

BCG vaccination and reduced risk of asthma

Vacinação com BCG e redução do risco de asma

Adelmir Souza-Machado, Álvaro A. Cruz

Since 1997, when Shirakawa et al. reported an inverse correlation between the incidence of asthma and reactivity to PPD among children in Japan,⁽¹⁾ there has been great interest in the possibility that BCG vaccination contributes to the prevention of asthma. There have been numerous objections to the methods and results of the study. However, due to the current global epidemic of asthma and the hygiene hypothesis to explain the increase in allergic diseases,⁽²⁾ as well as to the immediate availability of this safe, low-cost intervention, the expectations surrounding this issue have greatly increased. In its simplest form, the hygiene hypothesis suggests that early exposure to microbial products modulates the immune system away from the mechanisms related to the development of atopy. The infection generated by the attenuated mycobacterium of the BCG vaccine might perform this function, especially if the vaccine is administered in the first months of life.

Various studies in humans (in which different methods were used and different populations were investigated) have examined the issue and have obtained negative results or results of limited impact, frustrating the general expectation, which had increased due to evidence from experimental studies.⁽³⁾ In this issue of the Brazilian Journal of Pulmonology, Sarinho et al.⁽⁴⁾ make an important original contribution to the national debate by reporting their observations regarding the effect of the BCG vaccine, the number of doses of which varied, on 2,311 individuals between 10 and 70 years of age. The authors conducted a 10-year retrospective cohort study in which they evaluated those individuals in terms of the incidence of asthma (according to the number of BCG vaccine doses received). No statistically significant differences were found between the groups of individuals who received one, two or three or more doses of the BCG vaccine with regard to the prevalence of asthma, which was 16.4% (216/1,317), 16.6% (107/644) and 14.3% (50/350), respectively. Despite the methodological limitations of a

retrospective study, in which the intervention was not performed randomly (meaning that various uncontrolled environmental and individual factors might have been confounders), the study significantly contributes to the understanding of the issue, indicating that the limited protection provided by BCG vaccination is unlikely to increase with the use of multiple doses of the vaccine in the age bracket under study. Although the retrospective nature of the study implies a low level of evidence, it by no means negates the validity of the report. On the contrary, the authors should be congratulated for their willingness to gather information that might otherwise have been lost in archives and that is now shared with researchers worldwide. The same authors previously evaluated, from various perspectives, the relationship between BCG and asthma in other populations.^(5,6) However, care should be taken in extrapolating the findings reported in their most recent study (conducted in the state of Pará, Brazil) to other regions and communities in which the prevalence of infection with tuberculosis and atypical mycobacteria is different. It is likely that the BCG vaccine confers less protection against asthma in populations that are more exposed to antigens (such as the peoples of the Amazon region), just as it provides less protection against tuberculosis in those same populations.^(7,8)

Asthma is a syndrome that is expressed by different phenotypes; the immunopathological substrate of asthma is chronic airway inflammation, the characteristics and intensity of which vary.⁽⁹⁾ In 1986, one group of authors⁽¹⁰⁾ described CD4+ T lymphocyte subgroups (Th1 and Th2) based on the pattern of cytokines produced in mouse cells, which were subsequently identified in human cells as groups of cytokines with antagonistic properties, the balance between the two groups being important for health.⁽¹¹⁾ Individuals with atopic asthma are sensitized to at least one allergen and respond by producing specific IgE. In addition, there is a polarization of the T lymphocyte response, with activation of the Th2 subgroup, characterized by

the production of cytokines such as IL-3, IL-4, IL-5, IL-9, IL-13 and GM-CSF, all of which are related to elevated IgE levels and eosinophil attraction, as well as by the release of chemokines and mediators of the immediate response to allergens.⁽¹²⁾ In non-atopic asthma, the chronic inflammatory process is quite similar to that of atopic asthma; however, it is not possible to identify the production of specific IgE against a relevant aeroallergen.⁽¹³⁾ It is unlikely that the risk factors and potential protective factors for these two different asthma phenotypes are the same. Other T lymphocyte subgroups have been characterized, including regulatory T cells and follicular T helper cells (Th17, Th22 and Th9 cells), revealing the complexity of this microsystem, which has been described as playing an important role in modulating the interrelation between the innate immune response and the acquired immune response and, consequently, in maintaining health by mounting an effective immune response without autoimmunity or hypersensitivity.⁽¹⁴⁾

