

# The ISAAC Story



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## ISAAC's Beginnings

The International Study of Asthma and Allergies in Childhood is a unique worldwide epidemiological research programme established in 1991 to investigate asthma, rhinitis and eczema in children due to considerable concern that these conditions were increasing in western and developing countries, and that the causes of this increase were unknown.

ISAAC developed from a merging of two multinational collaborative projects each investigating variations in childhood asthma at the population level. These were an initiative from Auckland, New Zealand to conduct an international comparative study of asthma severity, and an initiative from Bochum, Germany to conduct an international study to monitor time trends and determinants of the prevalence of asthma and allergies in children.

This section charts the development of ISAAC from its early origins to its current global coverage and organisational structure. This history is summarised chronologically in a timeline and embellished with personal memories of some of the founder members of the consortium.

Here we present the global perspective on the ISAAC Story. More detail on the history within each region and study centre may be found under "Centres".

## Rationale for ISAAC

At the time that ISAAC was conceived, in the early 1990s, most previous research had looked at the reasons why some individuals rather than others develop asthma and allergic conditions such as allergic rhinitis and eczema. A major risk factor was a family history of atopic disease, but various environmental factors had been also considered important in the expression of disease. Such studies within populations had shed little light on the reasons why the occurrence of atopic disease varies from population to population.

Factors affecting the prevalence of disease at a population level may be different to those that determine which individuals within a population were at greatest risk. In addition, between populations the relationship between the three atopic conditions may be different. It was therefore considered likely that "ecological" (between-population) analyses might reveal further important determinants of asthma, allergic rhinitis and eczema. There was also widespread concern that these conditions were increasing in both developed and developing countries, but there was a lack of information on the burden of allergic diseases in many parts of the world.

One obstacle to the investigation of population differences (and of trends) had been the lack of a suitable and generally accepted method of measuring the prevalence and severity of asthma and other atopic diseases in children which could be used worldwide. Another obstacle was the absence of a coordinated research programme to obtain and analyse comparative data. The International Study of Asthma and Allergies in Childhood (ISAAC) programme was developed in 1991 to address these issues.

## Aims of ISAAC

ISAAC, the International Study of Asthma and Allergies in Childhood, was formed in 1991 to facilitate research into asthma, allergic rhinitis and eczema by promoting a standardised methodology able to be used in diverse locations around the world. From an early stage, it was conceived as comprising three phases:

The aims of ISAAC Phase One were:

1. To describe the prevalence and severity of asthma, rhinitis and eczema in children living in different centres and to make comparisons within and between countries;
2. To obtain baseline measures for assessment of future trends in the prevalence and severity of these diseases; and
3. To provide a framework for further aetiological research into lifestyle, environmental, genetic and medical care factors affecting these diseases.

The aims of ISAAC Phase Two were:

1. To describe the prevalence of 'objective' markers of asthma and allergies in children living in different centres, and to make comparisons within and between centres.
2. To assess the relation between the prevalence of 'objective' markers of asthma and allergies and the prevalence of symptoms of these conditions in children living in different centres.
3. To estimate to what extent the variation in the prevalence and severity of asthma and allergies in children between centres can be explained by differences in known or suspected risk factors or by differences in disease management.
4. To explore new aetiological hypotheses regarding the development of asthma and allergies in children.

The aims of ISAAC Phase Three were:

1. To examine time trends in the prevalence of asthma, allergic rhinoconjunctivitis and atopic eczema in centres and countries which participated in ISAAC Phase One.
2. To describe the prevalence and severity of asthma, allergic rhinoconjunctivitis and atopic eczema in centres and countries which did not participate in Phase One.
3. To examine hypotheses at an individual level which have been suggested by the findings of Phase One, subsequent ecological analyses and recent advances in knowledge.

## ISAAC Milestones

- 1991 Launch of ISAAC
- 1993 First publication
- 1994 Core questions
- 1995 Global coverage
- 1997 Phase 1 papers
- 1998 Phase 2 modules
- 1999 Phase 3 planned
- 2001 Phase 3 modules
- 2004 Guinness record
- 2006 Time trend paper
- 2008 Phase 3B maps
- 2011 500th publication



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Subsequently, ISAAC Phase Four was conceived as the development and expansion of the scope of website resources for ISAAC collaborators, especially those in low and middle income countries. It included the addition of management plans and other resources that are useful for managing asthma, eczema, and rhinitis.

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## Origins of ISAAC

ISAAC developed from a merging of two multinational collaborative projects each investigating variations in childhood asthma at the population level. These were an initiative from Auckland, New Zealand to conduct an international comparative study of asthma severity, and an initiative from Bochum, Germany to conduct an international study to monitor time trends and determinants of the prevalence of asthma and allergies in children. This section of the ISAAC Story collates the recollections of founder members of the consortium about the early development of ISAAC as a global study.

### Asthma epidemiology in the 1980s

*(Michael Burr)*

There is a long history of surveys of childhood asthma in various countries. When the findings of these surveys were compared, it was clear that reported asthma prevalence showed considerable geographical variation. Until relatively recently, each survey used its own methods, so that it was unclear whether the reported differences in prevalence could be attributable to variations in aspects of the methodology, e.g. the way children were selected, local diagnostic criteria, the way questionnaires were administered, the wording of the questions, and the conduct of challenge tests. But a comparison of surveys that used fairly similar methods suggested that the prevalence of childhood asthma was higher in New Zealand than in the United Kingdom.

The first survey planned to compare the prevalence in different countries was perhaps the study of Tokelau Islanders in New Zealand and Tokelau. In 1975-1976 surveys of asthma were conducted among Tokelauan children living in New Zealand and Tokelau, using the same methods (questionnaire and physical examination). Asthma, rhinitis and eczema were all substantially more common in New Zealand than in Tokelau; the differences were ascribed to environmental rather than genetic factors in that both groups of children were of predominantly Tokelauan descent.

In the early 1980s there was growing concern about a sudden rise in asthma mortality in New Zealand during the previous decade. This had not occurred in Australia, Canada, USA or England and Wales; furthermore, hospital admissions for asthma and sales per capita of asthma drugs had also increased disproportionately in New Zealand. The question obviously arose as to whether asthma prevalence was also higher in New Zealand. So in 1985 Innes Asher and others conducted a survey in Auckland, NZ, following the same protocol that had been used three years earlier in two areas of Australia. In each country the subjects were mostly 8 or 9 years old, and the survey employed a respiratory questionnaire and bronchial challenge with histamine. The prevalence of respiratory symptoms and bronchial hyperresponsiveness was similar in Auckland and inland New South Wales but lower in coastal New South Wales than in the other two sites.

The Auckland data were also compared with the findings of a survey in Croydon, England, which had been conducted in 1978. The prevalence of wheeze in the last month, the last 12 months and over the whole lifetime was significantly higher in Auckland than in Croydon; some uncertainty about the conclusions was expressed, however, in that neither the procedure nor the questions were identical, and during the 7-year interval between the surveys the prevalence in Croydon might have changed.

In order to compare asthma prevalence in several countries using the same protocol in each case, a survey was conducted in defined areas of Wales, New Zealand, Sweden and South Africa in 1988-1990. A questionnaire was completed by the parents of 12-year-old children asking about a history of asthma and respiratory symptoms, and the children performed a simple exercise challenge test. Asthma prevalence (determined by various criteria) was highest in New Zealand and lowest in Sweden; asthma mortality in children showed a similar pattern. Thus this study strengthened the evidence for real international differences in asthma prevalence, the disease being particularly common in New Zealand.

Interest in possible geographical variations in asthma was not confined to the disease in children. There was less information about asthma prevalence in adults, and valid comparisons between different areas were impossible because of the lack of any standardised methodology. During the 1980s, to rectify this situation, the International Union against Tuberculosis and Lung Disease began to develop standard methods for studying the epidemiology of asthma, including a questionnaire that would be suitable for large-scale surveys. In 1988 the European Commission funded a study that became known as the European Community Respiratory Health Survey (ECRHS), which would use this questionnaire and various tests to investigate asthma prevalence in people aged 20-44 years. The survey was conducted during the early 1990s in many countries; although it was primarily based in Europe, a few other areas participated, including four centres in New Zealand, where asthma prevalence was again found to be particularly high. Subsequent cross-fertilisation between ECRHS and ISAAC has occurred, including the enlisting of centres in one of these surveys leading to recruitment for the other.

Meanwhile, the development of a questionnaire for use in international surveys of children was stimulated by contact between investigators in Auckland and Bochum, Germany. The ensuing discussions led to a survey in New Zealand, Germany, England and Australia in 1991 that used the ISAAC protocol and was the forerunner of the main ISAAC study. Various indices of asthma (including the use of a video questionnaire) showed a higher prevalence in the Australasian centres than in Germany.

Thus New Zealand has played a prominent part throughout the development of international studies of asthma, arising out of concern about asthma mortality and morbidity in that country. It is entirely appropriate that the ISAAC International Data Centre should be located there.

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## The origins of ISAAC: a German perspective

(Ulrich Keil)

At the beginning of 1987 I had started to build up an Institute of Epidemiology and Social Medicine at the Medical Faculty of the University of Bochum. In 1987 the Federal Ministry of Research and Technology (BMBF) in Bonn approached a number of German epidemiologists to develop a manual for the planning and execution of epidemiological studies in the area of asthma and allergic diseases. They reported that a comprehensive research program would soon be announced to shed more light on the aetiology and medical care of asthma and allergies.

In light of the BMBF's experience with the German Cardiovascular Prevention Study (Deutsche Herzkreislaufpräventionsstudie, DHP) in the 1980's, which had cost a hundred million Deutsche Mark but had produced only meagre scientific output, the responsible people at the BMBF wanted to make sure that the envisaged nationwide research program for asthma and allergies should perform better. This is why they called on a number of leading epidemiologists in Germany to develop the above mentioned Manual.

Eight epidemiologists gathered in 1987 in Bochum and other sites in Germany and started developing the requested manual, resulting in a paper published in 1988 by "Berger J, Bergmann KE, Greiser E, Keil U, Lehmacher W, Schäfer H, Schwartz FW, Wichmann HE. Manual für die Planung und Durchführung epidemiologischer Studien auf dem Gebiet allergischer Krankheiten" was published in the journal *Allergologie* (*Allergologie* 1988;11:479-92). This manual was meant to be adhered to when studies in the field of asthma and allergies were being planned and developed, and research proposals being written.

My involvement in the writing of this manual in the years 1987 to 1988 acquainted me with the field of asthma and allergic disease epidemiology, which I had touched only sporadically, previously. Before, during and after the publication of this manual I had worked in the field of cardiovascular epidemiology and prevention and in the field of occupational epidemiology, and have continued to do so since.

In 1989 Stephan Weiland applied for a job at my institute in Bochum. He was a young physician from Cologne who had just returned from McGill University in Montreal with a Master of Science degree in epidemiology, but no practical experience in epidemiology. He expressed an interest in pediatric epidemiology and this coincided with the BMBF's official announcement of a comprehensive research program on asthma and allergic diseases and a request for proposals.

