

Early BCG and pertussis vaccination and atopic diseases in 5- to 7-year-old preschool children from Augsburg, Germany: Results from the MIRIAM study

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The role of immunization in the development of atopic disorders is still under debate. One reason might be, that because of high vaccination coverage in most countries only few and selected children are not immunized, leading to unstable and often biased effect estimates. In Germany, the situation was different between 1985 and 1991: bacillus Calmette-Guérin (BCG) and pertussis vaccination were not officially recommended leading to high numbers of non-vaccinated children in the 1990s. We report on a cross-sectional study with 1673 participants among 5- to 7-year-old preschool children conducted in 1996. We found no hint that BCG vaccination or whole-cell pertussis (WCP) vaccination may lead to higher prevalences of asthma, allergic rhinitis, eczema or allergic sensitization at preschool age. None of the associations was significantly positive. WCP vaccination may be protective against asthma OR 0.55 (95% CI: 0.31–0.98) and against symptoms of eczema in boys.

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The role of immunization in the development of atopic disorders is still under debate (1–9). One reason might be, that because of high vaccination coverage in most countries only few and selected children are not immunized, leading to unstable and often biased effect estimates. In Germany, the situation was different between 1985 and 1991: bacillus Calmette-Guérin (BCG) and pertussis vaccination were not officially recommended leading to high numbers of non-vaccinated children in the 1990s. Recently, Martignon et al. (11) reported a significant reduced risk to suffer from atopic diseases in adolescents being vaccinated (BCG, diphtheria-tetanus-poliomyelitis, pertussis) in contrast to a small number of non-vaccinated controls and this effect was strongest for atopic eczema and stronger in boys than in girls. We therefore analysed the association

between pertussis, BCG vaccination and atopic diseases combined and stratified by gender in our multi-centric international study for risk-assessment of indoor and outdoor air pollution on allergy and eczema morbidity (MIRIAM) with 1673 participants among 5- to 7-year-old preschool children, which was conducted in 1996 in the city of Augsburg, Germany.

Objectives

To assess the effect of BCG and whole-cell pertussis (WCP) vaccinations on diagnoses and symptoms of atopic disorders (asthma, hay fever and eczema) and allergic sensitization in an unselected cross section of preschool boys and girls.

Materials and methods

The study was performed after approval by the local ethic committee and after obtaining written parental consent. The source population included all 2444 children on admission to school; 1673 children participated which corresponds to 68%.

Data were derived by a parental questionnaire with regard to the performed vaccinations, symptoms and diagnoses of atopic diseases. Vaccinations were additionally recorded as documented in the official vaccination certificate of each participant.

Each participating preschooler underwent a detailed examination of the skin by an experienced dermatologist from the staff of the Department of Dermatology and Allergy Biederstein, Technical University of Munich (actual diagnosed eczema).

Parents were asked whether a physician ever had diagnosed asthma (lifetime asthma), hay-fever (lifetime hay-fever) or eczema (lifetime eczema) in their child. Symptoms of asthma, hay fever and eczema were assessed according to the questions of the International Study of Asthma and Allergies in Childhood (10) [past year wheeze, past year symptoms (hay-fever), past year rash] and sensitizations were determined by a skin prick test (SPT; allergens under survey: pollen of birch, grass, mugwort; alternaria, cat dander, house dust mite, cow milk, hen's egg; 'positive' score with a wheal diameter ≥ 2 mm).

Logistic regression analyses were used to adjust for confounding [sex, age, status (maximal education of either father or mother), passive smoking, nationality, playing predominately outdoors]. The analysis was done for the whole group and for girls and boys separately. The results are presented as adjusted odds ratios (OR) with 95% confidence intervals (CI). Careful adjustment for status was especially necessary because the group of academic parents was over-represented in those children without BCG or WCP vaccination.

Results

Data on BCG vaccination were available from 1496 children and data on WCP vaccination from 1562 children. Most data about vaccinations were taken from the vaccination certificate. Less children from the non-vaccinated groups than from the vaccinated group had their certificate available at the day of investigation (Tables 1 and 2), hinting at a certain recall bias

in those without certificate available. No such differences were visible when restricting the analysis to children of German nationality.

In regard to BCG and WCP, vaccination coverage was fairly low [non-vaccinated participating preschool children in respect to WCP (37%) and BCG (17%)], hereby allowing a reliable estimate of the effects of vaccination.

