Clinical and epidemiological picture of B pertussis and B parapertussis infections after introduction of acellular pertussis vaccines

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Pertussis is a highly communicable, vaccine preventable disease, which causes significant morbidity in unvaccinated individuals. In Germany, the general recommendation for pertussis vaccination was discontinued in 1975 because of concerns regarding the safety of whole cell pertussis vaccines. Vaccination coverage rates subsequently dropped from 50–60% to approximately 15% and, as a consequence, pertussis has become one of the most frequent endemic infections in German infants and children, with an estimated incidence of 180 cases per 100 000 per year.

Aims: To investigate the clinical picture and frequency of Bordetella pertussis and B parapertussis infections after introduction of acellular pertussis (acP) vaccines in Germany.

Methods: Prospective surveillance for B pertussis and B parapertussis in 14 144 toddlers. Pertussis vaccination coverage was 86%, either with acP (75%) or whole cell pertussis (wcP) vaccine (11%). All children presenting with cough for more than seven days were examined for B pertussis and B parapertussis by culture, PCR, and serology (for cough duration ≥ 21 days).

Results: There were 180 Bordetella infections; 116 (64%) were caused by B pertussis and 64 (36%) by B parapertussis. Incidence rates were 4.8 and 2.8 per 1000 person-years, respectively. Paroxysmal cough, posttussive whooping, and vomiting ≥ 21 days was found in 53%, 22%, and 8% of all B pertussis cases and in 22%, 5%, and 0% of all B parapertussis cases, respectively. A total of 81/116 (70%) B pertussis cases and 56/64 (87.5%) B parapertussis cases had received at least one dose of pertussis vaccine. Typical pertussis with paroxysmal cough ≥ 21 days was present in 29/35 (83%) unvaccinated B pertussis cases, in contrast to 33/81 (41%) vaccinated B pertussis cases.

Conclusion: Following the increase of pertussis vaccination coverage, we observed a relative increase of B parapertussis cases in comparison to B pertussis cases. In vaccinated children B pertussis disease frequently presented as a mild disease, clinically difficult to distinguish from diseases associated with coughing caused by B parapertussis and other viral or bacterial infections.

METHODS

Study population

A population based case-control study was carried out in Germany from February 1993 to May 1995 to determine the efficacy of Biken DTaP vaccine. The study population consisted of 16 780 children born between December 1992 and June 1994, recruited in 63 paediatric practices. The children were vaccinated at the age of 3, 5, 7, and 15–24 months, either with Biken acP vaccine (received by 75%) or with a whole cell pertussis vaccine (received by 11% of the study population), or were not vaccinated against pertussis (14%) by decision of their parents or guardian. Pertussis vaccine catch up vaccinations were offered to study participants after licensure of acP vaccines for general infant vaccination in 1995. The data presented here refer to the period 1997 to 1999, when pertussis surveillance was reestablished in 45 of the initial 63 paediatric practices to determine the long term efficacy of the pertussis vaccines in the study population. The 45 practices had initially recruited 14 144 children into the study population, of which 11 087 (78%) were still regularly seen in the practice in 1997. In addition to the children of the original study population the surveillance for Bordetella spp. was extended to all other children of the same age group presenting in the participating paediatric practices.

The vaccination status of the study population was determined in a random sample of 479 children; 88 (18.4%) were vaccinated with wcP vaccine, 263 (59.9%) with acP vaccine, 13.4% with both wcP and acP vaccine (usually three wcP doses followed by a acP dose), and 8.3% were not vaccinated against pertussis. Children were between 3 and 8 years of age and were considered to be fully vaccinated if they
Bordetella pertussis and Bordetella parapertussis surveillance
Between June 1997 and December 1999, nasopharyngeal swabs (NPS) were obtained from all children born between December 1992 and June 1994 who presented in the practice with any cough of ≥7 days duration. If children presented with any cough of ≥21 days duration, blood was taken for serological detection of pertussis antibodies.

Laboratory procedures
B pertussis and B parapertussis cultures were performed as described previously.14 The swabs were plated on charcoal horse blood agar supplemented with cephalin, and stored in sterile tubes containing 0.4 ml of NaCl solution (0.9%). Polymerase chain reaction (PCR) was performed in this solution using primers from insertion sequence elements IS481 and IS1001, specific for B pertussis and B parapertussis as described previously in detail.15 Single serum serology analyses for B pertussis and B parapertussis infections were performed using a standardised enzyme immunoassay to measure isotopic antibodies (IgG and IgA) to pertussis toxin and filamentous haemagglutinin FIIA. Antibody levels beyond the 95th centile of an age matched control cohort were regarded as indicative of recent contact, setting the specificity level at 0.95, as previously published by Wirsing von König and colleagues.16 Children who presented a significant anti-PT response either with or without an anti-FHA response, were classified as having B pertussis infection. Children who only showed significant FHA antibody response without anti-PT response were classified as having B parapertussis infection.

