Effectiveness of Acellular Pertussis Vaccine Assessed by Hospital-Based Active Surveillance in Germany


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We assessed the effectiveness of complete and partial pertussis vaccination in Germany—a country where acellular vaccine is predominantly used—for the prevention of cases of pertussis requiring hospitalization. Vaccine effectiveness was estimated by means of a screening method. Vaccine coverage of children born during the period of June 1996 through December 1998 was assessed by a telephone survey. Data from hospitalized children with pertussis in 1997–1998 and from patients with pertussis complications in 1997–2000 were acquired by a nationwide, hospital-based, active surveillance system. Age-adjusted vaccine effectiveness of completed primary vaccination was estimated to be 99.8% (95% confidence interval [95% CI], 98.9–100). After receipt of 1 dose of vaccine, vaccine effectiveness was as high as 68.0% (95% CI, 45.6–81.1), increasing to 91.8% (95% CI, 84.7–95.7) after receipt of the second dose. Vaccine effectiveness was even slightly higher for pertussis with complications. Thus, even after partial vaccination, acellular pertussis vaccine is highly effective in preventing hospitalizations for pertussis.

Pertussis is a vaccine-preventable disease in which the majority of severe complications occur in infants, particularly in those aged <6 months [1, 2]. Most national vaccination schedules recommend primary vaccination with 3 doses in the first 6 months of life; thus, vaccination is incomplete during the risk period most associated with severe complications. Moreover, relatively few data are available on the protection provided by partial pertussis vaccination under field conditions [3, 4].

Recently published coverage data showed that late vaccination is a problem in Germany [5]: completion of the primary pertussis vaccination series is delayed in ~80% of children. To a greater or lesser extent, a similar situation is found in other countries as well [6, 7]. Thus, the question of whether partial vaccination offers at least some protection against complications is of particular importance.

To improve coverage against pertussis, in 1995, Germany became the second country (after Japan) to license less-reactogenic acellular diphtheria-tetanus-pertussis (DTaP) vaccines for primary vaccination. This was followed by a sharp increase in vaccine coverage (the proportion of children who received 3 doses of DTaP at 24 months increased from 49% in 1994 to 91% in 1997) [5]. Since 1995, several DTaP vaccines have been licensed for use as primary vaccination. Currently, acellular vaccines are used for 90% of primary vaccinations (unpublished data from Institute of Medical Statistics, Munich, Germany; granted by Glaxo Smith Kline).

The vaccine effectiveness of acellular vaccine has been estimated to be ~70%–90% in several controlled
trials [8–12], depending on the immunization schedule, case definition, and other aspects of study design [13, 14]. Likewise, there are studies that have investigated the effectiveness of pertussis vaccines under field conditions [15–19]. Nevertheless, most of these studies investigated whole-cell vaccine. There are still few data regarding the effectiveness of acellular vaccine in broad conditions. Therefore, this study was conducted to assess the efficacy of pertussis vaccine after partial and completed primary vaccination series for preventing hospitalizations due to pertussis under field conditions in Germany, where an acellular vaccine program was established in 1995.

METHODS

Vaccine effectiveness was estimated by means of a modified screening method [20]. Vaccination status in children who had been hospitalized as a result of pertussis was compared with the vaccination status of a random sample of the German population of the same birth cohort.

Report system. Surveillance of hospitalized patients with pertussis was performed by Erhebungseinheit für seltene pädiatrische Erkrankungen in Deutschland (ESPED) [21], a nationwide, hospital-based surveillance system for rare pediatric diseases in Germany. Monthly report cards soliciting information about hospital admissions for up to 12 diseases are sent to all pediatric departments in Germany. Questions about pertussis in children younger than 16 years of age were included on the card from January 1997 through December 2000; in 1997 and 1998, information about all hospital admissions was solicited; in 1999 and 2000, the case definition was restricted to children with ≥1 of the following complications: pneumonia, apnea, encephalopathy, seizures, and death. Cards have to be returned even if there are no new patients with pertussis.

