Validation of the United Kingdom Working Party Diagnostic Criteria for Atopic Eczema in an African Setting

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Submitted in partial fulfillment of the requirements of Masters of Public Health (Epidemiology)

Declaration

I, Debra Ann Chalmers, Student Number CHLDEB002, declare that the work that I have submitted is my own and where the work of others has been used (whether quoted verbatim, paraphrased or referred to) it has been attributed and acknowledged.

Signature: Signed by candidate

Date: 15 August 2005

Acknowledgements

This study would not have been possible without support from the following people and organisations:

Benfara Scholarship Fund

Harry Crossley Foundation

KW Johnston Bequest Scholarship

The Wellcome Trust

The staff and clinicians who were responsible for designing the study as well as gathering and inputting the data, and specifically Professor Gail Todd, Professor Norma Saxe and Professor Hywel Williams. Thank you for your preparatory work on this study.

My supervisor, Professor Rodney Ehrlich, for all his patience, support, encouragement and countless corrections, always pushing me to achieve a better result.

My second supervisor, Professor Gail Todd, for her support and understanding, for encouraging me to question everything and to never ignore the scientist in me.

Valuable advice and support was provided many others, including members of the MPH class, family and friends. Thank you.

Finally, this thesis would not have been possible without the support of my partner, Eric. This thesis is dedicated to him and to my parents.

Summary

Background: In order to ensure accurate diagnosis of the condition and to allow for international comparisons to further the understanding of disease aetiology, the development of reliable diagnostic criteria for atopic eczema is of importance. Although the United Kingdom (UK) diagnostic criteria for atopic eczema have demonstrated good validity in an English language setting, limited data are available of their validity in situations where cultural and linguistic factors differ from those found in the United Kingdom.

Objectives: To determine the prevalence of atopic eczema in a Southern African setting using both a modified version of the UK Working Party diagnostic criteria for atopic eczema and a clinical assessment by a dermatologist, and to measure the validity of the UK criteria.

Methods: A cross sectional survey of 3067 children age 3-11 years was conducted in rural, peri-urban and urban settings in South Africa. The prevalence of atopic eczema was determined using the UK diagnostic criteria and a clinical assessment by a dermatologist. The prevalence of other skin conditions was also determined. The validity of the UK criteria was then determined by calculating the sensitivity, specificity, positive predictive value and negative predictive value.

Results: The point prevalence of atopic eczema following clinical examination was 1.0% (95% CI 0.6-1.4), with a one year prevalence of atopic eczema according to the UK criteria of 2.48% (95% CI 1.9-3.0). The sensitivity and specificity of the UK criteria in this setting were 43.7% and 97.9% respectively, values lower than those obtained in the UK setting. The positive predictive value was also lower than that obtained in the UK setting (18.4%; 95%CI

10.4-28.9) which is related to the low observed prevalence of atopic eczema in this study. The negative predictive value was 99.40% (95% CI 99.05-99.64). The presence of visible flexural eczema was the best predictor of atopic eczema, with a sensitivity and specificity of 81.2% and 99.0% respectively.

Conclusions: The point prevalence of atopic eczema was 1.0% with a period prevalence of 2.4%. These results are considerably lower than the period prevalence estimate of the ISAAC study of 8%. The UK criteria were not sensitive in predicting cases of atopic eczema in this study, a result similar to those found in Iran and Ethiopia. This may be related to problems with questionnaire translation, socio-cultural acceptability of the diagnosis of an itchy skin condition, or misclassification of subjects. At present, the UK criteria are not appropriate for use as an epidemiological tool in a South African setting.

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Chapter 1: Background & Definitions

1.1 Problem Statement

Atopic eczema refers to the skin manifestations of a hypersensitivity phenotype. In the past there was no clear definition of atopic eczema so that diagnosis of the condition varied between clinicians. In the early 1980's Hanifin and Rajka published a set of diagnostic features for atopic eczema in an attempt to guide physicians in their diagnosis (Hanifin & Rajka, 1980). The need for these criteria was clear as they would allow for agreement regarding diagnosis of the condition and therefore easier comparison of results between international studies. It was hoped that such comparisons would provide clues to the underlying aetiology of this poorly understood condition and allow for primary prevention in the future.

Hanifin and Rajka's criteria were followed by the development of the UK Working Party diagnostic criteria for atopic dermatitis in 1994 (Williams *et al.*, 1994a). The criteria have since been validated in hospital and community settings in the United Kingdom, and in other countries including Romania, Iran and Ethiopia (Popescu *et al.*, 1998; Firooz *et al.*, 1999; Haileamlak *et al.*, 2005). The demonstrated validity in these settings suggests that prevalence rates across populations can now be compared and can lead to hypotheses about the disease aetiology. However, the criteria have yet to be validated in a South African setting.

In the late 1990's the International Study of Asthma and Allergies in Childhood (ISAAC) sought to describe the magnitude and variation in the prevalence of atopic eczema, as well as other allergic conditions including asthma, on an international level. It was hoped that systematic international comparisons would facilitate an improved understanding of the global

epidemiology of these conditions as well as aiding in future research regarding aetiology. A cross sectional questionnaire survey was conducted in 56 countries and showed marked differences in prevalence of atopic eczema between countries (Williams *et al.,* 1999). In South Africa the urban prevalence of atopic eczema amongst English, Afrikaans and Xhosa speaking 13-14 year olds was approximately 8% according to a composite scoring system, with a self-reported diagnosis prevalence of 9.6%. The children completed their own questionnaires, responding to questions similar to those included in the UK criteria but not identical.

Current understanding of atopic eczema aetiology suggests that it arises from an interaction between an underlying genetic susceptibility and a variety of environmental influences which modulate phenotypic expression. Migrant studies provide an opportunity to assess how changes in environmental elements may alter disease occurrence or progression. Migrant studies involving Jamaican immigrants living in London showed an increased prevalence of atopic eczema as diagnosed by the UK criteria when compared to their Jamaican based counterparts (14.9% versus 5.6%) (Williams *et al.,* 1995a). Unfortunately the wide range of possibilities for environmental causes of atopic eczema means that migrant studies still involve a large degree of speculation.

In the case of South Africa, research has previously demonstrated a rural-urban gradient for asthma, with an urban prevalence of exercise induced bronchospasm of 3.17% and a rural prevalence of 0.14% (van Niekerk *et al.,* 1979). Recent research has shown the prevalence of exercise induced bronchospasm in children aged 8-13 years to be 14.9% in urban areas and

8.9% in rural areas (Calvert, 2003). The reduced difference in prevalence between the studies is thought to be due to a relative increase in the rural prevalence of asthma. Given that information regarding the rural prevalence of atopic eczema in South Africa is lacking, and that South Africa affords the opportunity for studying migrant populations, further research in this setting was prompted. However, before drawing conclusions about prevalence and possible aetiology, validation of the UK criteria as an epidemiological instrument is needed.

1.2 Aim

The study aimed to determine the prevalence of atopic eczema using clinical examination by a dermatologist, and subsequently to determine the validity of the United Kingdom Working Party diagnostic criteria for atopic eczema in a South African setting.

1.3 Objectives

- To determine the prevalence of atopic eczema in a South African setting using a clinical assessment by a dermatologist with a specific interest in paediatric dermatology;
- To determine the prevalence of atopic eczema in a South African setting using a modified version of the United Kingdom Working Party diagnostic criteria for atopic eczema;
- To determine the prevalence of skin diseases other than atopic eczema in these settings;
- To investigate the validity of the United Kingdom Working Party diagnostic criteria for atopic eczema in a South African setting.

Chapter 2: Literature Review

2.1 What is atopic eczema?

Atopic eczema is a chronic condition with significant impact on quality of life. The term atopy was used initially to refer to individuals with an inherited hypersensitivity such as asthma, with atopic eczema referring to the cutaneous manifestation of this condition (Borirakchanyavat & Kurban, 2001). More recently, a new definition of atopy has been proposed as "a personal or family tendency, usually in childhood or adolescence, to become sensitized and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins." (Johansson *et al.*, 2004). By extension, this refers to children and adults with an atopic constitution with primarily skin manifestations. Atopic eczema commonly presents in childhood, with early onset associated with a poorer prognosis (Williams, 1995). Approximately 80-90% of cases occur before the age of 5 years, and the condition is estimated to affect between 10-20% of children worldwide (Leung & Bieber, 2003; Williams, 1995).

There are as yet no objective laboratory markers of atopic eczema, and since clinical manifestations vary, accurate estimates of epidemiology are limited by the expertise of those making the diagnosis. An accurate diagnosis requires the clinician to have familiarity with a condition which often displays subtle cutaneous signs. These range across a spectrum from minor forms including pityriasis alba to major forms such as erythroderma (Leung & Bieber, 2003). The differential diagnosis of atopic eczema is large and depends on the country of residence. It may include other chronic dermatoses such as childhood skin infections and congenital disorders, malignant disease, immunological disorders, immunodeficiencies and metabolic disorders.

There appears to be a strong genetic basis to atopic eczema with approximately 75% of patients having a positive family history of atopic conditions. Twin studies suggest that there is up to 85% concordance for atopic eczema amongst monozygotic twins (Borirakchanyavat & Kurban, 2001; Williams, 1995). Genetic inheritance is probably on a polygenic basis, with some evidence pointing towards abnormalities in the high affinity IgE receptor and various interleukin (IL) genes, notably IL-4 and IL-5 (Levy *et al.*, 2003; Kang & Stevens, 2003; Borirakchanyavat & Kurban, 2001; Stevens & Cooper, 2000). Other inherited cytokine abnormalities have also been identified as possible candidate genes for the development of atopic eczema. The underlying immune mechanism remains unclear, and one should therefore continue to refer to the condition as atopic eczema. This is thus an aggregate term for skin conditions with similar clinical phenotype and a primary, as yet undetermined, genetic defect (Johansson *et al.*, 2004).

Many cells of the immune system display an abnormality in patients with atopic eczema, although the underlying dysfunction typically results in elevated IgE, hypersensitivity and T-cell dysregulation (Borirakchanyavat & Kurban, 2001; Stevens & Cooper, 2000). Dysregulation of the immune system results in inappropriate responses to otherwise innocuous immunological triggers. These triggers may in part be modulated by geographic and socioeconomic factors, but may also be ubiquitous and unavoidable. Food allergens are responsible for relapse in many children suffering from moderate to severe atopic eczema. In a recent cohort study of infants with a family history of atopy, an increase in severity of diagnosed atopic eczema was associated with an increased likelihood of having an IgE mediated food allergy, with a relative risk of 5.9 in the most severely affected group (Hill & Hosking, 2004). Applying aeroallergens such as house dust mite, animal dander and moulds

by patch test to unaffected atopic skin causes an allergic response in up to 50% of individuals who suffer from atopic eczema (Leung & Bieber, 2003; Levy *et al.*, 2003). Seasonal variation in atopic eczema has also been noted.

Individuals with atopic eczema have also been shown to have higher levels of *Staphylococcus aureus* bacteria than non-atopic eczema suffers, probably as a result of the loss of the protective barrier function of the affected skin (Leung & Bieber, 2003). It is thought that *S. aureus* infection facilitates ongoing inflammation through continued activation of T cells and macrophages. Increased bacterial binding may be facilitated by the underlying inflammatory nature of atopic eczema, so that an inflammation-infection-inflammation cycle is established. Establishment of *S. aureus* colonies also prevents colonization by commensals, predisposing individuals to further infections.

Interestingly, a lower occurrence of atopic eczema has been demonstrated in populations with higher exposure to infections at an early age, lending support to the hypothesis that childhood infections may be protective (Levy *et al.*, 2003). The exact mechanism is unclear, although it is thought that early infections preferentially stimulate the Th1-mediated immune response, thus reducing the Th2-response that is postulated to result in the hypersensitivity observed in atopic eczema. A recent study of children whose families' lifestyle advocates restricted use of antibiotics and limited vaccination showed a lower prevalence of atopy than in children from other families (Alm *et al.*, 1999). The premise is that this lifestyle could thus lead to an increase in childhood infections, promoting the Th1-response. Differences in diet and in rates of breast-feeding may also have contributed to the observed differences in prevalence. Similar conclusions were drawn following a cohort study in the United Kingdom, where

increased likelihood of early exposure to infections was associated with a decreased prevalence of atopic eczema (Harris *et al.*, 2001).

In contrast to these studies however, a recent Danish cohort study looking at sibling effect, infectious diseases and the risk of developing atopic eczema in the first 18 months of life showed that early infection did not seem to protect against allergic disease (Stabell Benn *et al.*, 2004). In fact, these data suggest that early infection is associated with an apparently paradoxical increased risk of atopic eczema. Their study was consistent with the emerging hypothesis that it is actually an increased number of older siblings which leads to a decreased risk of developing atopic eczema. In a recent review of the hygiene hypothesis of atopic eczema by Flohr *et al.*, it was proposed that the reduction in risk of atopic eczema amongst children with early exposures to infection may have been due to the presence of older siblings (Flohr *et al.*, 2005).

While knowledge of the cellular mechanisms of atopy has grown over recent years, development in epidemiological understanding of the subject has been slow (Williams, 1995; Williams, 2000). A summary of the most recent advances from studies conducted in Europe and Australia is shown in Table 2.1 (Larsen *et al.*, 1996; Child *et al.*, 1999; Marks *et al.*, 1999; Williams, 2000). Recent studies have also been conducted in North Africa (Yemaneberhan *et al.*, 2005), but South African data remain sparse.

Table 2.1: Ten recent advances in the understanding of the epidemiology of atopic eczema[1].

1.	Development of a valid definition of atopic eczema for use in epidemiological studies;
2.	Documentation of world wide burden of disease through studies such as ISAAC;
3.	Economic analysis showing the high cost of atopic eczema compared with other conditions;
4.	Studies showing geographical variation in atopic eczema which cannot easily be explained by current understanding of risk factors;
5.	Ecological studies that suggest a link between atopic eczema in young children and local water hardness;
6.	Migrant studies that suggest a strong environmental role in disease expression;
7.	A consistent positive association between socio-economic advantage and the development of atopic eczema;
8.	Improved understanding of the role of the immune system in atopic eczema;
9.	Improved understanding of the role of genetics and early environment in subsequent development of atopic eczema;
10.	Studies which suggest a proportion of atopic eczema may be preventable.

