A cross-sectional study of Ig-E mediated food sensitisation and food allergy in an unselected population of South African children aged 12-36 months.

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BSRWIS001

submitted in partial fulfilment of the requirements for the degree

MASTER OF PUBLIC HEALTH

in the

SCHOOL OF PUBLIC HEALTH AND FAMILY MEDICINE

at the

UNIVERSITY OF CAPE TOWN

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April 2014

PART 0

PREAMBLE

Declaration

I, Wisdom Basera (BSRWIS001), hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature _____

Date _____

Dedication

To the memory of my brother Emmanuel

and to Wayden my inspiration

Dissertation Abstract

Background

Food allergy (FA) is a significant and often life-threatening health problem affecting about 4-6% of children and their families globally. In some developed countries FA prevalence has reached 10% and it is believed that developing economies may follow a similar trend since there is a reported rise in the global burden of other allergic diseases like asthma, allergic rhinitis and eczema. However, there is a dearth of population studies at global level documenting challenge-proven Ig-E mediated food allergy (FA) prevalence. As such, we studied an unselected population of children attending crèches in Cape Town, South Africa.

Methodology

All children aged 12-36 months attending the selected crèches between February 2013 and October 2013 were eligible for the study. Participants were assessed with an allergy questionnaire, had skin prick tests (SPTs) done and if they qualified, were invited for an oral food challenge (OFC) at the Red Cross Hospital Paediatric Allergy Clinic (RCHPAC).

The SPT wheal size results were categorised into ≥1mm, ≥3mm and ≥7mm. We gave a general description of the study sample with respect to the demographic characteristics and compared participants and non-participants. We reported sensitisation pattern towards foods in the panel i.e. egg white extract, peanut, cow's milk, wheat (flour), soy, hazelnut and fish (cod) according to the SPT categories. The effects of age, ethnicity, sex and concomitant allergy on sensitisation patterns were assessed. Associations between the potential predictor variables and sensitisation were assessed by Z-test for proportions and Chi-square/Fisher's exact.

PART I presents the study protocol with a brief motivation for the relevance of the study and the methodology used.

PART II presents a structured literature review on FA and FS in large populations of selected and unselected cohorts. It provides an overview of empirical evidence on prevalence estimates from both the developed and developing world, and the potential risk factors causing FA.

PART III summarises the methodology, results and interpretation of the analysis conducted in a journal-ready manuscript according to Current Allergy and Clinical Immunology Journal requirements.

Results

The sample consisted of; 39% black African, 20% Caucasian and 41% mixed race participants, with a median age 26 months (IQR: 22-31). Amongst 121 participants (66% response rate, 92% participation rate and 94% completion rate), the prevalence of SPT≥1mm to any food was 16%, SPT≥3mm 12% and SPT≥7mm 4%. The prevalence of challenge-proven Ig-E mediated raw egg allergy was 1.7% and peanut allergy 0.8%. Black African participants had higher sensitisation rates (23%) of SPT≥1mm to any food, when compared to Caucasian (13%) and mixed race (10%) participants despite the difference not reaching statistical significance (p=0.17).

Conclusions

This study was acceptable and feasible in this population that has a low prevalence of Ig-E mediated FA that is comparable to other studies from developed countries using objective measures in unselected cohorts. The prevalence of FS is appreciably high in this sample and there are ethnic differences that require further investigation. The findings seem to suggest an existing burden of Ig-E mediated FAs in the South African context that is un-diagnosed and therefore not managed.

Acknowledgements

Thank you to my supervisor Professor Michael E. Levin for suggesting the dissertation topic, reading through countless drafts and his guidance and support throughout the process of developing this research since this was a new field to me. Thank you also to one of the Principal Investigators, Dr Claudia L. Gray for her constructive feedback and input during the thesis writing-up phase.

Thank you to Dr Maresa Botha and Sr Nurse Heidi Facey-Thomas for all the hard work in collecting the study data against all odds.

Thank you to the staff at the Red Cross Hospital Paediatric Allergy Clinic for coordinating and conducting the Oral Food Challenges.

