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Dana Goodenough Date

Factors Associated With Time to Appropriate Treatment in Pertussis Cases: Georgia 2009-2013

By

Dana Goodenough

MPH

Epidemiology

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Robert Bednarczyk

Faculty Thesis Advisor

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Dana Goodenough

B.S.
Emory University
2013

Faculty Thesis Advisor: Robert Bednarczyk, PhD

An abstract of
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Abstract

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By Dana Goodenough

Introduction: Pertussis is endemic in the United States, with periodic epidemics that continue to highlight its importance as a public health issue. Pertussis infection can cause a variety of symptoms, and the clinical presentation of pertussis can vary by age and vaccine status. However, little is known about the factors that affect time to treatment of pertussis cases. We analyzed five years of data from the Georgia Emerging Infections Program to understand how factors such as age, symptoms, and vaccine status can alter the clinical picture of pertussis and impact time to appropriate treatment.
Methods: We used multivariable linear regression to assess the impact of each variable on time to treatment.
Results: There was little consistency across age groups for symptom and demographic predictors of time to treatment. Overall, the multivariate liner regression showed that among patients aged 18 and younger, none of the variables had an impact on time to treatment greater than -0.25 to +1.47 days. Among patients over 18 years and older, most variables had little impact on time to treatment, though two (paroxysmal cough in 18-40 year olds and hospitalization in individuals over 40 years of age) were associated with at least a five day increase in time to treatment;
Conclusions: This study highlights how the difficulties in pertussis diagnosis can impact time to treatment, particularly for individuals aged 18 and older who may not begin treatment until there is an accumulation of symptoms. Healthcare providers need to recognize the variety of symptoms that pertussis can present with and consider confirmatory testing early.

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Chapter I: Literature Review

Background

Definition

Pertussis is a worldwide endemic and epidemic illness that continues to be a public health issue. Pertussis, caused by the bacterium *Bordetella pertussis,* is an airborne acute upper respiratory infection. The Centers for Disease Control and Prevention (CDC) defines a clinical case of pertussis as a coughing illness lasting two weeks with one classic sign of pertussis (paroxysmal cough, post-tussive emesis, or inspiratory whoop) and without another apparent cause. Furthermore, the CDC recommends the use of both culture and polymerase chain reaction (PCR) testing to confirm diagnosis(1). A probable case as defined by the CDC has the same criteria as a confirmed case without laboratory confirmation and the absence of epidemiologic linkage to a laboratory-confirmed case of pertussis. Several different case definitions are used around the world which can make it difficult to compare rates and examine disease burden (2). Nonetheless, for the purposes of this paper the CDC case definition for confirmed and suspected cases will be used.

Clinical Manifestations

A *B. pertussis* infection can cause a variety of symptoms. They range from severe disease, including paroxysmal cough, to milder illness with only rhinitis. Notably, many of the symptoms caused by *B. pertussis* are not atypical and mimic symptoms of other viral respiratory infections (3). For this reason, many pertussis cases are not recognized and are under-reported. Van den brink et al. found that doctors miss 1 in 5 pertussis cases in children when diagnosing on clinical suspicion alone (3).

In addition to there being a broad spectrum of symptoms associated with pertussis, there is also variability of clinical presentation across age groups and vaccination status. Infants less than 6 months old, partially vaccinated children, adolescents, and adults often do not have the typical whoop or cough paroxysm (4). In a pediatric hospital study on pertussis patients, unvaccinated children and adolescents had significantly more whooping cough compared to vaccinated children and adolescents (5). An inconsistent clinical picture can prolong proper diagnosis and treatment thus further exposing more individuals. Additionally, this variability in symptoms can lead to incorrect diagnoses and administration of ineffective antibiotics.

Prevalence

B. pertussis is highly contagious and can infect individuals of all age groups, however, children make up most of the cases. Severe complications of pertussis are most common in infants less than 12 months old. Since they have not finished their vaccination series, they only have partial immunity (1). For many years, in industrialized countries with high rates of infant immunization, an increasing proportion of cases has been reported in adolescents and adults whose symptoms vary from mild, atypical respiratory illness to the full whooping syndrome (4). Globally, pertussis is ranked among the top ten leading causes of childhood mortality (3). In 2003, despite estimated global vaccine coverage of about 75% with three doses of pertussis-containing vaccines, there were still an estimated 17.6 million pertussis cases, with an estimate 279,000 deaths (4).

Transmission

B. pertussis is highly transmissible and has an R_0 of 15-17 (6). It is spread through direct contact with respiratory droplets from infected individuals. In vaccinated populations, bacteria is often brought home by older siblings or parents which infects susceptible infants who are not fully protected. Secondary attack rates of up to 90% have been observed in non-immune household contacts (4). Also, the bacteria can colonize in the nasopharynx of healthy individuals resulting in asymptomatic cases (7). Although these individuals do not develop any clinical symptoms, they serve as reservoirs and can transmit the bacteria to susceptible individuals.

Pertussis clinical illness is characterized by a 7-10 day incubation period followed by a clinical course consisting of three stages: catarrhal, paroxysmal and convalescent. During the first stage, the catarrhal stage, the patient is the most contagious and presents with nonspecific symptoms such as malaise, rhinorrhea, sneezing, lacrimation, and mild cough. The catarrhal stage usually lasts one to two weeks in which the cough becomes more frequent. The next stage, the paroxysmal stage, is characterized by severe coughing spells often occurring in paroxysms. In some patients, these paroxysms are followed by a high pitched whoop. The paroxysmal stage can last several weeks. Once the paroxysms wane, the patient enters the convalescent stage which lasts about 1-2 weeks. The convalescent stage is characterized by waning symptoms (1). An individual infected with *B. pertussis* can spread the infection up to three or more weeks after cough onset (8). Clinical examination is important because undiagnosed infected adults can spread pertussis to inadequately immunized children who are more severely affected by the illness (9).

