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Dana Goodenough, Emory University
Ebony Thomas, Georgia Department of Public Health
Jessica Tuttle, Georgia Department of Public Health
Robert Bednarczyk, Emory University

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Factors Associated with Time to Appropriate Treatment in Pertussis Cases in Georgia, 2009 to 2013

Dana Goodenough,a,** Ebony Thomas,a Jessica Tuttle,b Robert A. Bednarczyka,c

Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia, USAa; Acute Disease Epidemiology Section, Georgia Department of Public Health, Atlanta, Georgia, USAa; Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, Georgia, USAa

Pertussis is endemic in the United States, with periodic epidemics that continue to highlight its importance as a public health issue. 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 to 19 years) (1). Both natural and acquired immunity is estimated to last only approximately 4 to 10 years (2).

Several factors may contribute to the increasing number of pertussis cases. These include waning immunity of the acellular pertussis vaccine, better diagnostics to confirm cases, and genetic changes in Bordetella pertussis (3). Additionally, many parents are choosing not to vaccinate or to partially vaccinate their children against pertussis among other vaccine-preventable diseases such that pertussis is being seen more often even in pediatric settings (4). Pertussis infection can cause a variety of symptoms, and the clinical presentation of pertussis can vary by age and vaccination status (5). The clinical presentation of patients with pertussis infection can range from severe disease, including paroxysmal cough, to milder illness with only rhinitis. Young infants may present with apnea and no other disease symptoms. Vaccinated adolescents and adults may exhibit mild symptoms or have the typical prolonged, paroxysmal cough. Notably, many of the symptoms caused by B. pertussis are nonspecific and mimic symptoms of other viral respiratory infections (6). For this reason, many pertussis cases progress without testing. This is problematic because the effectiveness of bacterial isolation and PCR diagnostic testing is subject to time and are not reliable after approximately 3 weeks of paroxysmal coughing (7). Delayed testing can lead to delayed treatment. Antibiotics are most effective within 3 weeks of onset of paroxysmal cough (8).

Little is known about the factors that affect time to antibiotic 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 increasing susceptibility due to waning immunity associated with acellular pertussis vaccines, determining how pertussis cases can be recognized sooner is important to prevent additional cases (9–11). By decreasing time to treatment, patients can begin treatment earlier and decrease the amount of time in which they are infectious. Early clinical recognition of pertussis would allow for earlier laboratory confirmation, which would diminish the gap between the start of antibiotics and confirmation, consequently reducing the occurrence of presumptive treatment. Prompt, correct treatment reduces the administration of inappropriate antibiotics and the further transmission of illness. We analyzed 5 years of data from...
the Georgia Department of Public Health (GDPH) to understand how factors such as age, symptoms, and vaccine status can alter the clinical picture of pertussis and affect time to appropriate treatment.

MATERIALS AND METHODS

Study population. This cross-sectional study was conducted using data from the GDPH. Data were collected, as part of routine passive surveillance, on confirmed and probable pertussis cases reported to the Georgia Department of Public Health from 2009 to 2013. A confirmed case as defined by the Centers for Disease Control and Prevention (CDC) and the Council of State and Territorial Epidemiologists (CSTE) is an acute cough illness of any duration with isolation of B. pertussis from a clinical specimen, or a clinical case with a PCR-positive laboratory test, or a clinical case that is epi-linked to a laboratory-confirmed case. A clinical case is defined as a cough illness lasting 2 weeks or greater with at least one of the following: paroxysms, whoop, or posttussive vomiting. A probable case is defined as a clinical case of pertussis without laboratory confirmation or epi-linkage to a laboratory-confirmed case. Serodiagnosis is not utilized as confirmatory testing in this surveillance system.

Data collection and analytic variables. Primary exposure variables and other variables were collected by the GDPH using the Georgia Department of Public Health Pertussis Reporting and Case Investigation form. The case report form included demographic, clinical, vaccine, and epidemiological information. Data identifying cough, paroxysmal cough, whoop, posttussive vomiting, apnea, hospitalization, seizures, acute encephalopathy, death, epi-linkage, and vaccination status were all reported as yes-or-no variables. Cough onset date and antibiotic start date were reported as day/month/year. Number of doses was a summation of the total number of pertussis-containing vaccines the individual received. The variable “completely vaccinated” was a yes-or-no variable that was created by the research team to reflect whether a patient was age appropriately vaccinated before cough onset according to the Advisory Committee on Immunization Practices (ACIP) recommendations.

