An examination of the roles of serologic, geographic, and demographic factors on the recurrence of pertussis in Minnesota

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Dedication

This dissertation is dedicated to my mother, Jeanne Cregan Sanstead.

Abstract

Pertussis (whooping cough) is a vaccine-preventable respiratory infection that can occur in all ages and can result in life threatening complications, particularly among infants. Although outbreaks have historically occurred cyclically every 2 to 5 years, recent outbreaks in the United States have been the largest on record since the 1950's despite high vaccination coverage. The effective control of pertussis is complicated by the inability to directly obtain true estimates of incidence and population immunity from surveillance data. Pertussis infections in adults and previously vaccinated children often have a mild presentation, which can result in undetected infections. Additionally, vaccine coverage is not a direct measure of immune status due to imperfect vaccine effectiveness, waning immunity, and natural boosting. Additional data sources and analyses are needed to better understand and ultimately disrupt the epidemic cycle of pertussis. This research (1) tests the feasibility of conducting a pertussis seroprevalence study in the University of Minnesota's Driven to Discover building at the Minnesota State Fair (2) identifies spatial and spatio-temporal clusters of pertussis vaccine exemptions and incidence in Minnesota, and (3) develops a model of pertussis transmission in Minnesota to explore the impact of model parameters on disease dynamics. The ability to predict the occurrence of an outbreak based on serologic, geographic, and/or demographic characteristics of a population may identify opportunities to implement supplementary prevention strategies.

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A. GENERAL BACKGROUND

A1. Clinical Presentation and Transmissibility of Pertussis

Pertussis (whooping cough) is a disruptive respiratory infection caused by the bacterium *Bordetella pertussis*. *Bordetella pertussis* adheres to epithelial cells that line the respiratory tract and releases damaging toxins that interfere with pulmonary secretion.[1] Pertussis illness is characterized by paroxysmal coughing (violent coughing spells) that may be followed by vomiting and a high-pitched "whooping" noise upon inhalation. The initial presentation of pertussis is similar to a common cold, consisting of a mild cough and runny nose. This catarrhal stage typically lasts 1 to 2 weeks and is followed by a paroxysmal stage, during which time the characteristic symptoms of pertussis manifest (Figure 1). The paroxysmal stage generally lasts 1 to 6 weeks and is the most identifiable stage of pertussis illness.[2] The subsequent convalescent stage may persist for months as the cough gradually diminishes in severity during the recovery process. Notably, adults often experience atypical cases of pertussis in which the pertussis specific symptoms of the paroxysmal stage are absent.[3,4] Life-threatening complications including pneumonia and encephalopathy can result from pertussis.

Transmission of *Bordetella pertussis* occurs through direct contact with respiratory secretions from infected individuals (droplet transmission), which is facilitated by coughing and sneezing. Transmission is possible between individuals of any age. Although contact with contaminated surfaces is not an effective mode of transmission, pertussis remains highly contagious with a secondary attack rate of 80%.[1,5] The incubation period of pertussis is typically 7 to 10 days, ranging from 4 to 21 days.[1] Individuals infected with *Bordetella pertussis* are considered infectious for 21 days following cough onset. Macrolide antibiotics reduce the infectious period to 5 days if an appropriate dosage is completed; however, antibiotics may fail to decrease the severity of disease if administered after pertussis toxins have damaged respiratory epithelial cells.[6]

A2. Epidemiology of Pertussis in the United States

A2.1 Historical Incidence Trends

Prior to the vaccine era, pertussis was a common childhood disease that resulted in over 100,000 reported cases and an average of 7,300 deaths each year in the United States.[7] The majority of cases occurred in children under the age of 5 years, with infants under the age of 1 year at greatest risk of developing life-threatening complications from infection.[7] Outbreaks recurred approximately every 2 to 5 years, with peaks exceeding 200,000 reported cases (Figure 2).[8] The introduction of a childhood pertussis vaccine in the 1940's drastically reduced pertussis incidence. Incidence reached a record low in 1976 with just over 1,000 cases reported nationwide.[8] However, a noticeable increase in reported cases began during the 1990's, a decade in which a modified pertussis vaccine and new diagnostic assay were introduced.

A2.2 Pertussis Vaccines

The first pertussis vaccine licensed for use in the United States was the diphtheria and tetanus toxoids and whole-cell pertussis vaccine, abbreviated DTP. Although DTP was effective in reducing pertussis incidence, the adverse effects of the vaccine included febrile seizures and painful local reactions.[9] The transition to a safer acellular vaccine, DTaP, was initiated in the 1990's with no changes to the timing of vaccine administration.[10] The recommended vaccination schedule remained one dose of pertussis vaccine at 2, 4, 6, 15-18 months, and 4-6 years.[11] The fourth and fifth doses of DTP were replaced with DTaP in 1992, and DTaP replaced all five doses of DTP in 1997.[12]

In 2005, Tdap was licensed for use in individuals aged 10 years and older as a single dose booster. Tdap is currently recommended at age 11 or 12 years for children who have completed the DTaP vaccination series.[13] Adults who have not previously been vaccinated with Tdap are also recommended to receive the vaccine, as are pregnant women in their third trimester of pregnancy. Notably, both Tdap and DTaP have been reported to provide a shorter duration of protection as compared to DTP. Numerous studies have shown that protection against pertussis wanes each year following the fifth dose of DTaP.[14,15,16] Protection provided by Tdap is estimated to last 2 to 4 years.[17,18] In comparison, a review by Wendelboe et al. suggests that protection provided by DTP lasts between 4 and 14 years, while protection following natural infection may have a longer duration.[19]

A2.3 Diagnostic Assays

Culture and direct fluorescent antibody testing (DFA) were the primary laboratory assays used to diagnosis pertussis during the early 1990's.[20] Faulker et al. examined pertussis diagnostic trends in the United States from 1990 to 2012 and found an increasing percentage of reported pertussis cased were diagnosed using polymerase chain reaction (PCR). By 2003, PCR had become the most commonly utilized diagnostic test. The sensitivity of PCR (>90%) is greater than the sensitivity of DFA (10%-50%), which is no longer recommended for diagnostic purposes.[13,20,21,22,23] During this same time frame, the use of culture decreased drastically. Although culture has near perfect specificity, sensitivity is low (<60%) and test results are not rapid.[21,24] Serology has consistently been utilized infrequently despite the fact that serology has greater sensitivity than PCR when testing is performed four weeks past cough onset (Figure 3).

A2.4 Recent Incidence Trends

Recent trends in pertussis incidence should be examined with consideration to diagnostic and vaccine changes. However, shifts in age-specific incidence suggest that the resurgence of pertussis is not solely an artifact of detecting a larger percentage of underlying infections. An increasing percentage of cases were reported among individuals over the age of 5 years as pertussis began to reemerge. Nationally, adolescents aged 11 to 19 years recorded the highest incidence of pertussis behind infants during the outbreak year of 2004 (Figure 4).[8] By 2012, the largest pertussis outbreak year since the 1950's (48,277 cases), incidence rates among children aged 7 to 10 years had surpassed incidence rates among adolescents.[8] These trends parallel changes to the vaccine composition and schedule. Incidence among adolescents as compared to children initially decreased following the introduction of Tdap in 2005. Conversely, disproportionately high incidence rates among children aged 7 to 10 years began after the first cohorts of children who were completely vaccinated with DTaP reached this age. This age group continues to experience high incidence rates due to waning vaccine-acquired immunity.[14,16] Thus, although more cases of pertussis are undoubtedly being detected due to more sensitive diagnostic methods, deficiencies of the currently recommended pertussis vaccines have in part reestablished pertussis as a legitimate public health concern.

A3. Knowledge Gaps in Pertussis Research

The effective control of pertussis is complicated by the incomplete understanding of its epidemiology. The circulation of pertussis within a population cannot be adequately assessed using incidence reports, as milder cases of pertussis often remain undetected. Research has shown that pertussis infections in both adults and previously vaccinated children are underreported, with missed diagnoses especially common (>90%) among adults.[4,25,26] Aguas et al. hypothesized that as pertussis transmission increases in a population, the frequency of mild (undetected) disease increases while severe (detected) disease decreases.[27] Integral to this hypothesis is Aguas et al.'s assumption that immunity has a greater effect on reducing disease severity than on reducing transmission. The proposed relationship between disease severity and transmission frequency is thus explained by the opportunity for natural boosting (boosting of immunity in partially immune individuals exposed to infection) when pertussis circulation is high and the parallel opportunity for immunity to wane due to lack of natural boosting when circulation is low. Through model simulations in a hypothetical population with high vaccination coverage, Aguas et al. concluded that peak incidence of severe disease (i.e., an outbreak year) is expected at intermediate levels of transmission.[27] Given that mild disease is not consistently detected, true peaks in pertussis transmission as compared to the observed epidemic cycle are not definitely known.

Lavine et al. explored natural immune boosting with the hypothesis that low pertussis circulation during the vaccine era explains the recent shifts in age-specific incidence.[28] Model simulations indicated that natural immune boosting requires exposure to a lower dose of pertussis antigen than does infection. Frequent natural immune boosting during the pre-vaccine era among adults and adolescents with primed immune systems (memory cells that have previously encountered pertussis antigen) from past infection may explain why pertussis historically occurred in young children. Conversely, adolescents and adults may no longer experience the benefits of natural immune boosting due to decreased pertussis circulation as the result of high vaccination coverage in children. Lavine et al.'s findings highlight the inadequacy of using vaccination records to assess population level immune status, as these records do not capture the effects of natural boosting and waning immunity. Estimating population immunity using routinely collected vaccination coverage data (e.g., National Immunizations Survey) is therefore deficient. Additionally, previous research has shown that aggregate measures of vaccination coverage at a high level (e.g., statewide) fail to capture local regions of unvaccinated individuals, which can be associated with pertussis outbreaks.[29,30] Thus, although outbreaks of pertussis can be reasonably expected to occur every 2 to 5 years, knowledge gaps pertaining to unobserved transmission and population immune status have prevented the epidemic cycle from being effectively understood and disrupted.

A4. Pertussis Seroprevalence Studies

For a disease such as pertussis, which does not induce lifelong immunity, the susceptible population is continually replenished and recurrence is to be expected.[31] However, the population susceptibility levels and the level of circulating bacteria at which pertussis outbreaks have the opportunity to occur are difficult to establish given that estimates of incidence and population immunity obtained from routinely collected data are imperfect. Alternative data sources are needed to assess undetected infections and immune status in order to understand their contributions to recurring pertussis outbreaks. Seroprevalence studies quantify antibody levels among individuals within a population, providing access to a measure that can capture the effects of both waning and boosting of immunity. *Bordetella pertussis* produces multiple antigens, however, only the pertussis toxin (PT) antigen is specific to *Bordetella pertussis*.[32] The anti-PT IgG antibody is accordingly the target of most serologic testing for pertussis. Inactivated PT is also a component of pertussis vaccine, meaning high anti-PT IgG antibody levels are evidence of either recent vaccination or recent infection.[23] Consequently, measuring this antibody is a useful tool for assessing both immunity (or susceptibility) and the prevalence of undetected infections within a population. Of note, vaccination history must be considered when interpreting positive serologic results.

A review by Barkoff et al. examined 44 pertussis seroprevalence studies conducted globally.[33] Many seroprevalence studies have been cross-sectional and restricted to one time point, limiting their ability to elucidate temporal trends.[34,35,36] Hallander et al. used samples from two non-consecutive time points (1997 and 2007) in a seroprevalence study in Sweden.[37] The first sample was taken before the introduction of a childhood vaccination program, and the second sampling occurred ten years after the introduction of the vaccination program. Studies have used this approach to observe changes in a population's immunity profile following modifications to a vaccination program. While these types of studies estimate population immunity levels at a given point in time, they do not observe how levels vary with respect to the 2 to 5 year epidemic cycle of pertussis.

Campbell et al. performed a seroprevalence study in Australia using serum samples from three time points that coincided with different stages of the pertussis epidemic cycle. They found that an increased prevalence of undetectable IgG anti-PT levels (<5 IU/mL), particularly among young children, preceded an outbreak year. However, these time points were non-consecutive (1997, 2002, and 2007).[38] To our knowledge, no study has taken repeated cross-sectional serum samples in consecutive years for the full duration of the 2 to 5 year outbreak cycle of pertussis. Utilizing serologic testing to estimate susceptibility and undetected infections in a single population over a time span that encompasses both outbreak and non-outbreak years may provide insight on demographic-specific trends.[39] These trends may expose targeted opportunities to disrupt the epidemic cycle. We have identified a novel venue, the Minnesota State Fair, in which such a study could potentially be conducted. For one of our aims, we conducted a pilot seroprevalence study to test the feasibility of performing annual serologic testing on independent samples of Minnesota residents attending the State Fair.

A5. Pertussis in Minnesota

The epidemic cycle of pertussis in Minnesota (Figure 5) has been similar to the national epidemic cycle with regard to temporality and age-specific incidence. Additionally, statewide incidence rates in Minnesota have been among the highest rates nationwide in the past decade. During the record outbreak year of 2012, Minnesota accounted for 8.6% of nationally reported cases despite representing less than 2% of the US population.[40] This disproportionately high burden of disease has occurred in Minnesota despite relatively consistent DTaP vaccination coverage that has exceeded national coverage.[41] Intervention strategies identified at the state level have the potential to reduce disease in an afflicted population and may prove to be effective on a larger scale given that Minnesota's incidence trends have mirrored national trends.

Additionally, Minnesota was selected as a study population due to the foundation of pertussis research that has been established using state surveillance data. Previous research conducted using Minnesota data has identified county-level variables associated with pertussis incidence, estimated the odds of pertussis each year following receipt of the 5th dose of DTaP, and used modeling techniques to estimate population immune status and the prevalence of undetected infections among adults and children.[16,26,42] The availability of state-specific estimates contributes to the validity of this research.

A6. Clustering of Pertussis & Vaccine Exemptions

Although statewide DTaP vaccination coverage has been consistently near 85% in Minnesota (Figure 6), unvaccinated individuals may not be randomly distributed throughout the state. Previous studies conducted using statewide pertussis vaccine exemption data from Michigan and California found 23 and 39 geographic areas, respectively, which contained statically significant clusters of children who had DTaP exemptions on record at their schools.[29,30] The relative risk of pertussis in these exemption clusters ranged from 1.27 to >30. Imdad et al. used county level data from New York to estimate that the incidence of pertussis increased by 5 cases per 100,000 population for each 0.1% increase in county exemption rate.[43] Notably, Feikin at el. found that the increased risk of pertussis in areas with high exemption rates is not restricted to unvaccinated children. In a study of Colorado counties, Feikin et al. reported that the risk of pertussis among vaccinated children between the ages of 3 years and 18 years was multiplied by 1.9 (1.7, 2.1) for each 1% increase in county exemptions.[44]

Furthermore, demographic and socioeconomic characteristics have been found to be associated with pertussis exemption clusters and vaccination clusters.[30] Thus, conducting spatial and spatio-temporal cluster analyses of pertussis incidence and vaccine exemptions in Minnesota highlights local areas that may be contributing to outbreaks in Minnesota. Additionally, this analysis sets the groundwork for continued surveillance by the Minnesota Department of Health (MDH) in which cluster analyses can be conducted as data become available, potentially providing an opportunity for targeted, early intervention in areas deemed to be at risk.

A7. Pertussis Models

Although serologic studies and spatial analyses provide additional data beyond the data that are obtained through routine surveillance, some parameters are inherently unobservable or uncertain and must be estimated. Modeling offers a means of using available data to inform estimates of unknown parameters. Through calibration, observed data (e.g., incidence) serve as targets to which a model is fit by varying uncertain parameters over plausible ranges.[45] In previous research, we used this approach to generate estimates of the prevalence of undetected infections and population immunity among adults and children in a metropolitan county in Minnesota.[26] Our model was limited by its restriction to discretely modeling outbreak years with no simulations of the inter-epidemic periods; however, models of pertussis transmission in other populations have been successfully implemented over the full epidemic cycle. [28,46,47]

Keeling and Rohani described the trade-off that exists between model accuracy and model transparency. Predictive models require a high degree of accuracy, whereas models used to gain insight on disease dynamics require a high degree of transparency.[48]

As additional components are incorporated in a model, the model is better able to fit to observed data (i.e., more accurate), but the ability to understand the impact of each model component on disease dynamic is diminished (i.e., less transparent). We developed a transparent model of pertussis transmission to simulate the epidemic cycle of pertussis, incorporating state-specific parameter estimates, where available. The model can be used to explore how the frequency and magnitude of the pertussis epidemic cycle is impacted by variation in population-level parameters. Additionally, the model allows us to investigate if individuals with a primed immune system from previous infection or vaccination experience a heightened immune response to secondary exposure, as suggested by Lavine et al.'s findings that natural immune boosting requires exposure to a lower dose of pertussis antigen than does infection.[28] In combination with serologic data and spatial analyses, our modeling study contributes to reducing the knowledge gap that exists regarding the true epidemiologic trends of pertussis.

B. MANUSCRIPT I

B1. Objective

The study objectives are 1.) To test the feasibility of conducting a pertussis seroprevalence study in the University of Minnesota's Driven to Discover building at the Minnesota State Fair; 1A.) To quantify pertussis antibody levels in a sample of Minnesota residents attending the State Fair to obtain age-specific estimates of population susceptibility and the prevalence of undetected infections; 1B.) To create a framework for conducting analyses on serologic and survey data by demonstrating methods to identify demographic factors associated with pertussis susceptibility and undetected infections.

B2. Introduction

Seroepidemiologic studies, which measure sera antibody levels produced in response to infection and/or vaccination, can be valuable tools for gaining insight on population level dynamics of infectious diseases.[39] Pertussis surveillance in the United States consists of case reports from health care providers and laboratories, resulting in an underestimation of true incidence by primarily capturing clinically apparent disease. Infections that remain undetected have contributed both to the persistence of cyclic pertussis outbreaks every 2 to 5 years and to the resurgence of pertussis following near elimination in the 1970’s.[8,49] In various populations, seroepidemiologic studies have been conducted to identify adults as a common source of unrecognized transmission.[4,50,51] Additionally, seroepidemiologic studies have been used to identify age groups with low pertussis antibody levels suggestive of susceptibility due to waning of vaccine-acquired immunity.[34] Because vaccination records cannot capture the unobserved effects of vaccine failure, waning immunity, and natural boosting (boosting of immunity in partially immune individuals exposed to infection), serologic data can complement vaccination records and provide a more accurate measure of population immunity.[16,28]

Pertussis seroepidemiologic studies have previously been conducted to identify potential areas for public health intervention and to assess vaccine impact on population immunity; however, seroepidemiologic studies are commonly restricted to one time point, limiting their ability to elucidate temporal trends. [34,35,51] To build upon previous seroepidemiologic research, one would ideally conduct a study that sampled a single population annually in consecutive years over the full epidemic cycle of pertussis. Understanding demographic-specific temporal trends in susceptibility and undetected infections as they relate to the recurrence of outbreaks would highlight opportunities for targeted interventions to disrupt sustained transmission. However, seroepidemiologic studies can be expensive and logistically difficult to conduct. Consequently, seroepidemiologic studies are not routinely used to assess population-based temporal trends of infectious diseases.[52]

The main challenge presented by prospective seroepidemiologic studies that aim to monitor changes in population-level immunity over time is collecting sera samples from a wide range of age groups drawn from the same population. Specimen collection for serologic testing is generally expensive, time consuming, and labor-intensive. Alternatively, relying on stored sera limits our ability to track immunity prospectively while monitoring changes in the epidemiology of a given disease in a given time and place. Previous pertussis seroepidemiologic studies that utilized population sampling to recruit several hundred participants to study centers have reported enrollment periods approaching one year, a rate that would be taxing for studies seeking to obtain annual samples.[35,51] In a study that measured immunity among school-aged children, Kelly et al. reported that the cost per specimen from a population-based random sample was 11 times greater than the cost per specimen obtained from residual sera.[53] Though immediately available, samples obtained from residual sera from diagnostic laboratories are subject to selection bias and may not be generalizable to a population of interest.[54] A trade-off therefore exists between expenditure of time and money and enrollment of a tailored study sample that can provide a complete picture of population level dynamics over time.

