

Reported pertussis infection and risk of atopy in 8- to 12-yr-old vaccinated and non-vaccinated children

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Pertussis infection has been suspected to be a potential causal factor in the development of atopic disease because of the effect of pertussis immunization on specific IgE antibodies. Although several studies found a positive association between pertussis infection and atopic disorders, this relationship has not yet been studied in a population stratified by vaccination status. To assess the association between pertussis infection and atopic disorders in pertussis-unvaccinated children and in pertussis-vaccinated children. Using data from a previously conducted study on the relationship between the diphtheria-tetanus-pertussis-(inactivated) poliomyelitis vaccination in the first year of life and atopic disorders, the study population of 1872 8–12 yr old was divided into children pertussis-unvaccinated and children pertussis-vaccinated in the first year of life. Within each group, the association between pertussis infection and atopic disorders (both as reported by the parents) was assessed. In the unvaccinated group, there were no significant associations between pertussis infection and atopic disorders. In the vaccinated group, all associations between pertussis infection and atopic disorders were positive, the associations with asthma [odds ratio (OR) = 2.24, 95% confidence interval (CI_{95%}): 1.36–3.70], hay fever (OR = 2.35, CI_{95%}: 1.46–3.77) and food allergy (OR = 2.68, CI_{95%}: 1.48–4.85) being significant. There was a positive association between pertussis infection and atopic disorders in the pertussis vaccinated group only. From the present study, it cannot be concluded whether this association is causal or due to reverse causation.

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The prevalence of atopic disorders has increased dramatically during the second half of the previous century, but explanations for this epidemic are still being sought. Vaccinations, having been an element of western lifestyle for decades, have been suggested to be involved. Especially, the pertussis component was suspected to be a risk factor following the finding in Swedish children that vaccination with diphtheria-tetanus-pertussis increased specific IgE antibodies to *Bordetella pertussis*, especially in individuals with a high risk of atopy (1). However, the epidemiological evidence so far does not appear

to support these suspicions (2–8). Not only pertussis vaccination, but also infection with *B. pertussis* has been hypothesized to change the risk of atopic disorders. Some support for this hypothesis was found in a murine model of allergic asthma. In this model, using a factorial design, it was found that while pertussis infection modulates immune mediators, it also exacerbates the allergic asthmatic response (9). Also, in several epidemiological studies, positive, albeit mostly weak or very weak, associations of pertussis infection with atopic disorders were found: with asthma in three follow-up studies

(10–12) and in a case-control study (13), with eczema in a cross-sectional study (14), and with allergic sensitization in a large cross-sectional study (15). In a small follow-up study of pertussis-infected children, the number of children with either elevated serum IgE or with a positive skin prick test had significantly increased about 1 yr after infection (16), especially in children with a family history or personal history of (suspected) allergy. An age-gender matched control group had IgE levels similar to those of the infected children at the time of infection, suggesting that high IgE was not a risk factor for infection. In contrast, in a follow-up study on the sequelae of whooping cough, in which no effect of pertussis infection in the first year of life on subsequent lung function and bronchial reactivity 9 yr later was found, pertussis cases were more likely to be atopic or to have a family history of wheezing illness than age-sex matched controls (17). The authors suggested that clinical symptoms of pertussis may occur more frequently, or may be more easily recognized, in children predisposed to respiratory morbidity. In all these studies, study populations were selected from the general population, and no distinction between vaccinated and unvaccinated children was made, presumably due to the fact that the vaccination coverage of the study populations in these studies was too high to make this distinction, and most children were probably vaccinated. However, vaccination clearly changes both the incidence and the clinical course of infection and therefore it would be worthwhile to study the relationship between pertussis infection and atopic disorders in pertussis unvaccinated and pertussis vaccinated children separately. This is feasible as even in vaccinated groups there is considerable morbidity due to pertussis infection (18). In the present study, the distinction between vaccinated and unvaccinated children could be made in the data collected in a previous study on the relationship between the diphtheria-tetanus-(whole-cell) pertussis-(inactivated) poliomyelitis vaccination (DTP-IPV) in the first year of life and reported atopic disorders at age 8–12 yr (7). We explored in vaccinated and unvaccinated children associations of pertussis infection with atopic disorders, both reported by the parents.