B. pertussis is a gram-negative coccobacillus (9). Although the bacterium has several virulence factors, including filamentous hemagglutinin, pertactin, and fimbriae, the most important virulence factor is the pertussis toxin. *B. pertussis* bacteria attach to the cilia of the respiratory epithelial cells and produce toxins that paralyze the cilia. This causes inflammation of the respiratory tract which interferes with the clearing of pulmonary secretions (10).

Also from the *Bordetella* genus is a bacterium called *Bordetella parapertussis*. *B. parapertussis* is similar to *B. pertussis* in that it can cause a similar clinical manifestation. However, because *B. parapertussis* does not express the gene that codes for the pertussis toxin, illness is often milder (4). *B. parapertussis* infection is much less common than infection caused by *B. pertussis*. In a 2012 pertussis outbreak in Minnesota, 265 nasopharyngeal swabs were taken from ill patients. Of those 265 swabs, 160 patients tested positive for *B. pertussis* while only 21 patients tested positive for *B. parapertussis* (11). *Bordetellae* are susceptible to macrolides, therefore, treatment with the recommended antibiotics for *B. pertussis* (discussed later) will also be effective against *B. parapertussis* (6).

Treatment

Pertussis can be treated with the early administration of antibiotics. The recommended antimicrobial agents for treatment or chemoprophylaxis of pertussis are azithromycin, clarithromycin and erythromycin (10). However, erythromycin is not recommended in infants less than one month of age. If a patient is diagnosed late, antibiotics will not alter the course of illness. Antibiotics are not effective after about three weeks of illness because at that point the bacteria is already cleared from the body, however, the toxins

and the damage done to the body remain which still cause symptoms. The current CDC guideline is to treat persons more than one year old within three weeks of cough onset, and infants less than one year old and pregnant women within six weeks of cough onset. The CDC also recommends that clinicians strongly consider treating prior to test results if clinical history is strongly suggestive or patient is at risk for severe or complicated disease (10).

Pertussis on the Rise

After the introduction of immunization against pertussis began in the United States in the 1940s, the number of pertussis cases decreased rapidly. However, since the 1980s, there has been a rise in the number of pertussis cases reported. In 2012, 48,277 cases and 20 pertussis-related deaths were reported in the United States. The largest increases have occurred in infants (age <12 months) and adolescents (age 10-19 years) (5). Both natural and acquired immunity is estimated to only last approximately 4-10 years (8).

Several factors may contribute to the increasing number of pertussis cases. These may include waning immunity of the acellular pertussis vaccine, better diagnostics to confirm cases, and genetic changes in *B. pertussis* (12).

Genomic analysis has found allelic variation in several *B. pertussis* virulence factor genes. Some of the genes affect those that code for the pertussis toxin A subunit (ptxA), pertactin (prn), serotype 2 fimbriae (fim2), serotype 3 fimbriae (fim3) and the promoter for pertussis toxin (ptxP) (13). Notably, a novel allele for the pertussis toxin (ptx) promoter ptxP3- in place of resident ptxP1 strains- has shown to increase *B. pertussis* virulence and immune suppression by producing more pertussis toxin (14).

Diagnostics

The standard pertussis diagnostic laboratory test is isolation of *B. pertussis* by bacterial culture. A properly obtained nasopharyngeal swab or aspirate is essential for optimal results. The ability to isolate *B. pertussis* is diminished if the patient has received prior antibiotic therapy effective against *B. pertussis*, if specimen collection has been delayed beyond the first 2 weeks of illness, and if the patient has been vaccinated (15). Additionally, PCR can be used in in conjunction with bacterial culture. However, the CDC does not recommend PCR as an alternative due to the possibility of false negatives and the absence of a standardized PCR assay for *B. pertussis*. Nonetheless, PCR has increased the number of pertussis diagnoses since its inclusion in the case definition in 1997. The effectiveness of bacterial culture and PCR diagnostics is subject to time and are not reliable after approximately three weeks of illness (15).

As stated earlier, the difference between a confirmed and probable case of pertussis is that a probable case lacks laboratory confirmation. Without laboratory confirmation, it is difficult to truly understand the burden of *B. pertussis.* Examining confirmed cases alone does not give us a complete picture of pertussis illness which makes understanding the epidemiology much more difficult. Studying probable cases in addition to confirmed cases helps us understand when physicians presumptively treat for pertussis. The CDC recommends that clinicians presumptively treat probable cases if the patient's clinical history is strongly suggestive of pertussis (10). Nonetheless, early and more frequent testing for pertussis are necessary to not only understand its epidemiology, but prevent transmission as well.

Impact

It is widely documented that the clinical presentation of pertussis can vary by age and vaccine status. However, little is known about the factors that affect time to treatment of pertussis cases. In the United States where diagnostic tools are so readily available, little is known about why pertussis cases often go so long without treatment. With the waning immunity associated with the current vaccine and rates of transmission increasing, it is important to determine how pertussis cases can be recognized sooner to prevent additional cases. By decreasing time to treatment, patients can begin treatment earlier and decrease the amount of time in which they are contagious. Through the early recognition of pertussis, laboratory confirmation can be obtained sooner, thus reducing the need for presumptive treatment. Prompt, correct treatment reduces the administration of inappropriate antibiotics and the further transmission of illness. This study will help to understand factors such as age, symptoms, and vaccine status that can alter the clinical picture of pertussis and prolong time to appropriate treatment.

