

BCG Vaccination and Risk of Atopy

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IT HAS BEEN PROPOSED THAT CHILDHOOD exposure to certain infections and vaccinations that induce T_H1-type immune responses may protect against atopic diseases, which are characterized by a T_H2-type cytokine expression.^{1,2} In particular, BCG vaccination has been suggested to have such an effect based on its ability to elicit a strong T_H1-type immune response in humans.³ In support of this theory, routine BCG vaccination has been stopped in most western countries where an increase in allergy has been observed.⁴ Results from the few epidemiologic studies that have addressed the hypothesized association between BCG vaccination and allergic diseases are conflicting⁵⁻⁹ and possibly distorted by selection bias, as they have been carried out in countries where BCG vaccination is either a part of the routine vaccination program or given only to high-risk subjects.

In Greenland, BCG vaccination was given routinely to all infants until 1990, when it was abruptly stopped.¹⁰ This provided a unique opportunity to compare the risk of atopy in unselected groups of children who were either all vaccinated with BCG or all unvaccinated. Furthermore, we obtained infor-

Context It has been suggested that BCG vaccination may protect against development of allergic diseases, particularly when given just after birth. BCG vaccination was given routinely to all infants in Greenland until 1990, when it was withdrawn from the vaccination program. Whether this resulted in an increased prevalence of atopy in children born after the stop of BCG vaccination is unknown.

Objective To determine whether BCG vaccination and age at BCG vaccination are associated with development of atopy.

Design, Setting, and Participants Cross-sectional study among schoolchildren aged 8 to 16 years in 4 towns on the northwest coast of Greenland. Participants had a blood sample drawn and information on BCG vaccination was obtained during 2 periods, November 1998 and November 2001. A total of 1686 children (79% of available children) participated, 1575 of whom had complete information on vaccination status. Atopy was defined as a positive test result in an assay that tests for IgE specific against the most common inhalant allergens in serum.

Main Outcome Measures Odds ratio (OR) of atopy in BCG-vaccinated compared with unvaccinated children and OR according to age at vaccination.

Results The risk of atopy was the same in BCG-vaccinated compared with unvaccinated children after adjustment for confounders (OR, 1.03; 95% confidence interval, 0.72-1.48). The risk of atopy in BCG-vaccinated children was not associated with age at vaccination ($P = .17$).

Conclusions BCG vaccination administered to infants is not associated with reduced risk of development of atopy.

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mation on exact date of BCG vaccination, enabling estimation of the risk of atopy according to age at vaccination.

METHODS

The study was conducted in the towns of Sisimiut, Ilulissat, Aasiaat, and Maniitsoq, located on the northwest coast of Greenland. These towns are similar in the number of inhabitants (3500-5200), climate, infrastructure, and living conditions. In November 1998, all children aged 8 through 16 years in Sisimiut alone were invited to participate. In November 2001, all children aged 9 through 13 years in all 4 towns were invited. The sample was limited to children born in Greenland. The children answered a self-administered questionnaire together with their parents re-

garding sociodemographic variables and had a venous blood sample drawn. Parental place of birth was used as an indicator of ethnicity. Thus, if both the child and his or her parents were born in Greenland, 96% of grandparents were also born in Greenland, making it highly likely that the child was of Inuit origin.¹¹ Children living in Sisimiut who were examined twice were only in-

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cluded at the time of their first blood sample. Ethics committee approval was obtained from the Commission for Scientific Research in Greenland. Written informed consent was obtained from all participating children and their parents.

Venous blood samples were analyzed for total IgE with the Unicap total IgE test (Pharmacia, Copenhagen, Denmark) and for specific IgE with the Phadiatop test (Pharmacia), which is a qualitative (yes/no) assay testing for the 8 most common inhalant allergens (grass, birch, mugwort, dog, cat, horse, *Cladosporium herbarum*, house dust mite) in 1 pool. Children with a positive specific IgE test result were considered atopic.

Information on child's place of birth, parents' place of birth, mother's age at first birth, and birth order was obtained for all children from the Danish Civil Registration System. All inhabitants of Greenland are registered in the system with a unique identification number. Information on birth weight was obtained from birth records.

