Pertussis Disease Burden in the Household: How to Protect Young Infants

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Background. We conducted a population-based, nation-wide, prospective study to identify who introduced pertussis into the household of infants aged ⩽6 months admitted to the hospital for pertussis in the Netherlands.

Methods. During the period 2006–2008, a total of 560 household contacts of 164 hospitalized infants were tested by polymerase chain reaction, culture, and serological examination to establish *Bordetella pertussis* infection. Clinical symptoms and vaccination history were obtained by a questionnaire submitted during sample collection and 4–6 weeks afterwards.

Results. Overall, 299 household contacts (53%) had laboratory-confirmed pertussis; 159 (53%) had symptoms compatible with typical pertussis infection, and 42 (14%) had no symptoms. Among children vaccinated with a whole-cell vaccine, 17 (46%) of 37 had typical pertussis 1–3 years after completion of the primary series, compared with 9 (29%) of 31 children who had been completely vaccinated with an acellular vaccine. For 96 households (60%), the most likely source of infection of the infant was established, being a sibling (41%), mother (38%), or father (17%).

Conclusions. If immunity to pertussis in parents is maintained or boosted, 35%–55% of infant cases could be prevented. Furthermore, we found that, 1–3 years after vaccination with whole-cell or acellular vaccine, a significant percentage of children are again susceptible for typical pertussis. In the long term, pertussis vaccines and vaccination strategies should be improved to provide longer protection and prevent transmission.

Vaccination has strikingly reduced the morbidity and mortality due to pertussis in developed countries [1]. However, in the past decade, a resurgence of pertussis has been experienced in many countries that has been attributed to increased awareness, waning immunity, and pathogen adaptation [2–6]. The high circulation of pertussis in vaccinated populations puts 0–6-month-old infants at risk, because they are too young to be completely vaccinated. Pertussis-related morbidity and mortality are highest in this group.

To protect infants against pertussis, the main sources of their infection must be identified. Several studies have demonstrated high attack rates for pertussis after household exposure, showing that adults played an important role in the transmission to children [7–13]. However, the contribution of various household members cannot be based on these studies, because they were designed for other aims. Moreover, they identified cases largely on clinical diagnosis, because laboratory confirmation was suboptimal or not available for all household members. Two multinational studies involving only small numbers of subjects recently attempted to clarify the sources of pertussis infection in young infants [14, 15] and concluded that parents, especially mothers, were the source in most cases. They suggested that vaccination of parents could substantially reduce the burden of infant pertussis.

We conducted a population-based, nationwide, prospective study to identify which household members had introduced pertussis to an infant hospitalized for pertussis. Both clinical and laboratory (culture, serological testing, and polymerase chain reaction [PCR])

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criteria were used to maximize diagnostic yield and to identify infected persons more reliably. Furthermore, we assessed the age-specific attack rate, severity, and impact of pertussis in a household setting and determined the effectiveness of vaccination in high-exposure settings.

METHODS

Population. From 1 February 2006 through 30 November 2008, pediatricians, microbiologists, and local public health services in the Netherlands reported any infant aged <6 months hospitalized with *Bordetella pertussis* or *Bordetella parapertussis* infection to the Centre for Infectious Disease Control of the National Institute of Public Health and the Environment (RIVM). Upon agreement of the parents or caretakers of the infant (hereafter denominated as "index infant"), a home visit was promptly conducted by the study nurse. Information on demographic characteristics, pertussis vaccination status, symptoms, hospital stay, family composition, and coughing contacts of the infant was collected by interviewing parents using a standardized questionnaire. Furthermore, household contacts (ie, persons living in the same house as the index infant) were enrolled in the study after providing informed consent and were interviewed using a standard questionnaire on demographic characteristics, vaccination history, pertussis history, clinical symptoms in the past 2 months, coughing contacts, and work loss. To identify *B. pertussis* or *B. parapertussis* by PCR or culture, nasopharyngeal and buccal swab specimens were collected from all household contacts, and a blood sample was obtained for pertussis serological testing. Four to 6 weeks after the initial home visit, follow-up data on symptoms were collected by phone for all participants.

