Effectiveness of Adolescent and Adult Tetanus, Reduced-Dose Diphtheria, and Acellular Pertussis Vaccine against Pertussis

Stanley C. Wei,1 Kathleen Tatti,1 Kimberly Cushing,1 Jennifer Rosen,1 Kristin Brown,1 Pamela Cassiday,1 Thomas Clark,1 Richard Olans,2 Lucia Pawloski,1 Monte Martin,1 Maria Lucia Tondella,1 and Stacey W. Martin

1National Center for Immunization and Respiratory Diseases, Division of Bacterial Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, and 2US Virgin Islands Department of Health, Christiansted, Virgin Islands

Background. Pertussis is among the most poorly controlled bacterial vaccine-preventable diseases in the United States. In 2006, a tetanus, reduced-dose diphtheria, and acellular pertussis (Tdap) booster was recommended for adolescents and adults. Tdap vaccines were licensed on the basis of antibody response without vaccine effectiveness data.

Methods. From 30 September 2007 through 19 December 2007, a pertussis outbreak occurred at a nursery through twelfth grade school on St. Croix, US Virgin Islands. We screened all students for cough and collected clinical history, including Tdap receipt. Coughing students were offered diagnostic testing. We defined clinical case patients as students with cough ≥14 days in duration plus either whoop, paroxysms, or post-tussive vomiting, and we defined confirmed case patients as students with any cough with isolation of *Bordetella pertussis* or those with clinical cases and polymerase chain reaction or serological evidence of pertussis; other clinical cases were classified as probable.

Results. There were 51 confirmed or probable cases among 499 students (attack rate, 10%). Disease clustered in grades 6–12, with a peak attack rate of 38% among 10th graders. Of 266 students aged ≥11 years with complete data, 31 (12%) had received Tdap. Forty-one unvaccinated students (18%) had confirmed or probable pertussis, compared with 2 (6%) of the vaccinated students (relative risk, 2.9); vaccine effectiveness was 65.6% (95% confidence interval, −35.8% to 91.3%; *P* = .092).

Conclusions. This first evaluation of Tdap vaccine effectiveness in the outbreak setting suggests that Tdap provides protection against pertussis. Increased coverage is needed to realize the full benefit of the vaccine program. Serological testing was an important tool for case identification and should be considered for inclusion in the Council of State and Territorial Epidemiologists case definition.

Following the introduction of combined diphtheria, tetanus, and pertussis vaccine in the late 1940s, the incidence of pertussis in the United States dramatically decreased. Cases that once numbered in the hundreds of thousands reached a nadir of 1010 cases in 1976 [1]. In the past 2 decades, reported rates have increased, and the age distribution of reported pertussis cases has shifted. Although pertussis was once thought of as predominately a childhood disease, 53% of cases reported to the National Notifiable Diseases Surveillance System in 2006 were in persons ≥15 years of age [2].

Increasing burden of disease in adolescents and adults and the potential role of adolescents and adults in the continued transmission of pertussis led the Advisory Committee on Immunization Practices (ACIP) in 2006 to recommend a single dose pertussis booster for all adolescents and adults <65 years of age given as a combined tetanus, reduced-dose diphtheria, and acellular pertussis vaccine (Tdap) [3, 4]. The infant and child combined diphtheria, tetanus, and acellular pertussis vaccine (DTaP) was licensed and recommended for the primary series and childhood boosters on the basis of efficacy, immunogenicity, and safety data from multiple studies, including randomized, controlled trials [5–7]. In contrast, US Food and Drug Administration approval of Tdap was based on serological bridging stud-
ies that compared the adolescent and adult immune responses to Tdap with the infant immune response to DTaP [8]. More recently, a post-licensure study has estimated the vaccine efficacy (VE) of an adolescent pertussis booster (Boostrix; GlaxoSmithKline) at 78% (95% confidence interval [CI], 60.7%–87.6%) [9] with use of the screening approach. No field evaluations of Tdap in the outbreak setting have, to our knowledge, been reported.

We investigated an outbreak of pertussis in a single-campus 499-student, nursery through twelfth-grade private school on the island of St. Croix, US Virgin Islands. The objectives of the investigation were to confirm pertussis as the etiologic agent, to implement prevention and control measures, to evaluate VE of routinely administered Tdap on prevention of pertussis, and to assess the performance of a combined diagnostic testing algorithm.

