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Lower risk of atopic disorders in whole cell pertussis-vaccinated children

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ABSTRACT: This study addressed whether whole cell pertussis-vaccinated children have a different risk of atopic disorders compared with children who did not receive this vaccination.

Data on vaccination status, atopic disorders and child and family characteristics of the children of 700 families were collected in this retrospective study. A minority of these 700 families refused vaccinations for religious reasons. The relation between pertussis-vaccination status and atopic disorders was analysed by means of adjusted logistic regression for repeated measurements in order to account for the correlation between sibship members.

The 700 families included 1,961 children. Data on vaccination status and atopic disorders were available for 1,724 children. Vaccinated children had a reduced risk of atopic disorders.

Whole cell pertussis vaccination is associated with a lower risk of atopic disorders, though other vaccine components (diphtheria, tetanus, poliomyelitis) or other vaccinations may also be involved.

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An increased risk of atopic disorders in pertussis or diphtheria tetanus pertussis (DTP) vaccinated children has been reported [1–4], but this was not confirmed by more recent observational studies [5–7], a randomised placebo-controlled trial [8], and an ecological study [9]. Reports of adverse effects of vaccinations usually cause controversy and debate between advocates and opponents of vaccination programmes. The current study evaluated the role of the pertussis vaccination as a risk factor for atopic disorders within a study of family size and birth order as risk factors for asthma, allergy and eczema in a population of 700 families in the Netherlands.

Material and methods

Study subjects

In a study in the Netherlands designed to determine the role of sibship size and birth order as risk factors for asthma, allergy and eczema 700 families with index children born in 1988, 1989 or 1990 were sampled from files administered by the Municipal Health Service covering the municipality of Zwijndrecht, a town with >40,000 inhabitants. A subgroup of these families adhere to the orthodox reformed religion and their children mostly attend orthodox reformed schools. Some of the parents of this group refrain from vaccinations for religious reasons. According to an official schedule in the Netherlands, children receive four vaccinations of DTP (whole cell), Poliomyelitis and *Haemophilus influenzae* type B at aged <1 yr (before 1998 at aged 3, 4, 5 and 11 months), mumps-measles-rubella (MMR) at aged 14 months, a booster of DT-Poliomyelitis at aged 4 and 9 yrs and a booster of MMR at aged 9 yrs. Since 2002 a booster of acellular pertussis is administered at aged 4 yrs.

Study design

This was a retrospective study using datafiles from routine health checkups from birth till adolescence.

Methods

Data on preventive health checkups of index children aged 6 yrs performed by the Municipal Health Service were collected from the files. Data from files of their siblings were also extracted. The following data were used: presence and type of allergy, asthma, eczema, current medication, birth order, sibship size, date of birth, sex, date of checkup, year of birth of the mother, postal code, country of birth of the parents, occupation of the breadwinner, atopic disorders of the parents, vaccination status, and duration of breastfeeding. A child was considered having asthma, allergy or eczema if this was mentioned in the file by the physician who did the checkup, in the questionnaire filled out by the parents or in a letter from a paediatrician/pulmonologist.

Analysis

The independent relation of pertussis-vaccination status with allergy, eczema, asthma and any atopic disorder (allergy, eczema or asthma) was evaluated within families by means of logistic regression for repeated measurements (Generalized Estimating Equations) [10], families being the units of

analysis, which takes correlation between family members into account. Analyses were performed both in univariate and multivariate models with adjustments for the subset of the following variables, which changed the univariate point estimate by at least 10% [11]: sibship size, birth order, year of birth, season of birth, sex, breast feeding for >1 month (yes/no), age at the time of checkup, allergy or asthma of the parents, level of occupation of the bread-winner (five levels), age of the mother at the time of delivery, level of urbanisation (two levels) and country of origin (both parents born in the Netherlands yes/no). A two-sided p-value of 0.05 was considered significant.

