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

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Pertussis is endemic in the United States, with periodic epidemics that continue to highlight its importance as a public health issue. The clinical presentation of pertussis can vary by age and vaccination status. However, little is known about the factors that affect time to antibiotic treatment of pertussis cases. We analyzed 5 years of data from the Georgia Department of Public Health to understand how factors such as age, symptoms, and vaccination status can alter the clinical picture of pertussis and affect time to treatment. We used multivariable linear regression to assess the impact of each variable on time to antibiotic treatment. There was little consistency across age groups for symptom and demographic predictors of time to antibiotic treatment. Overall, the multivariate linear regression showed that among patients ≤18 years old, none of the variables had an impact on time to antibiotic treatment greater than −0.25 to 1.47 days. Among patients >18 years old, most variables had little impact on time to treatment, though two (paroxysmal cough in >18- to 40-year-olds and hospitalization in individuals over 40) were associated with an additional 5 days in time to treatment from cough onset. 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.

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.

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**Analysis.** For analysis, cases were excluded if cough onset date or antibiotic start date was 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 percentage 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. We controlled for sex, race, and ethnicity and calculated exponentiated beta estimates to interpret the impact of individual variables on increasing or decreasing time to treatment.

**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
from analysis if time to treatment was missing or if the time to treatment recorded was not plausible. Sex, race, and ethnicity were included in the model but showed no significant or meaningful impact on time to treatment. There was little consistency across age groups for symptom and demographic predictors of time to treatment. Overall, the multivariate linear regression showed that among patients aged ≤18 years, none of the variables had an impact on time to treatment greater than −0.25 to 1.47 days. Among patients >18 years of age, most variables had little impact on time to treatment, though two (paroxysmal cough in >18- to 40-year-olds and hospitalization in individuals >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 (X-ray results in those >10 to 18 years old, seizures in those ≤3 months old, and hospitalization in those >3 years to 10 years old), none of the symptoms 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,
The Global Pertussis Initiative (GPI) developed an algorithm that defines for pertussis cases, as documented in the literature. It also emphasizes that proper sampling techniques, education, awareness, and recognition of pertussis should be top priorities. In addition, the GPI also emphasizes that proper sampling techniques are vital. 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. 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. In our study population, there were 71 confirmed cases with at least one negative 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 can take approximately 1 to 2 weeks to provide results, while PCR can be completed in a few days. For this reason, early laboratory 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. As per CDC recommendations, health care providers are strongly recommended to presumptively treat for pertussis when it is suspected.

In a children's hospital study conducted in Israel, Eidlitz-Markus et al. also found that symptom presentation varied by age group. They found that infants (up to 6 months old) suffering from pertussis were more likely to have cyanoosis 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 old (30.9%).

We also observed that infants ≤3 months old were more likely to have cyanoisis (55.9%) than children >10 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; \( P < 0.001 \))

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. In our study population, there were 71 confirmed cases with at least one negative lab result and 51 probable cases with at least one negative lab result. Thus, prompt specimen collection and testing are essential for pertussis confirmation.

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

<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>&gt;40 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal cough</td>
<td>0.96</td>
<td>1.16</td>
<td>1.02</td>
<td>0.98</td>
<td>1.09</td>
<td>1.18</td>
</tr>
<tr>
<td>Whoop</td>
<td>1.02</td>
<td>1.16</td>
<td>0.97</td>
<td>0.82</td>
<td>1.21</td>
<td>0.84</td>
</tr>
<tr>
<td>Posttussive vomiting</td>
<td>1.02</td>
<td>0.97</td>
<td>0.99</td>
<td>0.99</td>
<td>1.17</td>
<td>1.32</td>
</tr>
<tr>
<td>Apnea</td>
<td>1.09</td>
<td>1.18</td>
<td>0.94</td>
<td>0.94</td>
<td>0.32</td>
<td>0.77</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>1.02</td>
<td>1.16</td>
<td>0.97</td>
<td>0.94</td>
<td>1.47</td>
<td>0.69</td>
</tr>
<tr>
<td>X-ray result</td>
<td>1.02</td>
<td>1.16</td>
<td>0.97</td>
<td>0.94</td>
<td>1.17</td>
<td>1.32</td>
</tr>
<tr>
<td>Seizures</td>
<td>1.02</td>
<td>1.16</td>
<td>0.97</td>
<td>0.97</td>
<td>0.32</td>
<td>0.77</td>
</tr>
<tr>
<td>Acute encephalopathy</td>
<td>1.02</td>
<td>1.16</td>
<td>0.97</td>
<td>0.97</td>
<td>1.17</td>
<td>1.32</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>1.02</td>
<td>1.16</td>
<td>0.97</td>
<td>0.97</td>
<td>0.32</td>
<td>0.77</td>
</tr>
<tr>
<td>Combinations</td>
<td>0.91</td>
<td>1.02</td>
<td>1.26</td>
<td>0.95</td>
<td>0.91</td>
<td>0.95</td>
</tr>
<tr>
<td>Doses (mg)</td>
<td>0.91</td>
<td>1.02</td>
<td>1.26</td>
<td>0.95</td>
<td>0.91</td>
<td>0.95</td>
</tr>
<tr>
<td>Median age group</td>
<td>1.02</td>
<td>1.16</td>
<td>0.97</td>
<td>0.94</td>
<td>1.09</td>
<td>1.18</td>
</tr>
</tbody>
</table>

| Effect of variable on time to treatment of probable and confirmed pertussis cases by age group, adjusted for race, ethnicity, and sex \((n = 1,211)^{ab}\)

- **Time to treatment (days)**
- **Age group**
- **Doses (mg)**
- **Paroxysmal**
- **Whoop**
- **Posttussive vomiting**
- **Apnea**
- **Cyanosis**
- **X-ray result**
- **Seizure**
- **Encephalopathy**
- **Hospitalized**
- **Confirmed**

\( ^{a} \)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.

\( ^{b} \)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.

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

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**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.

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May 2016 Volume 60 Number 5 Antimicrobial Agents and Chemotherapy aac.asm.org 3055
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).

ACKNOWLEDGMENTS

We thank the Georgia Department of Public Health for providing the data utilized in this study.

The findings in this report solely represent the opinions of the authors. We have no conflicts of interest or financial disclosures to report.

FUNDING INFORMATION

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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