

# FOOD ALLERGY IN SOUTH AFRICA: JOINING THE FOOD ALLERGY EPIDEMIC?

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## ABSTRACT

The last 10-15 years have seen a steep rise in food allergies in westernised countries. South Africans, especially those of black descent, have traditionally enjoyed a low rate of food allergy and have long been thought to be protected against the food allergy epidemic. Previous food allergy prevalence studies in South Africa have focused on sensitisation and questionnaires which are not a true reflection of clinically relevant food allergy. A recent food allergy prevalence study in eczematous patients in Cape Town has shown a surprisingly high rate of challenge-proven food allergies in children of both Xhosa and mixed descent. These findings suggest that South Africa may not be spared from the food allergy epidemic. A large study investigating the prevalence of food allergy in an unselected group of young children is currently being planned, focusing on differences between urban and rural areas and between ethnic groups. Various factors which may contribute to the expression or suppression of food allergy, including exposure to foods, genetics, infections, diet and intestinal microbiota need further study. A better understanding of factors contributing towards food allergy expression will help us to define preventative strategies to curb the rise in food allergy.

## BACKGROUND

There is increasing evidence of a rise in the prevalence of food allergy, dubbed the 'second wave' of the allergy epidemic.<sup>1</sup> Enigmatically the food allergy epidemic has lagged behind the initial rise in respiratory allergies by several decades. This rise in food allergies has been described mostly in westernised countries by phenomenal statistics such as a two-fold rise in peanut allergy in the UK over the last 10-15 years.<sup>2</sup> A recent review also showed the incidence of challenge-proven food allergy in 10% of young children in Australia.<sup>1</sup> The importance of food allergies in westernised countries has received much recognition by large epidemiological studies such as the EuroPrevall study looking at food allergy and its impact in European countries.<sup>3</sup> Interestingly, peanut allergy in the UK seems to have stabilised,<sup>4</sup> implying that food allergy prevalence may already have peaked in certain parts of the world.

In South Africa, evidence suggests a significant increase in respiratory allergies,<sup>5</sup> which mirrors the pattern described in westernised countries, albeit lagging behind.

However, there is a dearth of studies looking at food allergies in South Africa, as with the entire African continent.<sup>6</sup> In the handful that have been performed, data reflect sensitisation or questionnaire-based allergies, both of which notoriously overestimate true allergy. Moreover, previous studies have lacked uniformity in the definition and diagnosis of food allergy, making it difficult to extrapolate the true allergy prevalence. In particular, there are few data on children younger than 3 years, the population with the lifetime peak prevalence of food allergy.

Anecdotally, true food allergy is deemed to be rare in South Africa, especially in the black African population.<sup>7,8</sup> However, South Africa is an ethnically diverse nation, with differences between ethnic groups in allergy expression. Moreover, the indigenous black population is rapidly urbanising and taking on a new 'westernised' diet and lifestyle. This may have an effect on prevalence of food allergy.

Recent studies indicate that food allergies may be gaining more prominence across ethnic groups in South Africa, as will be discussed in this article.<sup>9</sup> This could become a major health burden at an individual and public level.

## DIFFICULTIES IN DIAGNOSING FOOD ALLERGY

Before describing food allergy studies in South Africa, the diagnostic challenges in food allergy prevalence studies deserve mention. Worldwide, the marked heterogeneity in food allergy prevalence reflects different diagnostic methodology and definitions of allergy.