As shown in Tables 1 and 2, BCG and WCP vaccination were not associated with an increased risk of atopic diseases, symptoms and sensitizations. No decreased risk was associated with BCG vaccination either. WCP vaccination was negatively associated with doctor diagnosed asthma and eczema symptoms. The latter was only visible in boys. Because recall bias in the group of non-German children might be of concern the analysis was repeated in the group of German children only. Only minor changes in the ORs occurred, the associations remained.

Children without WCP vaccination had more pertussis than children vaccinated [24.3% ($n = 571$) compared to 8.3% ($n = 965$)]. When excluding children with pertussis from the analysis, the negative association between WCP vaccination and doctor-diagnosed asthma diminished and was not significant any more (OR 0.70; 95% CI: 0.36–1.33).

Discussion

Recently, Martignon et al. (11) reported a significant reduced risk to suffer from atopic diseases in adolescents being vaccinated (BCG, diphtheria-tetanus-poliomyelitis, pertussis; $n = 694$) in contrast to non-vaccinated controls ($n = 24$) (OR = 0.30; 95% CI: 0.10–0.92). The protective effect was strongest for atopic eczema and stronger in boys than in girls. However, the small number of non-vaccinated participants provides a limitation in any conclusions drawn from this study.

For BCG vaccination, among others, Shirakawa et al. (12), Aaby et al. (13), Grüber et al. (2), Marks et al. (14) and Garcia-Marcos et al. (15) were able to demonstrate a protective effect on the development of atopic disorders.

In contrast, like in our MIRIAM study, many other studies failed to substantiate a positive effect of BCG vaccination on the development of atopic sensitization or atopic eczema (16–20). In our study, there was a tendency for less asthma and wheezing in the group having been vaccinated against BCG (Table 1); however, this association was not significant.

Pertussis vaccine has been available for over 70 yr and WCP vaccines – which were in use for

Table 1. Association of bacillus Calmette-Guérin vaccination with atopy and allergies in boys and girls

	% in non-vaccinated (n)	% in vaccinated (n)	Adjusted OR (95% CI)	Adjusted OR (95% CI) boys	Adjusted OR (95% CI) girls
Vaccination certificate available	86.6 (247)	90.2 (1219)			
Girls	56.1 (253)	50.8 (1243)			
Mean age	6.5 (253)	6.5 (1239)			
Education academic	39.0 (249)	22.7 (1208)			
ETS exposure at home	30.0 (253)	34.8 (1241)			
Nationality – German	78.8 (245)	72.0 (1214)			
Asthma					
Past year wheeze	5.6 (231)	4.2 (1165)	0.53 (0.25–1.12)	0.67 (0.24–1.90)	0.35 (0.11–1.16)
Life-time asthma	4.4 (248)	3.4 (1222)	0.70 (0.33–1.50)	0.46 (0.17–1.29)	0.94 (0.29–3.03)
Allergic rhinitis					
Past year symptoms	4.4 (251)	4.1 (1233)	0.74 (0.35–1.56)	0.84 (0.32–2.22)	0.53 (0.16–1.82)
Life-time hay fever	4.0 (250)	4.7 (1219)	1.04 (0.47–2.27)	0.91 (0.30–2.75)	1.01 (0.33–3.09)
Eczema					
Actual diagnosed	3.6 (250)	5.0 (1230)	1.69 (0.74–3.87)	1.08 (0.30–3.90)	2.18 (0.73–6.51)
Past year rash	3.2 (250)	4.5 (1233)	1.27 (0.57–2.81)	1.01 (0.26–3.86)	1.54 (0.56–4.22)
Life-time eczema	16.5 (248)	12.9 (1221)	0.76 (0.49–1.16)	0.66 (0.34–1.26)	0.84 (0.47–1.50)
Sensitization (SPT)	30.5 (226)	30.9 (1096)	1.10 (0.78–1.56)	1.13 (0.69–1.86)	1.05 (0.65–1.70)

*p < 0.05; SPT, skin prick test; ETS, environmental tobacco smoke.

