Surveillance and epidemiology of the pertussis resurgence in the United States, 1990-2010

by

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Dedication

To Dr. Ching-Hwa Chi whose support of vaccination instilled a life-long appreciation for the preventive power of vaccines.

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This is a presentation not of my work, but of my understanding of the work of thousands: the physicians who examined patients, lab technicians who conducted testing, the state and local health department workers (most especially in Michigan) who collect and share data, and each pertussis case. To all of you, thank you. Special recognition of Sarah D., Kay L., and Meghan M. who shared their experiences with me, reminding me of the reality of pertussis in its strenuous and unending nature, and who kept the goal of prevention forefront in my mind throughout this dissertation process.

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Abstract

After a period of successful control, pertussis or whooping cough has, in the past decade, had large nationwide epidemics with a new adolescent risk-group. The surveillance confirmation criteria for pertussis included DNA testing by polymerase chain reaction (PCR) beginning in 1997, which is more sensitive than the culture gold-standard laboratory test, especially in adolescents and adults. This dissertation uses surveillance date from the state of Michigan to retrospectively assess the internal validity of reported pertussis surveillance cases. Data from the United States Centers for Disease Control and Prevention evaluated characteristics predictive of high incidence counties.

Michigan pertussis records (2000 - 2010) were evaluated according to the clinical case definition; a third included positive PCR results. Confirmed and probable cases comprised 69.4% of the data, and another 14% could have been confirmed had an adequate cough length been reported. An odds of insufficient cough duration was reported among PCR positive cases, 2.9 (95% CI: 1.57 - 2.79) times greater than in those without PCR positive results. Similar findings were observed for cases confirmed by culture and epidemiologic linkage. These findings show confirmatory criteria are frequently given precedence over the clinical case definition. We recommend that the case definition be more internally consistent with regard to the role of positive laboratory results. This dissertation illustrates that the current pertussis surveillance case definition has high internal validity. Surveillance cases need to be held to more stringent criteria for verification than for medical diagnosis, since it is the basis for allocation of time and resources for case and outbreak investigation.

County-level regression analysis of socio-structural risk-factors in national United States pertussis data (1990 - 2008), indicated that denser counties with a higher prevalence of healthcare barriers and poor child health were associated with decreased pertussis incidence. We observed an element of disease risk associated with county-level factors. Our findings could be explained either by low rates of disease or a less developed

surveillance structure. Further research to identify the county elements driving the risk differential is needed to tailor both vaccination and outbreak response efforts to local needs.

Chapter 1
Background of Pertussis Surveillance and Control in the United States

1.1. Introduction

Pertussis, commonly referred to as whooping cough, is one of the traditional childhood diseases preventable by vaccination. The illness was first described by Guillaume de Baillou, in 1578, as a highly fatal fever primarily affecting infants between four and ten months of age, producing severe bursts of coughing every four to five hours.[1] The causative bacterium, *Bordetella pertussis,* was first identified by Bordet and Genou in 1906.[2] The initial attempts at making vaccines had inconsistent results until Danish researchers in the late 1920s used whole, killed *B. pertussis* bacteria in the innoculum.[3] Large scale field trials were run between 1946 and 1948, and found that while there was a range of vaccine efficacy (61- 89%) the vaccine conferred considerable protection, with an estimated protective risk ratio of 0.22(0.18-.26).[3] The subsequent nationwide vaccination programs in United States were very effective in reducing the annual number of cases to less than 5,000 annually between 1968 and 1992.[4] Since routine vaccination began, mortality nationwide has declined dramatically and still remains well below pre-vaccination levels, with less than 50 annual pertussis-related deaths since 1966.[4]

The past twenty years have seen a resurgence of pertussis, resulting in endemic transmission with cyclic epidemics. The changing perception of the importance of pertussis is most clearly illustrated in the development of the pertussis objectives of the United States' Healthy People goals. These objectives, developed by the Centers for Disease Control and Prevention (CDC) and overseen by the Public Health Service, provide quantitative health objectives with ten year targets to improve the health of all people in the United States.[5] These goals are divided into topical areas, including an immunization and infectious diseases portion that specifies targets for both pertussis disease reduction and immunization coverage.[5-7] The original Healthy People 2000 goals for pertussis, established in 1988 when there were 3,450 annual cases, ambitiously targeted a low of 1,000 cases nationwide.[5] In 1999 there were 7,298 annual cases.[5] The

disease reduction goals for Healthy People 2010 narrowed in scope, focusing on children less than 7 years of age, in whom there were 3,417 cases, and revised a 2010 target of fewer than 2,000 cases.[6] However, the incidence of pertussis continued to rise during the first decade of the 21st century, with 4,166 cases less than seven years old reported in 2008.[6]

When creating the current 2020 infectious disease goals, pertussis control was operationalized in two high-risk populations, infants (< 1 year) with a target of less than 2,500 annual confirmed cases and adolescents (11 - 18 years) with less than 2,000 confirmed cases.[7] The current disease reporting based on a 4-year average from 2006-2010, shows just over 2,700 cases in infants and 3,300 cases in adolescents.[7]

The recalibration of these disease reduction goals illustrates the adjustment to the changing epidemiology of pertussis throughout the period from 1988 to the present. First, it recognizes that the number of pertussis cases continually increased well beyond the incidence goals that had been set. Secondly, it highlights the emergence of a new risk group, adolescents. Thirdly, the reclassification of the primary target population from the entire population to infants reflects that fact that greater incidence and severity of infection chiefly occur among the very young. The current 2020 infant target of less than 2,500 confirmed cases (62.5 cases /100,000 infants) is not necessarily a marker of disease reduction, but rather an acceptance of the difficulties of disease control, as the 2008 baseline was 2,777 reported infant cases. These changes reflect an unprecedented resurgence of pertussis, with a slightly older epidemiologic profile, having increased incidence among those 11-18 years old, and to a lesser extent adults.[8] This increase occurred most clearly during the 1990s but the foundational increase in cases can be traced back to the early 1980s.[9]

A component of the growing incidence may have resulted from better diagnostics with the faster and more sensitive polymerase chain reaction (PCR) test, genetic drift of the bacteria away from vaccine strains, lower vaccination rates and the lack of natural boosting of immunity in the presence of waning immunity from both disease and vaccination. In response to the increased incidence, booster immunizations were recommended for adolescents and adults in 2005.[8,10-12] This resurgence is most clearly

seen among infants, among whom 4,994 confirmed cases were reported in the 2012 calendar year (126.7 per 100,000 infants).[13] The year 2012 had many statewide outbreaks and may over represent infant cases, however a five-year average from 2008-2012 at 3,546 cases is still well above the targeted control goals.[14] Both the annual case counts and incidence estimates suggest that the transmission of pertussis is continuing to increase, as measured by confirmed disease in the most vulnerable portion of the population.

1.2. Surveillance

CDC statistics and recommendations are based on data collected via surveillance. Surveillance, the foundation of public health, is "the ongoing collection, analysis, and interpretation of outcome specific data for use in planning, implementation, and evaluation of public health practice."[15] The collection of such data is a proactive process, whereby the diseases and conditions are determined to be significant enough to warrant data collection. The analysis and interpretation of these data depend on the surveillance system objectives, which can be manifold. Since public health intends to protect and improve the health of populations, surveillance findings can identify risk factors, outbreaks, and changes in reporting or disease presentation. Ideally, such results will enhance prevention when they are shared with the public, and with those who work to improve the public's health, ranging from physicians at the micro-level to policy makers at the macro-level.

Disease surveillance systems are used to ensure a state of awareness and preparedness to specific, recognized health threats. These objectives include programmatic evaluation, risk group determination, and spatial distribution to better understand the epidemiology of the specified diseases. To be effective, surveillance systems require a formalized health system, a disease classification system, and a reliable means of diagnosis. The foundation of a surveillance system is derived of two fundamental components; the conditions that are reported, and the structural framework of the reporting process.

Continuing pertussis surveillance is justified because of its preventability, the resurgence of cases, the severity of illness in infants, and the extended morbidity in adults.

1.2.1. Reporting Process

The Michigan Public Health Code first formalized surveillance reporting in 1883, which required the reporting of specified communicable disease by physicians to the state health

department.[16] Public health legislative powers are retained at the state level, where communicable disease incidents are passively reported to state public health departments, then voluntarily shared with the federal CDC.[17] The data are collected to inform "the planning and evaluation of disease prevention and control programs, [and] in the assurance of appropriate medical therapy, and in the detection of common-source outbreaks."[14,16]

In the US, diseases are most frequently reported by private physicians and hospitals at the local city or county level, before being sent to that state's health department. Notifiable conditions are voluntarily reported to the CDC National Notifiable Diseases Surveillance System (NNDSS) by the health departments of states and territories.[17] As reports are received, the health departments review cases to examine larger trends and potential outbreaks. This should facilitate proper disease identification and follow-up of cases.[14] Additionally, automated reporting of laboratory test results is being incorporated at the state level to improve specific disease identification.[18-20] This is being done at the state level rather than in local health departments, due to the technical requirements of the process as well as the expertise needed to interpret the high volume of reports.

1.2.2. Notifiable Disease

Which conditions are determined to be notifiable, is based on various criteria which include: incidence, severity, communicability, preventability and public impact.[17] The approval of the Council for State and Territorial Epidemiologists (CSTE), comprised of epidemiologists working in state and local levels of government, is required for any addition to or alteration of the notifiable diseases list put forth by the CDC. Similar criteria are adopted by state health boards to determine the state-specific regulated list of reportable conditions; these generally include the federally notifiable diseases.

The goal of having specified notifiable conditions is to produce rapid disclosure to health authorities, which can then be capitalized on to minimize impact of diseases with high mortality or severe outcomes by preventing acquisition or speeding up identification of the causal agent to mitigate consequences. General classes of notifiable diseases are categorized by mode of transmission and include diseases: food or water borne, sexually transmitted, zoonotic or vector-borne, respiratory, blood borne and other. While the

response to a surveillance event is not part of the surveillance process per se, it should be the natural consequence of accurate and timely reporting of notifiable conditions and subsequently result in a qualified assessment and communication of the findings.

To ensure the validity and comparability of notifiable disease reporting, the case definition includes a standardized set of epidemiologic, clinical and laboratory criteria for both initial reporting and case verification. The case definitions are developed in collaboration between the CSTE and the CDC. Initial reporting guidelines indicate individuals with high probability of the disease in question. Disease-specific, case-validation criteria are intended to confirm the condition.

1.2.3. Pertussis, the Illness

Pertussis is the result of infection with the bacterium *Bordetella pertussis*. The infection is localized to the upper portion of the respiratory system, where these bacteria attach to the cilia and excretes a spectrum of toxins. This immobilizes and breaks the cilia, and impedes the clearing of the airways resulting in a prolonged cough illness. Infection has three stages, catarrhal, paroxysmal and convalescent. Individuals are communicable during the catarrhal period until two weeks after the onset of cough.[21] The incubation period of pertussis is a seven to ten days, from exposure to the onset of symptoms.[12] The catarrhal stage has a mild onset and presents as congestion with a low grade fever similar to other mild respiratory illnesses.[21] This stage usually lasts one to two weeks before coughing starts.[21,22] The patients generally cough at night, often in bursts or paroxysms that are so severe that the individual cannot breathe until the coughing has passed; often resulting in the inspiratory whoop from which the colloquial name whooping cough is derived. These bursts of coughing can also result in post-tussive vomiting. The paroxysmal stage lasts 1-6 weeks.[21-23] The individual generally feels fine between bouts of coughing.[21,23] There is a wide range in disease severity, vaccinated individuals and those who are older are less likely to have cough attributes (paroxysms, whooping or post-tussive vomiting) and tend to have fewer paroxysms per day when they do occur. This stage is clinically most severe in young infants, as they can turn blue from a lack of oxygen during the paroxysms, and have high hospitalization rates.[21] This type of cough also occurs in a variety of viral infections but tends to be mild and of short duration. During the convalescent stage the

frequency and severity of the paroxysms decreases. This stage can be as short as two weeks but can also last for months.[21,22]

Diagnosis of pertussis can be made on purely clinical characteristics, according the CSTE, if the individual has coughed for more than two weeks accompanied by whooping, severe bursts of cough, or vomiting after coughing. Laboratory confirmation of disease can identify the bacterium through culture or amplification of the bacterial DNA via PCR.[24,25] PCR tests were shown to have an increased sensitivity over culture testing improving the diagnostic sensitivity in adolescent and adult rates.[23,24,26-28] Pertussis can also be diagnosed through paired serology which looks for a significant fourfold rise in titer between samples taken at an interval of at least two weeks.[28] This delay in acquiring the second sample is problematic for public health purposes, not only because it requires a second healthcare visit, but also because an early diagnosis is critical for outbreak management. Therefore, research has been done on single serum samples to determine the normal level of IgG antibodies against pertussis toxin in healthy adults to be 99% below 20μg/mL.[27] These testing protocols were developed using healthy adults with no history of pertussis in the previous year, at a time when vaccination with the whole cell pertussis vaccine (DTP) was limited to children. The state of Massachusetts has incorporated this serology testing as a case confirmatory criterion for those ≥ 11years, but only when the testing is conducted at the Hinton State Laboratory Institute.[27,29] Since the serology testing cannot differentiate between antibodies from natural infection and immunization, this single serology test is not interpretable for three years after the receipt of a vaccine.[29]

The peak sensitivity is test specific: culture (week 1) PCR (weeks 1 & 2), serology (weeks 2+).[28,29] The sensitivity of both culture and PCR decreases significantly after the second week of cough and with age.[28] Though the PCR is more sensitive than culture, and serology more so than PCR in older age groups.[28] With the inclusion of PCR testing in the case definition in 1997, a portion of the increase in reported pertussis incidence may be attributed to the greater sensitivity of PCR testing in older populations over the previously accepted culture.[24,25]

Pertussis is treated with macrolide antibiotics commonly, erythromycin, azithromycin and clarithromycin.[12,30] Erythromycin was identified in the 1960s as the most effective

antibiotic; it is usually prescribed as 4 divided daily doses over 14 days.[12,31] This antibiotic is known to have low completion rates in part due to the length of the prescription and partly because of common gastrointestinal side-effects.[32] Azithromycin (prescribed 2x on day 1 and daily on days 2-5) and clarithromycin (prescribed twice a day for 7 days) both have shorter course of antibiotics, with fewer pills, are better tolerated and found to be equally effective as erythromycin.[30,32] These characteristics results in better compliance among pertussis cases.[33] Where allergies to macrolide antibiotics exist, trimethoprim-sulfamethoxazole (TMP--SMZ) is the recommended alternative.[12] The purpose of antibiotic treatment is to both kill the bacteria in infected individuals, and limit the period of transmission to others. It is not clear whether the final cough duration is improved. Macrolide therapy is also recommended for post-exposure prophylaxis to asymptomatic household contacts up to 21 days after cough onset in the primary individual, to decrease the probability of infection.

A recent case report of macrolide-resistant pertussis has been identified; it is possible that this bacterial type will become more frequent given the high use of macrolides for treatment, and prophylaxis.[34] This provides additional justification for promoting the use of culture testing for suspected cases, as having sample allows for further testing, including antibiotic sensitivity and variations in gene expressions.

1.3. Epidemiology

1.3.1. Traditional (before 1980 as disease declined)

Pertussis is diagnosed most frequently in very young children, usually under the age of one year, who typically present with more severe disease. Vaccination of these young children against pertussis was added to the recommended childhood vaccine schedule in the mid 1940s after a series of field and randomized control trials.[21] As a result, infection in older children and adults, most of whom have a primed immune system either via earlier infection or vaccination, have mitigated symptoms and exhibit a shorter duration of disease with less severe coughing. [35,36] Evidence of this immune response has been substantiated with bacterial load counts per nasopharyngeal swab where highest counts were found in infants (1.1x106 cells), followed by children ($2.1x10^4$ cells), and then adults (320 cells).[37] As pertussis is primarily diagnosed based on clinical presentation, these

older cases are less likely to be identified. Disease in adults was infrequent at the beginning of the twentieth century, when cases over 15 years of age accounted for 2.5% of the reported cases.[38] Re-infection has been reported showing that as many as 47% of children are infected by pertussis under outbreak conditions within five years of completing the initial vaccination series, three doses of the whole cell vaccine, suggesting that immunity is not life-long.[35,36,39]

1.3.2. Resurgence (1980 to present)

After having experienced the benefits of routine vaccination, pertussis is the only vaccine preventable disease (VPD) to have undergone a return to nationwide, endemic transmission. The increasing incidence of pertussis could be detected in the 1980s when the overall case count was still very low and diagnosis was still based on culture techniques (Figure 1.1).[9,40] This represents a true increase of disease as the incidence of pertussis in infants, which experience the most severe disease, has increased from a 1980s average incidence of 34.2 to 70.9 per 100,000 infants in 2011, a non-epidemic year.[14,41] Infants still face the heaviest disease burden and continue to exhibit the characteristic clinical presentation and high hospitalization rates.