A major pitfall is that sensitisation does not equate to allergy. This may be of particular significance in the black African population.<sup>9</sup>

Some of the inherent difficulties in diagnostic tests are mentioned briefly below:

- **Skin-prick testing (SPT):** not only is this operator-dependent, but racial differences in skin thickness and reactivity to histamine may influence outcomes.<sup>10</sup> The source of the allergen extracts may also influence results since these may not represent local allergens.<sup>10,11</sup>
- **Food-specific IgE (sIgE):** South Africa has a high prevalence of helminth infections, which may strongly amplify the IgE response and can lead to false elevation of specific IgE levels.<sup>12</sup>

Cross-reactivity between components of food allergens and environmental allergens are increasingly recognised. An example is grass pollen cross-reacting with cereals, soya and peanut by a specific IgE to similar carbohydrate determinants.<sup>13</sup> Interpreting a specific IgE level for food without considering cross-reactivity can lead to false positives for true food allergy. This is an important consideration since aeroallergen sensitivity has increased significantly in South Africa in the last few decades.<sup>14</sup> Component resolved diagnostics has refined the art of cross-reactivity recognition, but high cost and poor availability make it prohibitive in many parts of South Africa.

- **95% positive predictive value cut-off levels** for skin-prick tests and specific IgE are still commonly

used to diagnose food allergy.<sup>15,16</sup> However, our experience in South Africa indicates that these cut-off values may not be applicable to our population and need further consideration.<sup>9,17</sup>

- **Questionnaires** are limited by local culture and language. Furthermore, self-reporting significantly overestimates allergies.<sup>18</sup>
- **Oral food challenges:** The most definitive method of assessing the prevalence of IgE-mediated food allergy in young children is by oral food challenges. The gold standard is the double-blind placebo-controlled food challenge,<sup>19</sup> but open challenges suffice in most cases. However, food challenges are resource-demanding, both financially and expertise-wise. Logistically, travel limitations and expense in Africa create more issues. Moreover, the non-participation or refusal to undergo food challenge may lead to over- or underestimation of allergy.<sup>19</sup>

Food challenges have been sorely underused in African countries to date and previous food prevalence studies have omitted them entirely. A recently completed food allergy prevalence study in Cape Town, involving children with atopic dermatitis, is the first study in South Africa to use challenges to diagnose food allergies.

## PREVIOUS EVIDENCE FOR FOOD ALLERGY PREVALENCE IN SOUTH AFRICA

Although South African children have significant sensitisation rates to foods, the prevalence of clinically significant food allergy is, anecdotally, extremely low.<sup>7,8</sup> This is most pronounced in those of black descent. In particular, peanut allergy, with the sensational increase in the western world, was virtually unheard of among black South Africans until recently. This experience led to the belief that black South African children may be protected from the food allergy epidemic. Possible protective factors include rural diet, high microbial load and unique gut microflora in the context of genetic and epigenetic influences, as will be discussed later.<sup>10-12</sup>

### Previous studies in South Africa looking at sensitisation and allergy to foods

In the late 1980s in Bloemfontein, Mercer *et al.*<sup>20</sup> looked at 771 patients (age range 3 months to 15 years) attending the paediatric allergy clinic. Patients were predominantly Caucasian (personal communication, MJ Mercer). As part of allergic rhinitis evaluation, SPT and

slgE to certain foods were performed. slgE in the entire group was positive for wheat (24.4%), milk (9.9%) and fish (5.9%). Similarly, SPT in 275 children over the age of 6 years showed sensitisation mainly to wheat (30.6%), milk (30.6%) and fish (26.2%). Some of the positive SPT/slge can be attributed to cross-reactivities, e.g. wheat and grass cross-reacting. None of the patients had symptoms typical of food allergy, although foods were reported as a possible trigger of allergic rhinitis in 3.5%.

In the mid 1990s in Gauteng, SPT to foods were performed in 58 of 468 Caucasian patients (age range 4-18 years) participating in a survey at a paediatric asthma clinic.<sup>21</sup> SPT positivity was defined as 2 mm greater than the negative control. Sensitisation patterns in these selected patients were as follows: wheat (30.4%), peanut (18.2%), fish (15.1%), soy (12.7%), egg (6.9%) and milk (5.4%). Only one patient had a history consistent with food allergy, but specific details were not provided.

