Can multiple doses of BCG vaccine protect against asthma?*

Múltiplas doses de vacina BCG podem proteger contra asma?

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Abstract

Objective: To compare BCG vaccination involving a single intradermal dose and that involving multiple doses, one given with the multiple puncture technique, in terms of the protective effect against the subsequent onset of asthma. **Methods:** A retrospective cohort study involving 2,311 individuals having received the BCG vaccine. The patients were classified according to the number of doses of BCG vaccine administered (one; two; or three or more). The minimum follow-up period in order to determine whether there was any protective effect of BCG vaccination regarding the diagnosis of asthma was 10 years. **Results:** The sample included 1,317 individuals (56.99%) who had received only one BCG dose, 644 (27.87%) who had received two doses, and 350 (15.14%) who had received three or more doses. The number of patients diagnosed with asthma among those who had received one dose, two doses and three or more doses was, respectively, 216 (16.40%), 107 (16.61%) and 50 (14.28%). There were no significant differences among the groups. **Conclusions:** In the study sample, the prevalence of asthma among individuals having received multiple doses of the BCG vaccine was no different than that observed among those having received a single dose.

Keywords: Asthma; BCG vaccine; Immunization, secondary.

Resumo

Objetivo: Comparar a vacinação com uma única dose de BCG intradérmica com a vacinação com múltiplas doses, uma das quais pela técnica de multipuntura, em relação ao efeito protetor contra o aparecimento posterior de asma. **Métodos:** Estudo de coorte retrospectivo com 2.311 pessoas vacinadas com BCG. Os indivíduos foram classificados de acordo com o número de doses de vacina BCG recebidas (uma dose, duas doses e três ou mais doses). O tempo mínimo de acompanhamento para verificar se houve algum efeito protetor da vacina BCG em relação ao diagnóstico de asma foi de 10 anos. **Resultados:** A amostra incluiu 1.317 pessoas (56,99%) que receberam apenas uma dose do BCG, 644 (27,87%) que receberam duas doses e 350 (15,14%) com três ou mais doses. O número de pacientes diagnosticados com asma entre aqueles que receberam uma dose de BCG, duas doses e três ou mais doses foi, respectivamente, 216 (16,40%), 107 (16,61%) e 50 (14,28%). Não houve diferenças significativas entre os grupos. **Conclusões:** Na amostra estudada, não foi observada uma redução na prevalência de diagnóstico de asma com a revacinação ou com o uso de múltiplas doses da vacina BCG.

Descritores: Asma; Vacina BCG; Imunização secundária.

Introduction

The BCG vaccine is widely used in many parts of the world to protect against the miliary and meningeal forms of tuberculosis.[1] In Brazil, the BCG vaccine is offered as part of the National Immunization Program and is administered in a single dose in the first month of life. Use of the second dose of BCG vaccine was discontinued in the country after a study showed that the second dose offered no protection against pulmonary tuberculosis.[2]

The BCG vaccine, when administered intradermally, induces, even in newborns, a significant increase in the response of cytokines derived from T helper 1 (Th1) lymphocytes, and the reaction at the BCG vaccination site seems to be proportional to the production of INF-γ in response to the mycobacterial antigen.[3]

In addition to its possible preventive effects against tuberculosis, BCG vaccination has been reported to reduce the frequency of atopy in

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children; since the BCG vaccine influences the cellular immune response, it has also been hypothesized that BCG vaccination provides some protection against asthma.[4,5]

The prevalence of allergic asthma and other atopic diseases has dramatically increased in recent decades, especially in industrialized countries.[6] This increase cannot be explained solely by genetic factors, since substantial genome changes do not occur rapidly, appearing only after many generations. In seems unlikely that this increase is wholly attributable to changes in diagnostic procedures or exposure to etiologic agents of asthma and atopy. One possible explanation for this increase is the hygiene hypothesis, which states that the relative lack of infections in the first years of life could promote the development of allergic diseases in genetically predisposed individuals.[6,7]

