Epidemiologic and Laboratory Features of a Large Outbreak of Pertussis-Like Illnesses Associated With Cocirculating \textit{Bordetella holmesii} and \textit{Bordetella pertussis}—Ohio, 2010–2011

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Background. During 9 May 2010–7 May 2011, an outbreak of pertussis-like illness (incidence, 80 cases per 100 000 persons) occurred in Franklin County, Ohio. The majority of cases were identified by IS481-directed polymerase chain reaction (PCR), which does not differentiate among \textit{Bordetella} species. We sought to determine outbreak etiology and epidemiologic characteristics.

Methods. We obtained demographic, clinical, and vaccination-related data from the Ohio Disease Reporting System and Impact Statewide Immunization Information System. We tested sera from 14 patients for anti-pertussis toxin (PT) antibodies and used species-specific PCR on 298 nasopharyngeal specimens.

Results. Reported cases totaled 918. IS481 results were available for 10 serologically tested patients; 5 of 10 had discordant anti-PT antibody and IS481 results, suggestive of \textit{Bordetella holmesii}, which lacks PT and harbors IS481. We identified specific \textit{Bordetella} species in 164 of 298 specimens tested with multitarget PCR; \textit{B. holmesii} and \textit{Bordetella pertussis} were exclusively detected among 48 (29%) and 112 (68%), respectively; both were detected in 4 (2%). Among 48 patients with \textit{B. holmesii} infections, 63% were aged 11–18 years, compared with 35% of 112 patients with \textit{B. pertussis} infections ($P = .001$). Symptoms were similar among \textit{B. holmesii}– and \textit{B. pertussis}–infected patients. Adolescent pertussis (“Tdap”) booster vaccinations were more effective against \textit{B. pertussis} than \textit{B. holmesii} (effectiveness: 67% and 36%, respectively; 95% confidence intervals, 38%–82% and –33% to 69%, respectively).

Conclusions. We report the first documented mixed outbreak of \textit{B. pertussis} and \textit{B. holmesii} infections. \textit{Bordetella holmesii} particularly affected adolescents. Although laboratory capacity limitations might inhibit routine use of multitarget PCR for clinical diagnosis, focused testing and enhanced surveillance might improve understanding the burden of \textit{B. holmesii} infection.

Keywords. pertussis; \textit{Bordetella holmesii}; PCR; outbreak; \textit{Bordetella pertussis}.

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The incidence of reported pertussis has increased in the United States despite widespread use of effective vaccines [1, 2]. Clinical presentation can include cough illness persisting 4–8 weeks or longer, paroxysms, posttussive vomiting, and inspiratory whoop. *Bordetella pertussis* is the primary pathogen associated with the disease, and *Bordetella parapertussis* can produce illness resembling mild or moderate pertussis [3]. Additionally, *Bordetella bronchiseptica* and *Bordetella holmesii* have been detected in respiratory tracts of patients with pertussis-like symptoms. *Bordetella bronchiseptica* primarily infects nonhuman hosts; however, it has been reported to cause opportunistic upper respiratory tract infections among immunocompromised persons [4]. *Bordetella holmesii* was originally identified as a rare cause of bacteremia, predominantly among young adults with hypoplenism [5–9], but has been isolated from respiratory specimens obtained from otherwise healthy persons with pertussis-like illness [6, 10–15].

Clinical diagnosis of pertussis can be difficult because infection can present with nonspecific signs or symptoms. Laboratory testing typically relies on testing of nasopharyngeal (NP) secretions by real-time polymerase chain reaction (PCR) assays that target various nucleic acid sequences. The insertion sequence IS481 is often targeted for clinical diagnosis because 50–238 copies of IS481 are present per *B. pertussis* genome, which contributes to assay sensitivity [16, 17]; however, 8–10 copies of IS481 are present per *B. holmesii* genome [18] and the sequence is detected in 1%–5% of *B. bronchiseptica* strains [19, 20], potentially leading to incorrect diagnoses. Additional PCR targets can be used to improve specificity by differentiating among *Bordetella* species [17, 21–23].

During May 2010–May 2011, an outbreak of pertussis-like illness occurred in Franklin County, Ohio (population approximately 1.15 million [24]), which includes the city of Columbus. A majority of cases were classified on the basis of an IS481 PCR assay performed at a local hospital laboratory, and a limited number of *B. pertussis* isolates were obtained. We sought to describe outbreak epidemiologic characteristics, determine etiology, evaluate vaccination coverage among patients, and develop recommendations for prevention and control of future outbreaks.

