ORIGINAL ARTICLE

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

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**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, post-tussive 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.

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.[1] Pertussis infant vaccination was generally recommended again in 1991, but vaccination coverage only increased rapidly after the licensure of acellular pertussis (acP) vaccines in 1994. This was due, firstly, to the better acceptance of the less reactogenic acP vaccines, and secondly, to the availability of acP vaccines in combination vaccines.[2 3] A survey of vaccination coverage in 1999 found a pertussis vaccination coverage of 91% in a German infant population for the first three doses given at 2, 3, and 4 months of age.[4] Another survey in 2001/2002[5] found a pertussis vaccination coverage in former West Germany of 27% in 12–17 year old adolescents compared to 61% in 7–11 year olds and 83% in 2–6 year old children, documenting the change from a predominatly non-vaccinated population to a population with high pertussis vaccination coverage over the course of about 10 years.

An ongoing pertussis vaccine, long term efficacy study permitted us to introduce prospective long term surveillance in a highly vaccinated population of children between 3 and 8 years of age in German paediatric practices.[3] Our objective was to determine the the incidence and to describe the clinical spectrum of *B pertussis* and *B parapertussis* disease in this population after the introduction of acP vaccines. In addition, we investigated whether we could find an increase in *B parapertussis* infections in a situation involving questionable or, at the most, a low efficacy of licensed acP vaccines against *B parapertussis*.[6 7]

## 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.[3] 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 paedatric 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 vaccines, 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

had received at least four doses of any pertussis vaccine.All other children, who had received three or less doses of pertussis vaccine, were considered to be partially vaccinated. As there were only 13 *Bordetella* spp. cases who were partially vaccinated, most of whom had received three doses of pertussis vaccine, several of the following analyses combine fully and partially vaccinated *Bordetella* spp. cases into one group.

### *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.[8 9] The swabs were plated on charcoal horse blood agar supplemented with cephalexin, 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.[10–12] Single serum serology analyses for *B pertussis and B parapertussis* infections were performed using a standardised enzyme immunoassay to measure isotypic antibodies (IgG and IgA) to pertussis toxin and filamentous haemagglutinin FHA. 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.[13] 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 $\chi^2$ distribution or Fisher's exact test, where appropriate. Calculations were peformed 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 1997 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.

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: wcP vaccine (n = 8, 6.9%); acP (n = 60, 51.7%); both wcP and acP vaccine (usually three wcP 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 vaccinated *B parapertussis* cases did not show significant differences with regard to the duration of any cough, but revealed significant differences with regard to the

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

| | *B pertussis* n=116 (64%) | *B parapertussis* n=64 (36%) | p value |
|---|---|---|---|
| Cough >42 days | 74 (64%) | 24 (38%) | 0.0007 |
| Paroxysmal cough | 87 (75%) | 39 (61%) | 0.049 |
| Paroxysm >21 days | 62 (53%) | 14 (22%) | 0.0001 |
| Whooping | 63 (54%) | 19 (30%) | 0.0015 |
| Whooping >21 days | 26 (22%) | 3 (5%) | 0.002 |
| Vomiting | 58 (50%) | 16 (25%) | 0.0011 |
| Vomiting >21 days | 9 (8%) | 0 (0%) | 0.0276 |

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

| | *B pertussis* cases (n=116) | | |
|---|---|---|---|
| | *B pertussis* vaccinated (n=81) | *B pertussis* unvaccinated (n=35) | p value |
| Cough >21 days | 74 (91%) | 35 (100%) | 0.1038 |
| Paroxysmal cough | 54 (67%) | 33 (94%) | 0.0023 |
| Paroxysm >21 days | 33 (41%) | 29 (83%) | 0.0001 |
| Whooping | 38 (47%) | 25 (71%) | 0.024 |
| Whooping >21 days | 11 (14%) | 15 (43%) | 0.0019 |
| Vomiting | 32 (40%) | 26 (74%) | 0.0012 |
| Vomiting >21 days | 3 (4%) | 6 (17%) | 0.0182 |

*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).

occurrence and duration of paroxysmal cough and in post-tussive whooping. Thirty three of the 81 (41%) vaccinated *B pertussis* cases had more than seven days duration of paroxysmal cough in comparison to 14/57 (25%) of the vaccinated *B parapertussis* cases ($p < 0.05$). More than seven days duration of whooping was present in 33/81 (41%) of the vaccinated *B pertussis* and in 8/57 (14%) of the *B parapertussis* cases ($p < 0.05$).