Thank you once more to Dr Maresa Botha for keeping the SAFFA boat afloat with all the day to day administrative work.

Final thank you; to my funders during my studies i.e. UCT Postgraduate Funding and Canon Collins Educational and Legal Assistance Trust; my friends and family for all the support and the God Almighty for affording me this opportunity to study.

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List of Abbreviations

AD Atopic Dermatitis

AHNS Australia HealthNuts Study

DBPCFC Double Blind Placebo-Control Food Challenge

DSD Department of Social Development

EPAAC^{TM} Early Prevention of Asthma in Atopic Children

FA Food Allergy

FS Food Sensitisation

FHS Food Hypersensitivity

Ig-E Immunoglobulin E

NHNES National Health Nutritional Examination Survey

OFC Oral Food Challenge

PPV Positive Predictive Value

RCWMCH Red Cross War Memorial Children's Hospital

RCHPAC Red Cross Hospital Paediatric Allergy Clinic

sIgE Serum Immunoglobulin-E

SPT Skin Prick Test

UCT University of Cape Town

UK United Kingdom

USA United States of America

PART A

RESEARCH PROTOCOL

A cross-sectional study of Ig-E mediated food sensitisation and food allergy in an unselected population of South African children aged 12-36 months.

1 Protocol Executive Summary

There is no reliable South African data on the prevalence of food sensitisation (FS) and challenge-proven Ig-E mediated food allergy (FA) in an unselected cohort of children who are believed to have the lifetime peak prevalence of FAs. Most of the studies done are on selected populations and report questionnaire or FS rates that are not true estimates of FA. Findings from these studies suggest high rates of FS in the selected populations and inter-ethnic differences in sensitisation and challenge-proven Ig-E mediated FA. There is a need to determine the current FS rates and the challenge-proven Ig-E mediated FA prevalence in an unselected sample of South African children aged 12-36 months and to ascertain possible inter-ethnic differences and the public health burden.

This study of 114 children in the Cape Town Metropolis will lay a platform for the larger study of a total of 1200 children in Cape Town and 400 in the rural Eastern Cape. The immediate aims of the study are to determine the following:

1. Prevalence of sensitisation and challenge-proven Ig-E mediated FA for the common food allergens (cow's milk, egg, fish (cod), hazelnut, peanut, soya and wheat.
2. Pilot the questionnaires that will be used for the participants and non-participants.
3. Explore some risk factors as potential predictors of FS and Ig-E mediated FA.

The participants will be recruited from Cape Town crèches and data will be collected via a participant allergy questionnaire and a non-participant questionnaire will be used to assess for participant selection bias. Data on demographics and risk factors will be gathered and skin prick tests (SPT) performed. FS will be recorded based on degrees of sensitisation viz SPT≥1mm, SPT≥3mm and SPT≥7mm while Ig-E mediated FA will be defined as a positive SPT (SPT≥1mm > the negative control) and a positive oral food challenge (OFC). Rates of sensitisation and challenge-proven Ig-E mediated FA to foods under review will be computed and analysed based on particular risk factors.

2 Introduction

2.1 Background

FA has over the years become an issue of public health importance with evidence of an increasing prevalence (1). This rise in prevalence has however lagged behind by decades to the initial rise in respiratory allergies. Studies in westernised countries have reported remarkable statistics like a three-fold increase in peanut and tree nut allergy between 1997 and 2008 from a United States of America (USA) survey (2) and a two-fold rise in peanut allergies in the United Kingdom (UK) over the last 10-15 years (3). However, in the UK (Isle of Wight) the follow-up study shows that peanut sensitisation and reported allergy has since plateaued (4). The increasing concern over FAs is based on the fact that it has been shown to significantly affect morbidity, mortality and quality of life (5).