The BCG vaccine against tuberculosis is derived from an attenuated bacterium of bovine origin (*Mycobacterium bovis*), which is similar to the microorganism that causes the disease (*M. tuberculosis*). The ability of mycobacteria (which stimulate Th1 lymphocytes and regulatory T cells) to modulate the Th2 response has been documented in vitro and in various models of asthma.^(3,15) In a cross-sectional study investigating the impact of BCG vaccination and revaccination on the prevalence of asthma among adolescents in Salvador, Brazil, the overall analysis of the sample of individuals who received one or two doses of the BCG vaccine revealed no significant protection; however, neonatal BCG vaccination provided some protection to individuals who presented with symptoms of chronic rhinitis and who therefore were at a higher risk of developing asthma.⁽¹⁶⁾ A recent meta-analysis of 23 studies concluded that early BCG vaccination was associated with a small reduction in the risk of asthma (OR = 0.86; 95% CI: 0.79-0.93).⁽¹⁷⁾ In a randomized controlled study in humans, in which multiple intramuscular injections of BCG were used, BCG vaccination was found to have limited effects on asthma and allergic rhinitis.⁽¹⁸⁾

The levels of Th1 cytokines (TNF- α and IFN- γ) are increased in the inflammatory process

of asthma, indicating that activated Th1 and Th2 responses might coexist.^(12,13) The exposure of the immune system to infectious agents or microbial products, especially during childhood, seems to promote a balanced immune response, with modulation or regulation of the Th1 and Th2 systems.^(19,20) However, the lack of exposure, in a less septic environment, would facilitate the incidence of allergic and autoimmune diseases in subgroups of predisposed individuals. Based on this premise, various studies have been conducted in an attempt to identify interventions that might be incorporated into strategies to attenuate or prevent inflammation in asthma.^(3,15) In practice, however, this theory is not tenable. Because of the plurality of the immune response, the various inflammatory phenotypes of asthma, the genetic diversity, the environmental diversity and the various opinions regarding the timing of the intervention, this is a complex issue. Although BCG vaccination can reduce the risk of atopic asthma, it does not reduce the risk of non-atopic asthma, which might be the most common form of asthma in low-income children in Latin America. Among children in the state of Rio Grande do Sul, Brazil, the risk of asthma associated with infections has been shown to be higher than is that of asthma associated with atopy.⁽²¹⁾ A study investigating a cohort of low-income children in Salvador, Brazil, reported that the prevalence of asthma attributable to atopy was only 20% and that asthma is most strongly correlated with poor housing conditions and sanitation (unpublished data). One group of authors⁽¹⁵⁾ investigated the effect of BCG vaccination on an experimental model of asthma in mice and confirmed the previous reports of suppression of the Th2 inflammatory response in the airways, accompanied by the activation of regulatory T cells. However, concomitant neutrophilic inflammation related to the stimulation of Th1 cells was also observed.

In the context of a dynamic, complex and redundant immune response, there is certainly much more to the association between BCG vaccination and asthma than our (albeit advanced) knowledge of immunopathology allows us to understand. One aspect that merits careful investigation is the possibility that BCG vaccination is a protective factor in atopic asthma but not in non-atopic asthma.

Adelmir Souza-Machado
Adjunct Professor,
Institute of Health Sciences,
Federal University of Bahia;
Coordinator of the *Programa para o*
***Controle da Asma na Bahia* – ProAR,**
Bahia State Asthma and Allergic Rhinitis
Control Program – Salvador, Brazil

Álvaro A. Cruz
Associate Professor.
Federal University of
Bahia School of Medicine;
Director of the Center of Excellence in
Asthma, Salvador, Brazil