Objective

To assess the association between reported pertussis infection and reported atopic disorders in pertussis-unvaccinated children and in (whole-cell) pertussis-vaccinated children.

Patients and methods

Study area, population and design

The present study was conducted in the framework of a previous study designed to assess the relationship between the DTP-IPV vaccination and reported atopic disease (7). Briefly, in 2003 and 2004, we sent questionnaires to 4480 children (aged 8–12 yr) of 38 Orthodox Reformed (Protestant) primary schools in the Netherlands. Many parents of children attending these schools refuse vaccinations for religious reasons. A total of 1872 questionnaires (42%) were returned and suitable for analysis of which 671 pertained to reportedly DTP-IPV-unvaccinated children. A subsequent non-responder investigation found no evidence of any selection bias (7). The DTP-IPV provided by the National Vaccination Programme contained a whole-cell pertussis vaccine at the time the children in our study population were in their first year of life (since 2005 this vaccine has been replaced by an acellular pertussis vaccine). For the present study, we divided the population into two groups:

- I. Pertussis-unvaccinated children (i.e. no pertussis vaccinations in the first year of life). Almost all children of this group (94%) were completely DTP-IPV-unvaccinated.
- II. Pertussis-vaccinated children (at least one pertussis vaccination in the first year of life).

Data collection

The questionnaire asked for asthma (wheezing in the past 12 months or ever had the disease), hay fever (symptoms in the past 12 months or ever had the disease) and eczema (itching rash in the past 12 months or ever had the disease) (Dutch translation of the ISAAC questionnaire), physician-diagnosed food allergy ever, childhood vaccinations, gender, passive smoking history, date of birth, perinatal data, birth order, ZIP code, year of birth of the mother, any atopic disorder (asthma, hay fever or any allergy, such as allergy for house dust mite or pets) of parents or siblings, family composition, education, income, living conditions (current and during the first year of life), day care attendance, breast feeding, nutrition during the past month, frequency of exercise, body length and weight, and having had common infectious diseases preventable by vaccinations (measles, mumps, rubella and pertussis).

Reliability of vaccination status

After determination of tetanus toxoid IgG and diphtheria IgG antibodies in an unvaccinated subgroup of 80 children and after comparison of reported vaccination status with official registration data in a subgroup of 120 children, we concluded that vaccination status was reported fairly reliably (7).

Statistical analysis

The relationship between pertussis infection as independent variable and (current symptoms or ever had) asthma, (current symptoms or ever had) hay fever, asthma and/or hay fever, (current symptoms or ever had) eczema, physician-diagnosed food allergy ever, and 'any atopic disorder' (anyone of these disorders) as dependent variable, while adjusting for confounders, was estimated by means of series of logistic regression. As the first approach to multivariate modeling we fitted multivariate models (i.e. models including potential confounders as independent variables) only if there was a significant ($p < 0.05$) univariate relationship between pertussis infection and atopic disease and in that case included only variables (confounders), which changed the univariate point estimate [$\log(\text{odds ratio})$] by at least 10% (19). These potential confounders are listed elsewhere (7) and included, apart from the characteristics shown in Table 1, perinatal data, data on day care attendance, nutrition, physical exercise, housing, family history of atopic disease and socioeconomic data. If a potential confounder turned out to be a candidate for a multivariate model in either of the two groups (vaccinated or unvaccinated), we also included it in the corresponding multivariate model for the other group. As the second approach, we adjusted all univariate models for sibship size and a family history of atopy as these two characteristics could obviously be related to both pertussis infection and atopic status of the child.

Table 1. Characteristics of the pertussis-unvaccinated group and the (whole-cell) pertussis-vaccinated group

	Unvaccinated* n = 622 (%)	Vaccinated† n = 1033 (%)
Gender (male)	52.1	50.8
Age (years) (≥ 10)	56.9	56.3
Any atopic disorder	62.5	66.1
in parents and/or siblings (yes)		
Highest education of parents		
Lower professional or less	33.7	22.8
Medium professional	27.7	28.7
Higher secondary	11.8	15.4
High professional & university	26.8	33.2
Number of children in the family (≥ 4)	87.1	52.9
Pertussis infection (yes)	47.1	8.9

*Unvaccinated means: no pertussis vaccination in the first year of life.

