Association Between Undervaccination With Diphtheria, Tetanus Toxoids, and Acellular Pertussis (DTaP) Vaccine and Risk of Pertussis Infection in Children 3 to 36 Months of Age

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IMPORTANT Implications of reduced vaccine uptake on the risk of pertussis in children 3 to 36 months of age.

OBJECTIVE To examine the association between undervaccination and pertussis in children 3 to 36 months of age.

DESIGN Matched case-control study with conditional logistic regression analysis.


PARTICIPANTS Each laboratory-confirmed case of pertussis (72 patients) was matched to 4 randomly selected controls (for a total of 288 controls). The case patients were matched to controls by managed care organization site, sex, and age at the index date. The index date was defined as the date of pertussis diagnosis for the case patients.

EXPOSURE Undervaccination for the diphtheria, tetanus toxoids, and acellular pertussis (DTaP) vaccine. Undervaccination was defined as the number of doses of DTaP vaccine that was either missing or delayed by the index date. Case patients and controls could be undervaccinated by 0, 1, 2, 3, or 4 doses of DTaP vaccine. Children undervaccinated by 0 doses were considered age-appropriately vaccinated by the index date.

MAIN OUTCOME AND MEASURE Pertussis.

RESULTS Of the 72 case patients with pertussis, 12 (16.67%) were hospitalized, and 34 (47.22%) were undervaccinated for DTaP vaccine by the date of pertussis diagnosis. Of the 288 matched controls, 64 (22.22%) were undervaccinated for DTaP vaccine. Undervaccination was strongly associated with pertussis. Children undervaccinated for 3 or 4 doses of DTaP vaccine were 18.56 (95% CI, 4.92-69.95) and 28.38 (95% CI, 3.19-252.63) times more likely, respectively, to have received a diagnosis of pertussis than children who were age-appropriately vaccinated.

CONCLUSIONS AND RELEVANCE Undervaccination with DTaP vaccine increases the risk of pertussis among children 3 to 36 months of age.

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Children who are not age-appropriately vaccinated according to the recommendations of the Advisory Committee on Immunization Practices are considered undervaccinated.1 A recent longitudinal study showed that the rate of undervaccination increased significantly among a cohort of insured children born between 2004 and 2008 in the United States.2 There are numerous potential reasons for undervaccination, including parental choice, missed opportunities, barriers to health care, and medical contraindication to vaccination.3 6 Amid the recent pertussis epidemics across the United States, undervaccination is a concerning trend that potentially places children at increased risk for serious infection. For the present study, we examined the association between undervaccination and the risk of pertussis in children 3 to 36 months of age.

Methods

Setting and Study Population

We conducted a matched case-control study that was nested within a large cohort of children born between 2004 and 2008 (n = 323,247). These children were members of 8 managed care organizations (MCOs) that comprise the Vaccine Safety Datalink, a project funded by the Centers for Disease Control and Prevention that links electronic administrative databases in order to conduct epidemiological studies of vaccine safety.7 These databases contain information on demographics; vaccination history; and pharmacy, laboratory, and medical encounters in the outpatient, emergency department, and inpatient settings. Each MCO site’s institutional review board approved the study.

Children in the study cohort had to be continuously enrolled in the MCO from 2 to 12 months of age and were then followed up until 36 months of age unless they disenrolled from their MCO. For each child, person-time follow-up accrued during periods of active membership enrollment.

Cases of Pertussis

In this large cohort, we identified potential cases of Bordetella pertussis infection using automated laboratory databases at each participating MCO. The automated pertussis laboratory results were primarily recorded as text and were not stored in a standardized data format across all sites. For this reason, a trained medical records abstractor—blinded to the child’s vaccination status—manually reviewed all of the laboratory results to confirm positive laboratory diagnoses of pertussis by a polymerase chain reaction test or by B pertussis culture. The date of a positive laboratory result for B pertussis represented the index date for the case-control analysis. All cases were diagnosed between 3 and 36 months of age.

Controls

Each case patient with pertussis was matched to 4 disease-free controls by MCO site, sex, and age at the index date (±7 days). The controls were selected from the cohort of children enrolled in the MCO health plans between 2004 and 2010. Eligible controls did not have a record of pertussis prior to the index date.