BCG Vaccination

Until 1990, infants in Greenland received the BCG vaccination once intracutaneously in the deltoid region; all infants received the same dose within a few days after birth. The BCG vaccine administered from 1980 to 1990 (Copenhagen strain No. 1331) has been widely used in many countries around the world. Due to a reduction in incidence of tuberculous meningitis and pulmonary tuberculosis, BCG vaccination was withdrawn from the vaccination program at the beginning of 1990¹⁰ and stopped completely at all hospitals in Greenland during the following year. Due to local outbreaks of tuberculosis, BCG vaccination was introduced again in 1997 to newborns in the routine vaccination program. As an exception, Maniitsoq children who were born from 1990 to 1997 but not vaccinated were all offered vaccination in 1997.

In most towns in Greenland, exact date of BCG vaccination is registered both in vaccination protocols kept at the

health center where the child is born and in hospital records kept at the health center in the town where the child is living. Information on BCG vaccination was primarily obtained from vaccination protocols (77%) available in Sisimiut, Aasiaat, and Maniitsoq. The remaining information was obtained from hospital records (23%).

Statistical Analyses

The odds ratio (OR) for the prevalence of atopy in vaccinated compared with unvaccinated children and the OR for prevalence according to age at vaccination were estimated using logistic regression. To identify variables confounding the association between BCG and atopy, we used the change-in-estimate method,¹² including the background variables presented in TABLE 1 with the categories as presented if a change in the BCG OR of more than 10% was present. Adjustment for age was made using quadratic splines with knots at ages 8, 12, and 16 years. Analyses were carried out using SAS v8.2 (SAS Institute Inc, Cary, NC); $P = .05$ was used to determine statistical significance.

RESULTS

In November 1998, 820 children aged 8 to 16 years (85% of available children) were enrolled and had a blood sample drawn, of whom 789 were born in Greenland. In November 2001, 1139 children aged 8 to 13 years (74% of available children) were enrolled and had a blood sample drawn, of whom 1102 were born in Greenland. A total of 205 children living in Sisimiut had been examined twice and were only included in the study with their first blood sample, resulting in a study group of 1686 children aged 8 to 16 years. Information on BCG vaccination was obtained for 1575 children (93%). Of these 1065 (68%) had been vaccinated, but 3 children had missing information on exact dates of BCG vaccination. A total of 81 children were vaccinated when they were older than 1 year. Of these, 62 (76.5%) lived in Maniitsoq and had been vaccinated as part of the vaccination campaign performed in that town in 1997. The BCG vaccina-

tion coverage before age 1 year was 94% among children born before January 1, 1990, 53% among children born in 1990, and only 2% among children born after January 1, 1991.

Children receiving the BCG vaccine were older than unvaccinated children (Table 1). Furthermore, a higher proportion of the BCG-vaccinated children were examined in 1998 compared with 2001. The number of persons per room in the home differed between BCG-vaccinated and unvaccinated children in univariate analysis but was similar after adjusting for age ($P = .46$). Otherwise, the distribution of background variables was similar in BCG-vaccinated and unvaccinated children.

The adjusted OR for prevalence of atopy according to BCG vaccination and age at BCG vaccination was examined in 2 logistic regression analyses (TABLE 2). In the first, only age was a confounder, whereas in the second, age, year at examination, and birth weight were confounders. The adjusted risk of atopy was the same in BCG-vaccinated compared with unvaccinated children (OR, 1.03; 95% confidence interval [CI], 0.72-1.48). There was no effect modification by geographical site ($P = .23$) or by source of BCG vaccination information (vaccination protocols vs hospital records) ($P = .39$). Furthermore, if children with repeated measurements of atopy ($n = 205$) and children living in Maniitsoq ($n = 176$) were excluded, the overall risk of atopy remained unchanged (OR, 0.94; 95% CI, 0.61-1.47 and OR, 1.00; 95% CI, 0.68-1.47, respectively). There was no effect of age at BCG vaccination on risk of atopy ($P = .17$ for heterogeneity). The data could not be described by a trend.

