMENTS

**Please Print Clearly, Complete all Fields, Use CAPITAL LETTERS ONLY**

**Child's Information**

First Name

Last Name

Street address or P.O. Box

City

State | Zip Code

Phone – 

Child's Grade

School Name

School Address

School City

School State | School Zip Code

Child's Date of Birth m m d d y y y y

**Please check appropriate boxes**

**Sex**: ◯ Male ◯ Female

**Ethnicity**: ◯ Hispanic ◯ Non-Hispanic

**Race**: ◯ Native American ◯ Black ◯ Other ◯ Asian ◯ White

*Mail or bring original to*:
**NM Immunization Program**
**1190 St. Francis/ Runnels S-1250**
**PO Box 26110**
**Santa Fe, NM 87502-6110**

**I object to my child receiving the following vaccines:**

◯ Tetanus
◯ Diphtheria
◯ Pertussis
◯ Hib - Haemophilus Influenza type B
◯ Measles
◯ Mumps
◯ Rubella
◯ Hepatitis A
◯ Hepatitis B
◯ Varicella (Chicken Pox)
◯ Polio

Directions:
Please complete this form. Then in the presence of a Notary Public, please sign and date the certificate and have it notarized. IT IS THE PARENT/GUARDIAN'S RESPONSIBILITY TO ENSURE AN APPROVED COPY OF THIS EXEMPTION CERTIFICATE IS FILED WITH THE CHILD'S SCHOOL.

In accordance with 7.5.3.8B NMAC, I hereby certify that my religious beliefs, held either individually or jointly by others, do not permit the administration of vaccine or other immunizing agents and I therefore request that my child as named above be exempted from the school immunization requirements of NMSA 1978 Section 24-5-2.

I UNDERSTAND THIS REQUEST IS SUBJECT TO THE APPROVAL OF THE NEW MEXICO DEPARTMENT OF HEALTH. I HAVE READ THE 'COMPULSORY IMMUNIZATION REGULATIONS' AND UNDERSTAND THE RISK OF NON-IMMUNIZATION FOR MY CHILD. I UNDERSTAND THAT THIS CERTIFICATE, IF APPROVED, IS VALID FOR A PERIOD NOT TO EXCEED NINE MONTHS AND WILL EXPIRE THEREAFTER. IF I WISH TO REQUEST ANOTHER EXEMPTION AFTER THE NINE MONTH PERIOD, I MUST COMPLETE ANOTHER CERTIFICATE OF EXEMPTION AND SEEK APPROVAL.

I ALSO UNDERSTAND THAT WHERE ANY CASE OF COMMUNICABLE DISEASE OCCURS OR IS LIKELY TO OCCUR IN MY CHILD'S SCHOOL, THE DEPARTMENT OF HEALTH MAY REQUIRE THE EXCLUSION OF INFECTED PERSONS AND NON-IMMUNIZED PERSONS (7.4.3.9 NMAC - Rp, 7 NMAC 4.3.9, 8/15/2003).

I swear that all the foregoing statements are true to the best of my information, knowledge and belief.

Parent/guardian's name (print clearly) ______________________________

Parent/guardian's signature: ____________________ Date: ____________

Subscribed and sworn before me this ________ day of __________, 20____.

GREAT SEAL OF THE STATE OF NEW MEXICO ·1912·

____________________ My Commission expires: ______________
Notary's Signature and Seal

DOH Use Only: ☐ APPROVED ☐ DISAPPROVED

Date approved m m d d y y y y

Revised May 2009

______________________________
*Authorized Signature*

# APPENDIX I: IRB APPROVAL

EMORY UNIVERSITY

Institutional Review Board

TO: Jessie Clippard
Principal Investigator

CC: Sullivan Kevin Epidemiology

DATE: December 17, 2010

RE: **Notification of Expedited Approval**
IRB00047604
Clustering of pertussis cases around nonmedical immunization exemption pockets in New Mexico

This is your notification that your above referenced study was reviewed and APPROVED under the Expedited review process per 45 CFR 46.110 and 21 CFR 56.110. The approval is valid from 12/17/2010 until 12/16/2011. Thereafter, continued approval is contingent upon the submission of a continuing review request that must be reviewed and approved by the IRB prior to the expiration date of this study. A complete waiver of HIPAA authorization and waiver of informed consent are included with this approval.

Any reportable events (serious adverse events, breaches of confidentiality, protocol deviation or protocol violations) or issues resulting from this study should be reported immediately to the IRB and to the sponsoring agency (if any). Any amendments (changes to any portion of this research study including but not limited to protocol or informed consent changes) must have IRB approval before being implemented.

All correspondence and inquiries concerning this research study must include the IRB ID, the name of the Principal Investigator and the Study Title.

Sincerely,

Sarah K. Clark, CIP
Senior Research Protocol Analyst
*This letter has been digitally signed*