Vaccination status of infants and children aged <13 years was obtained via the national register. During the study period, pertussis vaccination was offered within the National Immunization Program at 2, 3, 4, and 11 months and—since 2001—an acellular preschool booster was offered at 4 years of age. Since 2005, an acellular vaccine has replaced the Dutch whole-cell vaccine for vaccinations in infancy. Ethics approval for our study was obtained from the Medical Ethical Committee of the University Medical Centre of Utrecht.

Diagnostic laboratory procedures. Laboratory confirmation was based on culture, PCR, or serological test results. A nasopharyngeal swab was used to inoculate Regan-Lowe charcoal agar containing 40 μg/mL cephalexin. The Regan-Lowe plates were incubated at 35°C in high humidity and were examined daily for 14 days for colonies typical of *Bordetella* species. Colonies were confirmed by partial sequencing of the *Bordetella* pertactin and toxin gene [16]. Specimens for PCR were collected as a nasopharyngeal or buccal swab (Dacron). PCR tests were performed in the regional public health laboratory in Tilburg, the Netherlands. Swabs were rinsed in 1 mL of solution containing 150 mmol/L NaCl and 1 mmol/L EDTA. Nucleic acids were extracted from a 200-μL sample using the total nucleic acid protocol with the MagNA pure LC nucleic acid isolation system (Roche Diagnostics). Each sample was eluted in 50 μL of buffer. Detection of *B. pertussis* and *B. parapertussis* was performed in a multiplex real-time PCR assay, as described elsewhere [17], using an ABI 7500 Fast Real-Time PCR System (Applied Biosystems). In brief, samples were assayed in a 25-μL reaction mixture containing 5 μL of DNA, 12.5 μL of 2× TaqMan Universal PCR Master Mix (Applied Biosystems), 300–900 nmol/L of the forward and reverse primers, and 75–200 nmol/L of each of the probes. All samples had been spiked before extraction with an internal control virus (phocine herpes virus) to monitor for efficient extraction and amplification, as described elsewhere [18].

Serological diagnosis of pertussis consisted of measurement of immunoglobulin (Ig) G antibodies against purified pertussis toxin (IgG-PT) and IgA antibodies against a crude cell-membrane preparation of *B. pertussis* (IgA-Bp) with an in-house ELISA of the National Institute for Public Health and the Environment. From 2003 onwards, the reference serum used in this ELISA has been calibrated with the US Food and Drug Administration (FDA) lot 3 international standard serum for PT antibodies. Serum samples were tested in 1:400 dilution (equivalent to 100 FDA lot, 3 IU/mL). An IgG-PT titer greater than the diagnostic cut-off of 100 U/ml was considered indicative for recent pertussis infection. As assessed by Giammanco et al [19] this value of 100 FDA lot 3 IU/mL corresponds with 82 "Dutch" U/mL, as measured with the reference serum that was in use at our institute before 2003. The specificity of this cutoff was 98.3% when assessed in 7756 serum samples obtained from the general population and was independent of age [20]. IgA-Bp levels were interpreted in combination with IgG-PT levels by constructing height categories of IgA-Bp and IgG-PT combinations (height categories 1 to 12, from low to high). The diagnostic cutoff of IgA-Bp–IgG-PT combinations was defined to be the 99th percentile of the distribution of IgA-Bp–IgG-PT height categories in 7756 serum samples obtained from the general population. IgA-Bp concentrations in the serum samples obtained from the general population increased with age (the data are not shown here but have been demonstrated in previous studies [21, 22]). Consequently, the diagnostic cutoff of IgA-Bp and IgG-PT combinations was age dependent, with separate cutoffs for subjects aged <5 years, 5–14 years, and >14 years. In patients with PCR- or culture-proven pertussis and in control subjects with other respiratory disease, the sensitivity and specificity of those age-dependant cutoffs have been shown to be 80% and 97%, respectively [22].