MATERIALS AND METHODS

Population and human subjects determination. We collected descriptive epidemiology and laboratory data from nursery through twelfth-grade students who attended School A during the outbreak period from 30 September 2007 through 19 December 2007. VE analyses for Tdap were limited to students ≥11 years, consistent with ACIP recommendations for Tdap vaccination [4]. Survey and laboratory data were collected as part of a public health response and were not considered to be research; thus, institutional review for protection of human subjects was not required. Written informed consent for all laboratory tests was obtained from a parent or guardian of all students aged <18 years and from students and teachers aged ≥18 years.

Pertussis outbreak case determination. We collected pertussis symptom and other epidemiological data through a combination of written, telephone, and in-person surveys. For students in grade 7 or above, we accepted history reported from either the student or the parent. For students below grade 7, parental report of histories was used.

We used a modified Council of State and Territorial Epidemiologists (CSTE) reporting case definition [10]. Outbreak cases were defined as illnesses with onset occurring during the outbreak period in students or staff members of School A. A clinical case was defined as a cough for ≥14 days and at least 1 of the following signs: whoop, post-tussive vomiting, and paroxysmal cough. A confirmed case was defined as cough illness plus isolation of B. pertussis in culture or a clinical case of pertussis with either a positive polymerase chain reaction (PCR) or serological test result. Clinical cases that were not laboratory-confirmed were classified as probable cases. This definition differs from the CSTE definition in 2 ways: serological testing was considered to be confirmatory for pertussis to allow for late diagnosis, and epidemiological linkage was not considered for case confirmation, given the large number of cases within the school.

Specimen collection and laboratory testing. Specimen collection was conducted during 2 time periods, from 18 December 2007 through 19 December 2007 and from 17 January 2008 through 21 February 2008. During the first period, students who reported cough beginning ≤14 days earlier at the time of specimen collection were offered a nasopharyngeal (NP) aspirate or swab sample for pertussis PCR and culture testing, as well as venipuncture for serological testing. Students with a >14-day history of cough at the time of specimen collection were offered serological testing only. Students without cough were not offered either form of testing. During the second period, NP specimen collection criteria remained the same. However, to assess asymptomatic seropositivity, serological testing was offered to all students aged ≥11 years regardless of cough history.

All confirmatory laboratory testing was conducted at the Centers for Disease Control and Prevention (CDC). NP aspirates were collected using N-Pak kits (M-Pro) and aliquoted into sterile screw-cap tubes. Sterile rayon-tipped NP swabs (Copan) were dipped into each aspirate and inserted into Regan-Lowe (RL) transport agar tubes (Remel). Blood specimens were drawn using serum separator tubes (Becton Dickinson), separated by centrifugation, and aliquoted into sterile screw-cap tubes. Reagan-Lowe transports, aspirates, and serum samples were stored at 4°C and shipped with cold packs to the CDC within 48 h after collection.

NP specimens were plated directly onto RL agar plates with and without cephalexin. Plates were incubated for up to 10 days at 37°C. PCR assays were performed according to published methods [11]. A specimen was considered to be PCR positive if it showed amplification of both insertion sequence 481 (IS481) and pertussis toxin subunit 1 (ptxS1) nucleic acid sequences [11]. Serum samples were tested in a 1:100 dilution by an indirect enzyme-linked immunosorbent assay (ELISA) for detection of immunoglobulin (Ig) G antibodies against pertussis toxin (PT) [12]. Optical density was read at 450 nanometers with a BioTek ELx800 microplate reader, and concentrations were interpolated from a 4-parameter logistic regression curve created by Gen5 software, version 1.01 (BioTek). Specimens were considered to have positive serological test results if they showed concentrations of IgG antibody against PT of ≥94 ELISA units (EU)/mL [13]. Antibody concentrations ≥49 but <94 EU/mL were considered to be indeterminate for recent infection. Although the assay is being developed as a single-point test performed on specimens obtained ≥2 weeks from cough onset, paired specimens were collected when possible. Acute-phase serum samples were defined as serum samples collected ≤14 days from cough onset and convalescent.
Effectiveness of Pertussis Booster

CID 2010:51 (1 August)

317

Figure 1. Number of confirmed and probable cases of pertussis, by week, among all students at School A.

phase serum samples were those collected >14 days from cough onset.

