

Ecological correlation among prevalence of asthma symptoms, rhinoconjunctivitis and atopic eczema with notifications of tuberculosis and measles in the Brazilian population

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This study aims to assess the relationship among incidence of tuberculosis and measles, in the general population, within the year of birth and the prevalence of asthma, rhinoconjunctivitis and atopic eczema in teenagers from different Brazilian cities enrolled in the International Study of Asthma and Allergies in Childhood (ISAAC) phases I and III. Positive answers to the questions: 'Have you had wheezing or whistling in the chest in the past 12 months?', 'In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?' and 'Has this itchy rash at any 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?' identified the teenagers with asthma, rhinoconjunctivitis, and atopic eczema, respectively. The incidence of tuberculosis and measles, in the general population, observed in the year of birth of the enrolled teenagers (1981/82 and 1988/89) were obtained from governmental agencies: National Foundation of Health (FUNASA) and Brazilian Institute of Geography and Statistics (IBGE). They were compared with the prevalence of asthma, rhinoconjunctivitis and atopic eczema reported in both ISAAC phases I and III. Although we observed reduction of the incidence of tuberculosis and measles in the general population in all cities, the prevalence of asthma, rhinoconjunctivitis and atopic eczema remained stable in most of the centers. In Pernambuco and Paraná, there has been a significant increase in the prevalence of rhinoconjunctivitis. These data do not corroborate the findings of an inverse relationship between the prevalence of atopic diseases and the decreasing incidence of tuberculosis and measles.

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The hygiene hypothesis associates the western way of life to the increase in prevalence of asthma and allergic diseases (1–3). The early exposure to infectious agents and/or endotoxins, to live in an environment with great number of children, low use of antibiotics, prolonged breast feeding, and the diet: fresh fruits and vegetables,

long-chain polyunsaturated fatty acids, and vitamin A, during the first year of life could be some of the factors related to the protection against development of asthma and allergic diseases (3). Viral infections (upper respiratory tract, hepatitis A) (2, 4) and parasite infection were associated with low prevalence of atopic sensitization (2, 5).

Previous studies had documented a reverse relationship between asthma prevalence and some health indicators, as BCG vaccination rates, decreasing incidence of tuberculosis and measles (6). However, subsequent studies did not confirm unequivocally these results (7–12). In this study we evaluate the association of prevalence of current atopic disease (asthma, allergic rhinitis, and atopic eczema) in teenagers (13–14-yr-old), having as data source the International Study of Asthma and Allergies in Childhood (ISAAC) protocol, and the tuberculosis and measles incidence in the general population at the time of the teenagers birth as a surrogate for exposition to these agents (13).

Methods

Prevalence of asthma, rhinoconjunctivitis and atopic eczema were obtained in two occasions in: Recife (Pernambuco; 1994/95 and 2002), Salvador (Bahia, 1995 and 2001/02), São Paulo (São Paulo, 1995/96 and 2002), Curitiba (Paraná, 1995/96 and 2002) and Porto Alegre (Rio Grande do Sul, 1995/96 and 2002). These data were obtained as part of ISAAC protocol (phases I and III), having the standardized written questionnaire (13) filled by the adolescents. Teenagers who answered positively to the following questions: 'Have you had wheezing or whistling in the chest in the past 12 months?' or 'In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?' or 'Has this itchy rash at any 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?' were identified respectively as having asthma, rhinoconjunctivitis, or atopic eczema (13).

Exposure to tuberculosis and measles in the first year of life was assessed indirectly by their incidence in the general population in 1981/82 and in 1988/89, i.e. the years of birth of the teenagers evaluated in the two ISAAC phases, in each centre.

The incidence of tuberculosis and of measles in the general population, expressed as average, were obtained as the ratio between the number of cases reported, provided by the National Foundation of Health (FUNASA) (14), and the general population registered in July of the studied year (Brazilian Institute of Geography and Statistics, IBGE) in each state (14).

