Pertussis is a highly contagious, vaccine-preventable respiratory infection caused by the bacterium *Bordetella pertussis*. Infections typically result in prolonged morbidity characterized by paroxysmal cough, posttussive vomiting, and inspiratory whoop. Life-threatening cases can present with acute encephalopathy, seizures, or pneumonia [1]. Children most commonly present with classic “whooping cough”; life-threatening cases generally occur in a small subset of infants. The prolonged illness course causes significant morbidity with its associated social and economic burden [2, 3].

Despite initial successes from immunization, pertussis has been increasing since the 1980s, especially among adolescents, although the most severe disease is still seen among infants [4–6]. In 2000, the Advisory Committee on Immunization Practices (ACIP) recommended immunizations with acellular diphtheria, tetanus, and acellular pertussis (DTaP) vaccine at ages 2, 4, 6, and 15 months and 4 years [7]. In 2005, amidst concerns about waning immunity, ACIP recommended an additional booster (Tdap) for adolescents and adults [8].
2010 and 2012, the United States experienced its highest rates of pertussis in 5 decades [9]. During these years, studies found conflicting results about the effectiveness, durability, and protection provided by the current vaccines [10–14]. In Oregon during 2012, the state recorded its highest case counts since the 1950s, with >60% of patients aged <20 years up to date on their pertussis immunizations. Although vaccine breakthrough infections accounted for a high proportion of disease burden, unvaccinated persons were up to 50 times more likely to acquire pertussis [15].

Although international studies have reported decreased illness severity among patients with vaccine breakthrough [16, 17], we identified no US studies examining illness outcomes among such patients in the years since acellular DTaP and Tdap vaccines were introduced and routine polymerase chain reaction (PCR) testing was implemented. The latter is important, as the national Council of State and Territorial Epidemiologists (CSTE) case definition was updated to include this test [18]. Given the significant morbidity and societal costs associated with pertussis infections, reductions in the duration and magnitude of illness can have an important public health impact [2]. Utilizing data from the Portland metropolitan area’s enhanced pertussis surveillance program from 1 August 2010 to 31 July 2012, we tested the hypothesis that patients with vaccine breakthrough have decreased illness duration and severity.

METHODS

Study Population and Oregon’s Reportable Infectious Disease Surveillance System

In collaboration with the Centers for Disease Control and Prevention’s National Center for Immunization and Respiratory Diseases Meningitis and Vaccine Preventable Diseases Branch and Oregon’s Acute and Communicable Disease Program, the Multnomah County Health Department conducts enhanced pertussis surveillance for the Portland metropolitan area. The 1.7 million people in this area account for 43% of Oregon’s population, with >25% of the population aged <19 years [19, 20]. Pertussis vaccination is compulsory for Oregon children in school or licensed childcare facilities. Although Oregon’s nonmedical vaccine exemptions are higher than the national median, DTaP and DTP (whole cell) coverage reflects national levels (ie, 94% vs 95%, respectively, for kindergarten-aged children in 2012) [21].

Physicians and laboratories are legally required to report laboratory-confirmed and clinically suspected cases of pertussis to local health departments, along with patient demographic and clinical data. Within 24 hours of notification, community health nurses interview patients about symptoms, hospitalization status, clinical outcomes, and exposures. For enhanced surveillance, data monitoring for consistency and completeness is performed on a monthly basis; detailed immunization data are collected; and patients are contacted every 2–3 weeks until cessation of cough, cough duration exceeds 100 days, or inability to contact (3 phone calls and a mailed letter).

Pertussis Case Definition

We used the 1997 CSTE criteria [17]: Confirmed cases involved cough of any duration with a positive culture; or a cough of ≥14 days’ duration with paroxysms of cough, inspiratory whoop, or posttussive vomiting accompanied by (1) a positive PCR result or (2) epidemiological linkage to a confirmed case. We included CSTE-confirmed cases of B. pertussis from the Portland metropolitan area with onset between 1 August 2010 and 31 July 2012. Given limited availability of vaccination information for adults, we included only patients <19 years of age. Cases with nonpertussis Bordetella were excluded.

We considered a patient to have severe pertussis-related illness if the person developed pneumonia, acute encephalopathy, or seizures; or if the person was hospitalized with these or any other pertussis-related condition. We evaluated demographic information and risk factors for hospitalization and pneumonia separately, as well as assessing any indication of severe illness.

