

Is early BCG vaccination associated with less atopic disease? An epidemiological study in German preschool children with different ethnic backgrounds

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We investigated the association of bacille Calmette-Guérin (BCG) vaccination and atopic manifestations among children. Because many children in the study area were from minority ethnic groups, the effect of ethnicity on disease prevalence was also analyzed. A mandatory health survey included all preschool children from Berlin in 1994. Trained medical personnel asked parents whether their child had ever had a diagnosis of atopic dermatitis (AD), bronchial asthma (BA), and hay fever (HF) or symptoms suggestive of these conditions. BCG-vaccination status was recorded from official vaccination documents. Ethnicity of the child was defined by maternal citizenship. We included 38 808 children in our study (20 813 children from former west Berlin), on average aged 6 years. The proportion of children with a foreign family background was 2.1% in East Berlin and 27.5% in West Berlin. BCG vaccination was more common in East Berlin than in West Berlin (94.2% vs. 16.5%) and in West Berlin more common among children with a foreign family background compared with Germans (25.3% vs. 13.2%). The adjusted odds ratio (95% CI) for BA was 0.85 (0.71–1.00) for BCG-vaccinated individuals. BCG vaccination was not significantly associated with AD or HF. Among non-German children, the odds ratios were 0.35 (0.30–0.42) for AD, 0.58 (0.48–0.70) for BA, and 0.72 (0.54–0.92) for HF. The OR for AD among children living in eastern Berlin was 1.19 (1.04–1.36), no significant regional differences were found for BA or HF. This study demonstrated a weak protective effect of BCG vaccination against asthma but a much stronger protective effect of non-German ethnicity against atopic manifestations among preschool children from Germany.

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The prevalence of atopic diseases in children has increased over recent decades in several industrialized countries, for reasons that are not yet fully understood. A shift in the genetic disposition of rather stable populations within a short period of time is unlikely. The view that environmental factors may be responsible for the epidemiological trend is supported by results of recent studies in populations with a similar genetic background but profound lifestyle differences, such as former

West and East Germany, Scandinavia and the Baltic area, or Hong Kong and mainland China. Higher asthma or hay fever rates have been found in areas with a more affluent lifestyle (1–3).

Environmental factors such as differences in indoor climate or outdoor pollution seem to account for only part of the epidemiological trends. Recently, changes in exposure to infectious agents early in life have received more interest as potential modifiers of the course of

allergic disease (4). However, variations in vaccination patterns may also be contributory.

Exposure to mycobacteria results in preferential secretion of Th1-like cytokines (5). Hence, bacille Calmette-Guérin (BCG) vaccination may skew the cytokine microenvironment towards preferential selection of Th1-like cytokines and contribute to a decreased risk of Th2-dependent atopic disease. This hypothesis is supported by data from murine systems in which BCG-infected mice show a cytokine shift towards a Th1-like pattern, and subsequent development of airway allergy is inhibited (6). A recent study in Japanese BCG-vaccinated school children demonstrated an inverse association between purified protein derivative (PPD) skin test reactivity and atopic disease (7). However, two other studies found no statistically significant difference in the prevalence of atopy between Swedish BCG-vaccinated and non-vaccinated children (8,9). There is a need for further large-scale population-based studies on this issue.

Each year in Berlin, all children participate in a standardized health survey prior to school entry. Detailed information is obtained on medical conditions, socioeconomic characteristics, prior vaccinations, and living conditions. We analyzed data of the 1994 sample in order to investigate the association between BCG vaccination and atopic manifestations. Because a large proportion of the children in our study area are non-German, it was also possible to analyze the effect of ethnic background on disease prevalence.

Subjects and methods

The mandatory health survey included all children from Berlin who were due to begin school in 1994. This analysis was based on standardized questionnaire data obtained at screening for school maturity. Data were obtained by specifically trained school physicians. Parents were asked for present or past definitive diagnosis of diseases and/or characteristic symptoms of their children. Additional questionnaire items concerned socioeconomic and living conditions.

Ethnicity of the child was defined by the mother's citizenship. According to official population statistics and a follow-up study in a district with a high percentage of Turkish children the proportion of foreign-born children is small (about 7%). (C. Grüber et al., unpublished data)

BCG vaccination used to be mandatory in former East Berlin. In former West Berlin, BCG vaccination was no longer officially recommended because the tuberculosis prevalence was low and the efficacy of the BCG vaccine was

limited. However, some physicians continued to vaccinate, particularly when the child was considered to be at higher risk of tuberculosis due to frequent travel to countries with higher tuberculosis prevalence.

BCG-vaccination status was recorded on the basis of official vaccination documents, and in rare cases of missing documents the presence of a vaccination scar. BCG vaccination had usually been administered in the neonatal period. Vaccinations were performed with *Mycobacterium bovis* Bacillus Calmette-Guérin (Copenhagen strain 1331). In the former East, 10^5 bacteria of the Gothenburg/Jena substrain were injected intracutaneously, and in the West, 10^5 bacteria of the Behring substrain. We excluded 607 children with a history of PPD skin test conversion or tuberculous disease from the analysis.