Case classification and source identification. A household contact was regarded as having a confirmed case of pertussis if PCR, culture, or serological tests yielded positive results.

The first day of illness was set as the onset of coughing or as the onset of cough-preceding cold symptoms. Cold symptoms occurring >2 weeks before onset of coughing were seen as a separate episode and not related to pertussis infection. A case was considered typical pertussis if it entailed at least 2 weeks of coughing and ⩾1 of the following symptoms: paroxysmal coughing, posttussive vomiting, and/or inspiratory "whooping."

In families, household contacts with laboratory-confirmed pertussis and the index infants were classified according to the chronology of symptom onset as (co)first or (co)second case(s)—that is, (co)first cases were persons with laboratory-confirmed pertussis with earliest date of onset, and (co)second case(s) had laboratory-confirmed pertussis with onset of symptoms at least 1 week (minimum incubation period) after the (co)first case.

Multiple first cases per household could occur if all became sick in the same week. An household case was considered a "source case" if the onset of symptoms occurred >1 week before the onset of the case in the index infant. Infection of the index infant was assumed to have occurred outside the household if the parents reported contact between the infant and a nonhousehold contact with pertussis infection in the week before onset in the infant.

Statistical analysis. Characteristics of the index infants and household contacts were analyzed. Differences in percentages and medians were tested with χ^2 test, the Fisher exact test, or the Wilcoxon Mann-Whitney test, as appropriate. Linear regression was used to study the relationship between duration of hospital admission, age, and vaccination status of index infants. A P value <.05 was considered statistically significant. Analyses were performed using SAS software, version 9.1 (SAS Institute). Ninety-five percent confidence intervals were calculated using Episheet [23].

RESULTS

Of 294 reported infants and their families, 90 were excluded because caretakers refused participation (for lack of time or fear of venapuncture) or the index infant lacked laboratory confirmation. Three families were excluded because the index infant had infection with *B. parapertussis*, leaving 201 infected index infants and their families for further analysis.

Infant index cases. The median number of days between date of hospitalization of the index infant and the study nurse's visit to the family was 17 days (range, 4–88 days). All 201 index infants were born in the Netherlands; 104 (52%) were male. The median age at onset of symptoms was 49 days (range, 2–103 days). Twenty-four infants (12%) were born prematurely (<37 weeks gestation period). Table 1 reviews symptoms and complications reported in 201 index infants. All infants survived. The median duration of hospital stay was 8 days (range, 0–80 days); 33 infants (16%) were admitted for day care or treated in the outpatients' clinic. Among infants eligible for at least 1 vaccination (ie, those aged 56–84 days), the median duration of hospitalization was shorter in those receiving 1 dose than for unvaccinated infants (4 vs 11 days; $P = .03$).

Attack rate in household contacts. Laboratory diagnostics were performed for 723 (98%) of 738 household contacts: 335 were tested by PCR, serological examination, and culture; 353 were tested by PCR and serological examination; 31 were tested

Table 1. Clinical Symptoms and Complications in 201 Infants aged <6 Months Admitted to the Hospital for *Bordetella pertussis* Infection

Characteristic	Infants (n = 201)
Age at onset of symptoms, median days (range)	49 (2–103)
No. of doses of vaccine received	
0[a]	146 (73)
1	37 (18)
2	17 (8)
3	2 (1)
Comorbidity[b]	32 (16)
Duration of cough, median days (range)	30 (3–150)
Paroxysmal cough	198 (99)
No. of paroxysms per day, median days (range)	25 (1–240)
Nonpraoxysmal cough	3 (2)
Cough with whoop	192 (96)
Posttussive vomiting	147 (73)
Posttussive sticky sputum	189 (94)
Wheezing	177 (88)
Cyanosis	164 (82)
Apnea	112 (56)
Collapse	65 (33)
Fever	13 (6)
Complications	
Pneumonia	12 (6)
Weight loss	97 (48)
Convulsions	10 (5)
Conjunctival infection	36 (18)
Retinal bleeding	9 (4.5)
Otitis media	8 (4)
Encephalopathy	0 (0)
Intracranial bleeding	0 (0)
Administration of oxygen	106 (53)
Mechanical ventilation	8 (4)
ICU admission	22 (11)
Death	0 (0)

NOTE. Data are no. (%) of patients, unless otherwise indicated. ICU, intensive care unit.