In 2005, 100 children (age range 2 months to 20 years) attending a tertiary asthma clinic in Pretoria underwent SPT to common foods.<sup>22</sup> Racially, 67% were black and the remainder Caucasian. Sporik's cut-off points were used for food reactions<sup>15</sup> and were positive for peanut (9%), egg white (7%), wheat (4%), fish (4%) and milk (3%). There was no mention of clinical reports of allergy.

In 2008, a study on an unselected group of 212 Xhosa high school patients in Cape Town (age range 15-24 years) showed positive SPT for food allergens in 5.4% of subjects, most commonly to egg white (3.3%), peanuts (1.9%) and milk (1.9%).<sup>23</sup> None of these students reported intolerance to these foods.

The above studies are summarised in Table I. Marked heterogeneity in sensitisation rates reflect different age groups, intercurrent atopic conditions and aeroallergen cross-sensitisation rates. It is difficult to extrapolate actual food allergy rates from these studies since the focus is mainly on sensitisation with some patient reports of allergic symptoms. However, interestingly, of the total 645 patients who underwent SPT from these 4 studies, only 1 (0.2%) had symptoms suggestive of true food allergy.

### Previous studies in South Africa looking at food allergy and atopic dermatitis

Atopic dermatitis is a particular risk factor for food allergy, with a complex (and not necessarily causative) relationship between these two entities.<sup>24</sup> Studies in

**Table I. Summary of previous food sensitisation/allergy prevalence studies in South Africa**

Date (place)	Population (age range)	Sensitisation	Confirmed allergy
Late 1980s (Bloemfontein) <sup>20</sup>	761 children with allergic rhinitis (3 months-15 years)	slgE positive for wheat 24.4%, milk 9.9% and fish 5.9% SPT positive for wheat 30.6%, milk 30.6%, fish 26.2%	No reported food allergy symptoms except possible trigger for allergic rhinitis in 3.5%
Mid 1990s (Gauteng) <sup>21</sup>	58 Caucasian children with asthma (4-18 years)	SPT positive for wheat 30.4%, peanut 18.2%, fish 15.1%, soy 12.7%, egg 6.9% and milk 5.4%.	One patient reported food allergy
2005 (Pretoria) <sup>22</sup>	100 patients (67 black and 33 Caucasian) with asthma (2 months-20 years)	SPT over 95% positive predictive value for allergy: peanut 9%, egg white 7%, wheat 4%, fish 4%, and milk 3%.	None
2008 (Cape Town) <sup>23</sup>	212 unselected Xhosa high school patients (15-24 years)	SPT positive for egg white 3.3%, peanuts 1.9%, milk 1.9%.	None

westernised countries have shown high rates of sensitisation (60-80%) as well as challenge-proven food allergy (27-40%) in children with atopic dermatitis.<sup>25-28</sup>

Two previous studies in South Africa have examined food allergy in patients with atopic dermatitis.

The first study in 1998 involved parental questionnaire-based perceptions of food reactions in 112 children with atopic dermatitis.<sup>29</sup> By recall, the commonest triggers of cutaneous symptoms were tomatoes, oranges, sweets, pineapple, chocolate, and sulphur-dioxide-containing soft-drinks. These foods resulted in symptoms in up to 49% of the children. The foods that commonly cause IgE-mediated reactions, namely egg, fish, milk, and peanut, resulted in reactions in up to 25% of the children.

The second study formed part of the EPAAC (Early Prevention of Asthma in Atopic Children) study, in which children aged 12-24 months with eczema underwent sIgE tests to egg, milk and peanut.<sup>30</sup> A heterogeneous group of 161 South African infants from various centres was included. Rates of sensitisation were similar to those reported in westernised countries in the study, namely: egg 47.1%; cow's milk 28.4% and peanut 26.8%. Eleven infants (7.2%) in the South African cohort had peanut sIgE levels above 14 kU/l, more than the 95% predictive value for a positive food challenge.<sup>16</sup> However, there was no mention of clinical reports of symptoms of immediate food allergy.