**METHODS**

**Case Ascertainment**

We retrospectively searched the Ohio Disease Reporting System (ODRS) [25] to identify and classify illnesses among Franklin County residents reported to have had onset of pertussis-like illness during 9 May 2010–7 May 2011, a 52-week period centered at the week of highest incidence. Confirmed cases were either (1) cough of ≥14 days with at least 1 classical pertussis sign (ie, paroxysms, whoop, or posttussive vomiting) with a PCR result positive for a target present in *B. pertussis*, or (2) cough of ≥14 days with at least 1 classical pertussis sign with close contact to a patient with illness confirmed by either culture or PCR, or (3) a cough of any duration with isolation of *B. pertussis*. Probable cases were cough of ≥14 days with at least 1 classical pertussis sign, and without confirmation by culture or PCR or epidemiologic linkage to a lab-confirmed case [26]. Suspected cases were defined as cough of <14 days and at least 1 classical pertussis sign in either (1) a person with a PCR result positive for a target present in *B. pertussis*, or (2) a person with close contact to a patient with confirmed illness. For 32 cases where illness onset dates were unknown, we substituted the earliest of the following events in place of the date of illness onset as follows: diagnosis date, specimen collection date, or date reported to the Ohio Department of Health. In accordance with standard reporting procedures, patients or parents of patients were interviewed by local health department personnel, with the final interview occurring at least 14 days after cough onset. Coughs persisting beyond the final interview were not followed to resolution.

**Epidemiologic Data Sources**

We obtained demographic and clinical descriptions of patients from ODRS, population data from the 2009 US Census Bureau, National Center for Health Statistics Bridged-Race Population Estimates [24], and immunization records from the Ohio Impact Statewide Immunization Information System and ODRS, which includes immunization records reported by healthcare providers, patients, and parents or guardians of patients. A tetanus-diphtheria-acellular pertussis (Tdap) vaccination was defined as a record of any pertussis-containing vaccination in a person aged ≥10 years. We examined Tdap records for adolescents aged 11–18 years, an age group for which the Advisory Committee on Immunization Practices recommends a single dose of Tdap [27]. Antibiotic administration records were obtained from ODRS, which combines clarithromycin and azithromycin therapy into a single group, thereby preventing individual analysis of either antibiotic.

**Specimen Collection and Laboratory Testing**

During 10–16 December 2010, we requested blood samples from Franklin County residents aged 10–57 years who were reported to have onset of pertussis during 25 October–27 November, 2010. To detect recent infection by *B. pertussis*, we tested 14 serum specimens at the Centers for Disease Control and Prevention (CDC) Pertussis and Diphtheria Laboratory by using a single-point indirect enzyme-linked immunosorbent assay (ELISA) for detection of immunoglobulin G (IgG) antibodies against PT [28]; specimens with anti-PT IgG concentrations of ≥94 IU/mL were considered to be seropositive [28, 29]. IS481 results obtained from NP specimens submitted to the Molecular Diagnostics Laboratory at Nationwide Children’s...
Hospital (NCH) in Columbus, Ohio, for routine clinical testing for *B. pertussis* and *B. parapertussis* (see PCR assay methods below) were available for 10 of 14 patients who had blood collected for anti-PT IgG serology. In addition, residual NP samples archived at NCH were available from 6 of these 10 patients.

These 6 NP samples were tested at the CDC using 2 PCR assays. The first was a multiplex assay targeting IS\(_{481}\) (detected in *B. pertussis*, *B. holmesii*, and in a small percentage of *B. bronchiseptica* isolates), hIS1001 (detected in *B. holmesii* only), and pIS\(_{1001}\) (detected in *B. parapertussis* and infrequently in *B. bronchiseptica*) [23]. The 6 samples were also tested by NCH in 3 separate PCR assays. These included a multiplex assay targeting *IS\(_{481}\)* and *BparaIS\(_{1001}\)* (specific for *B. parapertussis*).