†Vaccinated means: at least one pertussis vaccination in the first year of life.

SPSS version 13.0 (SPSS Inc, Chicago, IL, USA) was used for all analyses.

Results

The original study population consisted of 1872 children with usable questionnaires. Figure 1 shows numbers of 'don't know'/missing values for pertussis vaccination and pertussis infection for the two groups and the remaining group sizes:

1. Pertussis-unvaccinated: n = 622 (40 were DT-IPV vaccinated, the rest totally unvaccinated).
2. Pertussis-vaccinated: n = 1033.

Thirteen per cent of the unvaccinated group did not know whether they had a pertussis infection in the past, while this was only 5% in the vaccinated group. Table 1 shows a pertussis history and other characteristic by vaccination group. Interestingly, almost half of the parents of unvaccinated children reported that their child had experienced a pertussis infection in the past, while in the vaccinated group this was 8.9%.

Prevalences of atopic disorders for the two groups, with and without reported pertussis

Fig. 1. Exclusion of participants due to unknown vaccination status or unknown pertussis infection.

*Out of these, 671 were DTP-IPV-unvaccinated.

**Out of these, 582 were DTP-IPV-unvaccinated.

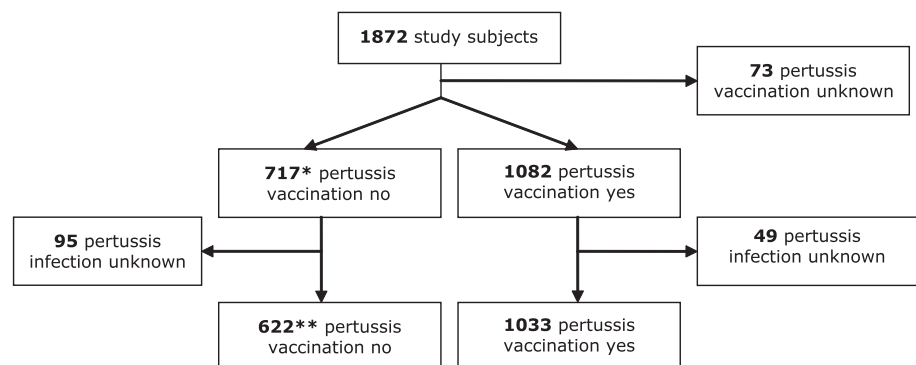


Table 2. Prevalences of reported atopic disorders by pertussis infection for the pertussis-unvaccinated group and the (whole-cell) pertussis-vaccinated group

	Pertussis infection?			
	Unvaccinated* (n = 622), %		Vaccinated† (n = 1033), %	
	No (n = 329)	Yes (n = 293)	No (n = 941)	Yes (n = 92)
Asthma	13.8	11.7	13.8	26.4
p-value		0.53		0.002
Hay fever	16.6	14.0	16.4	31.5
p-value		0.44		0.001
Asthma and/or hay fever	22.2	21.3	24.5	39.1
p-value		0.86		0.003
Eczema	29.5	33.3	34.3	34.8
p-value		0.35		1.00
Food allergy‡	4.9	7.9	7.3	17.4
p-value		0.17		0.001
Any atopic disorder	41.5	45.4	47.9	55.4
p-value		0.38		0.21

*Unvaccinated means: no pertussis vaccination in the first year of life.

†Vaccinated means: at least one pertussis vaccination in the first year of life.

‡Physician diagnosed.

infection, are presented in Table 2. In group I (unvaccinated) no important associations between pertussis infection and atopic disorders were found. In group II (vaccinated) however, all prevalences of atopic disorders were higher in the group of children who reportedly had a past pertussis infection, with the associations for asthma, hay fever, the combination of asthma and hay fever and food allergy being statistically significant. None of these associations changed more than the cut-off value mentioned in the Methods section when we added any of the possible confounders to the logistic model. The univariate odds ratios (OR) with 95% confidence intervals for asthma, hay fever, their combination and food allergy (pertussis infection yes/no) for both groups are shown in Table 3. Our second approach of multivariate modeling yielded similar results (results not shown).

