Epidemiology of pertussis in the Netherlands and implications for future vaccination strategies

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Pertussis in infancy and the association with respiratory and cognitive disorders on toddler age

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Abstract

Background: Pertussis in unvaccinated infants can run a severe course and is often accompanied by complications. We studied whether there is an association between pertussis hospitalisation in infancy and, respiratory symptoms, growth and cognitive development in early childhood.

Methods: A group of 89 children aged 13-45 months and hospitalised for laboratory confirmed pertussis within the first six months of their life were compared with 172 age-matched children without a history of pertussis. Multivariate logistic regression analysis was used to estimate risk ratios (RR) with 95% confidence intervals (95%CI) of the association between health outcomes and pertussis in infancy. Weight-for-length and length-for-age z-scores were calculated to investigate growth. Van Wiechen scores were compared to study cognitive development.

Results: Children with a history of pertussis in infancy had more often “asthma symptoms” (RR 2.8, 95%CI: 1.1 – 7.0) on toddler age and were more likely to report “respiratory infections” (RR 3.3, 95%CI: 1.6 – 6.6). A history of pertussis in infancy was associated with significantly lower weight-for-length in the first 40 months of life. No significant differences in cognitive development were found.

Conclusions: We found an association between severe pertussis in infancy and respiratory symptoms on toddler age. The mechanisms that may underlie this association require further investigation.
**Introduction**

Despite routine vaccination with high coverage, pertussis is still endemic in many countries including the Netherlands [1, 2]. Pertussis in unvaccinated infants can run a severe course and is often accompanied by complications such as hypoxia, apnoea, pneumonia or encephalopathy [3-5]. There is only limited data on possible consequences of severe pertussis in infancy in the long term. Results from several studies conducted in the 1980s suggested that children with a history of whooping cough were more likely to experience respiratory symptoms in childhood, though no differences could be demonstrated in physical examination of lung function indices [6-8]. It has been suggested that pertussis in childhood may result in a higher risk for atopic disorders, such as asthma, later in life [7, 9]. This was refuted by others who explained these results by confounding factors (such as socio-economic status and number of siblings) or by the greater susceptibility for pertussis of children predisposed to respiratory morbidity [7, 10, 11].

Studies from the 1950s describe severe intellectual difficulties or mental deficiencies in children who suffered from pertussis in infancy [12-14]. In later studies it was argued that these effects may be present in children with neurological complications, but are in general absent [15]. Interpretation of these findings is problematic, especially in the present time as most of these studies are outdated and medical care has improved since then. Furthermore, the diagnosis of pertussis in these studies is questionable as inclusion of subjects mainly relied on retrospective ascertainment of a history of whooping cough.

Previously, we conducted a nationwide prospective study to identify who introduced pertussis into the household of infants aged <6 months hospitalised for laboratory confirmed pertussis in the Netherlands [3]. In the current study we aimed to investigate whether there is an association between pertussis hospitalisation in infancy and respiratory symptoms, growth and cognitive development in infants aged 1-3 years.

**Methods**

**Participants**

In 2009, children born between July 2005 and February 2008, and hospitalised for laboratory confirmed pertussis (by PCR, culture or serological testing) in infancy (i.e., aged <6 months), were recruited from a previous nationwide study on pertussis in infants [3]. Hospitalisation for pertussis in these infants took place at least 12 months before enrolment in the current study. Based on the Dutch vaccination register, for each child hospitalised for pertussis in infancy three control children were invited from the same postal area and of the same sex and age. None of the controls reported to have had pertussis in infancy.
Data collection

Information on health status of both pertussis and control children, was collected by an extensive questionnaire which was adapted from the International Study of Asthma and Allergies in Childhood (ISAAC) [16].