2.1.1 Global estimates of food allergy

Many countries do not have accurate prevalence data for global estimates. Most prevalence measurements are based on self-report or surveys that are not based on objective confirmation of allergy through OFCs (6). Estimates from studies in developed countries using objective measures suggest that up to 2.5% of the adult population has FA with higher rates of up to 10% being reported in the first 3 years of life (7,8). A study in the UK followed birth cohorts from 2001-2002 to determine the incidence of confirmed FA and reported rates of 4%, 2.5% and 3% at 12 months, 2 years and 3 years respectively (9,10). A Danish study of an unselected population of children and adults showed the prevalence of challenge-proven FA to be 2.3% in children <3 years and 1% for children >3 years (11).

More recently in Australia, a large cross-sectional study assessing 2848 infants aged 12 months showed appreciably high levels of FS and challenge-proven Ig-E mediated FA using predetermined OFC criteria. The initial results show FS rates of 8.9% for peanuts and 16.9% to raw egg white. Overall, more than 10% of the infants have proven Ig-E mediated FA to one of the common allergenic foods of infancy (12).

2.1.2 Food allergy in Southern Africa

In Africa there is scarcity of data on the prevalence of FA possibly because much focus is on communicable and adult onset non-communicable diseases while allergic disorders are regarded as less important. Most of the studies available are from selected populations and questionnaire based surveys (13).

In Gaborone, Botswana, 55 patients from an allergy practice suffering from eczema, or those who had a history consistent with FA underwent testing for FS. Children with atopic dermatitis (AD) were mostly sensitised to egg (11%) and peanut (7%) (14). A case-control study in Pretoria checking for co-morbid conditions in 100 asthmatic children reported the following FS rates; 9% peanuts, 7% egg white, 4% wheat, 4% fish and 3% milk (15). In Cape Town, a cohort of 400 allergic children showed sensitisation to be common in eczematous children with an overall prevalence of 13%. Most sensitisation was with peanuts 35%, egg white 30%, milk 17%, fish 4%, tree nuts 3% and potato 3% (16).

In a multi-country study, the Early Prevention of Asthma in Atopic Children (EPAAC^{TM}), a heterogeneous group of South African infants aged 12-24 months showed high levels of sensitisation (not challenge-proven allergy) towards egg (47.1%), cow's milk (28.4%) and peanut (26.8%) (17). Gray et al assessing the prevalence of FA in children with Atopic Dermatitis (AD) observed high rates of sensitisation and challenge-proven allergy in black African and mixed race participants. Overall, FS level was at 66% and the confirmed FAs were 42% showing inter-ethnic differences in the South African context (18). In an unselected sample of black African high school students in Cape Town, 5.4% showed positive SPT towards the common food allergens. The prevalence of the reported allergens was 3.3% egg, 1.9% peanut and 1.9% milk (19).

The findings from the studies in selected populations suggest that there is appreciable sensitisation and confirmed FA towards the common food allergens in the local context. There are no studies in South Africa on unselected populations to help understand the prevalence of FAs in relation to global estimates.

2.1.3 Food sensitisation versus food allergy

In the EPAAC^{TM} study the South African overall level of sensitisation was 26.8% which was higher than the estimate for the whole group, 24.4%. The South African level of peanut sensitisation was higher (7.2%) than the rest of the group (4.9%). Despite such high FS rates, the prevalence of proven peanut allergy in South Africa is reportedly low. It stands to reason that the 95% positive predictive value (PPV) cut-offs for SPT values used in predicting positive food challenges may not be applicable in the South African context (17).

Based on anecdotal evidence, FA is believed to be uncommon especially in the black South African population (20,21). Should the prevalence be shown to be high in this population, it may provide some clues to the factors which could be driving the FA epidemic in the local context.

2.2 Rationale

There is evidence indicating that the prevalence of FA maybe much higher in the urban black African population than anticipated (19). The ethnic diversity in South Africa and the rapid urbanisation taking place in the indigenous black South African population may have an influence on the increase in FA as a result of the lifestyle differences (18). To avert missing children with a potential for challenge-proven Ig-E mediated FA, we will use any level of sensitisation (SPT ≥1mm) to denote positivity toward the allergen being tested and such subjects will undergo an OFC if they are not tolerating the food(s) on clinical history.