### Table 1. Sequences of Primers and Probes Used by Nationwide Children’s Hospital for Real-Time Polymerase Chain Reaction Assays

<table>
<thead>
<tr>
<th>Target</th>
<th>Species Specificity</th>
<th>Primer/Probes Sequence (5′ to 3′)</th>
<th>Amplicon Length (bp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IS(_{481})</td>
<td><em>B. pertussis</em> and <em>B. holmesii</em></td>
<td>F, TGA GCT GGG CAT CAA GCA R, TCG GCC TTG CCA TTG GT P, CGC TTT ACC CAA CCT TAC CGC CC(^a)</td>
<td>62</td>
</tr>
<tr>
<td>BparIS(_{1001})</td>
<td><em>B. parapertussis</em></td>
<td>F, CGT GGA TCA GGC CAA TCA AC R, AGC GAC TCG ATT TGA TCA TCC T P, ACG CCA GGA TCG TCC CGC AC(^b)</td>
<td>64</td>
</tr>
<tr>
<td>PtxA-Pr</td>
<td><em>B. pertussis</em> and <em>B. parapertussis</em></td>
<td>F, CAA TCC AAC ACG GCA TGA AC R, GGA CGG TGA CCG GTA CCA T P, CTC CTT CGG CGC AAA GTC GCG(^a)</td>
<td>63</td>
</tr>
<tr>
<td>BholIS(_{1001})</td>
<td><em>B. holmesii</em></td>
<td>F, TCA TCG CGC ATC AGA TAA GC R, CGG TAA AGT TGG ACG AGT TGC T P, TGA GCA AGG GCT GGT TGG CCT G(^b)</td>
<td>67</td>
</tr>
</tbody>
</table>

Abbreviations: bp, base pairs; F, forward primer; R, reverse primer; P, probe.

\(^{a}\) Probe 5′ end labeled with 6-carboxyfluorescein (FAM) and 3′ end labeled with 6-carboxytetramethylrhodamine (TAMRA).

\(^{b}\) Probe 5′ end labeled with 4,7,2′-trichloro-7′-phenyl-6-carboxyfluorescein (VIC) and 3′ end labeled TAMRA.

**Figure 1.** Temporal distribution of confirmed, probable, and suspected cases of pertussis-like illness in Franklin County, Ohio, by case classification. Data were obtained from the Ohio Disease Reporting System. White, light gray, and dark gray bars depict weekly counts of confirmed, probable, and suspected cases, respectively, with onset during 9 May 2010–7 May 2011. Weekly means of confirmed, probable, and suspected cases with onset during May 2005–April 2010 are depicted by a black line; error bars depict 1 standard deviation above and below weekly means.
a singleplex assay targeting the ptxA-Pr sequence (detected in B. pertussis and at high bacterial concentrations in B. parapertussis), and another singleplex assay targeting BhollIS1001 (specific for B. holmesii) (Table 1). Additionally, a convenience sample of 298 IS481-positive/BparaIS1001-negative NP swab specimens collected and archived (−70°C) during the outbreak interval were tested by NCH in their ptxA-Pr and BhollIS1001 PCR assays.

Statistical Analyses
We analyzed data by using SAS, version 9.2 (SAS Institute, Inc, Cary, North Carolina) and Microsoft Excel 2010 (Microsoft Corp, Redmond, Washington). Equality of age distributions was determined by using the Kolmogorov-Smirnov 2-sample test. We used 2-proportion z tests to compare proportions. Fisher exact tests were used to analyze clinical contingency tables because of frequent occurrence of cells with <5 expected values. Analysis of time from antibiotic administration to cough resolution was conducted using the Kaplan-Meier method with Wilcoxon tests to account for censoring. Cox proportional hazard regression was used to analyze potential relationships between patient age and time from antibiotic administration to cough cessation. We calculated vaccine effectiveness (VE) as follows:

\[ VE = 1 - \frac{PCV}{1 - PCV} \times \frac{1 - PPV}{PPV} \]

where PCV = proportion of cases vaccinated and PPV = proportion of population vaccinated [30], with Wald 95% confidence limits calculated by using logistic regression with only a constant (intercept) and the logit of PPV as the offset. We set PPV at 70% for Tdap VE calculations; although only a constant (intercept) and the logit of PPV as the offset.

Institutional Review Board Approval
Components of this study performed by the CDC were determined to be public health practice by the CDC and were exempted from institutional review board (IRB) review. Archival and testing of NP specimens was approved by NCH’s IRB (IRB11-00096).