Assessment of clinical presentation
Parents of children with laboratory confirmed bordetella infection were handed out diaries for a detailed daily documentation of typical symptoms for a total period of up to 42 days after start of cough. The recorded symptoms included: coughing, number of paroxysmal cough attacks, number of whooping attacks, vomiting, cyanosis, doctor visits, and hospitalisation.

Statistical analysis
Differences in symptoms and duration were evaluated with a χ² distribution or Fisher’s exact test, where appropriate. Calculations were performed with SSPS and SAS software. The incidence rates were calculated in the prospectively recruited study population for both study periods February 1993 to May 1995 and June 1995 to December 1999. Incidence rates were calculated as the number of new B pertussis and B parapertussis cases divided by the sum of person-months during which children were at risk of acquiring bordetella infections, assuming that all children remained part of the cohort throughout the study period.

RESULTS
Between May 1997 and March 1999, a total of 180 children (mean age 4.2 years, range 2.2–6.0 years) were diagnosed with bordetella infections. Among the 180 bordetella infections there were 116 (64%) B pertussis and 64 (36%) B parapertussis infections. Seventy nine of the 116 B pertussis infections (68%) were diagnosed either by PCR (75,79, 95%) or culture (39,79, 49%), whereas 37/116 B pertussis cases (32%) were diagnosed by serology only. Forty two of the 64 B parapertussis infections (66%) were diagnosed either by PCR (5/42, 12%) or culture (38,42, 90%), whereas 22/64 B parapertussis cases (34%) were diagnosed by serology only.

Table 1 Clinical symptoms in 116 children with B pertussis and 64 children with B parapertussis infection

<table>
<thead>
<tr>
<th>Symptom</th>
<th>B pertussis n=116 (64%)</th>
<th>B parapertussis n=64 (36%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough &gt;42 days</td>
<td>74 (64%)</td>
<td>24 (38%)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Paroxysmal cough</td>
<td>87 (75%)</td>
<td>39 (61%)</td>
<td>0.049</td>
</tr>
<tr>
<td>Paroxysm &gt;21 days</td>
<td>62 (53%)</td>
<td>14 (22%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Whooping</td>
<td>63 (54%)</td>
<td>19 (30%)</td>
<td>0.0015</td>
</tr>
<tr>
<td>Whooping &gt;21 days</td>
<td>26 (22%)</td>
<td>3 (5%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Vomiting</td>
<td>58 (50%)</td>
<td>16 (25%)</td>
<td>0.0011</td>
</tr>
<tr>
<td>Vomiting &gt;21 days</td>
<td>9 (8%)</td>
<td>0 (0%)</td>
<td>0.0276</td>
</tr>
</tbody>
</table>

In the prospectively recruited study cohort the incidence rate of B pertussis infections was 4.8 per 1000 person-years, whereas the incidence for B parapertussis infection was 2.8 per 1000 person-years. For comparison in the first study period between 1993 and 1995 the incidence rates of B pertussis was calculated to be 21.7 per 1000 person-years and 1.6 per 1000 person-years for B parapertussis infection.

A total of 124 of the 180 bordetella cases (69%) were fully vaccinated, 13 (7%) were partially vaccinated, and 43 (24%) were not vaccinated against pertussis. Of the 116 B pertussis cases, 72 (62.0%) were fully vaccinated and 9 (7.8%) were partially vaccinated against pertussis with the following vaccines: weP (n = 8, 6.9%); acP (n = 60, 51.7%); both weP and acP vaccine (usually three weP doses followed by an acP dose; n = 13; 11.2%). Thirty five children (30.2%) had never received any dose of pertussis vaccine. Twenty eight of the 35 unvaccinated B pertussis cases were diagnosed by either PCR (28/28, 100%) or culture (18/28, 64%); an additional seven cases were diagnosed by serology only. Of the 81 vaccinated B pertussis cases, 51 were diagnosed by either PCR (47/51, 92%) or culture (21/51, 41%); an additional 30 cases were diagnosed by serology only.