Separate analyses in group I for those who were DTP-IPV-unvaccinated and those who got their vaccination without the pertussis component yielded associations similar to those in the undivided groups (results not shown). Likewise, in group II results were similar for those who received the acellular pertussis vaccination at the age of 4 yr and those who did not.

Subsequently, to explore the effect of an uncertain pertussis history (in 13% of the unvaccinated group) on outcome, we repeated all analyses in this group twice, either assuming that all children with unknown pertussis history

Table 3. Crude odds ratios (OR) for atopic disorders (pertussis infection yes/no) with 95% confidence intervals (CI_{95%}) for the pertussis-unvaccinated and (whole-cell) pertussis-vaccinated group

	Unvaccinated* (n = 622)		Vaccinated† (n = 1033)	
	OR	CI _{95%}	OR	CI _{95%}
Asthma	0.83	0.52–1.34	2.24	1.36–3.70
Hay fever	0.82	0.53–1.27	2.35	1.46–3.77
Asthma and/or hay fever	0.95	0.65–1.40	1.98	1.27–3.10
Eczema	1.20	0.85–1.68	1.02	0.65–1.60
Food allergy‡	1.67	0.86–3.22	2.68	1.48–4.85
Any atopic disorder	1.17	0.85–1.61	1.35	0.88–2.08

*Unvaccinated means: no pertussis vaccination in the first year of life.

†Vaccinated means: at least one (whole-cell) pertussis vaccination in the first year of life.

‡Physician diagnosed.

had had a pertussis infection, or assuming that none of them had a history of pertussis infection. Neither of these sensitivity analyses affected our conclusions. Also, the prevalence of atopy in the group with unknown history of pertussis was similar to that in the group with a known history of pertussis.

Discussion

We found a positive association of reported past pertussis infection with reported airborne allergy and with reported physician diagnosed food allergy, but not with eczema, in a group of pertussis-(and DTP-IPV-)vaccinated children. This association was absent in pertussis-unvaccinated children.

Limitations

Our study has several limitations. First, the data were collected cross-sectionally and we, therefore, cannot establish the sequence of pertussis infection and the onset of atopic symptoms. However, this does not appear to invalidate our conclusions.

Secondly, pertussis infection was reported by the parents and diagnoses were not confirmed by laboratory tests. Also, some parents were uncertain about whether their child had experienced a pertussis infection or not, and this differed between the vaccinated (5%) and the unvaccinated group (13%). This would seem to suggest that this may be due to differences in family size, as families in the unvaccinated group were on average larger and mothers of large families may have poorer recall about the disease history of each of their children. However, family sizes were similar in children with known and unknown

history of pertussis, making this explanation unlikely. Perhaps, as clinical infections were more common in the unvaccinated group, there are also more cases of uncertain pertussis infection. Alternatively, parents of unvaccinated children may be reluctant to admit the occurrence of vaccine preventable diseases. This possible reluctance was, however, equally common in parents of atopic children and non-atopic children. Nevertheless, whatever their explanations, the uncertain histories of pertussis do not impact on our conclusions as reclassifying them as either pertussis or no pertussis did not change our findings.

Comparison of our prevalence of life-time atopy with other studies

We found prevalences of life-time atopic disorders in 8- to 12-yr-old children between 41.5% and 55.4% (Table 2), with an overall prevalence of 46.8%. This apparently somewhat high prevalence agrees well with another study conducted in the Netherlands in 13- to 14-yr-old children in the same year as that of our study (2003) that found a prevalence of life-time atopic disorders of 52.6% using the same data collection instrument (20). Our high prevalence of family history of atopy of around 65% (Table 1) is probably due to the large family size in this population.