Vaccination Status Determination

Only provider-documented doses of vaccine were included in our assessment of vaccination status. Vaccination history was obtained by (1) querying Oregon’s “ALERT” immunizations information system for dates, type, and manufacturer, and (2) faxing providers for vaccination dates and related information. The ALERT system contains immunization data entered by healthcare providers in Oregon.

Vaccination status was determined according to the ACIP recommendations for routine and catch-up vaccination schedules. ACIP-recommended doses include DTaP or DTP administered at 2, 4, 6, and 15 months, and 4 years and a single Tdap booster at age ≥11 years [5, 6]. Patients who had their fourth DTaP dose after the age of 4, or those who had their Tdap after age 7 are considered up to date. A 14-day grace period was allowed for persons to obtain vaccine prior to being considered not up to date. Per the ACIP schedule, shots were considered invalid if they were administered at <6 weeks of age; if spacing was <28 days for DTaP shots 1–3, <121 days between shots 3 and 4, and <182 days between shots 4 and 5; and if any vaccine shot was administered <14 days prior to symptom onset. Previous immunizations with whole-cell vaccine (DTP) were also considered valid if dose timing and spacing were appropriate.

Persons meeting the age-appropriate ACIP criteria for immunization were classified as up to date (UTD). Persons who received prior pertussis immunizations but failed to meet the age-appropriate ACIP criteria were classified as previously vaccinated, not up to date (NUTD). Persons with no documented doses were classified as unvaccinated.
Analysis
We assessed our primary exposure (vaccination status), outcomes (severe illness and cough duration), and potential confounders and effect modifiers using univariate and bivariate statistics. Potential confounders or effect modifiers included demographic variables (age, sex, race, ethnicity) and receipt of antimicrobial therapy. The latter has been shown to reduce cough duration [22]. Based on clinical trial findings, antimicrobial therapy was considered only when initiated within 20 days of illness onset [23].

To assess vaccination status with respect to severe illness, multiple logistic regression models were constructed including variables that were significant at the \( P < .25 \) level in unadjusted analyses. Further consideration was based on clinical importance or relevance for external validity. Predictor variables significant at \( P < .05 \) were retained in the final model, adjusted log odds ratios (aORs) were calculated, and model fit was assessed via the Hosmer-Lemeshow test.

To assess whether vaccination status influenced cough duration, we performed a time-to-event analysis with cessation of cough as the event. The Kaplan-Meier method was utilized for estimation of the cumulative probability of cough cessation. Demographic variables and risk factors were examined individually and log-rank tests were performed. Related linear regression and nonparametric analysis of variance was performed using the Kruskal-Wallis test. Cox proportional hazards models used variables that were significant at the \( P < .25 \) value. Variables significant at \( P < .05 \) were retained in the final model, and adjusted hazard ratios (aHRs) were calculated. Interactions were retained if significant at the \( P < .05 \) level. Model proportionality was confirmed in the final main effects model.

All analyses were performed using SAS version 9.2 software (SAS Institute, Cary, North Carolina). This study was considered public health practice and consisted only of analysis of routinely collected reportable disease data.

RESULTS

Descriptive Epidemiology
From 1 August 2010 to 31 July 2012, we received 753 case reports for pertussis that met the CSTE-confirmed case definition. Among these, 633 were for children aged 6 weeks to 18 years; of these, 624 (98.7%) had vaccination history and illness data including cough duration.

The median age was 9 years (interquartile range [IQR], 3–12 years). Just over half of patients (52.5%) were female (Table 1). Seventy-five percent (n = 457) of patients initiated therapy <20 days following cough onset (98% received azithromycin). Nineteen patients (3%) had positive chest radiography for pneumonia, and 12 (2%) were hospitalized. Two children developed acute encephalopathy, and 3 developed seizures. There were no deaths.

The majority of patients (54%) were either unvaccinated (171 [27%]) or previously vaccinated, NUTD (167 [27%]); 286 (46%) were UTD (Table 1). Of the 453 persons ever vaccinated, 93% (n = 422) received acellular pertussis vaccines only. Among the 31 persons receiving whole-cell vaccines, all were >7 years old (94% also received acellular vaccine). Nine (approximately 1%)
patients >10 years old received only a single Tdap (Supplementary Table 1).