Notably, the National Health and Nutrition Examination Survey (NHANES) has been collecting sera specimen annually in the United States since the 1980's. However, the manner in which the specimens are collected is intended to provide a sample that is representative of the nation as a whole. As such, the sample cannot be assumed to be representative of individual states.[55] This limits the usefulness of these data for understanding state-level trends in vaccine-preventable diseases. Importantly, Rohani et al. examined state-specific pertussis incidence rates over time and found that trends varied by spatial location.[56] States may experience varied trends in vaccine-preventable diseases due to demographics, state laws, and surveillance practices.[57] Consequently, nationwide samples may be inadequate for certain research questions. The need exists for state-specific venues that can provide an opportunity to collect sera specimens on an ongoing basis.

We hypothesize that state fairgrounds may provide a novel venue for conducting seroepidemiologic studies by enabling recruitment of a large number of individuals in a short period of time at a relatively low cost. The Minnesota State Fair attracts between 1 and 2 million visitors over a 12 day period each year, with visitors encompassing a large age range and representing diverse backgrounds.[58,59] We hypothesize that this venue will allow us to efficiently conduct a pilot pertussis seroepidemiologic study on a sample of Minnesota residents consisting of both adults and children. If this setting is deemed feasible following our pilot study, we foresee it facilitating larger seroepidemiologic studies for both pertussis and other infectious diseases, with an emphasis on studies dedicated to assessing temporal serologic trends in a specific population.

B3. Research Methods

B3.1 Study Overview

Participants completed a written survey regarding demographic information, receipt of pertussis vaccine, and recent history of cough illnesses. Following completion of the survey, participants provided a finger stick blood sample that was submitted for serologic testing. Serologic testing quantified pertussis antibody levels. Survey results were used to determine if elevated antibody levels were induced by recent vaccination or recent infection. Methods for identifying the association between demographic variables and serologic results are presented with the understanding that the limited sample size of this pilot studies prohibits statistical inference.

B3.2 Study Population & Sample

Because finger sticks are not recommended for children under the age of 1 year, the target population of this study was Minnesota residents aged 1 year or older. Individuals were eligible for participation if they were at least 1 year old and had a primary residence in Minnesota. Individuals under the age of 18 years were required to be accompanied by an adult. Enrollment was open to individuals of any gender, race, and ethnicity.

This research was a pilot study. As such, our sample size calculation was based on budget as opposed to statistical power. Our budget allowed for the enrollment of 90 participants. We used a stratified sampling mechanism based on the following age groups: 1-6, 7-17, and 18+ years. A total of 30 participants were targeted for enrollment in each age group. The bounds of these age groups were based in part on the recommended pertussis vaccination schedule, which calls for 5 doses of pertussis-containing vaccine by the age of 6 years.[60] As waning of vaccine-acquired immunity has been observed following completion of the pertussis vaccination series, we anticipated these age groups to differ with respect to estimates of susceptibility and undetected infections.[15,16,61] Although heterogeneity in exposure to vaccination recommendations and infection exists in these age groups, particularly among adults, the sample size of this study restricted further stratification.

B3.3 Participant Recruitment

Participant recruitment and enrollment occurred over a 3-day period (August 29, August 31, and September 1) at the 2016 Minnesota State Fair. The University of Minnesota (UMN) has an existing research facility at the fair, the Driven to Discover (D2D) building, in which the study was staged. In 2016, 12,476 fairgoers participated in 26 UMN research projects on the fairgrounds.[62] Two methods were used to recruit participants: 1.) a UMN D2D mobile application detailing the nature of the study and outlining study eligibility; 2.) active recruitment using study staff stationed outside of the D2D building.

B3.4 Participant Study Identification

Upon enrollment, each participant was assigned a unique four digit study identification (ID) number. Participant study ID and date of birth were recorded on the surveys. Participant study ID, date of birth, and gender were recorded on the laboratory submission forms (Appendix A). No direct identifiers were used to track study participants. Participant contact information was collected and stored separately from survey and laboratory results.

B3.5 Survey

Study participants completed a brief, paper-based survey (Appendix A). To distinguish between recent vaccination and recent infection in individuals with elevated antibody levels, participants were asked to self-report whether they had received a pertussis-containing vaccine (DTaP, DTP, or Tdap) within the past year. Additionally, participants were asked if they had been diagnosed with pertussis or experienced a cough illness lasting at least two weeks during the past year. Individuals reporting a cough illness were asked if the coughing occurred in spasms (paroxysmal coughing), if the coughing was followed by vomiting (post-tussive vomiting), and if the coughing was followed by a high-pitched "whoop" noise (whooping). The presence of one of these symptoms in addition to a two week cough meets the clinical case definition for pertussis and was used to determine if an infection was clinically apparent.[63] The distribution of cases that are subclinical vs. clinical is of interest to MDH because it could inform potential surveillance strategies.

Basic demographic information was collected from participants during the survey. These covariates included age, gender, race, ethnicity, education, and home zip code.

The response categories for these demographic variables were standardized across all studies conducted in the D2D building.

B3.6 Validity of Survey

Miles et al. conducted a systematic review on the validity of different sources of immunization reports and found that parental recall of childhood vaccination overestimated coverage in 11 of 15 studies included in the analysis.[64] The percentage point difference in vaccination coverage between self report and provider records ranged from 5% to 41% in the 11 studies. Of note, the studies included in this review varied in recall time and were not restricted to pertussis vaccines. Rolnick et al. surveyed adults and found that 61% of adults who reported receiving a tetanus booster were unable to recall if the booster included a pertussis component (i.e., Td vs. Tdap).[65] Difficulty in distinguishing between these vaccines may result in an overestimation of adult pertussis vaccination if previous receipt of Td is mistaken as Tdap. Although previous research suggests that self report of vaccination for our survey will result in false positives, the relatively short recall period of one year may attenuate overestimation of vaccine receipt. Recall of pertussis symptoms may affect the distribution of cases that are clinical vs. subclinical; however; the identification of all cases is dependent on serologic results.

B3.7 Serologic Testing

Serologic testing was conducted on participant blood samples to quantify pertussis antibody levels. A minimum of 50 µL of blood was collected by finger stick and allowed to clot for 30 minutes at room temperature. Specimens were centrifuged on site in Serum Separator Tubes (SST) for 90 seconds at 6,000 to 15,000 g to isolate serum from blood cells. Centrifuged samples were immediately refrigerated. Specimens were transported on ice to the Minnesota Department of Health Public Health Laboratory (MDH-PHL) for testing at the end of each day. Antibody levels were quantified using an IgG anti-PT ELISA assay that was developed by the Centers for Disease Control and Prevention and validated at MDH-PHL for use with acute or convalescent serum specimens.[61] This assay measures antibody levels against pertussis toxin, a pertussis-specific antigen that is produced by the bacterium *Bordetella pertussis* and is a component of pertussis vaccines. We categorized antibody levels according to commonly used cut-off values, with a concentration above 62.5 IU/mL indicating infection or vaccination within the past year (Table 1).[33] An undetected infection was defined as a participant who met all of the following criteria: 1.) had antibody levels >62.5 IU/mL; 2.) reported no pertussis vaccination within the past year; 3.) reported no diagnosis of pertussis by a healthcare provider within the past year. As the cut-off value that we are using to indicate a positive serology laboratory result is lower than the typically used MDH cut-off value (100 IU/mL), MDH did not conduct case investigations on individuals who tested positive in this study. The higher cut-off value used in routine MDH testing restricts case investigations to recent infections in which public health intervention is timely, whereas this study was assessing infections and vaccinations over the past year. Participants who reported symptoms consistent with pertussis received MDH recommendations on appropriate treatment and follow-up, if applicable. Participants with undetectable antibody levels (<5 IU/mL) were considered susceptible.

B3.8 Validity of Serologic Testing

Pertussis IgG antibody responses are considered to be more sensitive than both IgA and IgM responses. [23,66] Serologic testing for pertussis is therefore typically restricted to quantifying IgG antibody levels. Many commercial laboratories perform single-sample serologic testing for pertussis; however, cut-off values for antibody levels are not standardized. Guiso et al. compared results from serologic studies performed in three different countries and concluded that the IgG anti-PT cut-off value which optimizes sensitivity and specificity is likely between 60 and 75 IU/mL, with a value of 62.5 IU/mL generally accepted to indicate infection or vaccination within the past year.[67] Sensitivity and specificity at this cut-off value are estimated to be 80% and 95%, respectively; however, age and time since vaccination or infection impact these estimates.[23,67]

B4. Results

The primary aim of this study was to determine the feasibility of conducting a rapid seroepidemiologic study in the unique setting of a fairground. We were able to reach our total enrollment goal and obtain specimens that were satisfactory for testing (i.e., sufficient volume, integrity uncompromised). We conservatively anticipated processing 5 participants per hour during each of our 3 allotted study shifts on the fairgrounds. Each shift lasted 6 hours, totaling an expectation of 30 participants per day. We easily exceeded our projected rate of enrollment on the first day of the study with over 50 study participants. During the remaining 2 days of the study, we intentionally slowed recruitment efforts, as our study budget restricted testing to 90 specimens. Based on recruitment numbers from this pilot study, projected enrollment for a future seroepidemiologic study is shown in Table 2. Note that the projected numbers are based on conducting a study during 1 of the 2 available 6 hour shifts on the fairgrounds each day. Enrollment numbers would be greater if both shifts were used.

We over-enrolled 14 participants to ensure that we would have 90 testable specimens if any specimens were deemed unsatisfactory for testing. Children aged 1 to 6 years were difficult to enroll without active recruitment by study staff, which resulted in the decision to allow a larger percentage of participants in the older age groups. The demographics of study participants are shown in Table 3. We compared the demographics of study participants to Minnesota demographics from the 2016 American Community Survey to assess if our sample was representative of the state population. Study participants were primarily white and not Hispanic or Latino, similar to the state's racial and ethnic profile. Compared to the Minnesota population, study participants were more likely to be female and to reside within the seven county metro area.

The distribution of serologic results is shown in Figure 7. The prevalence of undetectable antibody levels was 53.8% (95% CI: 26.7%, 80.9%) in the 1-6 year age group, 72.3% (95% CI: 59.6%, 85.1%) in the 7-17 year age group, and 23.3% (95% CI: 8.2%, 38.5%) in the ≥18 year age group. Self-report of pertussis vaccination in the past year among individuals with undetectable antibody levels was 42.9% (95% CI: 6.2%, 79.6%), 14.7% (95% CI: 2.8%, 26.6%), and 14.3% (95% CI: 0.0%, 40.2%) in the 1-6, 7-17, and ≥18 year age groups, respectively. Of note, elevated antibodies suggestive of recent infection were found among two adults, neither of whom reported vaccination, pertussis diagnosis, or pertussis-specific symptoms in the past year.

B5. Discussion

The results of this pilot study demonstrate that a fairground setting is a viable option for efficiently conducting seroepidemiologic studies within the scope of a state population. Our ability to enroll participants and collect satisfactory specimens suggests that larger seroepidemiologic studies with 1,000 to 2,000 participants could feasibly be completed over the course of 12 days. Specifically, a fairground setting could facilitate annual population sampling to monitor serologic trends in a single population over time. Contrary to relying on residual sera or NHANES samples, our specimen collection allowed for sampling of tailored subgroups and collection of disease-specific variables (i.e., self-report of symptoms, vaccination history, and clinical diagnosis) via participant surveys.

The limited sample size of our pilot study prohibits statistical inference; however, our data suggest that children may have a higher prevalence of undetectable pertussis antibody levels than do adults. Heightened susceptibility among children as compared to adults has been observed in seroepidemiologic surveys in other countries.[37,38] Specifically, Campbell et al. observed an increased prevalence of undetectable antibody levels among children preceding a record outbreak in Australia. [38] Observing temporal variation in the prevalence of undetectable antibody levels among children despite consistent vaccination coverage may be suggestive of a change in the circulation of *Bordetella pertussis* within a population. Our pilot study demonstrates that we could feasibly use the Minnesota State Fair to obtain annual sera samples over the course of a full epidemic cycle in an attempt to find a surveillance measure that is indicative of an impending outbreak year. Additionally, demographic-specific trends interpreted in combination with routine surveillance data may highlight a subgroup in which targeted intervention could disrupt sustained transmission between outbreak years. Although cut-off values for serologic pertussis testing are not definitive, focusing on relative changes over time in a single population will produce directly comparable results that should be subject to less uncertainty as we use seroepidemiologic studies to better understand local dynamics of the epidemic cycle of pertussis.[33]

In addition to providing estimates of population susceptibility and infection prevalence for infectious diseases, large seroepidemiologic studies conducted on fairgrounds could be used to efficiently monitor vaccine impact.[37] Serologic data can inform public health policy by identifying susceptible subgroups that may benefit from an adjustment to vaccine recommendations. Importantly, the fixed timing of the state fair each year would control for seasonal effects.[68] Although our study focused on pertussis, this unique opportunity for serologic surveillance could be extended to other infectious diseases, including influenza. Miller et al. used sera samples collected in two consecutive years to establish an immunity profile in an English population before and after a wave of influenza infection.[69] The authors concluded that continued serologic studies would be beneficial to understanding the epidemiology of specific subtypes and providing data to inform parameters for prediction models. State fairgrounds present a logistically simple solution for such sustained research.

We acknowledge that our study sample may not be representative of the state of Minnesota. Metropolitan residents were overrepresented, which is not unexpected given that the fairgrounds are located in a metropolitan county. Future studies could stratify enrollment based on county of residence or adjust the target population to the seven county metro, which contains over half of the state's population. Additionally, selection bias in our study is possible if health status or vaccination status impacted participation. Under this assumption, we would expect participants to be less likely to have pertussis and more likely to be vaccinated as compared to non-participants. However, since we were assessing pertussis illness over the past year with serologic results, we would still expect to capture a high percentage of previously infected individuals. Of note, we did not meet our enrollment goal for children under the age of 6 years. Enrolling young children required active recruitment by study staff stationed outside of the research building, and this age group was not preferentially targeted for enrollment until the last day of the study. Studies seeking to enroll participants in this age group, or from any specific subgroup, would benefit from targeted recruitment for the duration of the study.

Our study's self report of vaccination within the past year would benefit from verification with vaccine records. Future studies could obtain pertussis vaccination records from the Minnesota Immunization Information Connection (MIIC), an electronic immunization database maintained by MDH. MIIC records, which contain date of vaccination and vaccine formulation, would allow time since vaccination to be considered in analyses. Studies with a larger sample size would also benefit from further stratifying age groups to capture the effect of the recommended dose of Tdap at ages 11 to 12 years. The age group of 7 to 17 years contains ages in which susceptibility would be expected to be both low (immediately after Tdap) and high (both prior to Tdap and when immunity from Tdap has waned). This heterogeneous grouping may obscure results in this age group.

We recognize that at this time, Minnesota may be uniquely positioned to leverage such an opportunity due to the existence of UMN's D2D building dedicated to staging research projects on the state fairgrounds. Additionally, Minnesota had the second highest total attendance among state fairs in 2016.[70] To our knowledge, no other state is utilizing a fairground setting to access a sample of residents for research purposes, specifically serological surveillance. Minnesota can serve as a model for implementing this novel sampling mechanism that bypasses many of the logistical challenges of seroepidemiologic studies.

B6. Conclusion

In conclusion, the results of this pilot study demonstrate that state fairgrounds can be utilized to recruit participants for seroepidemiologic studies with minimal expenditure of time or money. Our results raise the possibility of conducting routine population-based seroepidemiologic studies to supplement traditional public health surveillance in estimating disease prevalence, monitoring vaccine impact, and identifying at-risk groups.

C. MANUSCRIPT II

C1. Objective

The study objectives are 2.) To identify spatial and spatio-temporal clusters of pertussis vaccine exemptions and pertussis incidence in Minnesota; 2A.) To determine the association between the geographic location of exemption clusters and pertussis clusters in Minnesota; 2B.) To identify demographic and socioeconomic factors associated with pertussis clusters and exemptions clusters in Minnesota.

C2. Introduction

The association between non-medical vaccine exemptions and the occurrence of vaccine-preventable diseases, particularly pertussis, has drawn increased attention in recent decades. Pertussis incidence rates in the United States have risen to levels previously observed in the 1950's, with outbreaks continuing to occur cyclically every 2 to 5 years (Figure 2).[8] Numerous factors have been attributed to the resurgence of pertussis, including waning of vaccine-acquired immunity, bacterial evolution, and parental refusal of childhood vaccines.[56,71,72] Vaccine refusal is regulated at the state level by permissible exemptions to school immunization requirements. All states allow medical exemptions for vaccine contraindications, and a subset of states allow nonmedical exemptions due to religious and/or philosophical beliefs.[73] Non-medical exemptions to the childhood pertussis vaccine, DTaP, have been associated with an increased risk of pertussis at both the individual and population levels.[29,30,43,44,72,74,75] The risk of a non-medically exempt child contracting pertussis has been estimated to range from 6 to 23 times the risk of a vaccinated child.[44,75] From a population perspective, census tracts located within a cluster of non-medical exemptions have been estimated to be 2 to 3 times more likely to overlap with pertussis clusters as compared to census tracts located outside of exemption clusters.[29,30] Clusters in this context are geographic areas with more exemptions/pertussis cases than would be expected if their occurrence was proportionate to the population at risk. To date, the risks associated with clusters of DTaP exemptions have been derived from research restricted to non-medical exemptions and/or pertussis cases occurring among children, with exemption data often aggregated over multiple years.[29,30,43,44,74]

The focus of cluster analyses on non-medical exemptions has justifiably been driven by the opportunity for public health intervention, as vaccine refusal is the result of personal choice rather than medical contraindication. Studies that identify geographic overlap of areas with high non-medical exemption rates and areas with high pertussis incidence provide compelling data to combat vaccine refusal. However, medical exemptions, despite being less prevalent, also contribute to the susceptible population. For analyses that strictly aim to assess population risk, the distinction between exemption categories disregards a subset of susceptible individuals. Moreover, a recent study of school immunization data from California illustrated that this distinction is subject to misclassification.[76] Under a similar rationale, fully understanding the impact of exemption clusters on an entire population requires the inclusion of adults in the definition of persons at risk of pertussis, as transmission can occur between individuals of any age.[1] State health departments, in particular, are in a position to use this broader definition to further explore relationships between exemption status and incidence trends.

Schools report exemption data to state health departments at a fixed time each year as part of annual immunization reports. For example, immunization reports in

Minnesota are due by December 1 each year. These reports offer state health departments the opportunity to assess the association between DTaP exemption clusters and overlapping pertussis clusters on a recurring basis. Notably, previous cluster analyses have aggregated exemption data over multiple years under the rationale that exemption rates within schools are relatively stable over time.[29,30] Such studies cannot detect if a temporal pattern exists between cluster overlap (or non-overlap) and the cyclic occurrence of pertussis outbreaks every 2 to 5 years.[8] To expand upon previous research, we measured the association between DTaP exemptions and pertussis incidence with consideration of the following 1.) inclusion of both non-medical and medical exemptions 2.) inclusion of all ages in the population at risk of pertussis infection, and 3.) no temporal aggregation of annual exemptions. We implemented these methodological adjustments using immunization data from Minnesota kindergartners and incidence data from the Minnesota Department of Health (MDH). By routinely conducting these analyses, MDH could potentially use exemption data reported each December to forecast communities at increased risk of pertussis in the upcoming calendar year. The ultimate goal of these analyses would be to reduce transmission in high risk areas by modifying prevention efforts (e.g., expand recommendations for testing) when cases are first identified.

C3. Research Methods

C3.1 Study Overview

This study consisted of cluster analyses performed using Minnesota school-reported vaccine exemption data and pertussis surveillance data. Geographic areas which contained a greater number of pertussis cases or a greater number of vaccine exemptions than was expected based on population density were identified. We assessed the overlap of identified exemption clusters and pertussis clusters to determine if geographic areas with exemption clusters are associated with increased pertussis incidence. Using demographic and socioeconomic data aggregated at the census tract level, we assessed population characteristics inside identified clusters as compared to outside clusters.

