

Age at bacille Calmette–Guérin vaccination and risk of allergy and asthma

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Summary

Background It has been proposed that early age at bacille Calmette–Guérin (BCG) vaccination protects against the development of allergy.

Objective To study whether early age at BCG vaccination was associated with a decreased risk of atopy, allergic rhinitis, and asthma compared to BCG vaccination at later ages in childhood.

Methods The occurrence of atopy, allergic rhinitis, and asthma was studied in nearly 2000 women participating in the Danish National Birth Cohort study. Detailed information on age at BCG vaccination (age 0–15 years) was available from school health records. Atopic status was assessed serologically by a specific response to 11 common inhalant allergens using serum samples obtained from the women during the period 1997–2001. Information on allergic rhinitis and asthma was available from telephone interviews.

Results Approximately 85% of the women had been BCG-vaccinated. Age at BCG vaccination was not associated with risk of atopy, allergic rhinitis, or asthma. The odds ratio of atopy, allergic rhinitis, and asthma associated with being vaccinated during the first year of life was 1.05 (95% CI 0.71–1.56), 1.42 (95% CI 0.85–2.36), and 1.71 (95% CI 0.91–3.20), respectively, compared with being vaccinated at the age of 7 years. Adjustment for birth cohort, sibship size, age of the woman's mother at birth, and social class in childhood did not affect the results.

Conclusion Our findings suggest that age at BCG vaccination in childhood does not influence the development of allergy or asthma.

Keywords allergic rhinitis, allergy, asthma, atopy, BCG vaccination, epidemiology, risk factors

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Introduction

The prevalence of atopy [1, 2], allergic rhinitis [3–5], asthma [5, 6], and eczema [3, 5, 7] has increased in recent decades in many countries. The reasons for this increase are not fully understood, and it is evident that only a minor part of it can be ascribed to changes in genetic predisposition and diagnostic criteria [8, 9]. It has been proposed that changes in lifestyle with increasing industrialization have led to the loss of environmental factors that protected children from developing allergic disease [10, 11]. In this context, research has focused on the influence of childhood infections [12, 13] and of historical and present vaccinations [14] on allergy. In particular, it has been hypothesized that the past use of bacille Calmette–Guérin (BCG) vaccination was a factor that could have decreased the risk of developing allergy, and especially if it had been given early in life. This hypothesis is supported by several experimental studies suggesting that BCG vaccination or administration of mycobacterial antigens improves atopic dermatitis in children and inhibits immunoglobulin E (IgE)-mediated allergic sensitization and airway reactivity in animal models [15–17]. The hypothesis that tuberculosis (TB)

infection might have a similar effect is supported by findings in several countries of an inverse association between TB notification rates and allergic disease [18]. In addition, immunological studies have shown that BCG vaccination very early in life is capable of stimulating strong Th1 (T helper 1)-type immune responses [19, 20]. Immune reactions to BCG vaccine could help stabilize a natural balance between a Th1- and a Th2-type immunity, which is then not skewed towards the Th2-type that mediates allergic responses [21, 22]. BCG vaccination in childhood has even been suggested as a novel vaccine strategy against allergic disease [23, 24].

Despite the amount of experimental evidence in support of this hypothesis, few epidemiological studies have investigated the influence of early BCG vaccination on allergy [25–30]. We therefore aimed to study whether early age at BCG vaccination was associated with a decreased risk of atopy, allergic rhinitis, and asthma compared with BCG vaccination at later ages in childhood by using school health records from Copenhagen with detailed information on BCG vaccination.

Materials and methods

The Danish National Birth Cohort

The investigation was based on an ongoing nationwide Danish cohort study of pregnant women (The Danish

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National Birth Cohort) [31]. The Danish National Birth Cohort has consecutively recruited 100 000 pregnant women from 1997 to 2002. Pregnant women were invited to participate when they visited their general practitioner for the first time during pregnancy. All women who spoke Danish and intended to carry their pregnancy to term were eligible.

Ethics

Before initiation, the Danish National Birth Cohort was approved by the Danish Scientific Ethical Committees and the Danish Data Protection Agency, and all participants gave written informed consent. This particular study was furthermore approved by the Scientific Ethical Committee for Copenhagen and Frederiksberg, the Danish Data Protection Agency, the Steering Committee for the Danish National Birth Cohort, and the Municipality of Copenhagen.