A SPT≥3mm traditionally supports a diagnosis of Ig-E mediated FA with a good clinical history however, the SPT level has a low specificity (about 50%) to be of value in identifying clinically relevant FA. As a result we will also incorporate the category SPT≥7mm since for many of the foods that have been studied, a magnitude of skin prick test in this range has been shown to be associated with a positive outcome on incremental OFCs (22,23). We will denote the three categories; SPT≥1mm, SPT≥3mm and SPT≥7mm to represent low, medium and high levels of sensitisation. All SPTs are "corrected" for the negative control being 0 mm.

Most FA occurs in the first three years of life (24,25) we will therefore determine the Ig-E mediated FA prevalence in children aged 12-36 months to ascertain the possible public health burden. The findings can be used for advocacy regarding the provision of health services and food alternatives for the affected children and their families (26). Local studies have highlighted the need to evaluate the validity of the current cut-off values for the prediction of SPT and blood specific Ig-E levels in black South African children (18). This study will as well lay the platform for prediction studies and provide initial insights into modifiable and non-modifiable risk factors associated with FAs in South Africa.

2.3 Study objectives

This study will be conducted in the crèches located in the Cape Town Metropolis. The primary objective of the study is to determine the prevalence of sensitisation and challenge-proven Ig-E mediated FA in this sample that is presumed representative of the Cape Town population.

The following objectives are outlined for the study:

1. To determine the sensitisation levels to any one or more of the 7 common allergic foods (hen's egg, cow's milk, peanut, tree nuts, soy, wheat and fish (cod)).
2. To determine the challenge-proven prevalence of Ig-E-mediated FA to the above mentioned food allergens.
3. To explore the patterns of particular risk factors as possible predictors of FS and Ig-E mediated FA.

3 Methodology

3.1 Study design and setting

This is a cross-sectional (prevalence) study to be conducted at crèches in different areas of Cape Town and the OFCs will be conducted at the Red Cross Hospital Paediatric Allergy Clinic (RCHPAC).

3.2 Population and recruitment

The study population will be children aged 12-36 months attending crèches in the Cape Town Metropolis. This age group is notoriously difficult to access via child health clinics as their last scheduled post-natal visit is at 18 months. Therefore recruiting from the local registered crèches we will have a better age representation of those up to three years. A list of registered crèches in Cape Town is overtly available online and permission was obtained (Levin M 2012, personal email, July 11) from the Department of Social Development (DSD) to approach crèches to participate in the study.

Crèches selected from the sampling frame (using Microsoft Excel number generator) will be contacted and permission obtained from the manager/principal to conduct the study. Parents of eligible children will be sent an information leaflet regarding the study and will be invited to attend the crèche on study days as arranged with the crèche management. On study days, the team will meet with parents/guardians and details of the study will be discussed using an interpreter if necessary. If they choose to participate, informed consent will be obtained from the legal guardian in their language of choice. They will complete the study questionnaire, their child will be physically examined and undergo a SPT. In some cases SPT may be deferred to another day if the child has recently taken antihistamines. Furthermore, all children with a recent history (<6 months) of a reaction to any of the foods tested for will have their SPTs performed at the RCHPAC.

3.2.1 Inclusion criteria

- Children in the age range 12 months to 36 months.
- Children for who informed consent can be obtained from the parent or legal guardian.

3.2.2 Exclusion criteria

- Children with significant chronic illnesses (apart from that related to their atopic predisposition, such as asthma).
- Unwillingness or inability to comply with study requirements or procedures including the oral food challenge.

3.3 Sample size

The sample size is calculated using an expected proportion of 8% for challenge-proven Ig-E mediated FA to any particular food type. This is based on the primary study objective which is to determine the prevalence of challenge proven Ig-E mediated FA. Since there is no previous local data on the prevalence of confirmed allergy in an unselected population we assumed the expected proportion based on the preliminary results of the largest and most recent FA prevalence study (Australian HealthNuts Study (AHNS)) that has reported the prevalence of challenge-proven Ig-E mediated FA to be 10% (12).