This increase is evident nationally over the timeframe of the study, increasing from a 1990 average pertussis incidence of 1.7 to 6.1 per 100,000 persons in 2011, a year when few outbreaks were reported. [8,14] By 2009, adults (≥19 years) comprised 25.2% of the reported cases.[8] The percent of individuals infected in outbreak conditions 5 or more years after completing the primary acellular vaccination series (5 doses), is 28.8%.[42]

1.4. Prevention through immunization

1.4.1. Challenges of the Whole-cell Vaccine

Pertussis disease can be prevented or mitigated in individuals who receive routine childhood immunization. In the United States, the primary vaccination schedule is most frequently given using a combination of antigens against Diphtheria/Tetanus/Pertussis (DTP). The original DTP formulation contained inactivated cells of whole pertussis bacteria this was used in some form until the late 1990s, there were differences according to manufacturer and adjuvants. Because pertussis is toxin mediated and the vaccine contained the entire bacterium, the natural immune response results in transitory reactions

in as many as half of the children including pain and redness at the injection site.[43] Disease was effectively controlled reaching an all-time low in 1976, after which parental concern focused on the safety of the vaccine rather than the risks of infection.[44]

Side effects of vaccination have included convulsions and hyporesponsive episodes have also been reported, without subsequent neurological problems.[43] Due to the serious nature of these events there has been widespread negative publicity resulting from a number of reports noting encephalopathy following vaccination. As a point of reference the background rate of a first neurological episode within the five days following a notable event as been estimated to be 1 in 15,000 among children 3-6 months old.[43] There are three large epidemiologic studies that should be considered. The largest is the National Childhood Encephalopathy Study (NCES) a case-control study in the UK in the early 1980s, which reported that the pertussis vaccination was associated with a 1 in 140,000 risk of serious neurological illness in the first seven days after vaccination. These events were equally common after the first, second or third doses of vaccine.[43] The Institutes of Medicine (IOM) re-evaluated this study and subsequently concluded, "The evidence is consistent with a causal relation between DPT and acute encephalopathy."[45] The vaccine cannot be linked to serious long term neurologic sequellae, based on findings from NCES and both birth cohort studies, the Child Health and Education study and the Collaborative Perinatal study.[43]

The negative press that resulted after the NCES included a television program "Vaccine Roulette" and a book "A Shot in the Dark" which fueled concerns that DTP could cause brain damage, Reyes's Syndrome and sudden infant death syndrome (SIDS).[44] Since there was a low prevalence of disease many physicians and parents refused to vaccinate with DTP, either by using the alternative DT (Diphtheria/Tetanus) vaccine or refusing the vaccine entirely. These perceptions have been mitigated by strong advocacy within pediatric and primary-care organizations, and the school based vaccination requirements. In other countries this negative press resulted in dramatic reduction of DTP vaccination for a period of time, resulting in large pertussis outbreaks within five years.[44] When vaccination coverage was first estimated by the National Immunization Survey in 1994,

the DTP/DT coverage was at 70%. This is naturally an over-estimate of pertussis immunity as the DT immunization was included without differentiation at that time.[46]

1.4.2. Acellular Vaccine Formulation

Due to these concerns about reactivity of the DTP vaccine, an acellular formulation of the pertussis component (aP) was licensed in the USA in 1995, as an equally effective but less reactogenic vaccine and the DTP whole-cell formulation was phased out of use by 1999.[47-49] The formulation of the vaccine is manufacturer specific, all versions include the pertussis toxin (PT), filamentous haemagglutinin (FHA) and some include pertactin (PRN) and fimbriae (FIM).[50] The vaccination series consists of four initial doses given at 2, 4, 6, and 12-18 months, with a primary booster at 4 to 6 years. Efficacy of the full DTaP immunization series is 88.7 % against reported pertussis.[42] The unvaccinated have 8.9 times the odds of acquiring disease when compared to those fully vaccinated.[42] Since the changeover to DTaP, there has been some evidence that the acellular formation may have a lower efficacy compared to the whole cell vaccine.[48,49,51,52] Reduced efficacy estimates may partly be a reflection of bacterial adaptation under the immune selective pressure against the vaccine strains of the PRN component.[53,54]

Local reactions to vaccination still occur and include fever, redness, swelling and soreness and are estimated to occur in 1 of 4 children.[55] Some risk can be reduced if the vaccination is administered in the thigh rather than the arm in children younger than 36 months of age.[56] Some children with extremely serious reactions to a previous dose of DTaP including a life-threatening allergic reaction or suffered brain or nervous system disease within 7 days after a dose of DTaP should not receive any additional doses.[55] Children who had a seizure or collapsed, or cried non-stop for 3 hours, or had a fever over 105 degrees after a dose of DTaP are rare and the physician should be consulted as to whether further vaccination should be given, as these events could occur for other non-vaccine related reasons.[55]

Recognizing the new adolescent risk group, the Tdap vaccine was formulated adding the aP component to the tetanus and diphtheria booster (Td). The two licensed versions of this adolescent vaccine both contain PT, FHA and PRN, the one also licensed for use in adults also contains FIM elements. The Tdap vaccine has a smaller inoculum of each element

when compared to the DTaP vaccine.[50] The tetanus and diphtheria components are listed in order of the inoculum size. While the pertussis component is listed last since it was incorporated into a preexisting vaccine. Recent changes to the immunization schedule include an additional booster shot for adolescents and a one-time booster for adults recommended just following the peak of the first nationwide outbreak in the US in 2005. These changes have been reactive measures to control glaring increase of disease. .

1.4.3. Immunization Coverage

Vaccination prevalence against pertussis has increased from 70% in 1994 to 80.5% in 2008 for the initial 4-shot series among toddlers, though 95.6% had received the first three doses in the series.[46,57] This improvement in vaccinations in large part due to the outbreaks of Measles in the early 1990s which highlighted insufficient vaccination rates. With the implementation of the National Immunization Survey in 1994, solid state-based estimates of vaccination showed clearly where improvements were needed. The continued emphasis on immunization, along with the resurgence of disease has improved vaccination rates with 2011 estimates so that 4 dose coverage with DTaP is at 84.6%, and 3-dose coverage is estimated at 95.5%, these number have been steady since 2007 in nationwide estimates.[58]

Within three years since the new recommendation in 2008, Tdap coverage among adolescents was estimated at 40.8%.[10] With the continued press coverage of pertussis, the immunization rate has since improved. The most recent estimates (2010) of the Tdap adolescent booster, was at 68.7% among those 13-17 years of age in the US.[14] Since the introduction of the adolescent pertussis booster, the pertussis incidence of disease among this group has decreased, suggesting that the use of the vaccine was effective among this targeted population.[8,14] While initial uptake was low, numerous states have incorporated the adolescent booster as part of their school-based exclusionary immunization schedules (32 states for the 2011 school year), which has helped improve coverage.[59] Vaccination of adults (≥ 19yrs) with Tdap is estimated at around 8%. [11]

While the coverage of the primary immunization series has improved dramatically, most states (except for West Virginia and Mississippi) offer a religious or philosophical waiver which allows parents to refuse vaccination of their children for non-medical reasons. [59]

These refusals can be problematic, because such individuals tend to cluster in space. This increases the risk of infection not only to the unvaccinated children themselves, but to the entire community as they build a pocket of susceptible individuals in which an outbreak can easily occur.[60-62] In communities with more exemptors 11.0% of the disease is attributable to the exemptors, and the more exemptors the higher the reported incidence.[60-62]

The increased incidence of pertussis in older age groups allows for a more precise estimation of the duration of protection (waning immunity) following the initial vaccination series. Historic data suggest that infection-induced immunity is not lifelong, as individuals can experience disease again as adults.[35,36] Therefore, it is unlikely that vaccine stimulated protection will be more long-lasting than naturally induced immunity. An outbreak-based study in 1962 examined the duration of protection of a three dose series of the whole-cell DTP vaccination series and found that five years after the series was complete, 47% of individuals were reinfected.[39] Recent studies regarding the duration of protection following a full five-dose schedule of the acellular formulation (DTaP) found similar results. [42,63-66].

1.5. Summary and Specific Aims

1.5.1. Aims 1 & 2: Evaluating the Adequacy of the Surveillance Case Definition

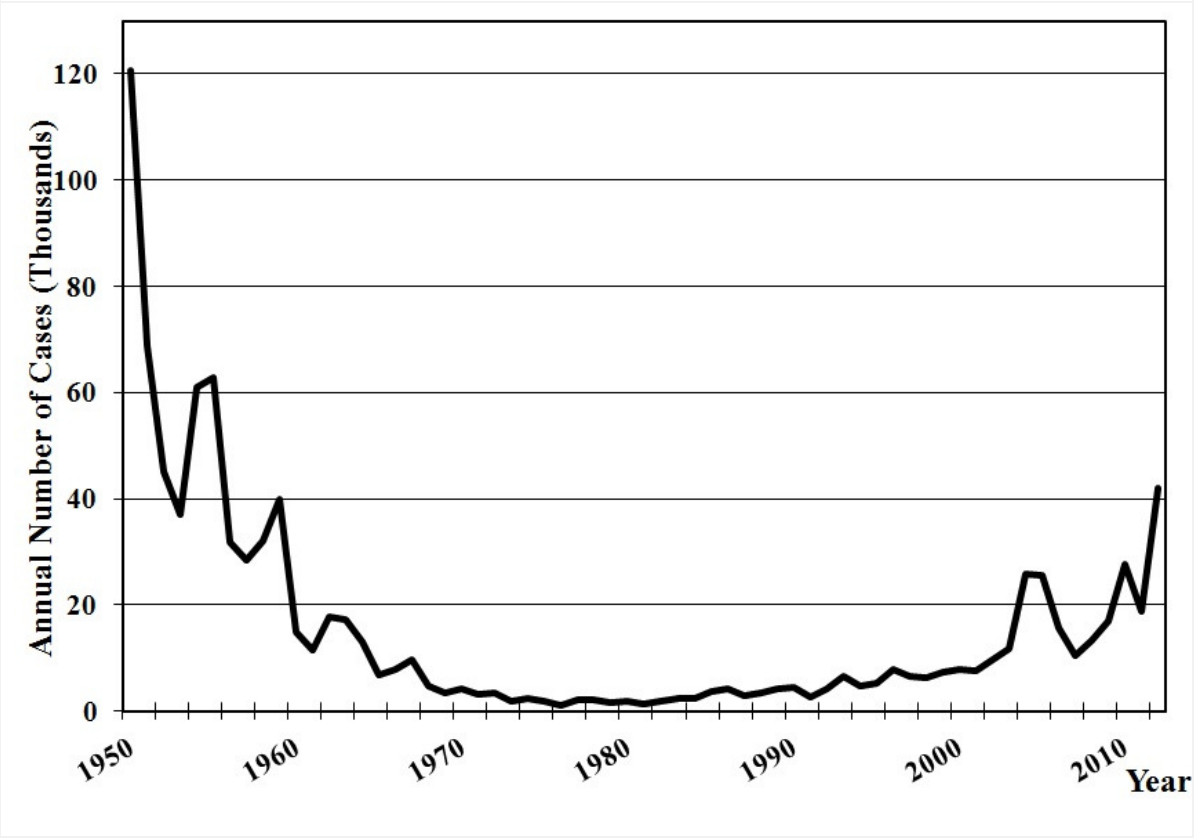
The resurgence of pertussis into the public conscience after 40 years of relatively few cases meant that many younger clinicians were not familiar with the disease, or the requirements for surveillance reporting when the collection of the data used in this dissertation was initiated. Because of the incorporation of DNA based diagnostic tests into the case definition in 1997 and the continuing increase of cases since then, we need to have a clear understanding of the nature of the surveillance data being collected, to appropriately identify pertussis outbreaks and to create effective immunization strategies. Chapter 2 addresses this need by evaluating the surveillance data from the state of Michigan for the period 2000-2010, according to the case classification requirements. This is the first population-based evaluation of the case classification requirements examining the role of PCR confirmation.

The primary element of case identification and the surveillance case definition is the unique and prolonged cough associated with pertussis. A case confirmation via a bacterial culture requires only the presence of a cough. However, a lab confirmation via the newer PCR testing accepted by the CDC in 1997 requires a two-week cough minimum duration. Because of this discrepancy in the importance of cough duration in case confirmation we need to better understand the reporting practices associated with cough duration in order to determine the efficacy of the current case definition. Chapter 3 addresses this need by identifying predictors of inadequate reporting of cough duration, in order to provide a scientific basis for simplifying and improving the case classification guidelines. Streamlining the confirmatory criteria in the surveillance case definitions will improve the quality and consistency of the data collected improving comparability of cases across state lines.

1.5.2. Aim 3: Defining Socio-Cultural Risk Factors of Pertussis

Vaccination is very effective in preventing severe pertussis both for the individual and in the local community. However, to be effective the population needs to maintain high vaccination levels. The Healthy People 2020 goals are to establish and maintain 95% coverage for both the primary vaccination series as well as the adolescent booster.[7] The use of immunizations is based on beliefs and behaviors that are developed based on the individual's environment. Because of the renewed endemicity of pertussis, a more complete understanding of the risk factors associated with the socio-structural components of the environment is needed so that public health workers can better identify at risk populations and develop more effective and targeted prevention programs. Chapter 4 assesses socio-structural risk factors across US counties for the period 1991-2008. This is the first nationwide assessment of county-level socio-structural risk factors for pertussis incidence.

Figure 1.1 Annual pertussis cases reported to the Centers for Disease Control and Prevention in the United States (1950-2012).[4]



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Chapter 2

Validity of Routine Pertussis Surveillance Data in Michigan, 2000-2010

2.1. Introduction

Pertussis is a highly communicable, respiratory infection caused by the *Bordetella pertussis* bacterium. Illness is characterized by bursts or paroxysms of coughing frequently followed by an inspiratory whoop which is the source of the common name, whooping cough. The clinical course of disease begins with a non-specific catarrhal stage, of general cold symptoms and a low-grade fever. After approximately one week, severe coughing spells begin where the patient cannot breathe between coughs; this is the paroxysmal stage it can last up to two months. The final stage of illness is the convalescent stage during which the severity and frequency of the coughing declines over time.[1,2] The most severe morbidity and mortality occur in children under 5 years, especially in those less than 1 year of age, and those who are not fully protected through immunization.[3] Additionally increasing morbidity is being seen among children in early adolescence, even in those fully immunized.[4]

The Council for State and Territorial Epidemiologists (CSTE) has established a case definition for each of the nationally notifiable diseases identified by the Centers for Disease Control and Prevention (CDC) (http://wwwn.cdc.gov/nndss/) this list has included pertussis since 1922.[5,6] The purpose of a case definition is to define illness using explicit, tangible criteria based on clinical, laboratory and epidemiologic information to maintain both validity and reliability in surveillance data collection, ensuring comparability across reporting source and time. Surveillance data are used to understand the magnitude and distribution of pertussis cases and changes in the epidemiology of the condition. Evaluation of the case definition criteria has become important with the U.S. national upsurge in cases, the recognition of a new risk group in adolescents, and the increased use of DNA tests for diagnosis. The 2010 outbreak in California reported significant disease among vaccinated individuals as soon as 5 years after the completion of the primary

immunization schedule, this has fueled concern regarding the long-term efficacy of the acellular vaccine formulation.[4,7,8] These concerns have justified the 2005 recommendation of a Tdap booster at 11-12 years and once among adults. Surveillance data is also used to evaluate the efficacy of programmatic changes in prevention and control efforts.[3] Therefore, it is imperative that the case definition be utilized consistently and as intended, to appropriately inform other public health decisions. Our analysis seeks to understand the utilization of each component of the case definition criteria, to determine the reliability of the data with regard to the intended standard.

The current CDC criteria (1997) for pertussis case status classification, the standard for ascertaining a case as confirmed or probable, are complex (Table 2.1). The distinction between the two is that a confirmed case has some laboratory indication of *B. pertussis*, either from the patient himself, or through epidemiologic linkage that is a close contact that tested positive, while a probable case is confirmed by the clinical presentation alone. These CDC case definitions have centered on cough as the central component of case identification, with a special focus on its duration. The cough criterion is necessary when laboratory testing is unavailable or when laboratory tests have low sensitivity among clinical cases, i.e. 7% sensitivity for culture.[9,10] The CDC case definition recognizes a positive bacterial culture as the gold standard, when an isolate is obtained diagnosis is definitive; any additional cough description cannot improve the certainty of diagnosis. However, other DNA tests like the polymerase chain reaction (PCR), included in 1997, while greatly increasing the sensitivity of laboratory diagnosis,[10-12] have the possibility for false positive results without the ability to verify the conclusion. In such cases cough attributes and duration increase the confidence in the diagnosis. Shakib et al. examined PCR-positive pertussis cases in light of the cough criteria and determined that a case definition with a cough of at least 7 days, rather than of 14 days, would allow an increase in confirmed case status from 88% to 95%.[13] The present study is designed to expand on that analysis by examining all pertussis cases reported in Michigan between 1 January 2000 and 31 December 2010, many of whom do not include a positive PCR test, with respect to the reported elements of the case definition, including cough duration.

The U.S. surveillance system functions primarily through a passive reporting mechanism, which minimizes resource expenditures until potential cases are identified. To function effectively, passive reporting systems must ensure an awareness of the conditions, and the willingness and capacity to report of the primary healthcare providers. This system is plagued by under-reporting and incomplete data collection.[14,15] During 1985-1988, the overall surveillance system sensitivity for routine passive data collection of pertussis, by the CDC, was calculated at 35% when compared with hospital discharge data.[16] Since then, the development of electronic reporting and automated laboratory reporting has increased the overall completeness, sensitivity, and timeliness of the reporting system.[14]

Evaluation of a surveillance system examines the data collected to either an external standard, or to another data collection system to evaluate data quality, timeliness of reporting, and efficiency of the reporting process. Such evaluations determine whether the surveillance system is functioning effectively in swiftly and appropriately identifying cases of pertussis. Additionally discrepancies can provide insight into informational misinterpretations, procedural gaps, and provide context to characterize the reported cases in reference to both the general population and unreported cases. There have been changes in the reporting of pertussis over the past decade, including the introduction of web-based reporting and automated lab result reporting against a background of a significant resurgence of cases. The objective of the present research was to qualitatively assess the validity of pertussis cases as reported through routine passive public health surveillance in the state of Michigan, and thereby address the utility of the reporting system as well as the effectiveness of the case definition criteria.

2.2. Materials and Methods

The database for this analysis included all cases of pertussis reported to the Michigan Department of Community Health (MDCH), between 1 January 2000 and 31 December 2010, as part of the state's routine surveillance of communicable diseases. The original data set contained 5,738 completed pertussis case investigations, of which 938 were filed as ‘Not a Case.’ The remaining 4,800 records were submitted with either a probable or confirmed pertussis case status and were, therefore, reportable. Six of these records had a laboratory result indicating *Bordetella parapertussis* infection, and were hence excluded

from all analysis. The data acquisition and analysis plan was approved by the Institutional Review Boards of the University of Michigan and MDCH.

2.2.1. Reporting Systems

During the study period, two electronic systems were used to transmit information regarding reportable diseases in Michigan from local health departments (LHDs), primary care providers and hospitals to the MDCH. The reportable diseases are specified in the Michigan Compiled Laws, specifically the Communicable Disease Rules, and include pertussis.[17]The first electronic system was a DOS-based, reporting system (1992-2004) which transmitted records on a weekly basis only from LHDs to the MDCH.[17]In June 2004, the Michigan Disease Surveillance System (MDSS) was implemented as a web-based disease reporting tool allowing for real-time access to communicable disease data by public health partners. The MDSS diversified the reporting sources to include not only LHDs, primary care providers and hospitals, but also includes automated reporting of laboratory results. With the numerous origins of case reports the system includes de-duplication functions, whereby the health department can choose to merge two reports into a single continuous record. MDSS also includes numerous other analytic and alert functions to facilitate public health response.

Providers entering data into the system are asked to complete the MDCH case report form, which includes demographic factors, contact information, and clinical information regarding the disease event. (See Appendix A for the MDCH pertussis case report form.) Healthcare providers and LHDs have the ability to review and edit data on their cases, immediately improving the overall completeness of demographic variables by roughly 20%.[17] Web-based reporting occurred on average five days earlier in the clinical course of illness, which is an expected improvement based on automatic updates rather than the weekly batch transmissions of the earlier system.[15,17] These values are comparable to other studies evaluating the implementation of electronic reporting systems,[14] and bidirectional data transfer.[15]

2.2.2. Data Modifications

While overall reporting has improved data completeness, many of the case report variables are still characterized by incomplete reporting. In order to improve the completeness of

key indicators, these variables were re-coded based on other information in the case report to minimize non-response, and increase the potential analytic sample size. For example, a case was coded as cough = 'Yes' when the record reported any of the following: a cough, a cough attribute, final cough duration, or an affirmative for still coughing at the final interview. For all variables a response of 'Yes' indicates a true response, a coded 'No' was interpreted as the absence of a yes, including both a negative and non-response.

Most pertussis cases received an antibiotic; the antibiotic date was one of the most completely recorded secondary dates (87.8% reported). Time to the first prescription of antibiotics was calculated in days from the cough onset date to the date of first antibiotic, and was used as a proxy for initial doctor visit. The time interval information was also calculated between cough onset and PCR test date, the most frequently reported lab test, as well as from cough onset to diagnosis date, to determine the timeline of medical care in regard to clinical and diagnostic assessment.

The date of disease was created to have a single variable indicating when in time the case occurred. In this analysis, occurrence was defined by year. Disease date was drawn from the reported date of cough onset whenever possible. This variable was utilized both for its completeness (91.3 %) and the fact that it is the single most memorable event for the patient to recall in the clinical disease timeline. The variable "onset date" was not selected because a large portion of the records report the same date for both general onset and cough onset. This is exceedingly improbable, since the initial catarrhal stage generally lasts seven days, generally with mild symptoms and insidious onset. Therefore, when both dates were equivalent it is more likely that the date reported was indeed cough onset due to its more dramatic presentation, which left only 6.9% of records with a valid onset date. If cough onset date was not available, or if it could not be calculated based on the final interview date, i.e. the final point of contact with the case, and the final cough duration date, other dates in the record were used to approximate the disease date. Estimated dates were selected based on dates of the following, in order of priority: illness onset, first antibiotic use, PCR or other test result, final interview.