References

1. Shirakawa T, Enomoto T, Shimazu S, Hopkin JM. The inverse association between tuberculin responses and atopic disorder. *Science*. 1997;275(5296):77-9.
2. Strachan DP. Hay fever, hygiene and household size. *BMJ*. 1989;299(6710):1259-60.
3. Herz U, Gerhold K, Grüber C, Braun A, Wahn U, Renz H, et al. BCG infection suppresses allergic sensitization and development of increased airway reactivity in an animal model. *J Allergy Clin Immunol*. 1998;102(5):867-74.
4. Sarinho E, Kunz FC, Bellesi N, Maia PF, Rizzo JA, Silva AR. Can multiple doses of BCG vaccine protect against asthma? *J Bras Pneumol*. 2010;36(3):281-85.
5. Oliveira FH, Sarinho SW, Montenegro S, Neuenschwander C, Queiroz R, Medeiros D, et al. Production of interferon gamma in asthmatic patients with small bacille Calmette-Guerin scars: a pilot study. *Allergy Asthma Proc*. 2006;27(6):516-22.
6. Sarinho E, Schor D, Veloso M, Lima M. BCG scar diameter and asthma: a case-control study. *J Allergy Clin Immunol*. 2000;106(6):1199-200.
7. Bierrenbach AL, Cunha SS, Barreto ML, Pereira SM, Rodrigues LC. Skin test reactivity to mycobacterial antigens parallels the phylogenetic structure of their genus. *Int J Tuberc Lung Dis*. 2001;5(7): 656-63.
8. Fine PE, Rodrigues LC. Modern vaccines. Mycobacterial diseases. *Lancet*. 1990;335(8696):1016-20.
9. Wenzel, SE. Asthma: defining of the persistent adult phenotypes. *Lancet*. 2006;368(9537):804-13.
10. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J Immunol*. 1986;136(7): 2348-57.
11. Parronchi P, Macchia D, Piccinni MP, Biswas P, Simonelli C, Maggi E, et al. Allergen- and bacterial antigen-specific T-cell clones established from atopic donors show a different profile of cytokine production. *Proc Natl Acad Sci U S A*. 1991;88(10):4538-42.
12. Holgate ST, Arshad HS, Roberts GC, Howarth PH, Thurner P, Davies DE. A new look at the pathogenesis of asthma. *Clin Sci (Lond)*. 2009;118(7):439-50.
13. Barnes PJ. Intrinsic asthma: not so different from allergic asthma but driven by superantigens? *Clin Exp Allergy*. 2009;39(8):1145-51.
14. Zhu J, Paul WE. Heterogeneity and plasticity of T helper cells. *Cell Res*. 2010;20(1):4-12.
15. Ahrens B, Gruber C, Rha RD, Freund T, Quarcoo D, Awagyan A, et al. BCG priming of dendritic cells enhances T regulatory and Th1 function and suppresses allergen-induced Th2 function in vitro and in vivo. *Int Arch Allergy Immunol*. 2009;150(3):210-20.
16. da Cunha SS, Cruz AA, Dourado I, Barreto ML, Ferreira LD, Rodrigues LC. Lower prevalence of reported asthma in adolescents with symptoms of rhinitis that received neonatal BCG. *Allergy*. 2004;59(8):857-62.
17. El-Zein M, Parent ME, Benedetti A, Rousseau MC. Does BCG vaccination protect against the development of childhood asthma? A systematic review and meta-analysis of epidemiological studies. *Int J Epidemiol*. 2010;39(2):469-86.
18. Li J, Luo DF, Li SY, Sun BQ, Zhong NS. Efficacy of intramuscular BCG polysaccharide nucleotide on mild to moderate bronchial asthma accompanied with allergic rhinitis: a randomized, double blind, placebo-controlled study. *Chin Med J (Engl)*. 2005;118(19):1595-603.
19. von Mutius E. 99th Dahlem conference on infection, inflammation and chronic inflammatory disorders: farm lifestyles and the hygiene hypothesis. *Clin Exp Immunol*. 2010;160(1):130-5.
20. Chatenoud L, You S, Okada H, Kuhn C, Michaud B, Bach JF. 99th Dahlem conference on infection, inflammation and chronic inflammatory disorders: immune therapies of type 1 diabetes: new opportunities based on the hygiene hypothesis. *Clin Exp Immunol*. 2010;160(1):106-12.
21. Pereira MU, Sly PD, Pitrez PM, Jones MH, Escoto D, Dias AC, et al. Nonatopic asthma is associated with helminth infections and bronchiolitis in poor children. *Eur Respir J*. 2007;29(6):1154-60.