

BCG Immunization at Birth and Atopic Diseases in a Homogeneous Population of Spanish Schoolchildren

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Key Words

BCG · Asthma · Hay fever · Atopic dermatitis · Schoolchildren · Spain

Abstract

Background: The role of immunization with bacillus Calmette-Guérin (BCG) in the prevalence of asthma, hay fever and atopic dermatitis is not definitely established and seems to be influenced by ethnic background. The aim of this study was to analyze the relationship between this immunization and the prevalence of those diseases in a homogeneous population of Spanish schoolchildren. **Methods:** The International Study of Asthma and Allergies in Childhood (ISAAC) core and environmental questionnaires were used in four different centers of the Spanish North Atlantic coast. Bilbao, San Sebastián and Asturias have a universal BCG immunization policy dur-

ing the first days of life, whereas La Coruña discontinued this practice in 1989. Except for this center, immunization coverage was above 90%. A random sample of schools of Asturias or all schools in the city district (rest of centers) with children 6 and 7 years old was surveyed. **Results:** The participation rate was above 70%. After excluding those children born outside Spain, the numbers were 6,762 immunized and 2,828 nonimmunized. After adjusting for gender, age, smoking habits of the father and mother, truck traffic near the household, older and younger siblings and having a cat or a dog during the first year of the child's life, the adjusted ORs of the BCG-immunized children suffering from asthma, hay fever and atopic dermatitis were respectively 0.87 (95% CI 0.76–1.00), 0.87 (0.75–1.01) and 0.89 (0.76–1.05). **Conclusions:** BCG immunization offers a weak but significant protection against asthma and hay fever in Spanish schoolchildren.

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Introduction

The hygiene hypothesis, which tries to explain the increase in the prevalence of asthma in western countries during the past decades, stresses the inverse relationships between the aseptic environment and the prevalence of asthma and allergic diseases. One of the reports that generated this hypothesis was that by Shirakawa et al. [1], who demonstrated an inverse relationship in Japanese schoolchildren between exposure to mycobacteria, size of the tuberculin response and subsequent development of atopy [1]. This relationship was explained from the immunological point of view by a shift towards a Th1 response – as opposed to a Th2 one – which is favored by contact with bacteria. In this context, some groups investigated the relationship between childhood immunization and the prevalence of those conditions. Immunization with the Calmette-Guérin bacillus (BCG) has attracted great attention as the BCG is able to elicit an important Th1 response and to influence its regulatory function in experimental animals [2–4] and in both healthy [5, 6] and asthmatic adults [7, 8] and schoolchildren [9]. In contrast to what was expected, most of the epidemiological studies, performed mainly in central and northern European countries as well as in Australia, show no effect of BCG immunization on the prevalence of asthma or atopy either when the vaccine is taken early in life [10–14] or when it is administered during adolescence [15, 16]. However, there seems to be a different result when the studied population originates from a different ethnic background: some investigations have shown that BCG immunization could in fact offer some protection in some immigrant populations [14, 17] in western countries or in less developed countries such as Guinea-Bissau [18].

The only study showing a somewhat protective effect of BCG immunization on asthma in a western country is the large German study by Gruber et al. [17] which found a weak but statistically significant protective effect of this immunization on asthma but not on hay fever or atopic dermatitis. This study surveyed children from East and West Germany. The fact that the children from the East had much higher immunization rates could have affected the results, as at the time of the study West and East German lifestyles were not totally comparable. Although controlling for the East-West effect in the logistic regression, it could be difficult to differentiate between the lifestyle effect and the BCG effect.

Three of the phase III centers of the Spanish International Study of Asthma and Allergies in Childhood

(ISAAC) are still using BCG immunization during the neonatal period, whereas another center on this coast (La Coruña) discontinued this immunization in 1989: we took advantage of this unique circumstance. These centers are all located on the northern coast of the country. The environmental conditions are quite comparable: all centers have a total yearly rainfall of between 1,000 and 1,600 ml, a mean maximum and minimum temperature range of between 23 and 27°C and between 5 and 8°C. The cities are fairly similar in size, ranging from 180,000 to 350,000 inhabitants. None of the centers is currently very polluted apart from vehicle traffic which is as intense as in all Spanish cities of this size. The genetic background of the population [19–22] is also very similar in the four centers. Therefore we are in a very good position to add some interesting information about the effect of BCG immunization on the prevalence of asthma, hay fever and atopic dermatitis in a homogeneous southern European population.