Comparison of our life-time prevalences of pertussis with surveillance data

The annual incidence of *B. pertussis* in the Netherlands in 1995–1996 for the age group 3–14 was roughly 5% according to a recent study that estimated annual age-specific incidences from serological data (21). This study could not estimate incidences for children younger than 3 yr. In the present study, we found, for a group of on average 10-yr-old unvaccinated children, a prevalence of reported life-time pertussis of almost 50%. This suggests, assuming an annual serological incidence of 5%, that most infections lead to recognized clinical disease in unvaccinated children. We found a prevalence of reported life-time pertussis of about 9% in the DTP-IPV vaccinated group, much higher than what we would expect from official notification rates. Specifically, from a study on the effect of a booster of acellular pertussis vaccination on the incidence of pertussis in the Netherlands (22), we estimated a life-time prevalence of notified pertussis of about 1.5% in a group of on average 10-yr-old (in 2003) children. While some over-reporting by the parents cannot be excluded, it

would seem plausible that notifications underestimate the true disease burden. This is, *inter alia*, suggested by the large ratio of serological cases to notified cases in the age group 3–14 [about 100 (21)]. Thus, considerable underreporting of clinical cases seems likely. Also, the infection may be circulating much more in this rather secluded, only partly vaccinated population. Therefore, the lifetime prevalence, even among vaccinated individuals, may be higher than that in the – less exposed – general population.

Possible explanations of our findings and comparison of our associations with those in other studies

Our finding of positive associations in vaccinated children is in line with associations found in other studies, but contrasts sharply with the results in our group of pertussis-unvaccinated children. This is puzzling, as in these children, the pathogen has more impact, and one would thus expect, if the relationship is causal, a stronger relationship between infection and atopy in the unprotected group. Also, with a higher prevalence of past pertussis infection in the unvaccinated group, we would expect a higher prevalence of atopic disorders in this group compared with the vaccinated group, but this is not the case (Table 2). This suggests that the effect of pertussis infection on atopy is restricted to pertussis-vaccinated children, an explanation supported by research in a mouse model (23). This study showed that infection with *B. pertussis* induced lung pathology and this induction was stronger after prior pertussis vaccination (both whole-cell and a-cellular). In this mouse model, however, no such differential effect of infection on allergy (total IgE) was shown. There are also simpler, non-causal explanations. First, it is possible that post-vaccination sero-conversion rates, and thus protection levels, are lower in children predisposed to atopic disorders, resulting in a positive, but non-causal association. Evidence for such an explanation appears to be contradictory. Although two studies found that anti-*B. pertussis* IgG levels were similar in atopic and healthy 5-yr-old (24) and in 10-yr-old vaccinated children (25), other studies found a decreased capacity for polyclonal production of both Th1 and Th2 cytokines in atopic neonates (26–28) and infants (29). The latter studies appear to support the hypothesis of decreased sero-conversion in atopic children, as most of the pertussis infections in our 8- to 12-yr-old study population possibly occurred at an age earlier than 5 yr. Secondly, the association between pertussis and atopy in vaccinated children may

be spurious. In unvaccinated children symptoms of pertussis infection are usually serious enough to get a pertussis diagnosis. In vaccinated children however, symptoms are, in general, less serious and specific (22) and if, as was suggested before (17), pertussis is more easily recognized and diagnosed in children predisposed to respiratory morbidity or other atopic disorders, the positive relationships found by several authors may well be due to diagnostic bias. Although one study found an increase in serum IgE 1 yr after pertussis infection, suggesting a causal association (16), the proportion of children evaluated in that study was only about 60% (25 out of the originally 42 included), which may have seriously biased their findings as children without respiratory symptoms may be more likely to withdraw. In summary, evidence for a causal association between pertussis infection and atopic disorders is still inconclusive. Therefore studies that avoid the methodological weaknesses of most studies to date are needed. Specifically a study to assess sero-conversion rates after pertussis vaccination in atopic and non-atopic young children (≤ 1 yr old) is recommended. Atopy could be assessed at a later age (prospective study) or children at risk of atopy could be compared with children not at risk (cross-sectional study). Moreover, a prospective study in vaccinated and unvaccinated children, repeatedly assessing immune responses to pertussis as well as including objective measurements of allergy (positive RASTs or positive skin prick tests) is recommended.

Conclusion

Evidence for a causal association between pertussis infection and atopic disorders is inconclusive. The positive association between *B. pertussis* infection and atopy in pertussis-vaccinated children could be either interpreted as a synergistic effect of pertussis vaccination and *B. pertussis* infection or as due to reverse causation or diagnostic bias. More research is needed to elucidate the underlying mechanism.

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