A questionnaire was sent to the pediatric department for each reported case; the questionnaire requested information on the patient’s demographic, clinical, and laboratory findings, as well as the number of doses of pertussis vaccine received and the type of vaccine used (acellular or whole cell). We used the national recommendations for pertussis vaccination to determine whether children underwent age-appropriate vaccination before the onset of pertussis; in contrast to the United States, where primary vaccination with 3 doses is recommended at 2, 4, and 6 months of age (with a booster during the second year of life), in Germany, primary vaccination with 3 doses is recommended at 2, 3, and 4 months of age, with a booster administered between the 12th and 15th month of life [22, 23]. Questionnaire responses with incomplete information were followed up by a telephone interview.

Case definition. A pertussis case was defined by ≥1 of the following, on the basis of information from the questionnaire: typical clinical symptoms, positive results of serologic tests, and positive results of culture, PCR, or a direct immunofluorescence test. All cases that did not meet this definition were excluded from further analysis. The criteria were applied after we received the questionnaire, and 2 members of our work group decided whether the case definition was met or not.

Typical clinical symptoms were defined as a cough lasting for ≥14 days or a paroxysmal cough with whoops lasting for ≥4 days. When the patient had been exposed to a patient with a confirmed case of pertussis, a cough of ≥7 days’ duration or a paroxysmal cough with whoops of any duration was accepted as typical. In children aged <6 months, apnea was also regarded as a typical clinical symptom. All results of serologic tests (ELISA or indirect immunofluorescence assay) were accepted as reported by the hospitals.

Pertussis vaccination coverage. The most-recent national vaccine coverage data for Germany is for children during the period of June 1996 through December 1998 [5]. The data were obtained by means of an established random-digit dialing method [24] by the Infratest Institute (Munich) from July through September 1999. An initial telephone call was made to screen families willing to participate. Parents were recontacted by a trained interviewer and asked to read the dates of vaccination and the brand names of the vaccines from the relevant pages of their child’s vaccination booklet. If records were unreadable, parents were asked to send a photocopy of the relevant pages, to give contact details of their pediatrician, and to sign a declaration authorizing the pediatrician to release vaccination information. If no vaccination booklet was available, the parents were asked whether the child had been vaccinated. If the child had been vaccinated, parental consent was sought to approach the pediatrician for the vaccination information.

Vaccine effectiveness calculation. Vaccine effectiveness is defined as 1 minus the RR for disease in vaccinated compared with unvaccinated people. This definition is equivalent to the screening method proposed by Orenstein et al. [20], which uses the formula \( \text{VE} = (\text{PPV} - \text{PCV}) / (1 - \text{PCV}) \times \text{PPV} \), where PCV is the proportion of cases vaccinated, PPV is the proportion of the population vaccinated, and VE is vaccine effectiveness.

Because the vaccine effectiveness can also be written as “1 – OR,” with OR being the OR of pertussis vaccination status for hospitalized patients versus that of the entire population, we used logistic regression to calculate age-adjusted interval estimates (95% CIs) of vaccine effectiveness [25]. The application of this method is justified, because, as a result of the low prevalence of hospitalization for pertussis, any statistical dependency between the random sample of the population and hospitalized patients with pertussis would be negligible.

For the estimation of vaccine effectiveness, only children who were eligible for ≥1 vaccination (≥2 months of age) were
RESULTS

Institute). Analyses were performed by use of SAS, version 6.12 (SAS Institute). Hospitalized children with complications in 1997–2000. Statistical analyses were performed by use of SAS, version 6.12 (SAS Institute). Of the 73 children aged ≥6 months who had known vaccination status, 71 (97%) had not received ≥3 doses of pertussis vaccine (table 2).

For 29 patients, the type of vaccine used was unknown. A total of 24 of these children had received 1 dose of vaccine, and 5 children had received 2 doses. Only 3 children had been vaccinated with whole-cell vaccine, all of whom had received a single dose.