Unfortunately true allergy rates in this population cannot be accurately extrapolated from these studies since the first study is questionnaire-based, while the other made use of sensitisation patterns.

### Current study in South Africa looking at food allergy and atopic dermatitis

Based on anecdotal evidence that food allergies are uncommon in South African children, especially those of black descent, we hypothesised that food allergies would be less common than in our westernised counterparts, even in children with atopic dermatitis (the population with inherently high risk of food allergy).

To test this hypothesis, a recent prospective, descriptive study was conducted in a tertiary medical centre in Cape Town to determine the prevalence of IgE-mediated food allergy in South African children with atopic dermatitis.<sup>9,31</sup> Foods tested were cow's milk, hen's egg, peanut, cashew nut, soya, wheat and codfish.

One hundred randomly selected children with atopic dermatitis from the dermatology clinic were investigated for IgE-mediated food allergy using a food allergy

questionnaire, SPT and sIgE (using immune solid phase allergen chip – ISAC Phadia). Open oral food challenges were performed in equivocal cases.

Allergy was defined as sensitisation to a food with a convincing history of a reaction to the food in the preceding year, or a positive food challenge.

Demographically, the mean age was 45 months. Of the group, 41% were of mixed race (mean age 50 months) and 59 were Xhosas (mean age 42 months). All patients had moderate or severe atopic dermatitis as measured by the SCORAD index.

Of the whole group, 66% showed sensitisation to at least one food, and 43% were polysensitised. Sensitisation was most commonly to egg (54% of patients), peanut (42%) and cow's milk (26%). A total of 68 open oral food challenges were performed. Overall 42% of patients had at least one food allergy, and 12% had multiple allergies. Allergy was most commonly to peanut (26% of patients), and egg (24%). Less common allergies were fish (3%), cow's milk (2%; but several gave a history of having outgrown cow's milk allergy), and cashew nut (1%). Surprisingly, among the Xhosa patients, 36% had at least one food allergy, 25% to egg and 17% to peanut (see Tables II and III). The latter were all proven by food challenges. Hence, out of our cohort of 59 Xhosa patients, 10 had challenge-proven peanut allergy, in an ethnic group with previously rarely reported peanut allergy.

Risk factors for food allergy included early-onset eczema before 6 months, and more severe eczema.

The authors concluded that IgE-mediated food allergy prevalence is high in this high-risk population of eczematous South African children and now equivalent to a comparable westernised population.

Table IV summarises all 3 above-mentioned eczema-food allergy studies.

### Preliminary evidence for food allergy increase in South Africa

Despite the lack of well-designed food allergy prevalence studies in the past, the surprisingly high prevalence of challenge-proven food allergies in the last study across mixed race and Xhosa patients with eczema suggests an increasing food allergy burden in South Africa. In addition, previously rare food allergy manifestations such as eosinophilic oesophagitis have been increasingly identified in South Africa in the past few years.<sup>32</sup>

Indeed food allergies may also be on the increase in other African countries. In a recent study in Ghanaian school children, 11% of 1 407 children reported adverse reactions to foods, and 5% of 1 431 children showed positive SPT reactivity. The most common sensitising foods were peanut and pineapple (2% respectively).<sup>33</sup> Food challenges were not performed as part of this study.

### WHAT FACTORS COULD BE DRIVING AN INCREASE IN FOOD ALLERGY IN SOUTH AFRICA?

Food allergy is usually associated with other atopic disorders and hence probably shares many common risk

**Table II. Overall sensitisation and allergy rates in recent atopic dermatitis/food allergy study**

	Any sensitivities % (n)	Any allergies % (n)
Mixed race (n=41)	61% (25)	51% (21)
Xhosa (n=59)	69% (41)	36% (21)
Total (n=100)	<b>66% (66)</b>	<b>42% (42)</b>