[1]Adapted from Williams, 2000

2.2 Diagnostic Criteria for Atopic eczema

Given the variation in clinical manifestation of atopic eczema the need arose for the development of criteria that would allow for consensus in diagnosis of the condition. Hanifin and Rajka published a set of diagnostic features for atopic eczema in 1980 (Hanifin & Rajka, 1980). These criteria were developed based on clinical experience, suggestions by experts in the field of dermatology and discussions at symposia. These resulted in what they referred to as a "unified outline of diagnostic criteria". Diagnosis rested on the presence of 3 or more of the 4 defined major criteria, and at least 3 out of the 22 minor criteria, as shown in Table 2.2.

Table 2.2: Guidelines for the diagnosis of atopic eczema[1]

Major criteria (must have 3 or more basic features)
Pruritis;
Typical morphology and distribution:
Flexural lichenification in adults;
Facial and extensor involvement in children;
Chronicity or chronically relapsing dermatitis;
Personal or family history of atopy.
Minor criteria (must have 3 or more basic features)
Xerosis;
Ichthyosis/palmar hyperlinearity/keratosis pilaris;
Immediate (type I) skin test reactivity;
Elevated serum IgE;
Early age of onset;
Tendency towards cutaneous infections;
Tendency towards non specific hand or foot dermatitis;
Nipple eczema;
Cheilitis;
Recurrent conjunctivitis;
Dennie-Morgan infraorbital fold;
Keratoconus;
Anterior subcapsular cataracts;
Orbital darkening;
Facial pallor/facial erythema;
Pityriasis alba;
Anterior neck folds;
Itch when sweating;
Intolerance to wool and lipid solvents;
Perifollicular accentuation;
Food intolerance;
Course influenced by environmental/emotional factors;
White dermographism/delayed blanch.

[1]Hanifin & Rajka, 1980

In the 1990's a working party of 13 dermatologists, two family practitioners and a pediatrician was assembled in the United Kingdom with the intention of deriving a minimum list of indicators for atopic eczema (Williams *et al.*, 1994a). Over two hundred cases were used to test the sensitivity and specificity of 31 diagnostic criteria which constituted a modified version of Hanifin & Rajka's criteria, shown in Table 2.2, placing a greater emphasis on applicability in population based studies. Of these criteria, thirteen were historical features, including the presence or absence of itch, the chronicity of the condition, a history of atopic conditions and the distribution of the condition (Hanifin & Rajka, 1980). The remaining eighteen criteria were clinical signs. These are listed in Table 2.3.

Table 2.3: The 31 criteria included in the derivation of a minimum set of discriminators for atopic dermatitis by the UK Working Party for atopic eczema[1]

Historical features (15)	
A: Itch	Presence/absence; Wool intolerance; Sweat-induced;
B: Chronicity	Duration; Age of onset;
C: Atopic background	Personal history of diagnosed asthma; Personal history of hay fever; Blocked nose in absence of colds; Family history of atopy;
D: Distribution / general	History of flexural involvement; History of a dry skin; Soap intolerance; Worsening of skin in winter;
Clinical signs(18)	
Visible dermatitis at any sight;	Extensor dermatitis;
Facial dermatitis;	Xerosis;
Perifollicular accentuation;	Infraorbital crease;
Periorbital pigmentation;	Infra-auricular fissure;
Palmar hyperlinearity;	Hand/foot dermatitis;
Flexural dermatitis;	Hypopigmented patches;
Truncal dermatitis;	Periorbital dermatitis;
Fine hair;	Cheilitis;
Periauricular dermatitis;	Keratosis pilaris.

[1]Williams *et al.*, 1994a

The six criteria which proved to be of the greatest predictive use for diagnosing atopic dermatitis were determined in logistic regression analysis to be: a history of flexural dermatitis; onset of the condition under the age of 2 years; the presence of an itchy rash; a

personal history of asthma; a history of generally dry skin and the presence of visible flexural dermatitis (Williams *et al.,* 1994a).

It is important to note that three of the four major criteria suggested by Hanifin & Rajka are included in the six criteria determined by Williams *et al.,* (1994a). Williams and co-workers went on to test the inter-observer variation of clinical diagnosis and signs of atopic eczema, using the criteria that they had established (Williams *et al.,* 1994b). They noted that between-observer agreement was good if the case represented a typical presentation of atopic eczema where the condition predominantly affected the flexures. However, atypical cases, which included those with mainly truncal lesions, resulted in reliability only slightly better than chance for inter-observer variation. The percentage agreement varied depending on the clinical signs used; those signs having a strict clinical definition showed a higher degree of agreement than those signs (e.g. keratosis pilaris) which had been poorly defined in the study. Physicians in other medical specialties have shown similar results for agreement with regard to a diagnosis based on clinical assessment (Spiteri *et al.,* 1988).

Independent hospital validation of the UK Working Party's diagnostic criteria for atopic eczema was conducted in the same year (Williams *et al.,* 1994c). The modified UK diagnostic criteria showed a sensitivity of 85% and specificity of 96%. The comparative instrument in this validation study was diagnosis of atopic eczema that had been made based on the Hanifin and Rajka criteria. The UK criteria were therefore considered attractive for use in an out-patient setting, as they require two minutes per patient to administer without the need for the patient to undress. The proposed diagnostic guidelines of atopic eczema are shown in Table 2.4.

Table 2.4: UK Working Party's diagnostic criteria for atopic eczema[1]

Must have: An *itchy* skin condition (or parental report of scratching or rubbing in a child)
Plus 3 or more of the following: 1. History of involvement of the skin creases such as folds of the elbows, behind the knees, fronts of the ankles or around the neck (including cheeks in children under 10 years of age); 2. A personal history of asthma or hay fever (or history of atopic disease in a first degree relative in children under 4 years of age); 3. A history of a general dry skin in the last year; 4. Visible flexural eczema (or eczema involving the cheeks/forehead and outer aspects of the limbs in children under 4 years of age); 5. Onset of the condition under the age of 2 years of age (not used if child is under 4 years of age).

[1]Williams *et al.*, 1994c

2.3 Variations in atopic eczema prevalence & the ISAAC study

The first international collaborative study on the world wide prevalence of atopic eczema was the International Study of Asthma and Allergies in Childhood (ISAAC) conducted in 1998. A questionnaire based survey as part of phase I of the study revealed a prevalence of approximately 8% of symptoms of atopic eczema amongst a Cape Town population of 13-14 year old English, Afrikaans and Xhosa speaking children (Williams *et al.*, 1999).

A more recent analysis of symptoms of atopic eczema and the relationship with socio-economic status has been conducted using the data collected in phase 1 of the ISAAC study. Analysis of responses given by a subset of 4947 children aged 13-14 years showed the self-reported prevalence of a recurrent itchy rash in the preceding year to be 11.9% (Mercer *et al.*, 2004). The self-reported prevalence of suffering from "eczema" was 10.5%. Mercer also

demonstrated amongst the 1746 pupils attending historically black schools that there was a small positive association between each additional year of residence in Cape Town and increased odds of experiencing a recurring itchy rash (OR=1.05, 95% Confidence Interval 1.01-1.09).

Following the publication of the ISAAC data there have been numerous independent studies describing the prevalence of atopic eczema in individual countries. A study in Australia amongst 2941 school children aged 4-18 years using both clinical examination and the UK criteria showed a point prevalence of 16.3% following clinical examination and a period prevalence of 10.8% based on the questionnaire results (Marks *et al.*, 1999). One must note that the point prevalence estimate in the Australian study is higher than the period prevalence estimate, in contrast to other validation studies. This was thought to be, in part, because some of the individuals found to have atopic eczema on clinical examination gave no history of itchy skin or a history of skin disease.

Recent New Zealand cohort data suggest the prevalence amongst children of less than 4 years of age to be approximately 15.8% (Purvis *et al.*, 2005). A slightly lower prevalence for atopic eczema of 11.2% was demonstrated in a Japanese study of 6-7 year olds and 11-12 year olds (Saeki *et al.*, 2005).

Studies of African populations are few. An Ethiopian study conducted by Yemaneberhan *et al.*, investigated the prevalence of and factors associated with atopic eczema in rural and urban Ethiopia (Yemaneberhan *et al.*, 2004). They demonstrated an overall prevalence of atopic eczema symptoms of 1.2% based on questionnaire responses, with a higher urban (1.5%) than rural (0.3%) prevalence. The questionnaire contained two questions relating to

atopic eczema symptoms – the first enquiring about an itchy skin rash which affected the skin creases of the arms and legs, and the second enquiring about the presence of this rash in the past year. They also showed that lifestyle factors linked with urbanization, like residing in a brick rather than mud house or exposure to cigarette smoke, were associated with an increased risk of atopic eczema symptoms.

Other than the ISAAC study, descriptive studies investigating the prevalence of atopic eczema in South Africa are lacking. In fact, dermatological studies in South Africa are fairly limited. A study of informal settlement dwellers in the Cape Town area showed "skin conditions" to account for 16.4% of major household health problems (Mathee & van Schirnding, 1995). Some hospital based studies have also been conducted, although these are not appropriate for commenting on the prevalence of the condition in the population as a whole (Hartshorne, 2003).

2.4 Validation of UK Working Party diagnostic criteria in other settings

Although the UK Working Party diagnostic criteria were validated in a hospital out-patient based setting, further validation in community settings and in developing countries is required. The comparison of a test with a single definitive reference, or gold standard, underlies validity testing. The concern with atopic eczema is that unlike most other medical conditions, the diagnosis was previously based on clinical judgment as there is no specific laboratory test which either confirms or refutes the presence of the condition. Given the wide range of clinical manifestations of the condition, the natural concern is a lack of standardization of the gold standard diagnosis. A protocol has therefore been described by Williams and co-workers for recording the signs of flexural eczema in children (Williams *et al.,* 1995b). This protocol aimed to standardize the assessment of atopic eczema in population studies of children and made

use of a standard set of photographs and instructions which clearly defined the terms eczema and flexural. This method was shown to improve percentage agreement between nursing staff when recording the sign as part of the UK Working Party diagnostic criteria.

The UK criteria were validated in a population setting in London in 1996 (Williams *et al.,* 1996). A cross sectional survey of 3000 children was conducted using a questionnaire of the UK criteria and clinical examination by a paediatric dermatologist. Initial analysis showed a sensitivity and specificity of 70% and 93% respectively, with a positive predictive value of 47%. It was found, however, that most of those individuals classified as false positives had been documented independently in the preceding year as cases of atopic eczema, but that their disease process was inactive at the time of examination. Adjustment for these "false positives" through reclassification resulted in a sensitivity and specificity of 80% and 97% respectively when compared with clinical examination by a dermatologist. It was concluded that the criteria were appropriate for use in a population setting, although further testing in other settings such as adult populations and other countries was required.

In the United Kingdom the criteria were validated in a population of Scottish infants using a postal questionnaire format, rather than the specified administration by a trained researcher. The results were encouraging as agreement between the mothers' postal and home interview responses were high, suggesting that the criteria are an easy to use, practical and reliable method of determining prevalence of atopic eczema in that setting (Fleming *et al.,* 2001). A second group of researchers tested the validity of the UK Working Party's criteria in a Danish setting. The Danish questionnaire was modified slightly to maintain integrity of the information content that might have been lost during the translation process. The Danish researchers referred to the lifetime experience of symptoms of atopic eczema rather than one year's

prevalence as suggested by the UK criteria. These results showed an overall sensitivity of 90% and specificity of 97% compared with diagnosis by an independent validator based on an interview and not clinical examination, suggesting that the criteria could be considered as appropriate for use in a Danish setting (Olesen *et al.*, 2001).

The United Kingdom diagnostic criteria have also been validated in Romania, Iran and most recently Ethiopia (Popescu *et al.*, 1998; Firooz *et al.*, 1999; Haileamlak *et al.*, 2005). In the Romanian study a total of 1114 children aged 6-12 years participated. The gold standard in this instance was clinical diagnosis by a dermatologist with a specific interest in atopic eczema. This study showed a sensitivity and specificity of 74% and 99% respectively, with a point prevalence of 2.4% based on clinical examination (Popescu *et al.*, 1998). By contrast, a similar study of 416 Iranian patients attending a clinic showed a sensitivity and specificity of 10% and 98.3% respectively (Firooz *et al.*, 1999). Point prevalence based on clinical examination was 14.4% in this study. The mean age of the individuals taking part in this study was considerably higher than in other studies mentioned here, with a mean of 22.4 years in the cases and 28.5 years in the non-cases. In a sub-analysis assessing the sensitivity and specificity of the UK criteria against clinical diagnosis in the patients younger than ten years of age, these measures were 12% and 100% respectively, although the numbers of patients were small (16 cases and 17 non-cases).

In Ethiopia a study of 7915 children aged 1-5 years showed an overall period prevalence of atopic eczema of 1.8% according to the UK criteria although only 52% of these were confirmed as having atopic eczema on clinical examination, with a point prevalence of 0.94% (Haileamlak *et al.*, 2005). The Ethiopian study also attempted to validate the ISAAC questionnaire, with a period prevalence estimate of 4.4% for symptoms of atopic eczema. The

authors cited linguistic and cultural factors as possible reasons for the poor performance of the UK criteria in this setting. These factors included translation problems and cultural concepts of terminology as well as doubts regarding the acceptability to parents of the diagnosis of atopic eczema compared with another itchy skin condition. The authors were not explicit about the nature of these factors, and thus one can only speculate that obstacles were encountered with the translation process, and that the concept of the word "eczema" is not conveyed adequately in its translated form. It is likely that with a low period prevalence of 0.94%, understanding of the construct of atopic eczema may be limited and thus comprehension of the questions may be affected. Access to health care will undoubtedly affect the understanding of the concept of eczema, and this too may have impacted on the efficacy of the questionnaire. The sensitivity and specificity of the UK criteria in Ethiopia were not quoted in the study. However, the low disease prevalence resulted in a poor positive predictive value.

2.5 Urbanization and atopic eczema

Migrant studies offer one way of demonstrating the relationship between exposures and disease outcomes, especially where environmental factors are thought to contribute to aetiology. South Africa is an ideal setting and provided the opportunity in this study to follow a population consisting of socio-culturally similar Xhosa speaking people originating in rural Transkei as they undergo rapid changes in urban Cape Town as part of an established migratory route pattern. In a study conducted in 1991, 30.3% of the residents of a peri-urban settlement in Cape Town had migrated from the previous apartheid "homelands", such as Transkei, within the preceding 5 years (Cooper *et al.*, 1991). Cooper suggested that this migration should be expected to increase, given the abolition of influx control and the change of government in 1994. In a separate study, Byarugaba suggested that the Transkei-Cape

Town migration pattern would continue given the discrepancy in infrastructure and employment opportunities in the two regions (Byarugaba, 1991). A more recent study showed that 3.72% of the rural population migrated to urban areas during the period 1986 to 1998 (Cox *et al.*, 2004). The Cape Magisterial district received the highest percentage of the sample of immigrants, with 7.65% of all immigrants from deep rural areas. Durban and Pretoria were the next most popular destinations with 7.58% and 5.45% of immigrants from deep rural areas respectively. The distribution of the remainder of immigrants was proportionately less than 5% per city.