We do not forsee our prevalence to be as high as 10% since we expect the incidence of FA to be reducing by the age of 36 months. The correlation between Ig-E mediated FA/FS outcome and the predictor variables will not be explored in-depth in the first phase of the study because of a possible lack in precision. The associations will be considered in the subsequent phases of the study, as such the risk factors will not be considered in the sample size calculation. In this phase of the study we seek to have a preliminary understanding of the association between some of the predictor variables that could be driving the allergy epidemic in this population and the Ig-E mediated FA/FS outcome.

In addition to the expected proportion we will use a precision of 5% and a power of 80%.

Assuming a challenge-proven Ig-E mediated FA proportion of 8%:

The sample size $= \{0.08(1-0.08)1.96^2\}/0.05^2 = 113.1$ **= 114**

3.4 Data collection tools

3.4.1 Questionnaire

A participant questionnaire will be completed with a study team member going through all the questions and collecting information on demographics and potential risk factors for FA with the parent/caregiver in their preferred language. Non-participants will be asked to fill in the non-participant questionnaire to assess for participant selection bias.

3.4.2 Skin prick testing

SPTs will be performed by trained medical/nursing staff. Children with no history of a reaction to food will have their SPTs performed at the crèche. Those with positive SPT (≥1mm > the negative control) will be invited to the RCHPAC for OFCs. Children who have a history of a reaction to food will have both their SPT and OFC performed at RCHPAC. Standardised solutions from ALK Abello (Thermo Fisher^{TM}) and ALK lancets will be used for the following food allergens: egg white extract, cow's milk, soya, wheat (flour), fish (cod), peanut, hazelnut, positive control and negative control. Sensitisation will be recorded based on the following SPT categories (> the negative control); SPT≥1mm, SPT≥3mm and SPT≥7mm.

3.4.3 Oral food challenges

In cases where there is evidence of any sensitisation to the foods being tested for (SPT≥ 1mm > the negative control), and there is no clear history of a recent severe allergic reaction to the food(s), and no clear history of tolerance, an incremental food challenge will be arranged. If children are sensitised to more than one allergen, they will need multiple food challenges on different days with an appropriate time interval between challenges.

3.5 Reliability and validity

The questionnaire was developed following the examples from the ongoing AHNS (27). This will serve as a comparing mechanism that will ensure validity in the tool we are using to collect data. Since this is the first phase of the larger study, the reliability of the data capturing tool will be assessed at the end of the first phase of the study and if need be, the questionnaire will be refined and re-conceptualised so that it measures what it is assumed to be measuring (22).

3.6 Potential study biases

There is the possibility that parents who have a concern that their child might have FA are more likely to choose to participate and complete the study than those without such a concern.

In an attempt to account for this bias we will ask parents who decline to participate if they would agree to complete a short non-participant questionnaire with questions regarding their child's allergy history.

There is also the possibility of misclassifying participants based on their clinical history i.e. those with a suspect allergy history are more likely to be classified as sensitised when reading the SPT measurements. To minimise on this we will rely on the judgement of another team member not performing the SPT to confirm the measurement. There will be continuous training as well to help reduce measurement errors in variables.

3.7 Measurement

The main outcomes of interest are the number of participants sensitised/truly allergic to a particular food as a proportion of the study sample. Using particular risk factors (ethnicity, age, sex and concomitant allergy status) we will determine the different proportions of participants that are either sensitised/truly allergic.