2.2.3. Data Analysis

This analysis was an evaluation of pertussis cases reported to the MDCH with a probable or confirmed cases status cases. These designations are given according to the reporting criteria established by CSTE and the case status definition criteria.[6] Reported clinical data were compared across the cases status classifications for comparability using frequencies and medians, as the continuous variables were not normally distributed. T-tests were used for comparisons of normally distributed data, and the Wilcoxon Two-Sample test was used for comparisons of medians when testing for significant differences between descriptive categories.

Records were also examined for the completeness of the auxiliary information recorded (e.g. dates, treatment, testing, demographics), with specific interest in changes over the study period. All records with at least a reported cough were examined (N=4,586: 95.7%). The variables examined included dates (cough onset, diagnosis, antibiotic, PCR), demographics characteristics (e.g. birth date, race, sex, Hispanic ethnicity) and clinical information (cough duration, whooping, paroxsysms, post-tussive vomiting, apnea, antibiotic prescribed). The temporal distribution of completeness was examined to evaluate changes in the reporting environment that occurred between 2000 and 2010 using simple linear regression.

The subset of investigations that were labeled 'Not a Case' was analyzed to determine the proportion of false negatives within each case status classification. The data were sorted first for any positive laboratory test (i.e. culture or PCR) and for epidemiologic linkage. Then each positive record was reviewed for the presence of a cough attribute and cough length. These records were also examined with respect to the year of occurrence to determine the distribution over the study period. The false negative rate was calculated to evaluate under-reporting.

2.3. Results

Of the 4,794 pertussis records reported to MDCH with a confirmed or probable status between 1 January 2000 and 31 December 2010, the breakdown according to the surveillance reporting pertussis criteria put forth by the CSTE for surveillance is shown in

Table 2.2. These criteria are the initial indicator which would lead the primary care provider to suspect pertussis and report the potential case. By definition, the entire dataset met reporting criterion 5, namely that a healthcare provider made a diagnosis of pertussis. Forty-five percent (N=2,157) of records met two reporting criteria, and 1,462 records (30.5%) met more than two reporting criteria. The breakdown of the full case status criteria in Table 2.1 is illustrated in Figure 2.1, where the CSTE confirmed case status criteria were met in 2,050 (42.8%) of records, and 1131 (23.6%) met the probable status criteria.

There was a significant difference in cough duration between those who reported at least one of the three required cough attributes (i.e. whooping, paroxysms or post-tussive vomiting), and those who did not (Table 2.3). Paroxysms were reported twice as frequently as either of the other two criteria. People reporting a specific cough attribute coughed at least 2.7 days longer on average than those who did not specify a cough attribute. This was most clearly evident with people who reported paroxysms and those who did not report paroxysms, where the mean cough duration differed by more than one week.

Comparison of the clinical characteristics by ascribed case status is shown in Table 2.4. Both confirmed and probable cases had a similar distribution of the median time from cough onset to seeking medical attention (Antibiotic Date). Of the cough attributes whooping was more frequent among the confirmed cases (6%, T-test $p< 0.01$) and paroxysms were less frequent (- 4% T-test< 0.01) when compared to the probable cases. PCR tests were frequently conducted on the day that antibiotics were first prescribed, except in those confirmed by epidemiological linkage where antibiotics were prescribed an average of 5 days prior to testing. The PCR test sample was collected roughly two days later than antibiotics were prescribed, an average of two weeks after the onset of cough, and often upwards of three weeks. (Data not shown.) This time to testing significantly decreases the probability of a positive result.[10,18] Those with a positive lab test compared to those without tended to be younger ($p<0.01$), less likely to be part of an outbreak ($p<0.01$), more likely to have post-tussive vomiting ($p<0.01$), and more likely to

have received antibiotics a earlier ($p<0.01$). Increasing age and longer time to diagnosis was seen with decreasing certainty of case status (moving from left to right in Table 2.4).

The cases labeled as "Suspect" in Table 2.4 include cases that failed to meet the confirmed or probable case status classification based on insufficient cough duration, but exhibited both a cough attribute and a positive laboratory indicator. The "Other" column describes cases which did not meet the proposed criteria. Those who failed the case status classification due to insufficient cough length, were of similar age and attribute distribution to their counterparts in the confirmed classification. They are distinct because they sought medical care in the first week of cough and were generally diagnosed prior to fourteen days.

Cases marked as part of an outbreak were most frequent among those confirmed by epidemiologic linkage. One quarter of those with a probable status were reported as occurring during an outbreak. There is no quantitative definition of a pertussis outbreak, but it would require a number of cases in the same place and time, linked in some manner. The frequency of outbreak associated cases among the epidemiologically linked and probable cases may be due to case ascertainment or follow-up differences that occur in high intensity outbreak situations, such as active case finding or more complete case follow-up. There was no significant difference in the use of PCR testing between outbreak cases (49.0%, 95%CI (47.6 – 52.7)) and endemic cases (46.1%, 95% CI(48.8 – 51.0)).

The completeness of variables that comprise the case report is selectively presented in Figure 2.2 to show the annual variability over the study period. Most variables remained at relatively constant levels of reporting. The reporting of critical disease variables like Cough Onset Date and the presence of a Whoop when coughing(data not shown), maintained a high reporting rate of 96.6% and 90.5% respectively. Other descriptive variables like Hispanic Ethnicity (62.9%) and Race (37.1%) held steady at lower levels. A slight decline was observed for Final Cough Duration and Cough Onset Date, most likely a by-product of the increasing volume of cases. Increasing completeness was seen in both Diagnosis and PCR dates. The Diagnosis Date change coincides with the introduction of the MDSS in 2004. The PCR increase is more gradual, roughly 5.7% per year and is not clearly linked to the introduction of the MDSS. Rather, it probably represents the

increased familiarity with and use of PCR testing as part of the diagnostic process. A consistently high level of reporting was evident for other clinical and demographic variables (Data not shown, see appendix B.*)* including: birth date, sex, whether antibiotics were prescribed, date of antibiotics, apnea, paroxysms, post-tussive vomiting.

The evaluation of records classified as "Not a Case," resulted in the identification of five additional confirmed cases, and thirteen suspect cases. The distribution over time is illustrated in Figure 2.3, and clearly occurs in parallel to outbreaks. Eight of these cases were still coughing at the final interview, including all confirmed cases. Of the three suspect cases one coughed 9 days the other 11 days while the third did not report a cough length. Seven of the ten remaining records failed to report cough length and the remaining three were no longer coughing. The overall false negative reporting rate was 4.2/1000 case reports since 2005.

2.4. Discussion

These results show that there was a high consistency in the data, over the study period, even with the changeover to internet-based reporting. The reported pertussis cases were correctly identified by the case definition and case classification criteria of CDC. Of the reported cases in this dataset 84.2% have a high clinical probably of being true pertussis cases; 66.4% met the reportable case definition, another 15.5 % had a positive PCR test and 2.3% were epidemiologically linked with a reported cough attribute. Of those reports that failed to verify the pertussis diagnosis, it is mostly based on incomplete cough duration. This brings into question two important factors in the utilization of the current case definition. Firstly, whether the of cough length criteria is necessary, in the presence of a positive laboratory indication (culture, PCR or epidemiologic linkage), and if so what duration would be required. Secondly, a PCR positive result is frequently being reported as a confirmed case, but only 70% of the cases meet the 14 day cough requirement. This is a misinterpretation of the classification criteria, where the process of confirming a case by culture and PCR testing differs. A case definition must be as straight forward as possible; the different requirements simply among the confirmed criteria make this a challenging case definition.

The current CDC clinical case definition for a probable case has been shown to have 96% sensitivity and 35% specificity among culture positive or direct fluorescent antibody (DFA) positive cases.[18]DFA is no longer considered a valid confirmatory test, and has been replace by PCR. As many as 81% of urgent care providers in another study were not aware that clinical pertussis is itself reportable, often waiting first for a positive laboratory result.[19] The inclusion of PCR as a confirmatory test has significantly increased the sensitivity of laboratory testing and the number of confirmed-status cases, as the PCR test detects the bacterium three times more frequently than culture.[10,20,21] This brings into question the importance of the cough criteria among PCR positive cases. As Shakib *et al* reported most PCR positive cases cough for more than seven days if they also present with a cough attribute, which agrees with our results.[13]

Due to the similarity between suspect cases and their confirmed counterparts, perhaps suspected cases with a cough attribute (whoop, paroxsysms, and/or post-tussive vomiting) who also have a positive lab indication (PCR or epidemiologic linkage) should be considered a confirmed case. It would seem that cough duration does not add much to these criteria, as the presence of a cough attribute already strongly indicates pertussis. Additionally, the pertussis case classification system is relatively complicated, and the presence of two cough durations would likely add to the confusion, especially since it is not critical for cases with a positive laboratory indicator. Based on our results, the current recommendations for confirmation via culture seem reasonable, as roughly 10% of these cases did not present with a cough attribute. The clinical case definition, used for probable cases, should also be maintained as currently recommended, 14-plus days of cough with a cough attribute, for those who either test negative by PCR/culture, or are unable to be tested in a timely or adequate manner.

Under these proposed guidelines 11.6% of those reported who currently fail the case definition due to insufficient cough length would also be confirmed cases. The 14.1% of cases listed as ‘Other’ in our analysis should not be reported due to lack of adequate clinical verification in the case report. After reviewing all events which had inaccurate case status labels base on information in the record, there was a slight over-reporting of

"true" cases at about 11/1000 reports. This may partially be due to incomplete reporting of classification criteria, most commonly the duration of cough.

The consistency of the completeness of most variables suggests the reliability of the reporting system even with the change to internet-based reporting. The implementation of an online reporting system probably mitigated the reporting burden of the four-fold increase of annual pertussis cases seen during the 2000s, resulting in only minor declines in completeness in a few variables such as cough onset date and cough duration. Disease-specific variable completeness did not fall below 90%, maintaining a high level of reliability. There were also some improvements in data completeness, for example, with the diagnostic date that stabilized in the high 70 % range, suggesting an increase in reporting capacity and "buy in" by healthcare providers. This represents an improvement in surveillance management, as a side benefit of the MDSS system, providing healthcare professionals the opportunity to review their cases. Pertussis is now recognized as an important contemporary issue, affecting an expanding age range of people. Nevertheless, one study in 2007 reported that nearly half of all family practitioners had never diagnosed a case of adolescent pertussis.[22]

Data consistency and accuracy are major challenges of a passive surveillance system, and reflects fluctuating resource availability including funding, personnel and interest. Our study covers a decade of increasing interest in both pertussis and reporting mechanisms, and while resources are known to fluctuate across time and within a given health department (e.g., when local outbreaks are recognized), there is a consistently high level of reporting the clinically important data. There is also occasional external resource supplementation in the form of personnel or finances from the state health departments or from the CDC, such as occurred during the study with the influx of post 9-11 bioterrorism funding to assist in the electronification of reporting systems, which in part helped facilitate the introduction of the internet-based MDSS system.[17]

The reported data were reliable with consistent and high completeness of the most important clinical variable, even with the increased work load and detailed case form. The internal validity of the reports is also adequate when compared to the CDC standard case definition, but is plagued by incomplete reporting such as submitting a cough length of

less than fourteen days but noting that the patient is still coughing. After an in-depth deconstruction of reported cases in light of the current pertussis case definition criteria, we recommend an update of the pertussis case definition, pertaining to cases with positive PCR tests or epidemiologic linkage and recommend that the cough attribute criteria be retained and the duration criterion be removed from the confirmed criteria.

Table 2.1 Criteria used to verify pertussis cases analyzed in this study

Probable Case (a clinical case):[*]

- Cough ≥ 2 weeks
  WITH
- One of the following: paroxysms, whoop, post-tussive vomiting

Confirmed Case[*] is a probable case with laboratory confirmation via:

- PCR positive
  OR
- Epidemiological linkage to a laboratory-confirmed case

A case can also be Confirmed if a cough case has a positive laboratory culture.[*]

Suspect Case:[†]

- Cough
  WITH
- One of the following: paroxysms, whoop, or post-tussive vomiting
  AND
- Bacterial confirmation via:
  - PCR positive
    OR
  - Epidemiological linkage to a laboratory-confirmed case

[*] This definition is established by and reportable to the CDC.[6]

[†] This is a NOT a CDC established case status definition; it was created for the purposes of this analysis.

Table 2.2 Criteria for reporting a suspected case of pertussis to public health authorities, and the total number and percent of 4,794 cases meeting that criterion.[23]

Reporting Criteria	N	%
1. An acute cough illness of any duration with an inspiratory whoop	1625	33.9
2a. Any person with isolation of *Bordetella pertussis* from a clinical specimen	472	9.8
2b. Any person with a positive PCR test for *B. pertussis*	2037	42.5
3. Any cough illness greater than 2 weeks duration in a person who is a contact of a laboratory-confirmed pertusiss cases.	624	13.0
4. Any cough illness greater than 2 weeks duration in a person who is a member of a defined risk group during an outbreak	570	11.9
5. A person whose healthcare record contains a diagnosis of Pertussis	4794	100.0
6. A person whose death certificate lists Pertussis as a cause of death or a significant condition contributing to death	2	<0.1

Table 2.3 Average cough duration by cough attribute among all reported pertussis cases in Michigan, 2000 - 2010.

Cough Attribute	N	Mean Cough Duration (Days)*
Any Attribute 1+	3,269	33.7
No Attributes	342	24.4
Whoop	1,326	34.4
No Whoop	2,009	31.7
Paroxysms	3,069	33.9
No Paroxysms	429	25.7
Post-tussive vomiting	1,827	33.9
No vomiting	1695	31.1

* There was a significant difference in mean cough duration, based on a pooled T-test, between those who reported the attribute and those who did not, in all categories at a p-value of < 0.01.

Table 2.4 Descriptive characteristics cases of pertussis in Michigan, 2000 – 2010, according to case status.

	Confirmed			Probable	Suspect		Other
Case Certainty	Culture N=467	PCR N=1230	Epi-Link N=353	14+ Cough & Attribute N=1131	PCR & Attribute* N=521	Epi-link & Attribute* N=111	N=773
Median Age (Yrs) Inter-Quartile Range (IQR)	0.8 (0.2 -12)	9.7 (3.2-19.9)	12.5 (5.8-33.0)	16.5 (6.2-41.8)	7.3 (0.5-16.7)	18.4 (5.9-38.8)	13.6 (4.5-39.2)
Median Cough Length (Days) (IQR)	24 (17-37)	26 (19-36)	33 (23-50)	33(22-50)	11(8-12)	10 (6-12)	17 (10-29)
Still Coughing (%)	85.3	87.9	68.1	81.4	80.6	70.8	66.4
Outbreak (%)	8.8	14.2	32.6	24.6	4.4	15.3	11.7
Cough Attribute Present (%)	90.8	100.0	100.0	100.0	100.0	100.0	41.2
Whoop	59.1	41.6	46.2	40.6	39.8	45.2	15.8
Paroxysms	87.1	95.2	97.7	97.6	94.4	96.4	42.6
Post-tussive Vomiting	62.6	59.2	45.4	56.9	54.3	45.5	25.2
Median Time from Cough Onset to:							
Antibiotics (IQR)	11 (6-18)	12 (7-18)	15 (7-23)	14 (7-24)	7(4-12)	9(3.5-13)	8.5 (3-17)
Diagnosis (IQR)	16 (10-25)	15 (10-23)	19 (11-29)	21 (13-37)	10(6-15)	13 (8-22)	15(7-30)

* These records would have met the confirmed case definition criteria had they coughed for more than 14 days.

Figure 2.1 Breakdown of cases according to case definition and case status criteria.

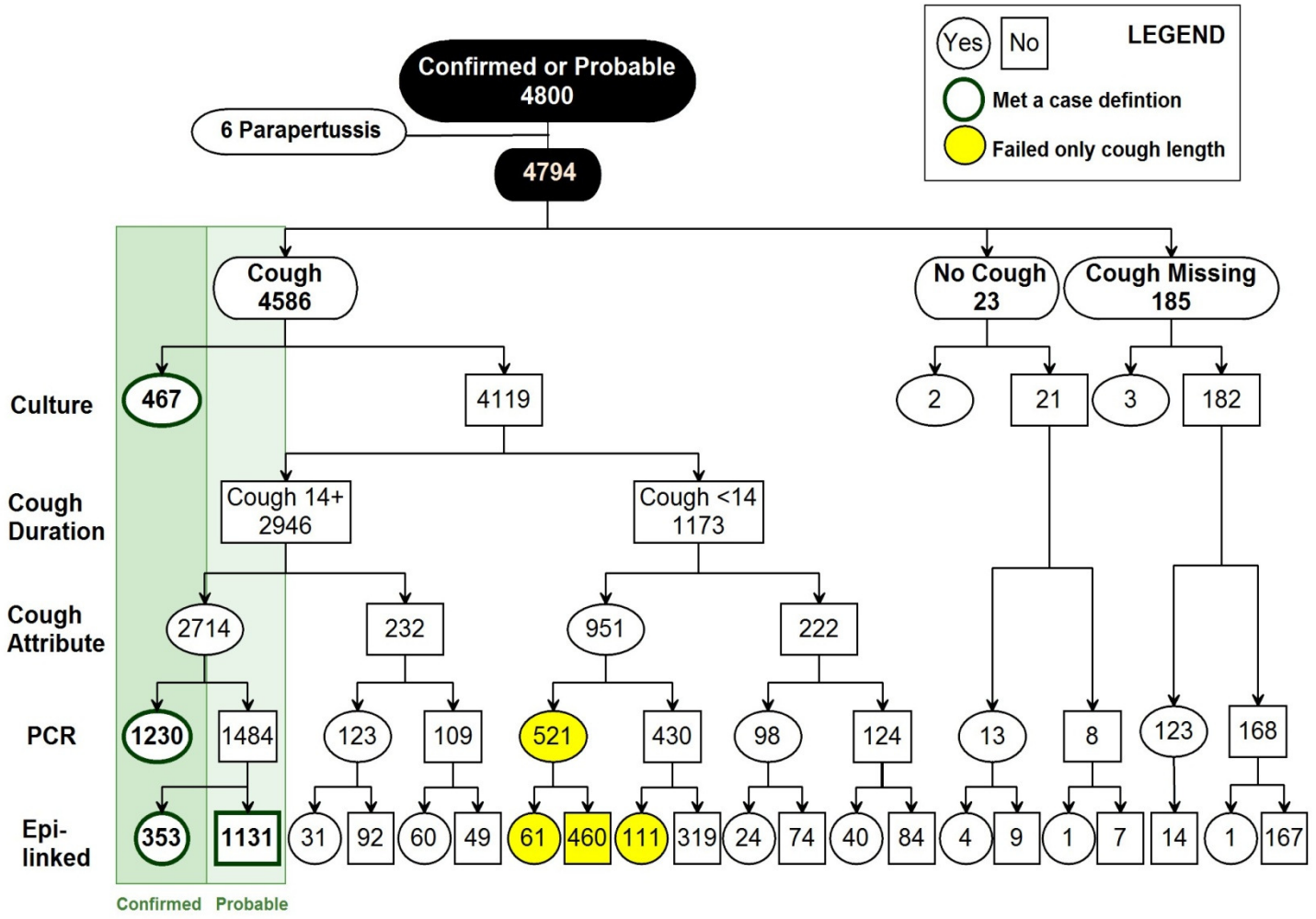


Figure 2.2 Completeness of select case report variables in Michigan by year.