 Patients with defined complications. From 1997 through 2000, a total of 462 patients with defined complications that met the case definition were reported to ESPED. There were 202 patients in 1997, 126 patients in 1998, 81 patients in 1999, and 53 patients in 2000. Forty-nine patients had to be excluded for the following reasons: 4 patients were reported to ESPED twice, 44 patients had complications that were not due to *Bordetella pertussis* or did not have defined complications, and 1 patient did not meet the case definition. A total of 209 patients were not born during the relevant time period (June 1996 through December 1998). Thus, 253 children remained for further analysis.

The complications most commonly reported in these children were apnea (in 151 patients) and pneumonia (in 143 patients). In addition, 10 cases of encephalopathy, 16 patients with seizures, and 2 deaths were reported. One hundred fifty-two (60%) of 253 children were old enough (i.e., age ≥2 months) to have received ≥1 dose of vaccine. For 13 of these children, vaccination status was unknown. Only 6 (4.3%) of the remaining 139 children were vaccinated in accordance with the German guidelines, and 114 patients (82%) had not been vaccinated. Eighty-five (55.9%) of 152 patients were reported to ESPED in 1997, 55 (36.2%) were reported in 1998, 10 (6.6%) were reported in 1999, and only 2 (1.3%) were reported in 2000.

Table 1. Population of a study assessing children with complete and partial pertussis vaccination in Germany.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of children aged &lt;16 years with reported cases of pertussis</td>
<td>895</td>
</tr>
<tr>
<td>Reason for exclusion from study, no. of patients</td>
<td></td>
</tr>
<tr>
<td>Infection with another pathogen</td>
<td>59</td>
</tr>
<tr>
<td>No questionnaire data</td>
<td>35</td>
</tr>
<tr>
<td>Did not meet case definition</td>
<td>48</td>
</tr>
<tr>
<td>Not born during relevant time period</td>
<td>224</td>
</tr>
<tr>
<td>Total no. of children considered for further analysis</td>
<td>529</td>
</tr>
</tbody>
</table>

Included. The proportion of the population vaccinated was estimated from the national coverage data. Vaccination status on 1 March 1999 was considered to be relevant for the comparison with hospitalized children with pertussis, because, at this time, all children in the survey were ≥2 months of age, and the age distribution was comparable to that of the hospitalized children with pertussis.

To ensure that subjects from the general population were similar to hospitalized patients with regard to vaccine coverage, only those persons born during the period of June 1996 through December 1998 were included in the calculation of vaccine effectiveness. Vaccine effectiveness was separately estimated for pertussis that required hospitalization by using data from patients hospitalized in 1997 and 1998, and, for pertussis with defined complications, it was estimated using the data for hospitalized children with pertussis.

Hospitalized Patients

From January 1997 through December 1998, a total of 895 hospitalized patients with pertussis aged <16 years were reported to ESPED. A total of 59 patients with a different pathogen (e.g., a pathogen other than *Bordetella parapertussis*) and 35 patients for whom no questionnaire data were available were excluded. Forty-eight (6.0%) of the remaining 801 patients did not meet the case definition. A total of 224 children were not born during the relevant time period. Therefore, the data for 529 patients born during the period of June 1996 through December 1998 remained for further analysis (table 1).

Vaccination Status

Hospitalized children with pertussis. A total of 371 children were eligible for ≥1 dose of vaccine (i.e., age of ≥2 months). Information about vaccination status was available for 349 children. A total of 319 (91.4%) of 349 patients had a condition that met the definition of clinical pertussis, 213 (61.0%) had a condition that met the laboratory case definition, and 183 (52.4%) had a condition that met both definitions. Only 8 (2.3%) of 349 children were vaccinated in accordance with the German guidelines, and 268 children (76.8%) had not been vaccinated. Of the 73 children aged ≥6 months who had known vaccination status, 71 (97%) had not received ≥3 doses of pertussis vaccine (table 2).

For 29 patients, the type of vaccine used was unknown. A total of 24 of these children had received 1 dose of vaccine, and 5 children had received 2 doses. Only 3 children had been vaccinated with whole-cell vaccine, all of whom had received a single dose.