The process of urbanization is linked to a number of transitions, namely demographic, educational, technological and cultural (Steyn *et al.*, 1997). South Africa, together with other developing countries, is likely to experience a protracted transition where chronic diseases and communicable diseases coexist for considerable time. The South African health system is disadvantaged in that it is facing a quadruple burden of disease: not only does the health system need to combat the pre-transitional diseases traditionally associated with poverty and the developing world, but there is also a rapidly emerging burden of chronic disease similar to that experienced in the developed nations of the west. Adding to this burden of disease is an extremely high level of accidents and injuries experienced in South Africa, together with the current epidemic of HIV and AIDS (Beaglehole & Yach, 2003; Bradshaw *et al.*, 2003).

Steyn *et al.* have shown that those individuals who had spent larger proportions of their life in an urban setting were more likely to lead "unhealthier" lifestyles and were at a higher risk for chronic diseases of lifestyle than those who were less urbanized (Steyn *et al*, 1999). Given that the increase in atopic eczema among those migrating from a developing to a developed

country suggests that atopic eczema is associated with urbanization (Williams *et al.*, 1998), it is possible that such a gradient exists within South Africa.

Research in this regard exists for asthma, another atopic disease. A study on the prevalence of asthma in the late 1970's showed an urban-rural gradient for 6-9 year old children (van Niekerk *et al.*, 1979). The prevalence of asthma was of 3.17% in the urban study area and 0.14% in the rural area. Further research into the presence of a rural-urban gradient for exercise induced bronchospasm was conducted recently by Calvert. Here the prevalence of exercise induced bronchospasm in children aged 8-13 years was 14.9% in urban areas and 8.9% in rural areas (Calvert, 2003). The reduction in prevalence gradient between the studies is thought to be due to a relative increase in the rural prevalence of asthma. Similar research is lacking for atopic eczema. The existence of an urban-rural gradient might provide important clues as to risk factors for the development of atopic eczema, especially if a high degree of socio-cultural similarity between study populations exists, thus allowing more accurate assessment of the impact of urbanization and environmental factors.

However, before inferences can be made about the presence of a rural-urban gradient for atopic eczema in South Africa, validation of the UK criteria in the local setting is necessary.

Chapter 3: Methodology

3.1 Study Design

A community-based cross sectional descriptive study was conducted.

3.2 Study Population

For the comparative study, three areas were defined: urban Cape Town (Langa), as defined by the local municipality; peri-urban; an informal or unplanned settlement within 10 kilometers of the local municipality of Cape Town (Joe Slovo, and later, Imizamoyethu); and a rural area, greater than 10 kilometers from the local municipality (Centane, Transkei) (Byarugaba, 1991).

The rural study area comprised villages or settlements within a 50 kilometer radius of the Thafalofefe Hospital in the Transkei which lies approximately 150 kilometers from East London on the East Coast of South Africa. A dwelling unit consists of one or more huts situated around a central pen area where cattle are corralled. Houses are built close together to form a village unit (Statistics South Africa Census 2001). These areas are sometimes referred to as tribal settlements.

The urban area was Langa, a township situated close to the Cape Town International Airport. The urban area was defined as such on the basis of infrastructure with a combination of permanent low and middle income housing. The two peri-urban informal areas selected were Joe Slovo, close to Langa, and Imizamoyethu which lies adjacent to the suburb of Hout Bay.

Informal settlements such as these are unplanned, usually on land which is illegally occupied and minimally or completely unserviced for all amenities (Statistics South Africa Census 2001). The study population consisted of children aged 3-11 years living within these four defined areas.

3.3 Sampling Methods

Each of the study areas was divided into grids using aerial photographs. These grid blocks were numbered and sampled through random selection using a random number table. All children between the ages of 3-11 years were interviewed within the chosen cluster. Division of the aerial photographs within the urban and peri-urban areas was to a level which included only households, whilst those in the rural areas these were defined to include schools within the sampling frame. This process of cluster sampling was repeated until a sample size of approximately 1000 for each sampling frame was reached. No record of cluster of origin was maintained, however, such that analysis allowing for cluster sampling was not possible.

Interviews and examinations took place at the local school or community centre which fell within a cluster. Interviews also took place at individual homes. At the time the study was conducted the prevalence of symptoms of atopic eczema in Cape Town was estimated at 8%, using data obtained during the 1995 ISAAC study. A sample size of 1000 per area would afford sufficient power to determine relative prevalence differences of 20% between the three locations (Williams *et al.*, 1998). For example, this would be sufficient where the observed prevalence in one area was 6.4% and in a second area 8%.

Initially, Joe Slovo was intended to be the only informal settlement included in this study. Unfortunately factors beyond the control of the researchers resulted in the need to abandon

the site and obtain the remainder of the sample from a second settlement. Imizamoyethu was chosen for this purpose as it was seen to be similar in many respects including housing structure, amenities and population type. Accurate division of Imizamoyethu into sampling frames using aerial photographs had not been performed, and thus sampling in this informal settlement was conducted on a house to house basis.

Further, selection bias may have been inadvertently introduced in Imizamoyethu. Without the researchers' knowledge at the time, the community became aware that the study was a dermatological one and began presenting children who were specifically suffering from skin conditions. Had sampling occurred correctly this should not have resulted in bias. Unfortunately Imizamoyethu was not initially chosen as a research site, and was only used as an alternative site after the researchers had experienced problems in Joe Slovo. Individuals began arriving at the central processing site and were also included in the study. It is not possible to determine how many were included in this manner. It was later discovered that these individuals had specifically sought treatment for pre-existing skin conditions. Thus the prevalence of all skin conditions is likely to be falsely elevated in Imizamoyethu on the basis of poor sampling strategy. For this reason the data from the two informal settlements have been kept separate in the analysis, although the required sample size of 1000 individuals was reached only by adding up the subjects in the two areas.

3.4 Pilot Study

A pilot study was conducted at the urban site (Langa). A total of 144 people were approached by field workers and asked to bring their children to be examined for possible skin complaints. A central church was hired for the pilot study. A response rate of 28% was achieved, with 38 of the 144 individuals taking part in the pilot study. The questionnaire was changed slightly as

a result of translation problems, especially with questions 1, 5 and 8 (see Appendix I). Individuals who took part in the pilot study were not included in the analysis.

3.5 Instruments

All parents of children aged 3 to 11 years were invited to participate in the interviewer assisted questionnaire. Atopic eczema was defined using a Xhosa translation of the UK modification of Hanifin and Rajka's criteria. A questionnaire was administered by trained research assistants and the child's skin examined by one of three dermatologists employed on this project (Hanifin & Rajka, 1980; Williams et al., 1994c). Questions included the mother's assessment of visible flexural eczema at the time of the questionnaire as well as specific enquiries regarding the sites of involvement. The questionnaire was developed in conjunction with Professor HC Williams. Given the difficulty with language and literacy in the study population, all questionnaires were administered by a trained bilingual Xhosa-English interviewer. Questionnaires were translated into Xhosa and then verified by back-translation prior to the commencement of the study. In some cases questions were modified in order not to lose information in the translation process.

In order to determine the prevalence of atopic eczema, the validity of the UK diagnostic criteria must first be established in a South African setting. The examination of the child by a qualified dermatologist served as the gold standard in order to assess the criterion validity of the questionnaire. This method has been successfully employed in other countries (Hon *et al.*, 2003; Yamada *et al.*, 2002; Chan *et al.*, 2001; Fleming *et al.*, 2001; Olesen *et al.*, 2001). Examination of the child also provided information regarding prevalence of other skin conditions. The child was examined in their clothes, usually their school uniforms. Only their arms, legs, chest and face were examined. If the lesions were extensive the children were

examined in their under garments in a private side room. The genitalia were not examined. The dermatologist was not aware of the results of the questionnaire at the time of clinical examination.

Children identified as suffering from atopic eczema in the first part of the study were then asked to participate in a second study, a case-control study to determine the risk factor profile of children with atopic eczema as well as the financial burden associated with the disease. All children identified in a particular geographical area of study constituted the relevant cases. Controls were drawn from the non-affected children in the same geographical area and were individually matched according to age and sex. These subsequent studies will be analyzed independently of this research and are not considered further here.

3.6 Definition of Terms

Atopy[1] Personal or family tendency to become sensitized and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins;

Atopic eczema[1] Dermatological manifestation of underlying IgE mediated hypersensitivity;

Allergic asthma[1] Asthma resulting from immunological reactions. Most cases are initiated by IgE antibodies;

Dermatitis[1] Umbrella term for a local inflammation of the skin;

Dry skin[2] A lusterless skin with fine white scaling, in the absence of visible dermatitis, involving one area greater than the size of the patients palm;

Eczema[1] Replacement term for the previously described atopic eczema/dermatitis syndrome;

Flexural eczema[2]	One or more patches of eczema affecting the popliteal fossae, antecubital fossae, infragluteal clefts, fronts or sides of the neck, front of the ankle, periorbital or periauricular areas;
Hypersensitivity[1]	Objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by a normal person;
Negative predictive value (NPV)[3]	The probability that someone with a negative test result is indeed free of the disease;
Non specific eczema	Eczema where no clear aetiology could be identified and where the pattern was not characteristic of the defined form of eczema described here;
Papular eczema[4]	Discrete eczematous papules with peri-follicular accentuation
Positive predictive value (PPV)[3]	The probability that someone with a positive test result does indeed have the disease;
Sensitivity[3]	The proportion of affected individuals with positive test results;
Specificity[3]	The proportion of unaffected individuals with negative test results.

[1] Adapted from Johansson *et al.*, 2004
[2] Adapted from Williams *et al.*, 1994a
[3] Adapted from Weinstock, 1989
[4] Adapted from Dorland's Illustrated Medical Dictionary, 2000

3.7 Statistical Analysis

The data collected were double captured into Microsoft Access XP-Professional. Statistical analysis was performed using STATA-8 (Licensed to Wolfson Library, UCT Medical School). Statistical analysis included the determination of prevalence of atopic eczema and other skin conditions. It was not possible to take cluster sampling into account during the analysis.

Descriptive statistics such as means, standard deviations and ranges were used to assess the demographics of the study population.

Validity is the extent to which a test measures what it purports to measure and is estimated by assessing the sensitivity and specificity of a particular test. Sensitivity is the proportion of true positives which were identified by the test, whilst specificity is a reflection of the number of true negatives identified by the test in question. These indicators are not dependent on the underlying prevalence of the condition. Positive and negative predictive values of a test are, however, dependent on the underlying prevalence of the condition. The positive predictive value is the probability of an individual deemed positive by the test of actually having the condition when diagnosed using the gold standard or reference test.

In order to assess the validity of the questionnaire the definitive test, or gold standard, was defined as the clinical examination by a dermatologist with a specific interest in paediatric dermatology. It was assumed that clinical examination more accurately represents the true presence or absence of disease than the questionnaire under evaluation (Weinstock, 1989). Other studies support this assumption and have shown that amongst dermatologists interested in atopic eczema, the percentage agreement on what constitutes a typical case of atopic eczema is high (Williams *et al.,* 1994c).

The validity of the questionnaire was then assessed by calculating sensitivity, specificity and predictive values. Youden's Index was also calculated and is the sum of the sensitivity and specificity minus one (Pekkanen & Pearce, 1999). These measurements of validity were also calculated for individual questions, and for combinations of questions as alternatives to the combination stipulated in the criteria.

Logistic regression analysis was performed to determine which questions were the best predictors of atopic eczema. The odds ratio is a measure of the association between an exposure and an outcome. In this case the "exposure" is the answer given for a particular question of the questionnaire, and the "outcome" is being diagnosed with atopic eczema following clinical examination by a dermatologist.

A logistic regression analysis model was constructed initially including only the outcome. Exposures variables, in this instance questions, are then added in a sequential manner and the deviance from the original model is then assessed. Using the "goodness of fit" criterion, the model with the smallest deviance is chosen as the preferred model. A likelihood-ratio test was performed of the null-hypothesis to assess for the deviance between models. The model with the lowest Aikaike's information criterion was selected as this represents the most appropriate model. A list of all models used and the corresponding Aikaike's information criteria can be found in Appendix II. Logistic regression allowed for investigation of possible confounding variables.

Model checking procedures were conducted to assess whether the assumptions underlying the model would hold, namely: the form of the linear predictor, the adequacy of the link function and the presence of outlying or influential observations. Pearson and deviance residuals were calculated.

Further analysis of the false positive and negative results was then performed, to try to throw light on the factors producing these false attributes.

Prevalence of other skin conditions was also determined at the time of clinical examination. Their impact on the sensitivity, specificity and predictive values of the questionnaire was also assessed.

3.8 Ethical Considerations

Consent was obtained from all the schools participating in the research as well as from local community leaders and the local authorities. Written or verbal consent was obtained from the parent or guardian of the child of interest. The parents then answered the questionnaire, with the understanding that they could refuse to answer particular questions should they wish. Disclosure of information was on a voluntary basis and subjects were informed that they could withdraw from the study at any stage if they were not satisfied with the process. Ethical approval was granted for this study by the UCT Research and Ethics committee (REC REF NO 116/98).

The physical signs of atopic eczema can be ascertained in less than one minute per subject and relies only on the exposure of arms, knees, ankles and neck. The examination technique was therefore acceptable for use in a school setting. No invasive procedures were required as part of this study.

Study participants could benefit from a definitive diagnosis of atopic eczema as they were counseled regarding the correct treatment of the condition. At the time of examination the study participants were encouraged to ask questions, and advice was given concerning current and future medications. If other skin diseases were diagnosed they were treated appropriately. Children who were identified as having non-dermatological illnesses were treated where possible, or else referred to the nearest appropriate health care facility. The

aim of this research was to provide a clearer understanding of the prevalence of atopic eczema and hence direct scarce health resources in a more appropriate manner.

3.9 Dissemination of Findings

The results of this study will be made available to the Department of Health in the Western Cape which covers the urban and peri-urban study area, as well as the Department of Health in the Eastern Cape. These results could be used to direct health service delivery. Finally, the results will be made available to all who participated in the study through a report back session at the relevant schools. Results of this study will be made available to the wider community through the Dermatological Society of Southern Africa and local and international medical journals.