*B. pertussis* isolates were tested by pulsed-field gel electrophoresis (PFGE) using a method described elsewhere [14]. PFGE profiles were analyzed and compared with a database of other *B. pertussis* isolates using BioNumerics software (Applied Maths).

**Vaccination history.** We solicited physician documentation of student vaccination status for all students from parents, the school nurse, and physicians. Students were considered to be fully vaccinated with DTaP if they had documented receipt of 5 doses of DTaP or 4 doses with the fourth dose given after 4 years of age and if appropriate timing and intervals had been followed [7]. Students were considered to be vaccinated with Tdap if they had documented receipt of Tdap prior to 30 September 2007. Students with documented vaccine histories during the current school year that did not show Tdap vaccination or showed vaccination on or after 5 December 2007 (14 days from the end of the outbreak) were considered to be unvaccinated. No students received Tdap between 30 September 2007 and 5 December 2007. Students who had no vaccine documentation were excluded from the vaccine effectiveness evaluation.

**Statistical analysis.** We performed data entry using Microsoft Access 2003 and data analysis using SAS, version 9.2 for Windows (SAS). VE was defined as

\[
(1 - [\frac{\text{AR}_{\text{vaccinated}}}{\text{AR}_{\text{unvaccinated}}}] \times 100\%
\]

where AR was the attack rate. Statistical comparisons were performed using Pearson’s χ² tests or Fisher’s exact test as appropriate. Analysis of the relationship between pertussis signs and symptoms, vaccination history, and serum anti-PT antibody concentrations was performed with general linear modeling, with the log of the antibody concentration as the dependent variable. Comparisons of study-enrolled and nonenrolled students were performed using a log binomial model.

**RESULTS**

**Outbreak description.** A total of 51 cases of pertussis, including 27 confirmed and 24 probable cases, occurred from 30 September 2007 through 17 December 2007 (Figure 1). In the 2 months after the outbreak, 2 additional probable cases were identified. Paroxysmal cough was the most common pertussis symptom (in 77% of cases), followed by whoop (46%) and then by post-tussive vomiting (35%). The median reported cough duration was 38 days (range, 14–127 days); however, 26 (51%) of the clinical case patients reported continued cough at the time of the last survey. Forty-eight percent of the case patients were seen in outpatient clinics, 3 went to emergency departments (7%), and none were hospitalized. Thirty-nine (84.8%) of the case patients received antibiotics. However, of 28 students for whom the date of antibiotic administration was known, 13 (46.4%) received antibiotics within 21 days of cough onset. The proportion of students with pertussis symptoms and measures of clinical severity did not differ significantly between those with confirmed and those with probable cases (data not shown).

The overall AR of clinical pertussis in the school during the
outbreak was 10% (Table 1). Although there was 1 probable case each in the second, third, and fourth grades, the AR was significantly higher among students grade six and higher, compared with younger students (relative risk [RR], 12.4; 95% CI, 3.9–39.3; P < .001). All laboratory-confirmed cases occurred in the older age group, and the AR of confirmed or probable pertussis in this group was 17%. Pertussis incidence was highest among tenth graders who had an AR of 38%. There were no statistically significant differences in pertussis incidence by sex, race, or ethnicity. Of the first 11 case patients, 5 participated in athletic team A, yielding a RR among all students of participation versus nonparticipation in team A during the first 5 weeks of the outbreak of 23.8 (95% CI, 8.5–66.2).

Laboratory results. Clinical specimens were obtained from 194 students (39%) and 10 staff members. Among students aged ≥11 years, 162 (56%) provided clinical specimens. Culture, PCR, and serological test results were concordant. There were 6 culture-confirmed cases, and these were the only PCR-confirmed cases. All 6 patients had positive convalescent serum samples. Of these patients, 4 had acute serum samples available, 2 of which had indeterminate results and 2 of which had negative results (Figure 2). Three additional clinical case patients had available NP specimens, and these had negative results by all 3 testing modalities. An additional 29 students with cough not fitting the clinical case definition had NP specimens collected and tested by PCR and culture. All of those test results were negative. All 6 isolates of B. pertussis from the culture-confirmed cases had a matching PFGE profile (46) that has been detected in US isolates of B. pertussis since the 1990s [14].