Four dichotomous health outcomes were defined:

- Mild asthma like symptoms: mucus/sputum production without having a cold, and/or dry cough without having a cold, and/or at least one episode of wheezing or dyspnoea in the past twelve months.
- Respiratory infections: a doctors’ diagnosis of pneumonia above 1 year of age, and/or doctors’ diagnosis of bronchitis in the past in combination with symptoms of or medication for bronchitis in the past twelve months, and/or more than six episodes of severe respiratory symptoms in the past (such as flu, pharyngitis, otitis media or sinusitis).
- Asthma symptoms: more than 4 episodes of wheezing or dyspnoea in the past twelve months, and/or doctors’ diagnosis of asthma in the past in combination with symptoms of or medication for asthma in the past twelve months.
- Skin disorders: itching rash and/or eczema in the past twelve months.

Information on length and weight was obtained from growth curves monitored during routine visits of the child at the Child Health Centre (CHC). Information on cognitive development of participating children was obtained from ‘Van Wiechen developmental investigation form’ routinely collected for each child by CHCs. The Van Wiechen classification scheme is an internationally accepted method to assess motor behaviour, speech, communication, and social skills based on physicians’ observations and parental questioning in order to early detect developmental delays [17]. Two clinicians calculated – independently of each other and blinded from the pertussis history of the child – sum scores on age-specific milestones over the first 15 months of age and of age 15-48 months, based on the number of positively or correctly answered items. Items were grouped to distinguish between language skills and other skills. Sum scores were classified as “good”, “unsatisfactory” or “uncertain”. An unsatisfactory score was given if at least one of the language items, or two items of the other skills, were scored negative. An uncertain score was given if too much data was lacking. In general, 90% of children have a satisfactory score on age-specific milestones.

The study design was approved by the Medical Ethics Committee of the University Medical Centre in Utrech, and all parents of participating children signed written informed consent.
Statistical analysis

The questionnaires and Van Wiechen scores were analysed with SAS version 9.1, Microsoft Excel, and Episheet [18].

Differences in potential confounding variables (Table 1) between the pertussis group and control group were tested by the $\chi^2$ test, Fisher’s exact test or Student’s t-test, as appropriate. We considered the study to be a retrospective cohort study and multivariate logistic regression analysis with “modified Poisson” approach [19] was used to estimate risk ratios (RR) with 95% confidence intervals (95%CI) of the association between each outcome and pertussis in infancy. To adjust for potential confounding we fitted multivariate models if there was a significant association between pertussis and the outcome in the univariate model, and included only variables which changed the univariate point estimate of the effect of pertussis with at least 10% [20].

The growth curves of the CHC files were analysed in R. Weight-for-length and length-for-age z-scores were calculated using Dutch references [21]. A z-score, or standard deviation score, is computed to determine the outcome of an individual in relation to reference measurements of a comparable population with the same age and sex. Weight-for-length scores account for individual differences in weight with respect to length, length-for-age scores account for differences in length with respect to age. Z-scores were analysed using a linear mixed effect regression model, where the pertussis group and the control group were compared, adjusted for birth weight, breastfeeding and birth order. Between-child variability was allowed for by including a random slope for length in the weight-for-length analysis, and for age in the length-for-age analysis. We tested if z-scores differed between both groups and whether this difference changed during the period of follow-up. In all analyses, a P-value<.05 was considered statistically significant.

Results

For 89 (57%) of 155 children with a history of pertussis the questionnaire was returned. In the control group, for 172 (37%) of 465 invited children the questionnaire was returned.

Characteristics of the pertussis and control group are presented in Table 1. Children in the pertussis group were less frequently completely vaccinated in infancy (i.e., less likely to have received four doses), had more often (older) siblings and were more often living outside the city than control children.

Adjusted for confounding variables, the RR for the association between pertussis and “respiratory infections” amounted to 3.3 (95%CI: 1.6 – 6.6) and for “asthma symptoms” amounted to 2.8 (95%CI: 1.1 – 7.0) (Table 2).
A history of pertussis in infancy resulted in significantly lower weight-for-length in the first 40 months of life, the z-score for the pertussis group differed on average -0.26 (95%CI: -0.51 − -0.01) standard deviations from the control group (P = 0.04). No interaction between group and length was found (P = 0.52), indicating that during this period the pertussis children did not catch up with the control group children. Length-for-age z-scores in the pertussis group differed on average -0.16 (95%CI: -0.41 − 0.09) standard deviations from the control group (P = 0.21). No significant interaction between group and age was found (P = 0.28).