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Table 2. Vaccination status of German hospitalized children with pertussis who were born during the period of June 1996 through December 1998.

<table>
<thead>
<tr>
<th>Age, months</th>
<th>No. of children</th>
<th>Unknown</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>158</td>
<td>3</td>
<td>155</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2–3</td>
<td>185</td>
<td>10</td>
<td>153</td>
<td>21</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4–5</td>
<td>105</td>
<td>4</td>
<td>63</td>
<td>30</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6–11</td>
<td>71</td>
<td>8</td>
<td>43</td>
<td>11</td>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>12–32</td>
<td>10</td>
<td>0</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>529</td>
<td>25</td>
<td>423</td>
<td>62</td>
<td>17</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Vaccine Coverage in Germany and Vaccines Used

Of 24,292 households screened, 1384 (5.7%) included a child born on 1 June 1996 or later, of which 818 (59%) participated in the second interview. A similar reporting rate was observed with the random-digit dialing technique in the United States (66.3%) [26]. There were no selection or rejection biases based on sex, age, socioeconomic or geographic characteristics, or household composition of participants and nonparticipants (data not shown). After completion of the second stage, data were available for 667 children with known vaccination status and who were born during the period of June 1996 through December 1998.

By the age of 6 months, 89.1% of children had received ≥1 dose of pertussis vaccine, but only 34.3% had completed primary vaccination at that time. By the age of 12 months, ∼95% of children had received ≥1 dose of vaccine, and 84.1% had completed primary vaccination.

At 1 March 1999 (the relevant date for calculation of vaccine effectiveness, because all children were ≥2 months of age), the age range of children in the telephone survey was 2–32 months. A total of 611 (91.6%) of 667 children had received ≥1 dose of vaccine, and 511 (81.5%) of 627 children who were old enough to have completed primary vaccination had received 3 or 4 doses of vaccine (table 3). The type of vaccine used was known for 519 patients; 481 (92.7%) of these patients had been vaccinated with acellular vaccine, 22 (4.2%) had been vaccinated with both acellular and whole-cell vaccine, and only 17 (3.3%) had been vaccinated exclusively with whole-cell vaccine. A total of 1559 doses of acellular vaccine were given to 503 children. In 1389 doses (89.1%), the 3-component vaccine (pertussis toxoid, filamentous hemagglutinin, pertactin) Infanrix DTaP (GlaxoSmithKline Biologicals) was used, mostly in a fixed combination with Haemophilus influenzae type b vaccine and/or inactivated poliovirus vaccine. The 2-component vaccine (pertussis toxoid, filamentous hemagglutinin) of Aventis Pasteur MSD (Tetravac or Pentavac; Pac Mérieux) contributed to 7.9% of doses. Other acellular vaccines were used in <2% of doses each.

Table 3. Results of a telephone survey assessing pertussis vaccine coverage in German children, according to age distribution and vaccination status.

<table>
<thead>
<tr>
<th>Age, months</th>
<th>No. of children</th>
<th>No. of doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unknown</td>
<td>0</td>
</tr>
<tr>
<td>2–3</td>
<td>40</td>
<td>26</td>
</tr>
<tr>
<td>4–5</td>
<td>46</td>
<td>3</td>
</tr>
<tr>
<td>6–11</td>
<td>136</td>
<td>0</td>
</tr>
<tr>
<td>12–32</td>
<td>445</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>667</td>
<td>56</td>
</tr>
</tbody>
</table>

Vaccine Effectiveness

Pertussis requiring hospitalization in 1997–1998. Vaccine effectiveness was estimated for all hospitalized children old enough (i.e., ≥2 months of age) to have received the first dose of pertussis vaccine. A total of 137 (70.1%) of 529 hospitalized patients with pertussis met this criterion. The vaccination status was unknown for 22 patients. Thus, 349 patients remained for the analysis of vaccine effectiveness.

