

# Editorial

## The International Study of Asthma and Allergies in Childhood (ISAAC): what have we learned?

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Knowledge of asthma prevalence has been increased greatly, especially in the last decade, through the development of two international collaborative studies: the *International Study of Asthma and Allergies in Childhood* (ISAAC) for children and adolescents; and the *European Community Respiratory Health Survey* (ECRHS) for adults. These studies were created as a response to the need for reliable data, obtained by reproducible methods and capable of providing categorical evidence of the increased prevalence of asthma and allergic diseases, which was frequently reported in the early 1990s.

The ISAAC was designed to maximize the value of epidemiological studies of asthma and allergic diseases, establishing a standardized methodology in order to facilitate the international collaboration. This study had the following specific objectives: a) to describe the prevalence and severity of asthma, rhinitis and eczema among children living in various locations and to draw comparisons among countries and among locations within specific countries; b) obtain baseline values in order to assess future tendencies in the prevalence and severity of these diseases; c) provide a structure for further etiologic studies into genetics, lifestyle, medical care and environmental factors that may affect these diseases<sup>(1)</sup>. The ISAAC was born out of two collaborative multinational studies of asthma in children, making it possible to standardize the written questionnaire (WQ) and video questionnaire (VQ) research instruments, both of which had been validated through pilot studies conducted in various countries, confirming their applicability and reproducibility<sup>(1)</sup>. The WQ, composed of three modules (asthma, rhinitis and atopic eczema), each comprising up to eight easily-understood, self-administered questions that do not depend on the presence of the interviewer (significant source of error)<sup>(1)</sup>.

Similarly to questionnaires used in other epidemiological studies, the ISAAC WQ (asthma module) consists of questions pertaining to asthma-

related symptoms, asthma severity and asthma diagnosis. In order to avoid memory errors, the majority of these questions refer to the preceding year. The VQ deals only with asthma, containing scenes of patients with asthma-related symptoms<sup>(1)</sup>.

When conducting an epidemiological study, some fundamental criteria must be met in order to guarantee comparability among results obtained at the various health care centers involved. In addition to the study design (sample size calculation, age bracket, sample selection, etc.), definition of the “cases” is essential. Most studies evaluating asthma identify “asthma sufferers” and categorize severity based on self-reported asthma-related symptoms. On the standard ISAAC WQ, the question “Have you ever had asthma?” refers to physician-diagnosed asthma. In locations where asthma is referred to by synonyms, this question has very low sensitivity, despite presenting high specificity. Various factors can interfere with responses to this query by those who have been diagnosed with asthma. Among such factors are understanding, acceptance and recollection of the diagnosis. On the standard ISAAC WQ, the question presenting the highest rates of sensitivity and specificity is “Have you experienced any wheezing within the last 12 months?”. Some authors have correlated this question with “current” or “active” asthma.

After the standard ISAAC WQ had been translated into (Brazilian) Portuguese, it was validated (by criteria) and applied in asthmatic adolescents who had been in regular follow-up treatment at a specialized clinic for over a year. Analysis of the responses given by these patients showed that nearly all reported “wheezing within the last 12 months”, and only half responded positively to the “Have you ever had asthma?” question, confirming the underdiagnosis caused by using the latter question as a criterion for the selection of cases<sup>(2)</sup>.

The initial phase of the ISAAC terminates with the publication of the results obtained from the various researchers who employed the protocol in an independent fashion, some of whom made

modifications to the standard WQ. The most significant change was the inclusion of a synonym for asthma (“bronchitis”) in the question about the medical diagnosis. The modified WQ identified similar frequencies of affirmative responses to the questions “Have you experienced wheezing within the last 12 months?” and “Have you ever had asthma or bronchitis?”. However, since the standard WQ was altered, direct comparison of these results with those from other locales was not possible. In a previous study, we added the question “Have you ever had bronchitis?” to the standard WQ and determined that the frequency of affirmative responses to this question was identical to that of the question “Have you experienced wheezing within the last 12 months?”, reinforcing the assumption that, in our milieu, the inclusion of synonyms for asthma is unnecessary.

Despite this evidence, there is still uncertainty regarding the power of the question “Have you experienced wheezing within the last 12 months?” in identifying “cases”. In an attempt to lay this question to rest, we determined the constructive validity of the standard WQ, using patients with bronchial hyperreactivity (proven by bronchoprovocation with methacholine) as a reference for comparison. We found that, in the identification of “cases”, this question presented higher rates of sensitivity, specificity, concordance, positive predictive values and negative predictive values than did any other<sup>(3)</sup>.