Statistical analysis

Chi-squared tests were used to compare proportions between groups. Logistic regression analysis was performed to adjust for potential confounding factors of the association between BCG-vaccination status and the outcome variables (atopic dermatitis, bronchial asthma, hay fever) and to investigate possible interactions. Variables were kept in the regression model if they improved it significantly, based on the likelihood ratio statistics.

Results

The study population consisted of 38 808 children (52.7% male), mean age 6 years. 20 813 children resided in former West Berlin. The proportion of children with a non-German family background was 2.1% in East Berlin and 27.5% in West Berlin ($p < 0.001$). The largest minority were Turkish children (56.8% of the children with a non-German ethnic background).

Of all children, 52.5% had been BCG vaccinated. BCG vaccination was more common in East Berlin than in West Berlin (94.2% vs. 16.5%, $p < 0.001$) and among German children compared with those with a non-German family background (57.6% vs. 25.5%, $p < 0.001$). However, in West Berlin BCG vaccination was less prevalent among German than among non-German children (13.2% vs. 25.3%, $p < 0.001$; East Berlin 95.6% vs. 28.7%, $p < 0.001$).

The overall prevalence rates were 10.9% for atopic dermatitis, 5.0% for asthma, and 1.8% for hay fever. In univariate analysis, BCG-vaccinated children were more likely to be afflicted with atopic dermatitis than non-vaccinated children,

Table 1. Prevalence of atopic diseases in relation to bacille Calmette-Guérin (BCG) vaccination status and sociodemographic characteristics

Variable	(n)	Atopic dermatitis (%)	p	Bronchial asthma (%)	p	Hay fever (%)	p
BCG vaccination							
Yes	(20 383)	12.5		5.0		1.8	
No	(18 425)	9.2	<0.001	5.1	0.713	1.8	0.909
Gender							
Male	(20 437)	10.9		6.1		2.2	
Female	(18 371)	11.0	0.972	3.9	<0.001	1.3	<0.001
Nationality							
German	(32 696)	12.4		5.4		1.9	
Non-German	(6112)	3.3	<0.001	3.0	<0.001	1.4	0.008
Residence							
in former East	(17 995)	13.2		5.2		1.9	
in former West	(20 813)	10.5	<0.001	4.9	0.141	1.7	0.390
Children per household							
One	(11 377)	12.2		5.3		2.0	
Two	(17 968)	11.5		5.1		1.8	
Three	(5743)	9.8		4.9		1.5	
Four	(1846)	7.3		4.8		1.0	
Five or more	(1221)	4.4	<0.001	3.0	0.013	1.5	0.007
Close to busy traffic							
Yes	(3008)	15.3		7.7		2.2	
No	(35 800)	10.6	<0.001	4.8	<0.001	1.8	0.108
Damp apartment/moulds							
Yes	(765)	11.5		10.2		2.6	
No	(38 043)	10.9	0.618	4.9	<0.001	1.8	0.082

whereas no statistically significant differences were found for asthma and hay fever. Non-German children were significantly less likely to have had atopic dermatitis, asthma, and hay fever. The ethnicity of the child was coded as German ($n=33\,163$), Turkish ($n=3569$), or other nationalities ($n=2683$). In these three groups, the prevalence of atopic dermatitis was 12.4%, 2.6%, and 4.2% ($p < 0.001$), of BA 5.4%, 3.1%, and 2.8% ($p < 0.001$), and of hay fever 1.9%, 1.3%, and 1.5% ($p = 0.022$), respectively. Atopic dermatitis was more prevalent among children in East Berlin, no significant regional differences were found for asthma or hay fever (Table 1).

Male gender and living in a damp apartment was associated with higher prevalence of respiratory allergies. A protective effect of more children at home was seen for all three conditions. Living close to busy traffic was associated with higher prevalences of atopic dermatitis and asthma (Table 1).

To adjust for potential confounders (e.g. gender, age, number of children at home, attended day care and traffic) a logistic regression analysis was performed. The adjusted odds ratio for asthma was 0.85 for BCG-vaccinated individuals and the 95% confidence interval just included unity. No interactions were found. BCG vaccination was not significantly associated with atopic dermatitis or hay fever. Foreign ethnicity proved to be highly protective with

regard to all three clinical manifestations of atopy (Table 2). Children living in former East Berlin were more likely to have atopic dermatitis than those in West Berlin (Table 2).

Discussion

The results of this large questionnaire-based study are consistent with a moderate protective effect of routine BCG vaccination against asthma. The finding is in concordance with animal models in which BCG induced a shift of the cytokine microenvironment towards a Th1-like pattern and prevented airway hyper-reactivity (6) and human studies that suggested an inverse association of mycobacterial infection or immunization and asthma or atopy (7,10). Our results were adjusted for important confounders. However, we cannot entirely rule out residual confounding by unknown factors. Differential misclassification of atopic disease with respect to BCG vaccination is unlikely because at the time of the study no possible association between BCG status and atopic disease had yet been proposed as a scientific hypothesis. Non-differential misclassification cannot be ruled out but would have resulted in a dilution of the effect of BCG vaccination on disease prevalences.