The age-adjusted vaccine effectiveness of 3 doses of acellular vaccine was estimated to be 99.8%, and the effectiveness of 4 doses was estimated to be 98.6%. After receipt of 1 dose of vaccine, vaccine effectiveness was 68.0%, and it increased to 91.8% after the second vaccination (table 4). Estimates of vaccine effectiveness after receipt of the third dose of vaccine, which were calculated for the subgroups of persons with conditions that met the clinical case definition, the laboratory case definition, and both definitions, did not differ significantly (99.6%, 99.8%, and 99.6%, respectively).

Hospitalized patients with pertussis with defined complications. A total of 152 (60.1%) of 253 patients with pertussis who had defined complications were ≥2 months old at the time of hospitalization. Vaccination status was unknown for 13 patients. Thus, 139 patients remained for the analysis of vaccine effectiveness.

Age-adjusted vaccine effectiveness for patients hospitalized with pertussis complications was 75.6% after the first dose, 95.9% after the second dose, 100% after the third dose, and 98.6% after the booster dose (table 4). No child with pertussis complications was hospitalized during the study just after finishing primary vaccination and before receiving the booster dose.

Sensitivity Analyses

The vaccination status of 22 hospitalized children with pertussis was unknown. Assuming that all of these children had been vaccinated in accordance with the German vaccination guidelines, age-adjusted vaccine effectiveness after the first dose of vaccine was 68.7% (95% CI, 46.3–81.7); after the second dose, it was estimated to be 98.6%. After receipt of 3 or 4 doses of vaccine, vaccine effectiveness increased to 99.8%, and the effectiveness of 4 doses was estimated to be 100%.

Table 4. Age-adjusted effectiveness of pertussis vaccine in hospitalized German children aged ≥2 months.

<table>
<thead>
<tr>
<th>No. of doses</th>
<th>Patients with and patients without defined complications, 1997–1998</th>
<th>Patients with defined complications, 1997–2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68.0 (45.6–81.1)</td>
<td>75.6 (53.6–87.4)</td>
</tr>
<tr>
<td>2</td>
<td>91.8 (84.7–95.7)</td>
<td>95.9 (89.1–98.8)</td>
</tr>
<tr>
<td>3</td>
<td>99.8 (98.9–100.0)</td>
<td>100 (99.2–100.0)</td>
</tr>
<tr>
<td>4</td>
<td>98.6 (91.5–99.9)</td>
<td>98.6 (91.1–99.9)</td>
</tr>
</tbody>
</table>
it was 88.8% (95% CI, 79.9–93.9); after the third dose, it was 96.7% (95% CI, 93.6–98.4); and after the booster dose, it was 97.3% (95% CI, 83.9–99.9). For the effectiveness of vaccine against pertussis with severe complications, the corresponding estimates were 73.8% (95% CI, 50.7–86.4) after the first dose, 92.8% (95% CI, 83.9–97.2) after the second dose, 98.3% (95% CI, 95.6–99.5) after the third dose, and 92.7% (95% CI, 73.3–98.3) after the booster dose.

**DISCUSSION**

Estimates of acellular pertussis vaccine effectiveness outside controlled trials are still rare. Our data show that the vaccine effectiveness of pertussis vaccine for completed primary vaccination (3 doses) was as high as 99.8% (95% CI, 98.3–100) in children aged 2–32 months who are at risk of hospitalization. The small decrease in the point estimate of vaccine effectiveness observed with an additional booster dose may be a random effect or the result of a dilution with older children.

Even partial pertussis vaccination is effective, with protection against hospitalization of 68% after 1 dose and 91.8% after 2 doses. This is important, because infants are at the highest risk of developing complications at a time when they will be, at best, only partially immunized. We found no postlicensure studies of either whole-cell or acellular vaccines that addressed the issue of partial versus complete vaccination with hospitalization as an end point.