Study population

Women who participated in the Danish National Birth Cohort during the period of September 1997 to October 2001 were eligible for inclusion in the present study. Furthermore, they had to have attended primary school in Copenhagen (the capital of Denmark) and to have their school health record identified in the Archives for School Health Records from the municipality of Copenhagen. The entire cohort of pregnant women ($n = 82\,257$) from all of Denmark was linked via the unique personal identification number assigned to all Danish residents with a database registering the school health records from Copenhagen belonging to persons born before 1978. Overall, 2269 women were identified based on this linkage. Since information on vaccination had not been computerized previously, the school health records were searched manually in the archive, and 2224 (98%) of the women were found using information on date of birth, maiden and present name, as well as the personal identification number often presented on the record.

Exposure data

The Danish TB Eradication Programme started in the 1930s. At the beginning, infants and children living in a TB contagious environment, and also adults at special risk of TB exposure were vaccinated. The target groups were expanded several times. During the period 1946–1989, which includes the birth period of the present study population (1953–1977), a school law dictated that all Danish children in primary school with a negative tuberculin test should be offered BCG vaccination free of charge. A routine BCG vaccination of the total Danish population has, however, never taken place and the vaccination has always been voluntary.

The Archives for School Health Records contains information from regular, mostly annual, health examinations of children who attended school in the municipality of Copenhagen between 1930 and 1990, as described elsewhere [32]. Detailed information about BCG vaccination had been obtained from vaccination cards presented at school entry (average age: 7 years). In general, all children in Denmark possess a standardized vaccination card where all vaccinations are recorded at the time they are given. Information on

BCG vaccination at school entry and during school years (age 7–15 years) was recorded on the school health records by the school physician. A total of 2185 (98%) women had information on BCG vaccination available on their records; the remaining women were excluded from the study. The time of vaccination was recorded either as the exact date (94%), the month and year (3%), the year (1%), or as 'yes' (2%). Since BCG vaccination was voluntary, the record also provided spaces for noting whether or not the parents would permit BCG vaccination if a tuberculin test turned out to be negative.

Information on sibship size at school entry and age of the woman's mother at birth was available from the school health records or could be obtained from the Civil Registration System. Social class (I–V) in childhood was derived from the father's occupation recorded on the school health records at school entry [33]. Nine women were excluded because of missing information on sibship size, leaving 2176 women in the study.

Atopy

The atopic status of the women was determined by serologic analyses. We used serum samples obtained around gestational weeks 6–12 (95.5%) or around gestational week 24 (4.5%) as part of the Danish National Birth Cohort study. Sera were available for 1956 of the 2176 women (90%). The sera were stored at -30°C . Sera were analysed for specific IgE against 11 common inhalant allergens using the Phadiatop Unicap[®] test (Pharmacia, Copenhagen, Denmark), which tests for all allergens in one pool (horse, dog, cat, grass (*Phleum pratense*), birch (*Betula verrucosa*), olive (*Olea europaea*), dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), herbs (*Artemisia vulgaris* and *Parietaria officinalis*), and mould fungus (*Cladosporium herbarum*)). Women with specific IgE levels ≥ 0.35 kU/L were classified as atopic [34].

Asthma and allergic rhinitis

Information on allergic rhinitis and asthma was obtained from the women using telephone interviews performed around gestational week 12 and was available for 1925 (88%) of the 2176 women in the study. All women were asked if they had ever had allergy and, if so, whether a physician had diagnosed it. Women who answered in the affirmative were asked further questions as to what kind of allergy they had. Women who reported allergic rhinitis and/or hayfever were considered to be cases of allergic rhinitis. All women were also asked if they had ever had asthma and, if so, whether a physician had diagnosed it. Those who responded in the affirmative were considered to be cases of asthma.

Statistical analyses

All risk ratios were calculated as odds ratios (ORs) using logistic regression. We assessed the independent effect of age at BCG vaccination on risk of atopy, allergic rhinitis, and asthma among vaccinated women.

In an additional analysis, unvaccinated women whose parents had not refused BCG vaccination were used as a reference group when assessing the independent effect on risk of atopy, allergic rhinitis, and asthma of BCG vaccination

administered at the age of 0–15 years. This reference group consisted of 61% unvaccinated women whose parents had permitted BCG vaccination and 39% unvaccinated women whose parents had not been asked whether or not they would permit BCG vaccination. This group was chosen as the preferable reference group since it was less likely to contain women whose parents had refused BCG vaccination because of diseases such as atopic dermatitis or other allergic conditions.