Stephan started working at my institute in January 1990 and we decided to apply for a research grant from this BMBF program. As we were rather ignorant about asthma and allergies we decided to travel to London and see Ross Anderson and David Strachan at St George's Hospital Medical School. We received a warm welcome by Ross and David, who put aside a full working day for us and informed us about all they knew about asthma and allergic disease epidemiology. (Bonnie Sibbald informed us about the epidemiology of rhinitis). Coming from the German university system we were quite surprised how well we strangers from Germany were treated.

On our return to Bochum we were full of new ideas and had a good feeling that we might be successful in developing a grant proposal. One request of the BMBF program was that we should get together with other research groups in Germany and develop a collaborative research program. Following this line we contacted a number of interested colleagues in Germany but our major interest was to stay in close contact with international groups. From Ross and David we had learned about research initiatives in Auckland, New Zealand, and from my 1986 sabbatical in Chapel Hill, North Carolina, I knew Neil Pearce from Wellington and his interest in asthma research.

In light of my 10 year experience with the World Health Organisation's MONICA (Monitoring trends and determinants in cardiovascular disease) project we planned for an international workshop with the title "Monitoring Trends of Asthma and Allergies". This workshop took place in Bochum on December 2-5, 1990 and was funded by the BMBF. The research groups from London, Auckland, Wellington and Bochum and additional groups from Germany were well represented. Stephan Weiland wrote the minutes of this workshop and they formed the basis for further developing our ideas and planning for the next international workshop with the title "Monitoring Trends of Asthma and Allergies in Childhood" which again took place in Bochum one year later, namely from December 8-11, 1991. This time the Institute of Social Medicine and Epidemiology of the Ruhr Universität Bochum funded the workshop which was instrumental in choosing the target population, namely children and adolescents, discussing the study design and protocol and the data collection instruments, thus laying the foundation for the worldwide International Study of Asthma and Allergies in Childhood (ISAAC).

I have very good memories of those two December workshops in Bochum, not only because of the wining and dining, but also because participants were very open and positive and because there were excellent presentations and a lot of fruitful discussion which helped producing the ISAAC protocol (Manual) with the written and video questionnaires in 1992.

In the same year a pilot study was started, comprising populations of 12-15 year olds in Wellington (New Zealand), Adelaide and Sydney (Australia), West Sussex (England) and Bochum (Germany). The results of this pilot study were published in 1993 in the *European Respiratory Journal* under the title "Self-reported prevalence of asthma symptoms in children in Australia, England, Germany and New Zealand: An international comparison using the ISAAC written and video questionnaires." *Eur Resp J* 1993;6:1455-1461. A year later the pilot study data from Bochum served for another paper with the topic "Self-reported wheezing and allergic rhinitis in children and traffic density on street of Residence", published in *Ann Epidemiol* 1994;4:243-247.

In the beginning of 1993 I moved from the Ruhr Universität Bochum to the University of Münster and again built up an Institute of Epidemiology and Social Medicine. Stephan Weiland followed me to Münster, enabling us to continue our work with ISAAC. For ISAAC Phase One we established two study regions in Germany, one in the city of Münster (northwestern part of Germany) and one in Greifswald, which lies in the northeastern part of the country. The irony of the ISAAC story is that we started out in Bochum to develop a research proposal for the

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BMBF to receive funding for a collaborative asthma study in Germany. However, our international contacts and the two workshops in Bochum helped to pave the way for the worldwide ISAAC Study; the original intention to start a Verbundprojekt in Germany (Collaborative asthma study in Germany) materialised only in the mid 1990's, when we established study sites and regions in Dresden and Munich, loosely connected also to the study in Leipzig. The Verbundprojekt targeted 10 year olds and unlike ISAAC Phases I and III incorporated clinical measurements and blood samples, thus helping to create ISAAC Phase II.

## The origins of ISAAC: a New Zealand perspective

*(Innes Asher)*

Origins of ISAAC - New Zealand perspectives

New Zealand started focusing on asthma in earnest in 1979 when it became apparent that a new epidemic of asthma deaths had arisen in 1977, affecting New Zealand more than any other country. This stimulated a range of programmes of research exploring the reasons for this epidemic starting with a prospective national asthma mortality study which confirmed the epidemic. A focus on admission to hospital for asthma found that these were increasing dramatically in New Zealand, Australia, The United Kingdom, Canada and USA and the highest rates were in New Zealand children.

Although deaths from asthma among children are relatively uncommon, the escalating admission rate combined with anecdotal reports of increasing severity, awakened a great deal of interest in finding out more about the prevalence and severity of asthma in New Zealand children, and comparisons with other countries. There had been a few previous childhood asthma prevalence studies in New Zealand, and none used identical methods, so comparison between centres and over time were limited. This led to the design of a study of asthma prevalence in children using standardised methods in centres across countries - Auckland, New Zealand and Belmont and Wagga Wagga, New South Wales, Australia - one of the first international comparison of asthma prevalence using standardised methods. The prevalence of current wheezing and bronchial hyper-responsiveness (using an abbreviated histamine challenge) did not differ between Auckland and Wagga Wagga, but the rates were lower in Belmont.

The finding of little difference in prevalence of asthma between New Zealand and Australia, combined with continuing concern about the possibility of a higher prevalence of severe asthma in New Zealand led our interest in developing a study to explore international differences in severity of asthma in children using standardised methods. Hospital admission rates were available for some English -language countries and showed international differences, but that may have reflected variations in provision or use of health services. Both hospital admissions and mortality rates could not be interpreted easily without better information on prevalence and severity.

During 1990 I contacted centres in Australia, Canada and the United Kingdom about collaborating on an international study of the severity of asthma in children. The concept was to use the "core protocol" approach to the asthma questionnaire developed by Ed Mitchell, Colin Robertson and Ross Anderson in London 1988. The concept of simple but standardised tools designed for widespread use (and based on questionnaires, rather than measures such as bronchial hyperactivity) was accepted, and the questionnaire was further developed. By 15 September 1990 investigators in eighteen centres in five countries were committed in principle to the project: Australia: Melbourne, Sydney, Perth; Canada: Gainesville, Seattle, Tucson; New Zealand: Auckland, Christchurch, Dunedin, Hastings, Nelson, Wellington; United Kingdom: Cardiff, Edinburgh, London, Southampton; USA: Hamilton and Saskatoon.

We were awarded a grant from the Health Research Council of New Zealand (HRCNZ) on 29 November 1991 to compare the prevalence and severity of childhood asthma in two age-groups of children both between countries and within New Zealand (by area and ethnic group). This covered fieldwork in Auckland, Wellington and Christchurch, a full-time data manager, and secretarial and computing support. The funding remained conditional upon at least one other centre outside New Zealand obtaining funds for a similar survey in their own centre. (On 1 April 1992 David Strachan of The Department of Public Health Sciences St Georges Hospital wrote confirming they had funding for a centre in southern England). The HRCNZ funding was activated on 1 July 1992 and did not extend to future studies to assess time trends, nor to detailed investigation (by case-control studies) of aetiological and medical care factors (genetic, cigarette smoke, aeroallergens, pollution, infections, drug use, preventive care, management of acute attacks). Some concerns had been expressed by the Health Research Council about the validity of questionnaire-based- measures, including their reproducibility, correlation with BHR and validation between centres, particularly where translation was involved. There were also issues relating to the choice of centres within each country and the statistical effects of cluster sampling by school.

At about the same time Ulrich Keil and Stephan Weiland were developing ideas for epidemiological studies of asthma and allergic disease in Germany, including baseline surveys for future assessment of time trends. During the first Bochum meeting in December 1990, international comparisons were also discussed and a similar conclusion was reached about the desirability of a core protocol. The original Auckland proposal had focused on asthma, whereas the German interest also included allergies. At the same time Julian Crane and Neil Pearce introduced the idea of a video questionnaire to overcome cultural and linguistic barriers in ascertaining the prevalence of respiratory symptoms. In March 1991, the Bochum and Wellington groups met with Innes Asher in Auckland and the two proposals were merged. This was welcomed by all parties.

By the time of the Bochum meeting in December 1991 there were fewer than 30 centres in the world where the prevalence of asthma in children had been studied at all, and most had used different methodology.

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## The origins of ISAAC: a United Kingdom perspective

*(Ross Anderson)*

During 1990, an informal meeting was held at St George's Hospital Medical School, London, between ourselves and Colin Robertson. We discussed ideas for developing an asthma questionnaire which would include measures of severity which were relevant in children. Colin's interest and expertise related to the long standing follow-up study of wheezy children in Melbourne originated by Howard Williams in the 1960s. We drew on ideas from the surveys that had been completed in Croydon, south London, during 1978 and which we planned to repeat in 1991 to obtain information on time trends in our area. Specifically, the question about wheeze that caused difficulty with speaking had been validated in terms of hospital admissions for asthma in Croydon.

Later in 1990, Ulrich Keil and Stephan Weiland contacted us "out of the blue" requesting a meeting. They had made a day trip from Bochum to St George's and explained that there was a desire by the German Government for research into allergy and Ulrich was seeking expert advice on methods.

Ross had already had some contacts with a number of the Auckland and Wellington investigators. Neil had visited St George's to talk about the fenoterol studies. Innes had been to the UK with the results of her children's survey and in 1988 Ross had been a visiting lecturer at the annual Boehringer respiratory symposium. Thus, there was already the basis for collaboration between St George's and New Zealand.

At the end of 1990 was the first meeting organised by Ulrich at Bochum. Attending from St George's were Ross Anderson, David Strachan and Bonnie Sibbald. The meeting included several classic dialogues and debates between epidemiologists and clinicians over methods (diagnostic accuracy versus unbiased ascertainment; the need to consider allergic disease not just asthma) and beginnings of understanding that factors affecting prevalence in populations may be different from risk factors within populations. The meeting had difficulty in agreeing on details of questionnaires. Just as the discussion seemed to be going nowhere, David produced from his briefcase the draft questionnaire that had been developed between the St George's group and Colin earlier in the year. This put something on the table and helped to focus the discussions, at least concerning asthma.

Eventually the epidemiologists "won" on the principle of using symptoms (manifestational criteria) rather than doctor diagnosis for international comparisons. However, at this stage, we had very little independent validation of the specific questions. There was a natural tendency to promote questions that we had used in our own surveys. Examples which were eventually included in ISAAC instruments are the difficulty in speech question (Croydon), the frequency of attacks question (Auckland) and the video questionnaire (Wellington).

In retrospect, we think that one of the greatest mistakes was not to include, as core, some non-asthma respiratory questions such as cough and phlegm. This would have made the questionnaire a general respiratory one, not just an enquiry about asthma symptoms. (Within ISAAC UK Phase One, carried out in 1995, we added questions on cough and phlegm which proved interesting in relation to indoor environmental risk factors.) Indeed, there is still no general respiratory equivalent to the ISAAC asthma questionnaire, as has become apparent recently while Ross has been reviewing the air pollution literature for developing countries. The range of questionnaires used in published studies is considerable, which makes international comparisons and meta-analysis problematic.