In childhood, respiratory infections such as measles, pertussis and tuberculosis can alter the development of the immune system, promoting a Th1 response, in which IL-12, IFN-γ and TNF are the cytokines predominantly released. The absence of such infections could stimulate Th2 responses, promoting atopic diseases.[8] According to this hypothesis, lower frequency and lesser severity of infection, as well as the prevention of infections with the use of antibiotics and vaccines (despite the many indisputable advantages of their use in the control of infectious processes) facilitates the development of allergic diseases.[9] Since the BCG vaccine activates the immune system, any protective effect it has against asthma would be of great interest to public health, given that it is a low-cost, safe and widely used vaccine.[4] Therefore, the objective of this study was to compare BCG vaccination involving a single intradermal dose at birth and that involving multiple doses, one given with the multiple puncture technique, in terms of the capacity to avert the subsequent onset of asthma.

Methods

This was a retrospective cohort study based on a database containing information about individuals treated at an immunization and allergy clinic in the state of Pará, Brazil. The individuals involved were in a relatively high socioeconomic class and could therefore afford private health insurance. Each of the individuals had been monitored for a minimum of 10 years by the same physician. Anonymity was guaranteed for all participants.

Taking into consideration the fact that the prevalence of asthma in this age bracket is 20%, the sample size required to allow a cohort study to detect protection (defined as a 25% reduction in prevalence—from 20% to 15%) should be at least 1,714 (1,142 individuals who had received one BCG dose and 572 who had received two or more doses), with an alpha error of 5% and a beta error of 20%.

The chi-square test was used in order to compare the study groups. The level of significance was set at $p < 0.05$. Since it is a characteristic of cohort studies, relative risk was assessed.

The database included information on 2,311 individuals (10-70 years of age), of whom 1,215 were female and 1,096 were male. There were no sample losses because this was a retrospective cohort study. Since all individuals were monitored for at least 10 years, the minimum age for inclusion in the study was 10 years, and the median age was approximately 25 years. All individuals had received one intradermal dose of the BCG vaccine in the first month of life, as recommended by the Brazilian National Ministry of Health. Of those 2,311 individuals, 640 received the booster dose, as recommended at the time the first dose was administered, and 315 received a third dose, given with the multiple puncture technique, because of the possible protective effect against allergic diseases.

Among the 2,311 individuals, there were 373 cases of asthma, which were diagnosed in accordance with the guidelines established in the III Brazilian Consensus on Asthma Management and confirmed through clinical testing.

All 2,311 individuals had received the BCG vaccine and, for analysis purposes, they were classified according to the number of doses of BCG vaccine administered (one; two; or three or more).

The diagnosis of asthma was made during the 10-year follow-up period.

Results

Of the 2,311 individuals in the study sample, 1,317 (56.99%) had received only one BCG dose, 644 (27.87%) had received two doses, and 350 (15.14%) had received three or more doses.

Table 1 - Prevalence of asthma in the study sample (minimum follow-up period of 10 years) by number of doses of BCG vaccine administered.

Doses of BCG vaccine, n	n	Individuals with asthma, n (%)
1	1,317	216 (16.40)
2	644	107 (16.61)
3 or more	350	50 (14.28)

$p > 0.05$; chi-square test = 1.062.

The sample consisted of 1,215 females and 1,096 males; the median age was 25 years.

As can be seen in Table 1, 373 (16.14%) of the 2,311 individuals developed asthma within the 10-year follow-up period: 216 (16.40%) of the 1,317 individuals who had received only one BCG dose; 107 (16.61%) of the 644 who had received two BCG doses; and 50 (14.28%) of the 350 who had received three or more BCG doses.

There were no significant differences among the three study groups.