**Table III. Breakdown for individual foods in recent atopic dermatitis/food allergy study**

	Egg sensitised % (n)	Egg allergic % (n)	Peanut sensitised % (n)	Peanut allergic % (n)	Cow's milk sensitised % (n)	Cow's milk allergic % (n)
Mixed race (n=41)	46% (19)	24% (10)	49% (20)	39% (16)	34% (14)	4.8% (2)
Xhosa (n=59)	59% (35)	25% (15)	37% (22)	17% (10)	20% (12)	0% (0)
Total (n=100)	<b>54% (54)</b>	<b>24% (24)</b>	<b>42% (42)</b>	<b>26% (26)</b>	<b>26% (26)</b>	<b>2% (2)</b>

**Table IV. Summary of food sensitisation/allergy prevalence studies in children with atopic dermatitis (AD) in South Africa**

Study population	Food allergy diagnosis	Results
112 children with atopic dermatitis (1994) <sup>29</sup>	Questionnaire	Perceived allergy to tomatoes, oranges, sweets, pineapple, chocolate, soft drinks in up to 49%, and egg, fish, milk, and peanut in up to 25%
161 children (12-24 months) with AD from various centres and ethnic backgrounds (2005) <sup>30</sup>	Sensitisation (specific IgE > 0.35 U/l)	Sensitisation to egg 47.1%; cow's milk 28.4% and peanut 26.8%. Peanut sIgE greater than 95% positive predictive value for allergy in 7.2%
100 children (6 months-10 years) with atopic dermatitis (2011) <sup>31</sup>	Sensitised AND convincing recent history of reaction, or positive food challenge	Sensitisation to egg 54%, peanut 42% and milk 26%. Allergy to peanut 26%, egg 24%, cow's milk 2%

factors. However, unique food allergy considerations such as the delayed epidemic, the potential life-threatening nature and related public-health measures make the identification of specific risk factors a priority.

### Early life influences

The distinct sequence of the allergic march suggests that certain individuals are prone to manifesting their atopic conditions under the influence of environmental factors within a particular timeframe (depicted in Fig. 1). Expression of food allergy in very early infancy dictates that early postnatal events and likely antenatal events play a critical role in abrogating the normal default response of tolerance to food allergens.<sup>1</sup>

Factors which could play a role in the expression of food allergy include:<sup>18,34,35</sup>

- Allergen exposure
- Gut microflora
- Gastric acid
- Changes in diet
- Infections
- Eczema and other atopic conditions
- Genetic and epigenetic factors

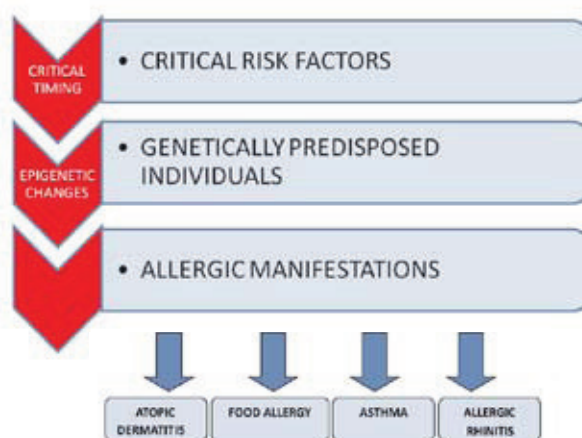


Fig. 1. Model for the development of allergic conditions

### Migrant populations

The rapid urbanisation, adoption of a westernised lifestyle and diet in South Africa simulate the characteristics of a large 'migrant' population. In migrant populations, the change in environment and lifestyle may affect genotype expression, thus leading to the mani-

festation of an allergy. Three factors are important in migrant populations (Fig. 2):

- The population must have an innate genetic predisposition to development of allergies
- Environment or lifestyle factors in their place of birth actively prevented/suppressed the expression of allergy
- Exacerbating factors in an altered environment actively allow the genetic potential for allergy to become unveiled.<sup>10</sup>

Some of the factors influencing the expression of allergy and their change in South Africa over the last decade or two are discussed.