C3.2 Data Sources

C3.2.1 Exemption data

Under Minnesota law, children enrolled in school must receive either vaccinations consistent with medically acceptable standards or an exemption to vaccination.[77] For children entering kindergarten, the pertussis vaccination requirement consists of having completed five doses of DTaP, with four doses considered acceptable if the fourth dose was administered after the age of four years. Exemptions from immunizations are allowed if 1.) a health care provider submits a signed note to the school indicating a medical contraindication or laboratory confirmation of existing immunity or 2.) a legal guardian submits a notarized statement of conscientious objection.[78] Schools are required to submit an Annual Immunization Status Report (AISR) to MDH by December 1 each year. The AISR provides school-specific counts of the number of enrolled kindergartners and the number of kindergartners who have received an exemption (either medical or non-medical) to vaccination.[78] Reported exemptions are vaccine specific. Because addresses for each exempt individual are not reported with AISR data, we used school addresses as a proxy for home address to geocode exemptions using a composite addresses locator in ArcMap 10.4 (Esri, Redlands, California). The composite locator matched school addresses against a street locator, then subsequently against a ZIP Code locator if a street level match was not found. Geocoded AISR data were aggregated to produce annual counts of kindergartner enrollment and DTaP exemptions by census tract. Minnesota contains 1,338 census tracts.

C3.2.2 Case Data

Confirmed and probable pertussis cases with cough onset between 2013 and 2016 were identified using the Minnesota Electronic Disease Surveillance System (MEDSS), an MDH database that houses case investigation data for reportable diseases. The Minnesota Communicable Disease Rule, Chapter 4605 requires that health care providers and other entities report suspected cases of pertussis to MDH within one working day.[79] MDH subsequently conducts case investigations on all suspected cases of pertussis. Clinical, demographic, and epidemiologic information are collected from both the case (or case's parent) and the case's provider, if applicable. The Health Insurance Portability and Accountability Act (HIPPA) permits providers to share patient medical history without patient authorization when the information is related to the case investigation of a reportable disease.[80] Consequently, the clinical information needed to define an illness as pertussis can be collected and entered into MEDSS regardless of the outcome of an interview attempt with a suspected case.

Confirmed and probable cases of pertussis are defined based on information collected during the MDH case investigation. A case of pertussis is considered confirmed if symptoms meet the clinical case definition of pertussis and 1.) the diagnosis is laboratory confirmed by culture or polymerase chain reaction or 2.) the case had contact with a laboratory confirmed case.[63] The clinical case definition of pertussis is defined as a cough illness lasting at least two weeks with either paroxysms of coughing, inspiratory whooping, and/or post-tussive vomiting as reported by a clinician or the case.[63] A case of pertussis is considered probable if it meets the clinical case definition of pertussis but does not meet the additional criteria needed to be confirmed.[63] The confirmed and probable case definitions for pertussis did not change between 2013 and 2016. Case addresses were geocoded using a composite address locator in ArcMap that matched addresses against a street locator, then subsequently against a ZIP Code locator if a street level match was not found. Geocoded cases were aggregated to produce counts of cases by census tract and cough onset date.

C3.2.3 Demographic and Socioeconomic Data

Demographic and socioeconomic variables were obtained from 2010 Census data. All variables were aggregated at the census tract level. These variables include race, ethnicity, highest level of education, median household income, and average household size (number of residents per household). Previous research has shown that affluence (measured by kindergarten tuition) is associated with vaccine refusal, and possessing at least a college level education is associated with vaccine uptake.[81,82] Variables that impact the number and type of contacts that individuals have (e.g., average household size) have been shown to be associated with pertussis incidence.[42]

C3.3 Exemption Cluster Identification

SaTScan software (Information Management Services, Inc., Boston, Massachusetts) was used to identify spatial clusters of exemptions. Clusters in this context are geographic areas with more exemptions than would be expected if their occurrence was proportionate to the population at risk. The population at risk of exemptions was defined as Minnesota kindergartners, estimated from AISR data. To assess spatial clustering of exemptions, observed data (i.e., geocoded exemptions aggregated by census tract) were compared to data simulated from a Poisson distribution. The null hypothesis was that exemptions were randomly distributed over space.[83] Each school year of AISR data (2012-2013, 2013-2014, 2014-2015, 2015-2016) represented a distinct period within which exemption clusters were identified. This design allowed for the assessment of geographic overlap of exemption clusters in a given school year and pertussis clusters occurring in the following calendar year. Because AISR data are reported annually and do not contain a more granular time component, the exemption cluster analyses were strictly spatial.

C3.4 Pertussis Cluster Identification

SaTScan software was used to identify space-time clusters of pertussis cases with cough onset between 2013 and 2016. Clusters in this context were geographic areas and time periods with more pertussis cases than would be expected if their occurrence was proportionate to the population at risk and the length of the time period. The population at risk of pertussis was defined as Minnesota residents of all ages, estimated from 2013 through 2016 American Community Surveys. Because vaccinated individuals may be at risk of pertussis due to primary vaccine failure or waning immunity, they were included in the population at risk. To assess space-time clustering of pertussis cases, observed data (i.e., geocoded pertussis cases aggregated by census tract and cough onset date) were compared to data simulated from a Poisson distribution. The null hypothesis was that pertussis cases were randomly distributed over space and time.[83]

C3.5 SaTScan Statistics

SaTScan generates circular scan windows to compare observed and expected data in a given geographic area. In our spatial and space-time analyses, the center of each window was a grid point defined by the centroid of census tracts. Scan windows vary in size and were allowed to include up to 50% of the population at risk.[83] This limit is a recommended SaTScan setting that allows both large and small clusters to be identified. The radius of the scan windows can be restricted by geographic area; however, a population-based restriction is recommended when the size of clusters are uncertain.[83] In space-time analyses, SaTScan scan windows have an added component of height to represent time. With this added dimension, the scan window becomes a cylinder.[83] Cough onset served as the time variable in our space-time analysis of pertussis cases. The temporal window was limited to include at most 50% of the study period and had a precision of one month.

SaTScan generates scan windows with varying centers and radiuses to assess for clustering. The scan window that produces the most likely cluster is the scan window which maximizes the likelihood function for the Poisson model. The likelihood function for a given scan window is defined as:

$$\left(\frac{c}{E[c]}\right)^{c}\left(\frac{C-c}{C-E[c]}\right)^{C-c}$$

where C is the total number of cases/exemptions, c is the observed number of cases/exemptions within the window, and E[c] is the expected number of cases/exemptions within the scan window under the null hypothesis.[83] Thus, the likelihood is a product of functions of observed to expected ratios within and outside the scan window. An indicator variable in SaTScan can restrict analysis to clusters of high rates only (i.e., scan windows must contain more cases/exemptions than expected). The likelihood equals 1 when observed data match expected data both inside and outside the scan window. As the number of observed cases/exemptions within the scan window exceeds the number of expected cases/exemptions, the likelihood increases.

Monte Carlo simulations were used to generate data sets under the null hypotheses. For both the spatial and space-time analyses, the maximum likelihood from the observed data was compared to the maximum likelihoods from the simulated data. For example, with 999 data sets simulated under the null hypothesis, the null hypothesis was rejected at the $\alpha = 0.05$ level if the maximum likelihood from the observed data ranked among the 50 highest simulated likelihoods.[83] The rejection of the null hypothesis for a given cluster was independent of the location of cases/exemptions outside of the cluster, as the observed versus expected numbers of cases/exemptions *within* the window was being compared.[83] We retained only the statistically significant clusters that did not overlap with a previously reported cluster.

C3.6 Regression analyses

We used logistic regression to assess the geographic overlap of spatial clusters of exemptions among kindergartners in a given school year and space-time pertussis clusters among individuals of all ages with a cluster start date in the following calendar year (e.g., 2012-2013 school year exemption clusters based on December 2012 ASIR data in relation to pertussis clusters with start date in 2013). From the cluster analyses, each census tract was assigned a value of 1 or 0 indicating if the centroid of the census tract was located inside or outside of a pertussis cluster. The same assignment was made to census tracts for exemption clusters. The logistic regression odds ratio represented the odds of a census tract within an exemption cluster being located in a pertussis cluster compared to the odds of a census tract outside an exemption cluster being located in a pertussis cluster. This odds ratio was calculated using both an unadjusted model and a model that was adjusted for demographic variables obtained from 2010 census data aggregated at the census tract level. We used univariate logistic regression to identify demographic variables associated with census tracts located in pertussis clusters and with census tracts located in exemption clusters. Demographic variables included in this analysis represented race, ethnicity, education, household income, and average household size (number of residents per household). Regressions were performed with Stata 13.1 (StataCorp LP, College Station, Texas).

C4. Results

C4.1 Geocoding Results

AISR data were reported by a total of 1,285 schools between the 2012-2013 and 2015-2016 school years, resulting in 4,706 school years of exemption data. AISR response rates from Minnesota schools ranged from 95.7% to 97.8% during the study period.[84] A total of 45 (1.0%) school years of exemption data were excluded from the analysis due to school addresses that could not be geocoded. Of the 3,431 confirmed or probable cases of pertussis reported to MDH during the study period, 24 (0.7%) were excluded from the analysis due to an insufficient address for geocoding. Twenty-one (0.6%) of the 3,407 geocoded cases were geocoded to the zip code level after failing to match an address on the street level. The final data set used for analysis consisted of 4,661 school years of exemption data and 3,407 pertussis cases. The distribution of geocoded cases across calendar years was 858 (25.2%) in 2013, 945 (27.7%) in 2014, 593 (17.4%) in 2015, and 1011 (29.7%) in 2016.

C4.2 Exemption Clusters

A total of 6 spatial exemption clusters were observed in the 2012-2013 school year, 8 in 2013-2014, 4 in 2014-2015, and 5 in 2015-2016 (Table 4). Census tract demographic variables positively associated with increased odds of being located in an exemption cluster were the percentage of households with income over $100,000 and average household size. The percentages of non-white and Hispanic residents and the percentage of residents with less than a high school degree were inversely associated with the odds of being located in an exemption cluster.

C4.3 Pertussis Clusters

Nine spatiotemporal clusters of pertussis cases spanning 505 (37.7%) census tracts were identified during the study period (Table 5). The 2013 and 2016 calendar years each contained 4 pertussis clusters. One pertussis cluster had a start date in 2015, with cases that extended into 2016. Additionally, one of the 2013 pertussis clusters included cases that extended into 2014. Census tract demographic variables associated with statistically significant increased odds of being located in a pertussis cluster were the percentage of non-white residents, the percentage of households with income over $100,000, and average household size (Table 6). The percentage of residents in a census tract with less than a high school degree was inversely associated with the odds of being located in a pertussis cluster.

C4.4 Overlap of Pertussis Clusters with Exemption Clusters

Figure 8 shows census tracts with exemption clusters identified from annual immunization school reports and pertussis clusters with onset during the following calendar year. The unadjusted odds ratio for 2012-2013 exemption clusters and 2013 pertussis clusters was 9.83 (95% CI: 6.05, 15.97), compared to 8.64 (95% CI: 6.07, 12.28) for 2015-2016 exemption clusters and 2016 pertussis clusters. The adjusted odds ratios for these years were 10.01 (95% CI: 5.97, 16.79) and 9.81 (95% CI: 6.62, 14.55), respectively. The odds ratio for 2014-2015 exemption clusters and 2015 pertussis clusters, 0.35 (95% CI: 0.08, 1.58), was not statistically significant. As no pertussis clusters with a start date in 2014 were observed, no association was calculated using the 2013-2014 school year exemption data.

C5. Discussion

Our results suggest that temporal differences may exist in the relationship between geographic clustering of DTaP exemptions and overlapping clusters of pertussis cases in the subsequent year. Specifically, the strength of this association may be dependent on the 2 to 5 year epidemic cycle of pertussis. Minnesota experienced a record outbreak year in 2012 with over 4,000 reported pertussis cases. In contrast, the number of reported pertussis cases dropped to 595 in 2015. These 2 years represented high and low points of the epidemic cycle in Minnesota, respectively. The 2012 outbreak extended into 2013, which was of 1 of 2 calendar years in our analysis in which we observed a statistically significant overlap of pertussis clusters with exemption clusters. Statistically significant overlap was also observed in 2016, a year which represented a nearly twofold increase in pertussis incidence from the previous year. These results suggest that exemption clusters may not be predictive of pertussis clusters in years which represent low points of the epidemic cycle of pertussis, as herd immunity may be high enough to combat the risk posed by exemption clusters. This notion is supported by the serologic finding from Campbell et al. that high population prevalence of undetectable antibody levels (i.e., susceptibility) among children immediately preceded an outbreak in Australia, while low prevalence of undetectable antibody levels was observed during a lull in the epidemic cycle.[38] Seroprevalence studies conducted between outbreak years may complement cluster analyses in identifying areas and/or demographics that contribute to sustained transmission.

Notably, previous cluster analyses of a similar nature have reported smaller odds ratios. Omer et al. aggregated kindergarten exemption data from Michigan between 1991 and 2004 and restricted pertussis cases to individuals aged 18 years or younger in an analysis that produced an odds ratio of 2.7. Atwell et al. aggregated kindergarten exemption data from California between 2005 and 2010 and estimated an odds ratio of 2.47. In our analysis, odds ratios for the two statistically significant years (9.83, 8.64) were considerably larger than these estimates. The stronger association observed in our study may be due in part to the inclusion of medical exemptions and pertussis cases of all ages, which we consider an appropriate method for assessing overall population risk. Medical exemptions, however, only accounted for approximately 4% of all exemptions during the study period. More so, our results suggest that temporally aggregating exemption data to arrive at a single risk estimate may diminish the observed association between exemption clusters and pertussis clusters in some years (i.e., high points of the epidemic cycle) while overestimating the association in other years (i.e., low points of the epidemic cycle). To our knowledge, this study is the first to measure the association between pertussis clusters and DTaP exemption clusters on an annual basis.

Our findings regarding predictors of pertussis clusters are consistent with a previous ecological analysis that assessed factors associated with increased pertussis rates in Minnesota. At the county level, Iroh Tam et al. similarly found educational attainment of less than a high school degree to be inversely associated with pertussis incidence rates, while income and average household size were positively associated with pertussis incidence rates.[42] Our results are also consistent with research that found vaccine refusal or delay to be positively associated with non-Hispanic white race, educational attainment, and household income.[85] Interestingly, the percentage of non-white residents in a census tract was associated with decreased odds of being in an exemption cluster and increased odds of being located in a pertussis cluster. This disparity could be reflective of access to healthcare, as white children in the United States are more likely to have a source of usual care than are non-white children.[86] Therefore, although census tracts with a higher percentage of non-white residents may be less likely to experience exemption clusters, the ability to contain pertussis outbreaks in these census tracts may be hindered by lack of access to healthcare providers for testing and treatment.

We acknowledge that our study design presents limitations. Exemption status is a proxy for susceptibility and is not necessarily reflective of true susceptibility status. Schools may incompletely report exemptions, and conversely, the report of an exemption does not necessarily mean that a child is completely unvaccinated (i.e., a child may partially complete the five dose DTaP series). For the purpose of this analysis, we assumed that exempt children are not up-to-date on pertussis vaccines. Vaccination history would be required to determine the effect of partial vaccination verses no vaccination on clustering of pertussis incidence.

Of note, our analysis represented pertussis cases occurring during a single epidemic cycle and consisted of cases that were reported to MDH. Pertussis infections, particularly among adults, often remain undetected due to non-specific clinical presentation.[87] We previously estimated that approximately 90% of pertussis infections in adults remain undetected.[26] In future research, serologic testing and models can be used to address uncertainty regarding the prevalence of undetected infections. However, we would not expect detection of pertussis to differ differentially with respect to clustering of census tract level exemptions. Importantly, census tract level observations may not hold true at the individual level.

Identified clusters are restricted by census tract boundaries and should not be interpreted as exact locations. The impact of aggregating individual data for cluster analysis is depicted in Figure 9. Because school address was used as a proxy for home address for exemptions, exempt individuals may not have resided in the same census tract to which their exemption was attributed. We selected a maximum cluster size of 50% of the population at risk, which would likely capture exemptions assigned to home address or school address in the same cluster assuming the two locations were in nearby census tracts. With a smaller setting for maximum cluster size (e.g., 10% of the population at risk), some larger exemption clusters were separated into several smaller clusters. Notably, the 50% of the population at risk setting is recommended to prevent selection bias due to cluster size.[83] Additionally, the choice to aggregate or not aggregate data impacts the total number of exemptions or pertussis cases that are randomly distributed when producing expected data to compare to observed data, which in turn influences the statistical significance of clusters. SaTScan analyses are thus dependent on user settings, and results should be interpreted with consideration to these settings. Our particular study design and SaTScan settings were selected under the notion that health departments may apply these methods as data become available each year.

C6. Conclusion

In conclusion, our study suggests that DTaP exemption clusters identified on an annual basis may not identify areas at increased risk of pertussis for the upcoming year if the epidemic cycle of pertussis is in a lull. During high points in the epidemic cycle, the risk of pertussis associated with DTaP exemption clusters may be greater than previously estimated. We encourage continued monitoring of this potential trend by state health departments. Given our findings, state health departments may consider monitoring areas with exemption clusters to provide increased messaging of pertussis prevention and response recommendations to schools, local public health, and healthcare providers when cases are first identified.

D. MANUSCRIPT III

D1. Objective

The study objective is to implement a deterministic compartmental model of pertussis transmission in R Studio using Minnesota-specific parameter estimates where available. This transparent model will be used to provide insights into the drivers of local outbreaks.

D2. Introduction

Models have been increasingly used in efforts to explain the resurgence of pertussis in the United States and to inform prevention strategies.[27,28,47] Infectious disease models range from complex predictive models that replicate historic incidence trends and forecast future trends, to minimal models that retain only the parameters necessary to qualitatively understand disease dynamics.[48,88] As the complexity of models increase, the ability to clearly identify the impact of individual model components on population-level dynamics decreases. While such models are better suited to accurately reproduce observed data, they do so at the expense of transparency.[48] Transparent models provide a means to explore the drivers of epidemiologic patterns, with the opportunity for additional complexities to be added as underlying dynamics are better understood.

Aguas et al. implemented a minimal model of pertussis transmission in a hypothetical population to generate hypotheses regarding the relationship between severe disease and transmission frequency.[27] By only modeling parameters necessary to replicate a generic pertussis epidemic, the authors were able to clearly observe the impacts of high and low transmission on the prevalence of severe disease within a hypothetical population. However, because populations have different characteristics – some measured (e.g., vaccine uptake, age composition) and some unmeasured (e.g., likelihood of seeking treatment) – observed disease dynamics may differ depending on the population modeled.[89] In a review of published pertussis models, Campbell et al. noted the importance of using contemporary data relevant to the study population for model parameterization whenever possible.[47] To examine the individual contributions of parameters on the epidemic cycle of pertussis in a local setting, we developed a compartmental model of pertussis transmission using Minnesota-specific population and vaccination estimates. Case data from the Minnesota Department of Health (MDH) served as qualitative calibration targets to inform base estimates of unobservable parameters. We varied parameters estimates over plausible ranges to observe their impact on the frequency and magnitude of recurring pertussis outbreaks.

D3. Research Methods

D3.1 Model Population

The model consisted of seven age groups: 1.) 0-1 year 2.) 2-6 years 3.) 7-10 years 4.) 11-12 years 5.) 13-21 years 6.) 22-64 years and 7.) 65-100 years. Age groups were based on the pertussis vaccination schedule and contact patterns, with the intent of capturing differences in immune status and population mixing by age. Specifically, the child age groups of 2-6 years and 11-12 years represented ages for DTaP and Tdap vaccinations, respectively.[11] The age groups of 22-64 years and 65-100 years were selected to differentiate contact patterns between working adults and retired adults. The initial age distribution of the model population (Table 7) was derived from 2010

Minnesota census data.[90] The model population was dynamic, with births and age-dependent deaths (Table 8) reflecting Minnesota rates.[90] All inputs were converted to weekly rates, as each model time step represented one week.