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## The origins of Phase Two surveys in Germany

*(Erika von Mutius)*

At the end of the 1980's, epidemiological studies were scarce in Germany. The prevalence of asthma and atopy was unknown, and risk factors have not been investigated in German populations. A colleague of mine, Thomas Nicolai and I designed a cross-sectional survey, enrolling all children in primary schools in Munich and the rural area around Munich. Since the potential adverse effects of air pollution were a major theme in these days, we wanted to compare prevalence rates between urban and rural areas. We designed questionnaires according to our clinical history taking approach and asked the children to perform spirometry and cold air challenges as well as to undergo skin prick tests as objective markers of disease. We had started the fieldwork in September 1989.

Then, in November 1989 the Berlin wall fell. Thomas Nicolai and I had always argued that West Germany was just not polluted enough to show adverse effects on asthma but that studies on pollution levels such as those encountered in the GDR would prove that there was indeed an effect. Such studies had been politically impossible until this time. With the sudden opening of the German border we thought that there was an opportunity. Through various contacts that were difficult to establish we found colleagues in East Germany, i.e. Hans-Heinrich Thielemann in Halle and Christian Fritzschn in Leipzig. These were wonderful people full of excitement and optimism for a better future and were willing to conduct the first East/West German study without any funding. We copied questionnaires in Munich, collected all our lung function equipment from the Munich survey and transported it to Leipzig. A colleague from North Germany, Professor Helgo Magnussen sponsored a cold air challenge device, and we instructed the colleagues in Leipzig to perform exactly the same study as in Munich, with the exception of skin prick testing which we could not afford. The statistical team at GSF in Munich entered the data and performed the statistical analyses. We were rather incredulous when we saw the results, which indicated less asthma and hay fever in polluted Leipzig as compared to Munich. In fact, we discussed whether the data needed to be re-entered.

Meanwhile, Stephan Weiland had appeared on my scene. Stephan had trained in epidemiology at McGill and upon his return he had a dream. Like the big cardiovascular MONICA study he wanted to establish a large survey for asthma. Ulrich Keil had contacts with David Strachan and Ross Anderson in London and Neil Pearce in Wellington, New Zealand. Stephan invited them to Bochum for a meeting - the first meeting of what would become ISAAC, the International Study of Asthma and Allergies in Childhood. This meeting on a grey December day in 1990 at the University of Bochum was decisive. ISAAC was born! At this first ISAAC meeting I met Fernando Martinez who had come as a substitute for Ben Burrows from Tucson, Arizona, USA.

Later I showed Stephan our first East/West German findings from Leipzig. He immediately understood the impact and offered to help write the paper as he was fluent in English after his fellowship whereas I was struggling with this foreign language. Stephan also strongly recommended that I should leave for a fellowship to the US or Canada. Given that Fernando was the only American I knew and that he had impressed me at the first ISAAC meeting, I asked him if I could come for a fellowship to work with him. At the second ISAAC meeting one year later he confirmed that I would become his first fellow. Meanwhile, the political landscape in Germany was strongly in favour of collaborative studies between East and West Germany. Stephan and I applied for a second survey in Halle and Leipzig, East Germany, to include skin prick testing to corroborate the questionnaire data. The first ISAAC phase II study was performed in Halle, East Germany, and Munich, West Germany. In the ISAAC phase II study we corroborated the findings of the first study using skin prick tests and hypertonic saline challenges as the ISAAC protocol had recommended. We had also developed a large and comprehensive questionnaire, inquiring about the ISAAC core questions for outcome definitions and a number of environmental exposures. This questionnaire was then used for the further development of the ISAAC Phase II questionnaire.



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## The ISAAC Toolbox

Early in the development of the ISAAC study it became apparent that there were no widely accepted tools for international surveys of asthma prevalence in children. Although many questionnaires and measurement tools had been used successfully for epidemiological studies within a single centre, they were often heavily dependent upon the local patterns of clinical diagnosis and were therefore poorly suited for international comparisons. From the beginning, therefore, ISAAC developed its own epidemiological instruments, initially for asthma, but soon extending to questionnaires for other allergic conditions, and to objective measurements of bronchial hyperresponsiveness, allergic sensitisation and atopic eczema. This section charts the development of these tools, which are now widely used both within ISAAC and by other investigators.

### The written questionnaire for asthma and wheezing

*(David Strachan, Ross Anderson, Colin Robertson)*

During 1990, an informal meeting was held at St George's Hospital Medical School, London, between Ross Anderson, David Strachan and Colin Robertson. We discussed ideas for developing an asthma questionnaire which would include measures of severity which were relevant in children. Colin's interest and expertise related to the long standing follow-up study of wheezy children in Melbourne originated by Howard Williams in the 1960s. We drew on ideas from the surveys that had been completed in Croydon, south London, during 1978 and which we planned to repeat in 1991 to obtain information on time trends in our area.

Two key concepts guided the development of specific questions. Firstly, the principle of using symptoms rather than diagnosis for international comparisons, and secondly, the recognition that there were several dimensions to asthma severity: frequency of attacks, intensity of attacks, and persistence of symptoms. Thus, a child could have only one or two attacks in a year, but if these were intense enough to result in admission to hospital, that would be considered severe. On the other hand, a child might be persistently troubled by wheezing but they or their parent might not recognise discrete episodes or attacks of symptoms.

At this stage, we had very little independent validation of specific questions, so there was a natural tendency to promote questions that we had used in our own surveys. Frequency of attacks of wheezing had been used in surveys in Auckland, and speech-limiting wheeze and sleep disturbance due to wheezing had been included in the Croydon surveys. The question about wheeze that caused difficulty with speaking had been validated in terms of its correlation with hospital admissions for asthma among 8-9-year-olds in Croydon.

It is important to note that the questions were selected because of prior experience with their use in English-speaking populations, with children mainly of primary-school age and with responses by the parent rather than by the child. Their adoption within the ISAAC core questionnaires led to their use in teenage children (self-reporting their own symptoms) and translation into many languages. Uncertainties about how reliably the written questions would perform in a different age group and in different languages and cultures led to the interest in developing a video questionnaire for administration alongside the written one. This is described in the next section.

### The video questionnaire for asthma and wheezing

*(Julian Crane)*

The idea for the video questionnaire and for using video sequences in questionnaires came from my early research in the Tokelau Atolls. We conducted a couple of surveys in Tokelau on 2 out of the 3 atolls and during development of the questionnaires and their translation and back translation from English to Tokelauan and Tokelauan to English I was struck by problems around the term wheezing. It turned out, as in other languages, that the term for wheezing also had many other meanings in Tokelauan including shortness of breath and coughing. This led to quite a lot of difficulty of questionnaire preparation.

When I was actually in Tokelau we conducted our surveys through the schools and as Tokelauan was an entirely oral language and in fact while we were on the atolls was in the process of having its first grammar developed by a Norwegian linguistic anthropological group of researchers (that's another story), it was evident that in the school environment there were relatively few books but video tape recorders and many video recordings and indeed amongst the general, few books in anyone's houses but many videos and it was clear that much of the information that Tokelauans collected and learnt came from video recordings. That first gave me the idea that a recording showing wheezing with a good soundtrack might be useful.

We thus started to film asthmatic adults and children initially in the wards and in outpatients and occasionally in Accident and Emergency and started to develop sequences which included exercise, nocturnal coughing and wheezing and then more severe cases and then as you know we developed an initial version in which we did some validation work.

This was a group effort to validate the questions both against the written questions that had been developed for ISAAC and also against airway hyper responsiveness to methacholine. This process was actually led by Robyn Shaw, whom I am sure you will know, now a paediatrician at the Hutt Hospital, who was working with us as a Research Fellow at the time and I think she incorporated some of this into her MD thesis as well as the publications.

We undertook the validation here in schools and subsequently published that. Other people have of course validated various other aspects of the video questionnaire along the way. The video questionnaire, I think, at some stage won the TSANZ poster prize with some confusion as to whether it was a poster or an audiovisual presentation as we presented it on video screens at the poster site.

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Subsequently when it was begun to be thought about to use it internationally there were issues of, for example having men and women exercising together which wouldn't be acceptable in the Islamic community and also that it was very European 'white' based. That led us to ask for sequences from various people. We received one from India, some from Chris Lai in Hong Kong and others and put together the final series of sequences that were used in the ISAAC study although as you know the European ISAAC was used first and then later we used the international version with the first sequence retained throughout all videos.

A number of groups around the world have used the video often in conjunction with the written ISAAC questionnaire and I did make two attempts to have funded a much wider development of the video concept given that I think using audiovisual presentation of symptoms could actually be very valuable in many different circumstances where the visual and or audio presentation might be most useful. For example, breathlessness I thought would be one, possibly distinguishing fits and faints and also in the assessment of sleep apnoea and snoring amongst others, however we never managed to achieve funding for this. I think this was a shame as video questionnaires would have been very useful for international studies.

The ISAAC video has been an interesting exercise and has provided some additional novelty in relation to the ISAAC studies.

## **Asthma alone, or asthma and allergies?**

*(David Strachan)*

Originally, the Auckland proposal had focused mainly on asthma, whereas the German group had been asked by their Federal Ministry to develop a study of time trends and determinants of asthma and allergic disorders. A broader perspective was also considered to be relevant to the Auckland grant application, since allergen sensitisation, indoor allergen exposure and infant eczema were putative determinants of asthma occurrence and severity. At the second Bochum meeting, in December 1991, the aims of ISAAC were agreed to include studies of the prevalence and severity of asthma, allergic rhinitis and atopic eczema.

The challenge was to develop, within a tight timescale, questionnaire measures of allergic rhinitis and atopic eczema that were similar in style and length to those that had been piloted successfully for wheeze and asthma. The UK group (Ross Anderson, Bonnie Sibbald and David Strachan, with substantial advisory input from Hywel Williams, who later joined the Steering Committee) had prepared, in advance of the December 1991 workshop, draft questionnaires based on preliminary analysis of a national case control study in Britain to determine a minimum list of reliable criteria (symptoms and signs) for eczema. These followed the conventions set by the asthma questionnaires, by following the same time periods for enquiring about symptoms and by placing questions about diagnostic labels (hay fever and eczema) after enquiry about the relevant symptoms and severity measures.

## **Development of the rhinitis questionnaire**

*(David Strachan and Bonnie Sibbald)*

Bonnie Sibbald, who was working at that time as an epidemiologist with Ross Anderson and David Strachan at St George's, London, had completed a population survey of rhinitis symptoms in south west London, with follow-up interviews and skin prick tests to define seasonal and perennial rhinitis and their relationship to aeroallergen sensitisation. The combination of rhinitis symptoms (sneezing, blocked or runny nose) with itching or watering of the eyes had the best predictive value for skin prick test positivity, and the questionnaire was therefore developed to include all these symptoms.

This was a study of adult respondents and some concerns were expressed about the generalizability of the results to children. However, at that time there was no comparable study of rhinoconjunctivitis in younger children, and it was felt that results for adults could be applied with caution at least to the teenage group. Two further issues which were resolved by discussion at the 1991 workshop were related to seasonality and severity of symptoms.