Chapter 4: Results

4.1 Demographics

Unfortunately, it is not possible to comment on the total number of questionnaires or clinical examinations completed during the study, because a portion of the questionnaires and clinical examination results were lost as a result of migration, hijacking and displacement of study participants by fires in the Joe Slovo informal settlement.

Of the remaining participants, 3069 of the 3144 children were examined by one of three dermatologists, representing a response rate of 97.6%. Virtually all study participants completed both the questionnaire and the clinical examination, but in a few cases (n=75) only the questionnaire was completed because the children could not be located for the dermatological examination. The distribution of loss to follow up cases was as follows: none from Centane, 32 from Langa, and 43 from the peri-urban areas (n=36 in Joe Slovo and n=7 in Imizamoyethu). Loss to follow up was largely due to the transitory nature of the accommodation of some families and ongoing migratory patterns. Since the prime objective of this study was to validate the applicability of the UK Working Party diagnostic criteria, and this could not be done in the absence of a clinical examination, those cases represented only by questionnaires were excluded from the analysis. An additional two cases were excluded because they did not meet the age inclusion criteria, to leave a total of 3067 individuals included in the study.

A complete demographic breakdown by area is shown in Table 4.1. In 8 cases the sex of the child was not recorded.

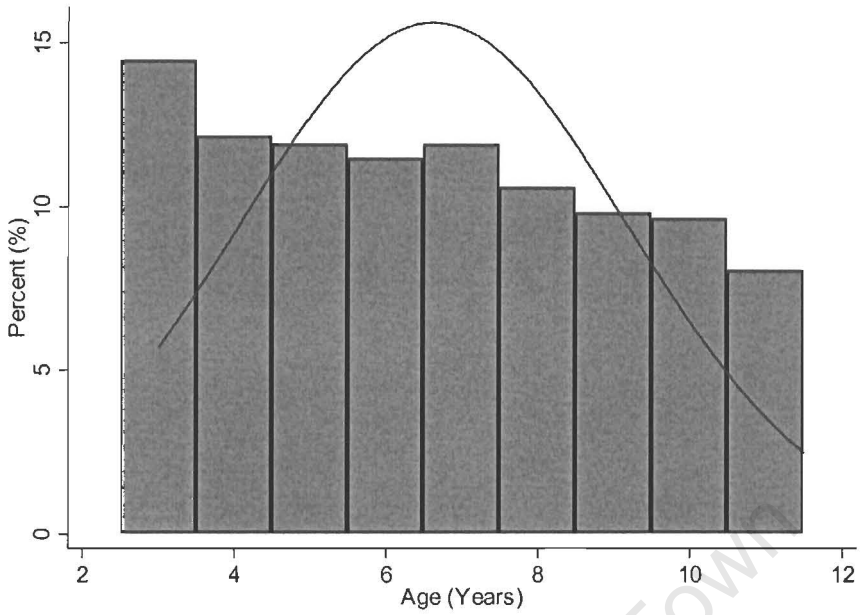
Table 4.1: Sex of study participants according to study area

	Rural: Centane n(%)	Urban: Langa n(%)	Peri-urban (1): Joe Slovo n(%)	Peri-urban (2): Imizamoyethu n(%)	Total
Female	531 (50.8)	513 (51.3)	325 (53.9)	235 (57.0)	1604 (52.4)
Male	513 (49.1)	486 (48.6)	278 (46.1)	178 (43.0)	1455 (47.5)
Total Number	1044	999	603	414	3060
Total in Area	1048	1002	604	413	3067

In total 1605 females and 1455 males were included in the study. There was no statistically significant difference in sex distribution between study areas (p=0.139).

The age ranged from 3 to 11 years, with a mean value of 6.6 (standard deviation 2.5). The median age was 7 years. The distribution of the age of study participants in shown in Graph 4.1. As one can see, a large proportion of individuals were aged three years at the time of the study.

Graph 4.1: Frequency distribution of age of study participants for the total study. A normal distribution line is also shown. n=3067



There was a statistically significant difference in the age distribution between study areas, with the mean age being lower in the peri-urban areas than in either the rural or urban areas. These values are listed in Table 4.2. The mean age was highest in the rural area.

Table 4.2: Age distribution of study participants according to study area.

	Total	Mean	Standard deviation
Rural: Centane	1048	7.0	2.5
Urban: Langa	1002	6.8	2.4
Peri-urban (1): Joe Slovo	604	5.6	2.4
Peri-urban (2): Imizamoyethu	413	6.5	2.5

In the majority of cases the mother of the study participant was responsible for providing the information for the questionnaire (Table 4.3). One way analysis of variance showed a statistically significant difference in the distribution of person interviewed by study area (p=0.000). The person interviewed was more likely to be the mother in the urban and peri-urban areas, while the proportion of grandmothers and grandfathers providing information was highest in the rural area.

Table 4.3: Distribution of person interviewed according to study area

	Rural: Centane n(%)		Urban: Langa n(%)		Peri-urban (1): Joe Slovo n(%)		Peri-urban (2): Imizamoyethu n(%)		Total n(%)	
Mother	489	(46.6)	767	(76.5)	429	(71.0)	221	(53.3)	1906	(62.1)
Father	15	(1.4)	24	(2.4)	6	(0.9)	6	(1.4)	51	(1.6)
Grandmother	137	(13.0)	2	(0.2)	1	(0.1)	1	(0.2)	141	(4.6)
Grandfather	30	(2.8)	0		0		0		30	(0.9)
Other	377	(35.9)	209	(20.8)	168	(27.8)	185	(44.7)	939	(30.6)
Total	1048		1002		601		413		3067	

4.2 Prevalence of atopic eczema using clinical assessment by a dermatologist

The results of the clinical examinations are shown in Table 4.4. A total of 32 children were found to be suffering from atopic eczema at the time of the clinical examination, a figure substantially lower than those who were deemed to be positive according to the questionnaire.

Table 4.4: Prevalence of diagnoses of various forms of eczema, according to study area

	Rural: Centane	Urban: Langa	Peri-urban (1): Joe Slovo	Peri-urban (2): Imizamoyethu	Total
Total number of observations	1048	1002	604	414	3068
Atopic eczema n(%)	4 (0.3)	21 (2.1)	3 (0.5)	4 (0.9)	32 (1.0)
Non specific eczema n(%)	30 (2.8)	39 (3.8)	23 (3.8)	9 (2.1)	101 (3.2)
Papular eczema n(%)	118 (11.2)	42 (4.1)	27 (4.4)	3 (0.7)	190 (6.1)
Any form of eczema n(%)	148 (14.1)	97 (9.6)	50 (8.2)	15 (3.6)	310 (10.1)

The distribution of atopic eczema cases was not equal across areas. The highest prevalence (2.1%) identified in the urban area of Langa than in other areas (p=0.001), whilst the distribution of cases between other areas was similar. A higher percentage of individuals suffering from papular eczema (11.2%) was identified in the rural area of Centane than in other areas (p=0.000).

4.3 Prevalence of atopic eczema using the modified UK criteria

The prevalence of atopic eczema was determined using the UK criteria and the clinical examination. The distribution of positive responses by study area is shown in Table 4.5. In total, 76 cases (2.4%) were classified as having atopic eczema according to the UK Working Party diagnostic criteria.

Table 4.5: Distribution of positive responses for each question, according to study area

	Rural: Centane n(%)	Urban: Langa n(%)	Peri-urban (1): Joe Slovo N(%)	Peri-urban (2): Imizamoyethu n(%)	Total
Total number of observations	1048	1002	604	413	3067
q1: In the last year has your child had an itchy skin	514 (49.0)	427 (42.6)	328 (54.3)	293 (70.9)	1562 (50.9)
q2: Has your child had itchy skin in the last week	486 (46.3)	365 (36.4)	393 (65.0)	246 (59.5)	1490 (48.5)
q3: Age of onset of this skin condition under 2 years*	29 (2.7)	41 (4.0)	5 (0.8)	2 (0.4)	77 (2.5)
q4: Has this skin condition ever affected the skin creases	375 (35.7)	295 (29.4)	278 (46.0)	201 (48.6)	1149 (37.4)
q5: In the last year has your child suffered from generally dry skin	162 (15.4)	273 (27.2)	118 (19.5)	26 (6.3)	579 (18.8)
Personal history of asthma or hayfever	10 (0.9)	58 (5.7)	16 (2.6)	6 (1.4)	90 (2.9)
Family history of asthma, hayfever or eczema for children under 4 years	15 (1.4)	15 (1.5)	5 (0.8)	2 (0.4)	37 (1.2)
Personal history of eczema	20 (1.9)	133 (13.2)	9 (1.4)	4 (0.9)	166 (5.4)
Visible flexural eczema	7 (0.6)	37 (3.6)	6 (0.9)	4 (0.9)	54 (1.7)
Positive according to UK criteria (using q1 as discriminator)	19 (1.8)	47 (4.6)	9 (1.4)	1 (0.2)	76 (2.4)
Positive according to UK criteria (using q2 as discriminator)	16 (1.5)	42 (4.1)	12 (1.99)	1 (0.24)	71 (2.3)

*there were 331 individuals where the age of onset of the condition was not known. These individuals were excluded from analyses pertaining to question 3.

4.4 Prevalence of other skin conditions by area

The distribution of other skin conditions according to area is shown in Table 4.6, below.

Table 4.6: Prevalence of other skin conditions diagnosed at clinical examination by a dermatologist

	Rural: Centane n(%)	Urban: Langa n(%)	Peri-urban (1): Joe Slovo n(%)	Peri-urban (2): Imizamoyethu n(%)	Total n(%)
total (n)	1048	1002	604	414	3069
Dennie-Morgan infra orbital lines	42 (4)	146 (14.6)	199 (32.9)	191 (46.1)	578 (18.8)
Ecthyma	32 (3.1)	17 (1.7)	18 (3.0)	5 (1.2)	72 (2.3)
Atopic	4 (0.4)	21 (2.1)	3 (0.5)	4 (1.0)	32 (1.0)
Non specific eczema	30 (2.9)	39 (3.9)	23 (3.8)	9 (2.2)	101 (3.3)
Papular eczema	118 (11.3)	42 (4.2)	27 (4.5)	3 (0.7)	190 (6.2)
All forms of eczema	148 (14.1)	97 (9.7)	50 (8.3)	15 (3.6)	310 (10.1)
Occlusive folliculitis	286 (27.3)	444 (44.3)	451 (74.7)	385 (93.0)	1566 (51.0)
Herpes simplex	14 (1.3)	13 (1.3)	17 (2.8)	7 (1.7)	51 (1.7)
Impetigo	266 (25.4)	197 (19.6)	242 (40.1)	233 (56.3)	938 (30.6)
Insect bites	908 (86.6)	477 (47.6)	470 (77.8)	374 (90.6)	2229 (72.7)
Perleche	39 (3.7)	67 (6.7)	49 (8.1)	99 (23.9)	254 (8.3)
Pityriasis alba	493 (47)	483 (48.2)	453 (75.0)	301 (72.7)	1730 (56.4)
Tinea capitis	402 (38.4)	174 (17.3)	188 (31.1)	71 (17.1)	835 (27.2)
Trauma	604 (57.6)	543 (54.1)	486 (80.5)	387 (93.7)	2020 (65.9)
Urticaria	3 (0.3)	1 (0.1)	3 (0.5)	2 (0.5)	9 (0.3)
Warts	29 (2.8)	42 (4.2)	19 (3.1)	20 (4.8)	110 (3.6)
Xerosis	342 (32.6)	242 (24.1)	302 (50.0)	325 (78.7)	1211 (39.5)

There was a higher proportion of occlusive folliculitis in the peri-urban areas than in other areas, together with a high proportion of infective conditions such as herpes, impetigo, tinea and warts. Insect bites were seen to be prevalent in both the rural and peri-urban areas. The proportion of trauma related conditions was also higher in the peri-urban settlements.

The skin conditions can be grouped according to basic morphology or aetiology. The eczematous group includes atopic, papular, and non-specific eczemas. The infective group includes ecythma, herpes simplex, impetigo, perleche, tinea capitus and warts. The dry or scaling skin group includes pityriasis alba and xerosis. The remaining conditions fall into a non specific category, including Dennie-Morgan lines, insect bites, urticaria, occlusive folliculitis and trauma.

Ecthyma is an ulcerative pyoderma which is usually caused by a staphylococcal or streptococcal infection at the site of minor trauma. It predominantly involves the shins and the dorsum of the foot and often heals with scar formation. There was a low prevalence of ecthyma with an overall prevalence of 2.3% and a range of 1.2% to 3.1% between study areas. There was no statistically significant difference in the distribution of ecthyma according to study area (p=0.057).

Herpes simplex lesions are due to infection by the human herpes virus type 1 and result in gingivostomatitis and pharyngitis. Primary infection is usually in childhood. There was no statistically significant difference in herpes simplex occurrence by study area (p=0.093). The total prevalence was determined to be 1.7% with a range of 1.3% to 2.8% across the study areas.

Impetigo is similar to ecthyma in that it is caused by staphylococcal or streptococcal infection of cutaneous abrasions or damaged skin. It is usually seen on the face of children, near the nose and mouth, and consists of pus filled vesicles with an erythematous border. These vesicles rupture and the pus forms a characteristic honey coloured crust. In this study there was a statistically significant difference in the distribution of cases of impetigo according to study area (p=0.000) with the greatest proportion of cases occurring in the peri-urban informal settlements.

Perleche is single or multiple fissures at the corners of the mouth. It may be due to a primary or superimposed infection with *Candida albicans*, *Staphylococci* or *Streptococci*; poor hygiene or drooling of saliva (Dorland's Illustrated Medical dictionary, 2000). There was a disproportionately high number of cases (n=99, 23.9%) of perleche in Imizamoyethu which may again relate to poor living conditions or poor oral hygiene.

Warts are caused by an infection with human papilloma virus. Warts occur at any age, but are uncommon in infancy and early childhood with the incidence increasing during school years. The prevalence of warts was 3.6% with no statistically significant difference between study areas (p=0.150).

Tinea capitus is a fungal infection of the scalp and was seen in 27.2% of the study population. There was a statistically significant difference in the distribution of tinea capitus between study areas (p=0.000) with the greatest proportion of cases occurring in rural Centane (n=402, 38.4%).

