Evidence of Efficacy of the Lederle/Takeda Acellular Pertussis Component Diphtheria and Tetanus Toxoids and Pertussis Vaccine but Not the Lederle Whole-Cell Component Diphtheria and Tetanus Toxoids and Pertussis Vaccine Against Bordetella parapertussis Infection

Ulrich Heininger, Klemens Stehr, Peter Christenson, and James D. Cherry

A subanalysis of a recent cohort efficacy trial of a pertussis vaccine was performed to determine its efficacy against cough illnesses due to Bordetella parapertussis infections. Infants received four doses of either the Lederle/Takeda acellular pertussis component diphtheria and tetanus toxoids and pertussis (DTaP) vaccine or the Lederle whole-cell component diphtheria and tetanus toxoids and pertussis (DTP) vaccine at 3, 4.5, 6, and 15–18 months of age; controls received three doses of diphtheria and tetanus toxoids (DT) vaccine only. All subjects were prospectively followed for cough illnesses of ≥7 days’ duration; cases of B. parapertussis infection were confirmed by positive culture, household contact, or serology. Seventy-six cough illnesses due to B. parapertussis were identified; 24 occurred in 929 DTaP recipients, 37 in 937 DTP recipients, and 15 in 321 DT recipients, resulting in an efficacy of 50% for DTaP vaccine (95% CI [confidence interval], 5% to 74%) and 21% for DTP vaccine (95% CI, −45% to 56%). The data in the present analysis suggest that the Lederle/Takeda DTaP vaccine but not the Lederle whole-cell component DTP vaccine has efficacy against B. parapertussis infection.

Pertussis is caused by Bordetella pertussis and, less frequently, by Bordetella parapertussis [1]. Although B. pertussis and B. parapertussis have a number of similar antigens, it is generally believed that diphtheria and tetanus toxoids and pertussis (DTP) vaccines do not prevent illness due to B. parapertussis infection [2].

However, in our primary analysis of data from our recent cohort efficacy trial, in which the Lederle/Takeda acellular pertussis component DTP (DTaP) vaccine and the Lederle whole-cell component DTP vaccine were compared, we found suggestive evidence that the DTaP vaccine but not the DTP vaccine had efficacy against B. parapertussis cough illnesses [3]. Specifically, the point estimate of efficacy of DTaP against laboratory-confirmed B. parapertussis cough illnesses of ≥7 days’ duration was 31%, but the lower bound of the 95% confidence interval was <0%.

In a recent substudy of our cohort efficacy trial, we found that efficacy of the DTaP vaccine against B. pertussis cough illnesses correlated inversely with study physician compliance with the study protocol regarding the monitoring of cough illnesses [4]. In the group of highly compliant study physicians, we noted that the efficacy of the DTaP vaccine against B. parapertussis was more clearly identified; these data are the subject of this report.

Methods

The methods relating to several analyses of our vaccine efficacy trial have been previously presented in detail [3–5] and will therefore only be summarized herein. The study was performed at 227 sites, which were mainly private pediatric office practices. This present analysis includes the findings at 59 of the most compliant practices, based on a reporting rate of cough illnesses of >20% per year or a referral rate of >10% per year (see below).

Healthy 2- to 4-month-old infants received three doses of DTaP or DTP at 6- to 8-week intervals and a fourth dose at 15–18 months of age. Controls (diphtheria and tetanus toxoids [DT] recipients) received three doses of vaccine at 2–4 months, 4–6 months, and 15–18 months of age.

All cough illnesses of ≥7 days’ duration in study subjects were to be reported by the parents to study physicians. In addition, the study physicians or their office personnel were to call all study families every 2 weeks. All cough illnesses in study patients were to be evaluated by the physicians, and nasopharyngeal specimens for culture and acute blood samples for serological study were to be obtained. When cough illnesses...
Table 1. Method of diagnosis of Bordetella parapertussis cough illnesses according to vaccine category.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>No. of cases</th>
<th>Culture</th>
<th>Household contact</th>
<th>Serologically*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTaP</td>
<td>24</td>
<td>3 (13)</td>
<td>0</td>
<td>24 (100)</td>
</tr>
<tr>
<td>DTP</td>
<td>37</td>
<td>9 (24)</td>
<td>2 (5)</td>
<td>34 (92)</td>
</tr>
<tr>
<td>DT</td>
<td>15</td>
<td>2 (13)</td>
<td>2 (13)</td>
<td>13 (87)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. positive (%). DTaP = diphtheria and tetanus toxoids and pertussis, acellular pertussis component; DTP = diphtheria and tetanus toxoids and pertussis, whole-cell pertussis component; DT = diphtheria and tetanus toxoids (control).

*Significant rise in IgA or IgG titer to filamentous hemagglutinin and/or pertactin without evidence of Bordetella pertussis infection (i.e., culture-negative for B. pertussis and no rise in IgA or IgG titer to pertussis toxin).

Discussion

For many decades, conventional whole-cell pertussis vaccines have been effective in preventing cough illnesses caused by B. pertussis [2]. Although efficacy of these vaccines against cough due to B. parapertussis has not previously been prospectively studied, the past literature suggests that they had no efficacy. Eldering and Kendrick [7] evaluated 55 children with B. parapertussis infection, of whom 32 (58%) had a history of pertussis immunization; Borska and Simkovicova [8] diagnosed 173 children with B. parapertussis infection, and 95% of them had previously been vaccinated against pertussis; finally, our group observed 82 children with B. parapertussis infection with known immunization histories, and 25% had had three or more doses of pertussis whole-cell vaccine compared with only 4% of 165 age-matched children with B. pertussis infection [9]. Moreover, there are numerous observations in humans in which B. pertussis infection was followed by B. parapertussis infection or vice versa, which served as arguments for a lack of cross-protection between the two organisms [10–13]. Finally, in a murine respiratory model, neither filamentous hemagglutinin nor pertactin from B. pertussis, antigens that are very similar to B. parapertussis antigens, provided cross-protection against infection with B. parapertussis, whereas protection against B. pertussis occurred [14].