Chapter II: Manuscript

Abstract

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By Dana Goodenough

Introduction: Pertussis is endemic in the United States, with periodic epidemics that continue to highlight its importance as a public health issue. Pertussis infection can cause a variety of symptoms, and the clinical presentation of pertussis can vary by age and vaccine status. However, little is known about the factors that affect time to treatment of pertussis cases. We analyzed five years of data from the Georgia Emerging Infections Program to understand how factors such as age, symptoms, and vaccine status can alter the clinical picture of pertussis and impact time to appropriate treatment.

Methods: We used multivariable linear regression to assess the impact of each variable on time to treatment.

Results: There was little consistency across age groups for symptom and demographic predictors of time to treatment. Overall, the multivariate liner regression showed that among patients aged 18 and younger, none of the variables had an impact on time to treatment greater than -0.25 to +1.47 days. Among patients over 18 years and older, most variables had little impact on time to treatment, though two (paroxysmal cough in 18-40 year olds and hospitalization in individuals over 40 years of age) were associated with at least a five day increase in time to treatment.

Conclusions: This study highlights how the difficulties in pertussis diagnosis can impact time to treatment, particularly for individuals aged 18 and older who may not begin

treatment until there is an accumulation of symptoms. Healthcare providers need to recognize the variety of symptoms that pertussis can present with and consider confirmatory testing early.

Background

Pertussis is endemic in the United States, with periodic epidemics that continue to highlight its importance as a public health issue. Pertussis infection can cause a variety of symptoms, and the clinical presentation of pertussis can vary by age and vaccine status (2). Pertussis presentations range from severe disease, including paroxysmal cough, to milder illness with only rhinitis. Notably, many of the symptoms caused by *B. pertussis* are not atypical and mimic symptoms of other viral respiratory infections (3). For this reason, many pertussis cases progress without testing. This is problematic because the effectiveness of bacterial culture and PCR diagnostics is subject to time and are not reliable after approximately three weeks of illness (15). Delayed testing can lead to delayed treatment. Antibiotics are not effective after about three weeks of illness because at that point the bacteria is already cleared from the body, however, the toxins and the damage done to the body remain which still cause symptoms (10).

Little is known about the factors that affect time to treatment of pertussis cases. In the United States where diagnostic tools are so readily available, little is known about why pertussis cases often go so long without treatment. With the waning immunity associated with the current acellular vaccine, increased risk of pertussis due to clusters of children with exemptions to vaccination mandates, and rates of transmission increasing, it is important to determine how pertussis cases can be recognized sooner to prevent additional cases (4, 16, 17). By decreasing time to treatment, patients can begin treatment earlier and decrease the amount of time in which they are infectious. Through the early recognition of pertussis, laboratory confirmation can be obtained sooner, thus reducing the need for presumptive treatment. Prompt, correct treatment reduces the administration

of inappropriate antibiotics and the further transmission of illness. We have analyzed five years of data from the Georgia Emerging Infections Program to understand how factors such as age, symptoms, and vaccine status can alter the clinical picture of pertussis and impact time to appropriate treatment.

Methods

Study Population

This cross-sectional study was conducted using data from the Georgia Emerging Infections Program (EIP). Data were collected, as part of routine active surveillance, on confirmed and probable pertussis cases reported to the Georgia Department of Public Health from 2009-2013. A confirmed case as defined by the Georgia EIP is a culture with cough of any duration or a clinical case and PCR positive or a clinical case that was epi-linked to a laboratory confirmed case. A clinical case is defined as a cough lasting two weeks or greater and one of the following: paroxysms, whoop, or post-tussive vomiting. A probable is defined as a clinical case of pertussis without laboratory confirmation or absence of an epi-link with a confirmed case.

Data Collection and Analytic Variables

Primary exposure variables and other variables were collected by the Georgia EIP using the Georgia Department of Public Health Pertussis Reporting and Case Investigation form. The case report form includes demographic, clinical, vaccine receipt, and epidemiological information. Data identifying cough, paroxysmal cough, whooping cough, post-tussive vomiting, apnea, hospitalization, seizures, acute encephalopathy, death, epi-linked and vaccine status were all reported as yes/no variables. Cough onset

date and antibiotics start day were reported as day/month/year. Number of doses is a summation of the total number of pertussis containing vaccines the individual received. The variable, "completely vaccinated," is a yes/no variable that was created by the research team to reflect whether a case was age appropriately vaccinated before cough onset according to the Advisory Community on Immunization Practices (ACIP) recommendations.

The time to treatment variable was calculated by subtracting the cough onset date from the antibiotics start date. We also computed a "total symptoms" variable by summing the number of the following symptoms the patient experienced: cough, paroxysmal cough, whooping cough, post-tussive vomiting, apnea, cyanosis, positive x-ray results, seizures, and encephalopathy. Age was divided into categories according to distribution and medical relevance: 3 months or less, greater than 3 months to 3 years, greater than 3 years to 10 years, greater than 10 years to 18 years, greater than 18 years to 40 years, and greater than 40 years. The variable "doses before illness" was a variable created by summing the number of pertussis containing vaccine the individual received prior to cough onset.

Analysis

For analysis, cases were excluded if cough onset date or antibiotic start date were missing, or if time to treatment was negative or implausible. We computed the proportions of study participants who presented with each symptom overall and by age group. Additionally, we calculated the percent of cases that were confirmed by age group.