The first ISAAC phase, concluded in 1996, brought together groups never before evaluated. In this phase, 119 facilities in 45 countries spanning every populated continent (Europe, Asia, Africa, North America, South America and Oceania) participated. In 74 facilities (in 34 of those countries), 208,723 school children (aged 6 to 7) and 366,106 adolescents (aged 13 to 14) were interviewed. The preliminary analysis of the data shows great variation among the results. The prevalence of “wheezing within the last year” ranged from 1.6% to 27.2% in the 6 to 7 age bracket and from 1.9 to 34.1% for those from 13 to 14 years of age. Physician-diagnosed asthma varied from 1.3% to 30.8% among the school children and from 1.8% to 30.2% among the adolescents. The lowest values were reported in the Republic of Georgia, in the Republic of Estonia and in the areas of higher elevation in Australia<sup>(4)</sup>.

In Brazil, seven health care centers (located in the cities of Recife, Salvador, Uberlândia, Itabira, São Paulo-Sul, Curitiba and Porto Alegre) participated in

the study. A total of 13,604 school children (6 to 7 age bracket) and 20,554 adolescents (13 to 14 age bracket) were evaluated. The mean prevalence of physician-diagnosed asthma was higher among boys than among girls, (7.3%, 4.9%, 9.8% and 10.2% for 6-, 7-, 13- and 14-year-old boys, respectively)<sup>(5)</sup>. The prevalence of “wheezing within the last 12 months” among school children ranged from 16.1% (in Itabira) to 27.2% (in Recife and Porto Alegre), whereas, among the adolescents, this ranged from 9.6% (in Itabira) to 24.7% (in Recife) to 27.1% (in Salvador)<sup>(5)</sup>. These data confirm that the prevalence of physician-diagnosed asthma is lower than that of “wheezing within the last 12 months”, supporting the proposition that use of the former criterion leads to underdiagnosis. Another important point is regarding asthma severity, which was unrelated to prevalence, as evidenced by the fact that the more severe forms of asthma were observed at a greater frequency in Itabira<sup>(5)</sup>. In comparison to the other participants in phase I of the ISAAC, Brazil is in eighth place among the countries with higher rates<sup>(4)</sup>.

The results obtained in phase I confirm that the ISAAC is a protocol of great value in epidemiological studies of asthma in children and adolescents. It has made it possible for researchers other than those involved in the project to use the same method and instrument to obtain data in other locations, as was done in the study conducted by Boechat et al., published in this issue of the *Jornal Brasileiro de Pneumologia* (Brazilian Journal of Pulmonology)<sup>(7)</sup>. The data collected by the authors showed prevalence rates that were higher than those obtained in Brazil by the end of phase I of the ISAAC. Even when compared to the combined data from children evaluated at all other Brazilian health care centers using the standard WQ (23,457 school children and 40,111 adolescents), the mean prevalence of “wheezing in the last 12 months” in the Boechat et al. study was higher among school children (27.7% for 6 year olds and 25.7% for 7 year olds) and lower among adolescents (21.4% for 13 year olds and 19.9% for 14 year olds).

In conclusion, the ISAAC was a landmark global study of asthma and allowed us to determine that the prevalence of asthma in Brazil is high, reaching levels seen in more developed countries. Employing physician diagnosis of asthma as a criterion for identifying “cases” resulted in underdiagnosis and prevented us from determining the true dimensions of asthma in our country. The results of ISAAC

phase III, recently completed and as yet unpublished, will be important for assessing whether in Brazil, as in other countries, the prevalence of asthma in Brazil is on the rise.

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## Pursuing MEDLINE

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The MEDLINE system, sponsored by the United States National Library of Medicine (NLM) is the most important online database of scientific journals in the area of biomedicine. The system evolved out of the union of the Index Medicus, last published in 2004, and other, lesser, databases. Access to MEDLINE is available for free on the Internet, and the database is consulted daily by thousands of researchers and professionals in the areas of health and biological sciences. In these fields, there are approximately 14,000 journals in current publication worldwide. Of those, approximately 4800 are listed in MEDLINE<sup>(1)</sup>.

The members of the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Society of Pulmonology and Phthisiology) have long hoped that the *Jornal Brasileiro de Pneumologia* (JBP, Brazilian Journal of Pulmonology) would be selected for indexing in MEDLINE. We are frequently asked when this will occur. To answer to this question, it is necessary to explain the process by which journals are evaluated by the NLM.

The decision as to whether or not a journal will be indexed in MEDLINE is ultimately made by the director of the NLM, based on advice given by the Literature Selection Technical Review Committee (LSTRC). The final decision should be made in accordance with the general policies adopted by the LSTRC, which are in turn dictated by the Board of Regents of the Library<sup>(2)</sup>. The LSTRC is composed of fifteen members, each affiliated with the National Institutes of Health, and meets three times per year. At every meeting, approximately 140 indexing requests, from journals the world over, are evaluated<sup>(1,2)</sup>. The committee analyzes the last four issues of each petitioning journal. On average, only 25 to 30% of the journals evaluated are selected for indexing.

The LSTRC evaluates a journal in various aspects<sup>(2)</sup>:

a. Scope and coverage: The journal should contain articles predominantly on core biomedical subjects.