Material and Methods

The Spanish version of the ISAAC phase III questionnaire was addressed to parents of children 6 and 7 years old in four centers: three cities (Bilbao, San Sebastian, and La Coruña) and one province (Asturias) of the North Atlantic coast of Spain. The three cities included all schools within the city district. Asturias included a random sample of schools. The main part of the study was carried out in 2002.

Among those ISAAC centers, at the time children included in the study were born, three had a universal newborn BCG immunization policy (Bilbao, San Sebastián and Asturias); the fourth discontinued this policy in 1989. The immunization was carried out with 10^5 bacteria of *Mycobacterium bovis* BCG (Copenhagen strain 1331, Pharmacia Upjohn). The immunization coverage for the years 1995 and 1996 (when the children were born) was respectively 92 and 95% for Bilbao, 97 and 96% for San Sebastián and 94 and 97% for Asturias.

The ISAAC phase III questionnaire included three core questionnaires on symptoms of asthma, hay fever and atopic dermatitis. Additionally, a fourth questionnaire on environmental risk factors was included in this phase.

We defined having asthma as a positive answer to the question: 'Has your child had wheezing or whistling in the chest during the last 12 months?' We considered that a child had hay fever when the mother or father answered the following two questions positively: 'In the past 12 months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she did not have a cold or the flu?' and 'In the past 12 months, has this nose problem been accompanied by itchy watery eyes?' Atopic dermatitis was defined as an affirmative answer to each and every one of these three questions: 'Has your child ever had an itchy rash which was coming and going for at least six months?' 'Has your child had this itchy rash at any time in the past 12 months?' and 'Has this itchy rash at any

Table 1. Number of participants, participation rate and exclusions due to birth outside Spain in each center

Center	Targeted children	Participating children	Participation rate %	Born outside Spain	Included in the analysis
Asturias	3,698	3,197	86.5	241	2,956
Bilbao	4,082	3,185	78.0	257	2,928
San Sebastián	1,495	926	61.9	48	878
Total BCG immunized	9,275	7,308	75.5	546	6,762
La Coruña, not immunized	4,088	3,017	73.8	289	2,828

Table 2. Prevalence of asthma, hay fever and atopic dermatitis in each individual center

	Asthma	Hay fever	Atopic dermatitis
Bilbao	12.3	9.0	7.9
Asturias	11.4	10.4	7.3
San Sebastián	8.5	7.1	9.0
La Coruña	12.9	10.6	8.7

time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?

Every child from Bilbao, San Sebastian or Asturias was considered to be immunized with BCG. As not every child was actually immunized, the error would deviate the results to the null hypothesis, thus further challenging the protective effect of immunization. On the contrary, all children from La Coruña were considered not to be immunized. The number of children affected by asthma, hay fever or atopic dermatitis by each risk factor was compared by means of the χ^2 test. Logistic regression analysis was used to calculate the odds ratio (OR) and the adjusted OR (aOR) for suffering from any of these diseases when risk/protective factors were present (Intercooled Stata 7.0, College Station, Tex., USA). The following factors were entered in the logistic regression: gender, age (years), older siblings (yes/no), younger siblings (yes/no), current maternal smoking (yes/no), current paternal smoking (yes/no), presence of cat in the household during the first year of the child's life (yes/no), presence of a dog in the household during the first year of the child's life (yes/no), mother with university studies (yes/no), and truck traffic on the street where the child lived (never, seldom, frequently through the day, almost the whole day).

Results

The number of immunized children was 7,308, whereas the number of nonimmunized children was 3,017. After excluding those children born outside Spain, these

figures were 6,762 and 2,828, respectively. The participation rate was well above 70% in both groups (table 1). The prevalence of asthma, hay fever and atopic dermatitis is shown in table 2.

In the univariate analysis, the prevalence of asthma and hay fever was lower in the immunized group, reaching statistical significance for asthma. Other factors significantly related to a lower prevalence of asthma were: female gender, having a nonsmoker mother or father and a mother with university studies. There was a significant trend for a higher asthma prevalence with increasing truck traffic on the street where the child lived. The factors associated with a lower prevalence of hay fever were quite similar to the aforementioned. The only factor associated with an increased risk of atopic dermatitis was truck traffic, but the trend was not as clear as in the case of asthma and hay fever (table 3).