Table 1.1: List and definition of variables that will be considered in the study

Name/Type	Scale	Possible Values
Age	Numerical - continuous	12 – 36 months
Sex	Categorical - binary	Male, Female
Ethnic origin	Categorical - nominal	Caucasian, Mixed race, Black African
Food exposures	Categorical - binary	Yes, No
Reactions to foods	Categorical - binary	Yes, No
Reaction Doctor diagnosed	Categorical - binary	Yes, No
Self-reported Asthma/Hayfever/Eczema status	Categorical - binary	Yes, No
Diagnosed made by	Categorical - nominal	Self, Doctor, Nurse
Clinical confirmed Asthma/Hayfever/Eczema status	Categorical - binary	Yes, No
Family member history of allergic disease	Categorical - binary	Yes, No
SPT result	Numerical - continuous	≥0mm
SPT≥1mm, ≥3mm & ≥7mm	Categorical - binary	Yes, No
Child tolerant to food if SPT≥1mm	Categorical - binary	Yes, No
Oral food challenge indicated	Categorical – binary	Yes, No
Oral food challenge result	Categorical - nominal	Positive, Negative, Equivocal

3.8 Potential benefits of study participation

Potential benefits of positive allergy tests/OFC include a conclusive diagnosis of Ig-E mediated FA demonstrating the need for counselling in strict avoidance of the food, reduction of the risk of inadvertent exposures, reduction of anxiety about the unknown, and validation of the child's family's efforts to avoid a food. The benefits of negative allergy testing/OFC are reassurance, expansion of the diet, improvement of the child's nutrition and quality of life.

4 Data management and analysis plan

Data will be collected by study personnel and recorded in participant questionnaires for entry into a Microsoft Access database for storage. The data will be cleaned using Microsoft Access pivot tables and exported to STATA version 11.1 (Stata Corp. College Station Texas) for analysis. Raw data will be stored in a specified locked cupboard in the Child Health Allergy Department at Red Cross War Memorial Children's Hospital and only the Principal Investigators and named study staff will have access to it. Each participant will be assigned a unique study number. The Microsoft Access database will only use the study number and not the name or hospital number.

The correlation between study number and respective name will be kept on a separate Microsoft Excel database to which only the study staff will have access. Confidentiality will be maintained at all times in the study and the name, hospital number, address, telephone number, or any other direct personal identifiers will not identify the participant in the study records, except when required by law. The data collected remains the property of the University of Cape Town.

Basic descriptive statistics of the sample will be reported i.e. age, sex and ethnic distributions. For each participant we will also report the history of allergic diseases for the first degree relatives (i.e. parents and siblings).

4.1 Objective 1

We will report the number of participants for particular SPT category (i.e. ≥1mm, ≥3mm and ≥7mm) as a proportion of the study sample for each of the foods tested.

4.2 Objective 2

For the participants who undergo OFCs, we will report the number of those who are positive for the food tested as a proportion of the study sample.

4.3 Objective 3

In order to examine the association between particular predictor variables and the Ig-E mediated FA/FS outcomes, we will examine the patterns of sensitisation by ethnicity, age, sex and concomitant allergy using Pearson chi-square tests and Z-test for proportions, Kruskal Wallis and Wilcoxon rank-sum tests to compare medians for numerical variables. We will also report the number of participants with self-reported food allergies, self-reported concomitant allergy and clinical confirmed concomitant allergy as a proportion of those with any sensitisation (SPT≥1mm > the negative control).

5 Ethical considerations

5.1 Consent

All parents/legal guardians will be required to give consent prior to entering the study. Consent will be taken in the caregiver's language of choice and the consent forms will be available in English, Xhosa and Afrikaans. Consent will cover all aspects of the study, including taking a dietary and allergy history, performing SPTs, performing the food challenges if indicated, and for data collection and reporting. We will also take consent for the taking of blood, stool and house dust samples from participant parents where these tests are indicated for further research.

The consenting process will consist of a detailed verbal description of the study as well as a written consent form and information sheet. If required, a trained translator will assist with the interpretation. Consent forms will be in triplicate, with one copy for the family, one for the study personnel, and one for the study folder.

5.2 The primary ethical issues in this study

5.2.1 Risks related to skin prick tests

A SPT can cause sensitisation and also acute allergic reactions theoretically, including anaphylaxis but both are extremely rare. In a recent Swedish study that reviewed findings from a sample of 5908 children <18 years undergoing SPTs found that 0.0024% had a reaction and 0.12% had a generalised reaction mostly involving the skin only. Children <1 year and those with eczema were more likely to have a reaction whereas older children mainly had vasovagal reactions. There were no severe anaphylactic reactions and only 2 of the 14 participants who had a reaction required adrenaline but no further treatment (28).