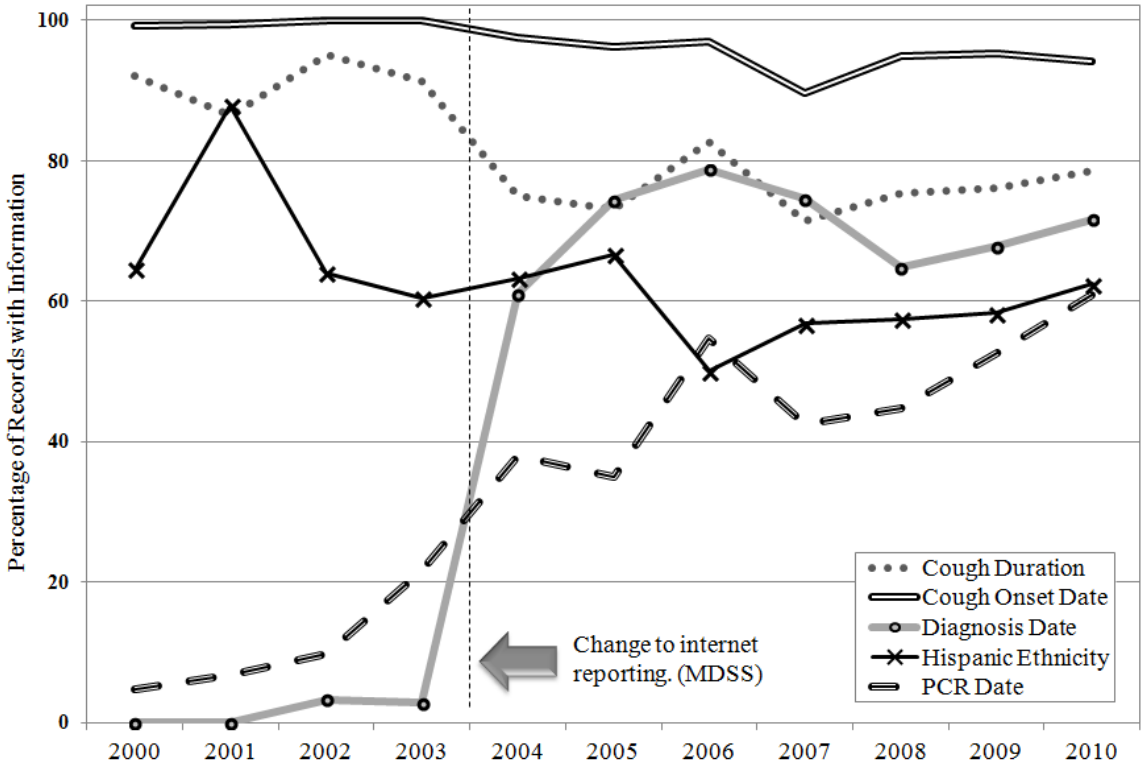
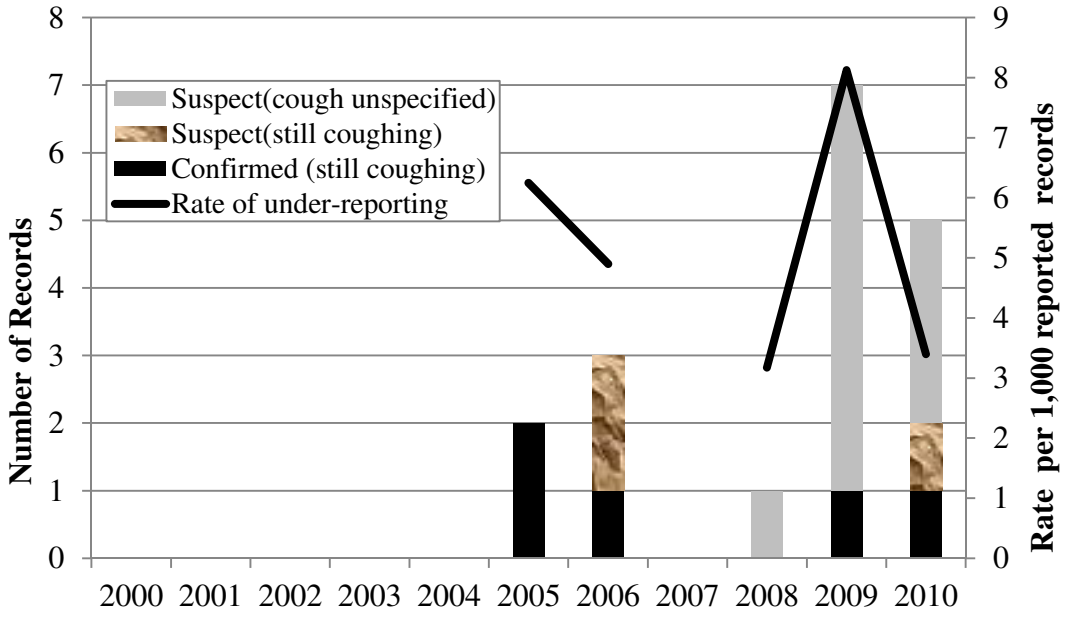


Figure 2.3 Unreported records according to case status classification



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Chapter 3
Routine Surveillance of Pertussis in Michigan, 2000 – 2010: Analysis of the Cough Criteria of the Clinical Case Definition.

3.1. Introduction

Pertussis, a common pediatric respiratory illness caused by the bacterium *Bordetella pertussis,* is clinically diagnosed based on cough characteristics. The most important of those characteristics is cough duration, which has been the primary component of the formal case definition used for the purposes of public health surveillance. More descriptive factors known as cough attributes are also key to the case definition and include the paroxysmal nature of the cough, inspiratory whooping, and post-tussive vomiting. Previously, the pertussis case definition used by the World Health Organization (WHO) (1991) required 21 or more days of spasmodic cough.[1] In 1990, the U.S. Centers for Disease Control and Prevention (CDC) instituted a pertussis case definition which requires a minimum of 14 days of cough, with the presence of at least one cough attribute.[2] Clinical diagnosis can be confirmed using laboratory testing for the presence of *B. pertussis* based on either culture or polymerase chain reaction (PCR) testing, although it is progressively more difficult to detect the bacterium after the second week of cough. Currently, cough duration is not required for disease confirmation if a positive laboratory culture of *B. pertussis* has been obtained.

The cough's attributes and its protracted duration are definitive of a *B. pertussis* infection; 95% of pertussis cases can be correctly diagnosed if coughing lasted for at least 21 days and was accompanied by choking fits. In the presence of a cough attribute, the diagnosis could be made earlier.[3] A clinical diagnosis of pertussis is highly preferred because culture sensitivity is very low as evidenced in one study where only 7% of specimens were culture positive in a sample of serology-positive, suspected cases.[4] Cough duration is also important to prove the accuracy of diagnosis when introducing a new laboratory test, such as the more sensitive PCR tests, which had 21% sensitivity among the previously mentioned suspected cases tested by culture.[4] PCR testing was

formally accepted as a confirmatory test for pertussis by the CDC in 1997 but only in cases where a clinical diagnosis had been made.[2] As noted in chapter 2, Michigan physicians have been using PCR test with increasing frequency over the last decade to diagnose and confirm cases. In the context of this increased use of PCR, Shakib *et al* re-evaluated the cough duration criteria among PCR-positive cases that also had a cough attribute.[5] They found that 88% of PCR-positives met the 14-day cough duration as specified in the CDC case definition, but if the required cough length was shortened to 7 days, then 95% of the cases would have been confirmed.

As a notifiable infectious disease, all cases of pertussis are required to be reported to local public health authorities. All surveillance data are the result of an unintentional case exclusion bias, which means that people who tend to delay medical care will be under-represented in surveillance data. When more active case finding occurs, due to recognized outbreaks, this bias may be reduced because those who would otherwise delay care are brought to the attention of healthcare providers earlier in the course of illness. This bias will make delayed cases appear to be more severe. Initially this is due to cough length, but secondarily because the less serious cases will never seek care and therefore not be included in the surveillance data. Cases may also be excluded for other unrelated reasons due to misdiagnosis or lack of reporting, as in all public health surveillance data.

3.1.1. Role of Antibiotic Treatment

Some antibiotics such as erythromycin, a macrolide, have shown bactericidal capacity that results in negative specimen samples in as few as two days in both hospitalized patients and laboratory cultures.[6] However, the frequently prescribed ampicillin, a beta-lactamase, is not effective in treating *B. pertussis* infection and can extend the period of positivity to an average of 20 days after the start of treatment; this is a week longer than would be seen in untreated patients.[6] The cough symptoms are not as sensitive to antibiotic treatment, though ampicillin results in about 10 extra days of cough.[6] Similar results showing the effectiveness of erythromycin, but not ampicillin, have been reported in other studies.[7,8] While the CDC pertussis treatment bulletin reports that use of antibiotics result in a shorter course of disease,[9] studies with active physician follow-up

of cases until coughing ends show no effect of antibiotic therapy on cough length, even when erythromycin is prescribed as prophylaxis.[6,10,11]

Studies based on surveillance data rarely consider the case exclusion bias, and by ignoring this will suggest that earlier treatment shortens cough duration. [1,12,13] However, the timing of treatment in such datasets creates an artificial association between treatment and cough duration, as those who seek care earlier would have a shorter average cough duration when compared to others who came in later, especially when there is incomplete reporting of cough length. Since there is insufficient compelling data to suggest that cough duration is shortened with antibiotic treatment, the primary purpose of treatment is to stop transmission by reducing and eliminating the pathogen from the respiratory tract.[6,14]

3.1.2. Objectives

The pertussis case definition components (Table 3.1) shown in their entirety, involve five different ways to identify pertussis cases for surveillance purposes. Four of these require a 14-day cough in addition to other criteria. The fifth, those cases defined by a positive culture test (#4) are not required to meet a specific cough length. As indicated in chapter 2, those who were reported with an insufficient cough (less than 14 days) according to the pertussis cases confirmation criteria sought medical attention earlier and were also diagnosed prior to 14 days. Thus, analyses in chapter 3 aim to evaluate the predictors of sufficient clinical cough criteria among surveillance cases reported as either probable or confirmed. In particular, this analysis determines whether there are systematic differences between those who reportedly met the 14-day criterion and those who did not, and determine whether and how this should affect the case definition.

3.2. Materials and Methods

The database for this analysis included cases of pertussis reported to the Michigan Department of Community Health (MDCH), during the 11 years from 1 January 2000 through 31 December 2010, as part of the state's routine surveillance of communicable diseases. The original data set contained 4,800 records submitted as either a probable or confirmed pertussis case. Six of these records had laboratory results indicating *Bordetella parapertussis* infection, and were excluded from analysis. After data cleaning, records

were excluded when no evidence of cough was contained in the record, this totaled 184 reports. An additional 1,177 records lacked valid information for at least one of the following variables: age, cough duration, or antibiotic, leaving a total of 3,433 records (71.5% of the original database) for analysis. Records which are complete for this additional information are more likely to have had a closer relationship with either the primary care provider or a health department worker for disease follow-up. The data acquisition and analysis plan was approved by the Institutional Review Boards of the University of Michigan and the Michigan Department of Community Health.

3.2.1. Reporting Systems

During the study period, two electronic systems were used to transmit information on reportable diseases from local health departments (LHDs), primary care providers (PCPs), and hospitals to the MDCH. These reportable diseases are specified in the Michigan Compiled Laws, Communicable Disease Rules, and include pertussis.[15] A DOS-based reporting system that functioned during 1992-2004 transmitted records on a weekly basis from only LHDs to the MDCH.[15] In June 2004, the Michigan Disease Surveillance System (MDSS) was implemented as a web-based disease reporting tool, allowing for real-time access to communicable disease data by public health partners. The MDSS included information from not only LHDs, PCPs, and hospitals; but has emphasized the inclusion of electronic laboratory reporting as well.

Any provider entering data into either electronic system was asked to complete a standardized MDCH pertussis case report form, which included demographic factors, contact information, and clinical information regarding the disease event. (See Appendix A for the MDCH pertussis case form.) Healthcare providers and LHDs can review and update their case reports, improving the overall completeness of demographic variables by about 20%.[15] The MDSS system also shortened the reporting interval to MDCH by roughly five days, depending on the disease.[15,16] These values are comparable to those reported in other studies evaluating the implementation of electronic reporting systems,[17] and bidirectional information transfer.[16]

3.2.2. Variable Re-coding

As these data are passively reported to the MDCH, most variables have some missing values. Thus, variables were re-coded to minimize the effects of missing data, as described below, thereby increasing the potential sample size that was analyzed. The MDCH pertussis investigation form (Appendix) codes the prescribed antibiotics with the numbers in first column in Table 3.2; the 'Original' column shows the data as submitted. Records with an unknown or missing code but with information on antibiotics in free-form text were coded manually for both the first (579 records) and second antibiotic (27 records), shown in the final three columns. Information on the second antibiotic was only used when there was missing or unspecified information in the previous two columns.

The coding prioritized use of an MDCH code when included in the free-form text, where it was considered the primary antibiotic. For multiple entries, the initial antibiotic was selected. In the absence of an MDCH antibiotic code the following were selected in order of preference: a macrolide, a specified antibiotic, otherwise the first listed. Trade names (e.g. Bactrim, Ketek, Keflex, Omnicef, Rocephin, and Z-pak) were assigned to their appropriate classification. Group 11 was redefined as second generation cephalosporins, and group 12 as third generation cephalosporins. The coding scheme was collapsed into three broader antibiotic classes, due to the small sample size in specific sub-categories.[18]

Two aspects of cough length were examined; the first was reported cough length at the final visit, and the second a constructed minimum duration cough length. Duration of cough was reported in 75.2% of all records. Of those who reported a final cough length, 81.4% were still coughing at the time the report was made. The minimum cough duration was created by using either the reported cough duration, or the time from cough onset to antibiotics, whichever was longer. The rational for this was that the individual would not have returned to the doctor's office if their coughing had resolved.

The first reported date of antibiotic prescription was used as a proxy for healthcare seeking behavior, or the initial healthcare visit. The data were separated into four groups that related the date of antibiotics to the cough duration: pre-cough, 0 – 6 days, 7–13 days and ≥14 days. However, this means that individuals who did not seek immediate medical

attention, and stopped coughing, would not be included in the dataset, thus inducing selection bias. To the extent that this occurred, the dataset does not fully represent the entire ill population.

The date of disease onset was drawn from the reported date of first cough, whenever available. This variable was used due to the extent of completeness (91.3 %) and because it is the most distinctive event in the course of disease, therefore likely to be accurate. If the cough onset date was not available, or if it could not be calculated based on the final interview date and the final cough duration, other dates in the record were used to approximate the disease onset. Estimated onset was selected based on dates of the following, in order of priority: disease onset, first use of antibiotic, PCR or other testing, final interview. The disease onset date was simplified to year of event for this analysis.

The data include a number of dichotomous variables. A summary of the data as received is reported in Table 3.3. Due to the high proportion of unknown or missing responses, and to retain records for other analysis, these dichotomous variables were re-coded so that a 'Yes' is retained, but that 'No' could refer to either a reported absence of the clinical characteristic, or an absence of report. Additionally the variable regarding vaccination should be interpreted as evidence of a DTP/DT vaccination record, and the unknown and missing records were included with the 'No' category meaning that no record of vaccination was available. This interpretation was based on the free-form responses provided with the conjunct variable asking about the "reason not vaccinated with three or more doses".

3.2.3. Quantifying the effects of the case exclusion bias

Since the Suspect Cases identified in Chapter 2 who failed only cough length also appeared to seek medical attention earlier in the course of disease, it was thought that earlier treatment may have resulted in shorter cough duration. To determine whether early and late healthcare seekers produce different cough duration data regardless of antibiotic use, out data was simulated in SAS using a log-normal distribution of reported cough duration, based on the cough durations reported in the MDCH data.) The dataset was left truncated by week to mimic the effects of delayed care seeking and the resulting case exclusion bias. The mean cough duration in five time periods, representing the delay

of seeking medical attention, were considered: <7 days, 7-13 days, 14-20 days, 21-27 days and 28+ days. As a result those went to the physician in week 2 (7-13 days) could not have coughed less than 7 days. These simulated data do not take into account any cases who sought care prior to coughing, or those who did not receive antibiotics. This process assumes that the use of antibiotics has no effect on cough duration.[6,11]

Stratifying on a variable within the causal pathway between time of expose and outcome can induce bias.[19] In our data, healthcare seeking behavior is affected by both the severity and duration of disease. Therefore, stratifying on when an individual first sought care (week of antibiotic prescription) could bias the association between exposures such as age, cough attributes, and epidemiologic linkage or outbreak status and the outcome, reporting of a cough compliant with the clinical case definition. For this reason, analyses by week antibiotics were prescribed are not pursued beyond the simulation in this manuscript.[19]

3.2.4. Predictors of adequate cough duration report

To evaluate whether the case's medical timeline and the association with other known cases varied over the study period, a table that annually summarized the raw data was examined. Records that did not report cough duration were excluded.

Next, logistic regression was run to determine variables associated with accurate reporting of the requisite 14-day cough, the minimum in the CDC's clinical case definition. Insufficient cough duration was termed a cough duration failure, as the case failed to meet the clinical case definition. This duration failure may be a result of the reporting process, and may not accurately represent the case history. Analysis was restricted to cases who sought care before 14 days of cough, and for whom duration of cough was reported. Those who sought care on or after 14 days were examined to estimate the overall accuracy of the reported duration; they were excluded from the predictors of adequate reporting since they by definition met the cough criteria.

All the predictors of cough length reporting were examined in univariate logistic regression to determine the strength of the association. After identifying all significant associations, numeric variables were examined for collinearity, which occurs when two or more variables are similar and therefore become redundant in predicting the outcome.

The collinear variables having a condition index over 30 were excluded from the model creation process. The model was constructed based on the remaining variables using a two-stage backward model selection. The initial stage included all significant, non-collinear individual predictors, which were selected for removal in reverse order of significance. The second stage examined potential interactions of age with the remaining individual predictors. The final decision on whether to include a predictor or interaction at either level was based on model fit criteria as quantified by the lowest AIC value. All analyses were conducted using SAS version 9.2 (Cary, NC).

3.3. Results

The distribution of reported cases varied widely by year and age group (Figure 3.1). Most notably, there was a trend toward increased reporting of pertussis in adolescents and adults, both in absolute numbers and in overall proportion. Infants however bear the highest incidence of disease. Table 3.3 describes the characteristics of health seeking behaviors and diagnostic patterns in Michigan during this 11 year period. No temporal patterns were obvious for length of cough (ranging from a mean of 28.0 to 38.7 days), time to antibiotic treatment (14.5-20.5 days) or time to PCR testing (15.0-26.0 days). PCR testing was positive in more than 90% of cases reporting testing in all but one year. Less than a quarter of cases were considered "outbreak" associated in most years, except in both 2001 and 2006, when more than 40% of cases were considered outbreak associated. In the last two years (2009, 2010) the proportion of cases associated with a defined outbreak were exceedingly low (Table 3.3). There were no clear patterns associated with cases reported as epidemiologically linked, not even in the last two years with many reported cases. The years 2004, 2006, and 2010 had atypically short times from cough onset to initial healthcare visit (14.9, 14.7 and 14.5 days), which was paralleled with a slightly shorter mean duration of cough.