D3.2 Model Health States

Individuals in the model were classified as susceptible, infectious, vaccine immune, or naturally immune. Distinct health states existed for naïve (never infected or vaccinated) and primed (memory cells that have previously encountered pertussis antigen) susceptibility and infectiousness. The transition diagram in Figure 10 shows possible movements between model health states. The rate at which susceptible individuals became infected was dependent on the prevalence of infectious individuals, age-specific contacts, and naïve/primed status. Previously infected or vaccinated individuals who returned to the susceptible state were allowed to have a lower likelihood of a subsequent infection as compared to naïve susceptible individuals due to a primed immune system.[91] Similarly, primed individuals with a secondary infection were allowed to be less infectious than naïve individuals who became infected. Infected individuals were infectious for three weeks before transitioning to a naturally immune state.[6] We assumed that both naturally immune and vaccine immune individuals were fully protected from infection for one year, after which immunity began to wane. Because neither pertussis infection nor vaccination induces lifelong immunity, previously immune individuals had the opportunity to return to a primed susceptible state.[19] Conversely, individuals with waning immunity also had the opportunity to return to a fully immune state under the assumption that exposure to infectious individuals can result in immune boosting.[28] Complete model equations and parameter definitions can be found in Appendix B.

D3.3 Model Input Parameters

D3.3.1 Vaccination Coverage and Efficacy

Average National Immunization Surveys (NIS) estimates for Minnesota were used to parameterize vaccination coverage for individuals under the age of 18 years.[92] NIS coverage estimates are available for children aged 19 to 35 months who have received four doses of DTaP or DTP and for adolescents aged 13 to 17 years who have received Tdap. For model parameterization, we assumed that vaccinated individuals received vaccines at ages recommended by the Advisory Committee on Immunizations Practices schedule. NIS estimates for DTaP/DTP coverage were applied to individuals in the 2-6 year age group. NIS estimates for adolescent Tdap were applied to individuals in the 11-12 year age group. Behavioral Risk Factor Surveillance System estimates of Tdap coverage in adults was applied to the 22-64 and 65-100 year age groups.[93] The estimates for DTaP and Tdap efficacy were both assumed to be 85%.[94]

D3.3.2 Waning Immunity

McGirr et al. conducted a meta-analysis of studies that assessed the long-term immunity provided by 5 doses of DTaP.[95] The reviewed studies varied in design and included cohort studies, case-control studies, and a randomized clinical trial. The predicted probability of vaccine failure (i.e., loss of immunity) each year following the fifth dose of DTaP was calculated using meta-regression. McGirr et al. estimated that 10% of vaccinated children would be immune 8.5 years following their fifth dose of

DTaP, assuming an initial vaccine efficacy of 85%.[95] We assumed that after a maximum of 10 years post vaccination with DTaP and in the absence of boosting, immunity waned completely and previously vaccinated individuals return to the susceptible health state. The duration of waning DTaP immunity was allowed to vary between 1 and 10 years. Base estimates for Tdap failure were obtained from a Wisconsin cohort study that used surveillance data and vaccination records to estimate vaccine efficacy.[17] The duration of waning Tdap immunity in the absence of boosting was allowed to vary between 1 and 5 years.

D3.3.3 Population Mixing

We assumed that transmission occurred via age-specific mixing. Mossong et al. conducted a survey to estimate the daily number and type of contacts made by individuals of different ages.[96] Surveys conducted across eight European countries produced similar results. We generated a contact matrix representative of model age groups by averaging Mossong et al.'s survey results to estimate the number of age-specific contacts individuals were assumed to make each day (Table 9). Although these data were generated from a European population, the pattern of children most frequently coming into contact with individuals of the same age and with individuals of a parental age is subjectively in agreement with the pattern that would be expected in the United States (i.e., contacts made primarily at school and at home).

D3.3.4 Transmission and Detection

Force of infection is defined as the per capita rate at which susceptible individuals contract infection.[31] The rate at which susceptible individuals contract infection is a function of the number of infectious individuals in the population and the product of contact rates and transmission probability. We assumed that transmission probability is not age-dependent. We applied a multiplier to the force of infection for secondary exposures, as implemented by Campbell et al., to allow for the possibility of a heightened immune response among individuals subject to immune boosting.[47] The range for this multiplier was 1 to 5. In a previous model, Rohani et al. assumed that 10% of infections are detected, which is consistent with CDC estimates of 5-10%.[97,98] We estimated a similar percentage of undetected adult infections in a transmission model of pertussis in a metropolitan county in Minnesota.[26] When varying model parameters, we assumed that at most 10% of adult infections were detected, with the potential for greater detection among children.

D3.4 Model Calibration

MDH surveillance data (confirmed and probable pertussis cases in Minnesota) were used to calibrate the model. We qualitatively compared model output to weekly pertussis prevalence (assumed to be incidence multiplied by duration of infectiousness) in Minnesota between 2005 and 2018. Model parameters were varied across plausible ranges during model calibration to obtain a good fit of the model to observed data. A good fit was qualitatively defined as model output that produced 1.) recurring outbreaks every 2 to 5 years 2.) outbreaks of similar magnitude to observed data, and 3.) a ratio of adult to child pertussis cases similar to observed data (Table 10). Variations of model parameters over plausible ranges were then further explored to observe their impact on model output (Table 11). All models simulations had a fixed burn in period. Model results are presented for a 20 year time period.

D4. Results

D4.1 Base Case Scenario

We established a base case scenario that provided a good fit to the data per our qualitative criteria. Recurring peaks occurred roughly every 4 years, with the weekly number of prevalent cases ranging from approximately 500 to 1,100 (Figure 11). The average proportion of cases occurring among children each year in the model base case was 73%, compared to the annual average of 76% in MDH case data. Parameter values for the base case are listed in Table 13. The overall percentage of detected infections in the base case was 7.6%, with infections among children over 6 times as likely to be detected compared to infections among adults. Children accounted for 29% of total infections on average each year in the base case scenario. In this scenario, the duration of naturally acquired immunity was 20 years, and the duration of vaccine acquired immunity was 8 years (DTaP) or 4 years (Tdap). The relative risk of infection among primed individuals was 0.75. In the base case scenario, the rate of transmission did not differ between primed and naive infections, and the boosting coefficient was 1.

D4.2 Exploratory Scenarios

In comparison to the base case, setting the duration of waning DTaP and Tdap immunity to the lower end of their plausible ranges – 1 year – increased the magnitude of recurring peaks. Although the peaks were higher, the difference in case counts between high and low points of the cycle was diminished (Figure 12B). The epidemic cycle was not greatly affected by increasing the duration of natural immunity from 20 years to 50 years (Figure 12C). Conversely, shortening the duration of natural immunity had an effect similar to decreasing the duration of vaccine acquired immunity. A scenario in which the risk of infection among primed individuals relative to the risk among naïve individuals was 50% decreased both the frequency and magnitude of recurring peaks (Figure 12D). The model was sensitive to the boosting coefficient, with a change from 1 to 2 producing steep peaks and valleys that ranged from approximately 200 prevalent cases per week to almost 2,000 prevalent cases per week (Figure 12E). All scenarios had a distribution of cases among children that was similar to the base case scenario.

D4.2 Trends in Susceptibility

The susceptible fraction of the population fluctuated around 45% throughout the epidemic cycle in most scenarios, including the base case. The base case susceptible fraction consisted largely (approximately 80%) of primed individuals, and on average was roughly two thirds adult. The cyclic pattern of susceptibility among adults did not differ from the pattern among children with respect to timing of peaks. Among adults, susceptible individuals were more likely to be primed than naïve, while the inverse was true for children. In the scenario in which transmission from primed infections was half as effective as transmission from naive infections (Figure 12F), the susceptible fraction of the population fluctuated around 70%. The scenario with a decreased relative risk of infection among primed individuals likewise had an elevated fraction of the susceptible population (approximately 60%) relative to the base case.

D5. Discussion

In this study, we implemented a model of pertussis transmission using Minnesota data to explore how individual parameters contribute to the epidemic cycle. Our base case scenario suggests that although children account for the majority of detected pertussis cases, adults account for the majority of total infections (detected and undetected). This finding is consistent with adult infections often lacking pertussis specific symptoms.[3,4] The similar temporal patterns of susceptibility among adults and children showed no age group driving the epidemic cycle. These results differ from findings by Campbell et al. in which increased prevalence of undetectable antibody levels among children was observed to precede an outbreak year in Australia.[38] Campell et al.'s study followed a change to the pertussis vaccination schedule (18 month booster replaced with 15-17 year booster), which may have contributed to the observed results. Worby et al. noted that relative to other age groups, 8 to 14 year olds had a larger depletion of their susceptible fraction during the ascent of Minnesota's record outbreak in 2012 and therefore had a driving role.[99] When viewing the percentage change in the susceptible population over time in each age group, we did not observe a similar trend. A possible explanation for this difference is the inability of our model to replicate outbreaks in specific settings, such as schools, which could be captured in the case data used in the study by Worby et al.

Our results suggest that the majority of the susceptible population has an immune system that has been primed from previous vaccination or infection. Children were the exception to this finding, as they are predominately still under the window of coverage from vaccination. Because of the high level of primed individuals, scenarios in which primed infections were not as transmissible as naïve infections severely dampened the epidemic cycle and raised the underlying level fraction of the population that was susceptible (i.e., lower circulation of pertussis in the population). The pertussis epidemic cycle that we have historically observed may not have been able to persist if infections among primed individuals were not as transmissible as infections among naïve individuals. However, the base case scenario supports the notion that primed individuals face a decreased risk of infection upon exposure relative to naïve individuals.[47] If less antigen is necessary for immune boosting than is necessary for a primary infection (boosting coefficient > 1), the peaks in the epidemic cycle are more dramatic. In contrast, the cycle is not greatly impacted by prolonging the duration of natural immunity. Together, these results show that the opportunity for boosting and loss of immunity allows for more volatility in the susceptible population than does a simple extension (or shortening) of immunity.[99]

Assumptions made to simplify the model impact validity and restrict its current use. The broad application of NIS vaccination estimates and the assumption of timely vaccine receipt prevented heterogeneity in vaccination coverage (with respect to age, geography, or timing) from being represented in the model. Future iterations of the model can be strengthened by the addition of time-varying parameters, expanded age groups, and quantitative calibration. Without these more sophisticated elements, the model does not capture cohort effects that may modify the epidemic cycle.[47] Additionally, the model does not distinguish between mild or atypical cases and more severe cases, which does not allow for exploring potentially differential contributions to transmission.[100] In its current state, the model provides a means to test the influence of parameters on a generic pertussis epidemic cycle in a population that has an age distribution and vaccine rates similar to Minnesota. Importantly, the base case scenario represents a single parameter set that provides a qualitatively good fit of the model to the data. Other plausible parameter sets that provide a similarly good fit potentially exist, particularly if parameters are correlated. Different parameter sets may result in different conclusions. If uncertainty in model inputs and outputs are of interest, a more systematic calibration approach with a specified search criteria and goodness-of-fit measure could be used to identify a collection of top fitting parameter sets.

D6. Conclusion

In conclusion, this model represents a foundation to begin exploring drivers of the epidemic cycle of pertussis. With the small proportion of infections that manifest as detected cases, relying on cases data to understand trends provides an incomplete picture of the epidemic cycle that can be supplemented with modeling.

E. GENERAL CONCLUSIONS

This dissertation used alternative methods to analyze routinely collected pertussis surveillance data and propose supplements to existing surveillance measures as part of work to understand the resurgence of pertussis. The combined results of these analyses contribute to identifying opportunities to disrupt the epidemic cycle of pertussis.

Manuscript I tested the feasibility of monitoring population immunity through serologic testing conducted in a research venue at the Minnesota State Fair. High prevalence of undetectable antibody levels among individuals is an indication of increased population susceptibility. We demonstrated that a sample of 2,000 Minnesotans of all ages could be tested over the 12 day course of the fair. The fairground setting bypasses many logistical issues that may otherwise prohibit routine serosurveillance. Temporal seroprevalence data can supplement trends in case data and vaccine uptake by capturing undetected infections and providing estimates of immunity that are subject to waning and immune boosting.

In Manuscript II, we used SaTScan software to identify areas in Minnesota where children with exemptions to DTaP were spatially clustered. We assessed the timing of these exemption clusters and spatio-temporal pertussis clusters in relation to the epidemic cycle of pertussis. Our key finding was that temporally aggregating exemption data to arrive at a single risk estimate may diminish the observed association between exemption clusters and pertussis clusters in some years (i.e., high points of the epidemic cycle) while overestimating the association in other years (i.e., low points of the epidemic cycle). This association can continue to be measured on an annual basis using data that are collected during pertussis case investigations. Local public health officials can use this knowledge to adapt messaging to potential high risk areas.

In manuscript III, we implemented a model of pertussis transmission using Minnesota-specific parameters where available. Modeling provided a means to estimate parameters that are not directly observable. Our results suggested that although children account for more detected cases of pertussis, infections are more prevalent among adults. Because the majority of the model population had an immune system that was primed from previous infection or vaccination, the model was sensitive immune boosting. The model can serve as tool to investigate the impact of different parameters on the frequency and magnitude of recurring pertussis outbreaks.

In summary, this dissertation used serologic, spatial, and modeling techniques to identify opportunities to reduce the occurrence of pertussis, a vaccine-preventable disease that has reestablished itself as a public health concern. The continued use of these research methods will contribute to reducing the knowledge gaps that exist in our understanding of the pertussis epidemic cycle.

Table 1. Interpretation of IgG anti-PT ELISA results

IgG ELISA result	Interpretation
<5 IU/mL	Undetectable (susceptible)
5 - 62.5 IU/mL	Non-recent vaccination or infection with pertussis
> 62.5 IU/mL	Recent* vaccination or infection with pertussis

*Note. Recent refers to past 12 months.

Table 2. Enrollment numbers for pilot study and projection to future studies

	Pilot study	Future study
Total participants	104	1200
Study duration (days)*	3	12
Recruitment rate (participants/hour)	5.8	16.7

*One study shift per day

Table 3. Participant demographics compared to 2016 population of Minnesota

Variable	Study N (%)	Minnesota 2016 ACS (%)
Age group		
1 to 6 years	18 (17.3%)	N/A*
7 to 17 years	53 (51.0%)	N/A*
18+ years	33 (31.7%)	N/A*
Race		
American Indian or Alaskan Native	0 (0.0%)	1.1%
Asian	2 (1.9%)	4.7%
Black or African American	4 (3.9%)	6.0%
Hawaiian or Other Pacific Islander	0 (0.0%)	0.0%
White	88 (84.6%)	83.3%
Multiracial	6 (5.8%)	2.8%
Other	3 (2.9%)	2.0%
Unknown	1 (1.0%)	0.0%
Ethnicity		
Hispanic or Latino	7 (6.7%)	5.2%
Not Hispanic or Latino	95 (91.3%)	94.8%
Unknown	2 (1.9%)	0.0%
Highest level of education completed		
≤ High school diploma or GED	69 (66.3%)	N/A*
High school diploma or GED	14 (13.5%)	N/A*
Associate's or Bachelor's degree	13 (12.5%)	N/A*
Graduate or professional degree	5 (4.8%)	N/A*
Unknown	3 (2.9)	N/A*
Metropolitan resident		
Yes	68 (65.4%)	55.0%
No	33 (31.7%)	45.0%
Unknown	3 (2.9%)	0.0%
Gender		
Female	60 (57.7%)	50.2%
Male	44 (42.3%)	49.8%

*Study data not compared to Minnesota population due to age-stratified sampling.

Table 4. Annual spatial clusters of DTaP exemptions among Minnesota kindergartners, 2012-2013 to 2015-2016 school years

Observed Exemptions	Expected Exemptions	Population	RR	School Year
62	4.08	177	15.74	2012-2013
381	273.11	11,834	1.51	2012-2013
329	233.3	10,109	1.51	2012-2013
16	3.95	171	4.08	2012-2013
149	102.01	4,420	1.51	2012-2013
77	44.68	1,936	1.76	2012-2013
208	130.38	5,028	1.67	2013-2014
15	1.69	65	8.97	2013-2014
248	169.45	6,535	1.54	2013-2014
58	24.97	963	2.37	2013-2014
26	7.26	280	3.62	2013-2014
31	10.99	424	2.85	2013-2014
10	1.4	54	7.18	2013-2014
4	0.1	4	38.65	2013-2014
655	477.26	19,334	1.62	2014-2015
14	1.14	46	12.43	2014-2015
5	0.12	5	40.63	2014-2015
158	105.6	4,278	1.55	2014-2015
34	5.71	211	6.05	2015-2016
436	307.8	11,381	1.55	2015-2016
13	1.24	45	10.52	2015-2016
17	2.62	97	6.53	2015-2016
31	10.49	388	2.99	2015-2016

Table 5. Spatiotemporal clusters of pertussis cases in Minnesota 2013-2016

Observed Cases	Expected Cases	Population	Census tracts	RR	Start Date	End Date
168	13.32	166,576	37	13.2	04/01/2016	09/30/2016
190	50.75	276,625	62	3.9	10/01/2013	11/30/2014
26	0.18	4,663	1	143.9	02/01/2016	04/30/2016
60	5.12	77,598	21	11.9	07/01/2013	11/30/2013
28	0.44	8,231	2	64.7	04/01/2013	07/31/2013
72	8.95	61,043	14	8.2	09/01/2015	07/31/2016
31	1.48	16,191	3	21.2	06/01/2016	12/31/2016
164	64.90	1,606,725	364	2.6	10/01/2016	12/31/2016
6	0.05	2,038	1	110.3	04/01/2013	05/31/2013

Table 6. Association between census tract demographic variables and clusters of pertussis and kindergarten DTaP exemptions in Minnesota by univariate logistic regression

Variable	Exemption cluster OR (95% CI)	Pertussis cluster OR (95% CI)
Percent non-white	0.96 (0.95, 0.97)	1.02 (1.01, 1.02)
Percent Hispanic or Latino	0.86 (0.83, 0.89)	1.00 (0.98, 1.02)
Percent less than high school degree	0.96 (0.94, 0.97)	0.96 (0.94, 0.98)
Percent of households with income over $100,000	1.01 (1.00, 1.02)	1.03 (1.02, 1.04)
Average household size	1.60 (1.17, 2.17)	1.53 (1.13, 2.07)

Table 7. Initialized model age structure

Age group	Model population
0-1 year	2.7%
2 -6 years	6.6%
7-10 years	5.3%
11 -12 years	2.7%
13-21 years	12.3%
22-64 years	57.4%
65-100 years	12.9%

Table 8. Model death rates by age group

Age group	Weekly death rate
0-1 year	0.0000446
2-6 years	0.0000038
7 -10 years	0.0000025
11-12 years	0.0000027
13-21 years	0.0000084
22-64 years	0.0000501
65-100 years	0.0008724

Table 9. Average number of age-dependent contacts (physical or non-physical) assumed each day for model simulations

Age group	0-1	2-6	7-10	11-12	13-21	22-64	65-100
0-1 year	0.95	1.78	0.59	0.11	0.40	3.67	0.75
2-6 years	0.76	2.42	2.04	0.25	0.60	3.94	0.81
7-10 years	0.40	2.73	3.83	1.27	1.98	4.35	0.95
11-12 years	0.18	0.80	2.65	3.72	5.21	4.33	1.12
13-21 years	0.13	0.41	0.93	1.22	7.59	6.36	1.13
22-64 years	0.25	0.65	0.52	0.25	1.42	8.96	2.32
65-100 years	0.12	0.32	0.27	0.13	0.48	3.78	3.87

Table 10. Age distribution of confirmed and probable pertussis cases in Minnesota

Year	Percentage of cases in adults	Percentage of cases in children
2005	32%	68%
2006	28%	72%
2007	28%	72%
2008	23%	77%
2009	20%	80%
2010	26%	74%
2011	22%	78%
2012	21%	79%
2013	22%	78%
2014	18%	82%
2015	22%	78%
2016	24%	76%
2017	25%	75%
2018	23%	77%

Note: Adult defined as age 18 years and older.