The third group of skin conditions are those relating to dry or scaling skin, including pityriasis alba and xerosis. Pityriasis alba is a condition of unknown origin in which erythematous scaly patches subside to leave areas of depigmentation. It occurs predominantly in children between the ages of 3 and 16 years, and while it is considered to be a manifestation of atopy, it is not confined to individuals suffering from atopic eczema. The prevalence of pityriasis alba was 56.4%, considerably higher than that of atopy (1.0%), and there was a statistically significant difference in the distribution of cases according to study area (p=0.000). The greatest proportion of cases was identified in Joe Slovo (n=453, 75.0%) whilst Centane had the lowest proportion (n=493, 47%). It is likely that the cases of pityriasis also are largely not as a result of an underlying atopic eczema.

Xerosis is a mild form of icthyosis and is characterized by dry, rough, discoloured skin which becomes scaly and desquamates. There was a statistically significant difference in the distribution of xerosis according to study area (p=0.000) with the greatest proportion identified in the peri-urban areas. The overall prevalence of xerosis was 56.4%.

The final group of skin conditions to be discussed is those which do not fall into any clearly specified category, including Dennie-Morgan lines, insect bites, urticaria, trauma and occlusive folliculitis. Dennie-Morgan infra orbital lines are folds of skin under the lower eyelid and commonly, although not exclusively, found in children with atopic dermatitis. The distribution of Dennie-Morgan lines does, in part, mirror that of atopic eczema, although the proportion of Dennie-Morgan lines observed was greater than atopic eczema (18.8% versus 1.0%, respectively). The greatest proportion of cases of Dennie-Morgan lines was observed in the peri-urban areas (n=199, 32.9% and n=199, 46.1%). It would seem that a great proportion of those identified as having Dennie-Morgan lines were suffering from conditions other than

atopy which would account for the lines, conditions such as contact dermatitis or other non-specific eczematous conditions, or relating to exposure to indoor smoke from coal and paraffin stoves.

There was also a statistically significant difference in the distribution of insect bites according to study area (p=0.000) with the greatest proportion occurring in the rural and peri-urban informal settlement areas, and the lowest proportion occurring in the urban formal settlement.

Trauma was wide ranging, from minor abrasions to digital amputation. The proportion of trauma was highest in the two peri-urban areas which reflect differences in living conditions. A complete analysis of the trauma cases is not possible given the variation in entity included in this category.

Urticaria is a vascular reaction in the dermis caused by dilation and increased permeability of the capillary bed in response to a variety of stimuli. Urticaria may be immune mediated, complement mediated, physically induced, induced by stress or idiopathic in origin. The aetiology of the urticaria was not recorded in this study. The overall prevalence of urticaria was low at 0.3% and a range of 0.1% to 0.5% across areas.

The last group to warrant discussion is those suffering from occlusive folliculitis. This is a localized inflammatory reaction of the hair follicles in response to emollient use, usually Vaseline. There was a statistically significant difference in the difference between study areas (p=0.000) with the greatest proportion observed in Imizamoyethu (n=385, 93.0%) and an overall prevalence of 51%.

4.5 Analysis of the validity of the UK diagnostic criteria

The UK diagnostic criteria were translated into Xhosa as described in section 3.5. A number of difficulties were encountered during the design and administration of the questionnaire. It is therefore appropriate to discuss these issues in greater detail before the validity of the questionnaire is assessed.

4.5.1 Analysis of criteria using either question 1 or question 2 as discriminator

According to the UK criteria a diagnosis of atopic eczema requires a positive response given for question 1: "in the last year has your child had an itchy skin?", plus a combination of responses for the other questions. In this study a second question, not part of the original criteria, was included as a form of internal validation. Question 2, which states: "has your child had itchy skin in the last week?". Logic would dictate that in the majority of cases a positive response to the second question should be accompanied by a positive response to the first. This was not the case, however. There was a statistically significant difference between the responses given for questions 1 and 2.

Table 4.7: 2x2 table comparing responses given for questions 1 and 2.

		q2: Has your child had itchy skin in the last week		Total
		Negative	Positive	
q1: In the last year has your child had an itchy skin	Negative	1289	216	1505
	Positive	288	1274	1562
Total		1577	1490	3067

The kappa statistic was 0.67 implying good agreement. However, 216 (7%) individuals provided a positive response to the question of itchy skin in the last week, but a negative

response to a history of itchy skin in the last year. These discordant answers were surprising, and it was thought that they might relate to mis-interpretations of the phrases "in the last week" and "in the last year" when translated into Xhosa. Thus, a decision was taken to calculate the UK criteria in two separate ways, once using question 1 as the discriminator, and the second time using question 2 as the discriminator. Thus two groups were generated using the two methods of calculating the criteria. Surprisingly, the kappa statistic between these two groups was 0.92 suggesting almost perfect agreement. This would suggest that the effect of logically discordant answers for questions 1 and 2 are minimal and do not impact on the outcome of the criteria. Validation of the questionnaire using both methods of discrimination is included in this analysis for interest's sake.

4.5.2 Translation Problems

One possible explanation for the logically discordant answers given for questions 1 and 2 relates to conceptual differences in translation of the phrases "in the last week" and "in the last year" into Xhosa. Similar translation problems were encountered with the second set of internal validation questions included in the questionnaire. As part of the criteria, individuals are asked if their child "suffers from eczema". This form of self reporting was thought to be sufficient in other studies. In this study, a second question was included later in the interview which enquires whether the child has "suffered from eczema in the past year".

There is no direct translation of the word "eczema" into Xhosa. In fact, the translation of the word "eczema" used in this study is simply an anglicized version, "*i-eczema*". Thus, conceptual understanding of the word "*i-eczema*" in Xhosa is limited by understanding of the English version of the word. No further explanation of the term was provided during the questionnaire process. Therefore answers to these questions are likely to have been limited

through poor understanding of the word "*i-eczema*". This understanding is modified by differences in access to health care as well as exposure to the Western conceptual reference of the word "eczema", and therefore it is likely not to have been uniform across study areas.

Table 4.8: 2x2 table comparing responses given for questions relating to previous eczema diagnosis.

		In the last year has your child suffered from eczema?		Total
		Negative	Positive	
Does your child suffer from eczema?	Negative	1941	960	2901
	Positive	56	110	166
Total		1997	1070	3067

One would assume that children answering yes to the second question relating to symptoms in the past year, would also answer yes to ever having suffered from eczema. This was not the case, with a kappa statistic of 0.09, showing poor agreement. Thus poor validity of the questionnaire may relate to inherent faults in the translation process where a lack of understanding of the concept of "*i-eczema*" and no provision of an explanation limited responses.

4.5.3 Measurements of validity

The sensitivity and specificity of each question in the UK Working Party diagnostic criteria was then determined, comparing the results with the clinical diagnosis of atopic eczema as the gold standard are shown in Table 4.9.

Table 4.9: Assessment of validity of UK diagnostic criteria, by question and in total, for atopic eczema when compared with diagnosis by a dermatologist.

	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV[1] % (95% CI)	NPV[2] % (95% CI)	Youden's Index
q1: In the last year has your child had an itchy skin	71.8 (53.2 86.2)	49.2 (47.4 51.0)	1.4 (0.9 2.2)	99.4 (98.8 99.7)	21
q2: Has your child had itchy skin in the last week	68.7 (49.9 83.8)	51.6 (49.8 53.4)	1.4 (0.9 2.2)	99.3 (98.8 99.7)	20.3
q3: Age of onset of this skin condition under 2 years	9.3 (1.9 25.0)	97.5 (96.9 98.0)	3.9 (0.8 10.9)	99.0 (98.6 99.3)	6.8
q4: Has this skin condition ever affected the skin creases	68.7 (49.9 83.8)	62.8 (61.1 64.5)	1.9 (1.2 2.8)	99.4 (99.0 99.7)	31.5
q5: In the last year has your child suffered from generally dry skin	62.5 (43.6 78.9)	81.5 (80.1 82.9)	3.4 (2.1 5.2)	99.5 (99.1 99.7)	44
Personal history of asthma or hayfever	6.2 (0.7 20.8)	97.1 96.4 97.6)	2.2 (0.2 7.8)	98.9 (98.5 99.3)	3.3
Personal history of eczema (not in criteria)	18.7 (7.2 36.4)	94.7 (93.8 95.5)	3.6 (1.3 7.7)	99.1 (98.6 99.4)	13.4
Family history of asthma, hayfever or eczema for children under 4 years	0.0 (0.0 10.8)	98.8 (98.4 99.2)	0.0 (0.0 10.0)	98.9 (98.5 99.2)	-1.2
Visible flexural eczema	81.2 (63.5 92.7)	99.0 (98.6 99.3)	48.1 (34.3 62.1)	99.8 (99.5 99.9)	80.2
Positive according to criteria using q1 as discriminator (q1 plus 3 or more)	43.7 (26.3 62.3)	97.9 (97.3 98.4)	18.4 (10.4 28.9)	99.4 (99.0 99.6)	41.6
q1 plus 4 or more	12.5 (3.5 28.9)	99.7 (99.4 99.8)	30.7 (9.0 61.4)	99.0 (98.6 99.3)	12.2
q1 plus 1 or more	71.8 (53.2 86.2)	63.8 (62.1 65.5)	2.0 (1.3 3.0)	99.5 (99.1 99.7)	35.6
q1 plus 2 or more	65.6 (46.8 81.4)	87.7 (86.5 88.8)	5.3 (3.3 8.0)	99.5 (99.2 99.7)	53.3
Positive according to criteria using q2 as discriminator (q2 plus 3 or more)	40.6 (23.7 59.3)	98.0 (97.5 98.5)	18.3 (10.1 29.2)	99.3 (99.0 99.6)	38.6

[1] Positive Predictive Value
[2] Negative Predictive Value

Only the presence of visible flexural eczema reliably predicted the clinical diagnosis of atopic eczema (sensitivity 81.3%, specificity 99.1%). Questions designed to elicit a personal history of hayfever, asthma or eczema had particularly low sensitivity, as did questions relating to the age of onset of the condition and a family history of atopy. Other questions in the questionnaire showed a moderate degree of sensitivity, although they appeared not to be specific for the diagnosis of atopic eczema.

A similar analysis was then performed comparing the criteria with the clinical diagnosis of any form of eczema. The results are shown in Table 4.10.

Table 4.10: Assessment of validity of UK diagnostic criteria, by question, for diagnosis of any form of eczema when compared with diagnosis by a dermatologist

	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV[1] % (95% CI)	NPV[2] % (95% CI)
q1: In the last year has your child had an itchy skin	49.0 (43.3 54.7)	48.8 (43.3 54.7)	9.7 (8.3 11.3)	89.5 (87.8 91.0)
q2: Has your child had itchy skin in the last week	48.0 (42.3 53.7)	51.3 (49.4 53.2)	9.9 (8.5 11.6)	89.8 (88.2 91.2)
q3: Age of onset of this skin condition under 2 years	3.2 (1.5 5.8)	97.5 (96.9 98.1)	12.9 (6.4 22.5)	89.9 (88.8 91.0)
q4: Has this skin condition ever affected the skin creases	39.6 (34.1 45.3)	62.7 (60.9 64.5)	10.7 (8.9 12.6)	90.2 (88.8 91.5)
q5: In the last year has your child suffered from generally dry skin	21.2 (16.8 26.2)	81.3 (79.8 82.8)	11.3 (8.9 14.2)	90.2 (88.9 91.3)
Personal history of asthma or hayfever	2.5 (1.1 5.0)	97.0 (96.3 97.6)	8.8 (3.9 16.7)	89.8 (88.7 90.9)
Personal history of eczema (not in criteria)	7.4 (4.7 10.9)	94.8 (93.9 95.6)	13.8 (8.9 20.0)	90.1 (88.9 91.1)
Visible flexural eczema	10.6 (7.4 14.6)	99.2 (98.8 99.5)	61.1 (46.8 74.0)	90.8 (89.7 91.8)

[1] Positive Predictive Value
[2] Negative Predictive Value

Given that the criteria were specifically designed for the diagnosis of atopic eczema, it was not surprising that the sensitivity obtained when using the questionnaire as a predictor of any form of eczema was lower than when using it as a predictor of atopic eczema, although specificity results are comparable. The positive predictive values are higher when diagnosing any form of eczema, although the negative predictive values are lower. This is a function of the increased prevalence of any form of eczema when compared with the prevalence of atopic eczema.

4.5.4 Logistic regression analysis

Logistic regression analysis was performed to explore the relationship between the diagnosis of atopic eczema and the questions included in the questionnaire. A detailed description of the logistic regression process has already been discussed in section 3.7.

In Table 4.11, the odds ratios, p values and confidence intervals are shown for each question from the results of univariate analyses – in other words, unadjusted for each other factor in the table. Family history of atopy was excluded from the analysis as no individuals in the study who were diagnosed with atopic eczema had a family history of atopy. Table 4.12 shows the results of a multivariate model where there was adjustment for all other factors.

Table 4.11: Results from logistic regression models of individual questions from the UK criteria (unadjusted for one another and for other factors)

	Odds ratio	P value	95% Confidence Interval	
q1: In the last year has your child had an itchy skin	2.4	0.021	1.1	5.3
q3: Age of onset of this skin condition under 2 years	4.1	0.021	1.2	13.8
q4: Has this skin condition ever affected the skin creases	3.7	0.001	1.7	7.8
q5: History of generally dry skin in the last year	7.3	0.000	3.5	15.1
Personal history of asthma or hayfever	2.2	0.277	0.5	9.4
Family history of asthma, hayfever or eczema for children under 4 years	Dropped because predicts failure perfectly			
Presence of visible flexural eczema	465.3	0.000	177.7	1218.3
Age of the individual	1.0	0.988	0.8	1.1
Sex of the individual	0.9	0.937	0.4	1.9
Study area	1.0	0.603	0.7	1.5
Person interviewed	0.9	0.404	0.7	1.1

Table 4.12: Logistic regression model based on questions from the UK criteria with adjustment for other factors.