The mean time to treatment was calculated across levels of each study variable. We used multivariable linear regression to assess the impact of each variable on time to treatment. Because time to treatment was heavily right skewed, it was log transformed for use in the regression analysis. Exponentiated beta estimates were computed to interpret the impact of individual variables on increasing or decreasing time to treatment.

All data was analyzed using SAS 9.4. Because the study consisted of secondary analysis of de-identified, previously collected data, it was exempted from IRB review.

Results

This study examined a population of 1,313 probable and confirmed cases of pertussis reported through the Georgia EIP. The average age of study participants was 12.7 years old (SD 17.3) and the median was 7 years old (IQR 0.42-14 years). Most study participants were white (78.4%), and the majority were female (57.1%). Nearly all cases had paroxysmal cough (92.8%); other symptoms were reported less frequently (e.g., the next two most common symptoms were post-tussive vomiting [57.1% of cases] and apnea [25.2% of cases] and with more variability by age (Table 1).

Overall, average time to treatment increased with age. On average, the youngest age group (3 months old or less) was treated 12.3 days after cough onset (SD 11.1), the lowest time to treatment among all age groups. Time to treatment increased to 21.7 days after cough onset in those over 40 years of age (SD 22.7) (Table 2).

While 92.9% of younger individuals (3 months old or less) had their pertussis cases confirmed through laboratory testing, the case confirmation proportion dropped with increasing age (greater than 3 months-3years, 92.4%; greater than 3 years-10 years,

82.1%; greater than 10 years-18years, 70.8%; greater than 18 years-40 years, 33.9%; over 40 years, 23.9%) (Table 3).

Variable symptom prevalence and number of symptom combinations were observed within age groups. The youngest age category (3 months old or less) had the greatest number of combinations of symptom presentation. In these cases, the combination that presented the most was only recorded 9 times out of 91 children with all symptoms reported (Table 4).

Multivariate Linear Regression

There were 1,211 cases available for multivariate linear regression analysis. Cases were exempt from analysis if time to treatment was missing or if the time to treatment recorded was not plausible. There was little consistency across age groups for symptom and demographic predictors of time to treatment. Overall, the multivariate liner regression showed that among patients aged 18 and younger, none of the variables had an impact on time to treatment greater than -0.25 to +1.47 days. Among patients over 18 years and older, most variables had little impact on time to treatment, though two (paroxysmal cough in 18-40 year olds and hospitalization in individuals over 40 years of age) were associated with at least a five day increase in time to treatment; (Tables 5 and 6) (Full tables of multivariate analysis are available in the appendix.).

By age group, the symptoms most commonly associated with increased time to treatment were paroxysmal cough and whooping cough (Table 5). For example, paroxysmal cough was associated with increased time to treatment for children 3 months old or less (1.16 days), greater than 3 months old to 3 years (1.16 days), greater than 10 years to 18 years

(1.30 days), and most meaningfully in adults older than 18 years to 40 years old (5.11 days). Although three of the measures were statistically associated with decreased time to treatment (X-ray results in >10-18years old, seizures in 3 months old or greater, and hospitalization in >3years-10 years old), none of the symptoms were associated with decreased time to treatment of at least one day (Table 5).

When considering the number of symptoms presented, for all probable and confirmed cases, having more symptoms was associated with longer time to treatment in all age groups except in infants three months old or less (-0.94 days) and children greater than 3 months to 10 years old (-0.95 days) (Table 6).Additionally, case confirmation was associated with longer time to treatment in all age groups except 3 months old or less and greater than 10 years to 18 years. (Table 6)

Discussion

We identified patterns in the length of time to treatment for pertussis that may be related to clinical presentation and case confirmation. The patterns that emerged from this study are important for recognizing the difficulty in diagnosing pertussis and initiating treatment based on clinical manifestations. This study further exemplifies that there is no one golden rule for clinically diagnosing pertussis. The high number of combinations of symptom presentations adds to the existing evidence of the varying presentations of pertussis clinical illness (2). Inconsistent clinical manifestations of pertussis makes it difficult to quickly and correctly diagnose pertussis. Lab cultures, the gold standard of pertussis diagnosis, can take approximately one to two weeks to provide results while

PCR can be completed in a few days (15). For this reason, early laboratory testing is pertinent.

In a children's hospital study conducted in Israel, Eidlitz-Markus et al. also found that symptom presentation varied by age group (5). They found that infants (up to six months old) suffering from pertussis were more likely to have cyanosis and a whooping cough than older children (7-18 years old). Similarly, we found that infants 3 months old or less were more likely to have a typical whoop (48.7%) than children greater than 10 years to 18 years old (30.9%). We also observed that infants 3 months old or less were more likely to have cyanosis (55.9%) than children greater than 10 years to 18 years old (3.1%) The researchers also noted that there was a significant difference between the infant and older groups in mean time to diagnosis (1.1 ± 0.06 weeks and 5.84 ± 4.19 weeks, respectively $p < .01$) (5). We also found that, on average, time to treatment for infants 3 months old or less (11.1 days) was less than time to treatment for children greater than 10 to 18 years old (15.6 days). Our study examined a greater range of age groups and symptoms which adds to the literature on pertussis clinical manifestations.