Vaccinated Patients Are Less Likely to Develop Severe Illness

Both UTD and NUTD patients had decreased odds of hospitalization compared with unvaccinated patients (odds ratio [OR], 0.1 [95% confidence interval [CI], .0–.6] and OR, 0.1 [95% CI, .0–.9], respectively). Similarly, UTD and NUTD patients had reduced frequencies of pneumonia compared with unvaccinated patients (OR, 0.5 [95% CI, .2–1.4] and OR, 0.5 [95% CI, .1–.7], respectively). For the combined outcomes reflecting any severe illness, both UTD and NUTD patients were significantly less likely than unvaccinated patients to suffer severe illness (OR, 0.4 [95% CI, .2–.8] and OR, 0.3 [95% CI, .1–.8], respectively).

Given similar point estimates for all illness outcomes, we assessed confounding after collapsing UTD and NUTD groups to improve statistical power (“ever-vaccinated”). Sex, race, and ethnicity did not confound the observed associations. Treatment was not assessed as it was coincident with severe illness and lacked temporality (no patients completed treatment prior to severe illness onset or diagnosis). Age confounded the association between vaccination status and the severe illness.

After adjusting by age, ever-vaccinated patients were 5 times less likely to be hospitalized and 2.5 times less likely to develop severe illness compared with unvaccinated patients (Table 2). Ever-vaccinated patients were less likely to develop pneumonia, although this association was not significant. Stratified analysis of infants aged 6 weeks to <6 months, 6 weeks to <1 year, and patients aged 1–18 years yielded consistently protective point estimates, with the largest magnitude of protection observed among infants (Supplementary Tables 2–4).

Table 2. Associations of Vaccination Status With Clinical Outcomes, Multiple Logistic Regression Analysis—Portland, Oregon, Metropolitan Area, 2010–2012 (n = 624)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>% Ever Vaccinated</th>
<th>OR (95% CI)</th>
<th>Age-Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>612</td>
<td>73.5</td>
<td>Referent</td>
</tr>
<tr>
<td>Yes</td>
<td>12</td>
<td>25.0</td>
<td>0.1 (0.0–4)</td>
</tr>
<tr>
<td>Positive radiograph for pneumonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>605</td>
<td>73.1</td>
<td>Referent</td>
</tr>
<tr>
<td>Yes</td>
<td>19</td>
<td>57.9</td>
<td>0.6 (2–1.3)</td>
</tr>
<tr>
<td>Severe illness*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>593</td>
<td>73.9</td>
<td>Referent</td>
</tr>
<tr>
<td>Yes</td>
<td>31</td>
<td>48.4</td>
<td>0.3 (2–7)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.

* Illness that resulted in hospitalization, pneumonia, acute encephalopathy, or seizures.

Vaccinated Patients Have a Shortened Duration of Illness

Patients were followed for 35,629 person-days (median, 56 [IQR, 33–81]; range, 14–100 person-days). Sixty-seven percent of patients (n = 420) stopped coughing during the study period and 19% (n = 117) were lost to follow-up. Persons lost to follow-up (censored) accounted for 5,219 person-days of follow-up (median, 34 [IQR, 21–70]; range, 14–98 person-days). A higher proportion of unvaccinated patients were lost to follow-up (23%) compared with UTD (17%) and NUTD patients (17%), although this was not significant (P = 0.08 and P = 0.17, respectively). There was no significant difference in the follow-up time among unvaccinated and vaccinated patients who were censored (median, 36 vs 31 person-days, respectively; P = 0.41).

To evaluate whether vaccination status was a proxy for access to healthcare, we examined the interval from illness onset to treatment initiation. Vaccinated patients initiated treatment later than unvaccinated patients (median, 10 vs 8 days, respectively; P = 0.05). The percentage of vaccinated vs unvaccinated patients who received treatment did not significantly differ (76% vs 68%, respectively; P = 0.10). These data suggest that vaccinated and unvaccinated patients did not have healthcare access differences.

Race, ethnicity, sex, and age were not associated with cough duration. However, any vaccination and antimicrobial therapy were associated with cough resolution (Figure 1). To confirm that severe illness outcomes alone did not independently explain these associations, a dichotomous severe illness variable was fixed in all models. No interactions were identified. The final model included vaccination status, antimicrobial therapy (time-dependent), severe illness, and age (Table 3). This model did not depart from proportionality (P = 0.16).

