SHORT COMMUNICATION

Does BCG revaccination protect against the development of asthma?

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Received 8 August 2012; accepted 17 October 2012
Available online 6 November 2012

KEYWORDS
Allergic rhinitis; Asthma; BCG vaccination; Prevalence

Summary
Single BCG vaccination has been considered as a protective factor against asthma. However, the effect of a second dose of BCG on the prevalence rate of asthma and asthma—allergic rhinitis—eczema comorbidity has not been studied exclusively among adolescents. In this ISAAC protocol-based cross sectional study we assessed the association between one single versus two doses of BCG among 2213 individuals aged 13–14 years old. We found no association between BCG revaccination and asthma, associated (OR = 0.68, 95% CI, 0.37–1.25) or not to allergic rhinitis and/or atopic eczema (OR = 1.07, 95% CI, 0.84–1.36).

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Introduction
Bacillus Calmette–Guérin (BCG) vaccination is purported to promote T lymphocyte polarization, and to induce Th1 lymphocytes to produce antagonist cytokines to the ones that promote atopic conditions. 1 Considering that atopy is a well-known risk factor for asthma, single BCG vaccination has been studied as a protective factor against that disease. In the study of Shirakawa et al., positive tuberculin response predicted a lower incidence rate of asthma, 1 similarly to the results from a recent published meta-analysis. 2 Furthermore, four other published studies found conflicting results of the effect of BCG vaccination on the prevalence of asthma. 3–6

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http://dx.doi.org/10.1016/j.rmed.2012.10.009

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Respiratory Medicine (2013) 107, 317–319

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Materials and methods

Between 2001 and 2002 several surveys on asthma and allergic diseases were conducted in Brazil and other countries taking part of the phase three of the ISAAC (International Study of Asthma and Allergies in Childhood) that included schoolchildren and adolescents.7 We took the opportunity of the ISAAC survey carried out in Belo Horizonte, Southeastern Brazil, to assess a poorly studied association between BCG revaccination (i.e., a second vaccination administered 7–10 years after the neonatal one and 3–8 years before data collection) and the prevalence of asthma, allergic rhinitis and atopic eczema among teenagers (13–14 years old).

In the present study, all the adolescents from 14 randomly selected public schools were recruited. Data were collected through a translated and validated Portuguese version of the ISAAC questionnaire.7 Subjects were classified as having one scar (related to the dose received within the first weeks of life) or two BCG scars (i.e., revaccinated from 6–7 to 10 years of age). Scars were considered as markers of BCG vaccination if they had a typical aspect, with 3–10 mm of diameter, and located in the lower insertion of the right deltoid muscle. Scar characterization was verified by trained health workers.

The main outcomes were predefined according to the ISAAC protocol, i.e., current asthma was defined in the case of an affirmative answer to the following question “Have you had wheezing or whistling chest in the past 12 months?” while the presence of allergic rhinitis was considered if the adolescent responded affirmatively and simultaneously to the both following questions: 1) “In the past 12 months, have you had a problem with sneezing, or a runny, or a blocked nose when you did not have a cold or flu?” and 2) “In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?” Flexural lesion suggestive of eczema was defined if there were affirmative answers to all the 3 questions, as follows: 1) “Have you ever had an itchy rash which was coming and going for at least 6 months?” and 2) If yes, “Have you had this itchy rash at any time in the last 12 months?” and 3) If yes, “Has this itchy rash at any time affected any of the following places, as follows, the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?” The concomitant presence of asthma and allergic rhinitis and/or eczema, as defined above, was considered as a proxy of ‘atopic’ asthma. Our work hypothesis was that BCG revaccination has not any effect on asthma prevalence.

The association between BCG revaccination and the prevalence of asthma was estimated through odds ratios (OR), adjusted for cluster effect and obtained through logistic regression with random-effects, considering each school as a cluster.

Results

The original sample encompassed 2771 adolescents, but 558 of them (20.1%) were excluded due to missing data. In the remaining 2213 included in the final analysis, there were 47.7% boys, and 1445 (65.3%) of them were revaccinated (i.e., had two BCG scars), while 768 had one single BCG scar (34.7%). Both, current asthma and ‘atopic’ asthma, were reported by 394 (17.8%), and 93 (4.2%) participants, respectively. Among them, 375 (95.2%) had also reported at least one of the following: diagnosis of asthma ever, wheezing with exercise in the last 12 months, more than 3 episodes of wheezing in the last 12 months, and waking up at night because of wheezing in the last 12 months, demonstrating a high likelihood of suffering from asthma.

From the adolescents with current asthma and from the ones with current asthma and allergic rhinitis and/or atopic eczema, 67.7% and 68.0% were revaccinated, respectively. As shown in Table 1, no association between revaccination and presence of symptoms of current asthma and ‘atopic’ asthma in the studied population was found. Moreover, there was no association when each school was evaluated separately (data not shown).

Discussion

Prevalence of current asthma in Brazilian adolescents is by 20% despite of virtually 100% single BCG vaccination coverage in the first weeks–months of life. These epidemiological data are in accordance with the results obtained in the present study. Sarinho et al. observed similar results in a Brazilian retrospective cohort study in which the mean age of the studied population was 25 years, which hampers comparison with our results.6

According to a recent published meta-analysis2 and the study carried out by Linehan et al.,9 single BCG vaccination could be a protective factor for asthma, but probably genetic and environmental factors might be involved with this effect. For instance, tobacco exposure, air pollution, intestinal parasites and viral respiratory infections probably affect asthma development, preventing the potential protective effect of BCG on both atopic and non-atopic asthma in our study population. Differently from results reported by Shirakawa et al., concomitant atypical mycobacteria infection is not frequent in Southeastern Brazil, and therefore exposure to nontuberculous environmental mycobacteria was probably not a confounding in our results.

Taken into account that we randomly selected 14 schools, it is reasonable to assume that these previously mentioned factors were equally distributed into our studied population, i.e., single or two BCG-related scar groups and probably did not interfered in the final results. We argue that the multifactorial (and not only BCG vaccination or revaccination itself) pathogenesis of asthma could explain the controversial results verified in studies that assessed the relationship between BCG vaccination and asthma conducted in different

Table 1 Logistic regression analysis adjusted for cluster effect, for BCG revaccination and both current and ‘atopic’ asthma.

<table>
<thead>
<tr>
<th>BCG scar</th>
<th>Current asthma</th>
<th>Current ‘atopic’ asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N (%)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>One scar</td>
<td>128/768</td>
<td>(16.7)</td>
</tr>
<tr>
<td>Two scar</td>
<td>269/1445</td>
<td>(18.6)</td>
</tr>
</tbody>
</table>

Note: 0.37–1.25
countries and therefore they can not be generalized. Further studies on this subject in different settings would be necessary to a better understanding of this issue.

Funding

P. Camargos is supported by the Brazilian research agencies CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico, Grant 303827/2009-2) and FAPEMIG (Fundação de Amparo à Pesquisa do Estado de Minas Gerais, Grant PPM00129-12). These research agencies had no influence in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Statement of contribution

PC, C Andrade, C Alvim, MJF, designed and supervised the research (i.e., project conception, development of overall research plan, and study oversight); C Alvim, C Andrade, MJF, RB, HB, undertook data collection, wrote the manuscript, and has primary responsibility for the final content of the manuscript; SC undertook the statistical analyses and wrote the manuscript. All authors assisted in the interpretation of analyses and revision of the manuscript and read and approved the final manuscript.

Conflict of interest statement

The authors had no personal or financial conflicts of interest.

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