The aOR and OR of the different factors included in this study are shown in table 4. The ORs were quite consistent and those which were statistically significant before adjustment remained so afterwards. The only clear protective factor for asthma was BCG immunization. Having at least one younger sibling and a mother with university studies were also protective factors which, after adjustment, did not reach full statistical significance. On the other hand, there were some clear risk factors such as male gender, current maternal smoking and truck traffic. The protective and risk factors for hay fever were very similar to those found for asthma. With the exception of very heavy truck traffic, no other risk factor was associated with atopic dermatitis.

A summary of the risk and protective factors of asthma, hay fever and atopic dermatitis is shown in figure 1.

Table 3. Number of children, prevalence of asthma, hay fever and atopic dermatitis by each factor studied

	n	Asthma %	p	Hay fever, %	p	Atopic dermatitis, %	p
BCG immunization							
Yes	6,762	11.4		9.4		7.8	
No	2,828	12.9	0.04	10.6	0.06	8.7	0.13
Gender							
Male	4,733	13.0		11.4		7.8	
Female	4,847	10.7	0.001	8.1	<0.001	8.3	0.39
Age							
6 years	4,773	12.3		9.3		8.36	
7 years	4,810	11.3	0.13	10.2	0.12	7.75	0.28
Older siblings							
Yes	4,447	12.4		9.5		8.1	
No	5,143	11.3	0.10	9.9	0.57	8.0	0.88
Younger siblings							
Yes	3,711	11.0		9.5		8.3	
No	5,879	12.4	0.05	9.9	0.55	7.9	0.38
Current maternal smoking							
Yes	3,745	13.3		10.7		9.2	
No	5,807	10.8	<0.001	9.0	0.007	7.9	0.66
Current paternal smoking							
Yes	3,944	12.8		9.7		7.9	
No	5,426	10.9	0.005	9.4	0.65	8.2	0.63
Had a cat 1st year							
Yes	395	14.2		10.9		8.7	
No	9,195	11.7	0.14	9.7	0.43	8.0	0.54
Had a dog 1st year							
Yes	863	13.6		11.4		8.1	
No	8,727	11.7	0.10	9.6	0.09	8.0	0.94
Mother with university studies							
Yes	3,421	10.8		8.1		8.7	
No	6,169	12.5	0.01	10.7	<0.001	7.7	0.09
Truck traffic							
Never	1,476	8.7		7.9		7.7	
Seldom	4,366	11.5		8.9		7.5	
Frequently through the day	3,332	13.5		10.9		8.6	
Almost the whole day	341	15.0	<0.001	17.0	<0.001	12.3	0.01

Discussion

The results of this study show a weak but significant protective effect of BCG immunization on asthma and hay fever. There was also a tendency that suggested this immunization was protective in the case of atopic dermatitis. With respect to asthma, those results are very similar to the ones obtained by Gruber et al. [17] showing a protective effect of early BCG immunization in a very large number of German children with a mean age of 6 years. The magnitude of this protection (aOR 0.85, CI 95% 0.71–1.00) bears great similarity with the present

study. However, Gruber et al. did not find a beneficial effect of this immunization on the prevalence of hay fever, whereas our results show that BCG vaccination also has a protective effect against this disease of the same magnitude as against asthma. In contrast to the present study, the German investigation had a somewhat diverse population of children with some confounders that could have affected the results: for example, BCG immunization was much more frequent among children from East Berlin (94%) than among those from West Berlin (16%), and although the children were born shortly before the German reunification and their ‘westernization’ could have been