RESULTS

Outbreak Description
Among residents of Franklin County, 645 confirmed, 29 probable, and 244 suspected cases of pertussis were reported with onset 9 May 2010–7 May 2011 (Figure 1); illness occurrence was highest during 24 September–12 November 2010. Overall incidence was 80 cases per 100 000 persons; highest incidences were reported among infants aged <1 year (619 cases per 100 000 persons) and among persons of Hispanic ethnicity (151 cases per 100 000 persons) (Table 2). No pertussis-related deaths were reported.

Paroxysmal cough was the most commonly reported clinical sign (82% of patients), followed by posttussive vomiting (42%) and whoop (20%); 81% had cough of ≥14 days; 18 (2%) patients were hospitalized (Table 2). Among 645 confirmed cases, 62% were classified on the basis of a positive PCR result and lacked reported contact with a confirmed case; 20% had a positive PCR result and reported close contact with a confirmed case; and 18% lacked PCR confirmation and were classified on the basis of an epidemiologic link to a confirmed case. No positive cultures were reported.

Serologic Investigation
Among 14 (5 suspected and 9 confirmed) serologically tested patients (response rate 14%, Table 3), IS481 PCR results were available for 10; PCR data were obtained from NP specimens
Table 3. Tests for Antibodies to Pertussis Toxin and Polymerase Chain Reaction Testing Using Multiple *Bordetella*-Related Targets Among Patients with Onset of Pertussis-Like Illnesses, Franklin County, Ohio (25 October–27 November 2010)\(^a\)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Case Classification</th>
<th>Age (y)</th>
<th>Anti-PT IgG ELISA (IU/mL)(^b)</th>
<th>IS481 RT-PCR (C(_T))(^b)</th>
<th>IS481 RT-PCR (C(_T))(^c)</th>
<th>ptxS1 RT-PCR (C(_T))(^b)</th>
<th>ptxA-Pr RT-PCR (C(_T))(^c)</th>
<th>hIS1001 RT-PCR (C(_T))(^b)</th>
<th>Bhol IS1001 RT-PCR (C(_T))(^c)</th>
<th>pIS1001 RT-PCR (C(_T))(^b)</th>
<th>Species Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Confirmed</td>
<td>16 (&lt;15)</td>
<td>20.3</td>
<td>20.3</td>
<td>(nd)(^a)</td>
<td>19.3</td>
<td>19.1</td>
<td>(nd)(^d)</td>
<td>(nd)(^d)</td>
<td>(nd)(^d)</td>
<td>Bh</td>
</tr>
<tr>
<td>2</td>
<td>Confirmed</td>
<td>17 (&lt;15)</td>
<td>28.5</td>
<td>29.0</td>
<td>(nd)(^d)</td>
<td>26.5</td>
<td>27.6</td>
<td>(nd)(^d)</td>
<td>(nd)(^d)</td>
<td>(nd)(^d)</td>
<td>Bh</td>
</tr>
<tr>
<td>3</td>
<td>Confirmed</td>
<td>11 (&lt;15)</td>
<td>25.2</td>
<td>25.3</td>
<td>(nd)(^d)</td>
<td>23.5</td>
<td>29.5</td>
<td>(nd)(^d)</td>
<td>(nd)(^d)</td>
<td>(nd)(^d)</td>
<td>Bh</td>
</tr>
<tr>
<td>4</td>
<td>Confirmed</td>
<td>10 (&gt;480)</td>
<td>18.7</td>
<td>18.3</td>
<td>27.8</td>
<td>31.1</td>
<td>(nd)(^d)</td>
<td>(nd)(^d)</td>
<td>(nd)(^d)</td>
<td>(nd)(^d)</td>
<td>Bh</td>
</tr>
<tr>
<td>5</td>
<td>Confirmed</td>
<td>14</td>
<td>126</td>
<td>27.0</td>
<td>29.0</td>
<td>34.2</td>
<td>37.3</td>
<td>(nd)(^d)</td>
<td>(nd)(^d)</td>
<td>(nd)(^d)</td>
<td>Bh</td>
</tr>
<tr>
<td>6</td>
<td>Confirmed</td>
<td>17</td>
<td>246</td>
<td>—(^o)</td>
<td>22.5</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Confirmed</td>
<td>57 (&lt;15)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Confirmed</td>
<td>19</td>
<td>450</td>
<td>—</td>
<td>20.4</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Confirmed</td>
<td>14 (&lt;15)</td>
<td>—</td>
<td>36.8</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Suspected</td>
<td>13</td>
<td>195</td>
<td>24.0</td>
<td>23.6</td>
<td>33.6</td>
<td>35.5</td>
<td>23.2</td>
<td>27.3</td>
<td>(nd)(^d)</td>
<td>Bh and Bp</td>
</tr>
<tr>
<td>11</td>
<td>Suspected</td>
<td>12</td>
<td>(22)</td>
<td>—</td>
<td>36.8</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Suspected</td>
<td>17</td>
<td>(16)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Suspected</td>
<td>16 (&lt;15)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Suspected</td>
<td>14 (&lt;15)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Bh, *Bordetella holmesii*; Bp, *Bordetella pertussis*; C\(_T\), cycle threshold; ELISA, enzyme-linked immunosorbent assay; IgG, immunoglobulin G; RT-PCR, real-time polymerase chain reaction.