[a] One hundred twenty-one infants were too young to be vaccinated.

[b] Includes other respiratory disorders (respiratory syncytial virus infection, 4 cases; influenza A, 1 case; human metapneumovirus infection, 2 cases; rhinovirus infection, 4 cases; rotavirus infection, 2 cases; and infection with an unspecified pathogen, 2 cases); reflux, 13 cases; gastrointestinal infection, 2 cases; urinary tract infection, 1 case; and damaged pulmonary lobe, 1 case.

Table 2. Attack Rates of *Bordetella pertussis* Infection, by Age and Disease Manifestation, in Household Contacts of Infants Hospitalized for Pertussis

Household contact	No. of persons	Disease manifestation, no. (%) of persons			Total attack rate
		Typical	Mild or atypical	Asymptomatic	
Mothers	164	58 (35)	34 (21)	18 (11)	110 (67)
Fathers	155	29 (19)	20 (13)	11 (7)	60 (39)
Other adults[a]	28	3 (11)	6 (21)	3 (11)	12 (43)
Adolescents aged 14–19 years	8	2 (25)	0 (0)	1 (13)	3 (38)
Siblings aged 9–13 years	27	12 (44)	3 (11)	3 (11)	18 (67)
Siblings aged 5–8 years	85	22 (26)	15 (18)	2 (2)	39 (46)
Siblings aged 1–4 years	92	32 (35)	20 (22)	4 (4)	56 (61)
Siblings aged 0 years (ie, twins)	1	1 (100)	(0)	0 (0)	1 (100)
Total	560	159 (28)	98 (18)	42 (8)	299 (53)

[a] Seventeen of 28 were grandparents.

by PCR only, and 4 underwent serological testing only. A positive test result was found for 391 (54%) of the tested persons; 36 (11%) of 335 cases were culture proven, 262 (38%) of 692 were serologically confirmed, and 213 (30%) of 719 were PCR confirmed. In symptomatic, laboratory-confirmed cases, the median duration of symptoms at time of sampling was related to the diagnostic method: cases confirmed by PCR had a shorter duration of symptoms than did serologically confirmed cases ($P = .01$). To maximize the diagnostic yield and to reliably identify infected contacts, taking into account the delay of sampling, a combined PCR and serological test result was considered optimal laboratory diagnosis. In 164 (82%) of 201 families with an infant index case, this optimal laboratory diagnosis was available for all household contacts ($n = 560$). Table 2 shows the attack rates for symptomatic and asymptomatic *B. pertussis* infection, by type of household contact. Omitting the twin-brother of 1 index infant, the highest attack rates of infection were seen in mothers (67%) and siblings aged 9–13 years (67%). Attack rates were lowest for adolescents aged 14–19 years (38%) and fathers (39%). A similar pattern was seen for the attack rate of typical pertussis. Of the 205 children with verified vaccination status, 180 (89%) had been completely vaccinated in infancy. Within 3 years after completion of the primary series, 9 (29%) of 31 children who received acellular vaccine had typical pertussis, compared with 17 (46%) of 37 children who received whole-cell vaccine (Table 3). Of the unvaccinated children aged 1–3 years 4 (67%) of 6 had typical pertussis.