Whereas hay fever or other forms of seasonal allergic rhinitis have a characteristic monthly pattern within any given country, it was clear that for international comparisons it would be difficult to refer to a specific season without loss of standardisation in the questionnaire. Therefore, it was decided to enquire about the occurrence of rhinitis symptoms in each of the 12 months of the year, and leave the task of defining seasonality to the statistical analysts. In practice, little use has been made of the seasonality responses in the main ISAAC papers, partly because of concerns that they may be biased by the month of fieldwork, and partly because many of the centres who eventually took part in ISAAC were from tropical countries. On reflection, perhaps more use could be made of these data.

As there were no widely accepted measures of severity of rhinitis (allergic or otherwise), there was a lively discussion at the 1991 workshop about how to assess this. Neither sleep disturbance nor night waking were felt to be appropriate, and school absence due to allergic rhinitis was considered to be rare and probably culture-dependent. There was some debate about whether quality of life measures should be included at all, but in the end, it was agreed that a single question on interference with daily activities was justified as a simple severity marker. It was recognised, however, that there were no supporting data, in either adults or children, to validate this choice.

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## Development of the eczema questionnaire

(David Strachan and Hywel Williams)

Hywel Williams, a trainee dermatologist, who was working at that time as a Wellcome Trust Clinical Epidemiology Fellow at St Thomas's Hospital in London, did not attend the 1991 workshop but had been in close liaison with David Strachan over the preceding year as they collaborated on analysis of eczema data from 1958 British birth cohort study. Hywel was planning to do a study to look at the differences between eczema prevalence between London-born Afro-Caribbean children and those living in Kingston, Jamaica, as the main focus of his PhD, but found a complete absence of valid diagnostic criteria that could be used for epidemiological studies. Prior attempts at developing diagnostic criteria for eczema, such as the Hanifin and Rajka criteria, were based on empirical grounds by a group of experts working in secondary care settings. Whilst many of the proposed criteria had good face validity, many were poorly defined (eg tendency towards infections) and some were uncommon (keratoconus), and trying to determine the presence or absence of 33 minor features in an epidemiological survey was going to be quite impractical. It was this topic that was to become to the main focus of Hywel's PhD. He set up a UK working party of 16 leading dermatologists to try and identify a minimum list of reliable discriminators for diagnosing a typical case of eczema. The aim was to develop a much smaller list of diagnostic features that could be reliably ascertained by trained nurses in epidemiological studies, rather than criteria that were the exclusive domain of clinician experts in an outpatient setting.

The UK Working Party study included direct inspection of the skin among its diagnostic criteria, and although many aspects of skin examination were tested for in the national case control study, it became clear at an early stage that historical features such as a history of involvement of the skin creases was just as, if not more important than physical signs. Thus, the combination of itchy rash with flexural involvement had both high sensitivity and specificity for atopic eczema in the age range planned for ISAAC, and the specificity could be improved if the age at onset was less than 5 years. Although the age range of this UK study was wider than that proposed for ISAAC, this was the most relevant information available to guide the construction of an ISAAC questionnaire for eczema. The age at onset question was only included for the younger age group (parentally completed questionnaires), as it was considered unreasonable for teenagers to recall the age at which they had first suffered from itchy rash. Although the questions contained in the final set of UK diagnostic criteria for atopic eczema that appeared in 1994 were not identical to those used in ISAAC, they were very similar. Around that time, empirical questions for another epidemiological study - the Avon Longitudinal Study of Parents and Children (ALSPAC) had been suggested by Dr. Clive Archer (a dermatologist at Bristol with an interest in eczema) in discussion with Hywel Williams, which included an element of chronicity of flexural symptoms. The establishment of the ALSPAC questionnaire at around the same time influenced the inclusion of the phrase "which was coming and going for at least six months" in relation to an itchy rash.

German allergologists and dermatologists who were present at the 1991 meeting were concerned that there were multiple expressions for "eczema" in German and therefore that translation might prove to be a problem. However, this argued in favour of standardising on a symptom-based definition. There was also concern that scabies could be a common cause of itchy rash in developing countries and had not been included in the UK case control study, a point that was subsequently partially addressed in later validation studies.

Night waking, which had been agreed as a measure of severity for wheezing and asthma, was a natural choice of severity marker for eczema given the frequent sleep disturbance to child and family due to scratching at night. In addition, a single question was included to enquire whether the itchy rash had ever cleared completely in the last year as a possible indicator of less severe or more transient eczema. However, this second question has not been used widely in ISAAC publications, which tend to concentrate on sleep disturbance as a measure of eczema severity.

The 1991 workshop also discussed briefly the development of a skin examination module for inclusion in objective surveys of atopic eczema. Subsequently, the development of the ISAAC Phase Two skin examination protocol followed closely the recommendations of the UK Working Party and further validation work by Hywel Williams, who joined the ISAAC Steering Committee in 1992.

In retrospect, it is reassuring to note the results of ISAAC Phase Two surveys have shown a high correlation between the prevalence of eczema determined by ISAAC core questionnaire and by skin examination, at least in 9-11-year-old children. This suggests that the idea of measuring eczema by questionnaire alone, which was controversial in the early 1990s, has a sound epidemiological basis.

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## Bronchial responsiveness

(Innes Asher)

In Phase Two objective measures related to asthma and allergies were developed. In December 1991 it was decided to have a module on bronchial responsiveness. At this time several methods were being used, and there were pros and cons to each. In December 1993 an ISAAC Airway Responsiveness Satellite Workshop was held in Auckland, New Zealand to choose a method for Phase Two.

Attendees at the workshop were Sandra Anderson (Sydney), Innes Asher (Auckland), Tadd Clayton (Auckland), Julian Crane (Wellington), Philippa Ellwood (Auckland), Ed Mitchell (Auckland), Philip Pattemore (Christchurch), Jenny Peat (Sydney), Colin Robertson (Melbourne), Robyn Shaw (Wellington), Alistair Stewart (Auckland), Erika von Mutius (Munich). Apologies were received from Pierre Ernst (Quebec), Michelle Haby (Sydney), Alison Leversha (Auckland), David Strachan (London).

The meeting developed criteria on which to judge challenge tests. The greatest priority was given to ease of standardisation between centres, countries and cultures, reproducibility, safety, specificity, and availability of dose response information. Of a lesser priority were acceptance by parents, feasibility in all participating countries, costs, co-operation by children, state of knowledge concerning tests, and legality in participating countries.

The methods considered were cold air, PEFV variability, exercise challenge, hyperosmolar challenge, methacholine, and histamine.

*Cold air challenge* (-15 degrees C), 5% CO<sub>2</sub> did not result in a dose-response, and equipment costs were high. Isocapnic hyperventilation was replacing this kind of test, but still no dose response.

*Histamine* was illegal for use with humans in Australia. There were probably insurmountable regulatory obstacles to the use of histamine and methacholine in New Zealand, USA and Germany.

*PEFR variability* had a number of disadvantages relating to effort, and use of asthma drugs.

*Exercise challenge.* There is a large experience with this test, which met most of the criteria. However the response to exercise challenge would be altered by variations in ambient humidity. It is the absolute water content of the air that is the concern, given that a water content of >10mg/L will eliminate the exercise response.

*The hyperosmolar challenge using hypertonic saline.* This acts by rapidly altering the osmolarity of the airway surface liquid which causes mast cells to degranulate. A good test for current asthma. In school studies in Melbourne this test compared well with an exercise test. The ultrasonic nebulisation was not ideal, as time consuming and a bit cumbersome.

There was considerable discussion on the pros and cons of each method as a tool for ISAAC. The preferred option recommended was hypertonic (4.5%) saline challenge. The exercise test according to the Haby method was 'highly recommended'. If histamine or methacholine challenges were to be used for ISAAC then the Yan method was preferred.

Post script 2011: In future epidemiological studies dry powder mannitol would be a consideration – it is an hyperosmolar challenge which is safe and reliable, with individual capsules for dry powder inhalation. The only equipment needed is a laptop spirometer, the dry powder device and the capsules.

## Measuring eczema by questionnaire and examination

(Hywel Williams)

Whilst questionnaires were attractive in their ease of application and low cost for making broad prevalence comparisons involving many thousands of children across many countries, concerns arose about the complete reliance on questionnaires due to potential problems in translating or understanding the concepts contained in the questions. Whilst many elements of the questions had been shown to have reasonable sensitivity and specificity when validated in UK community settings, it was possible that their performance was less good in other countries, where other itchy conditions such as scabies was more prevalent in the ages studied. ISAAC Phase Two, with its child contact module, therefore provided an ideal opportunity to examine the skin in a standardised manner.

One of the advantages of skin disease is that it is immediately visible - it is either present or not present, although visible eczema at one point in time in a condition that classically comes and goes will only provide a point prevalence which is typically lower than a 1-year period prevalence. By the time the ISAAC Phase Two modules were being developed, the UK Working Party's refinement of the Hanifin and Rajka diagnostic criteria for atopic eczema was completed in terms of development and community validation. The UK criteria included the one physical sign of "visible flexural dermatitis" which had been carefully constructed to only include those flexural sites that were helpful discriminators from other skin diseases such as contact dermatitis or lichen planus or scabies.

For the first time ever, a photographic protocol defining what eczema looks like, which sites could be deemed as being flexural at different ages, and what size or pattern of involvement could be deemed as a positive response was developed. The visible flexural dermatitis protocol was shown to be a reliable tool when used by trained nurses, and a set of training photographs and a set of quality control photographs were also developed for use in the public domain. Given concerns about the validity of questionnaire-ascertained eczema, it could be argued that the visible flexural dermatitis protocol used in ISAAC Phase Two offers the most objective method for standardising the eczema phenotype for a host of scientific studies given its freedom from language and/or interpretation bias.

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## Development of Phase Two modules

*(David Strachan)*

The concept of developing objective tests for asthma and allergy was discussed in outline at the first Bochum workshop (December 1990) and at the second workshop, one year later, it was decided that a series of self-contained “modules” would be desirable. Bronchial hyper-responsiveness, serum IgE, skin prick tests, skin examination, and a questionnaire about medications & health services were discussed at this time. The following year, at the Steering Committee in London, the list was extended to include supplementary questionnaires about risk factors and other respiratory symptoms.

Work on the modules continued through 1993 to 1995, including a special workshop on bronchial responsiveness testing, described in a separate section. As much of the attention within ISAAC at this time was on the expansion of Phase One, the main stimulus to finalise the measurement protocols came from the Germans (Stephan Weiland and Erika von Mutius) who planned comparative studies of 9-11-year-old children in former West Germany (Munich) and former East Germany (Leipzig and Dresden) starting in 1995.

Although the risk factor questionnaire underwent some changes after the German fieldwork, the protocols were essentially fixed at this time, and after their successful implementation in Germany the modules were printed as a bound volume in 1998. The measurement modules were summarised in the Phase Two methods paper, published in 2004. By the time of that publication, 30 centres in 22 centres had used combinations of the modules and contributed data to the ISAAC Phase Two Data Centre, which moved with Stephan Weiland from Münster to Ulm in 2002.