All analyses were done with and without adjustment for potential confounding by birth cohort (1953–1960, 1961–1963, 1964–1966, 1967–1969, 1970–1972, 1973–1977), sibship size (1, 2, 3, 4+), age of the woman's mother at birth (≤ 20 , 21–24, 25–29, 30–34, ≥ 35 years, missing), and social class (I, II, III, IV, V, missing). None of these variables were significantly associated with the three outcomes, but they were chosen as adjustment variables because they have previously been associated with atopy, allergic rhinitis, or asthma, and may also be associated with vaccination coverage. Variables entered into the logistic model were treated as categorical variables. *P*-values were based on likelihood ratio tests, and 95% confidence intervals (CIs) were based on Wald's test. The statistical software program SAS version 6.12 was used for the analyses (SAS Institute Inc., Cary, NC, USA) [35].

Results

Among the 1956 women for whom sera were available, 1653 (85%) had been BCG-vaccinated and 551 (28.2%) were classified as atopic. Of the 1925 women for whom information on allergic rhinitis and asthma was available, 1622 (84%)

had been BCG-vaccinated, 265 (13.5%) had allergic rhinitis, and 164 (8.5%) were cases of asthma. The women were between 21 and 46 years old with an average age of 31 years (standard deviation: 4 years).

Table 1 shows the risk of atopy according to the history of BCG vaccination in childhood. There was no association between age at BCG vaccination and risk of atopy. The OR of atopy associated with being vaccinated at age 0–7 days was 0.83 (95% CI 0.38–1.85), at age 8 days–1 month 1.33 (95% CI 0.67–2.65), at age 2–5 months 1.28 (95% CI 0.47–3.51), and at age 6–11 months 0.96 (95% CI 0.53–1.74) compared with being vaccinated at age 7 years; overall, the OR of atopy associated with BCG vaccination during the first year of life was 1.05 (95% CI 0.71–1.56).

Overall, BCG vaccination was not associated with the risk of atopy (OR = 0.80 (95% CI 0.53–1.21)) compared with unvaccinated women whose parents had not refused BCG vaccination (see the footnote in Table 1). The corresponding OR of atopy for unvaccinated women whose parents had refused BCG vaccination was 1.30 (95% CI 0.79–2.14).

Table 2 shows the risk of allergic rhinitis and asthma according to the history of BCG vaccination in childhood. Age at BCG vaccination was not associated with risk of allergic rhinitis or asthma. The OR of allergic rhinitis and asthma associated with being vaccinated during the first year of life was 1.42 (95% CI 0.85–2.36) and 1.71 (95% CI 0.91–3.20), respectively, compared with being vaccinated at 7 year of age.

Overall, BCG vaccination during childhood was not associated with risk of allergic rhinitis (OR = 0.81 (95% CI 0.48–1.40)) compared with unvaccinated women whose parents had not refused BCG vaccination (see the footnote in Table 2). The corresponding OR of allergic rhinitis for

Table 1. Risk of atopy according to age at BCG vaccination in childhood

		Atopy*	
		OR (95% CI)	Adjusted OR† (95% CI)
Cases/all (%)			
BCG vaccination			
Yes‡			
Age			
0–7 d	9/36 (25.0)	0.83 (0.38–1.79)	0.83 (0.38–1.85)
8 d–1 mth	14/39 (35.9)	1.39 (0.71–2.73)	1.33 (0.67–2.65)
2–5 mth	6/18 (33.3)	1.24 (0.46–3.36)	1.28 (0.47–3.51)
6–11 mth	17/59 (28.8)	1.01 (0.56–1.81)	0.96 (0.53–1.74)
1 y	10/37 (27.0)	0.92 (0.44–1.94)	0.91 (0.43–1.93)
2 y	15/45 (33.3)	1.24 (0.65–2.36)	1.30 (0.67–2.51)
3–4 y	17/69 (24.6)	0.81 (0.46–1.44)	0.78 (0.43–1.39)
5–6 y	53/228 (23.2)	0.75 (0.53–1.07)	0.72 (0.51–1.03)
7 y	206/718 (28.7)	1 (reference)	1 (reference)
8 y	56/241 (23.2)	0.75 (0.54–1.06)	0.75 (0.53–1.06)
9–15 y	32/128 (25.0)	0.83 (0.54–1.28)	0.83 (0.53–1.28)
Unspecified¶	11/35 (31.4)	1.14 (0.55–2.37)	1.20 (0.57–2.52)

P = 0.60§

OR, odds ratio; CI, confidence interval; d, day(s); mth, month(s); y, year(s).