The time to treatment variable was calculated by subtracting the cough onset date from the antibiotic start date. We also computed a “total symptoms” variable by summing the following findings or symptoms the patient experienced: cough, paroxysmal cough, whoop, posttussive vomiting, apnea, hospitalization, seizures, acute encephalopathy, death, epi-linkage, and vaccination status were all reported as yes-or-no variables. Cough onset date and antibiotic start date were reported as day/month/year. Number of doses was a summation of the total number of pertussis-containing vaccines the individual received. The variable “completely vaccinated” was a yes-or-no variable that was created by the research team to reflect whether a patient was age appropriately vaccinated before cough onset according to the Advisory Committee on Immunization Practices (ACIP) recommendations.

The mean time to treatment was calculated across levels of each study variable. We used multivariable linear regression to assess the impact of individual variables on increasing or decreasing time to treatment.

All data were analyzed using SAS 9.4. Because the study consisted of deidentified, previously collected data, it was exempted from Institutional Review Board (IRB) review.

RESULTS

This study examined a population of 1,313 probable and confirmed cases of pertussis reported through the GDPH. The average age of patients was 12.7 years (standard deviation [SD], 17.3), and the median age was 7 years (interquartile range [IQR], 0.42 to 14). Most study participants were white (78.4%), and the majority were female (57.1%). There was a similar proportion of epi-linked cases in the older age groups. Among the three age groups greater than 10 years old, the proportions of cases that were epi-linked to a confirmed case were similar, ranging from 17.0% to 18.8%. Among the age groups 10 years and younger, the proportions of cases that were epi-linked varied from 7.1% to 31.4%. Nearly all patients had cough (99.9%), and most had paroxysmal cough (93.3%); other symptoms were reported less frequently (e.g., the next two most common symptoms were posttussive vomiting [57.6%] and apnea [25.5%]) and with more variability by age (Table 1).

Overall, average time to treatment increased with age. A one-way analysis of variance (ANOVA) showed that increasing time to treatment with increasing age categories was statistically significant (data not shown). On average, the youngest age group (3
months old or less) was treated 12.3 days after cough onset (SD, 11.1), the shortest time to treatment among all age groups. Time to treatment increased to 21.7 days after cough onset in those 10 years old (5.11 days). Although three of the measures were statistically associated with decreased time to treatment (X-ray results and hospitalization in those >40 years of age) were associated with at least a 5-day increase in time to treatment (Tables 5 and 6) (full tables of multivariate analysis are available in the supplemental material).

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 (1.16 days), >3 months old to 3 years (1.16 days), >10 years to 18 years (1.30 days), and most meaningfully in adults >18 years to 40 years old (5.11 days). Although three of the measures were statistically associated with decreased time to treatment, hospitalization in those >3 years to 10 years old, were associated with decreased time to treatment of at least 1 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 ≤3 months old (-0.94 days) and children >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 individuals ≤3 months old and >10 years to 18 years old (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 various presentations of pertussis clinical illness (5). Inconsistent clinical manifestations of pertussis make it difficult to quickly and correctly diagnose pertussis. Lab cultures, the "gold standard" of pertussis diagnosis,
can take approximately 1 to 2 weeks to provide results, while PCR
can be completed in a few days (7). For this reason, early labora-
tory testing is pertinent. The Georgia pertussis incidence rate in
2011 was 1.9 cases per 100,000 population; however, the pertussis
rate by county ranged from 0 to 79.6 per 100,000 population (12).
As per CDC recommendations, health care providers are strongly
recommended to presumptively treat for pertussis when it is sus-
ppected (8).