## The Phase Three risk factor questionnaire

*(Ed Mitchell)*

The aim of the Phase Three risk factor questionnaire (often referred to as the "Environmental questionnaire") was to achieve individual level data which would be novel because of the scope of the questions and the scope of Phase Three. A list of variables of potential interest was developed in June 2000. This list included variables that could not be obtained by questionnaire, but were included to ensure that the item was explicitly considered. The main focus of the questionnaire was on the 6-7 year age group (completed by parents) with a briefer version for the 13-14 year age group (self completed).

The list of variables and the potential questions was discussed at the ISAAC Steering Committee meeting in October 2000 in Auckland. It was decided that a core questionnaire would be developed. Each question was developed to address a specific hypothesis. This was led by Ed Mitchell with Neil Pearce, Ross Anderson and Colin Robertson.

A month later the document "Environmental Questionnaire Instructions and Hypotheses" was produced for each age group ([view 6-7 year document](#) | [view 13-14 year Document](#)). The format was to provide a referenced argument for the specific hypothesis, the source of the question used (in many cases the question was developed by the Steering Committee), and a brief outline of the analysis (key outcome variable and potential confounders).

The questionnaire was produced in record time and was used by some centres early in the following year.

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## The Development of ISAAC

ISAAC started as a collaboration between mainly European and Australasian investigators but rapidly expanded during the mid-1990s to become a network covering all six inhabited continents (we have yet to recruit a regional co-ordinator for Antarctica!). This section charts the development of this worldwide consortium and ends with some reflections on the place of ISAAC in the world of the 21st century.

### The globalisation of ISAAC

*(Neil Pearce)*

Although ISAAC was started by research groups based in New Zealand, the United Kingdom and Germany, it was recognised from the start that it was important that the study be conducted on a truly global basis. The major contribution of epidemiology to the study of chronic diseases such as cancer and cardiovascular disease has arisen from studies at the population level, including analyses of patterns of disease prevalence and incidence across demographic groups, geographic areas and across time periods (“person, place and time”). For example, it was in the 1950s that it was first realised that colorectal cancer rates were high in Europe and low in Africa and this gave rise to hypotheses about the roles of fruit and vegetable intake and dietary fibre; similarly, it was realised that liver cancer rates were high in Asia, and this led to the discovery of hepatitis B as the major risk factor for liver cancer worldwide; more recently, international and regional comparisons in cervical cancer rates gave rise to the hypothesis that an infectious agent may play a role, eventually leading to the discovery of human papilloma virus (HPV) as the major risk factor for cervical cancer.

In contrast, prior to the ISAAC study, such standardised international comparisons had not been done for asthma - with the exception of the European Community Respiratory Health Survey, which had mainly been done in Europe. In fact, a huge amount of funding had already been spent on studying the “known” causes of asthma in affluent countries (e.g. air pollution, allergen exposure), but little was known about whether such risk factors were important globally. It was therefore decided, from the outset, to make ISAAC into a truly global study. This required that the study used simple inexpensive validated methods that could be used anywhere in the world – a requirement which led to the splitting of the study into Phase I (which could be done anywhere) and Phase II (which would only be done in selected centres and countries). It also required that the ISAAC Steering Committee be truly global, and this was achieved by creating positions for Regional Coordinators.

### The recruitment of Phase One regional co-ordinators

*(David Strachan)*

At the time of the London Steering Committee meeting in December 1992, ISAAC officially consisted of only 4 centres from 2 countries. Just two years later, 107 centres from 42 countries had been recruited, and by the end of 1995, the Auckland Data Centre had received Phase One data from 110 centres. This remarkable expansion and successful completion of fieldwork relied critically upon the identification of able and willing regional co-ordinators around the globe. It was they who put the “I” into “ISAAC”!

The 1993 Steering Committee meeting was held in Geneva and followed by a meeting with representatives of the World Health Organisation who had expressed an interest in ISAAC. This early interest from WHO led to the definition of ISAAC regions along the lines of WHO regions. However, in retrospect, it was not these official channels so much as personal contacts which led to the establishment of an effective network of regional co-ordinators (and, later, national co-ordinators) within ISAAC. In particular, during a period of sabbatical leave during 1993-4, Richard Beasley played a key role in promoting the concept of ISAAC outside of Europe and Australasia.

By the time of the 1994 Steering Committee meeting, the basic framework of ISAAC regional co-ordinators had been established, with attendance by:

Gabriel Anabwani (Africa: 4 countries, 4 centres participating in Phase One)

Bengt Björkstén (Northern & Eastern Europe: 5 countries, 5 centres)

Chris Lai (Asia-Pacific: 10 countries, 19 centres)

Fernando Martinez (North America: 2 countries, 3 centres)

Steve Montefort (Eastern Mediterranean: 5 countries, 6 centres).

The original ISAAC partners were represented by: Innes Asher (Oceania: 2 countries, 10 centres) and Ulrich Keil (Western Europe: 6 countries, 32 centres).

The following year, Javier Mallol (Latin America: 8 countries, 8 centres) was able to attend the Steering Committee meeting in Barcelona, and there was welcome news that Jayant Shah had recruited 21 Phase One centres in India. Jayant Shah was unable to attend the Steering Committee meeting in person until the October 2000 meeting in Auckland, by which time co-ordination of the African region had been split between Anglophone Africa (Joseph Odhiambo) and Francophone Africa (Nadia Aït-Khaled).

The network of regional co-ordinators remained remarkably constant throughout the last 15 years of ISAAC, and this organisational stability no doubt contributed to the smooth and successful implementation of Phase Three, both in the original Phase One centres and in new locations. In recognition of the expansion of ISAAC outside of Australia and New Zealand to Pacific island nations, Sunia Foliaki was appointed regional co-ordinator for Oceania, replacing Innes Asher, for Phase Three.

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## The globalisation of ISAAC Phase Two

(David Strachan)

In contrast to Phase One, where globalisation was driven by the enthusiasm of regional co-ordinators, recruitment of Phase Two study centres followed a less structured approach. The original concept of Phase Two was to study in greater depth centres with diverse prevalences of asthma or allergy, as defined at Phase One, but this aim was never fully realised. Principally, this reflects the greater demands, both financially and logistically, involved in completing Phase Two fieldwork.

In the late 1990s, as the methods of Phase Two had been finalised, it appeared that it might become very largely a European study, and a small European Union Framework Programme 4 grant was awarded to create a “network of excellence” among the ISAAC centres in Europe. This later bore fruit in the form of a more substantive EU FP5 grant which supported the centralised analysis of data, serum IgE, dust and DNA from EU centres in Phase Two.

Phase Two fieldwork in many lower-income countries was supported by a partnership with another centre in a higher-income country. Examples include Albania, Ecuador and Ghana (partners with the UK), Estonia and Latvia (partners with Sweden), and centres on mainland China (partners with Hong Kong). These partnerships allowed some transfer of knowledge and expertise, and contributed to standardisation of methods across study centres.

In retrospect, the original plan to select Phase Two centres on purely scientific criteria based on the Phase One findings was perhaps too optimistic. As it turned out, there is considerable heterogeneity of asthma/allergy prevalence across the centres that were included and this has led to more informative between-centre analyses of symptom combinations and risk factor associations.

The incomplete overlap between the network of Phase Two centres and those involved in Phases One and Three has limited the extent to which the results from Phase Two can supplement and inform the Phase Three comparisons. Nevertheless, Phase Two has achieved its original aspiration to perform objective tests of asthma and allergy in diverse populations around the world.

### ISAAC in the context of other European initiatives

(Bert Brunekreef)

As with any good story, the ISAAC story must be one that’s rich, multifaceted and having all sorts of twists and turns. I’ll add a few of my own.

When ISAAC got started in the Bochum workshops, we had just completed a few fairly large respiratory symptom questionnaire studies among primary school children in the Netherlands. I say ‘we’ because there were two parallel activities, one based in the University of Wageningen where I was at the time focused on environmental determinants of respiratory disease in children – and one led by Bert Rijcken in Groningen, which was more focused on the use that school health services might have from respiratory symptom questionnaires in their daily practice. When we got invited to the second Bochum workshop, none of us could go but we sent a junior colleague, Bernard Groot, to find out what was going on at the time. We then decided we were unlikely to get funding for yet another series of symptom questionnaires, and that we better wait for an opportunity to join a phase two study if that was ever going to happen. Fairly soon after that, Bert (the other Bert...) made the brave decision to leave science to become an artist, and we in Wageningen became more and more involved in studies of outdoor air pollution.

I think it was in 1992 that I met a young German epidemiologist, Stephan Weiland, at the annual conference of the International Society of Environmental Epidemiology in Cuernavaca, and we got to talk about the interesting work that he had been doing on proximity to traffic and respiratory problems in kids. A few years later I was giving a speech on air pollution at our National Institute of Public Health and the Environment in which I briefly quoted one or two of those traffic studies. In the break, a man working for the province of South Holland came up to me and asked whether I was interested to do a study on proximity to freeways and respiratory health in children. His argument was that more and more homes and schools were being built near freeways (yes, it’s a small country, and space is precious...). We got some talented students involved in what was really a pilot study, but we did manage to include objective measures of air pollution exposure and respiratory health, and we found a fairly striking relationship between truck traffic density on the nearest freeway and lung function in the children we tested. That study stimulated our government to fund a much larger study on the topic, at a time when in Germany, the first ever ISAAC Phase two study had just gotten underway. I felt that the time was now right to try and jump on the ISAAC train and I contacted Erika von Mutius and Stephan to ask them whether they would be willing to let us use their protocols and apply those in our Dutch studies. Both were extremely helpful, and after a few visits to Muenster where Stephan and Ulrich Keil had moved at the time we were ready to launch our own ISAAC II study, focused on the role of traffic pollution in explaining variations in respiratory health among school kids.

Meanwhile, a concerted action had been launched in Europe led by David Strachan, and aimed at further cementing collaboration of ISAAC centers in Europe, including some work on serology and mite allergen determinations which we had going at the time. (For those of you not from the EU, the EU has a staggering variety of funding instruments, and ‘concerted actions’ are primarily meant to allow research groups to get together to discuss areas of mutual interest, without funding actual research). If my memory does not fail me too much, this action laid the ground work for a successful application for the ISAAC Phase II study which was coordinated by Stephan between 1999 and 2003 or so. We were privileged to be part of that effort with contributions from our own study population, and from our lab doing dust allergen and endotoxin analyses for all partners, and the harvesting from that seminal effort continues to this very day.

Then in 2003, Stephan asked me whether I would be willing to become part of the ISAAC steering committee, and I was truly honored to accept. It took me a while to actually get to the meetings but since 2005 I’ve missed only one, and they have been very enjoyable experiences indeed.