To assess whether including treatment in a time-dependent manner was influencing our results, a treatment interval-stratified model was constructed with the following strata:
<8 days, 8 to <14 days, 14 to <21 days, and ≥ 21 days or no treatment following cough onset. Upon stratification, we found no significant changes (>10%) for any of our point estimates (Supplementary Table 5). Therefore, we chose to retain antimicrobial therapy in the model as a time-dependent covariate.

Subanalysis including only patients who were retained throughout the study period produced the same overall model, and no point estimate was changed by >10% (Supplementary Table 6). Stratified analysis of DTaP-eligible (6 weeks to 10 years) and Tdap-eligible (10–18 years) patients yielded similar models (Supplementary Tables 7 and 8). Exclusion of patients who received any whole-cell pertussis vaccines yielded the same model (Supplementary Table 9).

In all models, ever-vaccinated patients (UTD and NUTD) were significantly more likely than unvaccinated patients to have stopped coughing within 100 days compared with unvaccinated patients (Table 3). Patients who initiated treatment within 20 days of illness onset were 30% more likely than untreated persons to have stopped coughing, whereas patients with severe illness were more likely to have had a persistent cough, although this was not significant. Finally, patients between 11 and 18 years of age were more likely to have a persistent cough compared with patients 6 weeks to 15 months of age.

We also modeled 20-day cough duration separately, as this is the period when patients are most infectious [21]. During this study period, UTD patients were significantly more likely than unvaccinated patients to have stopped coughing (aHR, 3.7 [95% CI, 1.1–13.2]; Supplementary Table 10). This association was preserved after adjusting for antimicrobial therapy, and age and did not violate the proportionality assumption (P = .58).

**DISCUSSION**

In our cohort of Oregon children and adolescents with pertussis, we found that previously vaccinated patients, especially infants, are less likely than unvaccinated peers to develop severe illness. Likewise, regardless of age, vaccinated patients exhibited a significantly reduced duration of cough, the primary cause of morbidity in uncomplicated pertussis. Vaccinated patients were also more likely to stop coughing within 20 days of illness onset, potentially representing a reduction in case infectivity. Our findings obtained in a US cohort covered by predominantly acellular pertussis vaccine, utilizing PCR-inclusive case definitions, build upon international studies performed during the pre–acellular vaccine era that suggested that pertussis vaccination reduces illness severity, duration, and disease transmission [15, 16].

We found that even incomplete vaccination conferred protection against serious disease. This finding has implications for future studies, as collapsing undervaccinated patients with

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. Events/Total No.</th>
<th>% With Event</th>
<th>HR (95% CI)</th>
<th>Parameter Estimate</th>
<th>Adjusted HR (95% CI)a</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccination status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>97/171</td>
<td>56.7</td>
<td>Referent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previously vaccinated, not up to date</td>
<td>118/167</td>
<td>70.7</td>
<td>1.4 (1.1–1.9)</td>
<td>0.38</td>
<td>1.5 (1.1–1.9)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Up to date</td>
<td>205/286</td>
<td>71.7</td>
<td>1.6 (1.3–2.1)</td>
<td>0.52</td>
<td>1.7 (1.3–2.2)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Antimicrobial therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>104/167</td>
<td>62.3</td>
<td>Referent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>316/457</td>
<td>69.2</td>
<td>1.3 (1.1–1.6)</td>
<td>0.25</td>
<td>1.3 (1.0–1.6)</td>
<td>.03</td>
</tr>
<tr>
<td>Severe illnessb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>403/593</td>
<td>62.3</td>
<td>Referent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17/31</td>
<td>54.8</td>
<td>0.6 (.4–1.0)</td>
<td>−0.46</td>
<td>0.6 (.4–1.0)</td>
<td>.07</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 wk to &lt;15 mo</td>
<td>54/87</td>
<td>62.1</td>
<td>Referent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 mo to &lt;4 y</td>
<td>54/85</td>
<td>63.5</td>
<td>0.8 (0.6–1.2)</td>
<td>−0.19</td>
<td>0.8 (0.6–1.2)</td>
<td>.33</td>
</tr>
<tr>
<td>4 to &lt;7 y</td>
<td>58/84</td>
<td>69.1</td>
<td>1.0 (0.7–1.5)</td>
<td>−0.07</td>
<td>0.9 (0.6–1.4)</td>
<td>.72</td>
</tr>
<tr>
<td>7 to &lt;11 y</td>
<td>104/148</td>
<td>70.3</td>
<td>0.9 (0.7–1.3)</td>
<td>−0.29</td>
<td>0.7 (0.5–1.1)</td>
<td>.09</td>
</tr>
<tr>
<td>11 to &lt;19 y</td>
<td>150/220</td>
<td>68.2</td>
<td>0.9 (0.7–1.2)</td>
<td>−0.35</td>
<td>0.7 (0.5–1.0)</td>
<td>.04</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