Of the 64 B parapertussis cases, 52 (81%) were fully vaccinated, 4 (6%) were partially vaccinated, and 8 (13%) had not received any vaccination against pertussis.

Table 1 shows differences in clinical symptoms between B pertussis and B parapertussis infections. Children with B pertussis infections presented with a significantly longer duration of all symptoms than children with B parapertussis infection. B pertussis cases showed cough ≥42 days in 64%, paroxysms ≥21 days in 53%, whooping ≥21 days in 22%, and vomiting in 50%, compared to 38% (p = 0.0007), 22% (p = 0.0001), 5% (p = 0.002), and 25% (p = 0.0011) for the B parapertussis cases, respectively.

Significant differences in the clinical presentation were also found between B pertussis cases who had received at least one dose of a pertussis vaccine and unvaccinated B pertussis cases (table 2). Besides the total duration of any cough, all other cough symptoms and their duration were clearly reduced in the cases vaccinated against pertussis compared to the unvaccinated cases. Forty one per cent of those vaccinated had paroxysms ≥21 days compared to 83% of the unvaccinated cases (p = 0.0001). Whooping ≥21 days was seen in 14% of the vaccinated and in 43% of the unvaccinated cases (p = 0.0019). Forty per cent of the vaccinated had vomiting compared to 74% of the unvaccinated cases (p = 0.0012).

A comparison between the symptoms of vaccinated B pertussis and unvaccinated B parapertussis cases did not show significant differences with regard to the duration of any cough, but revealed significant differences with regard to the
The objectives were to determine the incidence, epidemiology and clinical picture of bordetella infections and relative frequency rates of \( B \) parapertussis infections in Germany during the time of low vaccination were between 21% and 25%. A Finnish study in a highly vaccinated population found a very similar distribution to ours, with about one third of laboratory confirmed bordetella infections being caused by \( B \) parapertussis. The protective role of pertussis vaccines against \( B \) parapertussis infections remains unclear. Whereas \( B \) parapertussis infections in Denmark decreased following the introduction of whole cell pertussis vaccination, the circulation was not seen to have decreased in former Czechoslovakia, despite the widespread use of whole cell pertussis vaccination. A recent German study estimated the efficacy of the Lederle whole cell vaccine against \( B \) parapertussis to be 21% (95% CI: 45% to 56%), in contrast to a higher efficacy for the Lederle acP vaccine of 50% (95% CI: 5% to 74%). Other recent acP vaccine trials did not find efficacy of acP vaccines against \( B \) parapertussis infections. The high rate of pertussis vaccination among the \( B \) parapertussis cases in our study suggests only a very low or no efficacy against \( B \) parapertussis disease for the acP vaccines used. Formal efficacy analyses, using the method of a population based ("nested") case-control study, will be provided at the end of this ongoing long term efficacy study.

The typical clinical picture of \( B \) pertussis whooping cough disease was found in almost all unvaccinated children, whereas the majority of vaccinated children had a significantly shorter cough duration and milder symptoms. This observation confirms data of the previously published efficacy study in the same population, where the Biken acP vaccine showed a significantly better efficacy against typical pertussis disease than against mild or less typical pertussis disease. Other recent studies also confirmed that \( B \) parapertussis may cause symptoms similar to \( B \) pertussis. Therefore, clinical symptoms alone do not allow one to make a distinction between \( B \) pertussis and \( B \) parapertussis diseases, especially in populations with a high and sustained pertussis vaccination coverage. Further surveillance of Bordetella spp. in highly immunised populations is necessary in order to document changes in the epidemiology and clinical picture of bordetella infections and to target additional preventive measures.

**ACKNOWLEDGEMENTS**

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Table 2: Clinical symptoms of \( B \) pertussis infection in 81 pertussis vaccinated* children and 35 unvaccinated children

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Pertussis vaccinated (n=81)</th>
<th>Pertussis unvaccinated (n=35)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough &gt;21 days</td>
<td>74 (91%)</td>
<td>35 (100%)</td>
<td>0.1038</td>
</tr>
<tr>
<td>Paroxysmal cough</td>
<td>54 (67%)</td>
<td>33 (94%)</td>
<td>0.0023</td>
</tr>
<tr>
<td>Paroxysm &gt;21 days</td>
<td>33 (41%)</td>
<td>29 (83%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Whooping</td>
<td>38 (47%)</td>
<td>25 (71%)</td>
<td>0.024</td>
</tr>
<tr>
<td>Whooping &gt;21 days</td>
<td>11 (14%)</td>
<td>15 (43%)</td>
<td>0.0019</td>
</tr>
<tr>
<td>Vomiting</td>
<td>32 (40%)</td>
<td>26 (74%)</td>
<td>0.0012</td>
</tr>
<tr>
<td>Vomiting &gt;21 days</td>
<td>3 (4%)</td>
<td>6 (17%)</td>
<td>0.0182</td>
</tr>
</tbody>
</table>