*Atopy was defined as a specific IgE level > 0.35 kU/L. †Adjusted for birth cohort, sibship size, age of the woman's mother at birth, and social class in childhood.

‡The adjusted OR of atopy for BCG-vaccinated women was 0.80 (95% CI 0.53–1.21, cases/all = 446/1653) compared with unvaccinated women whose parents had not refused to let them be BCG-vaccinated (cases/all = 38/124); the adjusted OR of atopy for unvaccinated women whose parents had refused BCG vaccination was 1.30 (95% CI 0.79–2.14, cases/all = 67/179). §*P*-value for a homogeneity test, whereby we test for a differential effect of vaccination at different ages within the age span 0–15 y. ¶Positive history of BCG vaccination, but the age at vaccination was not specified.

Table 2. Risk of allergic rhinitis and asthma according to age at BCG vaccination in childhood

	Allergic rhinitis			Asthma		
	Cases/all (%)	OR (95% CI)	Adjusted OR* (95% CI)	Cases/all (%)	OR (95% CI)	Adjusted OR* (95% CI)
<i>BCG vaccination</i>						
Yes†						
Age (years)						
0	24/144 (16.7)	1.35 (0.82–2.20)	1.42 (0.85–2.36)	15/144 (10.4)	1.61 (0.87–2.95)	1.71 (0.91–3.20)
1–2	11/82 (13.4)	1.04 (0.53–2.04)	1.08 (0.55–2.14)	7/82 (8.5)	1.29 (0.56–2.95)	1.33 (0.57–3.09)
3–6	36/291 (12.4)	0.95 (0.63–1.43)	0.91 (0.60–1.39)	23/291 (7.9)	1.19 (0.71–1.99)	1.09 (0.64–1.84)
7	92/711 (12.9)	1 (reference)	1 (reference)	48/711 (6.8)	1 (reference)	1 (reference)
8–15	42/365 (11.5)	0.87 (0.59–1.29)	0.89 (0.60–1.32)	25/365 (6.8)	1.02 (1.62–1.68)	0.96 (0.58–1.61)
Unspecified§	5/29 (17.2)	1.40 (0.52–3.77)	1.64 (0.60–4.48)	7/29 (24.1)	4.39 (1.79–10.8)	4.35 (1.72–11.0)

OR, odds ratio; CI, confidence interval.

*Adjusted for birth cohort, sibship size, age of the woman's mother at birth, and social class in childhood. †The adjusted OR of allergic rhinitis for BCG-vaccinated women was 0.81 (95% CI 0.48–1.40, cases/all = 210/1622) compared with unvaccinated women whose parents had not refused to let them be BCG-vaccinated (cases/all = 18/121); the adjusted OR of allergic rhinitis for unvaccinated women whose parents had refused BCG vaccination was 1.40 (95% CI 0.74–2.63, cases/all = 37/182). The adjusted OR of asthma for BCG vaccinated women was 0.53 (95% CI 0.30–0.95, cases/all = 125/1622) compared with unvaccinated women whose parents had not refused to let them be BCG-vaccinated (cases/all = 16/121); the adjusted OR of asthma for unvaccinated women whose parents had refused BCG vaccination was 0.98 (95% CI 0.49–1.98, cases/all = 23/182). ‡P-value for a homogeneity test, whereby we test for a differential effect of vaccination at different ages within the age span 0–15 y. §Positive history of BCG vaccination, but the age at vaccination was not specified.

unvaccinated women whose parents had refused BCG vaccination was 1.40 (95% CI 0.74–2.63). Childhood BCG vaccination was associated with an OR of asthma of 0.53 (95% CI 0.30–0.95) compared with unvaccinated women whose parents had not refused BCG vaccination. The corresponding OR for asthma for unvaccinated women whose parents had refused BCG vaccination was 0.98 (95% CI 0.49–1.98). When additional adjustment for smallpox and whole-cell pertussis vaccination was carried out, childhood BCG vaccination was associated with an OR of asthma of 0.61 (95% CI 0.33–1.11) compared with unvaccinated women whose parents had not refused BCG vaccination.

Additionally adjusting the other presented estimates for smallpox and/or whole-cell pertussis vaccination had a marginal effect on the results (data not shown).