Results

The 700 families comprised 1,961 children. Both vaccination status and atopic status was available for 1,724 children; of these 44 (2.6%) were not vaccinated for pertussis, mostly for religious reasons. Of these, 39 had received no vaccinations at all, four received only the polio-vaccination, and one received DT-polio (without pertussis). The 1,724 children had their health checkup at a mean age of 5.9 yrs (SD: 0.6 yrs). The types of allergy mentioned were house-dust mite, pollen, furry pets, food allergy, hay fever and allergic rhinitis. The prevalence of atopic disorders in both groups is shown in table 1. Crude odds ratios (OR)s for atopic disorders (vaccinated/unvaccinated) varied between 0.33–0.69. Adjusted ORs ranged 0.23–0.40, consistent with a substantially reduced risk of atopy in pertussis-vaccinated children. The same analysis in the subgroup of children attending orthodox reformed schools (39 unvaccinated and 128 vaccinated children) yielded similar point estimates. For "any atopic disorder" the adjusted OR (vaccinated/unvaccinated) in this subgroup was 0.16 (95% confidence interval 0.04–0.67, data not shown in table).

Discussion

In the present study, pertussis-vaccinated children were at a considerably lower risk of atopic disorders than unvaccinated children. Most vaccinated children received the combined DTP-polio vaccine. Hence, the comparison of children with and without pertussis vaccination was almost equivalent to the comparison of DTP-polio vaccination and no vaccination at all. Data used for this study were not collected to answer the present research question, and consequently no sample sizes for vaccinated and unvaccinated groups were computed. A total of 44 unvaccinated children were found and the relations studied were significant. Adjustment for confounders could have been a problem with so few children at risk, with resulting empty cells and huge confidence intervals. However, this was not the case and the results of the adjusted analyses showed similar relations. All data were collected retrospectively from files and possibly misreporting, most likely underreporting, of atopic diseases may have occurred. It could be that this misclassification is differential, *i.e.* related to the risk factor under study. This may mean that parents of vaccinated children report less atopy than unvaccinated children. However, the relations found persisted and even became somewhat stronger when the analyses were restricted to the more homogenous group of children attending orthodox reformed schools. Even if within this more homogenous group underreporting would be differential, it would be more likely that parents of unvaccinated children (more orthodox religious families) would report less than parents of vaccinated children. However, this bias would lead to an attenuation of the OR and the unbiased OR would even be more extreme.

In the Netherlands pertussis is endemic in childhood and shows 4-yearly peaks [12]. The highest incidence is reported in infants aged <1 yr (35 per 100,000 per year during 1989–1993). Pertussis cases are reported both in vaccinated and unvaccinated children, the incidence in the latter group being roughly 10-fold the incidence in the vaccinated group. The relatively low incidence in the unvaccinated group (compared to completely unvaccinated groups in Germany) can be explained by herd immunity.

As only 0.7% of the study population was born after 1997, the role of acellular pertussis vaccine is negligible in this study.

Given the hygiene hypothesis, it would be expected that the immune system of the unvaccinated children would have shifted more towards the T-helper cell 1-side, inconsistent with a raised risk of atopy. On the other hand, the immune system of vaccinated children is triggered with the (albeit killed) microorganisms at a very young age and from this point of view the findings of the current study fit in the hygiene hypothesis and are biologically plausible.

The findings of the current study are consistent with a recent study in Germany by GRÜBER *et al.* [7]. Several studies found an increased risk of asthma and allergy in DTP or pertussis-vaccinated children [1–4], but this may be due to residual confounding or confounding by indication as the reasons for not vaccinating are not described and may be related to the outcome. A number of studies found no relation between the DTP or the pertussis-vaccination and atopy [5–9]. One of these is a randomised controlled trial [8], which compared three groups that received different cocktails of DTP with a control group that received DT only. However the age of evaluation at 2.5 yrs was rather young and this may account for the lack of an effect. HENDERSON *et al.* [5] found no difference, but in this study the outcome was wheezing at the age of not more than 42 months. All (but one) studies mentioned above are observational and residual confounding cannot be excluded, especially when the reason for refraining from vaccination is not known. It is important for future studies to include groups that are as homogenous as possible and adequately describe the differences between vaccinated and unvaccinated groups.