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In 2006 and 2007, we were getting ready in Europe to propose a large scale study of the effects of long term exposure to air pollution on a variety of health outcomes, and Stephan was an enthusiastic and active member of the preparatory team to get this up and running. We met in early March 2007 in Barcelona to hammer out the last details of the proposal, and I will always remember with great sadness the day, just a few weeks later, that Gudrun Weinmayr called me in tears to tell me that Stephan had suddenly died. I couldn't believe it. He was extremely fit, running marathons, and less than a year earlier I had accompanied him on a one hour plus jog at a meeting in (I believe) Salzburg which we both were attending. It just did not (and does not ) feel right that somebody so talented and vibrant would all of a sudden be taken away from us and (more importantly) from his wife and small children.

But then life, including ISAAC's life, goes on. ISAAC made it to no less than 20 years, and to a great many achievements for science and society. I am extremely grateful to be part of it, and to have been able to make a few modest contributions.

January 2011, Auckland – Kuala Lumpur, Bert Brunekreef

## ISAAC in the 21st century

*(Carsten Flohr)*

We joined the ISAAC Steering Committee only a few years ago to complement its expertise, at a time when the study was already well under way. At its outset, the world of allergy and its needs was very different from what is required now. Even simple prevalence data was scant. There was also a lack of validated and standardised tools that could be used in large population-based surveys, and there certainly was no world map of the burden of allergic disease. All of this was already delivered in Phase One. In Phases Two and Three we have been able to look at individual risk factors of allergic disease (Phases Two and Three) as well as providing further prevalence data to look at trends (Phase Three). Part of this work is still underway.

Apart from its sheer size, the strength of the ISAAC data set is that it provides information on risk factors in developing countries, where allergic diseases have been only occasionally studied rare commodities until recently. As more and more populations adopt a western lifestyle in the 21st century, especially in urban centres of less affluent nations, ISAAC can make a contribution to the identification of key risk factors that drive allergic disease with the ultimate promise to aid disease prevention. For instance, we will seek to find the main environmental risk factors that explain the significant prevalence differences between ISAAC study centres. Another important area of interest is the impact of climate on allergic disease, and for this ISAAC prevalence data could be used in combination with satellite information. Furthermore, we need to study the lifestyle ingredients responsible for urban-rural prevalence and severity gradients as well as the influence of diet (mother and child), obesity, indoor and outdoor pollution. A lot more remains to be done!

*(Gary Wong)*

I have been involved in the ISAAC work ever since Phase I started many years ago. It has been one of the most wonderful research endeavors that I have been involved through out my career. The achievements from the ISAAC work are clearly great examples of the results generated by collaborators who truly worked together for their common goals.

Behind this massive collaboration, one of the important driving forces to push things forward is the ISAAC Steering Committee. Members are from different parts of the world and each of them provides his or her unique expertise such that appropriate and important research questions are generated. More importantly, they would challenge each other regarding how these questions should be answered with what sort of methodologies and analyses.

I had the opportunities to join a couple of Steering Committee meetings as an observer such as the ones in Kenya and Tonga. I finally came face-to-face to the people with their names on many papers that I have read. In most instances, meetings are not my favourite activities, but the ISAAC steering committee meetings are different. There are honest exchanges of opinion and all members have one common goal in mind that is to ask the right questions to reveal the truth. From the genuine discussion during these meetings, one could feel the passion of each member for the work they were involved in. I was thrilled to have the opportunity to join this big family when I was invited to become one of the members in this Committee.

The ISAAC research network has provided answers to many of the questions that the research community has asked in the past 2 decades. Now, we have a lot more data with regards to the global variations and trends of asthma and allergies in childhood. What are the next important research questions in asthma and allergies? How can such large collaborative network help to answer some of these questions? These will be the biggest challenges for the ISAAC Steering Committee in the 21st century.

# The ISAAC Story



## The global context of ISAAC in the 21st century

ISAAC has been the subject of positive editorial comment in the International Journal of Tuberculosis and Lung Disease, the leading voice of respiratory disease in developing countries, for its unique role in fostering research and critical thinking<sup>[1]</sup>. They state "ISAAC is a model that should be followed by all those of us who are committed to improving public health in low-income countries." ISAAC uses a simple framework which enables standard measures and comparisons across geographic, cultural and linguistic boundaries which means it can be carried out relatively inexpensively, making it particularly suitable for use in developing countries and allowing "truly global participation". This inclusive and encouraging approach has resulted in ISAAC becoming the largest study of its kind.

As stated by the Commission on Health Research for Development, ". . .for the world's most vulnerable people, the benefits of research offer a potential for change that has gone largely untapped". Such research is essential to improve public health globally and equitably. A major barrier to achieving this is a lack of confidence of health care workers to involve themselves in research. ISAAC has addressed this obstacle and produced a body of knowledge that informs policy. The World Allergy organisation has reported that "studies such as ISAAC are a major step toward overcoming barriers to the worldwide diagnosis and treatment of asthma"<sup>[2]</sup>.

ISAAC has established worldwide networks with organisations concerned with health in developing countries such as The International Union against Tuberculosis and Lung Disease (IUATLD) and the World Health Organisation (WHO). The ISAAC program is the only global study of paediatric asthma and allergy currently in existence and there is a clear and vital need for it to continue. ISAAC findings are cited by any organisation involved in monitoring and preventing CRD's and are used to inform global health initiatives which include WHO, and its NGO the Global Alliance against Chronic Respiratory Diseases (GARD). ISAAC publications are included in the "GARD Basket", a package of information, offered to countries by WHO to assist policy decisions relating to CRD's<sup>[3]</sup>.

1. Enarson D. Fostering a spirit of critical thinking: the ISAAC story. *Int J Tuberc Lung Dis* 2005;9:1.

2. Pawankar R, Baena-Cagnani CE, Bousquet J, et al. State of World Allergy Report 2008: Allergy and Chronic Respiratory Diseases. *World Allergy Organisation Journal*. 2008(Supplement 1):s4-s17.

3. World Health Organisation. Global Alliance against chronic respiratory diseases (GARD) basket: a package of information, surveillance tools and guidelines, to be offered as a service to countries. Geneva: World Health Organisation; 2008

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## ISAAC International Data Centres

The success of ISAAC as a worldwide initiative has depended upon efficient co-ordination and communication. It has also benefitted greatly from central collation of data for checking and statistical analysis. This section includes reflections from the ISAAC International Data Centre team in Auckland, New Zealand who played these roles for Phases One and Three, and from the ISAAC Phase Two International Co-ordinating and Data Centre in Ulm, Germany.

### Phase One and Three (Auckland)

*(Tadd Clayton)*

The ISAAC data centre in Auckland (now known as the ISAAC International Data Centre [IIDC]) was established in 1992-3 with the appointments of Philippa Ellwood and Tadd Clayton in the Department of Paediatrics. The main tasks in the early years of the IIDC were to carry out the quality assurance checks of the data submitted by the Phase One centres, and to review the study methodology used by each centre to identify any cases where centres had failed to follow the ISAAC protocol. Philippa also had an important role in carrying out the data collection for the Auckland Phase One centre and providing support to the field workers in the other New Zealand Phase One centres.

Following the completion of these tasks for most Phase One centres, the IIDC had an important role in the analysis of Phase One data, preparation of data tables, maps and graphs, and preparation of papers for publication. The IIDC also had a similar important role in the preparation of the Phase One ecological analysis papers.

From 1999 the IIDC began to again receive data from the ISAAC Phase Three centres. Similar data and methodology checks were carried out for the Phase Three data. The greater participation in Phase Three meant that these checks did take a longer period than for Phase One and the preparation of publications presenting the Phase Three data did not begin until 2005. Since then the data centre has again been working to analyse and present the Phase Three data. Phase Three also included an environmental questionnaire and there has been a significant further effort required to analyse and present that data.

### Phase Two (Ulm)

*(Gudrun Weinmayr)*

In 2001 I listened to the talk given by Stephan Weiland in the course of his application to the Chair of Epidemiology in Ulm - without the slightest idea that the project he presented would become my main research interest for the years to come. In fact I was at the very beginning of transforming a zoologist into a Master of Public Health i.e. in my first year of the 2-year-course in Ulm. The first implication for us was that we would have a new professor in epidemiology who finally arrived in the end of 2001. In my second year, in February 2002, I joined the data centre in Ulm and got very soon to love the work in this international study appreciating deeply this worldwide diversity.

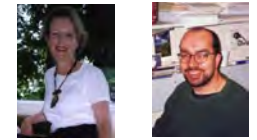
My knowledge of asthma and allergies – and of epidemiology - still had to develop. This first phase in Ulm was characterised by the moving from Münster to Ulm and the build-up of the department where on arrival just two technical staff were present. In Münster, Peter Rzehak and others had already developed a detailed coding and data transfer manual as well as a data check routine including the corresponding SAS-programs. The first centres had already sent their data but the main bulk was still to come. All this was moved to Ulm and for us, the Ulm-staff, in the beginning looked like, as you say in German, a “book with 7 Seals” - a riddle wrapped up in an enigma. The magical crystal ball was the “backup of Bernd’s Computer” where supposedly everything was to be found – if you just knew where... Peter introduced me to all this work that was completely new to me and together we continued and were joined in July by our new secretary Clarissa Schönlé and in October 2002 by data manager Claudia Pilz (now Dentler) and my fellow student Gisela Büchele. With her extensive past experience in biometry she had developed during her Master’s thesis the procedure on how to analyse the ISAAC bronchial hyperactivity (BHR) data. She joined us as the BHR-expert additionally bringing in also a strong experience in data management.

In Autumn 2002, organised by Clarissa, we held the ISAAC Phase Two Meeting with representatives from all study centres. It was a very informative and productive meeting and at the same time the exciting opportunity to get to meet all these people you just previously knew from e-mail exchange.

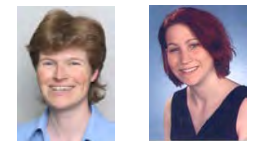
It took about another two years of solid and devoted work to compile the international data set and bring it into a form that could be reliably used for data analysis. In parallel, we had been developing statistical analysis tools to deal with the complexities of the data set, in particular the weighting procedures to take account of the stratified sub-sample used in Phase Two, and to incorporate all these particularities into SAS-Macros to allow the efficient analyses of the numerous centres.

So in 2004 just in time for the final report for the part of the project that had received funding from the EU, we could finally do the first analyses. With these first results we convened the first Meeting of the Phase Two Publication Group which at the time consisted of Stephan Weiland, Erika von Mutius, Bengt Björkstén, Bert Brunekreef, Bill Cookson, Francesco Forastiere and David Strachan. On this Meeting the outline of the publications to follow was developed. Work started with the publication round looking at the association of atopy with the disease outcome – the asthma paper being the first one to be developed fully but also being fuelled at the same time by discussion on the other papers – in collaboration with Hywell Williams and Carsten Flohr, at the time Hywell’s PhD-student, for the eczema paper and with Francesco Forastiere for the rhinitis paper.

## Auckland Data Centre



## Ulm Data Centre



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This was the time when we realised the full importance of the nonatopic part of disease and as well the concomitant variation of the association atopy-disease in the international context that seems to be in part related to the state of affluence of the country.