Discussion

The hypothesis that vaccination against TB or other exposure to mycobacteria could protect against allergy originates from a Japanese study on BCG-vaccinated children [36]. The authors reported that BCG-vaccinated children who responded to tuberculin skin testing were less likely to be atopic or to have atopic symptoms, and the authors suggested that this was caused by the BCG vaccination. The study has, however, been subject to critique because of the possibility of reverse causation. In addition, other studies on BCG-vaccinated children have not been able to reproduce the Japanese findings on atopy or allergic disease [37–41].

As BCG vaccination is a strong inducer of Th1 cytokine responses, even early in life [19, 20], and experimentally is capable of inhibiting allergic symptoms, the hypothesis was further examined under the assumption that a potential

protective effect comes from early age at BCG vaccination. All previous studies on BCG vaccination and allergy except one [30] have been limited to investigating the potential effect of vaccination *in infancy* [25–29], and Strannegard et al. [30] did not report on age at vaccination. Most studies have reported no association between BCG vaccination and allergy [26–29], while one found a protective effect of BCG vaccination very early in infancy [25]. One of these previous studies examined atopy and allergic diseases at age 0–7 years in Swedish children with atopic heredity and found no protective effect of infant BCG vaccination [26]. Another Swedish study, but based on an unselected material, examined parent-reported current allergy at age 4–9 years and found a non-significant protective effect of *previous* BCG vaccination, but only among immigrant children [30]. A third study, which examined the development of atopy and allergic diseases at age 0–7 years, found no persistent protective effect of infant BCG vaccination in a German cohort of 774 children [27]. Another German study of more than 38 000 pre-school children reported no association between neonatal BCG vaccination and a parent-reported history of hayfever or atopic dermatitis and a weak borderline significant protective effect on asthma [28]. A recent study of 1575 school children from Greenland who were born just before and after routine BCG vaccination in infancy was stopped did not find a reduced risk of atopy among those who were BCG-vaccinated in infancy overall or at specific age intervals during infancy [29]. Finally, a study of 400 African 3–14-year-olds reported a protective effect on atopy of BCG vaccination early in infancy and especially from vaccination within the first week [25].

In the present study, we did not find an association between age at BCG vaccination in childhood and risk of atopy, allergic rhinitis, or asthma among vaccinated women. Our study did not specifically focus on BCG vaccination in infancy as other studies have done since most vaccinations

took place at school entry, although vaccination at other ages also occurred. We did not have specific information on why some children had been vaccinated *before* school entry, and it cannot be excluded that bias could have occurred. Some of the children may have been vaccinated because they came into contact with institutions where vaccination was performed routinely at early ages. Others may have been vaccinated because they belonged to a high-risk group, e.g. due to TB in the family. Early exposure to TB would, however, according to the proposed hypothesis in the same way as BCG vaccination, have been expected to stimulate the immune system in a non-allergic direction. In addition, we were able to adjust for potential confounding by factors such as birth cohort, social class in childhood, maternal age, and sibship size. This, however, did not influence the results.

In an additional analysis, we compared BCG-vaccinated women with unvaccinated women whose parents had not refused to let them be BCG-vaccinated, and did not find an association between BCG vaccination and atopy or allergic rhinitis. BCG vaccination was, however, associated with a decreased risk of asthma, although the association was no longer significant after adjusting for smallpox and whole-cell pertussis vaccination. As BCG vaccination was optional, it is not clear what characterized children who had been vaccinated compared with those who had not been vaccinated, and bias of the results from this additional analysis cannot be ruled out. In the analyses, we tried to reduce bias by using unvaccinated women whose parents had not refused to let them be BCG-vaccinated as the reference group, since unvaccinated women whose parents had refused to let them be vaccinated could have done so specifically due to allergic conditions.

The present study has the advantage that information on BCG vaccination was obtained in a uniform manner prior to and independently of the blood samples and of the self-reported information on allergic rhinitis and asthma. Furthermore, atopy was measured objectively by serological testing. Bias from self-reporting was reduced by using questions on *physician-diagnosed* conditions, which have been found to be suitable for risk-factor studies because of their good specificity and positive predictive value [42]. Finally, we were able to adjust for birth cohort, social class in childhood, maternal age, and sibship size, but we can, however, not exclude that other factors previously related to allergy and/or asthma such as smoking habits, breastfeeding, birth weight, and gestational age could influence the results.

In conclusion, our findings suggest that age at BCG vaccination in childhood does not influence the development of allergy or asthma.

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