Table 11. Variable model parameters

Parameter	Base case	Plausible range
Duration of waning natural immunity	20 years	1 to 50 years
Duration of waning DTaP immunity	8 years	1 to 10 years
Duration of waning Tdap immunity	4 years	1 to 5 years
Transmission rate for primary infections	0.03	0.01 to 0.5
Transmission rate for secondary infections	0.03	0.01 to 0.5
Relative risk of infection among primed individuals	0.75	0 to 1
Boosting coefficient	1	1 to 5
Percentage of adult infections detected	3%	1% to 10%
Percentage of child infections detected	19%	1% to 50%

Figure 1. Timeline (weeks since cough onset) of pertussis illness.

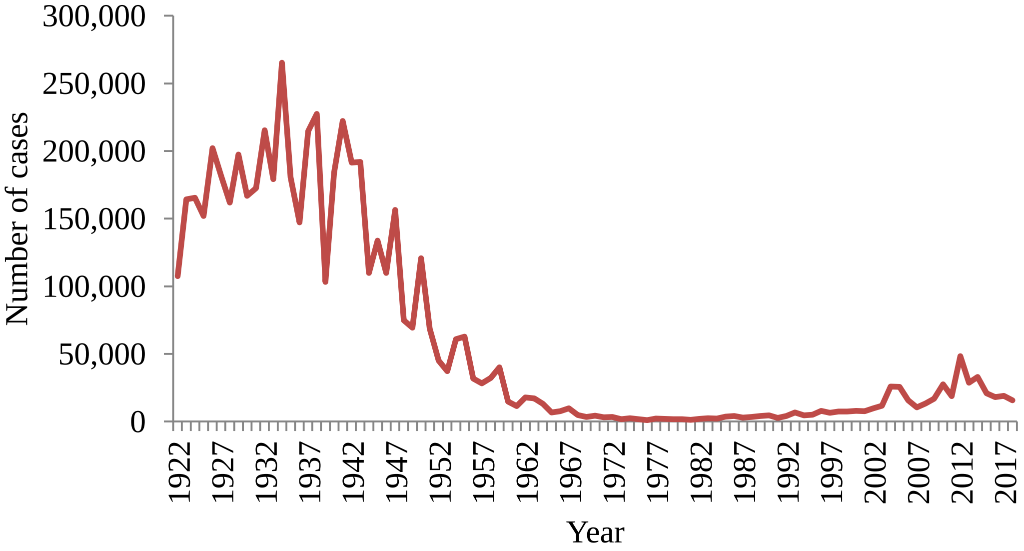


Figure 2. Nationally reported pertussis cases: 1922-2018.[8]

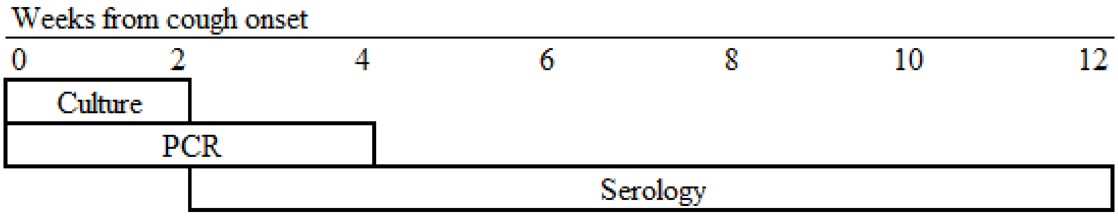
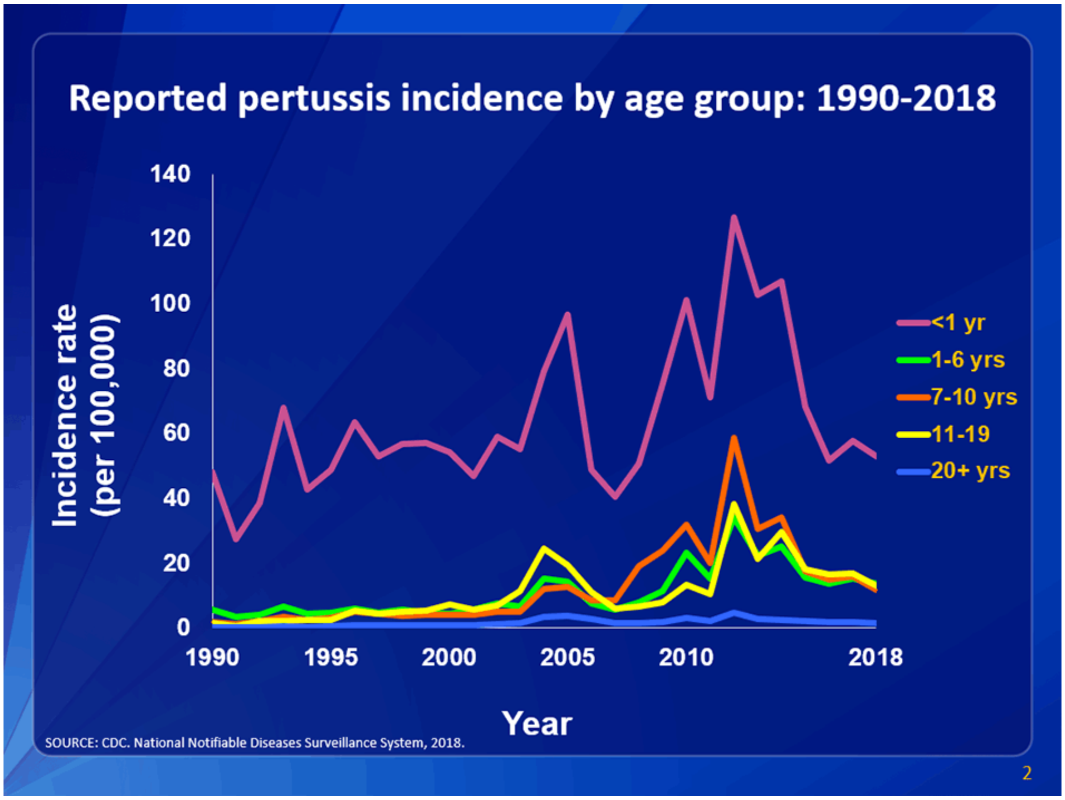


Figure 3. Optimal timing (weeks from cough onset) for pertussis diagnostic testing.[101]



Reported pertussis incidence by age group: 1990-2018

SOURCE: CDC. National Notifiable Diseases Surveillance System, 2018.

Figure 4. Nationally reported pertussis cases by age group: 1990-2018.[8]

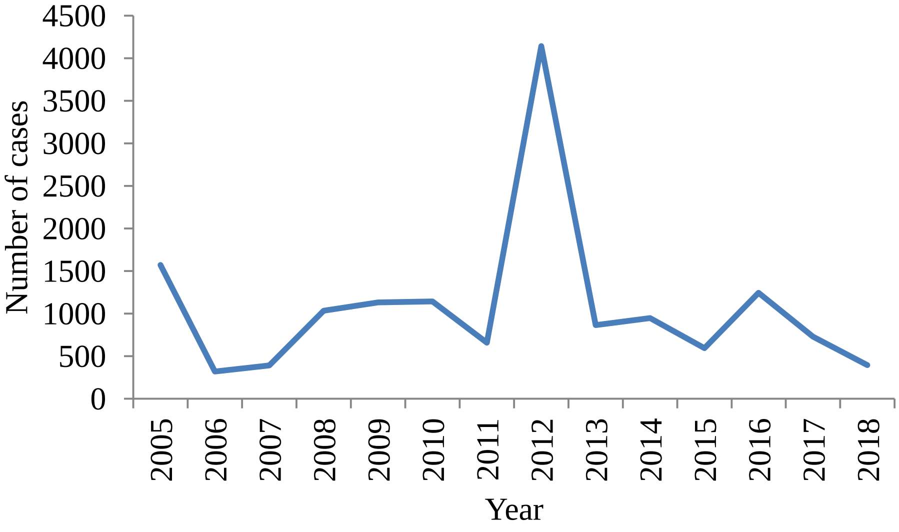


Figure 5. Reported pertussis cases in Minnesota: 2005-2018.[102]

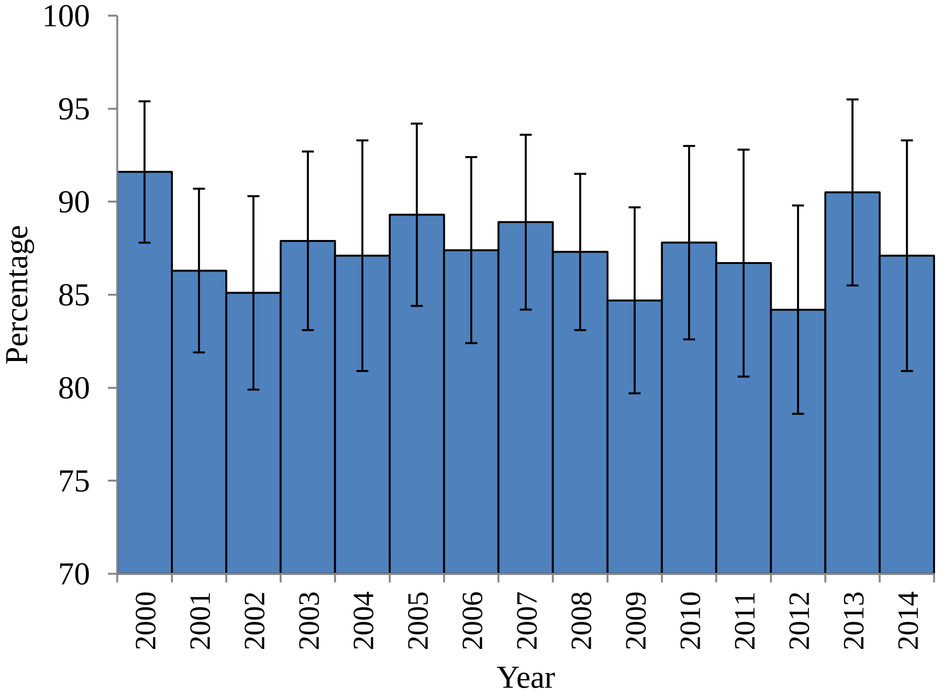


Figure 6. National Immunization Survey estimated percentage of Minnesota children aged 19-35 months with at least 4 DTaP vaccinations.

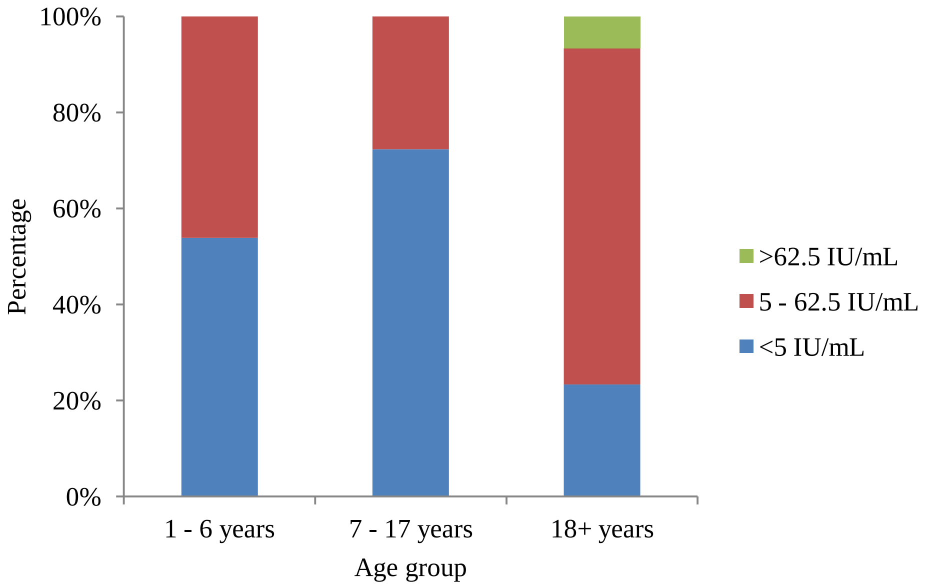


Figure 7. IgG anti-PT antibody levels (IU/mL) in 2016 sample of Minnesota residents.

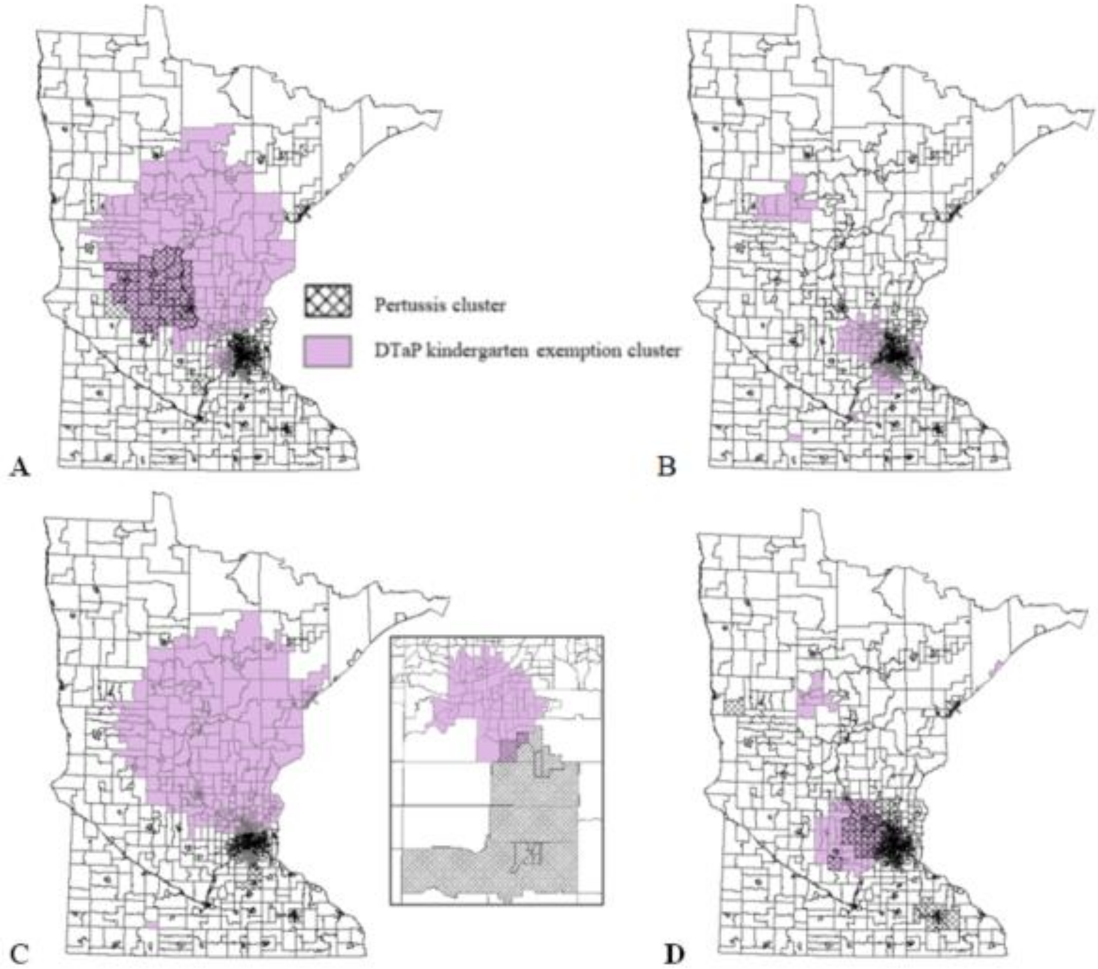


Figure 8. Spatiotemporal pertussis clusters in Minnesota relative to spatial DTaP exemption clusters identified from annual AISR kindergarten data A) 2012-2013 exemption and 2013 pertussis clusters B) 2013-2014 exemption and 2014 pertussis clusters C) 2014-2015 exemption and 2015 pertussis clusters D) 2015-2016 exemption and 2016 pertussis clusters. The insert shows a 2015 pertussis cluster in the Minneapolis-St. Paul metropolitan area.

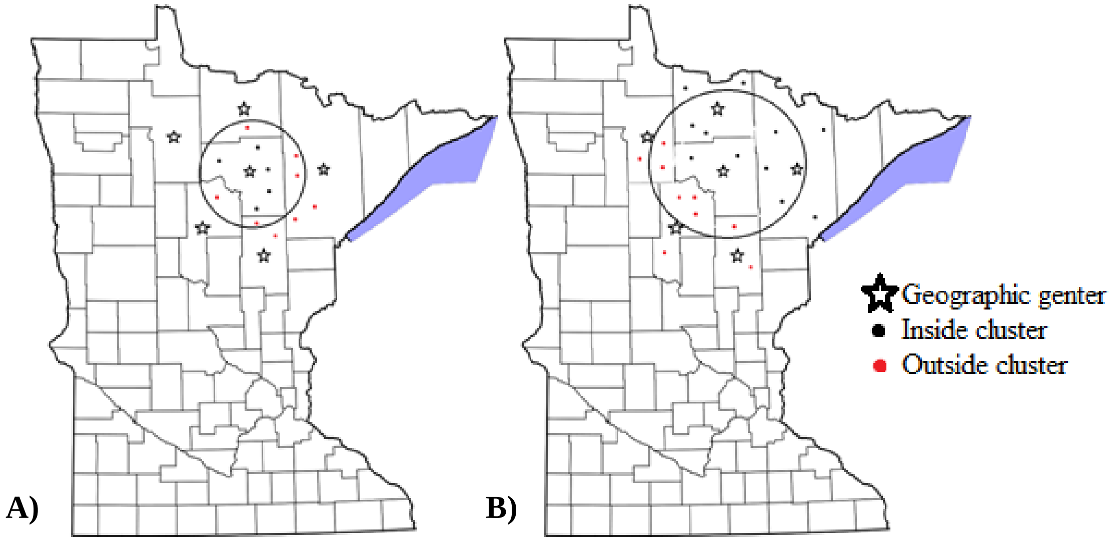


Figure 9. Depiction of cluster identification with cases aggregated at the county level A.) Cases within the scan window but in a county with a geographic center outside of the scan window are not part of the cluster. B.) Cases in counties with a geographic center in the scan window are part of the cluster, regardless if the individual case is within the scan window.

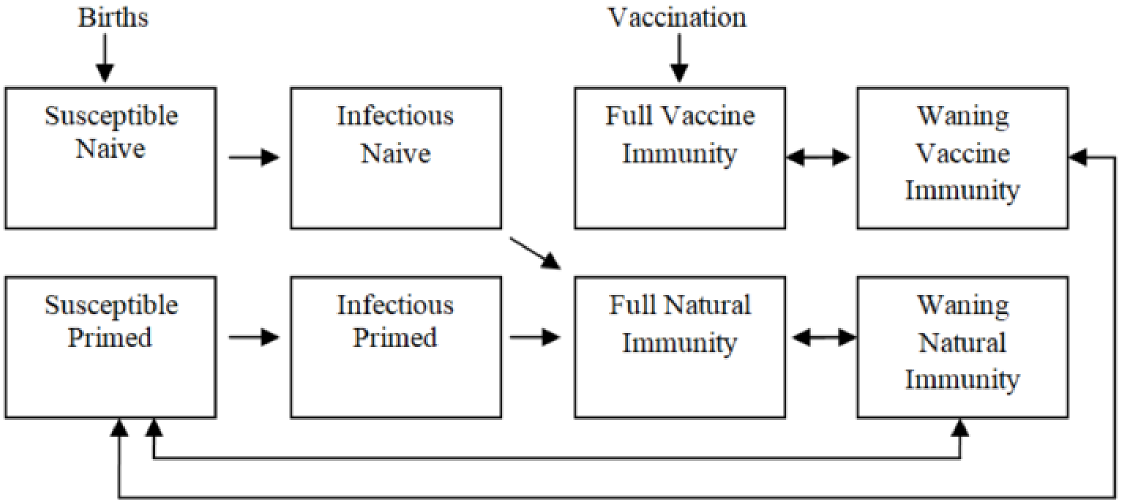


Figure 10. Transition diagram of compartmental pertussis model. Deaths can occur from any health state.