Our findings support the difficulty in establishing universal definitions for pertussis cases, as documented in the literature. The Global Pertussis Initiative (GPI) developed an algorithm that delineates the signs and symptoms of pertussis most common to 3 age groups: 0-3 months, 4 months to 9 years, and $\geq$10 years (2). However, in the era of waning immunity, it is important to understand the clinical presentation in adults as well. We found that not only did symptoms vary across younger age groups but they varied across older age groups as well. This study adds to the literature evaluating pertussis presentation, and highlights the complexity of pertussis diagnosis on the basis of

symptom presentation. As stated by GPI, early recognition and testing of pertussis is vital so that the sensitivity of diagnostic capacity is highest (2).

Only 23.9% of pertussis cases over 40 years old were confirmed. The low proportion of confirmed cases in the older adult groups highlights the importance of testing adults when pertussis is suspected. Delays in waiting to test can lead to delays in treatment overall. Our analysis showed that adults over 40 had the longest time to treatment (21.7 days after cough onset, SD 22.7). It is possible that low levels of confirmatory testing may be related to longer time to treatment, with health care providers making decisions to initiate treatment after symptoms accumulate to a point that pertussis is perceived to be a more plausible diagnosis. With the waning immunity attributed to the current pertussis vaccines, pertussis infection is possible in all age groups and probable cases should have confirmatory testing where feasible (12).

Cyanosis is considered a classic symptom of pertussis. In a retrospective study that reviewed the clinical charts of patients with suspected pertussis, researchers found that cyanosis independently predicted pertussis in patients less than 6 months old (18). These findings conflict with the longer time to treatment associated with cyanosis that we observed in infants 3 months old or less. However, time of cyanosis onset was not recorded, thus temporality could not be determined. If cyanosis presented later in the course of illness, then the results could be artificially inflated, especially if the later onset of cyanosis is what triggered the physician to begin antibiotic treatment. Nonetheless, cyanosis was present in approximately half of 0-3 month olds with pertussis, and its presentation or lack thereof should not rule out pertussis as a possibility.

Additionally, this study showed that presentation with more symptoms was statistically associated with longer time to treatment in 10-18 year olds; the time when immunity should be at its highest. This finding suggests that the clinical picture could be clouded when there are additional symptoms present. On the other hand, the total number of symptoms could be a marker of physicians waiting to treat until the clinical presentation worsened. This could also explain why additional symptoms was associated with increased time to treatment. However, time of symptom onset was only recorded for cough, thus we could not determine the temporality of the other symptoms. This is a potential limitation of the study because we do not know when symptoms occurred, therefore we cannot determine if the timing of certain symptoms is what lead to longer time to treatment.

Time to treatment for confirmed cases over 40 years of age was approximately 2 days longer compared to probable cases of the same age. This finding may have a few different explanations. First, in the older cohort there may be a delay in testing by physicians who do not suspect pertussis because there is a low index of suspicion among clinicians for pertussis in adults (18). Also, adults in this age range may not routinely seek health care thus leading to a delay in seeking treatment. Studies have shown that adults with pertussis are seen approximately 17.3 days after symptoms begin compared to 7.8 days for children aged 7 to 12 years (2). Finally, doctors could wait to get the lab results back before treating. Nonetheless, it is important that adults, especially those in contact with children, seek medical attention as soon as possible and that doctors test sooner when pertussis is suspected. The CDC recommends that clinicians strongly

consider treating prior to test results if clinical history is strongly suggestive or patient is at risk for severe or complicated disease (10).

Notably, whooping cough presentation was only associated with shorter time to treatment in children greater than 3 months to 10 years old. This finding is particularly interesting considering a whooping cough is the hallmark of pertussis infection. On the other hand, across age groups whooping cough was only present in 30-50% of cases suggesting that lack of a whooping cough should not immediately rule out pertussis infection. In another study, approximately 15% of confirmed cases across all age groups presented with a whooping cough (18). These findings further suggest that the lack of classical symptom presentation of pertussis is not necessarily conclusive.

Strengths and Weaknesses

This study has some limitations. One weakness of this study is missing data. In particular, there was a significant amount of data missing for vaccine history. However, every effort was made to derive the correct vaccine status information. This study exemplifies the importance of recording complete vaccine history and the sharing of vaccine history with healthcare providers. The utilization of Immunization Information Systems(IIS) can provide consolidated vaccine histories to clinicians so that they can have a more accurate immunization information for their patients It is difficult to get the complete clinical and epidemiological picture if vaccine history is not accurate. Another weakness of this study is that our data is surveillance data. The data we analyzed was not collected specifically for this study, therefore, we were limited to the variables and measures available. However, this study is unique because it utilized population based data and included information for cases of all ages.

Conclusion

Despite a widely available pertussis vaccine, pertussis is still a burden in the United States. This study exemplifies why cases of pertussis can be difficult to diagnose. Healthcare providers need to recognize the variety of symptoms that pertussis can present with and consider confirmatory testing early. Additionally, the CDC recommends that clinicians strongly consider treating prior to test results if clinical history is strongly suggestive or patient is at risk for severe or complicated disease (CDC).