Subjects with previous contact with patients with tuberculosis, and/or having suggestive symptoms of tuberculosis: cough with phlegm for at least 3 or more weeks, and/or fever, and/or weight

loss, and appetite loss, tuberculosis suggestive X-ray associated to at least one positive direct bacilloscopy or positive culture of sputum, were identified as having tuberculosis (14). Patients with high fever associated to cutaneous rash, plus to one or more of the following signals and symptoms: cough and/or coryza and/or conjunctivitis; previous contact with a patient with measles 7–18 days before, and/or positive measles IgM, were defined as having measles (14).

Data on prevalence of asthma, rhinoconjunctivitis and atopic eczema, obtained in both occasions were compared by the chi-square test. The level of significance (*p*-value) was 5%. This study was approved by the Ethical Committee of each involved institution and a signed informed consent for participation was obtained firstly from the School's principal and then from the adolescents' parents.

Results

Figures 1 and 2 show the annual incidence of tuberculosis and measles in the general population of Pernambuco, Bahia, São Paulo, Paraná and Rio Grande do Sul. It was observed a clear tendency of decreasing rates, considering those observed in 1980. Table 1 shows the incidence of tuberculosis and measles in the years of birth of the teenagers studied. In addition, Table 1 shows the prevalence of asthma, rhinoconjunctivitis and atopic eczema obtained from ISAAC phases I and III. A decrease in the incidence of tuberculosis and measles in the general population was observed in all studied states. In São Paulo and Rio Grande do Sul there was a significant reduction in the prevalence of asthma in 2002, compared with 1995/96. The prevalence of rhinoconjunctivitis significantly increased in Pernambuco and Paraná. In the other states there were no differences. Prevalence of atopic eczema was significantly reduced in 2002 only in Bahia compared with 1994/95.

Discussion

In Brazil, tuberculosis is a disease of compulsory notification for which the government provides free treatment, therefore, generating reliable epidemiological data. Besides the reduction in the incidence of tuberculosis in the general population observed in all Brazilian centers, there was a reduction, although not homogeneous, in the prevalence of asthma, rhinoconjunctivitis and atopic eczema in the last 12 months. These data are opposed to those observed by other authors (15–17).

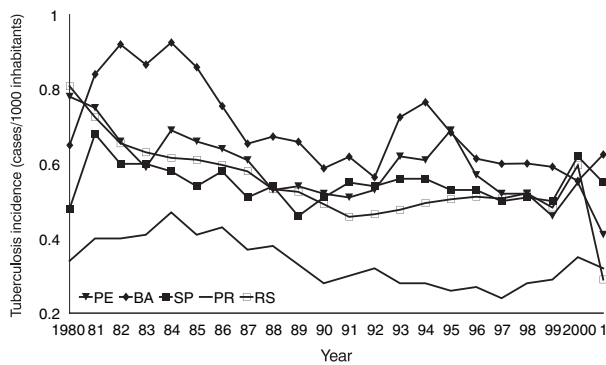


Fig. 1. Annual tuberculosis incidence (cases/1000 inhabitants) between 1980 and 2001 in Pernambuco (PE), Bahia (BA), São Paulo (SP), Paraná (PR), and Rio Grande do Sul (RS), Brazil.

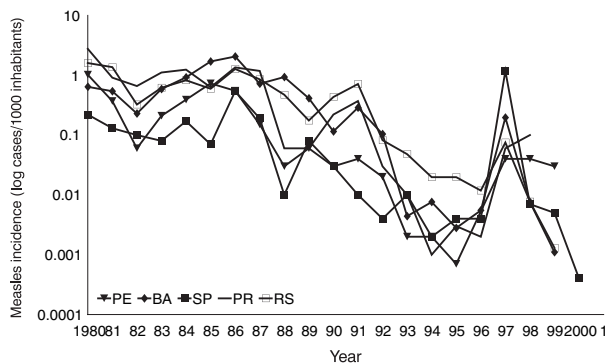


Fig. 2. Annual measles incidence (log cases/1000 inhabitants) between 1980 and 2001 in Pernambuco (PE), Bahia (BA), São Paulo (SP), Paraná (PR), and Rio Grande do Sul (RS), Brazil.