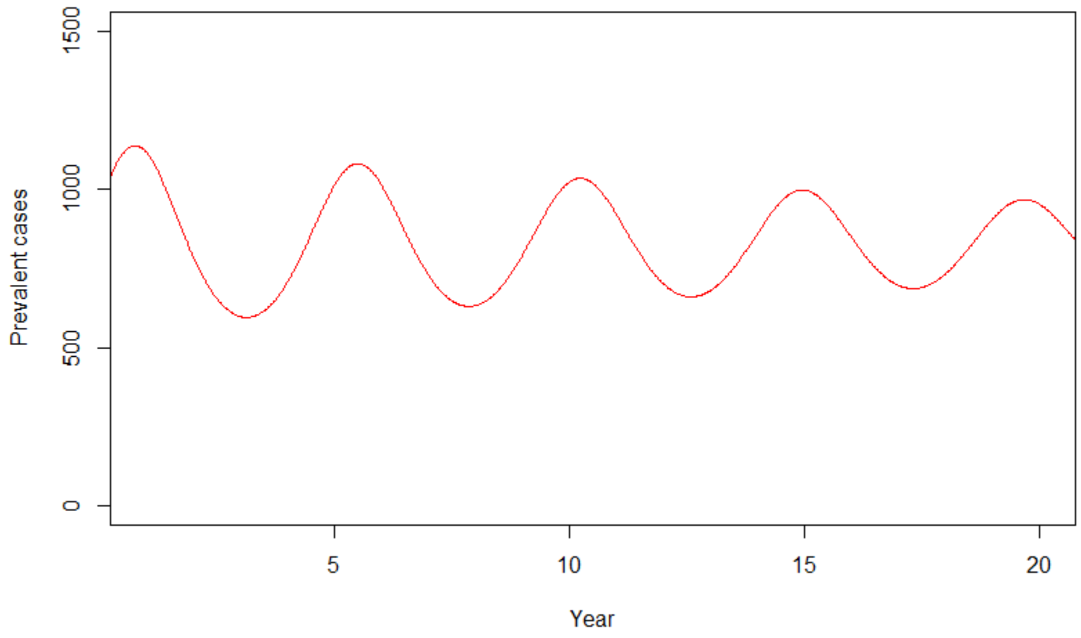


Figure 11. Model prevalent cases in base case scenario.

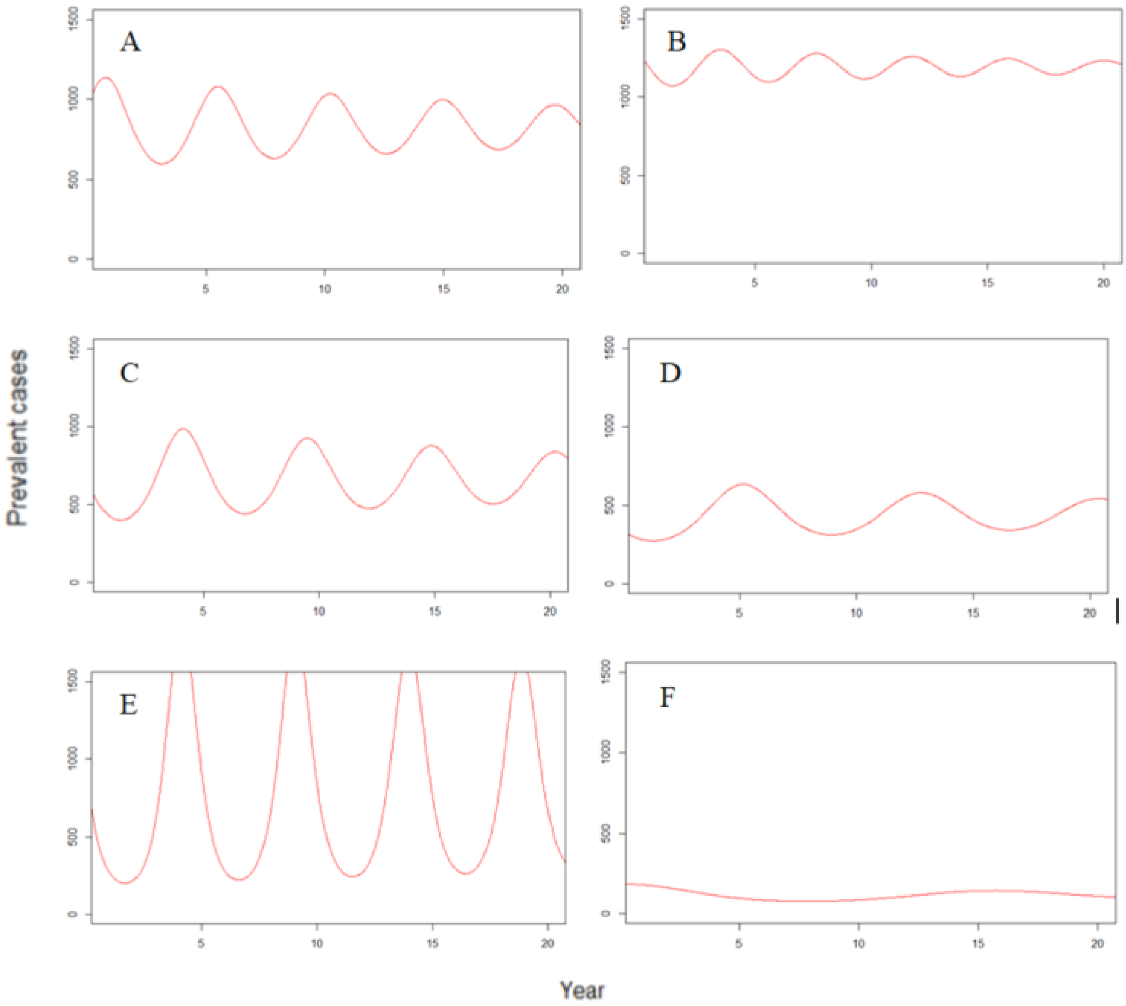


Figure 12. Comparison of model base case scenario to exploratory scenarios A) base case B) 1 year waning vaccine immunity C) 50 year natural immunity D) relative risk of infection among primed individuals is 0.5 E) boosting coefficient is 2 F.) primed individuals half as infectious as naïve individuals.

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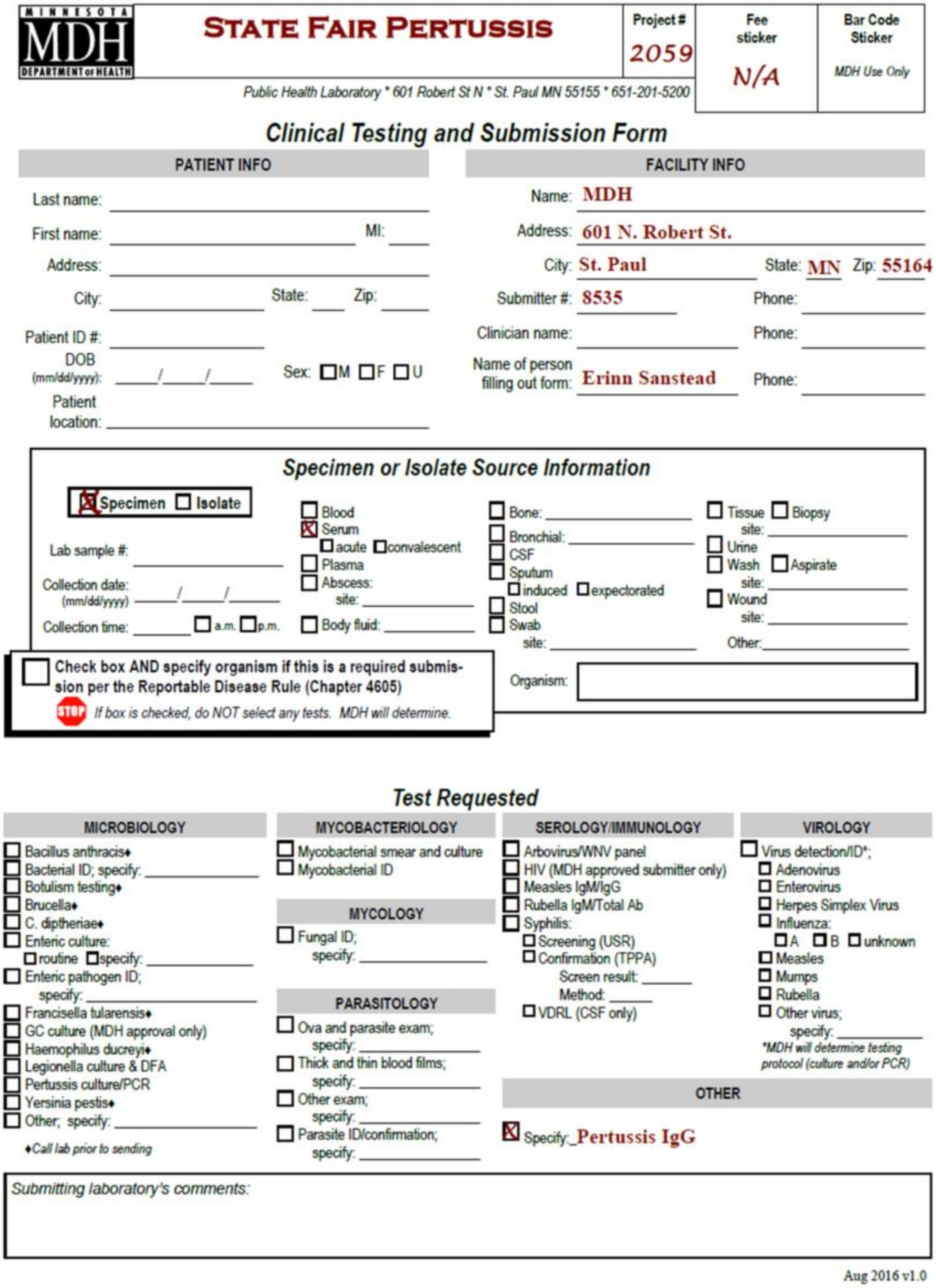
G. APPENDIX A



MINNESOTA MDH DEPARTMENT of HEALTH

STATE FAIR PERTUSSIS

Public Health Laboratory * 601 Robert St N * St. Paul MN 55155 * 651-201-5200

Project #	Fee sticker	Bar Code Sticker
2059	N/A	MDH Use Only

Clinical Testing and Submission Form

PATIENT INFO

Last name:
First name: MI:
Address:
City: State: Zip:
Patient ID #:
DOB (mm/dd/yyyy): ___/___/___ Sex: ☐M ☐F ☐U
Patient location:

FACILITY INFO

Name: MDH
Address: 601 N. Robert St.
City: St. Paul State: MN Zip: 55164
Submitter #: 8535 Phone:
Clinician name: Phone:
Name of person filling out form: Erinn Sanstead Phone:

Specimen or Isolate Source Information

☒ Specimen ☐ Isolate

Lab sample #:
Collection date: (mm/dd/yyyy) ___/___/___
Collection time: ________ ☐a.m. ☐p.m.

☐ Blood
☒ Serum
  ☐acute ☐convalescent
☐ Plasma
☐ Abscess:
  site: ________
☐ Body fluid: ________

☐ Bone: ________
☐ Bronchial: ________
☐ CSF
☐ Sputum
  ☐induced ☐expectorated
☐ Stool
☐ Swab
  site: ________

☐ Tissue ☐ Biopsy
  site: ________
☐ Urine
☐ Wash ☐ Aspirate
  site: ________
☐ Wound
  site: ________
Other: ________

☐ **Check box AND specify organism if this is a required submission per the Reportable Disease Rule (Chapter 4605)**

STOP *If box is checked, do NOT select any tests. MDH will determine.*

Organism:

Test Requested

MICROBIOLOGY

☐ Bacillus anthracis♦
☐ Bacterial ID; specify: ________
☐ Botulism testing♦
☐ Brucella♦
☐ C. diptheriae♦
☐ Enteric culture:
  ☐routine ☐specify: ________
☐ Enteric pathogen ID;
  specify: ________
☐ Francisella tularensis♦
☐ GC culture (MDH approval only)
☐ Haemophilus ducreyi♦
☐ Legionella culture & DFA
☐ Pertussis culture/PCR
☐ Yersinia pestis♦
☐ Other; specify: ________

♦Call lab prior to sending

MYCOBACTERIOLOGY

☐ Mycobacterial smear and culture
☐ Mycobacterial ID

MYCOLOGY

☐ Fungal ID;
  specify: ________

PARASITOLOGY

☐ Ova and parasite exam;
  specify: ________
☐ Thick and thin blood films;
  specify: ________
☐ Other exam;
  specify: ________
☐ Parasite ID/confirmation;
  specify: ________

SEROLOGY/IMMUNOLOGY

☐ Arbovirus/WNV panel
☐ HIV (MDH approved submitter only)
☐ Measles IgM/IgG
☐ Rubella IgM/Total Ab
☐ Syphilis:
  ☐ Screening (USR)
  ☐ Confirmation (TPPA)
  Screen result: ______
  Method: ______
  ☐ VDRL (CSF only)

VIROLOGY

☐ Virus detection/ID*;
  ☐ Adenovirus
  ☐ Enterovirus
  ☐ Herpes Simplex Virus
  ☐ Influenza:
    ☐A ☐B ☐unknown
  ☐ Measles
  ☐ Mumps
  ☐ Rubella
  ☐ Other virus;
  specify: ________

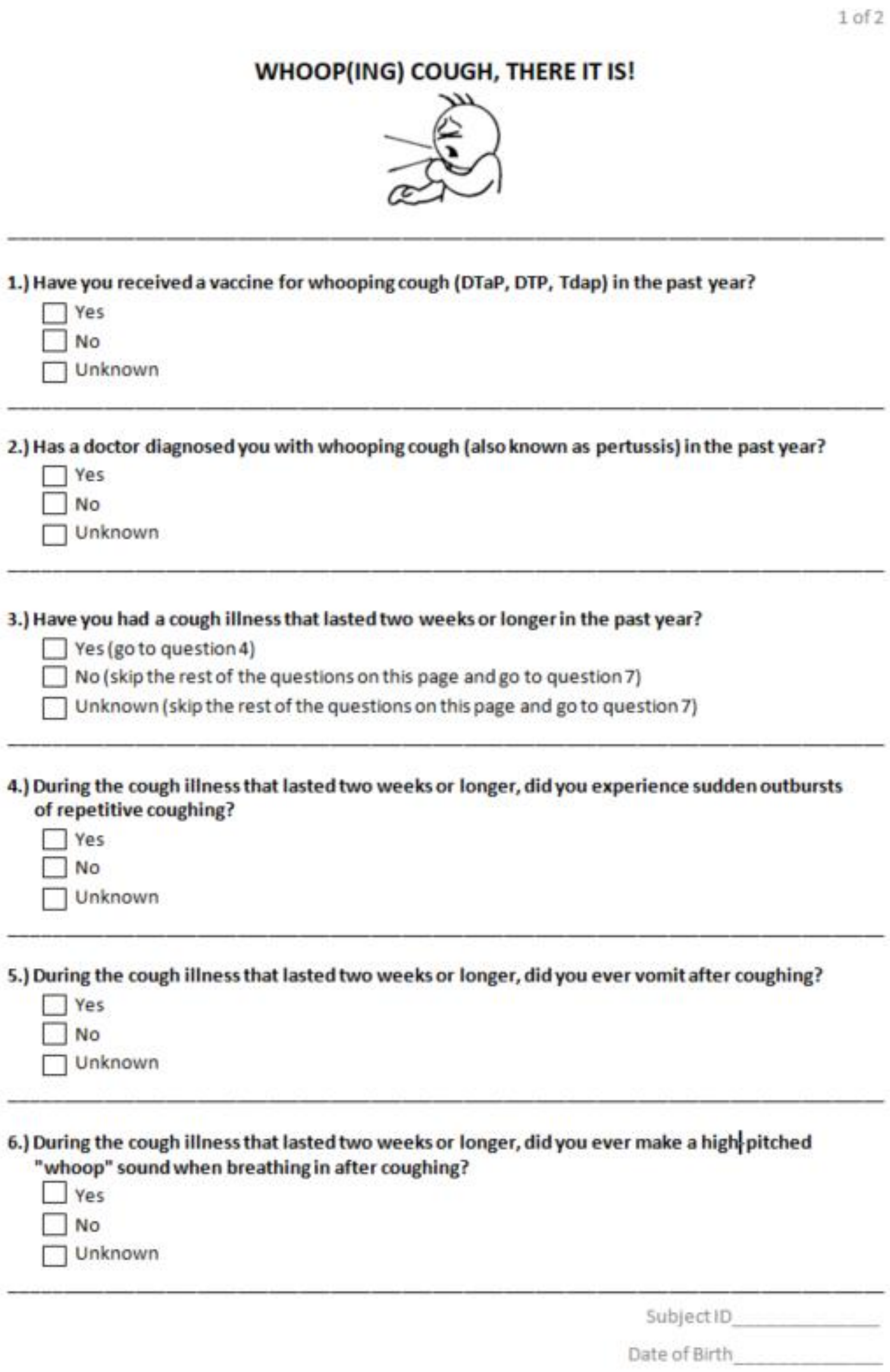
**MDH will determine testing protocol (culture and/or PCR)*

OTHER

☒ Specify: Pertussis IgG

Submitting laboratory's comments:

Aug 2016 v1.0



1 of 2

WHOOP(ING) COUGH, THERE IT IS!

1.) Have you received a vaccine for whooping cough (DTaP, DTP, Tdap) in the past year?

☐ Yes
☐ No
☐ Unknown

2.) Has a doctor diagnosed you with whooping cough (also known as pertussis) in the past year?

☐ Yes
☐ No
☐ Unknown

3.) Have you had a cough illness that lasted two weeks or longer in the past year?

☐ Yes (go to question 4)
☐ No (skip the rest of the questions on this page and go to question 7)
☐ Unknown (skip the rest of the questions on this page and go to question 7)

4.) During the cough illness that lasted two weeks or longer, did you experience sudden outbursts of repetitive coughing?

☐ Yes
☐ No
☐ Unknown

5.) During the cough illness that lasted two weeks or longer, did you ever vomit after coughing?

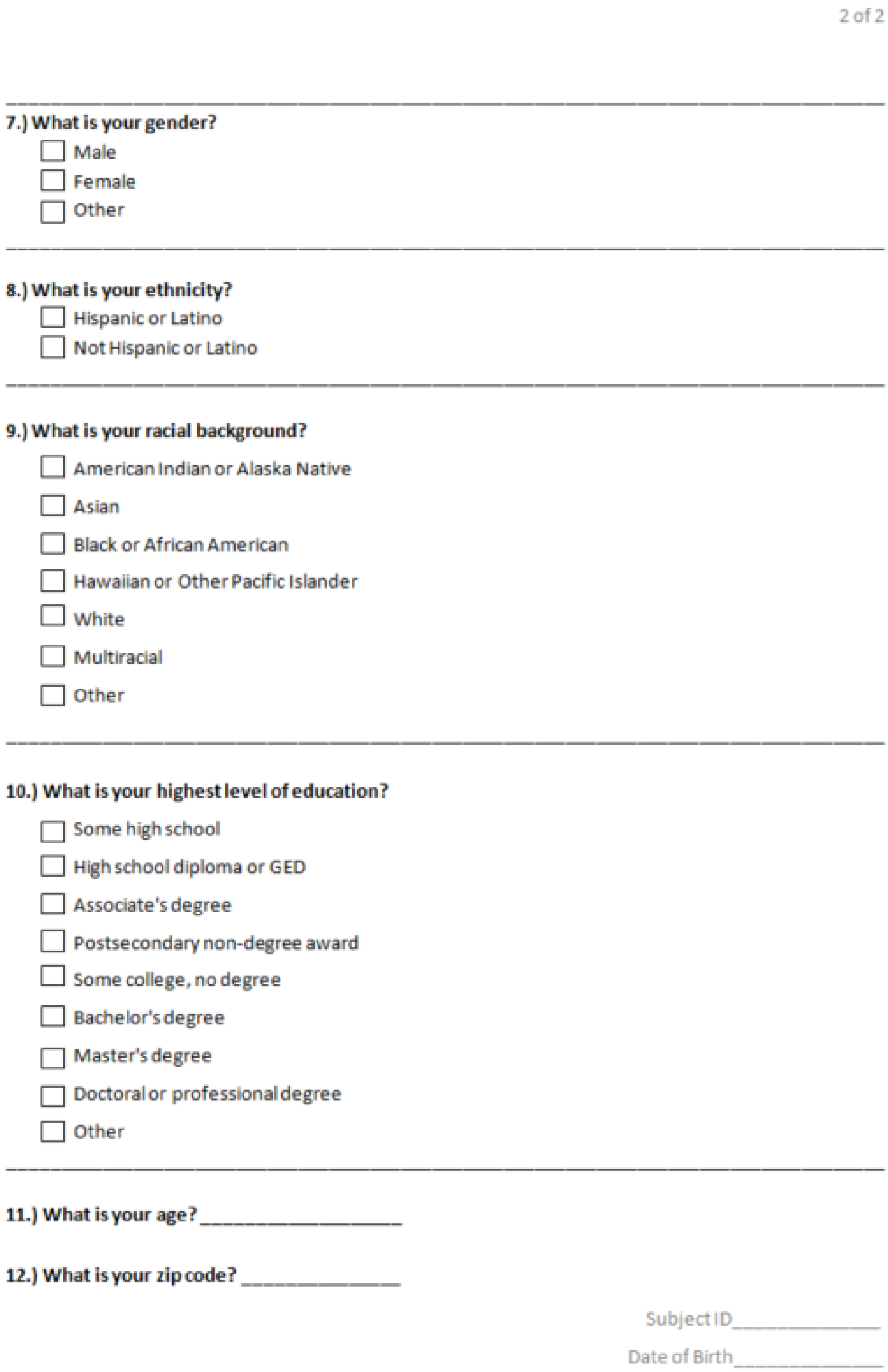
☐ Yes
☐ No
☐ Unknown

6.) During the cough illness that lasted two weeks or longer, did you ever make a high-pitched "whoop" sound when breathing in after coughing?