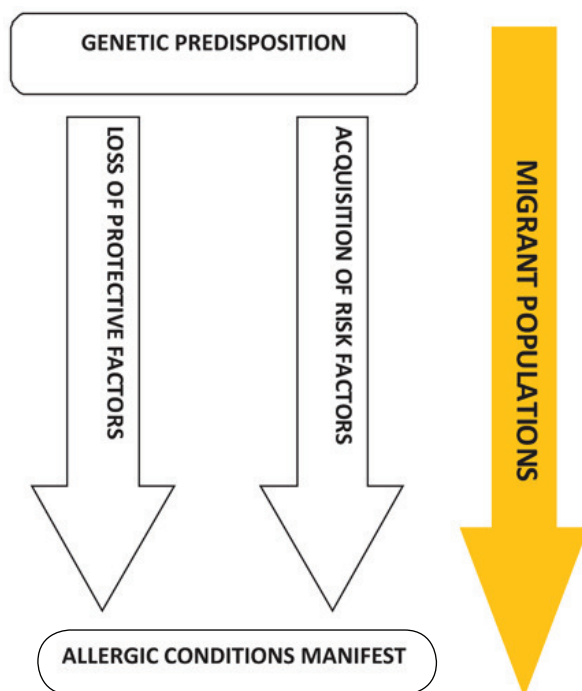


Fig. 2. Allergies in migrant populations.

### Allergen exposure

Whether a person becomes sensitised or tolerant to an allergen depends on multiple factors such as the timing, dose, route of exposure and possibly the nature of the allergen.<sup>36</sup> Allergen exposure via the inhaled or cutaneous route may abrogate the tolerance normally afforded via gut exposure.

There seems to be a window of opportunity for optimal allergenic solid food introduction between 4-6 months

of age.<sup>34,35</sup> Delayed introduction of allergenic foods such as wheat, egg and cow's milk has been associated with higher risk of food allergy in some studies.<sup>37,38</sup>

In South Africa, patterns of utilisation, consumption and exposure of foods need to be explored in depth as urbanisation occurs. Furthermore, the presence of potentially allergenic food components in non-food items, such as peanut oil in emollients, needs further clarification.

A comparison of peanut exposure between a cohort of Xhosa patients in 2006 and the eczema-allergy cohort in 2010/2011 shows an interesting trend in peanut consumption. In the first group, a dietetic study involved interviewing mothers ( $n=198$ ) of black infants aged 4-36 months in Cape Town about their infants' peanut intake using a peanut consumption questionnaire.<sup>39</sup> The mean age of introduction of peanuts and peanut products was found to be 10 months, and 64% of subjects started eating peanuts before 1 year of age. The median total peanut intake was 12 g/day (1-2 portions per day). In comparison, in the 59 Xhosa patients from the recent eczema-allergy study, the mean age of introduction of peanut was 22 months, and only 22% of children had consumed peanut before the age of 1.<sup>9,31</sup> Of those consuming peanut, the average consumption was 3 portions per week.

Although the eczema population may be preselected for more cautious introduction of solids, the trend towards later and more conservative introduction of peanut products is thought-provoking in the context of increasing prevalence of peanut allergy.

## Gut microflora

There is a delicate balance between bacteria and the immune system. Early colonisation of the intestinal tract by appropriate microbiota is important for healthy maturation of the immune system, especially appropriate programming of oral tolerance to dietary antigens.<sup>40,41</sup> Differences in certain bacterial populations between allergic and non-allergic infants have been noted.<sup>42</sup>

In South Africa, an increase in the rate of caesarian sections, changing diet in childhood, more frequent use of antibiotics and a changing maternal intestinal microbial milieu could all impact on a child's microflora. Much of the microbiome may be shaped by early exposures to environmental soil/dust by hand-to-mouth transmission (personal communication – Christine Cole, Detroit, USA). As the environmental dust and maternal microflora change in a migrant population, so too does the microbiome of children. This theory of gut microflora alteration merits further exploration, especially in view of possible rural-urban differences in allergy prevalence.