The twin brother of 1 index infant was hospitalized for pertussis for 9 days. Patients hospitalized for 1 day included 1 sibling (a 7-year-old child who had been vaccinated according to schedule, including the acellular preschool booster) and 1 father (age, 44 years). Five household contacts with pertussis

Table 3. Number of Pertussis Cases per Disease Manifestation, in Relation to Time Since Last Vaccine Dose for Children Who Were Completely Vaccinated (ie Children Who Had Received 4 Doses) with Either the Whole-Cell Vaccine or the Acellular Vaccine but Who Did Not Receive a Preschool Booster

Vaccine regimen received, duration since last dose	No. of patients			
	Total	Typical pertussis	Atypical pertussis	Asymptomatic pertussis
Four doses of whole-cell vaccine				
0 years	0	0	0	0
1 year	3	1	1	0
2 years	25	11	4	1
3 years	9	5	1	0
4 years	0	0	0	0
⩾5 years	38	16	4	2
Four doses of acellular vaccine				
0 years	2	0	2	0
1 year	15	4	8	0
2 years	12	4	2	1
3 years	2	1	1	0

Table 4. Classification of First Cases and Source Cases (ie, Household Contacts with Onset ⩾7 Days Preceding the Index Infant), by Relationship with the Infant

Relationship with index infant	No. of persons	First cases		Source cases	
		No. of persons	Percentage of persons (95% CI)	No. of persons	Percentage of persons (95% CI)
Index infant	164	68	35 (29–42)	…	…
Mother	164	46	24 (18–30)	52	38 (30–46)
Father	155	21	11 (7–16)	23	17 (11–24)
Other adult	28	4	2 (1–5)	6	4 (2–9)
Adolescents aged 14–19 years	12	0	0 (0–2)	0	0 (0–2)
Sibling aged 9–13 years	27	11	6 (3–10)	11	8 (4–13)
Sibling aged 5–8 years	85	17	9 (5–13)	20	15 (9–21)
Sibling aged 1–4 years	92	25	13 (9–18)	25	18 (12–25)
Sibling aged 0 years (ie, twins)	1	0	0 (0–2)	0	0 (0–2)
Total	560	192[a]	100	137	100

[a] Multiple first cases per household could occur.

reported having a diagnosis of pertussis confirmed by a general practitioner (GP) in the past (3–27 years ago, at the time that the subject was aged 0–4 years).

In total, 116 (39%) of 299 contacts with current pertussis infection consulted a GP for their infection. The GPs had ordered laboratory tests for 23 (20%) and treated 11 (9%) before onset in the index infant. Ten infected adult household contacts (5%) lost work days (median, 2 days; range, 1–10 days) because of their pertussis.

Introduction of pertussis in the households and transmission to neonates. Table 4 shows the distribution of first cases in the households, 93 (48%) had typical pertussis. Of the first cases, 28% were siblings, 24% were mothers, and 11% were fathers. Of the mothers, 14 (22%) of 46 had onset of symptoms during pregnancy. The index infant was the first case in 68 households, but in 11 infants (7%), the onset of symptoms coincided with onset of symptoms in a household contact. One index infant (0.6%) had been exposed to a child outside the household whose pertussis was diagnosed in the week before onset of symptoms in the index infant. When the index infant was the second, third, or fourth case in a household, 41% of the source cases were siblings, 38% were mothers, and 17% were fathers.

DISCUSSION

Currently in the Netherlands, an infant hospitalized for pertussis has most often been infected in the home by siblings or mother (in 33% and 28% of the cases, respectively). Of the possible sources of infection of the index infant (ie, contacts with onset of symptoms at least 1 week before onset in the index infant), 41% were siblings, 38% were mothers, and 17% were fathers.

Our finding that mothers play an important role in the transmission of pertussis in the household is consistent with previous studies [11, 12, 15]. Fathers have less importance in pertussis transmission, especially in the first 3 months of life, presumably because only mothers receive pregnancy leave in the Netherlands.

In contrast to other studies [14, 15], we found that siblings were the main source of infection in infants. The distribution of infection in contacts may reflect the demographic characteristics and family structures in the study households and is also influenced by vaccination history [24], characteristics of the circulating pathogen [6] and country-specific contact patterns [25]. The mean number of children (2.6; 95% confidence interval, 2.3–2.8) in the study households exceeded that of the general population in 2007 (1.8) [26], suggesting that having siblings is a risk factor for infant pertussis [27]. Alternatively, it could indicate that households with several children are overrepresented in our analyses, resulting in overestimation of sibling's importance. However, unlike previous studies, we included >80% of the infants hospitalized nationwide for pertussis in the study period, and our final analyses—with both PCR and serology results available for all household contacts—was based on 164 families. Therefore, our study population seems to be representative and yields a robust estimation of the role of various household contacts in the transmission of pertussis to infants.