In the mean-time changes occurred at the data centre: Claudia and Peter left in 2004/2005 and we were joined by Andrea Kleiner for data management, programming and performing statistical analysis and by Gabriele Nagel, a MPH with a medical background who had previously worked with EPIC.

Analyses continued, mainly with the three above papers, the corresponding paper for BHR, and Gabriele starting to look at the influence of breastfeeding on asthma. Also initiated were the Genetics analyses with mainly Jill Cantelmo and Miriam Moffat to be joined later on by Jon Genuneit, a medical doctor that had joined already during his training in Ulm - initially for his medical doctors thesis.

In February 2007 we got the good news that the asthma paper had been accepted by the AJRCCM – news that, very unusually, were celebrated in the library with a glass of Champagne and reflected all the “heartblood” as you say in German, i.e. the high amount of passion and thought, that Stephan Weiland had devoted to this first scientific output of Phase Two. It was only a month later, after having read the first draft of the Rhinitis paper, that he died completely unexpectedly on 19th of March. This shock deeply hit the whole department missing in addition to his excellent scientific guidance his enthusiastic and humane nature.

It left us with the desire to do our very best to continue this central piece of his work in his sense. In this endeavour we were wonderfully supported by the group and in particular by David Strachan who took over the role as Phase Two Coordinator. This helped us markedly not to only complete the work already started with Stephan Weiland but also to embark for new endeavours such as the round of overview papers sparked by Erika von Mutius during a discussion with David and the group in Ulm.

## Communications within ISAAC

*(Philippa Ellwood)*

When ISAAC began in 1991, the Auckland centre was one of the first centres to commit to participate in ISAAC and undertake data collection. In 1992, I was appointed as ISAAC research assistant, responsible for the Phase One fieldwork in the Auckland region, which led to overseeing the national data collection for the six New Zealand centres. In 1993, Auckland was established as the ISAAC International Data Centre (IIDC) and appointed Tadd Clayton as Data Manager. In 1993 my responsibilities were expanded to become the IIDC Research Manager which involved coordinating the international centres and ensuring the fieldwork followed protocol. This involved an enormous amount of communication with the centres.

In Phase One the principle method of communication with the Principal Investigators was by fax machine. It is amusing now to reflect on the amount of time spent standing beside the fax machine sending the centre report to collaborators, almost holding one’s breath in case the fax failed to send, (which it did on frequent occasions) and having to start all over again. Tadd also was an ‘avid’ user of the fax machine for his communications regarding the Phase One data checking and had similar experiences. When receiving documents back from the centres we would at times find pages missing due to failed fax attempts from the centres, which was as frustrating to the collaborators as to us in Auckland. As the fieldwork in Auckland was being undertaken I decided to document the methodology used to approach the schools and how it was undertaken in the schools. It became apparent that this information would be useful for other fieldworkers and these guidelines were subsequently circulated to the centres and made available from the ISAAC website (<http://isaac.auckland.ac.nz/phases/phaseone/fieldguide/young.html>). These have become a useful tool in assisting centres to follow the ISAAC protocol.

For Phase Three, the use of email had gained popularity and communicating with the centre Principal Investigators and collaborators became a lot less difficult. The centre report had been evaluated and was simplified for ease of understanding. This made it a lengthier document, so having email as the predominant mode of document transfer made life for the IIDC much easier (and less breath holding!).

The experience that Tadd and I have had communicating with the Phase One and Three Principal Investigators and collaborators has simply been a privilege. We have built up an amazing rapport with so many people, from so many different ethnically diverse communities. Due to the stability of the Data Manager and Research Manager, this rapport strengthened over time. With the ISAAC English language questionnaire having been translated into 53 languages, it would not be uncommon for misunderstandings to regularly occur. Although these did happen at times, usually about what the IIDC actually required, these were rare and very easily sorted out. It is humbling to have English as our primary language and have collaborators with English as a second language so enthusiastically embrace our language and have the determination to undertake the ISAAC fieldwork in their centre and to adhere to our documentation written in English. The international success of ISAAC is a tribute to the entire ISAAC worldwide collaboration.

*(Tadd Clayton)*

My communications with researchers were always concerning the checking of the data for its integrity, consistency and use of valid values. I prepared a report for each researcher on each version of their data which encouraged them to address as many of the unexpected features of their data as possible. The researchers responded to my reports, either providing a new revised version of the data, corrections for me to apply to the data or a statement that no further improvements were possible.

I would like to thank all of the researchers and the members of their teams who I have been in contact with throughout Phase One and Phase Three. Everyone has been extremely helpful and enthusiastic, as well as being patient with the occasional communication difficulty.

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## ISAAC Diary ISAAC Timeline Milestones

Year	Month	Phase One	Phase Two	Phase Three	Other	World/Other events
1989						Fall of Berlin wall
1990	Dec	6-7 yr and 13-14 yr age gps decided Core methods: written questionnaire on asthma, rhinitis and eczema Video questionnaire on asthma likely Pilot study underway	Idea of lung function in 9-10 yr olds		First meeting	ECRHS began
1991					Name of The International Study on Asthma and Allergies in Childhood (ISAAC) suggested by Bonnie Sibbald in a London café, and adopted by the founders	
	March				Ulrich Keil, Neil Pearce and Innes Asher meet in Auckland Merged the German and New Zealand initiatives	
	Aug					First website put online at CERN (the first webpage had been developed several months earlier)
	Dec	Aims, written and video questionnaires agreed Sample size 3000, unit school Decision to have Steering Committee (Auckland, Bochum, London, Tucson, Wellington) and Data Centre, but each centre owning own data, and find its own funding Decision to publicise ISAAC, and publish ISAAC ISAAC Manual and brochure planned	Phase Two modules concept agreed Develop modules for BHR, serum IgE, skin prick tests, skin examination, medications & health services			Dissolution of Soviet union
1992	Dec	ISAAC Phase One Manual printed 90% participation of children the goal Coding manual prepared Brochure produced Announcement in Lancet 2 countries, 4 centres Contact WHO Avoid competing with European Paediatric Asthma Study (EPAS) Decision to try and engage some centres in all WHO regions Develop translation guidelines Central coordinating, library and data analysis centre in Auckland Regional coordinating centres National coordinating centres Need registration form Innes Asher appointed Chair with Ross Anderson Deputy Chair In preference use electronic mail (fax and email) Bimonthly newsletter Annual Steering Committee meeting Central funding required ISAAC now 2 countries, 4 centres Study to continue to run on a cooperative basis	Further development of modules for BHR, serum IgE, skin prick tests, skin examination, medications & health services, risk factors indoor and outdoor, other respiratory symptoms			
1993	April				First ISAAC newsletter	
	August	Phase One coding and data transfer manual printed				



# The ISAAC Story



Year	Month	Phase One	Phase Two	Phase Three	Other	World/Other events
	Oct	European Paediatric Asthma Study (EPAS) will join ISAAC Regional coordinators assigned in all developing country regions North America lukewarm because lack of central funding Registration document agreed Centre questionnaire developed Enlarged Steering Committee - original steering committee plus Regional coordinators plus Phase Two module leaders Executive formed Four levels - The Steering Committee, Regional coordinators, National coordinators, participating centres ISAAC regions decided Coordinating Dta Centre Auckland International version of the video developed, and the preferred version Translation guidelines formalised Coding and Data transfer manual Completed Data collection completed Data collection completed in 4 countries, 13 centres ISAAC Field work guide written by Philippa Ellwood				
	Nov	Pilot study published in ERJ				
	Dec	Second edition of Phase One manual printed	ISAAC satellite workshop on the airway reactivity module in Auckland, New Zealand Preferred option hypertonic saline Methacholine and histamine unacceptable as availability and ethical issues rule them out in many countries Exercise challenge not feasible as water content of atmosphere too high in many countries			
1994	Oct	42 Countries 107 centres recruited, collecting data North Am 2 countries 3 centres W Europe 6 countries 32 centres Asia-Pac 10 countries 19 centres Latin Am 8 countries 8 centres Franco Afr 1 country 1 centre Anglo Afr 3 countries 3 centres India 1 countries 21 centres East Medit 5 countries 6 centres N & East Europe 5 countries 5 centres Oceania 2 countries 10 centres Funding from Glaxo International Double entry of data Stop encouraging recruitment of centres, but accept them Clean data set by 1 Dec 1995 to be included in initial Phase One publications	Decided age group 9-11 yr olds Modules on blood spots, aeroallergen measurement Structure for Phase Two decided David Strachan Chair of Phase Two implementation committee			
1995	March	Phase One rationale and methods paper published in ERJ				
	Sept	Data received from 36 centres in 18 countries Data checking and management decided Double entry of data essential Epi info package for ISAAC created Approach to ecological analyses of Phase One being developed Authorship approach decided ISAAC at ERS - Erika von Mutius gave a presentation 20 Sept 1995 First collaborators meeting at ERS 1995	Phase Two centres to be identified by 1996 Phase Two modules being finalised German Phase Two studies begin			
	Dec	Data received in Auckland from 110 centres				

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Year	Month	Phase One	Phase Two	Phase Three	Other	World/Other events
1996	Sept	Centre report developed Participation rates of <80% (13-14yr) and 70% (6-7yr) decided Independent back translations required Published maps to be in colour and to include enlargement of Europe ISAAC region formerly known as Eastern Europe/ Baltics will now be referred to as 'Northern and Eastern Europe', Scandinavian centre will be grouped with Western Europe	Confirmed hypertonic saline for BHR		ISAAC session at ERS	
1997	Sept					Domain name google.com registered
	Sept	Data from 48 additional centres received A small number of centres need to be excluded Authorship guidelines refined further ISAAC Executive will be representation of 4 founding groups and at least one regional coordinator Three subcommittees of the Steering Committee – Phase two, Phase Three and Data and publications Ecological analyses planned in detail	Munster and Munich will coordinate Phase Two Stephan Weiland will be the contact person Hypertonic saline – children not required to inhale 23 ml of saline			
	Nov	First Phase One worldwide paper published				
						ECRHS2 began
1998	May		ISAAC Phase Two Manual printed		ISAAC website being developed	
	Sept	Several ecological analysis papers drafted		Phase Three is to assess trends in prevalence Other centres not in Phase One will be distinct Data collection 2000 -2002 Same methods as Phase One Slide sets for SC and collaborators	First ISAAC collaborators meeting	
1999						First publication describing low prevalence of allergy among children of farmers (Braun-Fahrlander)
	Jan	First 4 Phase One worldwide papers published				
	March		Phase Two training seminar in Münster			
	Oct		At least 1000 subjects	Grant received from Glaxo Wellcome Objectives broadened to three aims Add environmental questionnaire Regional coordinators confirmed Advertise Phase Three Clean data to be received by Dec 2002		
2000	July			ISAAC Phase Three Manual printed		
	Sept			\$NZ500,000 received from GlaxoWellcome for Phase Three	Comparison with ECRHS published	
	Oct	Decision to put ISAAC Phase One summary data on website	Genetic analyses to be discussed	Environmental questionnaire piloted Expressions of interest in Phase Three 176 from 83 countries (47 new centres)	ISAAC letterhead with names of all Steering Committee	
2001	Feb	First Ecological analysis paper published				
	Sept		EU funding for 15 centres in Europe Genetics analysis agreement developed 25 centres in Europe 11 centres in 8 other countries Data centre in Münster	EOI 226 centres from 99 countries (91 new centres) 123 registrations Deadline for clean data 30 November 2002 ISAAC Publication policy notified to journals	ISAAC will continue beyond Phases Two and three	
2002	Sept		Phase Two Steering Group formed Data centre moved to Ulm	226 registrations from 89 countries Publication plan and writing groups finalised for time trend and world map papers	Principle of 'no survey without service' – principle for Phase Four	