In order to analyse the relation between age and clinical manifestation in both unvaccinated and vaccinated *B pertussis* cases, children were divided into a group aged <4.2 years and a group aged >4.2 years at the time of diagnosis of *Bordetella* spp. infection. No significant difference was found for cough duration and cough symptoms between vaccinated *B pertussis* cases of these two age groups. In unvaccinated *B pertussis* cases, however, children of the younger age group presented significantly more often with whooping of ⩾7 days ($p = 0.01$) or ⩾21 days ($p = 0.009$) and with vomiting of ⩾21 days ($p = 0.03$). There was no significant difference in the duration of cough or paroxymal cough.

## 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.[4 5] 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* still continue to circulate and cause relevant cough disease. Because of the incomplete efficacy of acP vaccines, especially with 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.[14]

We observed a relative increase 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%:36% 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%,[14] and the rates in Germany during the time of low vaccination were between 2.1% and 25%.[6] 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*.[14] 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,[15] the circulation was not seen to have decreased in former Czechoslovakia, despite the widespread use of whole cell pertussis vaccination.[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%).[7] Other recent acP vaccine trials did not find efficacy of acP vaccines against *B parapertussis* infections.[6 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.

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.[3] *B parapertussis* presented in general as a disease associated with milder symptoms of coughing. However, about one third of the children with *B parapertussis* infection had a disease presenting prolonged cough with typical whooping cough symptoms, as well as paroxysms, whooping, and vomiting. Other recent studies also confirmed that *B parapertussis* may cause symptoms similar to *B pertussis*.[14 18] 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.

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# POSTCARD FROM THE ROAD

## Shoeshine

On impulse I asked the lady having her shoes shined how much the boy was charging. Around 50p ($0.75 or €0.75) seemed good—cheap enough to afford while travelling on a tight budget, expensive enough to feel like there were two sides to the deal. The box on which he made me put my foot was roughly made but contained the tools he needed—soap, wax, polish, cloths, and brushes—to give my shoes a shine they'd not had since I first bought them.

About halfway through the shine I realised that I was breaking a UN convention. Forget that I was paying what was locally a good sum of money for the work. Forget that I was going to give him a pen too—big deal: have you ever met a doctor who needs another pen? Forget also that the money from my job would have gone towards the rental, lease, or purchase of his kit, moving him cent by cent closer to the prospect of owning his own chair and stool, with the pride, self respect, and status that this would give him.

The fact was that this was a child of about 11 years, kneeling before me, dirtying his hands with polish so that I might be able to see my face in my shoes. The UN convention states, in article 19, that children should be protected from exploitation. At 11 years old pretty much any true work is exploitation. Household chores, yes. Playing with friends after school, yes. Shining shoes in the street, no.

This was the first time I'd overtly—or knowingly—flaunted an international convention. But thinking about it I realised that covertly we flaunt this particular article on a daily basis. This happens every time we buy an item from an unknown source in a country which is itself unwilling or unable to abide by the convention. Looked at another way, our very way of life depends on exploitation. How else could we buy something as complex as a television for a mere few hundred pounds, or as simple as a T-shirt for less than ten? The worker, being paid a few dollars a day, is likely either to be a child, or an adult earning so little that there is no prospect of sending his or her own children to school. There is a direct link between the price we pay for the goods and the fact that the worker requires his or her own children to work as well.

We feel justifiably pleased—maybe even smug—about our own laws which aim to protect children. This is comparable to the smugness we felt in the days of empire, when we pointed out to less enlightened nations that we didn't use slaves. Well, not in Britain we didn't, because we had plenty working for us all over the rest of the Empire and beyond. We owe our current place towards the top of the developed world hierarchy to that exploitation, and we maintain our place there in a manner which is only slightly less exploitative.

The developing world—some parts more than others—is developing as a consequence of the efforts of its workforce, often employed under extraordinarily competitive conditions by companies who will move production from country to country to secure the lowest price—or, depending on your view, the highest efficiency. In some of these countries the underage workforce is an important contributor to that efficiency. Our position—the UN's position—is very threatening to the economic growth of these countries. After all, they say, badly paraphrasing Gandhi, that not every country can be a Britain, with an entire India to plunder and exploit. They have to create their economic growth from within, using what they regard as their own strengths—which often means their underage workforce.

At the heart of it, however, I cannot find fault in the UN convention. I'll continue to feel guilty until my shoes are scuffed again. Then perhaps I'll forget a bit, in the same way that I can deny the source of my prosperity when I'm back at home and can no longer see the polish blackened hands of the shoeshine boy. But a part of me will recognise that for too much of my life I live in the wrong half of another quote from Gandhi: "Earth has enough to satisfy the need of all the people, but not for satisfying the greed of some".

Later that evening in the same square the band set up and began to play. Lovers kissed and middle class families walked with their children, pausing sometimes to allow another child to clean their shoes.

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