\(^a\) ELISA values ≥94 IU/mL, IS481 C\(_T\) values ≤37, ptxS1 C\(_T\) values <40, ptxA-Pr C\(_T\) values <40, hIS1001 C\(_T\) values <40, Bhol IS1001 C\(_T\) values <40, and pIS1001 C\(_T\) values <40 were considered to be positive. ELISA values outside the linear range of measurement (15–480 IU/mL) are reported as being beyond either the upper or lower limit. Results indicative of negative findings are reported in parentheses. Nasopharyngeal specimens from patients 1, 2, 3, 4, 5, and 10 were analyzed independently at 2 laboratories to confirm results.

\(^b\) Performed at Centers for Disease Control and Prevention, Atlanta, Georgia.

\(^c\) Performed at Nationwide Children’s Hospital Columbus, Ohio.

\(^d\) (nd): PCR amplification was not detected.

\(^o\) —: not tested.
collected for clinical diagnosis at time of presentation with ill. IS481 PCR was positive for 10 specimens, including 5 seropositive (patients 4, 5, 6, 8, and 10) and 5 seronegative (patients 1, 2, 3, 9, and 11) patients. Among 6 patients with archived NP specimens available for further testing, NCH testing identified 3 seronegative patients who were positive for IS481, negative for ptxA-Pr, and positive for BholIS1001, indicating presence of B. holmesii and not B. pertussis DNA (Table 3, cases 1–3). These assays also identified 2 patients likely to have had B. pertussis without B. holmesii, and 1 patient likely to have had both (Table 3; cases 4, 5, and 10, respectively). Similar results were obtained from aliquots of these NP specimens tested by the CDC in a blinded fashion by using a multiplex and a singleplex PCR able to differentiate among Bordetella species, including B. parapertussis (Table 3). No patients with B. parapertussis were identified.

**Comparison of B. holmesii With B. pertussis**

Among the convenience sample of 298 IS481-positive NP swabs, we identified specific Bordetella species in 164, 48 (29%) were positive for B. holmesii (BholIS1001 positive only), 112 (68%) were positive for B. pertussis (ptxA-Pr positive only), and 4 (2%) were positive for both B. holmesii and B. pertussis (Figure 2). Among 48 patients with B. holmesii infections, 30 (63%) were aged 11–18 years and 13 (27%) were aged 15–18 years, compared with 39 (35%) of 112 patients with B. pertussis who were aged 11–18 years and 3 (3%) aged 15–18 years, excluding patients with evidence of both pathogens (P = .001 for 11–18 years). Among 70 IS481-positive adolescents aged 11–18 years who were identified as having evidence of a specific Bordetella species, 30 (43%) were positive for B. holmesii only, 39 (56%) were positive for B. pertussis only, and 1 (1%) was positive for both. Infants aged <1 year comprised a similar proportion of both illness types (15% of patients with B. holmesii, and 13% of patients with B. pertussis; P = .72) (Figure 3). Overall age distribution of patients tested for species-specific PCR targets differs from those not tested for species-specific PCR targets (P < .0001). However,
when the comparison was restricted to patients aged <24 years (comprising 89% of outbreak patients), the age distributions were similar ($P = .54$).

Among 48 patients with *B. holmesii* (excluding *B. pertussis* or *B. holmesii* coinfections), 42 (88%) had paroxysms, 21 (44%) had posttussive vomiting, 11 (23%) had whoop, and 42 (88%) had a cough duration of $\geq 14$ days. The frequencies of these clinical signs were similar among patients with *B. pertussis* infections, and no statistical differences were detected within the age strata examined (<1 year, 1–10 years, and 11–18 years) (Table 4). All *B. pertussis*– and *B. holmesii*–positive patients received antibiotics. Clarithromycin or azithromycin was administered to 45 (94%) patients with *B. holmesii* and 103 (92%) patients with *B. pertussis*. Following antibiotic administration, coughing persisted longer among patients with *B. pertussis*, compared with *B. holmesii* ($P = .01$) (Figure 4).