# The ISAAC Story



Year	Month	Phase One	Phase Two	Phase Three	Other	World/Other events
	Nov 2002— Jul 2003					Severe acute respiratory syndrome (SARS) pandemic 774 deaths among 8096 cases
2003	Nov			226 registrations from 89 countries Data at IIDC 218 centres Translations subcommittee formed Data deadline from Phase Three A centres delayed to 31 Dec 2003 Phase Three B mid 2004		
2004	Sept		Phase Two rationale and methods paper published in ERJ		ISAAC symposium at ERS Glasgow, with ECRHS	
	Nov			286 registrations from 107 countries	Phase Four will be an interventions study Proceed with plans for Phase Five 2010—2012 Infant wheeze study EISL initiated by Javier Mallol	
2005	Jan			Phase Three rationale and methods paper published in Int J Tuberc Lung Dis		
	Oct					Nobel Prize for Physiology or Medicine awarded jointly to Robin Warren and Barry Marshall for discovery of Helicobacter pylori infection as a cause of peptic ulceration
	Nov			Data centre will not accept any more centres	Link to Asthma Drug facility established ISAAC Monograph planned	
2006						Mutations in the flaggrin gene identified as a risk factor for eczema GABRIEL study begins
	Sept			First time trends paper published		
	Nov				Phase Four is about education and advocacy	
2007	19 March				Stephan Weiland died unexpectedly	
	June		First Phase Two results paper published			
	Sept			Tables of first EQ results compiled		
2008	Jan				Redevelopment of ISAAC website	
	Sept			First EQ paper published		
	Oct				ISAAC Monograph will be web-based	
2009	Feb			First world map paper published		
	June					H1N1 influenza ("swine flu") declared a pandemic by the WHO
	Nov				ISAAC will finish in Dec 2012 if no funding for Phase Five ISAAC Monograph renamed ISAAC Story	
2010		Last Phase One worldwide paper published Phase One individual level data on website to PIs only		ISAAC summary data on website		
	May				ATS ISAAC presentation on global disparities in asthma	
	Dec				ISAAC Story being written	First EISL publications
2011	Jan				ISAAC 20 year Symposium in Auckland	

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## ISAAC Diary

### ISAAC Timeline - Steering Committee meetings

Year	Month	Location	Activity	Who
1990	December 2-5	Bochum, Germany	International Workshop on Monitoring Trends of Asthma and Allergies	Anderson, Behrendt, Bergmann, Burr, Crane, Epstein, Frischer, Heilmaier, Hurd, Keil, Krämer, Martínez, von Mutius, Nowak, Pearce, Ring, Sibbald, Strachan, Wahn, Weiland, Wichmann
1991	December 8-11	Bochum, Germany	Second International Workshop on Monitoring Trends of Asthma and Allergies in Childhood	Anderson, Asher, Bergmann, Crane, Gergen, Groot, Habbick, Heilmaier, Hurd, Keil, Martínez, Pearce, Ring, Robertson, Sibbald, Strachan, von Mutius, Wahn, Weiland
1992	December 6-8	London, United Kingdom	Third International Workshop on ISAAC (Steering Committee meeting)	Anderson, Asher, Bauman, Beasley, Burr, Crane, Ernst, Hurwitz, Keil, Kremer, Landau, Langridge, Martínez, Pearce, Peat, Robertson, Schafer, Sibbald, Silverman, Strachan, Taylor, von Mutius, Warner, Weiland, Williams
1993	October 3-4	Geneva, Switzerland	Fourth International Workshop on ISAAC (Steering Committee meeting)	Anderson, Asher, Beasley, Martínez, Pearce, Strachan, Weiland WHO: Stober, Kjellstrom
1994	October 5-6	Nice, France	Fifth International Workshop on ISAAC (Steering Committee meeting)	Anabwani, Anderson, Asher, Beasley, Björkstén, Burr, Crane, Keil, Lai, Martínez, Montefort, Robertson, Stewart, Strachan, von Mutius, Weiland, Williams IIDC: Clayton NC: Charpin Other: Cropp, Persky
1995	September 15-16	Barcelona, Spain	Sixth International Workshop on ISAAC (Steering Committee meeting)	Anabwani, Anderson, Asher, Beasley, Björkstén, Keil, Lai, Mallol, Montefort, Pearce, Robertson, Stewart, Strachan, von Mutius, Weiland, Williams IIDC: Clayton NC: Garcia-Marcos
1996	September 6-7	Stockholm, Sweden	Seventh International Workshop on ISAAC (Steering Committee meeting)	Anderson, Asher, Beasley, Björkstén, Crane, Keil, Lai, Martínez, Mitchell, Montefort, Pearce, Robertson, Stewart, Strachan, von Mutius, Weiland, Williams IIDC: Clayton, Ellwood
1997	September 19-20	Berlin, Germany	Eighth International Workshop on ISAAC (Steering Committee meeting)	Anabwani, Anderson, Asher, Beasley, Björkstén, Burr, Keil, Lai, Mallol, Martínez, Mitchell, Montefort, Pearce, Stewart, Strachan, von Mutius, Weiland, Williams IIDC: Clayton, Ellwood
1998	September 18-19	Geneva, Switzerland	Ninth International Workshop on ISAAC (Steering Committee meeting)	Anderson, Asher, Beasley, Björkstén, Burr, Keil, Lai, Mallol, Mitchell, Montefort, Pearce, Robertson, Stewart, Strachan, von Mutius, Weiland IIDC: Ellwood Observers: Weber, Mégevand, Rylander
1999	October 8-9	Madrid, Spain	Tenth International Workshop on ISAAC (Steering Committee meeting)	Ait-Khaled, Anderson, Asher, Beasley, Björkstén, Burr, Crane, Lai, Mitchell, Pearce, Robertson, Stewart, Strachan, von Mutius, Weiland, Williams IIDC: Ellwood NC: Garcia-Marcos
2000	October 13-14	Auckland, New Zealand	Eleventh International Workshop on ISAAC (Steering Committee meeting)	Ait-Khaled, Anderson, Asher, Beasley, Björkstén, Burr, Crane, Lai, Mallol, Mitchell, Montefort, Odhiambo, Pearce, Robertson, Shah, Stewart, Strachan, von Mutius, Weiland IIDC: Clayton, Ellwood, Williams
2001	September 20-21	Gozo, Malta	Twelfth International Workshop on ISAAC (Steering Committee meeting)	Anderson, Asher, Björkstén, Cookson, Crane, Keil, Lai, Mallol, Mitchell, Montefort, Odhiambo, Pearce, Stewart, Strachan, von Mutius, Weiland, Williams IIDC: Clayton, Ellwood Phase Two DC: Rzehak
2002	September 12-13	Stockholm, Sweden	Thirteenth International Workshop on ISAAC (Steering Committee meeting)	Ait-Khaled, Anderson, Asher, Beasley, Björkstén, Cookson, Crane, Foliaki, Keil, Lai, Mallol, Mitchell, Montefort, Odhiambo, Pearce, Robertson, Stewart, von Mutius, Weiland, Williams IIDC: Ellwood Phase Two DC: Rzehak NC: Nilsson
2003	November 27-28	Lake Navaisha, Kenya	Fourteenth International Workshop on ISAAC (Steering Committee meeting)	Ait-Khaled, Anderson, Asher, Björkstén, Keil, Mitchell, Odhiambo, Pearce, Robertson, Stewart, Strachan, Weiland, Williams, Wong IIDC: Clayton Phase Two DC: Rzehak
2004	November 13-14	Nuku'alofa, Tonga	Fifteenth International Workshop on ISAAC (Steering Committee meeting)	Asher, Björkstén, Crane, Ellwood, Foliaki, Keil, Lai, Mitchell, Pearce, Robertson, Stewart, Strachan, Weiland, Williams, Wong IIDC: Clayton, Milne
2005	November 7-8	Hong Kong, SAR China	Sixteenth International Workshop on ISAAC (Steering Committee meeting)	Ait-Khaled, Asher, Beasley, Björkstén, Brunekreef, Crane, Ellwood, Foliaki, Lai, Mitchell, Montefort, Odhiambo, Pearce, Robertson, Stewart, Strachan, von Mutius, Weiland, Williams IIDC: Clayton Observer: Garcia-Marcos, Wong
2006	November 23-24	Santiago, Chile	Seventeenth International Workshop on ISAAC (Steering Committee meeting)	Ait-Khaled, Anderson, Asher, Brunekreef, Ellwood, Foliaki, Garcia-Marcos, Mallol, Mitchell, Pearce, Robertson, Stewart, Strachan, Weiland, Williams IIDC: Clayton
2007	September 12-13	Munster, Germany	Eighteenth International Workshop on ISAAC (Steering Committee meeting)	Ait-Khaled, Anderson, Asher, Björkstén, Brunekreef, Crane, Ellwood, Garcia-Marcos, Keil, Lai, Mallol, Mitchell, Odhiambo, Pearce, Robertson, Stewart, Strachan, von Mutius, Weinmayr, Williams, Wong IIDC: Clayton
2008	October 9-10	Casablanca, Morocco	Nineteenth International Workshop on ISAAC (Steering Committee meeting)	Ait-Khaled, Asher, Beasley, Crane, Ellwood, Flohr, Garcia-Marcos, Lai, Mitchell, Montefort, Odhiambo, Pearce, Robertson, Stewart, Strachan, Weinmayr, Williams, Wong IIDC: Clayton
2009	November 26-27	Mérida, Mexico	Twentieth International Workshop on ISAAC (Steering Committee meeting)	Asher, Brunekreef, Ellwood, Flohr, Foliaki, Garcia-Marcos, Mallol, Pearce, Robertson, Stewart, Strachan, Weinmayr, Williams IIDC: Clayton
2011	Jan 25-26	Auckland, New Zealand	Twenty-first International Workshop on ISAAC (Steering Committee meeting)	Ait-Khaled, Asher, Beasley, Brunekreef, Crane, Ellwood, Foliaki, Garcia-Marcos, Lai, Mallol, Mitchell, Montefort, Odhiambo, Pearce, Robertson, Stewart, Strachan, Weinmayr, Williams IIDC: Clayton, Ellwood E

Introduction

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(Time Line)

**ISAAC Steering**

**Committee**

**Timeline**