The tuberculosis notification rates are a better estimate of children's exposure to *Mycobacterium tuberculosis* than tuberculin responses (15).

Although the relationship among tuberculosis, BCG vaccination, delayed-type cutaneous hypersensitivity to tuberculin, exposure to Koch's bacillus and development of allergic diseases is very controversial. The findings of Shirakawa et al. (18) were not supported by other investigators, perhaps because of the differences in study protocols, examined population or in BCG preparations used (7–10), as well as in the pattern of natural exposure to *M. tuberculosis* and other Mycobacteria (8).

The protective effect of BCG vaccination performed in the first year of life on the development of asthma and allergic diseases in late childhood is controversial (2, 19–21). A cohort from a region with low incidence of tuberculosis and high incidence of allergic diseases had no differences in the prevalence of allergic sensitization between vaccinated and non-vaccinated subjects (20). However, in a subgroup of individuals with positive family history of rhinitis or eczema, BCG vaccination seems to have lower impact on asthma prevalence (20). In another cohort study, Grüber et al. followed-up BCG immunized and non-immunized German newborn as of birth and noticed a reduction in the prevalence of atopic eczema and wheezing in the last year among vaccinated subjects. This protection was sustained until the age of two, disappearing afterwards. There was no relationship among clinical features, total serum IgE levels and mean PPD wheal diameter (9). In a complementary study they observed a stronger protective effect of BCG early vaccination on those children with non-German ethnicity (21). English children did not show any interference of the BCG immunization with prevalence of

Table 1. Tuberculosis and measles incidence rates (cases/1000 inhabitants) in the year of birth of the adolescents evaluated at 13–14-yr-old (n) and prevalence of asthma (wheezing last year), rhinoconjunctivitis (nasal and ocular symptoms last year) and atopic eczema (skin lesions in characteristic locations) in Brazilian ISAAC (International Study of Asthma and Allergies in Childhood) phases I and III participants

Center	Year of birth	Incidence (cases/1000 inhabitants)		ISAAC year	n	Prevalence last year		
		Tuberculosis	Measles			Asthma	Rhinoconjunctivitis	Atopic eczema
PE	1981–82	0.71	0.21	1994–95	3085	19.7	11.3	4.6
	1988–89	0.53	0.04	2002	2774	19.1	14.5*	5.0
BA	1982–83	0.90	0.41	1995	3162	27.1	25.0	9.2*
	1988–89	0.67	0.67	2001–02	3022	24.6	24.4	6.5
SP	1982–83	0.60	0.09	1995–96	3008	23.3*	12.6	3.7
	1988–89	0.50	0.05	2002	3161	18.7	12.2	3.6
PR	1982–83	0.40	0.87	1995–96	3008	18.4	14.1	3.9
	1988–89	0.35	0.19	2002	3628	18.9	17.2*	3.7
RS	1982–83	0.70	0.47	1995–96	3195	24.7*	17.6	4.8
	1988–89	0.52	0.32	2002	3012	18.2	15.9	5.0

PE, Pernambuco; BA, Bahia; SP, São Paulo; PR, Paraná; RS, Rio Grande do Sul.

Data from National Foundation of Health (FUNASA) and Brazilian Institute of Geography and Statistics (IBGE).

*Significantly higher in comparison with the other year.

asthma and related symptoms (10). Similarly, Ota et al. (22) did not report any association between atopy, tuberculin response or BCG scar diameter in Gambian children.

In Brazil, BCG immunization is universal and recommended from the first month of life, being performed for more than 2 decades, in a program referenced by World Health Organization. Nevertheless, asthma prevalence was the eighth higher in the rank among centers that concluded ISAAC phase I (23). As the prevalence of atopic diseases before the beginning of vaccination is unknown, it is impossible to make comparisons.