*Pertussis vaccinated with either three (n=9) or four doses (n=72) of the following vaccines: wcP vaccine (n=8), acP vaccine (n=60), both wcP and acP vaccine (usually three wcP doses followed by an acP dose, n=13).

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The typical clinical picture of \( B \) pertussis whooping disease for the acP vaccines used. Formal efficacy analyses, using the method of a population based ("nested") case-control study, will be provided at the end of this ongoing long term efficacy study.

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**DISCUSSION**

The results of this study are based on a long term surveillance of Bordetella pertussis and parapertussis disease during a widespread increase of acP vaccination coverage in a German population from about 20% before 1994 to about 90% in 1999 to 2001. The objectives were to determine the incidence, clinical spectrum, and relative frequency of \( B \) pertussis and \( B \) parapertussis disease in vaccinated and unvaccinated children.

It may be expected that in Germany, as in other countries with a high coverage of pertussis vaccination, clinically significant \( B \) pertussis infections will decrease in the paediatric population. In our study we observed a clear decrease in the incidence from 21.7 per 1000 person-years during 1993–95 to 4.8 per 1000 person-years during 1997–99. However, even in highly immunised populations, \( B \) pertussis and \( B \) parapertussis disease continues to circulate and cause relevant cough disease. Because of the incomplete efficacy of acP vaccines, especially regard to mild disease, further circulation and a shift of \( B \) pertussis infections to older age groups, to adolescents and adults can be expected, as has already been shown in other countries.

We observed a relative decrease in the percentage of \( B \) parapertussis among all bordetella cases from 20% in the period 1993–95 to 36% in the period 1997–99. Since the larger part of \( B \) pertussis infections in this population might have been prevented by vaccination, this increase of \( B \) parapertussis infections may be both the effect of a decrease of \( B \) pertussis infections and a real increase in the incidence of \( B \) parapertussis infections. In contrast to the clear and expected decrease of \( B \) pertussis infections, the incidence of \( B \) parapertussis increased from 1.6 per 1000 person-years in 1993–95 to 2.8 per 1000 person-years in 1997–99.

We are confident that all symptomatic \( B \) pertussis infections were detected in both study periods, since prospective surveillance with a low trigger of any cough >7 days was used to initiate bordetella case investigations. However, the comparatively low sensitivity of \( B \) parapertussis PCR might have led to a certain underestimation of \( B \) parapertussis cases. If we consider the 77 Bordetella spp. cases diagnosed by culture alone, the ratio of \( B \) pertussis to \( B \) parapertussis was 51.49%, compared to a ratio of 64%. When PCR and serology positive cases were also included.

Among bordetella infections, relative frequency rates of \( B \) parapertussis have been reported between 1% and 35%,4,14 and the rates in Germany during the time of low vaccination were between 21% and 25%. A Finnish study in a highly vaccinated population found a very similar distribution to ours, with about one third of laboratory confirmed bordetella infections being caused by \( B \) parapertussis.4 The protective role of pertussis vaccines against \( B \) parapertussis infections remains unclear. Whereas \( B \) parapertussis infections in Denmark decreased following the introduction of whole cell pertussis vaccination, the circulation was not seen to have decreased in former Czechoslovakia, despite the widespread use of whole cell pertussis vaccination.4,16 A recent German study estimated the efficacy of the Lederle whole cell vaccine against \( B \) parapertussis to be 21% (95% CI: 45% to 56%), in contrast to a higher efficacy for the Lederle acP vaccine of 50% (95% CI: 5% to 74%).1 Other recent acP vaccine trials did not find efficacy of acP vaccines against \( B \) parapertussis infections.17 The high rate of pertussis vaccination among the \( B \) parapertussis cases in our study suggests only a very low or no efficacy against \( B \) parapertussis disease for the acP vaccines used. Formal efficacy analyses, using the method of a population based ("nested") case-control study, will be provided at the end of this ongoing long term efficacy study.

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REFERENCES