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Tables

Table 1 Study Population Characteristics among 1,313 probable and confirmed pertussis cases evaluated by the Georgia Emerging Infections Program, 2009-2013

Variable	Mean (SD)	n(%)
Demographics		
Age (years)	12.7 (17.3)	
Sex		
Female		750 (57.1)
Male		562 (42.8)
Race		
White		968 (78.4)
Black or African American		184 (14.9)
Other		82 (6.7)
Clinical Data		
Time to Treatment	15.6 (17.3)	
Cough		1300 (99.9)
Paroxysmal Cough		1200 (93.3)
Whooping Cough		482 (38.6)
Posttussive Vomiting		741 (57.6)
Apnea		299 (25.5)
Cyanosis		144 (15.7)
X-ray		
Negative		348 (79.8)
Positive		51 (11.7)
Acute Encephalopathy		11 (0.9)
Seizures		8 (0.6)
Hospitalization		291 (22.2)
Death		3 (0.2)
Vaccine History		
Number of Doses*		
0		384 (34.2)
1		132 (11.8)
2		34 (3.0)
3		58 (5.2)
4		93 (8.3)
5		335 (29.9)
6		86 (7.7)

*Received any doses of diphtheria, tetanus, and/or pertussis-containing vaccines BEFORE cough onset

Table 2 Average Time to Treatment among 1,211 probable and confirmed pertussis cases evaluated by the Georgia Emerging Infections Program, 2009-2013

Variable		Mean (SD)
Demographics		
Probable (n=303)		17.0 (16.8)
Confirmed (n=908)		14.7 (16.1)
Age (years)		
	0-3 mos (n=261)	12.3 (11.1)
	>3mos-3 years (n=233)	13.5 (11.4)
	>3years-10years (n=296)	16.2 (20.1)
	>10 years-18 years (n=190)	15.7 (15.6)
	>18 years-40 years (n=107)	16.2 (14.8)
	>40 years (n=124)	21.7 (22.7)
Sex		
	Female	15.4 (18.3)
	Male	15.1 (13.4)
Race		
	White	15.5 (16.5)
	Black or African American	15.4 (17.1)
	Other	17.1 (15.6)
Clinical Data		
Number of Symptoms		
	1	15.7 (17.5)
	2	15.4 (14.8)
	3	16.1 (19.1)
	4	15.9 (15.9)
	5	12.6 (11.7)
	6	12.0 (10.1)
	7	3 (0)
Vaccine History		
Number of Doses*		
	0	14.4 (15.0)
	1	13.4 (12.5)
	2	11.6 (9.8)
	3	14.5 (10.5)
	4	16.1 (14.6)
	5	15.7 (20.4)
	6	15.7 (20.4)

*Received any doses of diphtheria, tetanus, and/or pertussis-containing vaccines BEFORE cough onset

Table 3 Number of confirmed and probable cases by age group

Age Group	**Confirmed**	**Probable**	**Total**	**%Confirmed**
3 mos OR <	275	21	296	92.9
>3mos-3yrs	231	19	250	92.4
>3yrs-10yrs	262	57	319	82.1
>10yrs-18yrs	143	59	202	70.8
>18yrs-40yrs	38	74	112	33.9
>40yrs	32	102	134	23.9

Table 4 Prevalence of symptoms of pertussis cases by age category n(%), evaluated by the Georgia Emerging Program, 2009-2013

Symptom	**3 mos OR <**	**>3mos-3yrs**	**>3yrs-10yrs**	**>10yrs-18yrs**	**>18yrs-40yrs**	**>40yrs**
Paroxysmal Cough	265 (93.6)	230(93.5)	287 (91.4)	188 (94.5)	106 (95.5)	124 (93.2)
Whooping Cough	130 (48.7)	109 (45.8)	95 (30.8)	60 (30.9)	40 (36.7)	48 (36.1)
Posttussive Vomiting	184 (65.0)	167 (67.6)	163 (52.4)	120 (60.0)	50 (44.6)	57 (42.5)
Apnea	171 (61.3)	63 (27.8)	29 (10.3)	8 (4.7)	16 (15.7)	12 (10.5)
Cyanosis	99 (55.9)	23 (13.5)	8 (3.6)	5 (3.1)	4 (5.2)	5 (4.4)
X-ray (Positive)	21 (7.5)	8 (3.3)	4 (1.3)	4 (2.0)	5 (4.6)	9 (6.8)
Acute Encephalopathy	3 (1.1)	0	2 (0.6)	0	1 (0.9)	5 (3.8)
Seizures	3 (1.1)	1 (0.4)	1 (0.3)	2 (1.0)	0	1 (0.8)
Hospitalization	215 (72.9)	41 (16.4)	7 (2.2)	12 (5.9)	8 (7.1)	8 (6.1)
Combinations	50	23	17	11	16	18

Table 5. Table 5. Effect of variable on time to treatment of pertussis cases by age group, adjusted for race, ethnicity, and sex

Age Group	**Doses**	**Paroxysmal**	**Whoop**	**Postussive Vomiting**	**Apnea**	**Cyanosis**	**X-ray Results**	**Seizure**	**Encephal opathy**	**Hospitalized**	**Confirmed**
3 mos or less	0.96	1.16	1.02	0.98	1.09	1.18	0.94	**0.32**	0.77	0.97	1.04
>3 mos-3years	1.02	1.16	0.97	0.82	1.21	0.84	0.30	NA	NA	1.00	0.86
>3years-10years	0.92	0.92	0.97	0.99	1.17	1.32	0.82	0.92	0.53	**0.25**	0.98
>10years-18years	0.99	1.30	1.31	1.26	1.47	0.69	**0.15**	NA	NA	0.82	0.79
>18years-40years	1.15	5.11	2.77	4.13	0.11	0.11	NA	NA	NA	0.65	1.38
>40years	0.91	0.67	1.35	2.64	0.90	1.48	1.06	0.77	NA	7.08	1.19

Grey shading represents a negative parameter estimate indicating that the effect is a decrease in time to treatment

Bolded estimates are those that had a p value<0.05

Table 6. Effect of variable on time to treatment of pertussis cases by age group adjusted for race, ethnicity, and sex