The incidence of measles in the general population decreased in all centers, except in Bahia. Although evidence that infection by measles virus (6) and hepatitis A virus (4) in early life can promote some protection against development of atopy, this topic is still controversial. A cohort study held in Guinea-Bissau reported significant reduction of the prevalence of atopy among children who survived to measles, and higher prevalence of deaths because of measles among atopic children. A low production of gamma interferon in these patients could explain higher measles morbi-mortality and warrant the reverse relation observed (6). Atopic patients are believed to present more serious forms of the disease, and seek medical care more frequently that would generate under-diagnosis of measles among non-atopic subjects (11). Paunio et al. in a cross-sectional nationwide study in Finland observed that measles and atopy occurred more frequently together than expected, which does not support the hypothesis that experiencing natural measles infection offers protection against atopic disease (9).

Destefano et al. (24) and Anderson et al. (19) reported no protective effect from measles vaccination in the development of atopic disease. In Brazil, the rate of vaccination against measles is greater than 98%. In our study there was reduction in measles incidence in all studied centers, except in Bahia. Notwithstanding we did not observe a homogeneous pattern in the prevalence of asthma, rhinoconjunctivitis and atopic eczema. A failure in the routine measles vaccination during 1996 justified the epidemic trend in 1997 (Fig. 2).

According to the hygiene hypothesis, proposed by observations in developed countries, the early exposure to infectious agents or endotoxins could influence the development of Th2 diseases. This paradigm for Brazil, generates an apparent paradox, for the higher prevalence of asthma and of tuberculosis notification. The paradigm of imbalance in the relation Th1/Th2 should be

realized as a dynamic and complex process, and besides, perhaps it is not possible to extrapolate time and space in a global manner.

As an ecologic study, our study has some limitations. Ecologic studies are population-based epidemiologic studies that link geographic or secular trends in mortality or morbidity of a particular disease with corresponding trends in the use of medications for its treatment, association with another disease, etc. These studies are inherently limited because their analyses are based on general population rather than individuals. No individual information is available on confounding factors that might explain away any association between the studied variable and the outcome (25, 26). Therefore, such potential confounding factors can be neither examined nor controlled for in the analysis. Nevertheless, such studies might provide useful information on the potential population impact of a disease, drug, etc. In this study the rates are of the state and may not reflect accurately local patterns of infection or exposition (15). The long-term follow-up in all our centers reinforces our observations (26).

In conclusion, our data do not confirm the presence of an immunomodulatory effect of exposure to Koch's bacillus or to measles virus and development of atopic disease. More studies are necessary in order to determine the real importance of these external influences on the immunologic system in the neonatal period and the possible consequences in late childhood that can influence the expression of asthma.

References

- LIU AH, SZEFLER SJ. Advances in childhood asthma: hygiene hypothesis, natural history, and management. *J Allergy Clin Immunol* 2003; 111: S785-92.
- KEMP A, BJÖRKSTÉN B. Immune deviation and the hygiene hypothesis: a review of the epidemiological evidence. *Pediatr Allergy Immunol* 2003; 14: 74-80.
- WARNER JO. The hygiene hypothesis. *Pediatr Allergy Immunol* 2003; 14: 145-6.
- MATRICARDI PM, ROSMINI F, FERRIGNO L, et al. Cross sectional retrospective study of prevalence of atopy among Italian military students with antibodies against hepatitis A virus. *Br Med J* 1997; 314: 999-1003.
- MEDEIROS M, Jr, ALMEIDA MC, FIGUEIREDO JP, et al. Low frequency of positive tests in asthmatic patients infected with *Schistosoma mansoni* exposed to high levels of mite allergens. *Pediatr Allergy Immunol* 2004; 15: 142-7.
- SHAHEEN SO, AABY H, HALL AJ, et al. Measles and atopy in Guinea-Bissau. *Lancet* 1996; 347: 1792-6.
- ALM JS, LILJA G, PERSHAGEN G, et al. Early BCG vaccination and development of atopy. *Lancet* 1997; 350: 400-3.
- STRANNEGARD IL, LARSSON LO, WENNERGREN G, et al. Prevalence of allergy in children in relation to prior