The OR for atopy in children with missing information on BCG vaccination compared with BCG-vaccinated children was 0.89 (95% CI, 0.51-1.77). In a subanalysis we classified children with missing information on BCG vaccination as either BCG-vaccinated or unvaccinated according to year of birth (children born before 1990 and the first 6 months of 1990 as vaccinated and children born later as unvaccinated).

Table 1. Distribution of Background Variables in BCG-Vaccinated and Unvaccinated Children Aged 8-16 Years and Born in Greenland (N = 1575)

Variable	No. (%)		P Value for Heterogeneity
	BCG-Vaccinated (N = 1065)	Not BCG-Vaccinated (N = 510)	
Age at examination, y			
8	58 (5.4)	67 (13.1)	<.001
9	112 (10.5)	196 (38.4)	
10	124 (11.7)	171 (33.5)	
11	179 (16.8)	39 (7.6)	
12	208 (19.5)	20 (3.9)	
13	178 (16.7)	10 (2.0)	
14	76 (7.1)	7 (1.4)	
15	68 (6.4)	0 (0)	
16	62 (5.8)	0 (0)	
Sex			
Boys	526 (49.4)	254 (49.8)	.88
Girls	539 (50.6)	256 (50.2)	
Town and year of examination			
Sisimiut, 1998	654 (61.4)	75 (14.7)	<.001
Ilulissat, 2001	109 (10.2)	155 (30.4)	
Aasiaat, 2001	105 (9.9)	106 (20.8)	
Sisimiut, 2001	41 (3.9)	154 (30.2)	
Maniitsoq, 2001*	156 (14.6)	20 (3.9)	
Parental place of birth			
Greenland/Greenland	904 (84.9)	431 (84.5)	.14
Greenland/other	84 (7.9)	34 (6.7)	
Other/other	0 (0)	2 (0.4)	
Greenland/unknown	77 (7.2)	43 (8.4)	
Maternal age at first birth, y			
14-19	530 (49.8)	229 (44.9)	.19
20-29	517 (48.5)	272 (53.3)	
≥30	18 (1.7)	9 (1.8)	
Birth order			
1	415 (39.0)	180 (35.3)	.31
2	313 (29.4)	168 (32.9)	
3	184 (17.3)	96 (18.8)	
≥4	153 (14.4)	66 (12.9)	
Birth weight, g			
≤2499	35 (3.3)	21 (4.1)	.85
2500-3499	463 (43.5)	230 (45.1)	
3500-4499	485 (45.5)	220 (43.1)	
≥4500	34 (3.2)	17 (3.3)	
Unknown	48 (4.5)	22 (4.3)	
Maternal education (highest)			
Grades 8-12	152 (14.3)	75 (14.7)	.93
Trade/vocational	678 (63.7)	319 (62.5)	
Undergraduate, graduate	114 (10.7)	52 (10.2)	
Unknown	121 (11.4)	64 (12.5)	
No. of persons per room in home			
<1	135 (12.6)	55 (10.8)	.005†
1 to <2	608 (57.1)	264 (51.8)	
≥2	124 (11.7)	88 (17.3)	
Unknown	198 (18.6)	103 (20.2)	

*Twenty children remained unvaccinated despite Maniitsoq's 1997 vaccination campaign; of these, 10 were not living in Maniitsoq in 1997 and 3 did not live there during all of 1997.

†Possibly explained by differences in age distribution. After adjusting for age using logistic regression there was no difference ($P = .46$).

The overall estimate was unchanged (OR, 1.02; 95% CI, 0.70-1.48).

Total IgE levels did not differ between BCG-vaccinated and unvaccinated children (mean [SD] total IgE level among BCG-vaccinated and unvaccinated children: 233 [681] and 217 [590] kU/L, respectively, $P = .65$).

COMMENT

Based on a large cross-sectional study, we found BCG-vaccinated children to have the same risk of atopy as unvaccinated children. Furthermore, no significant differences in the risk of atopy were found according to age at BCG vaccination. Overall, these results do not support the hypothesis that BCG vaccination has a protective effect on the development of atopy.