Discussion

There is evidence that asthma results from a predominantly Th2 lymphocyte response to allergens, in contrast to the predominantly Th1 pattern found in non-atopic individuals.[10] Mononuclear cells from the umbilical cords of children who later develop asthma or other atopic diseases, or a combination of those diseases, produce lower quantities of INF-γ.[11] The Th1/Th2 balance in the neonatal period might be the determinant of the way in which the genetic predisposition to asthma is modulated, and can be useful as a predictor of the subsequent development of the disease.[12] It has been demonstrated that, among 12-year-old children, asthma is more prevalent in those with a weak response to the tuberculin skin test, which also depends on the immune response mediated by Th1 lymphocytes.[8]

The reciprocal regulation of Th1 and Th2 cells has been well documented. Various animal studies of Th2-mediated diseases, including asthma, have shown inhibition of the Th2 response after stimulation of Th1 cells.[13]

Immunization with BCG is a useful model to test the role of early stimulation of Th1 cells (during the critical period of maturation of the immune system), since BCG is a potent stimulator of Th1 response.[14]

Some human studies have indicated that there is an inverse relationship between exposure to *Mycobacterium tuberculosis* and the development of allergic disease. However, the role that neonatal BCG vaccination plays in the prevention of sensitization and the development of asthma remains unclear, and there is evidence that the induction of a Th1 response by the mycobacterium is insufficient to modulate allergic responses.[15] It is possible that, in the absence of a strong genetic influence, BCG vaccination provides some protection against the onset of allergic diseases.[16]

It is well known that the secondary immune response, which is mediated by memory cells, is more effective than is the primary response. One group of authors tested whether the Th1 immune response induced by BCG revaccination could be an antagonist of Th2 cytokines and improve pulmonary function in individuals with asthma.[13] The authors observed that BCG revaccination improved pulmonary function and resulted in an increase in the IFN-γ/IL-4 ratio, shifting the Th1/Th2 balance toward a Th1 response, thereby confirming the findings of a previous study conducted by the same authors.[17]

One group of authors studied children at 3 months, 6 years and 12 years of age.[8] The authors found that PPD positivity at 6 and 12 years of age was inversely associated with the presence of atopic symptoms at any age. In patients with positive PPD skin tests, the rate of atopic symptoms was one third of that found in those with negative PPD skin tests. The authors also found that the levels of Th2 cytokines (IL-4, IL-10 and IL-13) were significantly lower in positive PPD responders, whereas those of the Th1 cytokine IFN-γ were higher.[8] These data are consistent with the idea that atopic responses are limited by Th1 mechanisms.[8]

In our study, we found that BCG revaccination conferred no protection against asthma. Previous studies investigating the relationship between the BCG vaccine and atopy have yielded conflicting results.[4,18]

Two groups of authors[19,20] reported that they found no association between atopic diseases and BCG vaccination. Another study reported an association between BCG vaccination in the neonatal period and a reduction in the

prevalence of asthma in individuals with a family history of rhinitis or eczema.[14] Similarly, two studies[5,21] reported an association between BCG vaccination and lower rates of atopic diseases. It is important to emphasize that, in our study, we did not attempt to determine whether BCG vaccination protects against other atopic diseases: only asthma was considered.

Because of its retrospective cohort design, the present study has certain limitations. The confounding factors that might have influenced the findings of our study include the extremely wide age bracket and the above-average socioeconomic status of the individuals studied, as well as the fact that we did not classify asthma severity or investigate concomitant allergic rhinitis, both of which merit appropriate evaluation in further studies on the subject.

According to one recent study, BCG vaccination might offer greater protection against asthma when it is combined with an atopic component.[14] Another group of authors found that BCG vaccination protects against asthma in children with allergy and allergic rhinitis but not in those with asthma alone.[4] Other authors have also failed to find any association between BCG vaccination and a lower prevalence of asthma.[22,23] One study showed that neither BCG vaccination nor PPD positivity has any effect on asthma prevalence.[24] Conversely, one group of authors found that neonatal BCG vaccination was associated with a 27% reduction in the subsequent prevalence of asthma symptoms.[18] Therefore, the subject is controversial. In our study sample, the prevalence of asthma among individuals having received multiple doses of the BCG vaccine was no different than that observed among those having received a single dose. It is of note that the BCG vaccine is only one factor among many, and that other factors could be of much greater significance.

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