In a children’s hospital study conducted in Israel, Eidlitz-
Markus et al. also found that symptom presentation varied by age
group (1). They found that infants (up to 6 months old) suffering
from pertussis were more likely to have cyanosis and a whooping
cough than older children (7 to 18 years old). Similarly, we found
that infants ≤3 months old were more likely to have a typical
whoop (48.7%) than children >10 years to 18 years old (30.9%).
We also observed that infants ≤3 months old were more likely to
have cyanosis (55.9%) than children >10 years to 18 years old
(3.1%). The researchers also noted that there was a significant dif-
ference between the infant and older groups in mean time to di-
agnosis (1.1 ± 0.06 weeks and 5.84 ± 4.19 weeks, respectively; P <
0.01) (1). We also found that, on average, time to treatment for
infants ≤3 months old (11.1 days) was less than time to treat-
ment for children >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 to 3 months, 4 months to 9 years, and ≥10 years (5).
However, in the era of waning immunity, it is important to un-
derstand the clinical presentation in adults as well. We found that
not only did symptoms vary across younger age groups but also
they varied across older age groups. This study adds to the litera-
ture evaluating pertussis presentation and highlights the complex-
ity of pertussis diagnosis on the basis of symptom presentation.
The GPI says that in resource-rich countries where the sensitivity
of diagnostic capacity has already been reached, education, aware-
ness, and recognition of pertussis should be top priorities. In ad-
dition, the GPI also emphasize that proper sampling techniques
are vital (5). The standard pertussis diagnostic laboratory test is
isolation of B. pertussis by bacterial culture. The effectiveness
of bacterial culture and PCR diagnostics is subject to time, and these
tests are not reliable after approximately 3 weeks of illness (7, 13).
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 (7). In our study
population, there were 71 confirmed cases with at least one nega-
tive lab result and 51 probable cases with at least one negative lab
result. Thus, prompt specimen collection and testing are essential
for pertussis confirmation.

Only 23.9% of pertussis cases in individuals >40 years old were
confirmed. The low proportion of confirmed cases in the older
adult groups highlights the importance of testing when pertussis is
suspected. Delays in testing 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

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**TABLE 4** Prevalence of symptoms of probable and confirmed pertussis cases by age category, evaluated by the Georgia Department of Public Health, 2009 to 2013 (n = 1,313)

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

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**TABLE 5** Effect of variable on time to treatment of probable and confirmed pertussis cases by age group, adjusted for race, ethnicity, and sex (n = 1,211)*

<table>
<thead>
<tr>
<th>Age group</th>
<th>Time to treatment (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Doses</td>
</tr>
<tr>
<td>≤3 mo</td>
<td>0.96</td>
</tr>
<tr>
<td>&gt;3 mo–3 yrs</td>
<td>1.02</td>
</tr>
<tr>
<td>&gt;3 yrs–10 yrs</td>
<td>0.92</td>
</tr>
<tr>
<td>&gt;10 yrs–18 yrs</td>
<td>0.99</td>
</tr>
<tr>
<td>&gt;18 yrs–40 yrs</td>
<td>1.15</td>
</tr>
<tr>
<td>≥40 yrs</td>
<td>0.91</td>
</tr>
</tbody>
</table>

*Gray shading represents a negative parameter estimate indicating that the effect is a decrease in time to treatment. Bold estimates are those that had a P value of <0.05. NA, not available.

**a**Received any doses of pertussis-containing vaccines before cough onset.
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 (3). In this study, some probable cases did have testing; however, their test results were negative, and thus, they remained probable cases. This further exemplifies the need to test early to confirm pertussis diagnoses and confirm proper antibiotic treatment.

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 (14). These findings conflict with the longer time to treatment associated with cyanosis that we observed in infants <3 months old. 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- to 3-month-olds with pertussis, and its presentation or lack thereof should not rule out pertussis as a possibility. Even though pertussis was once rarely seen in the pediatric setting, it is imperative that health care providers consider pertussis in their differential diagnosis (4).

Additionally, this study showed that presentation with more symptoms was statistically associated with longer time to treatment in 10- to 18-year-olds. 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. There were more hospitalizations among 10- to 18-year-olds than among 3- to 10-year-olds (5.9% versus 2.2%), which could point to an accumulation of symptoms and more severe disease. This underlying symptom paradox could explain why additional symptoms were associated with increased time to treatment. However, time of symptom onset was recorded only 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 led to longer time to treatment.