Convalescent serum sample test results were generally consistent with clinical history. There were 157 convalescent-phase serum samples obtained from students for whom complete clinical data were available. Forty of the samples were obtained from patients with clinical or culture-confirmed cases, 45 were from students with a history of cough who did not meet the case definition, and 72 were from students without a history of cough. The geometric mean concentration (GMC) of anti-PT IgG in convalescent-phase serum samples among clinical or culture-confirmed cases was 107.2 EU/mL (95% CI, 68.0–170.2), compared with 20.2 EU/mL among students with a history of cough who did not meet the case definition (95%
CI, 13.6–30.1) and 29.4 EU/mL among students without a history of cough (95% CI, 22.5–38.6). Both of these comparisons were statistically significant (P < .001). Anti-PT GMCs did not differ significantly between those students who were not case patients with a history of cough and those without cough (P = .124).

Not all clinical case patients had positive serological test results. Of the 40 students with clinical or culture-confirmed cases and convalescent-phase serum samples, 26 had positive serological test results, 1 had indeterminate results; and 13 had negative results. Acute-phase serum samples were available for 7 students with clinical cases, 1 of whom had positive serological test results. The single positive acute-phase serum specimen was obtained 13 days after cough onset.

Tdap vaccination history was available for donors of 151 convalescent serum samples, 9 of whom had been vaccinated. The GMC among vaccinated students was 33.4 EU/mL, compared with 36.9 EU/mL among unvaccinated students. This difference was not statistically significant when controlling for cough history (P = .883).

**Tdap effectiveness.** A total of 287 students were ≥11 years of age, complete clinical histories were obtained for 282 (98%), and documented vaccination histories were obtained for 266 (93%). Students enrolled and students not enrolled in the study did not differ significantly by sex, age, or race and ethnicity (data not shown).

Among students aged ≥11 years, overall Tdap coverage was 12%. Coverage was highest among students 12–14 years of age, ranging from 15% through 21%. Tdap had a VE of 65.6% (95% CI, −35.8 to 91.3; P = .092) against confirmed or probable pertussis and 70.6% (95% CI, −110.3% through 95.9%; P = .180) against laboratory-confirmed pertussis (Table 2). When the analysis was limited to the students who were fully vaccinated against DTaP, the VE against confirmed or probable pertussis (61.3%; 95% CI, −52.5% to 90.2%) and laboratory-confirmed pertussis (68.3%; 95% CI, −126.4 to 95.6%) were similar.

**DISCUSSION**

Post-licensure VE studies are a critical component of vaccine program evaluation and are even more critical for new vaccines and vaccines for which licensure is based on serological surrogate end points, rather than direct VE data [8]. Although we did not show statistically significant benefit in the setting of limited sample size, we estimated Tdap effectiveness to be 65.6%, which is comparable to the findings from a recent Australian school-based VE study (78.0%; 95% CI, 60.7–87.6%) [9]. Working with passively reported notifiable diseases data, this previous study relied upon the diagnostic strategies of individual clinicians to define cases and used the screening method to indirectly estimate VE. The standard calculation of VE uses individual disease and vaccination status, whereas the screening method uses population-level data and estimates VE on the basis of the expectation that an effective vaccine will result in a lower proportion of vaccination among cases than among the general population. If vaccination coverage is not assessed by a uniform method, as it was not in this case, the VE estimate may be biased. The screening method is best viewed as a useful but preliminary assessment to more methodologically rigorous studies [15]. A strength of the current investigation is the confirmation of vaccination and disease status for both individuals with cases and those without cases. In addition, all specimens were collected and processed using a standardized algorithm and tested at a single laboratory.

Estimates of VE of the childhood acellular pertussis vaccine range from 59% through 89% [7]. Nationally, 96% of kindergarteners have met school entry requirements for DTaP [16], which optimizes the protection afforded by imperfect childhood pertussis vaccines. This outbreak occurred in a population with high DTaP vaccination coverage. Among students aged

<table>
<thead>
<tr>
<th>Case definition</th>
<th>No. (%) of students with cases</th>
<th>Total students</th>
<th>Vaccine effectiveness, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmed or probable</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tdap</td>
<td>2 (6.1)</td>
<td>33</td>
<td>65.6 (−35.8 to 91.3)</td>
</tr>
<tr>
<td>No Tdap</td>
<td>41 (17.6)</td>
<td>233</td>
<td>Reference</td>
</tr>
<tr>
<td><strong>Laboratory confirmed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tdap</td>
<td>1 (3.0)</td>
<td>33</td>
<td>70.6 (−110.3 to 95.9)</td>
</tr>
<tr>
<td>No Tdap</td>
<td>24 (10.3)</td>
<td>233</td>
<td>Reference</td>
</tr>
</tbody>
</table>

**NOTE.** The case percentages given in parentheses are the percentage of persons with a given vaccine status who had confirmed or probable cases. Vaccine effectiveness was calculated as 1 minus the relative risk. Confidence intervals (CIs) were calculated by χ² test.