Table 1. – Prevalence of atopic disorders among unvaccinated and vaccinated children and crude and adjusted odds ratios (OR)s for atopic disorders (vaccinated/unvaccinated) with 95% confidence intervals (95% CI) for adjusted ORs.

	Allergy	Eczema	Asthma	Any atopic disorder
Unvaccinated %	11.4	13.6	11.4	22.7
Vaccinated %	5.2	4.9	8.7	13.8
Crude OR	0.40	0.33	0.69	0.51
Adjusted OR[#]	0.23	0.26	0.40	0.37
95% CI	0.07–0.79	0.11–0.63	0.10–1.70	0.16–0.87

[#]: Variables included in the multivariate model were for allergy (birth order, family size, year of birth, atopy of the father, age of mother at birth), eczema (birth order, atopy of the father, age of mother at birth), asthma (birth order, family size, year of birth, atopy of the father, age of mother at birth) and any atopy (birth order, family size, atopy of the father, age of mother at birth). n=44 (unvaccinated) and 1,680 (vaccinated).

Conclusion

The results from this study suggest that whole cell pertussis-vaccinated children have a lower risk of atopic disorders.

However, other vaccine components (diphtheria, tetanus, poliomyelitis) or other vaccinations may also play a role.

References

1. Odent MR, Culpin EE, Kimmel T. Pertussis vaccination and asthma: is there a link? *JAMA* 1994; 272: 592–593.
2. Kemp T, Pearce N, Fitzharris P, *et al.* Is infant immunization a risk factor for childhood asthma or allergy? *Epidemiology* 1997; 8: 678–680.
3. Farooqi IS, Hopkin JM. Early childhood infection and atopic disorder. *Thorax* 1998; 53: 927–932.
4. Hurwitz EL, Morgenstern H. Effects of diphtheria-tetanus-pertussis or tetanus vaccination on allergies and allergy-related respiratory symptoms among children and adolescents in the United States. *J Manipulative Physiol Ther* 2000; 23: 81–90.
5. Henderson J, North K, Griffiths M, Harvey I, Golding J. Pertussis vaccination and wheezing illnesses in young children: prospective cohort study. *BMJ* 1999; 318: 1173–1176.
6. DeStefano F, Gu D, Kramarz P, *et al.* Childhood vaccinations and risk of asthma. *Pediatr Infect Dis J* 2002; 21: 498–504.
7. Grüber C, Illi S, Lau S, Nickel R, *et al.* Transient suppression of atopy in early childhood is associated with high vaccination coverage. *Pediatrics* 2003; 111: 282–288.
8. Nilsson L, Kjellman M, Bjorksten B. A randomized controlled trial of the effect of pertussis vaccines on atopic disease. *Arch Pediatr Adolesc* 1998; 152: 734–738.
9. Anderson HR, Poloniecki JD, Strachan DP, *et al.* Immunization and symptoms of atopic disease in children: results from the International Study of Asthma and Allergies in Childhood. *Am J Public Health* 2001; 91: 1126–1129.
10. Diggle PJ, Liang KY, Zeger SL. Analysis of Longitudinal Data. Oxford, Clarendon Press, 1994.
11. Rothman K. Modern Epidemiology. Philadelphia, Lippincott-Raven, 1998: pp. 256–257.
12. de Melker HE, Conyn-van Spaendonck MA, Rumke HC, Sprenger MJ, Schellekens JF. Whooping cough in The Netherlands, 1989–1994. *Ned Tijdschr Geneeskd* 1995; 139: 1280–1286.