Experience at the RCHPAC reflects the Swedish study experience where the most common reactions are itching and burning at the test site which is easily treated with antihistamines. These reactions are short lasting and can be relieved with oral antihistamine and topical cold compress (Levin M 2013, Paediatric Allergy Clinic report, November 28).

5.2.2 Risks related to oral food challenges

When introducing increasing amounts of allergen there is potential of allergic reactions of varying severity. Most allergic reactions during food challenges are mild and respond promptly to appropriate medical therapy e.g. short acting antihistamines. The more severe reactions (including lower respiratory and cardiovascular reactions) will require treatment with intramuscular adrenaline (29).

A large retrospective review showed that 28% of children had a severe reaction. These however, were all respiratory with no cardiovascular or anaphylactic reactions, and all responded to antihistamines, adrenaline, β-agonists and corticosteroids with no need for hospitalisation (29). The RCHPAC having performed over 120 OFCs in the last 2 years has had no severe reactions including anaphylaxis, and no one required adrenaline or hospitalisation (Levin M 2013, Paediatric Allergy Clinic report, November 28).

To minimise risk of morbidity associated with food challenges, they will be performed under medical supervision in a hospital setting with resuscitation facilities, and according to a standardised protocol with slowly increasing doses and adequate intervals between doses.

5.2.3 Risks related to venipuncture

As venipuncture may be painful, a local anaesthetic cream will be used prior to drawing blood. In order to minimise the risk of infection all standard sterile procedures will be followed.

6 No fault insurance

The participants in this study are covered by the no-fault insurance offered by the University of Cape Town. The participants' parents or guardians will be informed of this during the consenting process and it is specified in writing on the information sheets.

7 Funding

The bulk of the funding for the study is being obtained by the Principal Investigator mainly from grants.

8 Dissemination of study findings

Given the objectives of the research, the findings will robustly assess the FS rates and the prevalence of challenge-proven Ig-E mediated FA in the Cape Town sample. These findings will be used to inform the larger study involving a cohort of children from the Cape Town Metropolis and Bulungula area in the Eastern Cape.

The immediate beneficiaries of the information are the participants and the family members of the participants. Findings will be disseminated in the form of a preliminary report, seminars in the School of Public Health, UCT and presentations at appropriate meetings and conferences. An article will be submitted to a public health/paediatric allergy/clinical immunology peer-reviewed journal.

9 Logistics

Provisional enquiries have indicated that there are on average 10 children aged 12-36 months per crèche. We aim to visit 1-2 crèches per week (averaging 10 participants per week) and depending on the response rate (assumed to be at 60-80%) the data collection for the study is likely to be completed within 9 months (February 2013-October 2013). This time frame takes into consideration factors like delayed responses from the crèches and slow recruitment rates amongst other challenges that could be encountered as the study progresses.

An outline of the proposed study time is given below:

February 2013-October 2013 Data collection

November 2013-December 2013 Data capturing and cleaning

January 2014 Data validation and Baseline data exploration

February 2014-March 2014 Final analysis, preparation of manuscript

April 2014 Submission

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RESEARCH PROTOCOL LENGTH: 15 PAGES/4003 WORDS