### Table 2. Tetanus, Reduced-Dose Diphtheria, and Acellular Pertussis Vaccine (Tdap) Effectiveness Estimates by Confirmed or Probable and Laboratory-Confirmed Case Definitions among Students Aged ≥11 Years
which occurred in individuals who initially presented for testing. In contrast to the high DTaP coverage rates, the Tdap age-appropriate coverage rate in School A was only 12%, which is much too low to realize the greatest impact of herd immunity or the indirect benefits of vaccination in preventing transmission to susceptible individuals. Tdap coverage in the United States among adolescents 13–17 years of age has increased from 11% in 2006 to 41% in 2008, but the majority of adolescents have not received Tdap. Pertussis has secondary ARs as high as 80% in susceptible individuals [17, 18]. To prevent future school-based outbreaks among adolescents, higher Tdap coverage rates are needed to minimize the negative impacts of waning immunity, imperfect VE, and high secondary transmission rates.

During this investigation, we were able to demonstrate how targeted use of well-characterized assays improves case confirmation. Previous studies have shown that pertussis culture and PCR are most sensitive when performed on NP specimens collected <2 weeks and <3 weeks, respectively, after cough onset [16, 19, 20], whereas serological test results were uniformly negative among specimens obtained from coughing persons <13 days after cough onset. Conversely, convalescent-phase serological testing allowed for confirmation of 26 clinical cases, 20 of which occurred in individuals who initially presented for testing >2 weeks after cough onset. Although NP specimens were not obtained from these individuals, most cases would not likely have been confirmed by culture or PCR because of the timing of specimen collection. These observations support the testing algorithm employed during this outbreak. The positive PCR and convalescent-phase serological test results for the 6 individuals with culture-positive cases also provide strong evidence of the clinical usefulness of these assays. On the basis of experience from this outbreak, the CDC has adopted this testing algorithm as a standard for outbreak investigations. Modification of the CSTE case definition to include acceptance of a well-validated serologic assay would facilitate identification of cases, particularly among adolescents and adults who present late in the disease course.

Although serological testing is very useful, it does have some limitations. Although the GMC for students without a history of cough in this study was solidly in the negative range, 12 of the 72 noncoughing students who were tested had positive serological test results, ranging in concentration from 118 through 418 EU/mL (data not shown). None of these students had received Tdap. Positive serological test results in asymptomatic persons have been noted in other serologic studies [21–23], and our results provide additional evidence of asymptomatic infection and the potential for unrecognized transmission. For example, in a 2-year prospective study involving 2781 persons in which both clinical and serological data were obtained, Ward et al [23] found that, for every symptomatic case, there were an additional 5 asymptomatic infections. For serological testing to be most useful for the diagnosis of acute pertussis disease, the spectrum of illness, including asymptomatic seropositivity, must be more clearly understood.

In this investigation, we evaluated the effectiveness of routinely administered Tdap for prevention of pertussis in the outbreak setting. We also provided a clear, simple algorithm for optimal use of pertussis diagnostic tests, including serological testing, based on cough duration. As Tdap coverage levels increase, additional assessments of vaccine effectiveness are warranted, as are evaluation of the potential indirect effects of vaccination in preventing transmission to unvaccinated persons, including those at high risk for infection, such as infants.

Acknowledgments

We thank Tina Tobias, Bill Sinfield, and the Virgin Islands Department of Health, for their invaluable assistance, and Tiffany Jackson, for laboratory technical support.

Potential conflicts of interest. All authors: no conflicts.

References

5. Stehr K, Cherry JD, Heininger U, et al. A comparative efficacy trial in Germany in infants who received either the Lederle/Takeda acellular pertussis component DTP (DTaP) vaccine, the Lederle whole-cell component DTP vaccine, or DT vaccine. Pediatrics 1998; 101(1 Pt 1):1–11.
10. Case definitions for infectious conditions under public health sur-