Since our present results are different from past clinical observations and laboratory studies, our findings need to be carefully scrutinized. Since most of our cases were established serologically without culture confirmation, it might be argued that these cases are in fact B. pertussis—induced illnesses and not B. parapertussis illnesses. In our cohort analysis, we found that 10 (16%) of 64 subjects whose B. pertussis infections were documented by culture or by household contact did not have...
an antibody response to pertussis toxin. By our serological
definition, these cases would have been counted as *B. parapert-
tussis* illnesses when they of course were not. Therefore, in
our present analysis, at least 16% and perhaps more of our
serologically diagnosed cases may have been due to *B. pertussis*
rather than *B. parapertussis*.

However, if the above were the case, according to the results
of our cohort analysis [3], one would expect greater efficacy in
DTP rather than in DTaP vaccinees. Furthermore, if in the
present analysis, only the culture-positive and household con-
tact cases of *B. parapertussis* infection are counted, the attack
rate in DTaP recipients is 0.16 per 100 person-years and in
DT recipients is 0.35 per 100 person-years; the point estimate
of efficacy is 54%, which is similar to that noted in table 2. A
similar analysis in DTP recipients results in an attack rate (0.50
per 100 person-years) higher than that in DT vaccinees and
therefore no evidence of efficacy.

The question to be raised is why the DTaP vaccine but not
the DTP vaccine is efficacious against *B. parapertussis* illness.
The answer is not known, but the differential efficacy is Perhaps
due to good filamentous hemagglutinin antibody response follow-
ing DTaP vaccine but not DTP vaccine [15]. If this hypothe-
sis is correct, it is possible that other DTaP vaccines with
significant filamentous hemagglutinin content may also have
some efficacy against *B. parapertussis* illnesses as well as
against those due to *B. pertussis*.

Acknowledgments

The authors are grateful to Sabina Schmitt-Grohé and Michael
A. Überall (central investigators), the investigators in 59 study
sites, the staff of Wyeth-Lederle Praxis Vaccines and Pediatrics
and Quintiles Ltd., and the Study Advisory Board for their con-
tributions to this trial. The laboratory assistance by Carmen Lorenz
and Regina Rost is highly appreciated.

References

1. Cherry JD, Heininger U. Pertussis. In: Feigin RD, Cherry JD, eds. Text-
book of pediatric infectious diseases. 4th ed. Philadelphia: WB Saun-

2. Cherry JD, Brunell PA, Golden GS, Karzon DT. Report of the task force
81(suppl):93–84.

Germany in infants who received either the Lederle/Takeda acellular
pertussis component DTP (DTaP) vaccine, the Lederle whole-cell com-

4. Cherry JD, Heininger U, Stehr K, Christenson P. The effect of investigator
compliance on calculated efficacy in a pertussis vaccine trial. Pediatrics

5. Heininger U, Cherry JD, Stehr K, et al. Comparative efficacy of the Lede-
rlle/Takeda acellular pertussis component DTP (DTaP) vaccine and
Lederle whole-cell component DTP vaccine in German infants follow-

6. Kälbleisch JD, Pren KL. The statistical analysis of failure time data. New

7. Eldering G, Kendrick P. Incidence of parapertussis in the Grand Rapids
area as indicated by 16 years’ experience with diagnostic cultures. Am

8. Borska K, Simkovicova M. Studies on the circulation of *Bordetella pertus-
sis* and *Bordetella parapertussis* in populations of children. J Hyg Epide-

9. Heininger U. Gemeinsamkeiten und Differenzen von Pertussis und Para-


11. Vysoka B. The epidemiology of pertussis and parapertussis. J Hyg Epide-


14. Khleef N, Danve B, Quentin-Millet MJ, Guiso N. *Bordetella pertussis* and
*Bordetella parapertussis*: two immunologically distinct species. Infect

15. Heininger U, Cherry JD, Christenson P, et al. Comparative study of Led-
erle/Takeda acellular and whole-cell pertussis component diphtheria-
tetanus-pertussis vaccines in infants in Germany. Vaccine 1994; 12:
81–6.

Table 2. Attack rates of *Bordetella parapertussis* cough illnesses according to vaccine category and DTaP and DTP vaccine efficacy.

<table>
<thead>
<tr>
<th>Clinical category</th>
<th>Vaccine efficacy,* % (95% CI)</th>
<th>No. cases/person-years (attack rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTaP</td>
<td>DTP</td>
</tr>
<tr>
<td>Cough ≥7 days’ duration</td>
<td>50 (5 to 74)</td>
<td>21 (45 to 56)</td>
</tr>
<tr>
<td></td>
<td>Cough ≥21 days’ duration with paroxysms, whoop, or posttussive vomiting</td>
<td>58 (14 to 80)</td>
</tr>
</tbody>
</table>

NOTE. DTaP = diphtheria and tetanus toxoids and pertussis, acellular pertussis component; DTP = diphtheria and tetanus toxoids and pertussis, whole-cell pertussis component; DT = diphtheria and tetanus toxoids (control).

* Vaccine efficacy was calculated by use of Cox proportional-hazards regression with SAS software (SAS Institute, Cary, NC) for personal computers.

† Cases per 100 person-years.