Children with a history of pertussis hospitalisation in infancy had more often unsatisfactory language scores, although this difference was not statistically significant (Table 3).

| Table 1. Characteristics of children with and without a history of pertussis hospitalisation in infancy. |
|---------------------------------------------------|---------------------------------------------------|-------------------|
| Age, mean months (SD) | Pertussis (n=89) | No pertussis (n=172) | P-value |
| 27 (6.7) | 28 (7.5) | 0.05 |
| Number of males (%) | 42 (47) | 86 (50) | 0.67 |
| Birth weight, mean grams (SD) | 3,473 (797.5) | 3,491 (703.1) | 0.85 |
| Gestation period, mean weeks (SD) | 39.1 (2.3) | 39.4 (1.9) | 0.23 |
| Gestation period <37 weeks (%) | 10 (11) | 10 (6) | 0.12 |
| Breastfeeding during at least 1 month (%) | 56 (63) | 120 (70) | 0.26 |
| Completely vaccinated against pertussis (%) | 70 (78) | 153 (89) | 0.03 |
| Parent(s) of non-western origin (%) | 12 (13) | 25 (15) | 0.82 |
| Attending child day care (%) | 56 (63) | 121 (71) | 0.22 |
| Number of siblings in household, mean (SD) | 1.9 (1.6) | 1.1 (1.1) | <0.001 |
| At least one older sibling (%) | 73 (82) | 97 (56) | <0.001 |
| Pets in household (%) | 40 (46) | 97 (56) | 0.11 |
| Smoking in household (%) | 7 (8) | 13 (8) | 0.93 |
| Both parents low level of education (%) | 11 (12) | 16 (9) | 0.45 |
| Family member with allergy (%) | 51 (57) | 92 (53) | 0.55 |
| Family member with eczema (%) | 36 (41) | 57 (33) | 0.26 |
| Family member with asthma (%) | 22 (25) | 28 (16) | 0.10 |
| Living in city (%) | 33 (37) | 90 (52) | 0.02 |
| History of measles (%) | 0 (0) | 0 (0) | 1 |
| History of varicella (%) | 31 (35) | 68 (40) | 0.56 |
| Follows special diet (%) | 5 (6) | 10 (6) | 0.94 |
Table 2. Prevalence of respiratory symptoms and skin disorders in children with and without a history of pertussis hospitalisation in infancy.

<table>
<thead>
<tr>
<th></th>
<th>Pertussis (n=86)</th>
<th>No pertussis (n=151)</th>
<th>Crude RR (95%CI)</th>
<th>Adjusted RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild asthma like symptoms (%)</td>
<td>41 (48)</td>
<td>58 (38)</td>
<td>1.3 (0.8 – 1.9)</td>
<td>-</td>
</tr>
<tr>
<td>Respiratory infections (%)</td>
<td>22 (26)</td>
<td>14 (9)</td>
<td>2.8 (1.4 – 5.4)</td>
<td>3.3 (1.6 - 6.6)</td>
</tr>
<tr>
<td>Asthma symptoms (%)</td>
<td>14 (16)</td>
<td>8 (5)</td>
<td>3.1 (1.3 – 7.3)</td>
<td>2.8 (1.1-7.0)</td>
</tr>
<tr>
<td>Skin disorders (%)</td>
<td>20 (23)</td>
<td>35 (23)</td>
<td>1.0 (0.6 - 1.7)</td>
<td>-</td>
</tr>
</tbody>
</table>

* For 3 children in the pertussis group and 28 children in the control group information on confounding variables was missing.

b “Respiratory infections” adjusted for age, sex, and number of siblings; “asthma symptoms” adjusted for age, sex, number of siblings and family member with asthma.