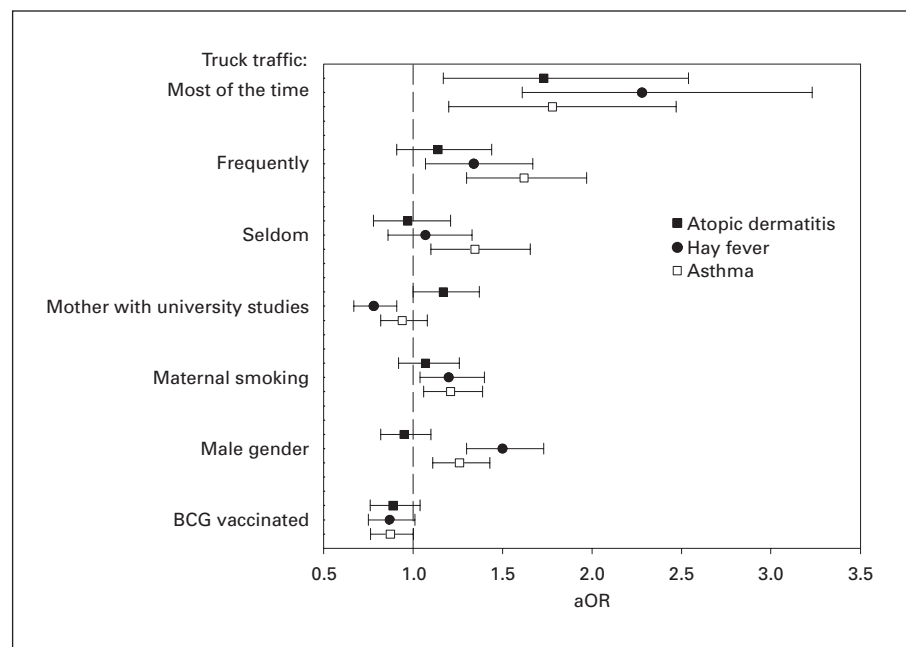


Fig. 1. Summary of the risk and protective factors of asthma, hay fever and atopic dermatitis. aOR = Adjusted OR.

Table 4. OR and adjusted OR (aOR) for asthma, hay fever and atopic dermatitis of the different factors studied (adjustment for all factors in the table)

	Asthma		Hay fever		Atopic dermatitis	
	OR	aOR	OR	aOR	OR	aOR
BCG vaccinated	0.87 (0.76–0.99)	0.87 (0.76–1.00)	0.87 (0.75–1.00)	0.87 (0.75–1.01)	0.88 (0.75–1.04)	0.89 (0.76–1.05)
Male gender	1.24 (1.09–1.41)	1.26 (1.11–1.43)	1.47 (1.28–1.68)	1.50 (1.30–1.73)	0.94 (0.81–1.09)	0.95 (0.82–1.10)
Age 7	0.91 (0.80–1.03)	0.91 (0.80–1.03)	1.11 (0.97–1.27)	1.11 (0.97–1.28)	0.92 (0.80–1.07)	0.92 (0.79–1.06)
Has older siblings	1.11 (0.98–1.25)	1.09 (0.96–1.25)	0.96 (0.84–1.01)	0.94 (0.81–1.08)	1.01 (0.87–1.17)	1.01 (0.87–1.18)
Has younger siblings	0.88 (0.77–0.99)	0.90 (0.78–1.03)	0.96 (0.83–1.01)	0.95 (0.82–1.11)	1.07 (0.92–1.24)	1.05 (0.89–1.22)
Current maternal smoking	1.26 (1.11–1.43)	1.21 (1.06–1.39)	1.20 (1.05–1.38)	1.20 (1.04–1.40)	1.03 (0.89–1.20)	1.07 (0.92–1.26)
Current paternal smoking	1.20 (1.06–1.36)	1.09 (0.95–1.25)	1.03 (0.89–1.18)	0.91 (0.79–1.06)	0.96 (0.83–1.12)	0.95 (0.81–1.11)
Had a cat first year	1.24 (0.93–1.65)	1.12 (0.83–1.53)	1.14 (0.82–1.57)	0.99 (0.70–1.41)	1.11 (0.78–1.59)	1.17 (0.81–1.69)
Had a dog first year	1.18 (0.96–1.46)	1.08 (0.87–1.34)	1.21 (0.96–1.51)	1.08 (0.85–1.38)	1.01 (0.78–1.30)	0.96 (0.73–1.26)
Mother with university studies	0.85 (0.74–0.97)	0.94 (0.82–1.08)	0.74 (0.64–0.85)	0.78 (0.67–0.91)	1.13 (0.98–1.32)	1.17 (1.00–1.37)
Truck traffic						
Seldom	1.36 (1.11–1.67)	1.35 (1.09–1.65)	1.13 (0.91–1.41)	1.07 (0.86–1.33)	0.97 (0.78–1.22)	0.97 (0.78–1.21)
Frequently through the day	1.64 (1.33–2.02)	1.60 (1.30–1.97)	1.42 (1.14–1.77)	1.34 (1.07–1.67)	1.14 (0.91–1.43)	1.15 (0.91–1.44)
Almost the whole day	1.85 (1.31–2.62)	1.72 (1.20–2.47)	2.38 (1.69–3.34)	2.28 (1.61–3.23)	1.69 (1.16–2.47)	1.73 (1.17–2.54)

well advanced at the time of the study, the possibility that BCG immunization could have been a marker of a non-western lifestyle during the first years of the children's lives (which is in itself a protective factor for asthma and allergy) cannot be ruled out. The results of our study support the fact that in certain western societies early BCG immunization can protect from allergic diseases, thus validating the German study.