Our estimates of vaccine effectiveness of complete primary vaccination were higher than those in efficacy studies of acellular vaccines [8–12]. This is because we assessed vaccine effectiveness for cases of pertussis that required hospitalization. Previous investigations dealing with hospitalizations found a similar effectiveness for complete primary vaccination with whole-cell vaccine [3, 26–28]. The estimates of vaccine effectiveness were even slightly higher for hospitalized patients with defined complications. Although these differences were not statistically significant, they are in line with previous observations that indicate that pertussis vaccine is shown to have higher effectiveness for complicated disease [12, 29].

The number of unvaccinated children among hospitalized patients with pertussis in our study (80% of the children eligible for ≥1 dose of vaccine) was higher than that in studies from Canada (49.5%) and the United States (25% of all cases) [30, 31]. This may be explained by a delay in vaccination in Germany [5], which accounts for there being a higher number of unvaccinated children exposed. Alternatively, this could be explained by the high effectiveness of partial vaccination with the acellular vaccines used in Germany. However, previous investigations hint at a lower hospitalization rate for children with pertussis in Germany compared with other nations [29, 32]. If only patients with more-severe cases were hospitalized in Germany, a higher percentage of unvaccinated children could be explained by a higher effectiveness of pertussis vaccine against severe disease [12, 29].

Several potential sources of bias were considered. In similar studies, completeness of ascertainment using hospital-based active surveillance, as assessed by capture-recapture analysis, was ~50%–80% [33–36]. Reporting bias by severity of disease—only the most severe cases are reported—cannot be excluded, because pertussis has been described as being milder in vaccinated children than it is in unvaccinated children [37, 38]; this would account for an overestimation of vaccine effectiveness. However, analyses of the reported cases by size of reporting hospitals suggest that, rather, some pediatricians simply do not report cases of pertussis at all (data not shown).

By beginning the observation period in January 1997, we missed a small number of patients hospitalized in 1996. However, age-adjusted estimates of vaccine effectiveness would only be influenced if immunization status of missed cases differed from that of children of the same age group hospitalized later. Because the rates of vaccine coverage in Germany were nearly unchanged from 1996 to 1998, this bias is unlikely. Moreover, only a few children were hospitalized with pertussis in 1996, because 1996 was a low point in the epidemic cycle, as our data and data of another study [39] revealed. This earlier study investigated hospitalizations resulting from pertussis complications in Germany during 1993–1996. In the second half of 1996, only 3 children aged ≤12 months of age were reported to have pertussis complications, all of whom were aged <3 months [39]. Assuming that all of these persons had been exactly 2 months of age and were immunized on schedule with 1 dose, vaccine effectiveness in preventing complications in hospitalized patients with pertussis would still be 72.4% and not 75.6% after the first dose of pertussis vaccine (data not shown). Because no child hospitalized during the end of 1996 was old enough to have received >1 vaccination, the estimates of the effectiveness of 2–4 immunizations are uninfluenced.

The participation rate for the telephone survey was 59%. Participants did not differ significantly from nonparticipants with regard to sociodemographic criteria [5], but participants may be more interested in the health of their own children. Therefore, vaccine coverage may be lower in children of nonparticipants, and overestimation of vaccine coverage would tend to increase vaccine effectiveness. However, the effect of this bias is small: assuming that vaccine coverage in nonparticipants was one-half that in participants, the effectiveness after 3 doses would still be still 99.2% (95% CI, 94.2–99.9; data not shown).

Although the net effect of the different biases is difficult to assess, their influence on the results is likely to be limited. Therefore, pertussis vaccination with acellular vaccines is effective under field conditions as well as in controlled trials. This
is valid not only for completed primary vaccination series, but also, importantly, for partial vaccination.

Because the effectiveness of acellular vaccine is high, many cases of pertussis resulting in hospitalization could be prevented. A high effectiveness was observed after partial pertussis vaccination of patients with pertussis who required hospitalization. The fact that vaccine-induced immunity was found after the first dose of pertussis vaccine was administered and the fact that severe pertussis cases mostly occur in young infants emphasize the importance of timely initiation of primary vaccination.

References