Table 3. Number of children with unsatisfactory scores, by age, and history of pertussis hospitalisation in infancy.

<table>
<thead>
<tr>
<th></th>
<th>Pertussis (n=90)</th>
<th>No pertussis (n=172)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. with sufficient data available</td>
<td>No. with unsatisfactory score (%)</td>
<td>No. with sufficient data available</td>
</tr>
<tr>
<td>&lt;15 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Language scores</td>
<td>64</td>
<td>2 (3)</td>
<td>124</td>
</tr>
<tr>
<td>Other skills</td>
<td>66</td>
<td>2 (2)</td>
<td>123</td>
</tr>
<tr>
<td>15-48 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Language scores</td>
<td>49</td>
<td>9 (18)</td>
<td>106</td>
</tr>
<tr>
<td>Other skills</td>
<td>49</td>
<td>3 (6)</td>
<td>105</td>
</tr>
</tbody>
</table>

Discussion
Adjusted for confounding factors, we showed that children with a history of pertussis in infancy had on toddler age about 3 times higher risk for “respiratory infections” and “asthma symptoms”. A higher risk for respiratory illness in childhood, may be a precursor for asthma in adulthood [22, 23].

Based on the current study we can only speculate on the explanation for the increased risk on respiratory morbidity in children with a history of pertussis in infancy. Many studies have suggested that children with bronchiolitis in infancy caused by viral infections, especially RSV, have a greater risk on developing recurrent wheezing and lower respiratory tract.
infections during early childhood [24-27]. The mechanism behind such an association may be multifactorial. Infections could induce allergic sensitization [25, 28, 29] and/or could affect lung development [30, 31].

Like RSV, pertussis may cause bronchiolitis in young children [32, 33]. Moreover, double infections with *B. pertussis* and RSV or other viruses often occur [34-36]. Possibly, pertussis infection in infancy may cause wheezing by increased bronchial hyper-reactivity either in a similar way as RSV or by co-infection with RSV. Although some of the children in this study had co-infection with RSV, we unfortunately did not inquire this in a standard way.

Alternatively, the association may reflect a genetic predisposition for respiratory infections. Previous studies showed that in the majority of children the association between infection in infancy and wheezing in early childhood was transient and related to congenitally smaller airways which predisposed these children to wheezing in association with infection [25, 28, 37, 38]. Conceivably, children with smaller airways may be more prone to severe infection with *B. pertussis* or pertussis is more easily recognized in children predisposed to respiratory morbidity.

Persistent wheezing in children has been shown to be associated with bronchial hyper-reactivity and IgE-mediated sensitization in the first year of life and may be a predictor for asthma in adulthood [23, 28, 39]. We did not measure IgE levels of the children in our study. It might however still be interesting to repeat the measurements in both groups in a few years to determine whether the increased risk on respiratory illness persists in children hospitalised for pertussis in infancy. Although the proportion of children with unsatisfactory scores on language skills in the group with a history of pertussis was higher, we found no statistically significant difference in cognitive development variables between both groups. This may be explained by the absence of children who had neurological complications during their pertussis infection [3]. In particular, hypoxia and brain haemorrhages may affect cognitive functions [5, 12, 40]. Further, the small differences observed may require the inclusion of a larger number of children to attain significant differences.

We acknowledge there are some limitations of the current study. First of all, selection bias may have occurred if participating children in the pertussis group are the ones who suffered most from their pertussis infection in infancy. However, there were no differences in (disease) characteristics between the selected group and the children in the study they were enrolled from [3]. Secondly, information bias may have occurred if parents of children in the pertussis group were more alert on respiratory symptoms since their child suffered from pertussis. The significantly lower weight-for-length in children with a history of pertussis hospitalisation may however be a consequence of an increased risk for respiratory disease. Alternatively, the control group could be overrepresented by children with high respiratory morbidity if their
Acknowledgements
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References