Significantly more cases met the CDC case definition before 2006 than after, 50.2% and 43.9% respectively (unpaired T-test=3.7, df =4788, p<.001) this is after the large outbreaks began and vaccination recommendations for adolescents and adults were instituted. Records where the individual was still coughing at the final healthcare visit, a potential source for failing to meet the CDC case definition were not associated with age

or outbreaks in chi-squared testing. Some individual years did show an association between a higher proportion of ongoing cough and outbreak status, including 2000, 2003 and 2005. However, in 2010 this association was reversed and outbreak cases were associated with a lower proportion of cases ongoing cough than in their non-outbreak counterparts. This ongoing cough was associated with age in those in reported outbreak settings, due to 1-4 year olds being twice as likely as all other ages (16%) to be still coughing.

Clarithromycin/Azithromycin was the most frequently prescribed antibiotic (69.8%) while another 14.0% of cases received Erythromycin (Table 3.2), all macrolides. The proportion of cases each year treated with Clarithromycin/Azithromycin increased over the study period, and a slight decline was evident in treatment with Erythromycin (Table 3.3).

The proportion of individuals reporting the clinical characteristics of illness increased over the first two weeks of cough, after which they did remained similar (Table 3.4). The most frequent clinical characteristic reported was paroxysms, which is similar to other surveillance studies.[12] Epidemiologic linkage occurred primarily with those seeking medical care in the first week of cough. Classification of cases as part of an outbreak was not reported frequently (3.2%) in those who received antibiotics prophylactically, but was greater in those diagnosed after they had already begun coughing. There was no association with history of vaccination.

Older patients exhibited a broader distribution of cough duration, and antibiotic prescription occurred later after cough onset (Figure 3.2). Only among children did the mean time to initiation of antibiotic therapy occur just prior to 14 days (13.3 days) (data not shown). Further investigation into the medical care timeline indicates that antibiotic prescription and laboratory testing were frequently conducted concurrently at 11-12 days, with diagnosis occurring about three days later (Table 3.4). Of these data only 11.3% did not have a cough attribute on file, 10.6% among infants and about 15% in all older age groups. (Data not shown.) The more delayed the initial visit and first antibiotic prescription, the longer the average cough duration and the more likely it was that cases were treated with macrolides. According to Figure 3.2 the age-specific, average cough

duration by week of initial antibiotic prescription relative to cough onset showed an increasing cough duration when the initial healthcare visit was delayed, this was significant in a Kaplan-Meier comparison (P< 0.0001)(data not shown).

However, those who took antibiotics prophylactically, in week 0 reported cough lengths that averaged longer than those who took antibiotics in the first two weeks of cough (Figure 3.2). This is also seen in Table 3.4,where the week 0 patients (N=251) reported cough duration was similar to those who took antibiotics in the second week of cough. The other descriptor variables of this prophylactic group matched those of the other groups but without a clear pattern. Some characteristics, including use of a macrolide antibiotic, clinical attributes, and lab testing, the prophylactically treated group had the lowest reported frequency. In other instances like the diagnostic timeline these prophylactic cases were similar to those who sought care in the first week after cough onset.

Had earlier antibiotic treatment resulted in shorter cough duration, then one would expect that those who received antibiotics prior to cough onset would have the shortest overall cough duration. This is not seen and leads us to suspect that the apparently longer cough duration observed among cases with a delayed initial healthcare visit may be the result of bias in data collection. If antibiotics have no effect on cough then those who sought care prior to cough onset [11] or those who did not use antibiotics [1] (N=397), would provide an unbiased subset of the database if the entire the cough duration was reported. However, among these potentially unbiased cases, only 171 (43.1%) reported any cough duration, and three-quarters of them were still coughing at the final interview. As these portions of data were not robust enough to support additional analysis a theoretical simulation was conducted comparing the average reported cough duration according to the week of the initial healthcare visit.

The log-normal simulated distribution was left-truncated over five time periods, representing the delay of seeking medical attention, <7 days, 7-13 days, 14-20 days, 21-27 days and 28+ days. The means were calculated for each of the four truncations 24.9, 25.8, 31.0, 38.0 and 45.3 days; the proportion of cases observed according to timing in the MDCH data was 24.6%, 31.5%, 18.6%, 10.3%, and 15.0%. Truncation showed that

care seeking bias results in longer mean cough duration with each successive week. An increase of 1 day of cough occurs between weeks 1 and 2, 5 days between weeks 2 and 3, and 7 days between successive weeks. This could mistakenly be interpreted as an effect of antibiotic therapy, however this comparison was made from data simulated under no treatment effect; it is therefore a direct result of the case exclusion bias. This case exclusion bias as illustrated through truncation describes the observed difference in cough duration seen in the actual MDCH data over the first five weeks when more than three-quarter of cases sought medical care (24.7, 25.7, 30.6, 34.8, and 58.3 days mean cough duration).

At the exclusion of antibiotic timing, the multivariable logistic regression found records with any one of the three confirmatory criteria, i.e. culture positive, PCR positive, or epidemiologic linkage, had increased odds of inadequate cough reporting (Table 3.5). This final statistical model contained only those records for which cough duration was numerically reported (N=1,755, 16 % reported cough failure). Because those who sought care after 14 days would, by definition, meet the criterion, they were excluded from this analysis. In addition, 18 of these 1,448 records reported insufficient cough values, representing reporting accuracy of 98.7%. A sensitivity analysis that included the records missing cough duration as insufficiently reported cough produced results that were comparable to the model presented (data not shown). The results indicate better odds of reporting a 14 day cough among, school-aged children, those presenting with post-tussive vomiting or paroxysms, and those initially treated with a beta-lactam class antibiotic. Positive lab testing by culture or PCR, as well as an indication of epidemiologic linkage, was associated with failure to report sufficient cough duration.

3.4. Discussion

The perceptions of pertussis have changed dramatically since 2000 among both healthcare providers and the general U.S. populace, now that pertussis is recognized as a contemporary public health issue. This has occurred primarily as a result of nation-wide media attention garnered from a large outbreak in 2004, the 2010 outbreak which resulted in 10 infant deaths in the state of California, and 2012 outbreaks in Washington and Minnesota.[20] Our data from Michigan show that during an outbreak year, cases were

reported to have received earlier treatment, and an increased proportion had PCR testing, as compared with non-outbreak years. This increase in PCR testing is critical as these cases fell under a new (1997) surveillance reporting category (Table 3.1 #3). Results in chapter 2 indicated that these cases were frequently misreported, with as many as 35% having inadequate cough length information. Our study found that all of the confirmation criteria (culture, PCR, epidemiologic linkage) were associated with increased odds of inadequate cough duration and subsequent failure to meet the clinical case definition.

Since the study began a change over from prescription of erythromycin to azithromycin was evident, after 2005 according to the CDC recommendation given their comparable effectiveness, but the lower side-effect profile, shorter course of therapy, and higher completion rates of patients taking azithromycin.[9] Individuals taking antibiotics prophylactically, before their cough began, required at least a second physical visit to a healthcare provider to verify illness, as cases are only reportable after diagnosis. These cases report a lower frequency of cough attributes because the second visit usually occurs early in the first week of cough, and the attributes may appear as late as the second week of coughing. There is also a possibility that early antibiotic use led to a decrease in disease severity as manifested in the clinical presentation, if antibiotics were able to curtail the extent of cellular damage.

Our simulated data examination on the effects of the case exclusion bias that occurs in all surveillance data, ignored any effect of antibiotics on cough length, and yielded a 13 days difference in reported cough length between those who received antibiotics in the first week since cough onset and those who waited until the third week of cough. This bias-based difference in cough duration is similar to that observed in the MDCH data after stratifying on week of antibiotics and suggests that antibiotics are not the cause of the shorter cough duration associated with earlier healthcare visits which coincides with initial antibiotic treatment. Since the cough is a physical response to overcome extensive cellular damage caused by the bacteria, and these ciliated epithelial cells have a long lifespan with a reported half-life of six months, the cough duration may depend more on physical cellular regeneration rather than the time required to clear the bacteria.[21]

While our simulation was based on the mean cough duration reported in the MDCH data (26.8 days), we found that 80% of all reported cases had ongoing cough at the final healthcare visit. Therefore, our analysis was based on incomplete cough data. Another study which followed pertussis cases to the end of their cough, 80% of cases had finished coughing after 60 days, more than twice the surveillance reported cough duration, which suggests that our surveillance cases are followed for just over a month.[12] This length of follow-up should be sufficient for most case management and even outbreak investigations; however statements pertaining to cough length and antibiotic effectiveness must be based on complete follow-up of a complete case cohort. While these bias effects should not be evident among either those who sought care prior to cough onset,[11] or those who did not use antibiotics,[1] these records were small in number and also plagued by the "still coughing" designation, so it was not possible to verify these conclusions in this subset of the MDCH data.

We recognize that missing data may have affected our findings, and probably reflects fluctuating accuracy and completeness associated with changing resources available to a local health department. Reporting and outbreak investigative capacity varies over time within a given health department, secondary to changes in workforce priority, resource availability and a number of other factors.[22,23] These limitations are common to all surveillance data. We assume that this was random and would have reduced the strength of associations that were observed.

As opposed to the incomplete cough duration reported in the surveillance data, there is also a high proportion of inadequate reporting, to the point where the reported case does not mean the surveillance case definition. The odds of such inadequate reporting of cough duration, reporting less than 14 days of cough, were more frequent when a confirmatory indicator was present (i.e. culture or PCR positive or epidemiologic linkage). The current case definition has no specified duration of cough for those cases confirmed by positive culture (OR: 2.1, 95%CI(1.4 – 3.2)). This finding suggests that there is a gross misinterpretation of the confirmatory criteria as sufficient in and of themselves to merit confirmatory status. However, the presence of a confirmatory indicator substantiates but does *not* supersede the need to meet the clinical case definition, this currently applies to

those confirmed by either PCR or epidemiologic linkage and requires at least 14 days of cough with a reported cough attribute.

This misunderstanding can be mitigated by streamlining the case definition so both confirmatory lab tests confirm cases using a single case definition formula. It seems reasonable that if a case is laboratory positive, the cough of any length must be accompanied by at least one cough attribute (i.e. whooping, paroxysms, or post-tussive vomiting). This simplification should clarify the role of laboratory confirmation in pertussis surveillance, and so should improve the accuracy of the reported cases in such a way that a great proportion will meet the case definition.

All cases without a positive laboratory test should continue to be required to meet the current clinical case definition, including the 14 day cough duration. A small proportion of these cases also identified as epidemiologically linked could also be given a confirmed status but only after meeting the clinical case definition. This later recommendation is consistent with the US CDC's case definition for probable cases and cases confirmed by epidemiologic linkage since at least 1990.[24] However some physicians were not aware that probable cases (Table 3.1 #1),[25] and this study has clearly indicated a misunderstanding of the role of confirmatory criteria with regard to the case definition. These recommendations would allow confirmation of 376 (7.8%) additional reported cases in the data. It did not affect those confirmed by epidemiologic linkage or probable case status, and would improve the confirmation rate among infants by 12% and sequentially fewer cases as age increases to 5% among adults. The sensitivity of the new recommendations among those currently confirmed by culture is 89.7%. The 44 culture confirmed cases without an attribute are evenly spread across the age groups, this may occur as a result of the current case definition which does not require any attributes when confirmed by culture. Bortolussi *et al* reported that among those less than two years of age a cough attribute was present in 80% by 7 days and in 97% coughing 14 days.[12] Therefore most infants would be confirmable under the new recommendations.

In addition to streamlining the case definition regarding laboratory positive case confirmation, a standardized protocol for PCR testing of pertussis should be created to minimize the risk of false positive testing. It is also important to define both

epidemiologic linkage and outbreak association status, as our study suggests that this information is reported in only 20% of cases. These categorizations are increasingly important with the upsurge of pertussis cases and statewide outbreaks. Having a clearer understanding of how cases are associated can be used to improve outbreak control strategies, by informing the targeting of vaccination campaigns and guiding case identification.

Table 05 Pertussis surveillance reporting criteria used during the study, as published by the Centers for Disease Control and Prevention, based on the 1997 case definition which is compatible with the 2010 edition. These definitions are established by and report.[2]

1.) Probable Case (**a clinical case**) defined as:
- Cough ≥ 14 days
  WITH
- One of the following: paroxysms, whoop, or post-tussive vomiting

2.) Confirmed Case requires an **epidemiologic link**, and the **clinical case** definition

3.) Confirmed Case requires a **positive PCR test**, and the **clinical case** definition.

4.) Confirmed Case requires a **positive bacterial culture** and **a cough**.

5.) Outbreak Case must occur in an **outbreak setting** and **coughs for 14 days** or more.

Table 3.6 The recoding of antibiotic information for reported pertussis case records in Michigan, 2000-2010 , to standardize additional information included as free form text in the original dataset (N=4800)

MDCH Code	Description	Original*	Recode of Antibiotic #1†	Recode of Antibiotic #2†	Antibiotic Class N(%)‡
1	Erythromycin (incl. pediazol, ilosone)	625	642	653	**Macrolide**
3	Clarithromycin /Azithromycin	2772	2867	3039	**3,692**
5	Amoxicillin	285	289	292	
7	Penicillin	4	4	4	**β-lactamase**
8	Ampicillin	14	16	17	**431**
10	Augmentin	46	50	49	
11	Ceclor	6	8	11	
12	Cefixime	17	21	27	
2	Cotrimoxazole (bactrim/septra)	58	64	70	***Other***
4	Tetracycline /Doxycycline	33	38	43	***312***
6	Other	104	110	134	
9	Unknown	89	100	96	
-	Missing	747	591	365	365

* These are the records coded as received from the Michigan Department of Community Health.
† This is the recode of the free-form text responses for the first and second antibiotic variables.
‡ Classification of the previous data according to antibiotic class. First generation cephalosporins were re-coded from the 'Other' classification to beta-lactams (N=31).

Table 3.7 Trends in reported data, describing the diagnostic timeline and the prevalence of case management characteristics among the probable and confirmed cases of pertussis in Michigan 2000 – 2010 (N=4790)

Year	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**
Total reported cases	127	148	61	139	313	334	631	270	347	918	1502
Illness timeline (mean)											
Cough duration (days)	36.1	38.7	36.3	34.4	30.4	32.5	28.0	31.5	32.8	31.3	29.0
Days to Antibiotic	18.6	20.5	20.2	16.5	14.9	16.3	14.7	17.4	17.1	16.0	14.5
Days to PCR test	26.0	16.6	18.0	16.4	16.6	16.9	16.1	19.0	15.8	16.1	15.0
Prevalence (%) of characteristic among those with information:											
Erythromycin	43.3	58.8	41.0	39.6	29.7	28.1	12.5	11.5	10.7	5.8	2.9
Other Macrolide	15.0	9.5	21.3	30.9	39.6	53.9	68.1	63.7	59.7	70.2	78.3
PCR positive	75.0	100.0	90.9	93.8	90.7	90.5	95.5	91.5	95.9	97.6	97.9
Outbreak	35.4	55.4	34.4	36.0	21.4	16.2	46.8	13.3	10.4	2.9	1.9
Epi-linked	16.5	19.6	9.8	23.0	20.4	19.2	11.6	12.2	15.6	22.2	20.4

Table 3.8 Descriptive statistics of time patterns of symptom onset, diagnosis, and treatment based on pertussis case records with reported cough from Michigan, 2000-2010.

				Week antibiotics were prescribed relative to cough			
		ALL		**0***	**1st**	**2nd**	**3rd+**
Variables	**N**	4,610		251	1,033	1,257	1,702
Male (%)	4,604	44.0		43.0	43.1	43.2	45.0
Age in years (median, IQR)	4,569	10.7	(2.8-33.6)	12.7	10.4	9.7	11.0
Days to 1st antibiotic (median, IQR) †	4,069	11	(6-20)	-6	3	9	22
Days to PCR (median, IQR) †	2,135	12	(7-21)	3.5	4	9	21
Days to diagnosis (median, IQR) †	2,819	16	(9-26)	8.5	7	12	24
Macrolide Antibiotic (%)	4,412	83.0		*78.8*	79.9	84.8	87.7
Coughing at final interview (%)	4,004	79.9		75.4	77.8	83.7	81.1
Cough duration days (final)	586	25	(15 – 41)	22	15.5	18	35
Cough duration days (still coughing)	2,708	26	(18 – 40)	25	19	21	34
Any cough attribute (%)	4,610	88.7		74.5	85.9	91.7	91.6
Whooping (%)	4,610	35.2		32.0	39.1	41.1	39.4
Paroxysms (%)	4,610	82.7		77.7	83.6	88.7	88.8
Post-tussive vomiting (%)	4,610	49.2		48.9	46.8	52.7	54.6
Apnea (%)	4,610	33.5		27.5	32.4	36.2	34.0
Laboratory positive test (%)	4,610	53.2		48.6	56.8	62.5	50.2
Culture (%)	4,610	10.2		8.4	11.1	11.0	9.8
PCR (%)	4,610	43.9		41.4	47.0	52.2	41.2
Epidemiologic linkage (%)	4,610	19.2		18.7	22.8	17.8	17.5
Outbreak (%)	4,610	16.1		3.2	14.13	17.0	17.9
Vaccination Record (%)	4,610	56.7		75.9	72.48	70.7	74.3

* These cases had their first medical visit prior to the onset of cough, and received antibiotics prophylactically.
† All time intervals are from cough onset date to the date mentioned.

Table 3.9 The odds of cases of pertussis in Michigan, 2000-2010 being reported with insufficient cough duration for confirmation of pertussis, according to the CDC guidelines.

Parameter	Odds Ratio	95% CI
Age Group		
Child (0-4yrs)	-Reference-	
School-aged(5-19 yrs)	0.429	(0.315 – 0.585)
Adult(20+yrs)	0.412	(0.292 – 0.582)
Post-tussive vomiting	0.585	(0.442 – 0.775)
Paroxysms	0.387	(0.287 – 0.523)
Whooping	0.721	(0.542 – 0.960)
Cough cessation	0.745	(0.545 – 1.017)
Culture positive	2.087	(1.357 – 3.211)
PCR positive	2.094	(1.571 – 2.791)
Epidemiologic linkage	1.440	(1.059 – 1.958)
Antibiotic		
Macrolides	-Reference-	
Beta-lactams	0.189	(0.189 – 0.608)
Other/Unspecified	0.703	(0.407 – 1.212)

Figure 3.3 Cumulative number of pertussis cases by quarter-year and age-group reported in Michigan, 2000-2010.