The dataset does not firmly support the hypothesis that BCG exposure protects against allergy in general. The point estimate of the

Table 2. Risk for clinical manifestations of atopic disease with respect to bacille Calmette-Guérin (BCG) vaccination, region of residence, and nationality (logistic regression analysis)

Manifestation	Risk factor	Crude OR (95% CI)	p	Adjusted* OR (95% CI)	p
Atopic dermatitis	BCG vaccinated (Baseline: non-vaccinated)	1.33 (1.25–1.43)	<0.001	0.99 (0.87–1.13)	0.92
	Non-German (Baseline: German)	0.24 (0.21–0.28)	<0.001	0.35 (0.30–0.42)	<0.001
	East Berlin (Baseline: West Berlin)	1.55 (1.45–1.65)	<0.001	1.19 (1.04–1.36)	0.01
Bronchial asthma	BCG vaccinated	0.93 (0.85–1.02)	0.15	0.85 (0.71–1.00)	0.05
	Non-German	0.53 (0.48–0.62)	<0.001	0.58 (0.48–0.70)	<0.001
	East Berlin	1.07 (0.98–1.17)	0.15	0.99 (0.82–1.19)	0.89
Hay fever	BCG vaccinated	0.97 (0.83–1.13)	0.70	0.97 (0.73–1.29)	0.82
	Non-German	0.72 (0.58–0.91)	<0.001	0.70 (0.54–0.92)	0.01
	East Berlin	1.07 (0.92–1.24)	0.38	0.94 (0.69–1.25)	0.64

OR, odds ratio; CI, confidence interval. *Adjustment for age, gender, number of children at home, attended day care, and the variables listed in the table.

adjusted odds ratio for asthma in BCG-vaccinated children was 0.85. The data indicate that BCG vaccination may be associated with a 15% reduction of the risk for asthma in school children. This would mean a substantial benefit in population terms. However, because the 95% confidence interval just included unity the findings are also compatible with no effect. Large-scale prospective studies are needed to further clarify this issue.

Scandinavian studies failed to demonstrate a statistically significant protective effect of BCG vaccination among Swedish children (8,9). However, there was a tendency towards lower allergy prevalence among immigrant children born in non-western countries (9). The Japanese study that boosted the discussion of a potential protective effect of Th1-inducing vaccines against allergy included exclusively BCG-vaccinated children and was based on the observation that a positive tuberculin response among the Japanese children predicted a lower incidence of atopic disorders (7). However, the immunological stimulus given by mycobacteria might have been different among Japanese and European children in several respects. The Japanese children received a 10-fold higher dose of a BCG strain that differs biochemically from the strain that was used in our population. The protective effect shown in the Japanese study might be related rather to additional environmental mycobacterial infections that are known to be more common at lower latitudes (11).

In addition to the weak effect of BCG vaccination on asthma, we found a strong protective effect of non-German ethnic background. Geographical studies suggest that ethnicity is an important determinant of atopic disease rates (3). In smaller studies, it has also been found that Turkish children, who form the largest minority

among our study population, were less likely to have asthma and atopic dermatitis (12,13). Currently it is unknown whether this marked protection is due to genetic factors, to a healthy immigrant effect, or to other environmental factors not covered by our instruments. However, the possibility that lifestyle factors play a key role should stimulate further studies of possible preventive determinants that could be adopted by other populations.

The Berlin Wall divided Germany into two states, one with a more affluent westernized lifestyle and another with socialist living conditions, and the fall of the Wall provided a unique situation to study the impact of such differences on allergy. Somewhat surprisingly, we could not demonstrate a systematic protective effect of residence in East Berlin on atopic manifestations. In fact, atopic dermatitis was even more prevalent in the east of the city. Lower prevalence of allergic airway diseases in eastern German than western regions have been shown previously (1,14,15). However, these populations were large distances apart. Two studies investigating time trends suggest that a more traditional lifestyle early in life provides sustained protection against atopic disease (16,17). The population investigated in our study was born shortly before unification. By the time they started school, the transition to a more Westernized lifestyle in East Berlin was already well-advanced. Assuming that directly after unification prevalence of asthma and hay fever in the east may have been lower than in 1994, our finding that respiratory allergies are not lower in East Berlin than in West Berlin does not suggest a sustained protective effect of an early more traditional lifestyle against respiratory allergies. The finding that atopic dermatitis was more prevalent in East Berlin is concordant with an earlier report (15).

In summary, our study results demonstrated that among preschool children early routine BCG vaccination possibly provides a weak protective effect against asthma, but not against hay fever or atopic dermatitis. However, other factors such as ethnicity proved to be a much stronger determinant for all three allergic diseases. Prospective studies are more suitable resolving the issue of BCG immunization and its potential to limit atopy. This retrospective study adds evidence from a large population-based sample that may facilitate future decisions about launching large prospective intervention studies.

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