The larger role of siblings in the transmission of pertussis in the Netherlands may result from using a less effective whole-cell vaccine [28]. In areas with low vaccine coverage, young children most often introduce pertussis into a household [10], whereas in high-coverage areas, adolescents and adults play a larger role [7, 29]. Despite high uptake in the 1990s, the relatively less effective Dutch whole-cell vaccine may have created an area with low immunity. The lower effectiveness of the Dutch whole-cell vaccine is underlined by the fact that 44% of completely vaccinated children got typical pertussis. However,

even among children completely vaccinated with the acellular vaccine (introduced in 2005), 29% got typical pertussis within 3 years after completion of the primary series of vaccination. Conceivably, intra-familial factors (such as host genetics or immunological background) may induce vaccine failure [30], and prolonged and intense exposure (as in a household) may overcome vaccine-induced protection. Besides, 71% of siblings in the current study had not received the acellular preschool booster, introduced in 2001. The role of siblings in the transmission of pertussis may diminish in the coming years as introduction of the preschool booster reduced the incidence of pertussis in infants, probably due to reduced transmission from siblings [5].

In one-third of the cases, we found no household contact with symptom onset preceding the infection in the index infant, although most households had $\geqslant$1 contact shown to be infected. It could be that contacts were asymptomatic, failed to recall symptoms, or that symptoms were slow to develop. Asymptomatic or subclinical infections may still transmit pertussis to vulnerable infants [9, 13]. Of course, the source of infection could have been a casual contact outside the household [31].

Pertussis may run a severe course in infants, especially those who are prematurely born, and hospitalization may exceed 1 week [7, 12, 32, 33]. Fortunately, none of the infants in the study died or had severe complications (eg, encephalopathy or intracranial bleeding), although we cannot exclude the possibility that those of nonparticipating parents may have been more severely ill. Most index infants in the study were too young to have been completely vaccinated. However, protection against severe pertussis can be achieved after one dose of vaccine [34, 35], and duration of hospitalization—a marker for severity—was significantly lower among infants who had received 1 dose.

Although most household contacts were vaccinated, the attack rate of symptomatic pertussis was high (46%). In a similar study in a highly vaccinated population in France [7], the attack rate of symptomatic pertussis in household contacts was equally high, although not all cases were laboratory confirmed. We showed that only 39% of infected household contacts consulted a GP, and 20% were tested. Importantly, only 9% were treated with antibiotics before onset of symptoms in the index infant, conforming to the protocol for prophylaxis to limit secondary spread to infants [36]. Only 5% of infected adults reported loss of working days because of disease. Thus, most pertussis infections beyond infancy are mild and go unnoticed by the health care system. In the short term, a number of other measures could be implemented to protect infants.

First, the vaccination schedule could start at 6 weeks of age [37], which theoretically would have prevented severe disease in almost 40% of the cases in this study. In fact, if proven safe, effective, and accepted by the population, vaccination directly after birth [38] or vaccination of mothers during pregnancy [39] could protect infants even in the first weeks of life.

Second, selective vaccination of new parents will reduce transmission to infants. In 35% of our study households, pertussis was introduced by a parent, and parents accounted for 55% of the source cases. Instead of selective vaccination of parents, overall adult vaccination has been suggested [40] and is recommended in some countries. However, since adult vaccination has so far obtained low coverage [41] and is unlikely to be cost effective [42], this strategy is not promising. Because expectant parents have regular contact with health care and are well motivated to protect their child, their selective vaccination needs consideration. In the long term, pertussis vaccines and vaccination strategies should be improved to give longer protection against both disease and infection.

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Potential conflicts of interest. All authors: no conflicts.

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