a Adjusted by age, vaccination status, antimicrobial therapy, and/or severe illness.

b Illness that resulted in hospitalization, pneumonia, acute encephalopathy, or seizures.
unvaccinated patients in assessments of vaccine efficacy could obscure important benefits of vaccination [10, 11, 24]. Furthermore, vaccination before and treatment after illness onset may be important for limiting pertussis transmission. In our cohort, we found reduced cough duration following receipt of antimicrobial therapy. The dual effects of vaccination before illness and treatment after onset could decrease disease transmission as well as severity. This point has programmatic implications for encouraging parents and providers to pursue a pertussis control strategy that includes vaccination, early diagnosis, and treatment, and may prove useful for future pertussis transmission modeling.

A strength of our approach was access to data from a large metropolitan enhanced surveillance system where 99.5% of reported patients had complete vaccination histories, >98% of patients completed disease interviews, and cough duration was assessed prospectively. Data was collected on a number of known and potential confounding factors before vaccination status was ascertained. Because defining vaccination status by calculating the interval from vaccination to illness onset or counting the number of immunizations can introduce biases due to the cyclical nature of pertussis disease and the age dependency of these classifications (Supplementary Tables 1 and 11), using the ACIP vaccination recommendations provided an appropriately conservative measure of vaccination status. These classifications, combined with CSTE case definitions, provided high specificity, improved generalizability, and minimized biases [5, 6, 18]. Significant findings from our distinct analyses suggest that these associations were unlikely to occur by chance. The pooled analysis of patients who received acellular and whole-cell pertussis vaccines was found to be appropriate based on results from acellular-only subanalyses (Supplementary Table 9).

The observational nature of this study has limitations. All surveillance data carry a risk of biased case ascertainment, which could have influenced our analyses if unvaccinated patients with severe illness were more likely to seek healthcare or be reported. However, analysis of treatment patterns suggested that access to healthcare did not differ by vaccination status. The use of provider-documented vaccinations and clear vaccine status definitions reduced the possibility that misclassification of vaccination status influenced our results. Missing immunization data for persons ever vaccinated would only have served to make our groups more alike, resulting in an underestimate of the true effect. Although differential loss to follow-up for cough duration could have influenced our results, we found no significant differences in loss to follow-up or duration of time followed with respect to vaccination status, suggesting that this potential bias was nondifferential. Reduced cough duration among vaccinated patients was not explained by a lower proportion of severe illness in this group, as this factor was controlled for in our analysis.

There are multiple plausible explanations for our findings. The acellular pertussis vaccines are formulated with 3–5 specific bacterial antigens and have been shown to induce both humoral and prolonged cellular immunity [25–27]. However, differentially waning immunity to some antigens could enable susceptibility to infection, whereas the residual immunity could explain the reduced illness severity. Alternatively, bacterial evasion of the humoral immune response could allow for establishment infection, whereas residual cellular immunity may limit severity and duration [28–30]. Research into the nature of the protective immune response may aid future vaccine development.

Pertussis has reemerged to epidemic levels in the United States despite high rates of vaccination [4, 10–14, 31, 32]. Although pertussis vaccination alone may not completely prevent illness, even incomplete vaccination decreases cough duration and protects against severe disease manifestations. Our results suggest that the current ACIP immunization guidelines are effective at limiting individual-level pertussis severity and morbidity. However, reducing the high proportion of breakthrough infections at the population level may necessitate improved vaccine formulations and wider coverage. Also, as the protective effect of vaccination was found to be independent of antimicrobial therapy, both vaccination and early treatment strategies are likely important for improving outcomes. We recommend adherence to the ACIP vaccination guidelines and early treatment initiation, and welcome future research into the relationship between pertussis vaccination and disease burden.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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