	Odds ratio	P value	95% Confidence Interval	
q1: In the last year has your child had an itchy skin	0.6	0.578	0.1	2.7
q3: Age of onset of this skin condition under 2 years	0.3	0.168	0.0	1.6
q4: Has this skin condition ever affected the skin creases	0.7	0.696	0.2	3.0
q5: History of generally dry skin in the last year	4.9	0.006	1.5	15.4
Personal history of asthma or hayfever	1.2	0.832	0.1	11.0
Family history of asthma, hayfever or eczema for children under 4 years	Dropped because predicts failure perfectly			
Presence of visible flexural eczema	596.5	0.000	185.2	1921.4
Age of the individual	0.9	0.420	0.7	1.1
Sex of the individual	1.5	0.372	0.5	4.3
Study area	1.3	0.276	0.7	2.5
Person interviewed	1.0	0.728	0.8	1.3

Whilst the odds ratios for the questions changed slightly upon the inclusion of the other factors, the presence of a generally dry skin in the preceding year and the presence of visible flexural eczema remained the only statistically significant predictors of atopic eczema. The age and sex of the individual, study area and person interviewed were not confounding factors in this case, as their presence did not have a statistically significant effect on the outcome.

A separate analysis (Model A shown in Appendix II) was performed where all study areas are compared to the rural area, but there is no change in the significance of the effect of study area.

Using the "goodness of fit criterion", the most appropriate logistic regression model was generated using the combination of a history of dry skin in the preceding year and the presence of visible flexural eczema. The log-likelihood was -77.9. When comparing the log-likelihood ratios between models, the model with the lowest Aikaike's information criteria was this combination, with AIC=161.8688. The results are shown in Table 4.13.

Table 4.13: Logistic regression model based on the model including a history of dry skin in the preceding year and the presence of visible flexural eczema.

	Odds ratio	P value	95% Confidence Interval	
q5: History of generally dry skin in the last year	3.0	0.018	1.2	7.6
Presence of visible flexural eczema	348.9	0.000	130.4	933.3

4.5.5 Analysis of false positive results

Of the 76 individuals classified as having atopic eczema according to the questionnaire, only 14 of those were diagnosed with atopic eczema following clinical examination (Table 4.14). These individuals thus had positive agreement on diagnosis between the two methods. The remaining 62 individuals classified as positive according to the questionnaire but negative on clinical grounds, with disagreement between the two measurements. These individuals are referred to as "false positives" in this analysis. Analysis was performed to see whether these discordant individuals were distributed unevenly according to study area, sex, person interviewed or age (Table 4.15). Analysis was also performed to assess the influence of the presence of other skin conditions on the likelihood of falling into the discordant group (Table 4.16).

Table 4.14: 2x2 table comparing the distribution of cases according to UK criteria versus dermatological examination

		Atopic eczema based on dermatological examination		Total
		Negative n(%)	**Positive n(%)**	
UK diagnostic criteria	**Negative**	2973 (99.4) **(Negative agreement)**	18 (0.6) **(False negative)**	2992 (100)
	Positive	62 (81.5) **(False positive)**	14 (18.4) **(Positive agreement)**	76 (100)
Total		3036 (98.9)	32 (1.0)	3067

An initial analysis was performed to assess the distribution of "false positives" according to study area and is shown in Table 4.15.

Table 4.15: Distribution of false positive cases according to study area (n=62)

	Rural: Centane n/N (%)	Urban: Langa n/N (%)	Peri-urban (1): Joe Slovo n/N (%)	Peri-urban (2): Imizamoyethu n/N (%)
False Positives	16/1048 (1.5)	37/1002 (3.6)	8/604 (1.3)	1/414(0.24)

The distribution of "false positives" was not equal between areas, with a larger proportion being found in Langa (p=0.000). In other words, more people were criteria positive but atopic eczema negative in Langa than in any other area.

There was no statistically significant difference in distribution of "false positives" according to sex (p=0.517). Of the false positives, 30 (48.3%) were female and 32 (51.6%) were male. There was also no statistically significant difference by the person interviewed (p=0.894). The age distribution for "false positives" was also not statistically different from the study population, (p=0.733).

Further analysis was performed to assess whether the prevalence of other skin conditions differed between the "false positives" and the whole sample. These results are shown in Table 4.16.

Table 4.16: Prevalence of other skin conditions among the total study population and for false positive individuals

	Total Sample Frequency n(%)(N=3067)		*95% Confidence Interval for total sample prevalence*		Number of observations n (%) for false positives (N=62)		95% Confidence Interval for false positive prevalence	
Non specific eczema	*101*	*(3.3)*	2.6	3.9	6	(9.6)	2.1	17.2
Papular eczema	*190*	*(6.2)*	5.3	7.0	6	(9.6)	2.1	17.2
Ecthyma	*72*	*(2.3)*	1.8	2.8	3	(4.8)	0	10.3
Dennie-Morgan lines	*578*	*(18.8)*	17.4	20.2	12	(19.3)	9.2	29.4
Occlusive folliculitis	*1566*	*(51.0)*	49.2	52.8	21	(33.8)	21.7	45.9
Herpes simplex	*51*	*(1.7)*	1.2	2.1	1	(1.6)	0	4.8
Impetigo	*938*	*(30.6)*	28.9	32.2	13	(20.9)	10.5	31.3
Insect Bites	*2229*	*(72.7)*	71.0	74.2	33	(53.2)	40.4	66.0
Perleche	*254*	*(8.3)*	7.3	9.2	9	(14.5)	5.5	23.5
Pityriasis Alba	*1730*	*(56.4)*	54.6	58.1	23	(37.1)	24.7	49.4
Tinea capitus	*835*	*(27.2)*	25.6	28.8	16	(25.8)	14.6	37.0
Trauma	*2020*	*(65.9)*	64.1	67.5	30	(48.3)	35.5	61.1
Urticaria	*9*	*(0.3)*	0.1	0.4	No observations			
Warts	*110*	*(3.6)*	2.9	4.2	1	(1.6)	0	4.8
Xerosis	*1211*	*(39.5)*	37.7	41.2	14	(22.58)	11.8	33.2

From Table 4.16, there was a statistically significant lower prevalence of folliculitis, insect bites, PSA, trauma and xerosis among false positives when compared with the total sample. Occlusive folliculitis occurs as a result of emollient use, such as Vaseline. Given that emollients are often prescribed in the management of eczema, it is possible that they may act as a protective factor and reduce the signs of eczema. Regression analysis (Appendix II, Model B) demonstrated that the presence of occlusive folliculitis in the total sample, unadjusted for other factors, reduced the odds of developing signs of any form of eczema

(OR=0.4, 95% CI 0.3-0.5, p=0.000). The relationship was similar when adjusted for age, sex and study area (Appendix II, Model C). It would therefore make sense if there was a higher proportion of occlusive folliculitis in the false positive group, and the low proportion of occlusive folliculitis in the false positive individuals is unexpected.

4.5.6 Analysis of false negative results

Of the 32 individuals diagnosed as having atopic eczema by clinical examination, 18 of those in fact were classified negative according to the questionnaire. These individuals are referred to as "false negatives" in this study. Analysis was performed to see whether these discordant individuals were distributed unevenly according to study area, sex, person interviewed or age.

An initial analysis was performed to assess the distribution of false positives according to study area and is shown in Table 4.17.

Table 4.17: Distribution of "false negative" cases according to study area

	Rural: Centane n(%)	**Urban: Langa n(%)**	**Peri-urban (1): Joe Slovo n(%)**	**Peri-urban (2): Imizamoyethu n(%)**
False negatives	1/1048 (0.10)	11/1002 (1.10)	2/604 (0.33)	4/414 (0.97)

The distribution of "false negatives" between areas was not equal, with a larger proportion found in Langa. There was no difference in the distribution according to sex, as there are equal numbers of males and females. The mean age of this group was 6.2 years with a standard deviation of 2.6 years. This is similar to the mean age of the population which was 6.6 (standard deviation = 2.5). Information for the "false negative" individuals was provided by 12 maternal interviews, one interview of a grandmother and 5 interviews with other individuals.

Chapter 5: Discussion

Two key findings emerge from this study – the first is the unexpectedly low point prevalence of atopic eczema, and the second is the poor validity of the UK criteria in a South African setting. There are a number of possible explanations for these findings, and these will be discussed independently below. First, however, some mention must be made of the demographics of the sample. It is also of interest to briefly mention the findings relating to the prevalence of other skin conditions.

5.1 Demographics

A response rate of 97.6% was obtained in the study, with a final sample size of 3067 participants. Those participants lost to follow up and hence excluded from the analyses lived primarily in the urban and peri-urban study areas. In the rural area questionnaires and clinical examinations were performed on the same day, thus loss to follow up was less problematic in the rural area. In the urban areas it was not always possible to schedule a clinician to be present at the time of administering the questionnaire, with the result that examinations may have taken place more than two weeks later. Researchers were also faced with other issues such as fire and theft which led to some cases not being examined, or questionnaires of individuals who had been examined going missing. Unfortunately there was no way to accurately assess the exact number of individuals lost to follow up or the number of questionnaires lost during the data collection phase of this study.

While there was no difference in the distribution of sex between areas, there was a difference in the age distribution across study areas, with a higher mean age in the rural area. Given the migratory nature of the study population, one possible explanation of the difference in age

noted between areas is that younger children are kept closer to their parents in urban or peri-urban settlements while the parents are looking for work. Older children are sent from the urban areas to live with relatives, either in the Transkei or other rural areas, or sent to receive schooling in these areas. Further supporting evidence for this theory is that the person interviewed was more likely to be a grandmother or grandfather in rural areas than in the urban or peri-urban areas.

While there was a statistically significant difference in the person interviewed according to study area, there was no statistically significant association between the person interviewed and the likelihood of being diagnosed with atopic eczema, either according to the questionnaire or on clinical grounds. It was noted, however, that while the association was not statistically significant (p=0.755), a high proportion of those deemed positive according to the questionnaire had information provided by an unclassified source (n=24, 31.5%). Misclassification may have occurred in this regard, and could have been limited had the older children been asked to complete the questionnaire themselves.

5.2 Prevalence of other skin conditions

A secondary aim of this study was to determine the prevalence of skin conditions other than atopic eczema. A brief discussion of these conditions is warranted. A high prevalence of skin diseases due to poor living conditions and access to sanitation emerged. Infective conditions such as impetigo were highest in the informal settlements. Insect bites were also highest in these areas, possibly relating to housing conditions, and the abundance of discarded refuse or stagnant pools of water which could act as breeding reservoirs for the insects. The striking prevalence of easily treatable skin conditions in all areas is a reflection of poor access to health care amongst the study population.

5.3 Prevalence of atopic eczema following diagnosis by a dermatologist

One of the primary aims of this study was to determine the point prevalence of atopic eczema by dermatological examination. To date, such studies in South Africa are sparse. The point prevalence for atopic eczema in this study was determined as 1.0% with a range of 0.3% and 2.1% between study areas. The highest proportion of cases was identified in urban Langa, and the lowest in rural Centane.

5.3.1 Prevalence of atopic eczema

It was surprising to note the low point prevalence of atopic eczema according to dermatological examination, given that the 1995 ISAAC study showed a period prevalence of 8%. In the ISAAC study individuals from all races and socio-economic groups were included while in this study only black Xhosa speaking children from generally low socio-economic areas were included.

Given the widely varying aetiology of atopic eczema, it is possible that a number of apparently similar phenotypes co-exist. The local phenotype expressed in black skinned individuals may differ on a subtle level from that observed in the white skinned population in the United Kingdom, and thus from the phenotype on which the UK criteria are based.

It is also possible, given the known seasonal variation of atopic eczema, that the questionnaire based on the UK criteria recorded the true prevalence as reflected over one year. Clinical examination is a reflection of point prevalence only and may not be an accurate estimate since it may not identify disease which is in remission at the time of examination.

5.3.2 Prevalence of atopic eczema by clinical diagnosis from other studies

No other large scale prevalence studies of atopic eczema in the South African population using diagnosis by a dermatologist have been conducted. Limited studies have been conducted in other developing countries. In rural Tanzania, examination of 1114 individuals of all age ranges showed a prevalence of dermatitis of 0.2% in the study population (Gibbs, 1996). The nature of the dermatitis was thought to be infective, as the author states that atopic eczema is very rare amongst individuals of this population. Recent studies in Ethiopia and Iran have involved determination of prevalence based on questionnaires rather than clinical examination (Firooz *et al.*, 1999; Yemaneberhan *et al.*, 2004).

Numerous studies have been conducted elsewhere in the world, and for the purposes of this discussion they will be divided into European and Australasian. In the United Kingdom, a cross sectional survey of 695 children age 3-11 years showed a point prevalence of 8.5% based on examination by a dermatologist (Williams *et al.*, 1996). A Swedish study of 1961 children aged 5-6 years showed a point prevalence of 8.5% in the one study area and 11.5% in the second study area (Broberg *et al.*, 2000). These results are similar to the prevalence rates observed in the United Kingdom study.

A lower prevalence of atopic eczema was demonstrated among Romanian school children, with a point prevalence of 2.42% (Popescu *et al.*, 1999). Although there are a number of differences between the study population in Romania and those included in this study, it noteworthy that there is a greater similarity between the prevalence observed in Romania and South Africa, than between Romania and the other European countries mentioned. It is possible that the difference in prevalence between Romania and the other European

countries is due to underlying differences in the socio-economic status and degree of urbanization of the populations studied.

Studies conducted in Australasia show a point prevalence of atopic eczema by dermatological examination similar to those observed in the United Kingdom and Sweden. In Australia the point prevalence among children aged 4-18 years was 16.3% (Marks *et al.,* 1999). Research in Japan showed a point prevalence of 11.2% among individuals ranging between 6 and 7 years, and in China the prevalence was 7.6% among children aged 3-5 years (Chan *et al.,* 2001; Saeki *et al.,* 2005).

While it is not appropriate to compare the point prevalence from dermatological examination with the period prevalence obtained in the ISAAC study, one can see that the comparative differences are similar. In the ISAAC study, the period prevalence rates in Eastern Europe were generally lower than in Northern and Western Europe, while the period prevalence rates in Japan and Australia were higher than those observed in China (Williams *et al.,* 1999). These differences would suggest underlying differences in socio-economic status and degree of urbanization, as mentioned, and may afford studies into disease aetiology in the future.

5.3.3 Limitations of prevalence determination using clinical examination

Of concern is the inter-observer variation which may have occurred during this study. Had each child been examined by more than one dermatologist, the agreement between dermatologists could have been assessed. In this study, three dermatologists examined the children individually, but there was no way to assess inter-observer variation. Records of which clinician was responsible for the examination were not kept, so it was not possible to

assess whether the different examiners were associated with different likelihoods of diagnosis with atopic eczema.