Vaccination Status

For case patients and their matched controls, vaccination status for diphtheria, tetanus toxoids, and acellular pertussis (DTaP) vaccine was ascertained retrospectively from the index date. The DTaP vaccine is recommended at 2, 4, 6, 15-18, and 48-83 months of age.8 Because the children in the present study were followed up through 36 months of age, we analyzed the first 4 doses of DTaP vaccine. Children were either age-appropriately vaccinated or undervaccinated at the index date. Undervaccination was defined as the number of doses of DTaP vaccine that was either missing or delayed by the index date (Table 1). The calculation for determining undervaccination was based on a published algorithm that measures the difference between when a vaccine dose was actually administered and when the dose should have been administered according to the Advisory Committee on Immunization Practices schedule. The algorithm accounts for age, grace periods, catch-up schedules, vaccine shortages, combination vaccines, and changes in vaccination policy.2 For our study, if a child received a diagnosis of pertussis at 5 months of age on January 15, 2008, he or she would be matched to 4 disease-free controls of the same sex at the same MCO who were also 5 months of age between January 7 and 22, 2008. For this matched stratum, age-appropriately vaccinated children are those who received 2 doses on time (with 0 doses missing or delayed), and undervaccinated children are those who received either 1 dose on time (with 1 dose missing or delayed) or 0 doses on time (with 2 doses missing or delayed). In the analysis, these 3 groups of children would be classified as being undervaccinated by 0, 1, and 2 doses of DTaP vaccine, respectively.

Analysis

The final case-control population was analyzed with conditional logistic regression to estimate odds ratios and 95% CIs. In the regression models, the outcome variable was pertussis.
case status, and the predictor variable was undervaccination status. Case patients and controls were undervaccinated by 0, 1, 2, 3, or 4 doses of DTaP vaccine at the index date. Children undervaccinated by 0 doses (age-appropriately vaccinated) represented the referent group. To examine a dose-response relationship, we compared the risk of pertussis for children undervaccinated by 1, 2, 3, or 4 doses of DTaP vaccine with the risk of pertussis for the referent group. The matched odd ratios from the conditional logistic regression models were used to calculate the attributable risk percent of pertussis in the total population.9

**Results**

**Cases and Controls**

In the automated laboratory databases, there were 1522 children between 3 and 36 months of age with a laboratory test result (positive or negative) for pertussis between 2004 and 2010. A manual review of the laboratory results revealed that 72 of these 1522 children (4.73%) received a laboratory-confirmed diagnosis of pertussis. The mean age of the case patients was 14.27 months (median age, 11.06 months), and 50% were male patients. Sixty-four (22.22%) of the controls were undervaccinated, and 4 of these 6 controls (6.25%) had an ICD-9-CM code for vaccine refusal.

**Risk of Pertussis**

Undervaccination was strongly associated with laboratory-confirmed pertussis in children 3 to 36 months of age (Table 3). There was an apparent dose-response relationship in which the risk of pertussis increased as the magnitude of undervaccination with DTaP vaccine increased. Although not statistically significant, children undervaccinated by 1 or 2 doses of DTaP vaccine were 2.25 (95% CI, 0.97-5.24) and 3.41 (95% CI, 0.89-13.05) times more likely, respectively, to have received a diagnosis of pertussis than children who were age-appropriately vaccinated. Children undervaccinated by 3 or 4 doses were 18.56 (95% CI, 4.92-69.95) and 28.38 (95% CI, 3.19-252.63) times more likely, respectively, to have received a diagnosis of pertussis than children who were age-appropriately vaccinated. The attributable risk percent in the entire population was 36.39% (95% CI, 19.65%-49.66%), suggesting that 36.39% of all cases in the population were attributed to undervaccination.

**Discussion**

In our case-control study of infants and young children from 8 MCOs across the United States, we found a significant increased risk for pertussis in undervaccinated children between 2004 and 2010. We used automated MCO health care databases and medical record reviews to identify laboratory-confirmed cases of pertussis and automated immunization records to ascertain vaccination status. Not surprisingly, we found that the risk of pertussis greatly increased as undervaccination with DTaP vaccine increased. Our data also suggest that approximately 36% of cases of pertussis in children 3 to 36 months of age could have been prevented with on-time vaccination with DTaP vaccine.