Age	Doses	Number symptoms	Confirmed case
3 mos or less	1.03	0.94	0.89
>3 mos-3years	1.10	1.03	1.03
>3years-10years	0.94	0.95	1.04
>10years-18years	1.00	**1.23**	0.97
>18years-40years	1.06	1.22	1.50
>40years	0.78	1.05	1.94

Grey shading represents a negative parameter estimate indicating that the effect is a decrease in time to treatment.
Bolded estimates are those that had a pvalue<0.05

Chapter III: Summary, Public Health Implications, Possible Future Directions

We identified patterns in the length of time to treatment for pertussis that may be related to clinical presentation and case confirmation. The patterns that emerged from this study are important for recognizing the difficulty in diagnosing pertussis and initiating treatment based on clinical manifestations. This study further exemplifies that there is no one clear definition for clinically diagnosing pertussis. Public health action is needed to address the complexity of pertussis infection to assist in prevention and control of future pertussis outbreaks. Our findings suggest that adults over 40 could play an important role in pertussis infection, due to less frequent confirmatory testing and potential lack of prioritization of pertussis as a cause of illness, which can impact time to treatment. If efforts are made to raise awareness among adults and clinicians about the signs and symptoms of pertussis in adults, a positive impact on time to treatment is attainable, which may help prevent the spread of pertussis to others in close contact with these adults. Future studies that include time of symptom onset for all symptoms is necessary to better understand the clinical progression of the disease. Additionally, future studies that document symptoms other than the classic pertussis symptoms across all age groups are needed to recognize how pertussis can manifest in different ways and in different populations.

Appendix A

This analysis was conducted using all probable and confirmed cases stratified by age group. Sex, race, and ethnicity were also controlled for in the model. The variable x-ray results is characterized as either positive or negative/unknown.

Table 5.a 3 mos or less (n=132)

Variable	exp(B)	Beta Estimate	Standard Error	95% CI		p-value
Doses	0.9631	-0.03758	0.16552	0.6963	1.3322	0.8208
Paroxysmal	1.1621	0.15025	0.25778	0.7012	1.9261	0.5611
Whoop	1.0213	0.02109	0.13621	0.7820	1.3338	0.8772
Postussive Vomiting	0.9791	-0.0211	0.14164	0.7418	1.2924	0.8818
Apnea	1.0875	0.08388	0.146	0.8169	1.4478	0.5667
Cyanosis	1.1767	0.16274	0.14525	0.8852	1.5643	0.2648
X-ray Results	0.9408	-0.06103	0.31752	0.5049	1.753	0.8479
Seizure	0.3175	-1.14721	0.53851	0.1105	0.9124	0.0352
Encephalopathy	0.7732	-0.25726	0.73544	0.1829	3.2681	0.7271
Hospitalized	0.9681	-0.03242	0.15299	0.7173	1.3066	0.8325
Confirmed	1.0369	0.03627	0.26979	0.6111	1.7596	0.8933

Table 5.b >3 mos to 3 years (n=112)

Variable	exp(B)	Beta Estimate	Standard Error	95% CI		p-value
Doses	1.018	0.01796	0.05214	0.9192	1.1277	0.7312
Paroxysmal	1.156	0.145	0.3341	0.6006	2.2252	0.6652
Whoop	0.967	-0.034	0.16204	0.7036	1.3279	0.8342
Postussive Vomiting	0.824	-0.19378	0.16739	0.5934	1.1437	0.2498
Apnea	1.206	0.18767	0.21384	0.7934	1.8345	0.3823
Cyanosis	0.837	-0.17783	0.25939	0.5035	1.3918	0.4946
X-ray Results	0.302	-1.198	0.62427	0.0888	1.0259	0.0579
Seizure	1.000	0	.			.
Encephalopathy	1.000	0	.			.
Hospitalized	1.003	0.00286	0.26596	0.5955	1.6890	0.9914
Confirmed	0.856	-0.1551	0.49565	0.3241	2.2623	0.755

Table 5.c > 3years-10 years (n=153)

Variable	exp(B)	Beta Estimate	Standard Error	95% CI		p-value
Doses	0.9199	-0.08352	0.0452	0.84188488	1.0051	0.0668
Paroxysmal	0.917	-0.08668	0.24846	0.5634585	1.4923	0.7277
Whoop	0.9742	-0.02615	0.15665	0.71663832	1.3243	0.8677
Postussive Vomiting	0.9944	-0.00565	0.13572	0.76211242	1.2974	0.9668
Apnea	1.1702	0.15716	0.30483	0.64383886	2.1268	0.607
Cyanosis	1.316	0.27457	0.35167	0.6605363	2.6218	0.4363
X-ray Results	0.8177	-0.2013	0.58992	0.25729212	2.5985	0.7335
Seizure	0.9184	-0.08517	0.83331	0.17934255	4.7026	0.9187
Encephalopathy	0.5254	-0.64364	0.60112	0.16172867	1.7067	0.2862
Hospitalized	0.2548	-1.36716	0.48888	0.09774778	0.6643	0.0059
Confirmed	0.9808	-0.01936	0.20966	0.65031813	1.4793	0.9266

Table 5.d >10 years- 18 years (n=102)