Table 2. Association of WCP vaccination with atopy and allergies in boys and girls

	% in non-vaccinated	% in vaccinated	Adjusted OR (95% CI)	Adjusted OR (95% CI) boys	Adjusted OR (95% CI) girls
Vaccination certificate available	87.3 (568)	91.9 (964)			
Sex % girls	52.0 (577)	51.5 (985)			
Mean age (Std)	6.5 (574)	6.5 (984)			
Education academic	29.6 (565)	23.9 (951)			
ETS exposure at home	34.0 (576)	34.6 (984)			
Nationality – German	74.1 (562)	73.7 (960)			
Asthma					
Past year wheeze	3.9 (537)	4.7 (921)	1.47 (0.79–2.75)	1.53 (0.71–3.29)	1.48 (0.46–4.76)
Life-time asthma	5.0 (564)	3.0 (970)	0.55 (0.31–0.98)*	0.60 (0.28–1.27)	0.49 (0.20–1.26)
Allergic rhinitis					
Past year symptoms	4.4 (573)	4.5 (979)	1.09 (0.61–1.92)	1.05 (0.53–2.07)	1.10 (0.37–3.28)
Life-time hay fever	3.9 (566)	5.2 (965)	1.13 (0.66–1.94)	0.84 (0.41–1.70)	1.73 (0.71–4.23)
Eczema					
Actual diagnosed	4.8 (569)	4.6 (977)	1.22 (0.69–2.15)	0.90 (0.37–2.16)	1.39 (0.65–3.00)
Past year rash	4.2 (574)	4.3 (977)	1.05 (0.59–1.85)	0.34 (0.13–0.91)*	1.94 (0.89–4.26)
Life-time eczema	13.2 (568)	13.7 (965)	1.20 (0.84–1.70)	0.95 (0.57–1.58)	1.47 (0.89–2.42)
Sensitization (SPT)	31.3 (499)	31.4 (878)	0.99 (0.76–1.27)	0.94 (0.66–1.33)	1.09 (0.74–1.59)

*p < 0.05; SPT, skin prick test; ETS, environmental tobacco smoke.

vaccination of the children in our study – were alleged to be responsible, at least in part, for the increase of atopic disorders worldwide (1, 4).

In this context, Nilsson et al. (3) were able to show only a higher prevalence of positive SPT results in 7-year-old children after an experimental 2-component vaccine administration, which is no longer in use. Interestingly, neither a 5-component nor a WCP vaccine administered in infancy was associated with allergic manifestations in the study population at age 7 (3).

Some observational studies have suggested an increased risk of allergies after pertussis vaccination. Odent et al. (4) found a 5-fold increased

risk of asthma in WCP-vaccinated children at the age of 8 yr in contrast to non-vaccinated. Although no specific symptoms were detected in a group of 23 non-vaccinated children, 23% out of 1011 WCP-vaccinated showed signs of asthma (5). Furthermore, Farooqi et al. (1) described an OR of 1.8 for atopic manifestations among WCP-vaccinated children in contrast to non-vaccinated.

Similar to Martignon et al. (11), we found a protective effect of vaccination with WCP vaccine with regard to asthma and eczema symptoms especially in preschool boys (Table 2). A protective effect has already been demonstrated

in other studies (5,7,21–23). Our results, however, are not consistent: we found a protective effect for ever doctor diagnosed asthma but not for wheezing and we found an effect for skin rash but not for doctor-diagnosed eczema, which might indicate a different time course of the protection. Although our results confirm results of the Martignon study (11), pertussis vaccination may not be an important protective factor but clearly the vaccination was not associated with more allergies. Our results may indicate a protective effect from WCP vaccination with regard to allergic disorders, but the protective effect of WCP vaccination against asthma might be an indirect effect: pertussis vaccination protects from pertussis for which an association with asthma has been demonstrated (25). The data from our study point in that direction, the protective effect of WCP vaccination was diminished after exclusion of children having had pertussis.

A review from the US Institute of Medicine stated that the evidence is inadequate to accept or reject a causal relationship between multiple immunizations and an increased risk of allergic disease, particularly asthma (24).

In conclusion, we found in our MIRIAM study no hint that BCG vaccination or WCP vaccination may lead to higher prevalences of asthma, allergic rhinitis, eczema or allergic sensitization at preschool age. None of the associations was significantly positive. In contrast, there were hints that WCP vaccination may be protective against asthma and against symptoms of eczema in boys.

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