Our study has limitations. Most notably, we believe that our analyses may not accurately estimate the true risks among children undervaccinated by either 1 or 2 doses of DTaP vaccine, owing to the heterogeneity of the children defined to be

**Table 2. Demographic Characteristics and DTaP Vaccination Status of the Study Population**

<table>
<thead>
<tr>
<th>Comparison of DTaP Vaccine Doses Undervaccinated by</th>
<th>OR (95% CI)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 vs 0</td>
<td>2.25 (0.97-5.24)</td>
<td>.06</td>
</tr>
<tr>
<td>2 vs 0</td>
<td>3.41 (0.89-13.05)</td>
<td>.07</td>
</tr>
<tr>
<td>3 vs 0</td>
<td>18.56 (4.92-69.95)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>4 vs 0</td>
<td>28.38 (3.19-252.63)</td>
<td>.002</td>
</tr>
<tr>
<td>1, 2, 3, or 4 vs 0</td>
<td>4.36 (2.23-8.55)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: DTaP, diphtheria, tetanus toxoids, and acellular pertussis; OR, odds ratio.

*To examine a dose-response relationship, we compared the risk of pertussis for children undervaccinated by 1, 2, 3, or 4 doses of DTaP vaccine with the risk of pertussis for the referent group (0 doses missed).
in these strata. For example, the stratum of children undervaccinated by 1 dose of DTaP vaccine included children 21 months of age who received 3 doses of DTaP vaccine on time and children 3 months of age who received 0 doses of DTaP vaccine on time. Similarly, the stratum of children undervaccinated by 2 doses of DTaP vaccine included children 24 months of age who received 2 doses on time, as well as children 5 months of age who received 0 doses on time. In these scenarios, it is reasonable to assume that the younger children who never received any doses on time would be at greater risk than the older children who received some doses on time. Although it is biologically plausible that there is an interaction between age and dose, there were too few cases in the first 2 strata of undervaccination to adequately examine the interaction in the analysis.

There are several potential confounding factors that may be associated with both vaccination status and exposure to pertussis, including geography, household size, presence of adolescents in the household, day-care attendance, and Hispanic ethnicity. Our analyses may have been limited because the Vaccine Safety Datalink databases do not routinely capture most of these variables. However, in our analysis, we were able to match case patients to controls on MCO site, which helped to control for geographic variation in vaccination status and pertussis.

Lastly, our results may have also been influenced by a diagnostic bias. It is possible that physicians are more likely to conduct pertussis tests on undervaccinated children than age-appropriately vaccinated children when they present to the clinic for acute infections. This, in turn, would lead to an overestimate of the association between undervaccination and pertussis. However, it has also been shown that undervaccinated children have lower outpatient visit rates than age-appropriately vaccinated children. Therefore, although more pertussis cases would be identified in the undervaccinated group because of increased testing, some cases in the undervaccinated group may have been missed because the children in this group use the medical system less frequently than age-appropriately vaccinated children. These potential biases would distort the odds ratio estimates in the opposite direction, and it is unlikely that they explain the large association between undervaccination and pertussis that we found in the present study.

The United States is currently experiencing the largest outbreak of pertussis in 50 years. There are numerous possible reasons for this outbreak, including an increased awareness of the disease and increased testing, more widespread use of polymerase chain reaction testing, and the fact that DTaP vaccines may be less potent and provide protection for less time than the old DTP vaccines. Our data suggest that undervaccination, whether due to parental refusal of vaccines or other barriers to health care, is an important contributing factor, especially given the documented increasing rates of undervaccination in 2 recently published studies.

Undervaccination with DTaP vaccine places infants and young children at increased risk for pertussis. Although not supported by our data, it is also possible that undervaccination indirectly threatens the health of surrounding populations that are at high risk for serious complications from pertussis, such as infants who are too young to be vaccinated. We believe that our study supports on-time vaccination with DTaP vaccine, as recommended by the Advisory Committee on Immunization Practices.

### References