Variable	exp(B)	Beta Estimate	Standard Error	95% CI		p-value
Doses	0.99101065	-0.00903	0.05514	0.8894923	1.1041153	0.8703
Paroxysmal	1.29633364	0.25954	0.56721	0.4264792	3.9403581	0.6484
Whoop	1.31332226	0.27256	0.18808	0.9083942	1.8987519	0.1508
Postussive Vomiting	1.26311387	0.23358	0.17067	0.9039934	1.7648985	0.1746
Apnea	1.47249759	0.38696	0.47157	0.5843137	3.7107618	0.4141
Cyanosis	0.6852168	-0.37802	0.79851	0.1432592	3.2774301	0.6371
X-ray Results	0.14743321	-1.91438	0.80297	0.0305558	0.7113727	0.0192
Seizure	1	0	.			.
Encephalopathy	1	0	.			.
Hospitalized	0.82248914	-0.19542	0.35236	0.4122829	1.6408356	0.5805
Confirmed	0.79308887	-0.23182	0.18856	0.5480452	1.1476973	0.2221

Table 5.e >18 years-40 (n=25)

Variable	exp(B)	Beta Estimate	Standard Error	95% CI		p-value
Doses	1.153	0.14234	0.13986	0.8765289	1.5166	0.3274
Paroxysmal	5.1074	1.6307	1.14274	0.5438562	47.965	0.1772
Whoop	2.7722	1.01963	0.73842	0.65202446	11.786	0.1906
Postussive Vomiting	4.1324	1.41885	0.69977	1.04843733	16.288	0.0636
Apnea	0.1089	-2.21771	1.2737	0.00896738	1.3215	0.1053
Cyanosis	0.1129	-2.18151	1.11421	0.01271006	1.0023	0.0721
X-ray Results	1	0	.			.
Seizure	1	0	.			.
Encephalopathy	1	0	.			.
Hospitalized	0.6529	-0.42628	1.14136	0.06971459	6.1152	0.7148
Confirmed	1.3838	0.32483	0.48712	0.53263164	3.5951	0.5165

Table 5.f >40 years (n=30)

Variable	exp(B)	Beta Estimate	Standard Error	95% CI		p-value
Doses	0.90927291	-0.09511	0.24304	0.5646956	1.4641112	0.7007
Paroxysmal	0.67448894	-0.3938	0.80113	0.140294	3.2427275	0.6297
Whoop	1.34759295	0.29832	0.67499	0.3589183	5.0596656	0.6644
Postussive Vomiting	2.64082139	0.97109	0.65395	0.7329689	9.5146432	0.157
Apnea	0.90425851	-0.10064	0.98903	0.1301407	6.2830705	0.9202
Cyanosis	1.47665589	0.38978	1.06792	0.1820738	11.975983	0.7199
X-ray Results	1.05753423	0.05594	1.43217	0.0638567	17.513871	0.9693
Seizure	0.7702193	-0.26108	1.56214	0.0360491	16.456399	0.8694
Encephalopathy	1	0	.			.
Hospitalized	7.07820256	1.95702	1.60286	0.3058729	163.79663	0.2398
Confirmed	1.18840254	0.17261	0.99398	0.1693833	8.3378951	0.8643

Appendix B

This multivariate linear regression analysis was conducted using all probable and confirmed pertussis cases evaluated by the GA EIP from 2009-2013, stratified by age group.
Sex, race, and ethnicity were controlled for in the model. Doses are the number of pertussis containing vaccines received before illness onset.

Table 6.a 3 mos or less (n=132)

Variable	exp(B)	Beta Estimate	Standard Error	95% CI		p-value
Doses	1.028056	0.02767	0.04115	0.9484	1.1144	0.5022
Number Symptoms	0.941689	-0.06008	0.06159	0.8346	1.0625	0.3306
Confirmed	0.89249	-0.11374	0.2995	0.4962	1.6053	0.7046

Table 6.b > 3mos-3 years (n=153)

Variable	exp(B)	Beta Estimate	Standard Error	95% CI		p-value
Doses	1.102378	0.09747	0.12844	0.8570	1.4180	0.4488
Number Symptoms	1.027799	0.02742	0.04698	0.9374	1.1269	0.56
Confirmed	1.030599	0.03014	0.19042	0.7096	1.4969	0.8744

Table 6.c > 3years-10 years (n=153)

Variable	exp(B)	Beta Estimate	Standard Error	95% CI		p-value
Doses	0.942188	-0.05955	0.03642	0.8773	1.0119	0.1034
Number Symptoms	0.954021	-0.04707	0.05887	0.8501	1.0707	0.4248
Confirmed	1.035848	0.03522	0.14916	0.7733	1.3876	0.8135

Table 6.d >10 years- 18 years (n=102)

Variable	exp(B)	Beta Estimate	Standard Error	95% CI		p-value
Doses	1.0045	0.00449	0.05167	0.9078	1.1116	0.9308
Number Symptoms	1.2321	0.20872	0.08394	1.0452	1.4524	0.014
Confirmed	0.965934	-0.03466	0.15293	0.7158	1.3035	0.821

Table 6.e >18 years-40 (n=25)

Variable	exp(B)	Beta Estimate	Standard Error	95% CI		p-value
Doses	1.058539	0.05689	0.07221	0.9188	1.2195	0.4362
Number Symptoms	1.224117	0.20222	0.20099	0.8255	1.8151	0.3215
Confirmed	1.503086	0.40752	0.37075	0.7268	3.1087	0.2794

Table 6.f >40 years (n=42)

Variable	exp(B)	Beta Estimate	Standard Error	95% CI		p-value
Doses	0.781797	-0.24616	0.17617	0.5535	1.1042	0.1711
Number Symptoms	1.0472	0.04612	0.16475	0.7582	1.4463	0.7812
Confirmed	1.942042	0.66374	0.41101	0.8678	4.3463	0.1153