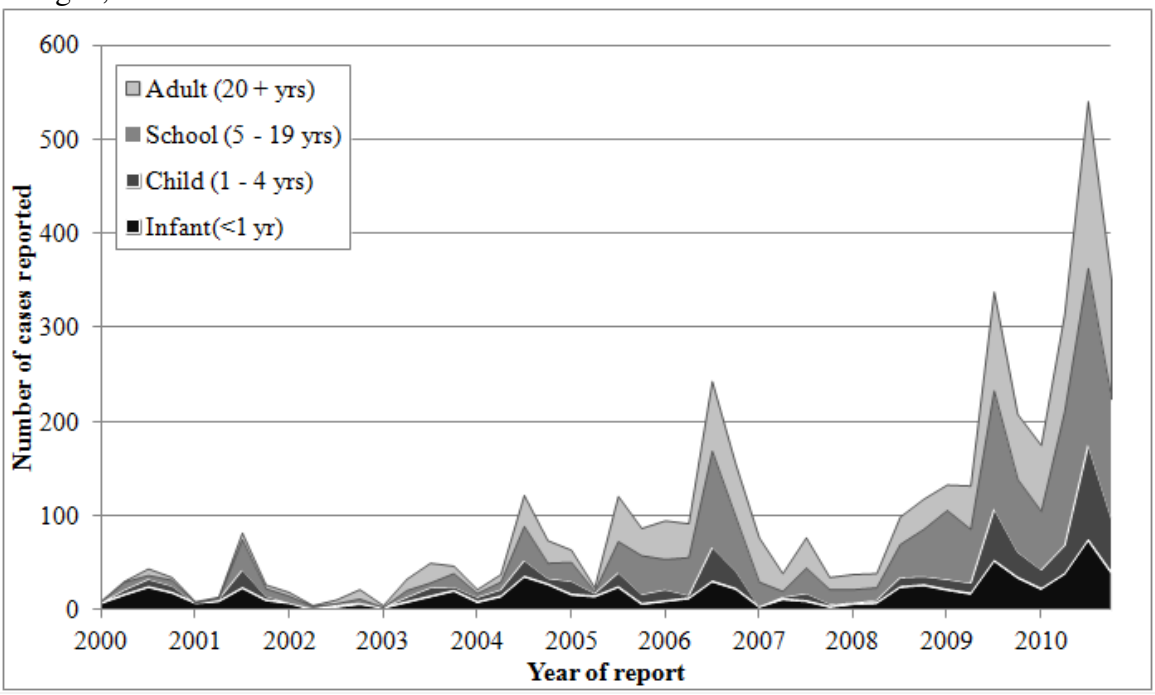
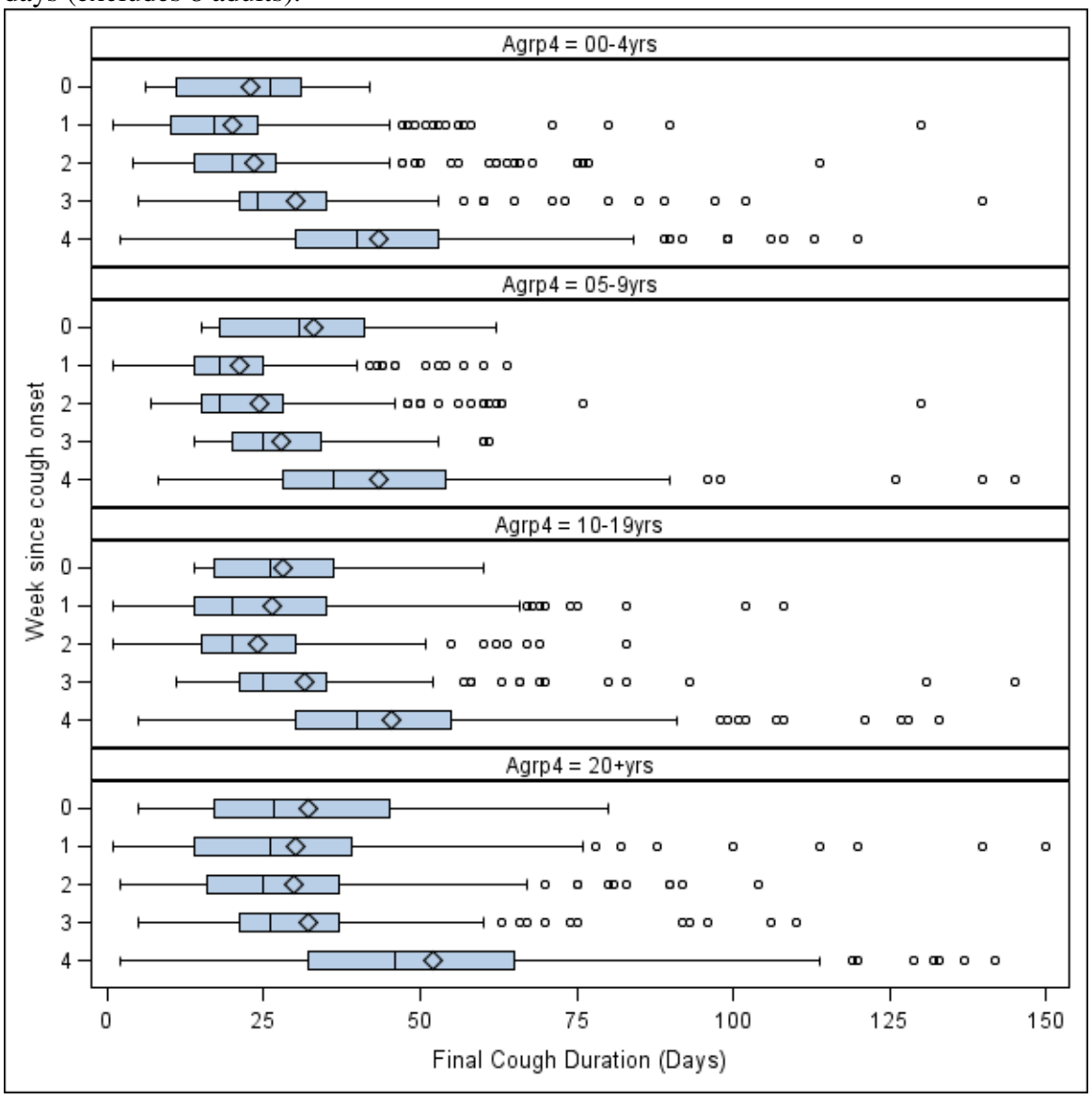


Figure 3.4 The distribution of reported cough duration by age-group and the week antibiotics were first prescribed relative to cough onset, where cough was less than 150 days (excludes 8 adults).



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Chapter 4
Population and County Risk Factors of Pertussis Incidence in the U.S.A., 1991-2008

4.1. Introduction

Pertussis, or whooping cough, is a prolonged cough illness that may result in hospitalization and mortality in very young children. While disease is experienced, diagnosed, and reported at the individual level, the factors leading to illness should be considered in a broader socio-cultural environment that contributes to risk; including social networks, health behaviors, and financial resources. These characteristics describe the nature of the local community and represent the greater context in which the individual moves and is potentially exposed to disease. The importance of the socio-structural construct is often discounted because medicine is evidence driven and practiced at the individual level. However, the intangible beliefs and perceptions of health are molded by the individual's friendships, past experience and what he recognizes as the norm in his community.

The field of social epidemiology characterizes these socio-structural factors which impact the distribution of health and disease and explores the mechanism of influence on both individual and population health.[1] Social epidemiology generally explores complex health outcomes of insidious onset, frequently associated with aging including obesity, mental health, and mortality. Vaccine preventable diseases like pertussis differ in that they: primarily affect pediatric populations; have a specific biological cause which is preventable; had a drastic decline of incidence secondary to introduction of a vaccine. The social epidemiologic approach is useful perspective as health behaviors are socially patterned derived from the physical and social environment of the individual.

There has been very little work in the field of social epidemiology directed at the study of vaccine preventable diseases; although a recent study examined community risk factors associated with immunization coverage levels, including pertussis containing vaccines.[2]

Some individual-level disease investigations have suggested potential community-level characteristics of disease risk, such as family size, age distribution, and commuting.[3,4] Community-level characteristics such as income inequality, unemployment, and the proportion of the workforce commuting, each describe a group of people among whom the case resides. As a communicable disease of exclusively human origins, pertussis infection would be strongly affected by the specifics of the local socio-cultural environment.[4,5] This plays out not only in the physical interactions and resources but also in the exchange of health beliefs and behaviors, that flow across social networks and establish social cultural. For a vaccine preventable disease (VPD), like pertussis, these environmental factors mold both the views on immunizations and healthcare preferences. As pertussis is primarily a disease of the young, most cases are passive recipients of the socio-cultural environment as filtered through the choices of their parents or guardians.

The social epidemiology perspective can develop our understanding of pertussis risk factors by through an examination of community-level, societal and environmental influences that result in a high risk setting. In this study, we examine three broad categories of population-level risk factors and their effects on pertussis incidence: factors of disease acquisition, healthcare access, and poverty.

4.1.1. Disease acquisition

An individual's potential exposures to a pathogen are a combined byproduct of the social-network structure of the community, both internally and with other communities.[6] In a consideration of county-level predictors for risk of pertussis exposure, there are two components to be evaluated; disease introduction and disease transmission. The more frequently people enter and exit a geographic area, such as a county, the greater the risk that the bacteria is introduced into the resident population.[7] At the county level, this introduction risk will be analyzed though estimates of community connectivity, assuming the more highly connected counties have more frequent importation of infection. This is captured in factors such as the proportion of the workforce commuting out of county and the connection to local urban or metropolitan areas, since disease tends to spread outward spread from large population centers.[8]

The within-community mixing relates directly to transmission risk, and describes the risk of exposure to *B. pertussis* at the community level. Factors such as family-size, group housing, household-level crowding, and county-level population density all quantify daily interaction patterns among the population.[4,6]These measures are somewhat crude but the intent, nonetheless, is to summarize routine personal interactions by quantifying the county population who live in high contact settings. The age composition of the population is included under this heading, as pertussis tends to be more distinctively symptomatic, and serious among young children, with less specific symptoms occurring in older and vaccinated individuals, making diagnosis more difficult.[9]

4.1.2. Healthcare access

Healthcare access is important to both pertussis prevention and diagnosis. Access can be considered from two different but equally viable perspectives. The first is the availability of clinical or healthcare services; the second is the ability or willingness to use said services. The availability of healthcare services includes any interaction where an individual has access to preventive immunization or for the clinical diagnosis of pertussis to be made. The ability to use services can be impeded by lack of health insurance, cultural barriers like language and ethnicity, and physical barriers such as distance or lack of transportation.

Healthcare services are most effective in impacting pertussis epidemiology through provision of clinical preventive services like routine vaccination of young children. The recommended vaccination schedule for pertussis requires multiple visits to a healthcare provider at 2, 4, 6 and 12-18 months of age. Additional boosters are recommended at 4-6 years and again at 11-12 years.[10] Immunization coverage studies have shown that immunization rates are highest in areas where there are more pediatricians per capita.[2] The age, training and specialties of local physicians might affect patterns.their views on the importance of preventive services as well as diagnostic

Utilization of services can be affected by a number of factors including a person's health insurance status and cultural barriers. Cultural incompatibility between an individual and those providing the health services is an important aspect of healthcare utilization, because it goes beyond the physical services and aims to describe avenues of perceived

inaccessibility. For example, reluctance to use conventional healthcare services can be due to wariness, cultural values, stigma, or personal beliefs.[11] This could be measured as the proportion of a population who are considered to be outside of the mainstream culture, minorities (proportion non-white), under-educated, foreign-born, or non-English speakers. In the long run, any reluctance to utilize healthcare services, whether due to financial constraints or social convention, has the potential to weaken the health profile of the community. As surveillance data originates through providers of conventional medical practices, the data represents those who are willing and able to seek care from these sources. Those who choose to use alternative medicinal practices are both more likely to be unvaccinated; [12] if there is critical mass of like-mindedness in a given area they can facilitate ongoing transmission.

4.1.3. Health & Economic Risk Factors

While access and use of conventional healthcare resources are important factors to consider when assessing community risk for pertussis, other secondary factors can affect pertussis incidence as well. For example, healthcare use patterns may be influenced by individual factors, relating to the personal resources of the individual or household-level constraints, such as finances, and transportation. The physical proximity of healthcare resources such as a hospital, clinic or doctor's office, where clinical diagnoses and care occur, vary by residence, and is tied to factors such as population density, rurality, financial resources of residents, and the resulting fiscal solvency of the local healthcare enterprise. While some of these factors are related to the affluence of the community, special governmental programs attempt to address these disadvantages and allocate resources to mitigate the effects of poverty, at both the household and community levels. Poverty, wealth inequality, and poor child health were considered factors that may increase disease risk in local communities. These descriptive measures can be quantified at the county level and used to describe the relative degree of disadvantage present in the county. In addition to poverty measures, other socio-economic factors, including unemployment, lack of health insurance, or the proportion of single-parent households diminish resources available to people and often occur concurrently, with clustering of these factors occurring within communities. In general, communities with a higher proportion of these disadvantages could be expected to experience a higher overall

incidence of pertussis. This study examined population composition and distribution, healthcare availability, cultural barriers and poverty quantified at the county level, as indicators of increased risked of pertussis.

4.2. Materials and Methods

4.2.1. Pertussis Case Data

The data for this analysis were provided by the United States Centers for Disease Control and Prevention (CDC) as all pertussis cases reported from physicians and hospitals, between 1 January, 1991 and 31 December, 2008. The CDC has designated pertussis and many other diseases as nationally notifiable. The legal basis for formally requiring the report of health conditions to public health authority is under state jurisdiction, and all 50 states, the 6 territories, and Washington DC explicitly require the reporting of pertussis.[13] The states, in turn, send reported pertussis cases to the CDC, and these case reports include identifying demographic characteristics and the county and state of case residence.

The original data set contained 167,122 records submitted as either probable (clinical cases) or confirmed (cases with laboratory evidence) pertussis case. Of these records, 163 were excluded as multiple cases were combined in a single entry. Another 970 records could not be assigned an age, and 2,863 more were not assigned to a specific county, although a valid state of residence was provided. The remaining 163,554 cases were analyzed by age and county but collapsed over time. This was done for statistical purposes to minimize the numbers of zero reports in the data. Of the 3,143 U.S. counties 13.6% (N=427) did not report any pertussis cases for the entire study period; they were included in the analysis. Counties without reported cases were distributed across the country, although 75% of these counties had a population of less than 260,000 people.

4.2.2. Demographic and Risk Factor Data

Residence of cases was provided as county and state which constitutes the finest spatial resolution in the analysis. County-level demographic data were collected primarily from federal sources and represent standardized values for all U.S. counties. Population data was aggregated by age group and county from the 2000 Census Bureau estimates. Census

data also provided household-based information summarized at the county level. The county-level predictors are the same for all age groups within a county.

County-level predictor variables were gathered from several sources, but primarily from the Health Resources and Services Administration's (HRSA) Area Health Resource File. This database contained healthcare availability factors, and data on cultural barriers, poverty and introduction risk. The variable of "Interstate Miles", representing risk of *B. pertussis* introduction, was created from spatial aggregation methods (available in ArcGIS version 9.2, Redlands, CA), using the road system base layer in ArcGIS. To facilitate comparisons, predictor variables were grouped into three broad categories involving bacterial transmission, healthcare barriers and poor child health. A disadvantaged county is one that has a higher proportion of healthcare barriers or poor child health.

4.2.3. Analysis

The county-level association of each predictor variable with the incidence of pertussis was first examined using standard regression methods for bivariate associations. Then, a negative binomial regression model was developed in which the count of the number of cases per age-group within each county was the outcome, with an offset being the log of the population for each age-group. The negative binomial distribution is appropriate for count data in situations where the variance is greater than that allowed for a Poisson distribution. This was done using generalized estimating equation (GEE) methods, which created a population average model where the average effect of each predictor is estimated across all counties. Clustering of county values was adjusted for by specifying an exchangeable correlation structure for the repeated measures (i.e., the count for each age group), and using the robust estimates of standard error. By taking into account the correlation among observations in the same county, the sandwich-type estimates of standard errors adjust the model-specific standard errors and are consistent, even in the presence of a mis-specified covariance structure.[14]The outcome was the aggregated 17-year count of reported pertussis cases by county for each age-group: infants <1 year, pre-school 1-4 years, school-aged 5-19 years and adults 20+ years. This count was offset by

county size using the log of the age-specific county population, due to the log-based link function.

County-level predictors were grouped into the following categories: interpersonal proximity and contact, pathogen introduction, healthcare availability, cultural barriers to healthcare, poverty and inequality, and poor child health. Within each grouping the individual variables were run in a bivariate GLM model to determine the explanatory power of the predictor, adjusting for age and controlling for clustering. Significant predictors ($p < 0.10$) from the bivariate analyses were entered into a single model and collinearity of the predictors was assessed. Where collinearity was found, as indicated by an Eigenvalue and condition index of >30,[15] these variables were removed from further analysis, and collinearity was re-assessed until the maximum condition index did not exceed 30. A category-specific model was then fit with each predictor, using a backward step-wise model building approach, including all significant, non-collinear predictors. Variables appearing as non-significant according to type-III tests were considered for removal from the model. Non-significant variables were retained when the model fit was improved by their retention, as determined by the QIC (Quasilikelihood under the Independence model Criterion) statistic, the goodness of fit criteria for GEE models.

The significant predictors for each category were then combined into an overall model, and assessed for correlation and then collinearity. Remaining variables were reviewed in a similar backward step-wise manner. All modeling was conducted using SAS version 9.3 (Cary, NC).

4.3. Results

Risk-factors for pertussis infection were identified under three broad categorical associations: pathogen transmission (1a,1b), healthcare barriers(2a-c) and poor child health(3). Initial bivariate analysis indicated that many of the significant associations involved an inverse relationship between indicators of disadvantage and pertussis incidence (Table 4.1). A positive association was seen among the pathogen introduction variables quantifying urbanicity, as well as the barriers of age, housing stress and the per capita rate of licensed medical personnel. Most socioeconomic characteristics, classified

as barriers to receiving healthcare, behaved in a consistent manner which seemingly contradicts the hypothesis that disadvantage results in more disease.

To explore the incongruent findings between the two classes within the pathogen transmission variables, risk of introduction and risk of contact, population mobility and density were selected as representative variables for stratification. This assessment attempted to determine whether these aspects of urbanization could account for the discordance, as urban areas are known to have a lower incidence of pertussis. Table 4.2 separated the counties according to the two classes of variables within pathogen transmission, and evaluated whether pertussis incidence showed a pattern indicative of either or both population density (above or below average) or the mobility of the county (presence or absence of an interstate highway within the county limits). The four columns on the right show a gradient from the more densely populated and connected counties, to more sparsely populated, less dense counties. The orientation of the four categorical columns is arbitrary and the current form was selected to parallel the visual decline in population density. Two-tailed Satterthwaite T-tests for unequal variances were conducted to determine if significant differences occurred across either population density or presence of an interstate. The association between each variable and pertussis incidence has been shown previously (Table 4.1).

Most of the predictors showed significant differences across both aspects of pathogen transmission, population density and mixing. The only other variable, that paralleled density, and decreased across all four groups was the rate of licensed medical personnel (MD and RN) per 1,000 persons. A few variables exhibited trends that increased while population density declined including: median age, the proportions of children in poverty, and the lack of health insurance. Only housing stress and the proportion of minorities showed a significant differences in pertussis incidence when an interstate was present or absent, but was not associated with density. The inverse, an observed discrepancy in pertussis incidence observed in high verses low density counties but not seen in the presence/absence of an interstate, was seen for crowding, low birthweight births, and workforce commuting out of county. Pertussis was found to be higher in low density

areas (Below average density=2.06, above average density=1.71 average age-adjusted, annual incidence per million persons).

In the national multivariable statistical model, as with the bivariate associations, most predictors were associated with decreased pertussis incidence (Table 4.3). Only two remaining variables were positively associated with pertussis incidence; the per capita rate of licensed medical personnel and housing stress, the latter of which was marginally non-significant. The per capita rate of licensed medical personnel shows inverted associations with both child poverty and those lacking health insurance (Table 4.2), suggesting this metric loosely mirrors affluence, therefore its absence marks disadvantage. Lower per capita rates of licensed medical personnel are associated with decreased incidence, consistent with the other healthcare barriers and indicators of disadvantage. The variables for pathogen transmission, population density and mixing (the commuting workforce) as well as adverse child-health outcomes were also significantly associated with lower pertussis incidence.

Stratifications of the national model on the presence of an interstate within county limits was conducted to determine whether there were any significant differences in risk factors bases on connectivity and isolation of the communities (Table 4.3). The interstate-free, isolated counties having theoretically fewer opportunities for pathogen introduction were similar to the national model. Counties with interstates showed a significantly higher incidence of pertussis associated with housing stress, defined by the Economic Research Council as the proportion of houses with at least one of the following characteristics: incomplete plumbing, incomplete kitchen facilities, renter or owner cost >30 % of household income, or >1 person per room.