The sample size for this study was calculated based on the estimate of a prevalence of 8% for atopic eczema (Williams *et al.*, 1998). In calculating sample size one must estimate a level of significance and the power of the test. In this instance a level of significance of 5%, desired power of 90%, to show a 20% relative difference between study areas, and estimated prevalence of 8%, resulted in a sample size requirement of 3000 individuals. The relative prevalence of atopic eczema was in fact lower than 8% and was determined to be 1.0% for the total study sample, with a 95% confidence interval of 0.6% to 1.4%. Thus even though the power of this study may have been reduced, the narrow confidence interval provides sufficient precision in the prevalence estimate.

5.3.4 Presence of a rural urban gradient for atopic eczema

There was a statistically significant difference between the rural area of Centane and the urban area of Langa but not between Centane and the two peri-urban areas. It would therefore seem that a rural-urban gradient exists for atopic eczema when using clinical examination as the means of diagnosis, assuming the peri-urban population to be "intermediate" between the rural and urbanized populations. The emergence of such a gradient is in keeping with other studies of atopic disease in Southern Africa. In Zimbabwe an assessment of the prevalence of reversible airways obstruction among 2055 rural and urban primary school children showed urban living to be associated with an increased prevalence of reversible airways obstruction (Keeley *et al.,* 1991). Similar results had been demonstrated in a South African study of rural and urban Xhosa speaking children, and more recently by Calvert (Van Niekerk *et al.,* 1979; Calvert, 2003).

The process of urbanization is associated with exposure to new environmental elements as well as the adoption of different dietary and social habits. In South Africa there has been an increase in excess weight and obesity, largely in the urban population, in keeping with the rapid urbanization and demographic transition characteristic of the last decade (Steyn *et al.*, 2005). While obesity is not associated with an increase in atopic disease, it can be used as a proxy for changes in lifestyle and habits that are associated with urbanization and westernization. A recent review of atopic eczema suggested that its development relies on the interaction of several factors, including genetics, exposure to allergens, exposure to infections during infancy and to various irritants which may disrupt the barrier function of the skin (Williams, 2005). It is likely that the exposure to these factors changes as an individual moves from a rural to an urban environment, and thus the prevalence of atopic eczema changes as well. A similar pattern was demonstrated in a recent study of prevalence and associated factors of atopic eczema in rural and urban Ethiopia; although in this study prevalence was determined using a questionnaire and not clinical diagnosis. Here lifestyle factors linked to urbanization were associated with an increased risk of atopic eczema symptoms (Yemaneberhan *et al.*, 2004).

The Zimbabwean study also showed higher socio-economic status to be associated with an increased prevalence of reversible airways disease (Keeley *et al.*, 1991). Similar research in the Cape Town Metropolitan area showed that the prevalence of allergic rhinitis symptoms increased from lowest to highest socio-economic status, although there was no gradient observed with the prevalence of eczema symptoms (Mercer *et al.*, 2004). Further research into risk factors and how they differ between rural and urban areas forms part of phase II of the study referred to in the dissertation and is not discussed further here.

5.4 Assessment of validity of the UK criteria in a South Africa setting

The period prevalence of atopic eczema using the modified UK criteria was determined to be 2.4% with a 95% confidence interval of 1.9% to 3.0%. The highest proportion of cases was identified in Langa, with a period prevalence of 4.6% in that area.

5.4.1 Prevalence of atopic eczema according to the UK criteria

There was a statistically significant difference between the study areas in the identification of cases (p=0.000). A difference was noted when comparing the rural area of Centane with the urban area of Langa and also when comparing the rural area of Centane with the peri-urban area of Imizamoyethu. However, there was no statistically significant difference in the distribution of cases between rural Centane and peri-urban Joe Slovo. These differences in distribution of cases according to study area suggest the presence of a rural – urban gradient in the prevalence of atopic eczema.

Of all the components of the UK criteria, only the presence of visible flexural eczema relies on identification of a physical sign of atopic eczema. Limitations of the criteria are discussed later in section 5.4.4, but it is important at this juncture to mention limitations relating to the identification of this key physical sign.

In an analysis of erythema scoring systems for atopic eczema it was found that difficulties in assessing the severity of eczema were more likely to be encountered among darkly pigmented children. Thus the severity of eczema may be underestimated in pigmented children and not treated appropriately (Ben-Gashir *et al.*, 2002). It is possible that the same holds true for recognition of signs of mild eczema. This may lead to under-reporting by respondents of visible flexural eczema as part of the criteria, although it is unlikely to have

affected the outcome of the dermatological examination as the clinicians in this study were experienced in examination of pigmented individuals.

5.4.2 Measurements of validity

The measurements of validity of the UK criteria were as follows: sensitivity 43.7%, specificity 97.9%, positive predictive value 18.4% and negative predictive value 99.4%, Youden Index of 41.6. In general, the most valid method of identifying atopic eczema in epidemiological studies is "the one that introduces the least bias to the measure of effect" (Pekkanen & Pearce, 1999). When comparing prevalence data between two groups, the focus is on the absolute prevalence difference. While a high specificity is desirable as this is the proportion of true positives identified by the test, sensitivity is also important. Here Youden's Index is a good composite measure of validity as it is calculated using both sensitivity and specificity. A question with a higher Youden's index can therefore be considered have greater validity than one with a lower index. When the test is no better than random, then Youden's index approaches zero (Pekkanen & Pearce, 1999). Positive predictive value is dependent on the prevalence of the condition and therefore cannot be used as a comparative instrument unless the prevalence of the condition is similar between the populations.

In this study the low sensitivity, and Youden Index, displayed by the criteria in the South Africa setting means that they are not appropriate for wide-scale epidemiological use as they are little more effective than chance at identifying true cases. If they were to be used, the period prevalence would be a poor reflection of the actual prevalence of the condition.

It is possible that the most appropriate use of the criteria would be to use the presence of itchy skin (question 1) plus the presence of two other positive responses (itch plus 2), rather

than the presence of three other positive responses as is required at present. Here the sensitivity rises to 65.63% whilst the specificity drops to only 87.75%, with a Youden Index of 53.3. The compromise in specificity is perhaps worth the overall gain in the sensitivity of the questionnaire, and this combination may be more appropriate as a epidemiological tool.

A more appropriate measure, however, may simply be the reported presence of visible flexural eczema. Whilst eczema is a complex disease, the presence of visible flexural eczema alone was the most sensitive and specific question in the questionnaire (81.25% and 99.08% respectively), and a Youden Index of 80.2. The use of this question alone may be the most appropriate in the South African context. The use of a single question as a screening tool has recently been adopted for the diagnosis of asthma.

5.4.3 Comparison with the results of validation studies conducted in other countries

Numerous other studies have been conducted to assess the validity of the UK criteria in other settings, although to date only one study in Africa has been published (Haileamlak *et al.*, 2005). Initial analysis of the criteria by the UK Working Party showed an overall sensitivity of 85% and specificity of 96% in a hospital based study (Williams *et al.*, 1994c). A population based study in the United Kingdom reported a sensitivity of 70% and specificity of 93% (Williams *et al.*, 1996d). This similarity can be accounted for by the fact that the populations tested would be similar to those used to derive the criteria, and cultural understanding of the terms in the questionnaire would be similar.

When looking at studies which involved translation of the questionnaire, as with this study, the results are mixed. In the Romanian, Danish and Chinese studies the results are similar to those observed by Williams *et al.*, while in Iran and Ethiopia the results are similar to those

observed in South Africa (Williams *et al.,* 1996c; Popescu *et al.,* 1998; Firooz *et al.*, 1999; Gu *et al.,* 2001; Olesen *et al.,* 2001; Haileamlak *et al.,* 2005).

In Romania the reported sensitivity and specificity was 74% and 99% respectively (Popescu *et al.,* 1998). However in this setting the point prevalence of atopic eczema was 2.4% and the authors recommended use of the criteria with care in cases of low prevalence. They showed that the systematic error of the criteria decreases as prevalence of atopic eczema increases, for a fixed sensitivity and specificity. They postulated that cthe riteria will therefore overestimate true prevalence for true prevalence values below 2% and similarly, underestimated for true prevalence values above 10%. It is therefore likely that problems will arise when trying to demonstrate small prevalence differences between countries, as underestimation of the prevalence will bias the absolute prevalence difference towards the null (Popescu *et al.,* 1998). The prevalence of atopic eczema in South Africa (1.0%) was lower than that observed in Romania and thus it is possible that overestimation occurred in the manner just described. This systematic error might account for some of the limitations of the criteria in a South African setting.

A recent Danish study showed a sensitivity of the UK criteria for atopic eczema of 90% and specificity of 97% (Olesen *et al.,* 2001). While this study had its flaws, with only 61 participants and an element of selection bias in the sampling strategy, the results remain in keeping with those observed in the United Kingdom.

Finally, the Chinese validation of the UK criteria demonstrated a sensitivity of 95.50% and specificity of 97.52% (Gu *et al.,* 2001). Unfortunately the ages ranged from 1 year to greater than 40 years of age, which means that the results are also largely not comparable with those

of this study. Of concern in the Chinese study is the fact that the method of translation was not clearly described and the prevalence of atopic eczema was not reported.

In contrast, the study conducted in Iran by Firooz *et al.*, reported a sensitivity of 12.50% and specificity of 100% in children aged 10 years and younger (Firooz *et al.*, 1999). Only 33 patients were included in this age group and so the results are limited by the small sample size. Possible reasons cited for the differences in sensitivity and specificity observed from those noted in the original UK validation study may be similar to causes of poor sensitivity and specificity in the South African setting. The authors also cited the possibility that the lack of socio-cultural acceptability of an itchy skin condition may limit positive responses to certain skin conditions. It is also possible that geographic variation, nutritional and environmental factors may be responsible for lower disease prevalence in Iran or for altered manifestations of the condition which may not be identified using the UK criteria.

The recent study in Ethiopia reported positive and negative predictive values of 55.5% and 90.1% on a population prevalence of between 4.4% (using the ISAAC questionnaire) and 1.3% (using the UK criteria) (Haileamlak *et al.*, 2005). In Ethiopia, as with this study, the sign of visible flexural eczema was also a strong predictor of atopic eczema. Haileamlak *et al.*, cite translation problems, socio-cultural issues and the transient nature of atopic eczema as possible reasons for their results. These reasons are similar to those applicable in the South African context. It is likely that the Ethiopian study is the most comparable to the South African context, as the study participants and study design are the most similar.

5.4.4 Limitations of the criteria

Issues regarding translation of the questionnaire have, to a certain extent, already been raised in sections 4.5.1 and 4.5.2. However, these issues play a critical role in the limitation of the criteria in South Africa, and warrant further discussion here.

There was a marked discordance between answers given to the questions relating to "itchy skin in the last year" (question 1) and "itchy skin in the last week" (question 2). In Xhosa there is recognized trouble with translation of the concept of the word eczema, and also with translation of "in the past year". For example, "in the past year" is translated to mean literally "in the past calendar year" which would include only the months of the year that had passed. If a child was seen in March 1997, "in the past year" could either have been interpreted as "during 1996" or as "in either January, February or March 1997", rather than "in the preceding 12 months" as was intended.

Further, discordant answers were also given for the two questions relating to previous eczema diagnosis. One explanation for these discordant answers is that "Does your child suffer from eczema" is understood to mean "Does your child have eczema now", whilst "in the past year" is open to more subtle mis-interpretation. It was believed after the piloting procedure of the questionnaire that the most accurate translation of the questions were chosen, but given the discordant answers received for these two questions this seems not to have been the case.

The proportion of discordant answers for questions relating to itchy skin "in the last year" and "in the last week" was smaller than for the questions relating to the diagnosis of eczema. This would suggest that some of the disagreement in the questions relating to eczema diagnosis

can be accounted for by the poor translation of the word "eczema", while the remaining discordant answers relate to the multiple interpretations of "in the last year".

In a recent validation of the Xhosa translation of the EQ-5D, a health related quality of life measure, the researchers also found that while translation of certain words into Xhosa may easily be done, the concept may not translate as effectively so that the desired interpretation of the word is lost (Jelsma *et al.,* 2004). Back-translation is an acceptable means of assessing accuracy of translation, but it is often only possible to pick up gross errors rather than subtle changes in the concept being conveyed (Sperber, 2004). Thus the two versions may be comparable in language, but not in meaning. In a recent review of translation methodology, comparisons were made between various methods of translation, including back translation with monoglot testing as was used in this study (Maneersriwongol & Dixon, 2004). They concluded that back translation is the most appropriate method for transcultural research, and while testing on bilingual subjects is perhaps the most desirable, they conceded that resource limitations may preclude this in most instances. In this study, although every effort was taken to ensure comparability of language and interpretation for the Xhosa translation of the questionnaire, it is still possible that systematic errors of translation occurred. Translation problems are therefore likely to have influenced the sensitivity and specificity of the questionnaire.

It is also possible that the Western cultural understanding of itchy skin and the negative connotations which may be associated with itchy skin are not as readily disclosed in a traditional Xhosa culture. Further investigation into the Xhosa cultural understanding of the phrases "itchy skin" and "eczema" are warranted before specific conclusions can be drawn in this regard, however.

Aside from issues related to translation of the criteria, some limitations with the criteria itself should be acknowledged at this point. As mentioned previously, the criteria established a period prevalence of atopic eczema, whilst dermatological examination establishes point prevalence. The difference between these two measurements should remain stable throughout the study, but it is nevertheless important to acknowledge that this difference exists. A recent validation study concluded that the UK diagnostic criteria will overestimate the prevalence if the true prevalence is below 2% and underestimate if the true prevalence is above 10% (Popescu *et al.,* 1998). Given that the point prevalence of atopic eczema was determined to be 1% in this study, it is possible that the UK diagnostic criteria prevalence estimate of 2.48% in the South African setting is an over estimation due to the low population prevalence.

Other sources of bias are also inherent in the questionnaire and the establishment of the period prevalence of atopic eczema according to the criteria. Aside from the translation problems discussed earlier, recall bias, relating to memory and information recall, may have occurred when asking about symptoms occurring in the preceding year. Information was also provided by individuals other than the study participant or indeed the parent of the study participant, and this may have also introduced a form of information bias. More accurate information may have been obtained if the information regarding symptoms had been gained from the children themselves. A further source of information bias may have arisen from differences in access to health care between the study areas, with consequent differences in exposure to the term "eczema".

Every attempt was made to assess the impact of the presence of other skin conditions on the validity of the questionnaire; it is possible that skin conditions not identified or not recorded in the survey may have contributed to the "false positives".