**Table 4. Clinical Features of Patients With *Bordetella holmesii* or *Bordetella pertussis* Infections, Excluding Patients Infected by Both Bacteria—Franklin County, Ohio (9 May 2010–7 May 2011)**

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>All Ages</th>
<th>&lt;1 Year</th>
<th>1–10 Years</th>
<th>11–18 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>B. holmesii</em></td>
<td><em>B. pertussis</em></td>
<td><em>B. holmesii</em></td>
<td><em>B. pertussis</em></td>
</tr>
<tr>
<td>Paroxysms</td>
<td>n = 48 (%)</td>
<td>n = 112 (%)</td>
<td>n = 4 (%)</td>
<td>n = 12 (%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>n = 48 (%)</td>
<td>n = 112 (%)</td>
<td>n = 4 (%)</td>
<td>n = 12 (%)</td>
</tr>
<tr>
<td>Whoop</td>
<td>n = 48 (%)</td>
<td>n = 112 (%)</td>
<td>n = 4 (%)</td>
<td>n = 12 (%)</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>n = 48 (%)</td>
<td>n = 112 (%)</td>
<td>n = 4 (%)</td>
<td>n = 12 (%)</td>
</tr>
<tr>
<td>Cough $\geq 14$ d</td>
<td>n = 48 (%)</td>
<td>n = 112 (%)</td>
<td>n = 4 (%)</td>
<td>n = 12 (%)</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

*Clinical data source: Ohio Disease Reporting System.*

*Percentages exclude cases missing all clinical records.*

*P* values were calculated by using 2-sided Fisher exact test.

![Figure 4](https://academic.oup.com/cid/article-abstract/56/3/322/428246/563324248246)
We found no association between patient age and time from antibiotic administration to cough cessation (P = .45).

Tdap receipt was confirmed for 18 (60%) and 17 (44%) patients aged 11–18 years with *B. holmesii* and *B. pertussis* infection, respectively (Table 5). We were unable to obtain immunization records for 1 *B. holmesii* patient and 4 *B. pertussis* patients. Although Tdap coverage was higher among patients with *B. holmesii*, compared with *B. pertussis*, this difference was not significant (P = .18). Estimated effectiveness against *B. holmesii* was 36% (95% CI, 33% to 69%) and 67% (38% to 82%) for IS.

**Table 5.** Effectiveness of Pertussis-Containing Vaccines Against *Bordetella holmesii* or *Bordetella pertussis*, Among Patients Aged 11–18 Years, Excluding Persons Infected by Both Pathogens—Franklin County, Ohio (9 May 2010–7 May 2011)

<table>
<thead>
<tr>
<th>Received Tdap, No. (%)</th>
<th>B. holmesii (n = 30)</th>
<th>B. pertussis (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine effectiveness (95% CI), including persons missing vaccination records</td>
<td>18 (60%)</td>
<td>17 (44%)</td>
</tr>
<tr>
<td>Vaccine effectiveness (95% CI), excluding persons missing vaccination records</td>
<td>17 (57%)</td>
<td>17 (44%)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; Tdap, tetanus-diphtheria-acellular pertussis.

a Effectiveness is calculated by the screening method, using 70% Tdap coverage among all Franklin County residents aged 11–18 years. Although precise Tdap coverage levels for adolescents aged 11–18 years in Franklin County are unknown, the 2011 National Immunization Survey-Teen reported estimated Tdap coverage among Ohio adolescents aged 13–17 to be 72.7% (95% CI, 67.2% to 78.2%).

b Vaccination data sources: Ohio Disease Reporting System and Impact Statewide Immunization Information System.