## Gastric acid

Most food allergens are susceptible to acid digestion in the stomach. This has raised the concern that changes in the stomach acid content may make subjects more susceptible to allergen sensitisation. Indeed, the increasing use of anti-acids in young babies with presumed gastro-oesophageal reflux disease has paralleled the rise in food allergies.<sup>43</sup>

## Changes in diet

In African countries, considerable changes in diet have occurred. Notably, the intake of plant foods has diminished, with increasing ingestion of animal products, and a decrease in fibre intake.<sup>7,44</sup> Anti-inflammatory immunomodulating factors in the diet such as prebiotics, fat-soluble vitamins and polyunsaturated fatty acids may be reduced in westernised diets, making them more 'inflammatory'.<sup>45</sup>

Large urban-rural differences in diet do not only affect allergen exposure to food allergens, but have been found to affect skin sensitivity to common aeroallergens – in other words they can shift the entire allergic 'make up'.<sup>46</sup>

The influence of maternal diet during pregnancy and lactation on allergy expression in the infant remains controversial and under study.

## Burden of infection

Developing countries including South Africa are plagued by poor sanitation and housing, overcrowding and lack of access to clean water. It seems that early exposure to such environments with high microbial and endotoxin levels, can be protective against allergic conditions (the hygiene hypothesis).<sup>12</sup> However, the degree of protection depends on the intensity and timing of the infections.

Certain helminthic infestations may protect an individual from allergic predisposition by mechanisms that are incompletely understood. These may include interleukin-10 (IL-10)-related suppression of the allergic response.<sup>10,47</sup>

In South Africa, the intensity of infection exposure may be lessening with urbanisation, more ready access to treatment and smaller family size. In addition, helminthic infections are treated more readily and regularly.

An interesting theory by Van Ree and Yazdanbakhsh<sup>10</sup> is that the increase in allergic burden in black Africans may be even more dramatic as parasitic infections could have primed the immune system for IgE responses.

## Genetic factors

A family history of atopy is a strong risk factor for developing atopic diseases later in childhood. Rising rates of maternal allergy, which is a strong direct determinant of allergic risk, may have implications for allergic burden in generations ahead.<sup>1</sup>

The rapidity of the increase in food allergies worldwide suggests that epigenetic changes modify disease expression under the influence of environmental changes. Epigenetic changes may be heritable, and even amplified across generations. It has been suggested that the new generation of food allergy patients is more likely to have a more severe or persistent clinical course.<sup>1</sup>

Moreover, evidence suggests that development of allergy in non-white populations is heightened in a westernised environment, over and above that of the local western population.<sup>44,48,49</sup> This suggests a strong genetic propensity that is amplified in a western environment.

## FUTURE DIRECTIONS

The results of the recent eczema-allergy study provide initial evidence for an increase in food allergy prevalence in South Africa. As opposed to other allergic conditions, when considering food allergies, a critical time and dose of the food, in conjunction with the delicate balance between exacerbating and protecting factors are vitally important. The question remains as to whether there are as yet unidentified factors influencing the food allergy epidemic, or whether it is simply an 'amplification' of allergic manifestations, the 'next step' as allergies domino from one generation to the next.

The imminent plan is to embark upon a large food allergy prevalence study in an unselected population of 1-3-year-old South African children in Cape Town and the rural Transkei. The aim is to address rural-urban differences and ethnic patterns in food allergy prevalence. The results of this forthcoming study will provide impor-

tant data on the possible food allergy epidemic in South Africa, allowing more targeted and informed planning of health-care services.

The South African population, previously seemingly untouched by food allergy issues, can now provide a platform for exploring factors which may influence the current food allergy epidemic. Such an understanding will hopefully enable us to modulate early determinants to modify and ultimately curtail the development of allergic disease.

### Declaration of conflict of interest

The authors declare no conflict of interest.

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