Five previous studies have addressed the hypothesis that BCG vaccination protects against allergic diseases by comparing the prevalence of atopy or allergic diseases in BCG-vaccinated and unvaccinated children. Strannegård et al⁵ found no protective effect of BCG vaccination on allergic diseases in Swedish 4- to 9-year-old children, while a nonsignificant effect was observed among foreigners. Similarly, Alm et al⁶ found no association with BCG vaccination and atopy or allergic diseases in 2- to 7-year-old children with atopic heredity. However, a potential protective effect of BCG vaccination may have been masked by the strong genetic predisposition to atopy in the children. Furthermore, in Sweden BCG vaccination is only given to children at high risk of tuberculosis, resulting in a BCG vaccination rate of 4%,¹³ a likely source of selection bias. In a study conducted in Africa, Aaby et al⁷ reported that BCG-vaccinated children had a lower prevalence of atopy compared with unvaccinated children, particularly when the vaccine had been administered in the first week after birth. Grüber et al⁸ found no effect of BCG vaccination given before age 6 months on development of atopy or allergic manifestations at age 7 years in a cohort study; in this study 13% of the children at high risk of tuberculosis were BCG-vaccinated, and

children born outside of Germany were overrepresented in the BCG-vaccinated group. In another cross-sectional German study among preschool children a weak protective effect of BCG vaccination against asthma was observed in German children, whereas a stronger protective effect on atopic manifestations was observed in children of non-German ethnicity.⁹

The strength of our study was its ability to minimize selection bias, as practically all children within a birth cohort were either vaccinated or not vaccinated. By examining children of the same age in 1998 and 2001 we were able to compare the prevalence of atopy in vaccinated and unvaccinated children within the same age group. The 2 examinations were performed in exactly the same manner at the same time of year, and we obtained high participation rates in both years. It could be speculated that an increase in the prevalence of atopy from 1998 to 2001 would bias our results. However, we found the prevalence of atopy according to age to be the same in 1998 and 2001, and we adjusted for year of examination in the analyses. Furthermore, an increase in the prevalence of atopy in the last 3 years would have tended to bias our estimates in favor of a protective effect of BCG vaccination. Our study was further strengthened by measuring atopy objectively in all children, and by obtaining information on BCG vaccination status and exact date of vaccination independently of the outcome for 93% of the children. The fact that the majority of the children were vaccinated just after birth, when the protective effect of BCG on atopy has been suggested to be strongest, reduced the risk of missing a potential protective effect of BCG vaccination, as did the fact that our study was not restricted to children who were genetically predisposed to atopy.

Although our study does not support the hypothesis that vaccination with BCG is capable of preventing the development of atopy, we cannot rule out that the effect of BCG vaccination may be different in populations with other ge-

Table 2. Prevalence of Atopy According to BCG Vaccination and Age at Vaccination in Children Aged 8-16 Years Born in Greenland (N = 1575)

Variable*	Total†	No. of Children With Atopy	Prevalence, %	OR (95% CI)	P Value for Heterogeneity
BCG-vaccinated‡					
Yes	1065	173	16.2	1.03 (0.72-1.48)	
No	510	62	12.2	Reference	
Age at vaccination, d§					
0-1	111	13	11.7	0.76 (0.38-1.52)	.17
2-3	212	38	17.9	1.19 (0.69-2.05)	
4-5	324	65	20.1	1.32 (0.80-2.16)	
6-7	128	23	18.0	1.15 (0.62-2.11)	
8-30	151	23	15.2	1.05 (0.57-1.91)	
31-180	53	3	5.7	0.34 (0.10-1.18)	
≥181	83	8	9.6	0.77 (0.35-1.67)	

Abbreviations: CI, confidence interval; OR, odds ratio.

*All other variables in Table 1 not mentioned in footnotes ‡ and § below were found not to affect the association between BCG and atopy.

†Total numbers of BCG-vaccinated children do not sum to 1065 because 3 children were missing data on exact date of vaccination.

‡Adjusted for age.

§Adjusted for age, year of examination, and birth weight.

netic constitutions.¹⁴ Furthermore, our primary focus was on the effect of early BCG vaccination. Thus, we had limited data regarding children vaccinated at ages outside the general recommendations.

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