☐ Yes
☐ No
☐ Unknown

Subject ID_______________

Date of Birth_______________



2 of 2

7.) What is your gender?

☐ Male
☐ Female
☐ Other

8.) What is your ethnicity?

☐ Hispanic or Latino
☐ Not Hispanic or Latino

9.) What is your racial background?

☐ American Indian or Alaska Native
☐ Asian
☐ Black or African American
☐ Hawaiian or Other Pacific Islander
☐ White
☐ Multiracial
☐ Other

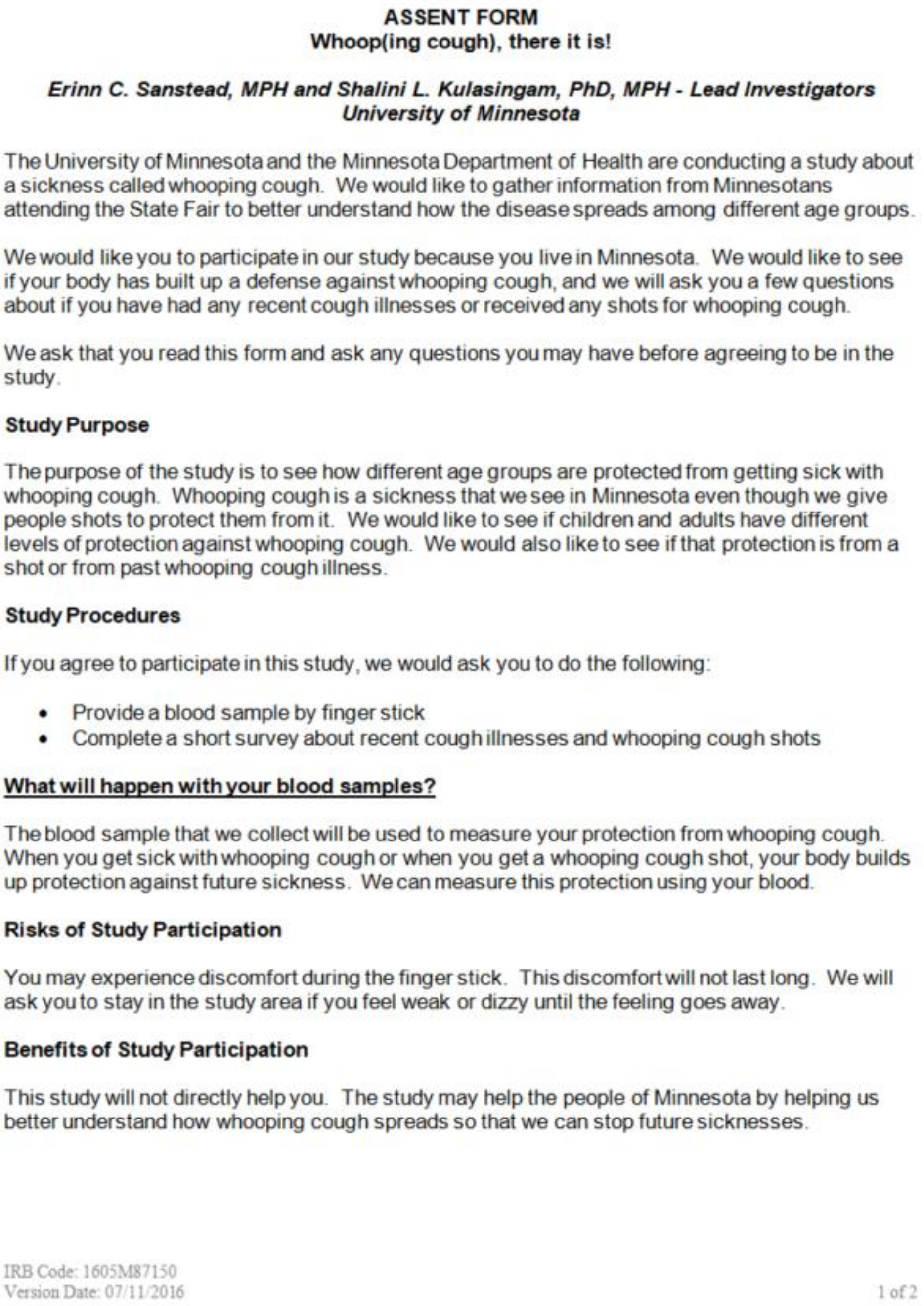
10.) What is your highest level of education?

☐ Some high school
☐ High school diploma or GED
☐ Associate's degree
☐ Postsecondary non-degree award
☐ Some college, no degree
☐ Bachelor's degree
☐ Master's degree
☐ Doctoral or professional degree
☐ Other

11.) What is your age? ___________________

12.) What is your zip code? _______________

Subject ID______________
Date of Birth______________



ASSENT FORM
Whoop(ing cough), there it is!

Erinn C. Sanstead, MPH and Shalini L. Kulasingam, PhD, MPH - Lead Investigators
University of Minnesota

The University of Minnesota and the Minnesota Department of Health are conducting a study about a sickness called whooping cough. We would like to gather information from Minnesotans attending the State Fair to better understand how the disease spreads among different age groups.

We would like you to participate in our study because you live in Minnesota. We would like to see if your body has built up a defense against whooping cough, and we will ask you a few questions about if you have had any recent cough illnesses or received any shots for whooping cough.

We ask that you read this form and ask any questions you may have before agreeing to be in the study.

Study Purpose

The purpose of the study is to see how different age groups are protected from getting sick with whooping cough. Whooping cough is a sickness that we see in Minnesota even though we give people shots to protect them from it. We would like to see if children and adults have different levels of protection against whooping cough. We would also like to see if that protection is from a shot or from past whooping cough illness.

Study Procedures

If you agree to participate in this study, we would ask you to do the following:

- Provide a blood sample by finger stick
- Complete a short survey about recent cough illnesses and whooping cough shots

What will happen with your blood samples?

The blood sample that we collect will be used to measure your protection from whooping cough. When you get sick with whooping cough or when you get a whooping cough shot, your body builds up protection against future sickness. We can measure this protection using your blood.

Risks of Study Participation

You may experience discomfort during the finger stick. This discomfort will not last long. We will ask you to stay in the study area if you feel weak or dizzy until the feeling goes away.

Benefits of Study Participation

This study will not directly help you. The study may help the people of Minnesota by helping us better understand how whooping cough spreads so that we can stop future sicknesses.

IRB Code: 1605M87150
Version Date: 07/11/2016

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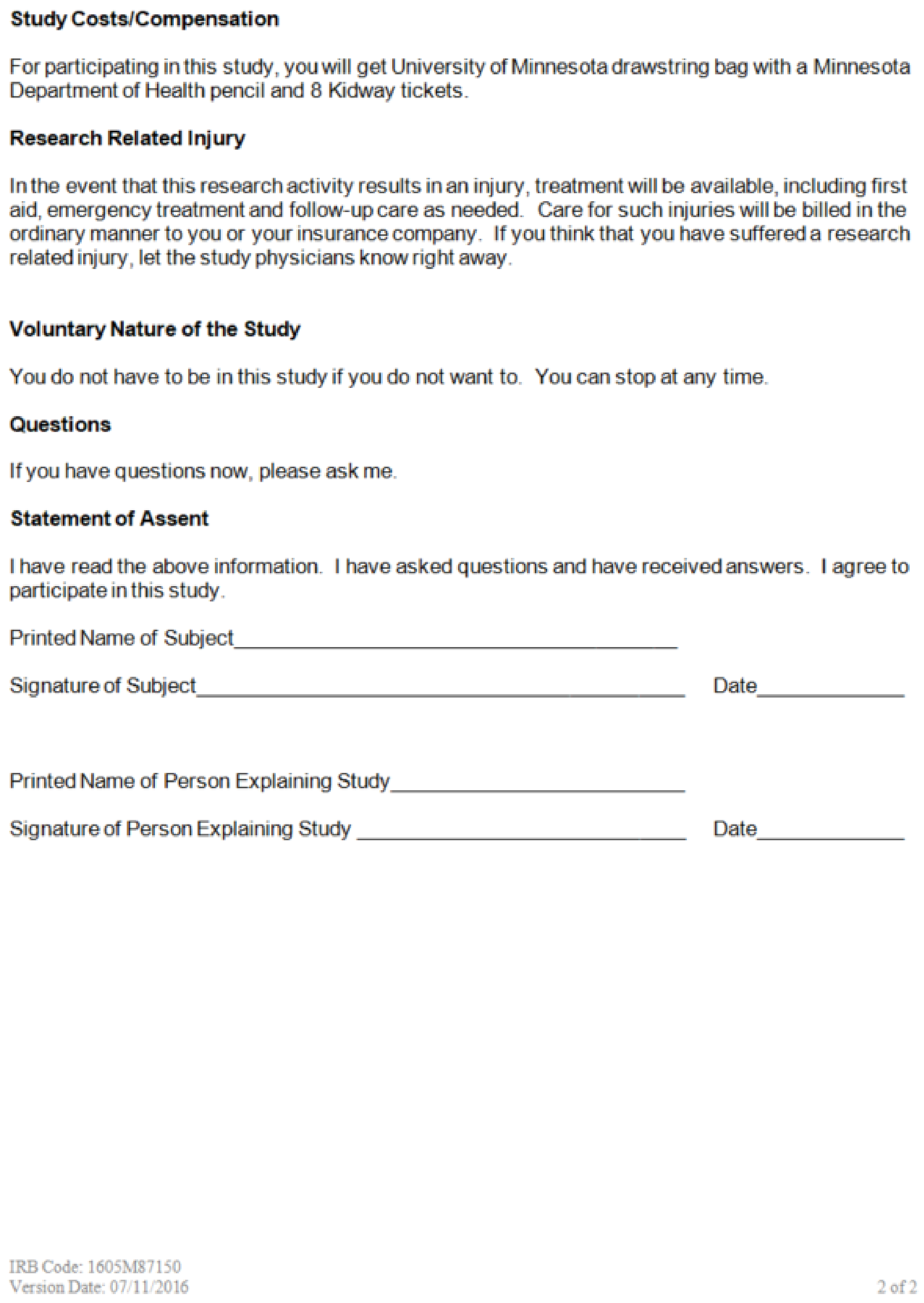

Study Costs/Compensation

For participating in this study, you will get University of Minnesota drawstring bag with a Minnesota Department of Health pencil and 8 Kidway tickets.

Research Related Injury

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to you or your insurance company. If you think that you have suffered a research related injury, let the study physicians know right away.

Voluntary Nature of the Study

You do not have to be in this study if you do not want to. You can stop at any time.

Questions

If you have questions now, please ask me.

Statement of Assent

I have read the above information. I have asked questions and have received answers. I agree to participate in this study.

Printed Name of Subject______________________________________

Signature of Subject____ Date_____________

Printed Name of Person Explaining Study_________________________

Signature of Person Explaining Study ____________________________ Date_____________

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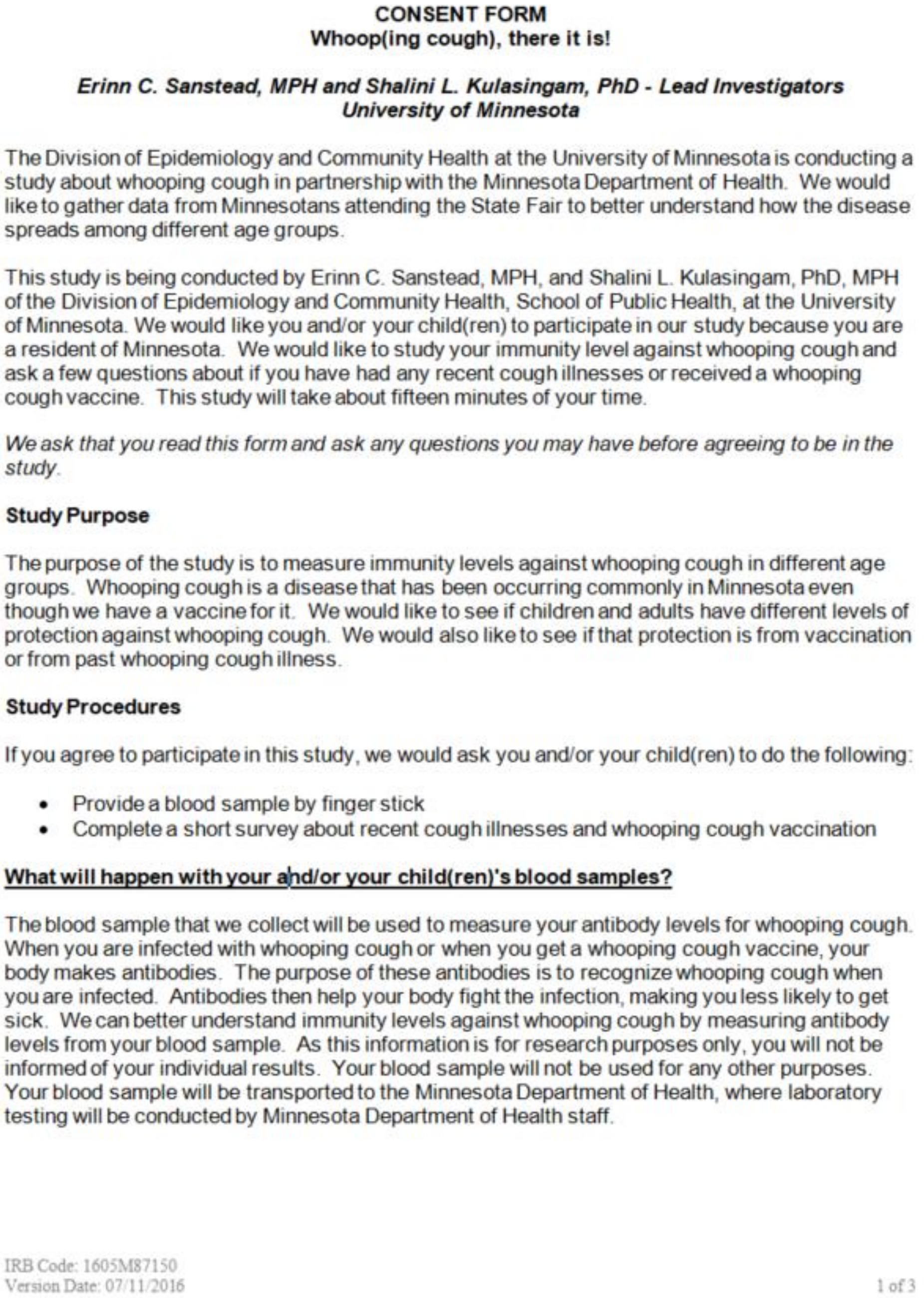

CONSENT FORM
Whoop(ing cough), there it is!

Erinn C. Sanstead, MPH and Shalini L. Kulasingam, PhD - Lead Investigators
University of Minnesota

The Division of Epidemiology and Community Health at the University of Minnesota is conducting a study about whooping cough in partnership with the Minnesota Department of Health. We would like to gather data from Minnesotans attending the State Fair to better understand how the disease spreads among different age groups.

This study is being conducted by Erinn C. Sanstead, MPH, and Shalini L. Kulasingam, PhD, MPH of the Division of Epidemiology and Community Health, School of Public Health, at the University of Minnesota. We would like you and/or your child(ren) to participate in our study because you are a resident of Minnesota. We would like to study your immunity level against whooping cough and ask a few questions about if you have had any recent cough illnesses or received a whooping cough vaccine. This study will take about fifteen minutes of your time.

We ask that you read this form and ask any questions you may have before agreeing to be in the study.

Study Purpose

The purpose of the study is to measure immunity levels against whooping cough in different age groups. Whooping cough is a disease that has been occurring commonly in Minnesota even though we have a vaccine for it. We would like to see if children and adults have different levels of protection against whooping cough. We would also like to see if that protection is from vaccination or from past whooping cough illness.

Study Procedures

If you agree to participate in this study, we would ask you and/or your child(ren) to do the following:

- Provide a blood sample by finger stick
- Complete a short survey about recent cough illnesses and whooping cough vaccination

What will happen with your and/or your child(ren)'s blood samples?

The blood sample that we collect will be used to measure your antibody levels for whooping cough. When you are infected with whooping cough or when you get a whooping cough vaccine, your body makes antibodies. The purpose of these antibodies is to recognize whooping cough when you are infected. Antibodies then help your body fight the infection, making you less likely to get sick. We can better understand immunity levels against whooping cough by measuring antibody levels from your blood sample. As this information is for research purposes only, you will not be informed of your individual results. Your blood sample will not be used for any other purposes. Your blood sample will be transported to the Minnesota Department of Health, where laboratory testing will be conducted by Minnesota Department of Health staff.