We report the first documented mixed outbreak of *B. pertussis* with *B. holmesii*, with nearly two-thirds of *B. holmesii* cases aged 11–18 years. A majority of cases were diagnosed and reported as pertussis on the basis of clinical presentations and IS481 PCR positivity. Although this methodology is widely practiced, these criteria are insufficient for differentiation among *Bordetella* species. Some misclassification of *B. holmesii* as *B. pertussis* as a result of a highly sensitive assay may be clinically acceptable [21, 32]. Until recently, data suggested that *B. holmesii* prevalence was low, even among patients with classic pertussis symptoms. For example, a study of 12,727 NP specimens obtained from persons suspected of having pertussis during 1994–1998 yielded 7% *B. pertussis* isolates and only 0.26% *B. holmesii* isolates [10], implicating *B. holmesii* for a small proportion of pertussis-like illnesses. Moreover, a review of 11,319 NP swabs obtained during 1992–2003 from Finnish and Dutch patients suspected of having pertussis produced no evidence of *B. holmesii* DNA [21], further indicating that prevalence of *B. holmesii* might be low. However, a study of 177 NP specimens obtained during 2009–2010 from French patients suspected of having pertussis revealed *B. holmesii* DNA among 20% [14], a result similar to our finding of *B. holmesii* among 17% of IS481-positive persons suspected of having pertussis (including 4 coinfections of *B. holmesii* with *B. pertussis*).

These results might be limited by sampling methodology, sample size, incomplete immunization reporting, presence of inconclusive samples (45% of 298 samples tested were positive for IS481, and negative for both species-specific PCR targets), and potentially differing sensitivities of ptxA-Pr and BhollIS1001-based assays. Among patients with *B. holmesii* infections, 51% had cough at the final interview, compared with 77% of those with *B. pertussis* infections; thus, cough durations and differences in cough durations between etiologic categories are likely underestimated. Our finding that patients with *B. holmesii* were older than those with *B. pertussis* is consistent with previous reports that described highest *B. holmesii* incidence among adolescents or adults [10, 14]. Factors contributing to the higher proportion of *B. holmesii* among adolescents are unknown and might include age-dependent clinical presentation, transmission-related factors, or other unknown causes. Because our data are limited to the outbreak period in Franklin County, we are unable to describe the larger temporal or geographic features of *B. holmesii* incidence. In the setting of a resurgence of pertussis, with strong evidence of widespread transmission of *B. pertussis*, the relative contribution of *B. holmesii* to the total burden of reported pertussis could be small, but enhanced surveillance is necessary to elucidate the epidemiological characteristics of *B. holmesii*.

In addition to *B. pertussis* and *B. holmesii*, *B. parapertussis* circulated during the outbreak period. Among all nasopharyngeal specimens submitted to NCH for testing for *Bordetella* species during 9 May 2010–8 May 2011, 7.5% were positive for IS481, and 1.4% were positive for *B. parapertussis BparaIS1001*. Specimens were obtained predominantly (but not entirely) from patients located in the outbreak locale. Culture findings were consistent with PCR results, further validating these data (M. Marcon, personal communication, e-mail, July 2012).
Cough illness among persons with *B. holmesii* might be caused by another etiology, with *B. holmesii* acting as a super-infecting agent or a subclinical colonizer. Carriage of *B. holmesii* among asymptomatic persons is unknown, and understanding of prevalence could aid in evaluation of these hypotheses [10]. After azithromycin or clarithromycin administration in this study, cough illness among patients with *B. holmesii* resolved more quickly than cough among persons with *B. pertussis*; PT, which is lacking in *B. holmesii*, might contribute to the relative recalcitrance of cough among patients with *B. pertussis*. Moreover, antimicrobial susceptibility testing of 15 *B. holmesii* isolates obtained from patients in the outbreak locale showed that most isolates were susceptible to azithromycin doses as low as 0.12 µg/mL (M. Marcon, personal communication); *B. pertussis* isolates were susceptible to lower doses of azithromycin. The apparent effectiveness of these antibiotics supports the probable bacterial etiology of cough among these patients, and these findings suggest that it would be reasonable for healthcare providers to apply standard pertussis care for either etiology.

Although differentiation might be unnecessary for treatment decisions, epidemiologic value is relevant in distinguishing among *Bordetella* species. Improved specificity would advance our understanding of burdens from *B. pertussis* and *B. holmesii*, reduce concerns arising from apparent vaccine failures after misdiagnosis, and might provide information on which vaccine-based outbreak response strategies can be based. Vaccinations remain important for prevention and control of pertussis, and vaccination campaigns should continue despite pertussis-like illness among certain vaccinated persons. Although a majority of pertussis cases in the United States are diagnosed at clinical laboratories where multistate PCR might not be feasible, limited multitarget PCR capacity, especially among public health laboratories, is important for pertussis outbreak investigations and surveillance.

**Notes**

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