TABLE 6 Effect of variable on time to treatment of probable and confirmed pertussis cases by age group adjusted for race, ethnicity, and sex (n = 1,211)∗

<table>
<thead>
<tr>
<th>Age group</th>
<th>Doses</th>
<th>No. of symptoms</th>
<th>Confirmed case</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 3 mo</td>
<td>1.03</td>
<td>0.94</td>
<td>0.89</td>
</tr>
<tr>
<td>&gt; 3 mo–3 yrs</td>
<td>1.10</td>
<td>1.03</td>
<td>1.03</td>
</tr>
<tr>
<td>&gt; 3 yrs–10 yrs</td>
<td>0.94</td>
<td>0.95</td>
<td>1.04</td>
</tr>
<tr>
<td>&gt; 10 yrs–18 yrs</td>
<td>1.00</td>
<td>1.23</td>
<td>0.97</td>
</tr>
<tr>
<td>&gt; 18 yrs–40 yrs</td>
<td>1.06</td>
<td>1.22</td>
<td>1.30</td>
</tr>
<tr>
<td>&gt; 40 yrs</td>
<td>0.78</td>
<td>1.05</td>
<td>1.94</td>
</tr>
</tbody>
</table>

∗Gray shading represents a negative parameter estimate indicating that the effect is a decrease in time to treatment. Bold estimates are those that had a P value of <0.05.

†Received any doses of pertussis-containing vaccines before cough onset.

Time to treatment for confirmed cases in persons >40 years of age was approximately 2 days longer than in persons of the same age with probable cases. 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 (14). Also, adults in this age range may not routinely seek health care, thus leading to a delay in 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 (5). 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 the patient is at risk for severe or complicated disease (8).

Notably, whooping cough presentation was associated with shorter time to treatment only in children >3 months to 10 years old. This finding is particularly interesting considering that a whooping cough is the hallmark of pertussis infection. On the other hand, across age groups, whooping cough was present in only 30 to 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 (14). These findings further suggest that the lack of classical symptom presentation of pertussis is not necessarily conclusive.

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, especially among adults. 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 health care providers. The utilization of Immunization Information Systems (IIS) can provide consolidated vaccine histories to clinicians so that they can have more accurate immunization information for their patients. It is difficult to get the complete clinical and epidemiological picture if vaccine history is not accurate. Utilization of IIS may help, but it still has its limitations because states cannot access others states’ IIS systems and adults are often not entered into the IIS system. Another weakness of this study is that our data are surveillance data. The data we analyzed were not collected specifically for this study; therefore, we were limited to the variables and measures available. Notably, because we did not know symptom onset, we were unable to discern if an increasing number of symptoms may be confusing the clinical picture or if delayed treatment leads to an increased number of symptoms. Consequently, there is an underlying symptom paradox in our study, and we recommend that future studies capture data on onset for each symptom to better understand time to treatment and categorize the stages of pertussis. Information about the type of physician prescribing treatment and the date medical treatment was sought was not available; however, this information can address questions related to behavior in future studies. While race and ethnicity were not statistically significant in our models, other socioeconomic status data were not available, and we recognize this as a potential weakness in our study. Furthermore, most of the cases reported presented with paroxysmal cough during (93.3%), suggesting that the data of cases reported are very skewed toward...
typical pertussis. This could have led to an underestimate of time to treatment.

However, this study is unique because it utilized population based data and included information for cases of all ages. There could be differences in physicians’ knowledge of pertussis and what signs and symptoms they know to look for and in which age groups. Unfortunately, little is known about the attitudes of different physician types in the United States toward pertussis diagnosis. More information is needed to understand pertussis awareness across health care providers. Nevertheless, in a 2012 Italian study of pediatricians and general practitioners, researchers found a decreasing trend of suspected pertussis diagnosis with increasing age of the patient ([15]). Additionally, a study done in the Netherlands of pediatric pertussis cases in university teaching hospitals found that doctors miss 1 in 5 pertussis cases in children when diagnosing on clinical suspicion alone ([6]). The findings of our study have important implications for improvement of pertussis recognition and diagnosis.

Conclusion. Despite a widely available pertussis vaccine, pertussis is still a burden in the United States. This study highlights how the difficulties in pertussis diagnosis, particularly among adults, can affect time to antibiotic treatment; adults may not begin antibiotic treatment until there is an accumulation of symptoms. Health care 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 a patient is at risk for severe or complicated disease ([8]).

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