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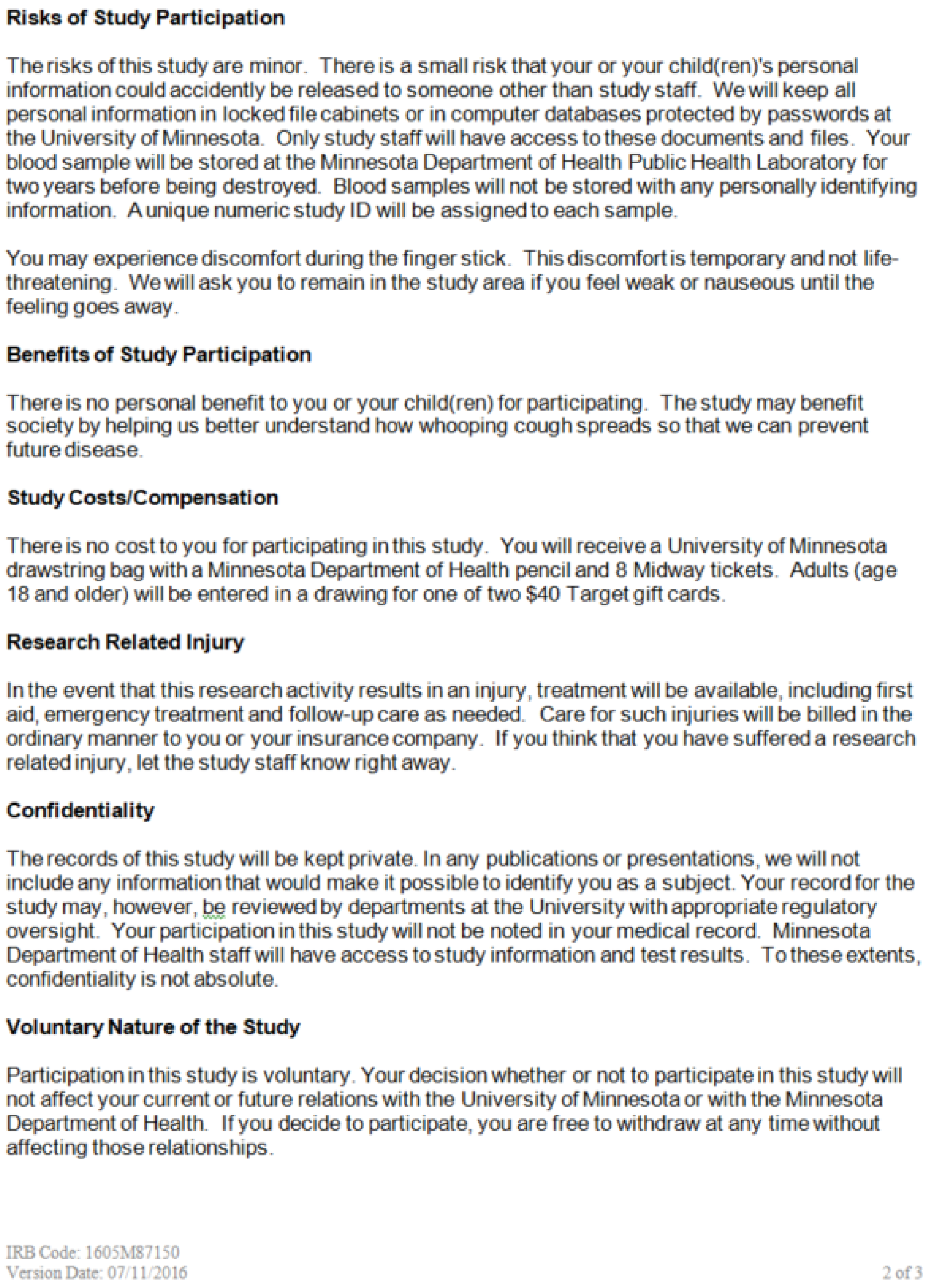


Risks of Study Participation

The risks of this study are minor. There is a small risk that your or your child(ren)'s personal information could accidently be released to someone other than study staff. We will keep all personal information in locked file cabinets or in computer databases protected by passwords at the University of Minnesota. Only study staff will have access to these documents and files. Your blood sample will be stored at the Minnesota Department of Health Public Health Laboratory for two years before being destroyed. Blood samples will not be stored with any personally identifying information. A unique numeric study ID will be assigned to each sample.

You may experience discomfort during the finger stick. This discomfort is temporary and not life-threatening. We will ask you to remain in the study area if you feel weak or nauseous until the feeling goes away.

Benefits of Study Participation

There is no personal benefit to you or your child(ren) for participating. The study may benefit society by helping us better understand how whooping cough spreads so that we can prevent future disease.

Study Costs/Compensation

There is no cost to you for participating in this study. You will receive a University of Minnesota drawstring bag with a Minnesota Department of Health pencil and 8 Midway tickets. Adults (age 18 and older) will be entered in a drawing for one of two $40 Target gift cards.

Research Related Injury

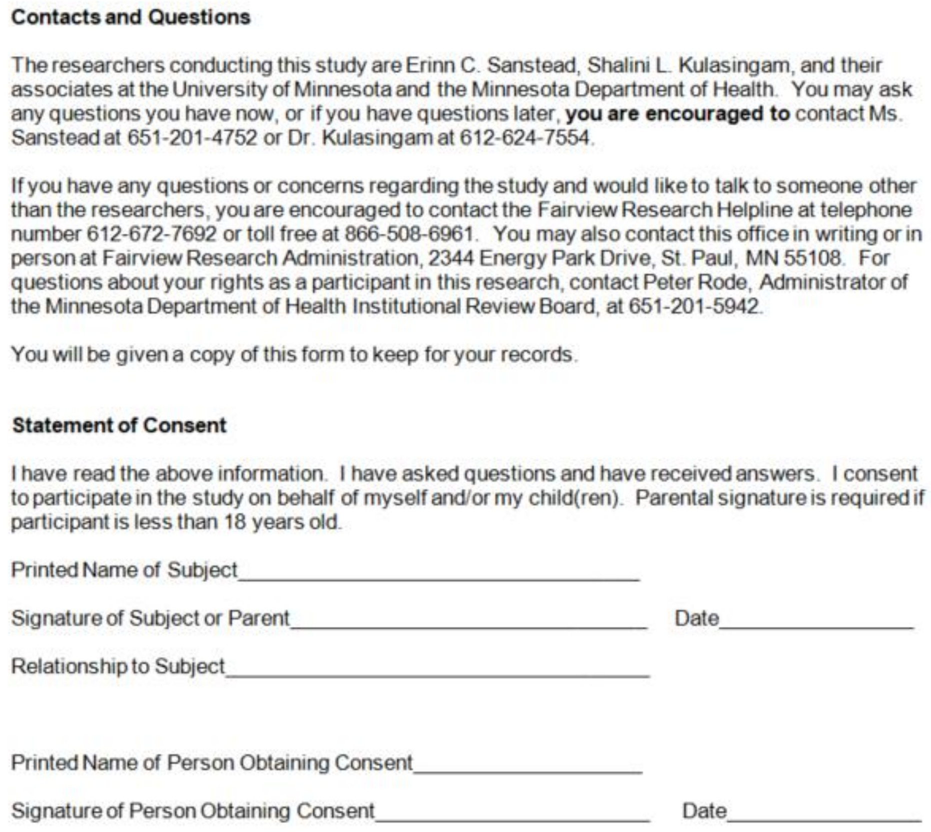
In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to you or your insurance company. If you think that you have suffered a research related injury, let the study staff know right away.

Confidentiality

The records of this study will be kept private. In any publications or presentations, we will not include any information that would make it possible to identify you as a subject. Your record for the study may, however, be reviewed by departments at the University with appropriate regulatory oversight. Your participation in this study will not be noted in your medical record. Minnesota Department of Health staff will have access to study information and test results. To these extents, confidentiality is not absolute.

Voluntary Nature of the Study

Participation in this study is voluntary. Your decision whether or not to participate in this study will not affect your current or future relations with the University of Minnesota or with the Minnesota Department of Health. If you decide to participate, you are free to withdraw at any time without affecting those relationships.



Contacts and Questions

The researchers conducting this study are Erinn C. Sanstead, Shalini L. Kulasingam, and their associates at the University of Minnesota and the Minnesota Department of Health. You may ask any questions you have now, or if you have questions later, **you are encouraged to** contact Ms. Sanstead at 651-201-4752 or Dr. Kulasingam at 612-624-7554.

If you have any questions or concerns regarding the study and would like to talk to someone other than the researchers, you are encouraged to contact the Fairview Research Helpline at telephone number 612-672-7692 or toll free at 866-508-6961. You may also contact this office in writing or in person at Fairview Research Administration, 2344 Energy Park Drive, St. Paul, MN 55108. For questions about your rights as a participant in this research, contact Peter Rode, Administrator of the Minnesota Department of Health Institutional Review Board, at 651-201-5942.

You will be given a copy of this form to keep for your records.

Statement of Consent

I have read the above information. I have asked questions and have received answers. I consent to participate in the study on behalf of myself and/or my child(ren). Parental signature is required if participant is less than 18 years old.

Printed Name of Subject______________________________

Signature of Subject or Parent__________________________ Date______________

Relationship to Subject______________________________

Printed Name of Person Obtaining Consent_______________

Signature of Person Obtaining Consent__________________ Date______________

H. APPENDIX B

$Ages\ 0\ to\ 1\ year$:

$$S_1 = n - (S_1)(B_1) - (S_1)(d_1 + a_1)$$

$$I_1 = (S_1)(B_1) - (I_1)(d_1 + a_1 + r)$$

$$R_1 = (X_1)(r) - (R_1)(d_1 + a_1 + w) + (RP_1)(b)(B_1)$$

$$V_1 = -\ (V_1)(d_1 + a_1 + v_1) + (VP_1)(b)(B_1)$$

$$SP_1 = (RP_1)(wp) + (VP_1)(vp_1) - (SP_1)(d_1 + a_1)\ - (SP_1)(rr)(B_1)$$

$$IP_1 = -(IP_1)(r) - (IP_1)(d_1 + a_1) + (SP_1)(rr)(B_1)$$

$$RP_1 = (R_1)(w) - (RP_1)(d_1 + a_1 + wp) - (RP_1)(b)(B_1)$$

$$VP_1 = (V_1)(v_1) -\ (VP_1)(d_1 + a_1 + vp_1) - (VP_1)(b)(B_1)$$

$Ages\ 2\ to\ 6\ years$:

$$S_2 = -(S_2)(B_2) - (S_2)\big(d_2 + a_2 + (f_2)(e_1)\big) + (S_1)(a_1)$$

$$I_2 = (S_2)(B_2) - (I_2)(d_2 + a_2 + r) + (I_1)(a_1)$$

$$R_2 = (X_2)(r) - (R_2)\big(d_2 + a_2 + w + (f_2)(e_1)\big) + (RP_2)(b)(B_2) + (R_1)(a_1)$$

$$V_2 = (F_2)(f_2)(e_1) -\ (V_2)(d_2 + a_2 + v_1) + (VP_2)(b)(B_2) + (V_1)(a_1)$$

$$SP_2 = (RP_2)(wp) + (VP_2)(vp_2) - (SP_2)(d_2 + a_2 + (f_2)(e_1))\ - (SP_2)(rr)(B_2) \\ + (SP_1)(a_1)$$

$$IP_2 = -(IP_2)(r) - (IP_2)(d_2 + a_2) + (SP_2)(rr)(B_2) + (IP_1)(a_1)$$

$$RP_2 = (R_2)(w) - (RP_2)\big(d_2 + a_2 + wp + (f_2)(e_1)\big) - (RP_2)(b)(B_2) + (RP_1)(a_1)$$

$$VP_2 = (V_2)(v_1) -\ (VP_2)(d_2 + a_2 + vp_1) - (VP_2)(b)(B_2) + (VP_1)(a_1)$$

$Ages\ 7\ to\ 10\ years$:

$$S_3 = -(S_3)(B_3) - (S_3)(d_3 + a_3) + (S_2)(a_2)$$

$$I_3 = (S_3)(B_3) - (I_3)(d_3 + a_3 + r) + (I_2)(a_2)$$

$$R_3 = (X_3)(r) - (R_3)(d_3 + a_3 + w) + (RP_3)(b)(B_3) + (R_2)(a_2)$$

$$V_3 = -\ (V_3)(d_3 + a_3 + v_1) + (VP_3)(b)(B_3) + (V_2)(a_2)$$

$$SP_3 = (RP_3)(wp) + (VP_3)(vp_1) - (SP_3)(d_3 + a_3)\ - (SP_3)(rr)(B_3) + (SP_2)(a_2)$$

$$IP_3 = -(IP_3)(r) - (IP_3)(d_3 + a_3) + (SP_3)(rr)(B_3) + (IP_2)(a_2)$$

$$RP_3 = (R_3)(w) - (RP_3)(d_3 + a_3 + wp) - (RP_3)(b)(B_3) + (RP_2)(a_2)$$

$$VP_3 = (V_3)(v_1) - \ (VP_3)(d_3 + a_3 + vp_1) - (VP_3)(b)(B_3) + (VP_2)(a_2)$$

$Ages\ 11\ to\ 12\ years$:

$$S_4 = -(S_4)(B_4) - (S_4)\big(d_4 + a_4 + (f_4)(e_2)\big) + (S_3)(a_3)$$

$$I_4 = (S_4)(B_4) - (I_4)(d_4 + a_4 + r) + (I_3)(a_3)$$

$$R_4 = (X_4)(r) - (R_4)\big(d_4 + a_4 + w + (f_4)(e_2)\big) + (RP_4)(b)(B_4) + (R_3)(a_3)$$

$$V_4 = (F_4)(f_4)(e_2) - \ (V_4)(d_4 + a_4 + v_2) + (VP_4)(b)(B_4) + (V_3)(a_3)$$

$$\begin{aligned} SP_4 = {} & (RP_4)(wp) + (VP_4)(vp_2) - (SP_4)(d_4 + a_4 + (f_4)(e_2)) \ - (SP_4)(rr)(B_4) \\ & + (SP_3)(a_3) \end{aligned}$$

$$IP_4 = -(IP_4)(r) - (IP_4)(d_4 + a_4) + (SP_4)(rr)(B_4) + (IP_3)(a_3)$$

$$RP_4 = (R_4)(w) - (RP_4)\big(d_4 + a_4 + wp + (f_4)(e_2)\big) - (RP_4)(b)(B_4) + (RP_3)(a_3)$$

$$VP_4 = (V_4)(v_2) - \ (VP_4)(d_4 + a_4 + vp_2) - (VP_4)(b)(B_4) + (VP_3)(a_3)$$

$Ages\ 13\ to\ 21\ years$:

$$S_5 = -(S_5)(B_5) - (S_5)(d_5 + a_5) + (S_4)(a_4)$$

$$I_5 = (S_5)(B_5) - (I_5)(d_5 + a_5 + r) + (I_4)(a_4)$$

$$R_5 = (X_5)(r) - (R_5)(d_5 + a_5 + w) + (RP_5)(b)(B_5) + (R_4)(a_4)$$

$$V_5 = -\ (V_5)(d_5 + a_5 + v_2) + (VP_5)(b)(B_5) + (V_4)(a_4)$$

$$SP_5 = (RP_5)(wp) + (VP_5)(vp_2) - (SP_5)(d_5 + a_5) \ - (SP_5)(rr)(B_5) + (SP_4)(a_4)$$

$$IP_5 = -(IP_5)(r) - (IP_5)(d_5 + a_5) + (SP_5)(rr)(B_5) + (IP_4)(a_4)$$

$$RP_5 = (R_5)(w) - (RP_5)(d_5 + a_5 + wp) - (RP_5)(b)(B_5) + (RP_4)(a_4)$$

$$VP_5 = (V_5)(v_1) - \ (VP_5)(d_5 + a_5 + vp_1) - (VP_5)(b)(B_5) + (VP_4)(a_4)$$

$Ages\ 22\ to\ 64\ years$:

$$S_6 = -(S_6)(B_6) - (S_6)\big(d_6 + a_6 + (f_6)(e_2)\big) + (S_5)(a_5)$$

$$I_6 = (S_6)(B_6) - (I_6)(d_6 + a_6 + r) + (I_5)(a_5)$$

$$R_6 = (X_6)(r) - (R_6)\big(d_6 + a_6 + w + (f_6)(e_2)\big) + (RP_6)(b)(B_6) + (R_5)(a_5)$$

$$V_6 = (F_6)(f_6)(e_2) - \ (V_6)(d_6 + a_6 + v_2) + (VP_6)(b)(B_6) + (V_5)(a_5)$$

$$SP_6 = (RP_6)(wp) + (VP_6)(vp_2) - (SP_6)(d_6 + a_6 + (f_6)(e_2)) - (SP_6)(rr)(B_6) + (SP_5)(a_5)$$

$$IP_6 = -(IP_6)(r) - (IP_6)(d_6 + a_6) + (SP_6)(rr)(B_6) + (IP_5)(a_5)$$

$$RP_6 = (R_6)(w) - (RP_6)\big(d_6 + a_6 + wp + (f_6)(e_2)\big) - (RP_6)(b)(B_6) + (RP_5)(a_5)$$

$$VP_6 = (V_6)(v_2) - (VP_6)(d_6 + a_6 + vp_2) - (VP_6)(b)(B_6) + (VP_5)(a_5)$$

$Ages\ 65\ to\ 99\ years$:

$$S_7 = -(S_7)(B_7) - (S_7)\big(d_7 + a_7 + (f_7)(e_2)\big) + (S_6)(a_6)$$

$$I_7 = (S_7)(B_7) - (I_7)(d_7 + a_7 + r) + (I_6)(a_6)$$

$$R_7 = (X_7)(r) - (R_7)\big(d_7 + a_7 + w + (f_7)(e_2)\big) + (RP_7)(b)(B_7) + (R_6)(a_6)$$

$$V_7 = (F_7)(f_7)(e_2) - (V_7)(d_7 + a_7 + v_2) + (VP_7)(b)(B_7) + (V_6)(a_6)$$

$$SP_7 = (RP_7)(wp) + (VP_7)(vp_2) - (SP_7)(d_7 + a_7 + (f_7)(e_2)) - (SP_7)(rr)(B_7) + (SP_6)(a_6)$$

$$IP_7 = -(IP_7)(r) - (IP_7)(d_7 + a_7) + (SP_7)(rr)(B_7) + (IP_6)(a_6)$$

$$RP_7 = (R_7)(w) - (RP_7)\big(d_7 + a_7 + wp + (f_7)(e_2)\big) - (RP_7)(b)(B_7) + (RP_6)(a_6)$$

$$VP_7 = (V_7)(v_2) - (VP_7)(d_7 + a_7 + vp_2) - (VP_7)(b)(B_7) + (VP_6)(a_6)$$

$Ages\ 100\ years$:

$$S_8 = (S_7)(a_7) - (S_8)(d_8)$$

$$I_8 = (I_7)(a_7) - (I_8)(d_8)$$

$$R_8 = (R_7)(a_7) - (R_8)(d_8)$$

$$V_8 = (V_7)(a_7) - (V_8)(d_8)$$

$$SP_8 = (SP_7)(a_7) - (SP_8)(d_8)$$

$$IP_8 = (IP_7)(a_7) - (IP_8)(d_8)$$

$$RP_8 = (RP_7)(a_7) - (RP_8)(d_8)$$

$$VP_8 = (VP_7)(a_7) - (VP_8)(d_8)$$

$Parameters$:

$S_i = susceptible\ (naive)\ fraction\ of\ population\ in\ age\ group\ i$

$I_i = infectious\ (naive)\ fraction\ of\ population\ in\ age\ group\ i$

$R_i = vaccine\ immune\ (full)\ fraction\ of\ population\ in\ age\ group\ i$

$W_i = naturally\ immune\ (full) fraction\ of\ population\ in\ age\ group\ i$

$SP_i = susceptible\ (primed)\ fraction\ of\ population\ in\ age\ group\ i$

$IP_i = infectious\ (primed)\ fraction\ of\ population\ in\ age\ group\ i$

$RP_i = vaccine\ immune\ (waning)\ fraction\ of\ population\ in\ age\ group\ i$

$WP_i = naturally\ immune\ (waning) fraction\ of\ population\ in\ age\ group\ i$

$X_i = (I_i + IP_i)\ in\ age\ group\ i$

$F_i = (S_i + R_i + SP_i + RP_i)\ in\ age\ group\ i$

$n = birth\ rate$

$i = transmission\ rate\ (naive)$

$ip = transmission\ rate\ (primed)$

$rr = relative\ risk\ of\ infection\ with\ primed\ immune\ system$

$r = rate\ of\ recovery\ from\ infection$

$c_{i,j} = number\ of\ contacts\ age\ group\ i\ has\ with\ age\ group\ j$

$$B_i = \sum_{i=1}^{N} (i)(I_i)\left(c_{i,j}\right) + (ip)(IP_1)(c_{i,j})$$

$f_i = fraction\ of\ vaccinated\ individuals\ in\ age\ group\ i$

$e_i = efficacy\ of\ DTaP$

$e_2 = efficacy\ of\ TdaP$

$v_1 = rate\ of\ transition\ from\ full\ DTaP\ immunity$

$v_2 = rate\ of\ transition\ from\ full\ Tdap\ immunity$

$vp_1 = rate\ of\ transition\ from\ waning\ DTaP\ immunity$

$vp_2 = rate\ of\ transition\ from\ waning\ Tdap\ immunity$

$w = rate\ of\ transition\ from\ full\ natural\ immunity$

$wp = rate\ of\ transition\ from\ waning\ natural\ immunity$

$b = boosting\ coefficient$

$a_i = rate\ of\ aging\ to\ age\ group\ (i+1)\ in\ age\ group\ i$

$d = mortality\ rate\ in\ age\ group\ i$