The present study has some limitations that deserve comment. The first one is the fact that the data on BCG immunization are not individual and it has been assumed that all children in one area were immunized and all children in the other were not. This is obviously not fully accurate as the coverage was not 100%. On the other hand, some children might have moved from one area to another. Also, but very unlikely, due to the time elapsed since the immunization was discontinued and to the way

immunizations are implemented in Spain, it is possible that some children of the nonimmunized center had in fact been immunized. A further limitation is the noninclusion of the family history of atopy in the information obtained from the parents and, consequently, in the multivariate analysis. Other studies finding either a protective effect of BCG on asthma [17] or not [23] have not included this factor in their analyses. It is quite unlikely that adjusting for the family history of atopy would have modified the effects of BCG immunization on asthma and hay fever found in this study, due to the homogenous genetic and environmental background of the population of the children surveyed. Those limitations would probably have weighed against the hypothesis rather than the contrary. A final limitation of our results is that they have been obtained by means of a questionnaire and not using objective measurements. However, many epidemiological studies which relied on questionnaires have gathered very important information, increasing our knowledge on different aspects of asthma and allergy.

The present study and the abovementioned German one are the only two that found a protective effect of BCG immunization in asthma (and also in hay fever in our case) in a western population. Other studies in Sweden, Norway and Australia have found no such association. For instance, Alm et al. [10] performed a case-control study on children with a parental history of atopy at the mean age of 5.5 years and studied both subjective (questionnaire) and objective (prick test and specific IgE) measurements. They could not find any association between early BCG immunization and any of the outcome variables. However, the authors state that their study had enough power to detect a high effect (50% reduction of symptoms). Effects of a lower size could have been missed due to the number of children included in their study: the small size of the effect found in both the present and in the German study would probably have been overlooked. However, the very large ecological study performed by Anderson et al. [11] at the international level using the ISAAC study data did not find any relationship between BCG vaccination and the prevalence of asthma, hay fever or atopic dermatitis either uncorrected or corrected for gross national product. The fact that the authors did not include a multilevel analysis could have led them to miss this effect at national or regional level.

Other studies that have shown no effect of BCG immunization have studied adult subjects that were immunized at the age of 14. Jentoft et al. [16] performed a survey in 136 tuberculin-negative and 250 tuberculin-positive men and women aged 22–40 years who were sub-

jected to a questionnaire together with objective measurements such as lung function, bronchial hyperresponsiveness and tuberculin testing. They could find no relationship between tuberculin reactivity and any asthma symptoms, asthma medication, FEV₁ level or bronchial hyperresponsiveness. Omenaas et al. [15] had previously reported an absence of relationship between BCG immunization at 14 years of age and total or specific IgE in the same population. However, these individuals were immunized quite late and it is quite possible that the immunomodulation of BCG has a window of opportunity while the immune system is adapting to extrauterine life. On the other hand, some other studies which included children immunized within the first days of life found no association. For instance, Krause et al. [13] studied a large group of children born in Greenland and concluded that early BCG immunization had no effect on atopy as measured by specific IgE. They did not provide information about asthma symptoms. However, these authors state that they could not rule out that the effect of BCG immunization may be different with other genetic backgrounds, as shown by Alm et al. [24]. In fact, Aaby et al. [18] found a lower prevalence of atopy as defined by prick tests in children 3–14 years of age from Guinea-Bissau, the protection being higher when immunization took place within the first week of life. In addition, a Swedish study [14] showed that BCG immunization had a protective effect on atopic dermatitis, hay fever and asthma only in immigrant children. More recently, Marks et al. [25] have shown that this type of immunization was associated with a lower prevalence of current asthma in genetically predisposed Australian children 7–14 years old of southeast Asian origin.

In summary, our study shows that BCG immunization could offer a weak but significant protection against asthma and hay fever in a western population sharing a very similar lifestyle and genetic background.

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