To determine whether these associations were consistent throughout the study period with the upsurge of cases and significant changes in diagnostic measures, the national model was run on subsets of the data, defined as follows: prior to 1997 when then case definition did not include PCR, 1998 through 2003 as PCR was being incorporated into diagnostic practice, and 2004 or later when large scale outbreaks began occurring. There were no substantial differences among these period-specific models, which were similar to the national model. (Data not shown.)

Because healthcare outcomes and unhealthy conditions are known to vary regionally throughout the United States, the model was stratified on the four census regions (Table 4.4). These individual, region-specific models did not vary significantly from the base model, except for the proportion of the population with very low education in the Midwest, which not only changed direction but became a risk factor for greater pertussis incidence. This finding resulted in a more detailed investigation of populations known to have less than a high school education. We focused on the distribution of the Amish population as they are known to complete schooling after the eighth grade, reside primarily in rural farm economy areas associated with the Midwest, and have been reliably enumerated by county in the 2010 Religious Congregations and Membership Study (www.RCMS2010.org), which takes a census of a wide range of religious affiliations.

"Amish counties" were operationalized as counties where the Amish congregation was greater than 1,000 members or where the Amish population comprised more than 5% of the country population. Two-thirds of all Amish counties were found in the Midwest region, though large populations are also found in adjacent states (i.e. Pennsylvania, New York and Kentucky). In states having at least one Amish county, Amish counties have an age-adjusted average annual incidence of 2.91 per 100,000 county residents while non-Amish counties report an average 1.74 incidence (Satterthwaite T-test $p<0.01$). Though there is not a significant difference within any of the three regions based on these states, excluding the western states. Nor is there a significant difference in pertussis incidence when Amish counties are re-defined as comprising a minimal 1% of the county population or greater than 1000 Amish members, in states with a minimum of five Amish counties. An average discrepancy between the Amish and non-Amish counties was a slightly elevated 0.41 cases per million in Amish counties (Satterthwaite T-test (unequal variances) $p=0.13$)). This risk difference may drive the increased pertussis incidence associated with under-education in the Midwestern region, but not elsewhere in the U.S.

4.4. Discussion

This county-level analysis of risk factors associated with pertussis in the U.S. produced unexpected results, with more disadvantaged counties experiencing a lower incidence of

reported pertussis. These associations were consistent for variables of increasing disadvantage identified by all three categorical areas: pathogen transmission, healthcare barriers and poor child-health outcomes. The directionality was strong and remained constant throughout the U.S., across time, and in counties both with and without interstate highways. Of particular interest was the decreased incidence of reported pertussis associated with lower population density and the greater proportion of the workforce commuting to other counties, and the increased risk of pertussis in the Midwest among those counties with a greater proportion of the population lacking a high school education.

The pathogen transmission factor, population density continued to be highly significant in most models, and was inversely associated with the incidence of pertussis. This association is historically consistent as far back as the 1910s.[16-18] Historic findings were attributed to delayed exposure in non-urban settings based on a comparison of infectious disease incidence rates between urban and rural military recruits in World War I and again in World War II.[18] While the magnitude of the observed urban/rural discrepancy in pertussis incidence has declined, it is still evident. The importance of the commuting workforce overall, but especially in counties without interstates, may continue to support this theory of delayed pertussis acquisition. The use of immunizations and the increased mobility of the U.S. population may mitigate the discrepancy in pertussis incidence rates between urban and rural areas.

The commuting workforce, a variable describing the risk of pathogen introduction, was seen to be important both nationally and in counties without interstate highways. This variable was selected to address population mixing; however, in counties with an interstate highway, county-to-county interactions occur more frequently and for purposes beyond employment. So, a single variable quantifying the commuting workforce cannot capture the full extent of these interactions. Stratification by region also nullified an observed effect of commuting and it is possible that commuting out of county in the national model may reflect regional effects, rather than county-level mixing patterns. This could be due to relative county size where northeastern counties have a much

smaller area, when compared to counties in the Midwest and West, where the size of a county would limit the proportion of the workforce commuting out of county.

The only indicator of disadvantage that was a risk factor for increased pertussis in the stratified analyses was the proportion of the population with less than nine years of education, in the Midwestern states. This change of effect may be result from a combination of factors based on the distribution sub-populations in modify the effect of what is traditionally identified as a disadvantage and the disease outcome. For example individuals in the Midwest are generally characterized as having a strong sense of social responsibility. This perspective may result in different cultural perspectives on the importance of vaccination, across all levels of society and where vaccine refusers are relatively rare, and low vaccination is the result of under vaccination. Both coastal regions, the West and Northeast, are more inclined promote individual rights over the collective benefit of the community, and have a more heterogeneous mixture of refusers and under-vaccinated. However it is possible that in the Midwest the inadequately vaccinated are more homogenously under-vaccinated and as a result this variable of low educational attainment acts as a proxy for low vaccination levels based on other social norms which describe a large proportion of under-vaccination. This may be the case with low educational attainment among the Amish, who predominantly reside in the Midwest, where low vaccination coverage rates have been reported.[19-22] These communities are supportive of immunizations, though most children have received only some vaccinations.[20,21] This suggests that low education may behave as a proxy for under vaccination in this region, and should be interpreted as a cultural barrier to healthcare access, rather than an indicator of disadvantage.

While economic and cultural disadvantage is frequently addressed in populated, urban settings, we observed child poverty, crowding, low educational attainment, and a lack of medical personnel to have been more prevalent in low density populations. These variables were inversely associated with pertussis incidence, as was population density itself. Therefore, the counterintuitive directionality of disadvantage being associated with lower reported pertussis incidence is consistent across our entire U.S. county sample, not just in urban areas as previously reported. This suggests that our findings are not the

result of underreporting based on resource differentials in urban verses rural health departments.

While our analysis was limited to a county-level analysis our findings indicate higher disease rates in more affluent counties. The State of Healthcare Quality 2012, published using the Healthcare Effectiveness Data and Information Set (HEDIS) reports, show that vaccination coverage rates are high among traditionally disadvantaged Medicaid enrollees at rates near commercial HMOs and above rates seen in commercial PPOs.[23] These higher disease rates in more affluent communities may be a consequence of a tendency towards vaccination refusal in white populations with higher education and higher income.[24,25] Regarding disease control, pertussis is observed to occur in both more affluent counties and areas of low vaccination. Local public health workers should target control measures to these population in incipient outbreak settings.

This is an ecologic study of disease risk as such our findings describe the risk of pertussis at the county level. A study at the county-level is unable to identify the effects of pocket populations, who reside within the county. If the sub-population is small then the county will generally describe the majority of the population. However if the population is divided more evenly the county descriptors will not accurately represent either sub-group. This study was also unable to control for vaccination coverage, a strong predictor of disease risk and an important descriptor of local healthcare cultural views. [12] Low vaccination coverage is comprised of two fundamental groups, those who are under vaccinated and those who refuse some or all vaccinations. These studies have very different demographic profiles. Under vaccination tends to be associated with disadvantage, while vaccine refusal is associated with higher education, income and maternal age.[12,25] Our findings are more consistent with the demographic profile of vaccine refusal, where affluence is associated with an increased incidence of pertussis.

These unexpected findings warrant further study, they seem to suggest that the risk of pertussis is associated more strongly with vaccine refusal than under vaccination. More research characterizing the effects of population density and health care barriers with disease specific outcomes will further our understanding of the socio-structural risks factors associated with pertussis. This will allow public health and medical care providers

to better understand the disease risks of their local communities and to develop specialized disease prevention programs.

Table 4.10 Initial bivariate analysis of county-level predictors of pertussis incidence grouped by risk category bacterial transmission (1), healthcare barriers (2), & poor child health (3), after controlling for age. Direction of the association is indicated to the left of each variable.

Pertussis Risk Category	Highly Significant ($p \leq 0.01$)	Significant ($0.01 < p < 0.10$)	Non-significant ($p \geq 0.10$)
1a. Inter-Personal Proximity and Contact	- Household size (mean) - Population <5 y.o. (%)* - Population in Group Housing (%) o Population Density	- Crowding - Family size (mean) o Housing Density	o Births per hospital o Urban population%
1b. Pathogen Introduction	- Commuting Out	o Interstate miles† + Urban influence code + Urban rural continuum codes	
2a. Healthcare Availability	+ Licensed Medical Personnel /1,000 persons - Uninsured (Health)(%)	o Medicaid Eligibility	- Hospital Beds/ 1000 o MD <35% + MD Preventive Medicine (%) - MD Public Health (%) - Rural Clinics
2b. Cultural Barriers to Healthcare	o Non-English Speaking - Racial Minority* - Less than High School Education (%)	+ Median age	- Foreign Born - Hispanic Ethnicity o Medicare eligibility
2c.Poverty and Inequality	- GINI o Median Family Income - Children in Poverty % - Persistent Poverty - Unemployment	- Home ownership + Housing Stress	
3. Adverse Child Health Outcomes	- Infant Mortality - Low Birth-weight		

*Data from the Census Bureau.
†Calculated from ArcGIS roadways map.
Symbol Key: (+) increasing risk, (o) IRR between 0.999 and 1.00, (-) decreasing risk

Table 4.2 Summary demographic and socioeconomic measures for United States counties grouped by county rurality (population density) and connectivity (presence of an Interstate highway).

		Interstate	NO Interstate	Interstate	NO Interstate	2-Tailed T-test	
	ALL	High Density	High Density	Low Density	Low Density	Density	Interstate
Variable	**N=3,143**	**N= 946**	**N= 627**	**N= 422**	**N= 1,148**		
Pertussis Incidence (mean)*	1.88	1.74	1.65	2.15	2.03	< 0.01	0.83
Age Median (Yrs)	37.32	35.91	36.95	37.47	38.63	< 0.01	< 0.01
Population Under 5yrs (%)	6.32	6.61	6.30	6.33	6.10	< 0.01	< 0.01
Children in poverty (%)	17.94	14.71	17.77	19.0	20.31	< 0.01	< 0.01
Crowding % (1+ person/room)	3.58	3.35	3.09	4.11	3.84	< 0.01	0.93
Density (persons/sq.mi)	242.87	670.06	161.45	20.08	17.21	< 0.01	< 0.01
Housing stress (%)	17.12	19.24	15.15	19.67	15.52	0.47	< 0.01
Interstate miles	17.38	38.74	N/A	42.58	N/A	< 0.01	< 0.01
Low birthweight births %	8.03	8.06	8.17	7.93	7.94	0.02	0.89
MDs+RNs per 1,000 pop	3.32	7.24	3.20	1.25	0.90	< 0.01	< 0.01
Racial minority (%)	15.65	17.08	14.08	15.88	15.25	0.44	< 0.01
Less than High School Education (%)	9.09	7.12	9.56	9.52	10.30	< 0.01	< 0.01
Unemployment (16+yrs) (%)	5.81	5.81	6.40	5.40	5.63	< 0.01	< 0.01
Uninsured (%)	14.75	12.69	13.61	16.27	16.52	< 0.01	< 0.01
Workforce Commuting out of county (%)	32.62	34.29	35.35	31.08	30.40	< 0.01	0.08

* Mean, annual, direct age-adjusted cases per 1,000,000 people per year, based on the period 1991-2008. The standard was the U.S. age-specific population, from the U.S. Census Bureau estimates.

Table 4.11 A negative binomial regression population average model of county-level risk factors associated with reported pertussis incidence between 1991 and 2008 in the United States, age stratified. Stratified Models A, separate the data according to whether an interstate highway crossed the county borders this is a rough estimate of the inter-county mobility of the population.

Parameter	National Model		Stratified Models A			
			Interstate (N=1,368)		**NO Interstate** (N=1,775)	
	IRR	Conf Int.	IRR	Conf Int.	IRR	Conf Int.
Age Group						
Infant (< 1 yr)	47.19***	(44.49 , 50.04)	47.00***	(43.63 , 50.63)	47.8***	(43.61 , 52.33)
Child (1-4 yrs)	6.98***	(6.51 , 7.48)	6.44***	(5.93 , 6.99)	7.52***	(6.75 , 8.37)
School-aged (5-19 yrs)	5.17***	(4.87 , 5.47)	5.19***	(4.83 , 5.56)	5.09***	(4.66 , 5.56)
Adult (20 + yrs)		-Reference-		-Reference-		-Reference-
Crowding (1+ person/room)	1.01	(0.98 , 1.03)	1.00	(0.95 , 1.03)	1.02	(0.99 , 1.05)
Population Density (Ln)	0.85***	(0.80 , 0.88)	0.84***	(0.78 , 0.89)	0.89**	(0.82 , 0.96)
Workforce commuting out of county (%)†	0.98**	(0.96 , 0.99)	0.99	(0.97 , 1.00)	0.96**	(0.93 , 0.98)
Medical personnel (MD& RN) per 1000 persons	1.36***	(1.20 , 1.53)	1.57***	(1.37 , 1.8)	1.05	(0.81 , 1.35)
Minorities (%)†	0.98	(0.94 , 1.00)	0.96	(0.92 , 1.00)	0.98	(0.93 , 1.02)
Less than high school education (%)†	0.85***	(0.76 , 0.93)	0.95	(0.80 , 1.10)	0.79***	(0.7 , 0.89)
Children in poverty (%)†	0.94*	(0.88 , 0.99)	0.96	(0.87 , 1.04)	0.93*	(0.86 , 0.99)
Housing Stress	1.16	(0.98 , 1.37)	1.25*	(1.01 , 1.54)	1.07	(0.83 , 1.38)
Low birthweight infants (%)†	0.88***	(0.83 , 0.92)	0.87***	(0.80 , 0.93)	0.89***	(0.83 , 0.94)

* Significant at $0.05 \geq p > 0.01$
** Significant at $0.01 > p \geq 0.01$
*** Significant at $p < 0.01$
† One increment increase in the percentage measure represents a 5% increase. For example: For every 5% increase in the proportion of the population with less than 9 years of education, the pertussis IRR decreases by 15%, in the national adjusted model.

Table 4.12 A negative binomial regression population average model of county-level risk factors associated with reported pertussis incidence between 1991 - 2008 in the United States, age stratified (*continued*). **Stratified Models B** separate counties by U.S. Census regions, to determine if there are regional distinctions in pertussis risk factors.

	Northeast (N=217)		Midwest (N=1,055)		West (N=447)		South (N=1,424)	
	IRR	**Conf Int.**	**IRR**	**Conf Int.**	**IRR**	**Conf Int.**	**IRR**	**Conf Int.**
Age Group								
Infant (<1 year)	27.31***	(23.36 , 31.9)	40.63***	(36.94 , 44.67)	29.50***	(26.38 , 32.92)	71.60***	(64.59 , 79.36)
Child (1-4 years)	4.95***	(4.14 , 5.92)	7.10***	(6.40 , 7.87)	5.92***	(5.13 , 6.82)	8.04***	(7.12 , 9.07)
School-aged (5-19 years)	7.53***	(6.78 , 8.36)	4.94***	(4.53 , 5.37)	3.97***	(3.57 , 4.4)	5.29***	(4.71 , 5.92)
Adult (20 + years)		-Reference-		-Reference-		-Reference-		-Reference-
Crowding (1+ person/room)	0.75***	(0.62 , 0.91)	1.02	(0.97 , 1.07)	0.97	(0.93 , 1.01)	1.02	(0.96 , 1.07)
Population Density(Ln)	0.79**	(0.66 , 0.93)	0.93	(0.85 , 1.01)	0.99	(0.91 , 1.06)	0.80***	(0.7 , 0.9)
Commute out of county (%)†	0.98	(0.93 , 1.02)	1.01	(0.98 , 1.03)	0.98	(0.95 , 1.01)	0.98	(0.94 , 1.01)
Medical personnel (MD& RN) per 1000 persons	1.36*	(1.01 , 1.82)	1.41***	(1.19 , 1.64)	1.10	(0.77 , 1.57)	1.18	(0.89 , 1.56)
Minorities (%)†	1.14	(0.94 , 1.38)	1.07	(0.99 , 1.14)	1.02	(0.96 , 1.08)	0.98	(0.94 , 1.02)
Less than high school education (%)†	0.95	(0.61 , 1.46)	1.20***	(1.05 , 1.35)	0.87	(0.72 , 1.05)	0.89	(0.74 , 1.05)
Children in poverty %†	1.02	(0.79 , 1.3)	0.91*	(0.83 , 0.98)	0.93	(0.84 , 1.01)	0.91	(0.82 , 1.01)
Housing Stress	1.46	(0.96 , 2.22)	1.03	(0.72 , 1.44)	1.05	(0.82 , 1.32)	0.88	(0.64 , 1.21)
Low birthweight infants (%)†	0.82	(0.64 , 1.05)	0.88***	(0.82 , 0.94)	1.01	(0.94 , 1.08)	0.90**	(0.82 , 0.97)

* Significant at $0.05 \geq p > 0.01$
** Significant at $0.01 > p \geq 0.01$
*** Significant at $p < 0.01$
†One increment increase in the percentage measure represents a 5% increase. For example: For every 5% increase in the proportion of the population with less than 9 years of education, the pertussis IRR increased by 20% in the Midwest age-adjusted model.

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Chapter 5
Conclusions

5.1. Summary of Major Findings and Research Implications

The introduction of the whole cell pertussis vaccine in the United States during the 1940s controlled pertussis transmission to an absolute low in 1976 of 0.46 cases per 100,000. The resurgence of pertussis in the United States with the return to widespread, year round transmission, and cyclic statewide outbreaks has posed a significant challenge for disease control. The addition of booster vaccination in adolescents and adults has not halted the increasing baseline incidence of disease. And the cocooning strategy, vaccinating the contacts of newborns, has not been effective as only 5% of adults with infant contact had received the vaccination.[1] The incidence of pertussis among infants has also continued to increase. The observations of the increasing incidence of pertussis, identification of emerging risk groups and vaccination control strategies are based on surveillance data.

This dissertation (Chapters 2 and 3) evaluates the comprehension of the pertussis clinical case definition, based on the secondary data included in the case report. The primary finding, presented in Chapter 2, was that only 69.4% of the records could be internally validated. An additional 14.0% reported a cough of insufficient duration to fulfill the 14-day minimum required of a clinical case. These later cases were termed "suspect," but we had high confidence in their diagnosis as valid pertussis cases. These records included both a cough attribute (whooping, paroxysms or post-tussive vomiting) and a confirmatory indication (PCR positive or epidemiologically linkage), and the average duration of cough had an inter-quartile range of 8-12 days. This duration is close to the 14-day minimum cough duration required in the clinical case definition for surveillance purposes. At least 70% of these cases acknowledged incomplete cough data as they were still coughing when last seen by the physician. Our results suggested a high validity for 83.4% of cases being reported.

These findings initiated an additional investigation of the factors associated with reporting an inadequate cough duration which fails to meet the clinical case criteria (Chapter 3). They also highlighted the incomplete nature of clinical cough length, in surveillance records and spurred another investigation of the average complete cough duration of illness (Chapter 3). In that comparison, the average duration of cough was not found to differ between those who reported cessation of cough and those still coughing, both averaging 25 days (IQR: 15-41 days). Rarely are cases identified by diagnosis tracked for the full course of disease. We recognize that an average cough duration of 3.5 weeks is quite sufficient for diagnostic and surveillance purposes, though an exhaustive follow-up averages 7 weeks and may exceed the resources of the healthcare provider.[2] Routine surveillance data is incomplete regarding reported cough length and should not be used to determine the effect of treatment on cough duration.