- BCG vaccination and infection of atypical Mycobacteria. *Allergy* 1998; 53: 249–54.
9. GRÜBER C, KULIG M, BERGMANN R, et al. Delayed hypersensitivity to tuberculin, total immunoglobulin E, specific sensitization, and atopic manifestation in longitudinally followed early Bacille Calmette-Guerin vaccinated and non-vaccinated children. *Pediatrics* 2001; 107: e36.
 10. PAHARI A, WELCH S, LINGAM S. BCG, tuberculin-skin-test results and asthma prevalence in school children in north London. *Indian Pediatr* 2002; 39: 254–8.
 11. REMES S, MAKELA M, MARSHALL J. Measles and atopy in Finland. *Allergy* 2000; 55: 973–4.
 12. PAUNIO M, HEINONEN O, VIRTANEN M, et al. Measles history and atopic diseases: a population-based cross-sectional study. *JAMA* 2000; 283: 343–6.
 13. ASHER MI, KEIL U, ANDERSON HR, et al. International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8: 483–91.
 14. National Foundation of Health (FUNASA), Brasilia, Brazil. Available at: <http://www.funasa.gov>. Accessed in July 2004.
 15. VON MUTIUS E, NEIL P, BEASLEY R, et al. International patterns of tuberculosis and the prevalence of symptoms of asthma, rhinitis and eczema. *Thorax* 2000; 55: 449–53.
 16. SHIRTCLIFFE P, WEATHERALL M, BEASLEY R, et al. An inverse correlation between estimated tuberculosis notification rates and asthma symptoms. *Respirology* 2002; 7: 153–5.
 17. VON HERTZEN L, KLAUKAKKA T, MATTILA H, et al. Mycobacterium tuberculosis infection and the subsequent development of asthma and allergic conditions. *J Allergy Clin Immunol* 1999; 104: 1211–4.
 18. SHIRAKAWA T, ENOMOTO T, SHIMAZU SI, et al. The inverse association between tuberculin responses and atopic disorder. *Science* 1997; 275: 77–9.
 19. ANDERSON HR, POLONIECKI JD, STRACHAN DP, et al. Immunization and symptoms of atopic disease in children: results from the International Study of Asthma and Allergies in Childhood. *Am J Public Health* 2001; 91: 1126–9.
 20. MARKS BG, NG K, ZHOU J, et al. The effect of neonatal BCG vaccination on atopy and asthma at age 7 to 14 years: an historical cohort study in a community with a very low prevalence of tuberculosis infection and high prevalence of atopic disease. *J Allergy Clin Immunol* 2003; 111: 541–9.
 21. GRÜBER C, MEINLSCHMIDT G, BERGMANN R, et al. Is early BCG vaccination associated with less atopic disease? An epidemiological study in German preschool children with different ethnic backgrounds. *Pediatr Allergy Immunol* 2002; 13: 177–81.
 22. OTA MO, VAN DER SANDE MA, WALRAVEN GE, et al. Absence of association between delayed type hypersensitivity to tuberculin and atopy in children in the Gambia. *Clin Exp Allergy* 2003; 33: 731–6.
 23. SOLÉ D, YAMADA E, VANA AT, et al. International study of asthma and allergies in childhood (ISAAC): prevalence of asthma and asthma-related symptoms among Brazilian schoolchildren. *J Invest Allergol Clin Immunol* 2001; 11: 123–8.
 24. DESTEFANO F, GU D, KRAMARZ P, et al. Childhood vaccinations and risk of asthma. *Pediatr Infect Dis J* 2002; 21: 498–504.
 25. SUISSA S, ERNST P. Inhaled corticosteroids: impact on asthma morbidity and mortality. *J Allergy Clin Immunol* 2001; 107: 937–44.
 26. FLETCHER RH, FLETCHER SW, WAGNER EH. *Epidemiologia Clínica: Elementos Essenciais*. 3rd edn. Porto Alegre: Artmed, pp. 281.