It is likely that selection bias occurred in Imizamoyethu because of the problems discussed previously in the section on sampling methodology, 3.3. Even though every attempt was made to reduce the possibility of selection bias through careful study design and sampling strategies, in the field it was not possible to adhere to the protocol. It is notable that the recorded prevalence of atopic eczema in Imizamoyethu was similar to that in the other peri-urban settlement of Joe Slovo. However, it is likely that the high prevalence of other skin conditions noted in Imizamoyethu is an over-estimation of the true prevalence because of the volunteer bias.

5.4.5 Analysis of the false positive and false negative results

Only 14 of the 76 individuals diagnosed using the questionnaire were in fact true positive cases. An understanding of the factors which contributed to the "false positive" and "false negative" results for the criteria is necessary if the limitations of the criteria in the South African setting are to be identified.

The "false positives" were not evenly distributed between areas, with the largest proportion being found in Langa. This may suggest that subtle differences in the administration or understanding of the questionnaire became more apparent, for whatever reason, in Langa and therefore resulted in a higher "false positive" rate. This may also reflect differences in access to health care between those individuals living in Langa and in the other areas, and

therefore differences in the understanding of the concept of "eczema", as mentioned previously.

There was also a difference in the frequency of certain skin conditions among the "false positives", specifically a lower prevalence of occlusive folliculitis, insect bites, pityriasis alba, trauma and xerosis. Xerosis is likely to have resulted in mis-classification since the dry skin condition may also have resulted in generalized itching, fulfilling the criteria, but subsequently not being associated with atopic eczema on examination. Insect bites may have resulted in mis-classification for similar reasons.

There were 18 "false negative" cases in this study. As with the false positive cases, the distribution was not uniform between study areas, with the highest proportion again being found in Langa, perhaps for similar reasons.

There was also a difference in the distribution of the age of the "false negative" cases from the general population, with "false negatives" more likely to be younger. In an assessment of Hanifin's and Rajka's minor criteria in 2 year olds, only dry skin, environmental influences and facial erythema were found to be useful in the diagnosis of atopic eczema (Bohme *et al.,* 2000). Xerosis is the only one of these included in the UK criteria, and hence included in this study. In a Swedish study of atopic dermatitis in 5 to 6 year olds using the UK criteria, dry skin (xerosis) was the most common differential diagnosis (Broberg *et al.,* 2000). Given the strong positive association demonstrated by logistic regression analysis with a history of dry skin and the diagnosis of atopic eczema (section 4.5.4), it was surprising that a history of generally dry skin was only reported in 38.89% of the "false negative" individuals. It is possible that this resulted from a mis-understanding of the question, especially relating to the phrase "in the last

year" and thus there was an underestimate of the number of positive responses to this question.

Of interest are the 12 individuals (66.67%) who were diagnosed as having atopic eczema on clinical examination, but did not have visible flexural eczema present at the time of administration of the questionnaire. This serves to illustrate that while visible flexural eczema is a good predictor of atopic eczema, other factors also play a role in diagnosis of this condition.

5.5 Contributions made by this study

The prevalence of atopic eczema, whether measured by clinical examination or UK criteria, was low. As with asthma, a rural-urban gradient seems to exist for atopic eczema. Further analysis of the differences in exposures between the urban and rural groups is warranted, and forms part of the phase II portion of this study.

The validity of the UK criteria in the South Africa setting is limited. This may be as a result of translation problems or underlying unspecified socio-cultural issues relating to the diagnosis of an itchy skin condition. The use of the criteria in a South African setting is therefore limited in their current format. The presence of visible flexural eczema was the strongest predictor of atopic eczema. Future epidemiological surveys should consider its use either alone, or in conjunction with a history of dry skin in the preceding year. It may, however, be more appropriate to derive South African criteria *de novo* rather than attempting to adapt the UK criteria.

Appendices

Appendix I: Questionnaire

A copy of the UK Working Party diagnostic criteria is shown below. Included are cross references (in bold face) to the modified version used in this study. The modified questionnaire follows.

UK Working Party diagnostic criteria for atopic eczema

Must have: An *itchy* skin condition (or parental report of scratching or rubbing in a child) **(question 1)**
Plus 3 or more of the following: 1. History of involvement of the skin creases such as folds of the elbows, behind the knees, fronts of the ankles or around the neck (including cheeks in children under 10 years of age); **(question 4)** 2. A personal history of asthma or hay fever (or history of atopic disease in a first degree relative in children under 4 years of age); **(question 6)** 3. A history of a general dry skin in the last year; **(question 5)** 4. Visible flexural eczema (or eczema involving the cheeks/forehead and outer aspects of the limbs in children under 4 years of age); **(question 9)** 5. Onset of the condition under the age of 2 years of age (not used if child is under 4 years of age). **(question 3)**

[1]Williams *et al.*, 1994c

The modified version of the UK Working Party's questionnaire on atopic eczema used in this study follows. The Xhosa translation appears first in italics and then the English translation. Demographic information was also obtained, but the questions are not shown here.

1. *Umntwana wahke wanorawuzelelo lofele ukuzi krwempa noku zihlikihla?*

   In the last year, has your child had an itchy skin? By itchy we mean scratching or rubbing the skin

2. *Kule veki indlulileyo ukhe umntwana wakho wanorawuzelo lofele?*

   Has your child had this itchy skin in the last week?

3. *Ube eneminyaka emingaphi umntwana wahko ukuqala kwalengxaki?*

   How old was your child when this skin condition began?

4. *Olurawuzelelo lukhe lwaxhaphaka kwindawo ezifana; nomphambili wengqiniba; umva wama madolo; amaqatha kunye nenkophe zamehlo?*

   Has this skin condition ever affected the skin creases – by skin creases we mean the front of the elbows, behind the knees, front of the ankles, around the neck, or around the eyes?

5. *Kulonyaka uphelileyo umntwana ukhe wahlutshwa yingxaki yofele olomileyo?*

   In the last year has your child suffered from generally dry skin?

For questions 6 and 7 the following combinations are noteworthy:

Yes to sub-questions 1 and 2 or 6 are equivalent to a history of hayfever

Yes to sub-questions 3, 4 and 5 or 7 are equivalent to a history of asthma

Yes to sub-questions 1 or 8 are equivalent to a history of eczema

6. *Ingaba umtwana unayo enye yezingxaki zilandelayo?*

   Does your child suffer from any of the following?

6.1 *Impumlo ezirawuzelelayo nezivuzayo kunye nofele olurawuzelelelayo xa edibene, ingca, ukutya, okanye izilwana?*

Itchy runny nose or itchy skin after contact with plants, grass, food or animals

6.2 *Ukuthimla akanye urawuzelelo lwamehlo ehlotyeni?*

Sneezing or itchy eyes in the summer?

6.3 *Utswino lwesifuba nomphefumlo obambekayo?*

Wheezy or tight chest with shortness of breath?

6.4 *Utswino lwesifuba nokhohlo-khohlo olumbambekileyo xa athe wanokukhawuleza nokuzilolonga ethubeni?*

Wheezing, chest tightness or coughing after exercise?

6.5 *Ukhohlo-khohlo olomileyo olunga nxulumelanga nefiva okanye ezinye izifo ebusuku?*

A dry cough at night not associated with a cold or chest infection?

6.6 *Inqaba umtwana wakho unayo ihayfever?*

Does your child suffer from hayfever?

6.7 *Inqaba umtwana wakho unayo iasthma?*

Does your child suffer from asthma?

6.8 *Inqaba umtwana wakho unayo ieczema?*

Does your child suffer from eczema?

7. *Ingaba kusapho lwalomntwana kukho owakhe wanezingxaki zilandelayo?*

Have family members ever suffered from any of the following:

7.1 *Impumlo ezirawuzelelayo nezivuzayo kunye nofele olurawuzelelelayo xa edibene, ingca, ukutya, okanye izilwana?*

Itchy runny nose or itchy skin after contact with plants, grass, food or animals

7.2 *Ukuthimla akanye urawuzelelo lwamehlo ehlotyeni?*

Sneezing or itchy eyes in the summer?

7.3 *Utswino lwesifuba nomphefumlo obambekayo?*

Wheezy or tight chest with shortness of breath?

7.4 *Utswino lwesifuba nokhohlo-khohlo olumbambekileyo xa athe wanokukhawuleza nokuzilolonga ethubeni?*

Wheezing, chest tightness or coughing after exercise?

7.5 *Ukhohlo-khohlo olomileyo olunga nxulumelanga nefiva okanye ezinye izifo ebusuku?*

A dry cough at night not associated with a cold or chest infection?

7.6 *Inqaba efamelini yenu yahko ukhona one ihayfever?*

Have any of the family suffered from hayfever?

7.7 *Inqaba efamelini yenu yahko ukhona one iasthma?*

Have any one of the family suffered from asthma?

7.8 *Inqaba efamelini yenu yahko ukhona one ieczema?*

Have any one of the family suffered from eczema?

8. *Kulo nyaka uphelileyo umntwana wakhe wakha thazwa zezi ngxaki zolfele?*

   a) *emkoma, nokrawezelo*

   b) *iintsumpa*

   c) *izilanda ezomileyo ezirawuzelayo*

   d) *amabala ebusweni*

   e) *akukho kwezi*

   In the past year has your child suffered from any of the following complaints?

   a) eczema

   b) warts

   c) psoriasis

   d) facial spots

   e) none of these

9. Presence of visible flexural eczema recorded as final part of criteria

Appendix 2: Logistic Regression Analysis

Comparing with an empty model	Log Likelihood	chi^2	P value	AIC
ATOPIC + q1	-174.9109	5.88	0.0153	353.8217
ATOPIC + q2 (not in criteria)	-175.1676	5.36	0.0205	354.3352
ATOPIC + onset	-175.9813	3.74	0.0532	355.9625
ATOPIC + q4	-171.3743	12.97	0.0003	346.7486
ATOPIC + q5	-162.9848	29.75	0.0000	329.9697
ATOPIC + asthma or hayfever	-177.3736	0.95	0.3290	358.7472
ATOPIC + eczema (not in criteria)	-174.2863	7.13	0.0076	352.5726
ATOPIC + family history	Dropped			
ATOPIC + visible flexural eczema	-80.7045	194.31	0.0000	165.409
ATOPIC + q1 + onset	-173.721	8.26	0.0161	353.4421
ATOPIC + q1 + q4	-171.1399	13.42	0.0012	348.2729
ATOPIC + q1 + q5	-162.6153	30.47	0.0000	331.2306
ATOPIC + q1 + eczema	-172.2491	11.20	0.0037	350.4983
ATOPIC + q1 + visible flexural eczema	-80.6943	194.31	0.0000	167.3887
ATOPIC + q4 + q5	-160.4633	34.79	0.0000	326.9266
ATOPIC + q4 + eczema (not in criteria)	-169.0297	17.64	0.0001	344.0594
ATOPIC + q4 + visible flexural eczema	-80.6691	194.38	0.0000	167.3382
ATOPIC + q5 + eczema (not in criteria)	-162.5696	30.56	0.0000	331.1392
ATOPIC + q5 + visible flexural eczema	-77.93439	199.85	0.0000	161.8688
ATOPIC + q1 + q4 + q5	-160.4472	34.81	0.0000	328.8944
ATOPIC + q1 + q4 + visible flexural eczema	-80.5958	194.51	0.0000	169.1916
ATOPIC + q1 + q5 + visible flexural eczema	-77.3670	200.97	0.0000	162.7341
ATOPIC + q1 + q4 + q5 + visible flexural eczema	-77.85	200.97	0.0000	164.7333
ATOPIC + sex	-177.7734	0.01	0.9373	359.5468
ATOPIC + study area	-177.7288	0.26	0.6079	359.4577
ATOPIC + age	-177.8604	0.00	0.9895	359.7208
ATOPIC + person interviewed	-177.4933	0.73	0.3915	358.9865

Logistic Regression Model A: Individual questions of UK criteria adjusted for age, sex and person interviewed and stratified by study area

```
Logistic regression                                     Number of obs   =       3022
                                                        LR chi2(12)     =     209.80
                                                        Prob > chi2     =     0.0000
Log likelihood = -72.465861                             Pseudo R2       =     0.5914
------------------------------------------------------------------------------
      ATOPIC | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          q1 |   .5448672   .4142253    -0.80   0.424     .1227949    2.417692
       ONSET |   .2550911   .2254201    -1.55   0.122     .0451337    1.441747
          q4 |    .920826   .6912151    -0.11   0.913     .2114589     4.00986
          q5 |   5.177288   3.114514     2.73   0.006     1.592366    16.83301
ASTHMAorHA~R |   1.133355   1.295357     0.11   0.913     .1206407    10.64727
     VISFLEX |   560.9496   340.2972    10.43   0.000     170.8232    1842.048
    ageinyea |    .925325   .0921683    -0.78   0.436     .7612182    1.124811
         SEX |   1.627487   .8484904     0.93   0.350     .5857919    4.521593
   INTERVIEW |   1.075305   .1541905     0.51   0.613     .8118501    1.424254
_Istudyare_2 |   1.925939   1.448185     0.87   0.383     .4411565    8.407997
_Istudyare_3 |   .9411906   .9201022    -0.06   0.951     .1385314    6.394506
_Istudyare_4 |   4.594495   4.400017     1.59   0.111     .7031798    30.0199
------------------------------------------------------------------------------
```

Logistic Regression Model B: Model showing the odds of having occlusive folliculitis if diagnosed with any form of eczema (unadjusted for other factors)

```
Logistic regression                                     Number of obs   =       3067
                                                        LR chi2(1)      =      42.94
                                                        Prob > chi2     =     0.0000
Log likelihood = -982.79118                             Pseudo R2       =     0.0214

------------------------------------------------------------------------------
   ECZEMATOT | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
FOLLICULITIS |   .4471863    .056434    -6.38   0.000     .3491955    .5726752
------------------------------------------------------------------------------
```

Logistic Regression Model C: Model showing the odds of having occlusive folliculitis if diagnosed with any form of eczema (adjusted for other factors)

```
Logistic regression                                     Number of obs   =       3059
                                                        LR chi2(4)      =      64.92
                                                        Prob > chi2     =     0.0000
Log likelihood = -968.76295                             Pseudo R2       =     0.0324

------------------------------------------------------------------------------
   ECZEMATOT | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
FOLLICULITIS |   .5525325   .0776828    -4.22   0.000     .4194536     .727833
    ageinyea |   1.068555   .0258411     2.74   0.006     1.019089    1.120422
    studyare |   .7834606   .0579521    -3.30   0.001     .6777262     .905691
         SEX |   .9845654   .1196859    -0.13   0.898     .7758372    1.24944
------------------------------------------------------------------------------
```

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