When stratified by the first healthcare visit after cough onset, as indicated by the receipt of an antibiotic, our findings illustrated an increasing association with the length of the reported cough (Chapter 3). The theoretical analysis of case exclusion bias, where individuals seeking care in the second week of cough could by definition cough no less than 14 days, showed sequentially longer average cough durations when artificially truncated over the first 5 weeks of cough. This magnitude of effect from our theoretical analysis was observed in the Michigan dataset when stratified by week of cough, suggesting that the differences seen in cough duration cannot be attributed to the timing of antibiotics. Surveillance data, in general, is not suitable to determine the average cough length or the effect of antibiotics on coughing, as both are predicated on knowledge of a complete cohort from disease identification (or exposure) until the cessation of coughing. [2] The 15.6% of cases in the data, who ceased coughing before the end of surveillance, are a biased subset who happened to finish coughing within the average follow-up time. They are not a representative sample of all cases, because those who reportedly were still coughing at the end of surveillance have a similar mean and distribution to those who had ceased coughing, suggesting that the follow-up time is the limiting factor and not the cough duration.

The suspect cases identified in Chapter 2 failed only this 14-day minimum cough length criterion and would otherwise have been reportable confirmed cases. They had sought care earlier in the course of illness than those with adequate reported cough durations, as in seen in other studies.[3] Logistic regression analysis of those who sought case prior to 14 days, associated inadequate cough report with the presence of a confirmatory indication. Positive bacterial tests confirmation, both culture and PCR, each had a two-fold greater odds of reporting inadequate cough duration. Epidemiologic linkage to a laboratory confirmed case increased the odds of inadequate cough duration by a half. These odds highlight a misinterpretation of the case definition of the individual assigning the case status, probably a health department worker, as a confirmatory indication does not supersede the need to fulfill the clinical case definition, except in the case of a positive culture, which was obtained in 10.2 % of the cases.

This excess of incomplete cough duration is most problematic among the PCR-positive cases as they comprised 43.0% of the reported cases during the 2000s, and a third of them did not include a sufficient cough length. Similar findings of individuals testing positive by PCR but having inadequate cough length have been reported.[3,4]An outbreak investigation in New Hampshire found that a number of the PCR-identified cases never coughed, and some of those who coughed did not have the classic cough attributes associated with pertussis. [4] When PCR-positive patients present with a cough attribute, it should be presumed they are true cases. Our surveillance data was hampered by the high proportion of cases still coughing when the surveillance report was finalized. In the presence of a cough attribute, other researchers have suggested reducing the minimum cough duration to one week.[3] However, our findings in Chapter 3 suggest that the case confirmation criteria are not accurately understood. Therefore, adding an additional criterion such as 7-day cough length for PCR cases to the 14-day cough for the clinical case definition could be detrimental to the consistency of surveillance reporting.

The case classification process should be efficient, containing the minimum number of criteria to identify highly probably pertussis cases. Based on the analyses in Chapters 2 and 3, we recommended that cases be defined by the presence of both a cough and cough attribute for all individuals with a positive lab test. The clinical case criteria should not be

altered, and those identified with an epidemiologic link should continue to be required to meet the clinical case definition. High quality pertussis surveillance data is crucial to the identification of cases and the commitment of resources in outbreak investigation. They are also the basis for vaccination recommendations.

Chapter 4 evaluated the county-level socio-structural risk factors for pertussis, focusing on disease exposure risk, barriers to healthcare and poor child health. We found that pathogen exposure risk factors were associated with lower incidence of pertussis. We also determined that having a larger proportion of the workforce commuting was a strong indicator of decreased risk in counties without an interstate highway. This might be attributed to regional differences in county size being inversely correlated with the volume of daily population movement into and out of a county. Curiously, barriers to healthcare and poor child health were also inversely associated with pertussis incidence.

Of these barriers, low educational attainment (<9 years) showed a 22% reduction in pertussis incidence for each 5% increase in low education within a county, whereas under regional stratification an increased risk of pertussis by 20% was seen in the Midwestern region. We considered the possibility that education should be interpreted as a proxy for healthcare access, as the age-adjusted pertussis incidence was 2.0/100,000 persons greater in counties with ≥5% Amish population. The U.S. Amish live primarily in the Midwest and adjacent states, and do not continue schooling after the eighth grade. They are also known to have low immunization rates, and consequently outbreaks of vaccine preventable diseases.[5-7] It is possible that in the Midwest low educational attainment is a proxy for county-level vaccination coverage.

Some of our healthcare barriers (e.g. physicians per capita, housing stress, children in poverty) had been associated with vaccination coverage in a previous study.[8] However, only housing stress correlated with decreased vaccination coverage and increasing pertussis incidence. Both a higher per capita prevalence of physicians and less child poverty were associated with increased vaccination, but counter-intuitively with increased pertussis. This suggests that our findings may reflect more complete reporting in more affluent counties.

5.2. Challenges Inherent with Pertussis

Pertussis occurs both seasonally and cyclically with epidemics occurring every 3-4 years on average, though this is location specific.[9] Epidemiologists need to be careful when interpreting year-to-year differences both cases and incidence to distinguish between cyclic epidemic occurrences and baseline transmission. The Healthy People 2020 goals have incorporated these epidemic cycles and now report 4-year averages rather than year-specific totals.[10] All analyses in this dissertation collapsed the data over time to create averaged the annual pertussis incidences resulting in more robust estimates of disease occurrence.

The highest disease rates occur in infants and adolescents, making it important that analyses account for the age distribution of the source population.[11] Reported pertussis rates in different geographic areas should be age adjusted, for comparability.[12] We used an external age adjustment to the 2000 U.S. population when comparing U.S. county-level pertussis rates in Chapter 4. The selection of generalized estimating equation models allowed us to offset the count of cases by the age-group specific, county population, resulting in age-adjusted rates.

The sporadic nature of disease, and a preponderance of cases in the young, results in low case counts among adults, and in counties with sparse populations. This produced situations where there were no cases for some county age-groups, in some years. As a result we used relatively broad age-groups and collapsed the data across more than a decade to help address the over-dispersion (variance greater than the mean) resulting from excessive zeros, while using a negative binomial distribution in analyses. This excess of zeros could also have been addressed through the use of zero-inflated negative binomial (ZINB) regression models. This ZINB analytic method would assess the association between predictors, given that a case was reported in a given county. It is based on the theory that the initiation of disease, that first case, results from a different process than the one that drives the quantity of subsequent cases. For pertussis, this would be true as the first cases would be the result of a combination of susceptibility and means of contact with a pertussis source outside the county, as chronic carrier states have not been identified.

5.3. Suggestions for Future Research

There is growing literature suggesting the reevaluation of the 1997 pertussis surveillance case definition. This is usually based on one or more common points of concern:[13]

1. The reduced sensitivity of the current case definition for infant cases.
2. The requisite 14-day minimum duration of cough.
3. The exclusion of serology as a confirmatory disease indicator.

One 2013 recommendation put before the Council of State and Territorial Epidemiologists was to include apnea as a clinical indication among infants.[13] This recommendation is based in part on ability of apnea to help differentiate between the frequently similar clinical presentations of pertussis and respiratory syncytial virus (RSV) infections. Pertussis was noted to have a higher proportion of apnea, cyanosis and lymphocytosis, while RSV infections had more frequent fever, vomiting and respiratory distress.[14] The multiple facets of case confirmation are confusing, and while simplicity and continuity should be the primary aim of the case definition, further research into the proportion of infant cases excluded by the current case definition will help determine the possible benefits of refining the case definition by including infant-specific criteria. Current estimates suggest 10-20% of infant cases are being excluded.[13] Many states, including Michigan, recognize the importance of apnea, incorporating in the case report form. (Appendix) However, more research is necessary to determine its value as part of passive surveillance.

This dissertation was unable to include vaccination coverage in the analysis, primarily because nationwide county-level estimates were not available. Vaccination is the primary means of prevention and while there was a significant effort to increase vaccination in the 1990s, many states are lessening the stringency of their exemption policies, either by including a philosophical exemption or by reducing the difficulty of gaining an exemption. Exemption frequency has been shown to cluster in space, and both frequency and clustering are associated with substantial increases in pertussis incidence.[15-17] Imdad et al., showed that even in states where waivers are not easily obtained, religious waivers are increasing among public school children.[17] To better understand pertussis transmission in the community setting further work should quantify the cost of these policy changes in terms of disease outcomes.

County-level vaccination rates were not included in analyses presented in this dissertation (Chapter 4), due to a lack of standardized nationwide estimates. Thus, there is the possibility that small clusters of low vaccination prevalence may exist within counties. As a large proportion of vaccination assessment is done through the public school system, it overlooks the populations most inclined to refuse vaccination; those educating their children in private schools or at home. Even the National Immunization Survey is not able to capture an adequate statistical sample of minority populations within states, particularly when the subgroup is not easily classified. As a result, immunization estimates may over-estimate coverage by failing to detect pockets of high risk which increase the county-wide risk of pertussis.[16] Further study could better elucidate how unvaccinated children who are outside the public school system affect accuracy of county-specific vaccination estimates, and influence disease outbreaks.

The study of immunization coverage lends itself well to the inclusion of other socio-structural investigations. Analyses in Chapter 4 could have been improved with a finer spatial resolution of both case occurrences and vaccination coverage. It would be beneficial to determine whether the reduced incidence of pertussis observed in Chapter 4 was the result of lower reporting rates (county resource availability), or lower disease occurrence perhaps related to higher vaccination coverage. It would allow state and federal public health agencies to more effectively target disease reduction strategies. While it is unlikely to be feasible at a national level working closely with a state health department should provide sufficient data and expertise to adequately describe the interplay between resource availability, vaccination coverage and pertussis.

Vaccine coverage is the major cornerstone of pertussis prevention, yet the efficacy of the vaccine has also recently been drawn into the discussion of pertussis control. The observed waning of immune competency within the first five years following vaccination by whole cell diphtheria, tetanus and pertussis (DTP)[18]and diphtheria, tetanus, acellular pertussis (DTaP)[19-21] formulations, suggests further research into vaccine efficacy is needed. The presence of antigenic-drift in *B. pertussis* away from the vaccine strains is much more problematic for the acellular formulation due to the limited number of antigenic components. Currently *B. pertussis* filamentous hemagglutinin (FHA), fimbriae

(FIM), pertactin (PRN), and pertussis toxin (PT) are the virulence factors included in the acellular pertussis vaccines.[22] Some researchers have shown that having initial doses of DTP rather than a complete DTaP series provides greater protection in subsequent years.[23-25] Research is needed to determine whether modification to the DTaP components can produce a more robust immune response, or whether providing a combination of DTP and DTaP, would be most effective for the long-term control of pertussis. This also affects the booster vaccination recommendations for adolescents and adults which currently use the tetanus, diphtheria, acellular pertussis (Tdap) vaccines.

The discussion of vaccine formulation would benefit greatly from further research to identify additional *B. pertussis* antigenic components for inclusion in the acellular vaccines (beyond the FHA, FIM, PRN and PT that are currently included).[22] Research on the PRN component of the vaccine has shown variants occurring in the Dutch population as early as 1980.[26] This gene product is used in adhering to host tissue and is therefore an ideal vaccine target. Within a decade, 90% of *B. pertussis* isolates were of the newer non-vaccine strains.[22,26] This coincides with the resurgence of pertussis and suggests bacterial adaptation in response to the whole cell DTP formulation. The shift to the acellular vaccine with four basic components can be rendered ineffective by bacterial adaptation much more rapidly than the whole cell vaccine. The rate at which each component undergoes mutation is important in determining bacterial response to the selective pressure of vaccination. This would help determine which vaccine components are likely to have reduced effectiveness with time.

5.4. Conclusion

The control of vaccine preventable disease like pertussis is an intricate struggle between bacteria and humans. The bacterium *B. pertussis* struggles for survival to evade the human immune system and vaccine-derived immunity. In surveillance data the bacteria is noted as a means of diagnosis, though fewer culture tests are being ordered making bacterial research more of a challenge. Humankind has developed vaccines as a mean of self-protection, though with the decrease of natural infection parental concern has shifted to the safety of the vaccines rather than the protection they provide. Vaccination status is assessed on a case-specific basis in disease surveillance, though separate monitoring

systems are in place. The effects of both disease and vaccination extend beyond the immediate individual affecting their immediate community. The role of surveillance data in pertussis control is to provide timely, reliable information regarding affected populations, primarily for disease control endeavors. This dissertation highlighted the validity of the current surveillance system case definition, though the role of the clinical case definition is misunderstood. Surveillance data are a good source of data for further research into the nature and mechanisms of pertussis transmission.

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Appendix

Pertussis Case Report Form, Michigan Department of Community Health

Pertussis

Michigan Department of Community Health

Communicable Disease Division

Investigation Information

Investigation ID	Onset Date mm/dd/yyyy	Diagnosis Date mm/dd/yyyy	Referral Date mm/dd/yyyy	Case Entry Date mm/dd/yyyy	Case Completion Date mm/dd/yyyy

Investigation Status
○*New* ○*Active* ○*Completed* ○*Superceded* ○*Cancelled*

Case Status
○*Confirmed* ○*Not a Case* ○*Probable* ○*Suspect* ○*Unknown*

Patient Status I=inpatient O=outpatient D=died	Patient Status Date mm/dd/yyyy	Part of an outbreak? N=NO Y=YES U=unknown	Outbreak Name	Case Updated Date mm/dd/yyyy

Patient Information

Patient ID	First	Last	Middle

Street Address

City	County	State	Zip

Home Phone ###-###-####	Ext.	Other Phone ###-###-####	Ext.

Parent/Guardian (required if under 18)

First	Last	Middle

Demographics

Sex	Date of Birth mm/dd/yyyy	Age	Age Units
○*Male* ○*Female* ○*Unknown*			○*Days* ○*Months* ○*Years*

Race
○*Caucasian* ○*African American* ○*American Indian/Alaska Native* ○*Hawaiian/Pacific Islander*
○*Asian* ○*Unknown* ○*Other (Specify)*_____

Ethnicity	Worksites/School	Occupations/Grade
○*Hispanic/Latino* ○*Non-Hispanic/Latino* ○*Unknown*		

Referral Information

Person Providing Referral

First	Last	Phone ###-###-####	Ext.	Email

Primary Physician

First	Last	Phone ###-###-####	Ext.	Email

Street Address

City	County	State	Zip

Hospital Information

Patient Hospitalized	Hospital	Hospital City	Hospital Record No.
○ Yes ○ No ○ Unknown			

Admission Date mm/dd/yyyy	Discharge Date mm/dd/yyyy	Days Hospitalized	Patient Died
			○ Yes ○ No ○ Unknown

Clinical Information

Any Cough?	Cough Onset Date mm/dd/yyyy	Paroxysmal Cough?	Whoop?
○ Yes ○ No ○ Unknown		○ Yes ○ No ○ Unknown	○ Yes ○ No ○ Unknown

Posttussive Vomiting?	Apnea?
○ Yes ○ No ○ Unknown	○ Yes ○ No ○ Unknown

Final Interview Date mm/dd/yyyy	Cough at Final Interview?	Duration of Cough at Final Interview (Days)
	○ Yes ○ No ○ Unknown	

Chest X-ray for Pneumonia	Seizures Due to Pertussis	Acute Encephalopathy Due to Pertussis
○ Positive ○ Negative ○ Not Done ○ Unknown	○ Yes ○ No ○ Unknown	○ Yes ○ No ○ Unknown

Treatment Information

Were Antibiotics Given?
○ Yes ○ No ○ Unknown

First Antibiotic Received

○ Erythromycin (incl. pediazole, ilosone)	○ Cotrimoxazole (bactrim/septra)	○ Clarithromycin/azithromycin
○ Tetracycline/Doxycycline	○ Amoxicillin	○ Penicillin
○ Ampicillin	○ Augmentin	○ Ceclor
○ Cefixime	○ Unknown	○ Other _____

Date Started First Antibiotic mm/dd/yyyy	Number of Days First Antibiotic Actually Taken

Second Antibiotic Received

○ Erythromycin (incl. pediazole, ilosone)	○ Cotrimoxazole (bactrim/septra)	○ Clarithromycin/azithromycin
○ Tetracycline/Doxycycline	○ Amoxicillin	○ Penicillin
○ Ampicillin	○ Augmentin	○ Ceclor
○ Cefixime	○ Unknown	○ Other _____

Date Started Second Antibiotic mm/dd/yyyy	Number of Days Second Antibiotic Actually Taken

Laboratory Information

Was Laboratory Testing for Pertussis Done?
○ Yes ○ No ○ Unknown

Test Name	Testing performed? Y=YES N=NO UNK=unknown	Result P=positive N=pending U=unknown N=negative I=indeterminate S=parapertussis	Date Specimen Taken mm/dd/yyyy
Culture			
DFA			
Serology 1			
Serology 2			
PCR			

If paired sera were tested, was there a significant rise (four-fold or greater) in antibody titer to Bordetella pertussis?
○ Yes ○ No ○ Not Tested or Unknown

Vaccine Information

Vaccinated? (Received any doses of diphtheria, tetanus, and/or pertussis containing vaccines)
○ *Yes* ○ *No* ○ *Unknown*

Vaccination Date	Vaccine Type*	Vaccine Manufacturer	Lot Number
mm/dd/yyyy	W=DTP Whole cell A=DTaP H=DTaP-Hib K=DTaP-IPV K=DTaP-IPV-Hep B N=DTaP-IPV-Hib D=DT or Td T=DTP-Hib P=Pertussis only O=Other X=Tdap U=Unknown		

Date of Last Pertussis-Containing Vaccine Prior to Illness Onset
mm/dd/yyyy

Number of Doses of Pertussis-Containing Vaccine Prior to Illness Onset
○ *Zero* ○ *One* ○ *Two* ○ *Three* ○ *Four* ○ *Five* ○ *Six* ○ *Unknown*

Reason Not Vaccinated With 3 or More Doses of Pertussis Vaccine
○ *Religious exemption* ○ *Medical Contraindication* ○ *Philosophical Exemption* ○ *Previous Pertussis Confirmed by Culture or MD*
○ *Parental refusal* ○ *Age Less Than 7 Months* ○ *Unknown* ○ *Other*_____

Epidemiologic Information

Imported?
○ *Indigenous* ○ *International* ○ *Out of State* ○ *Unknown*

Epi Linked to Another Culture Confirmed Case?
○ *Yes* ○ *No* ○ *Unknown*

Age of the person from whom the case contracted Pertussis

Age Type
○ *Days* ○ *Months* ○ *Years*

Transmission Setting (Where did this case acquire pertussis)?
○ *Church* ○ *College* ○ *Community* ○ *Correctional Facility* ○ *Daycare* ○ *Doctor's Office*
○ *Home* ○ *Hospital ER* ○ *Hospital Outpatient Clinic* ○ *Hospital Ward* ○ *International Travel* ○ *Military*
○ *School* ○ *Unknown* ○ *Work* ○ *Other*_____

Specify Transmission Setting (name of school, daycare, etc.)

Setting (Outside Household) of Further Documented Spread
○ *Church* ○ *College* ○ *Community* ○ *Correctional Facility*
○ *Daycare* ○ *Doctor's Office* ○ *Hospital ER* ○ *Hospital Outpatient Clinic*
○ *Hospital Ward* ○ *International Travel* ○ *Military* ○ *More Than 1 Setting Outside Household*
○ *No Documented Spread Outside Household* ○ *School* ○ *Unknown* ○ *Work*
○ *Other*_____

Specify Setting (Outside Household) of Further Documented Spread (name of school, daycare, etc.)

Number of Contacts in Any Setting Recommended Antibiotics