PART B

LITERATURE REVIEW

2. Literature Review

1. Introduction

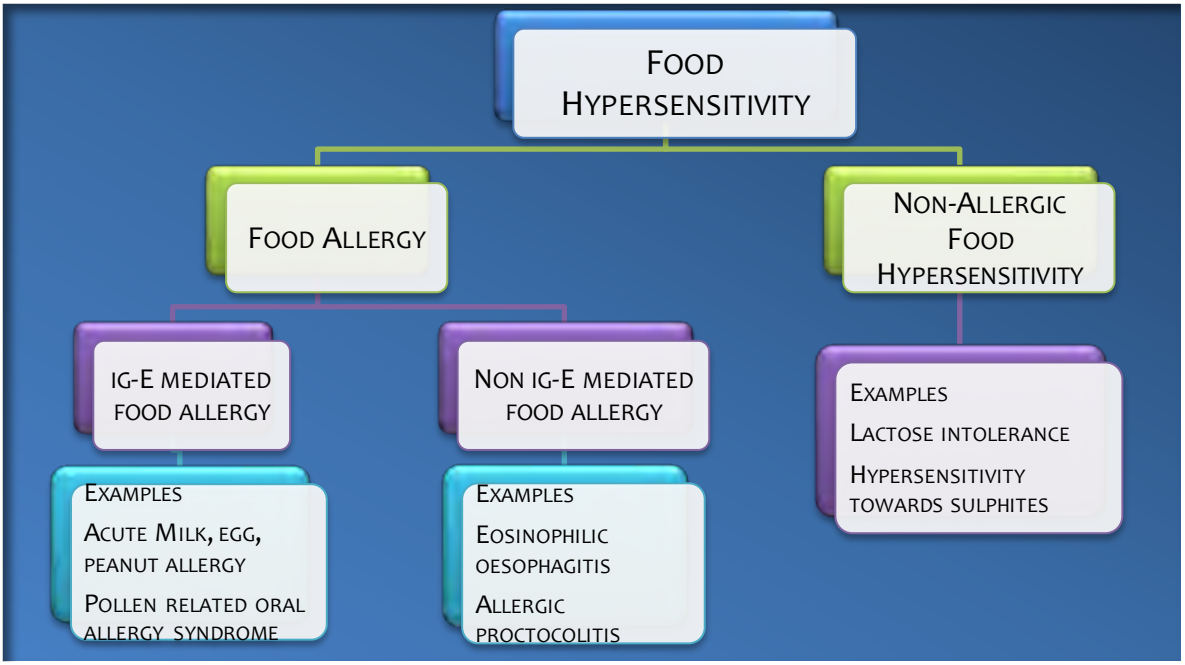
1.1 Definition of food allergy and food sensitisation

The term food allergy (FA) is used to describe adverse reactions to foods mediated by the immune system, and non-allergic food hypersensitivity to describe those not immune mediated. Food hypersensitivity (FHS) represents the umbrella term for both reaction patterns (1,2). FA is specifically defined as an adverse immune reaction arising from a specific response that occurs reproducibly on exposure to a particular food (3). The individuals with such allergies are therefore at risk of developing life-threatening Ig-E mediated systemic reactions upon ingestion of the particular allergen (4).

Food sensitisation (FS) is the production of a particular type of allergic antibody (Ig-E) to a particular food by the immune system resulting in a positive allergy test (Skin Prick Test (SPT) or immunoCAP). It is possible for a person to be sensitised without experiencing an adverse reaction upon food ingestion (3).

Figure 2.1: Terms used for adverse food reactions and examples

Adapted from Johansson et al (2).



1.2 Clinical signs and symptoms of food allergy

The symptoms of Ig-E mediated FA vary, ranging from mild discomfort to life threatening reactions that require immediate medical attention. Symptoms may involve many body systems but usually they are localised in the GIT, the skin/mucous membranes, the respiratory tract and/or the cardiovascular system. Adverse food reactions may occur within a few minutes to an hour after ingestion and can last for days to even weeks (5).

1.3 Consequences of having food allergies

Those found to have lg-E mediated FA have their quality of life altered in a negative way. The sufferers and the family have to deal with the disbelief concerning their condition and face the challenges of managing their day to day lives. Food avoidance is challenging and subjects may need to alter their habits, limit their activities and organise special diets during social events, communal activities and during hospitalisation. There is a risk of severe reactions and patients often experience increased anxiety leading to social isolation and possible mental health problems (6,7).

2. Background

2.1 Common allergenic foods

There has been a steady increase over the past decades in the understanding of FA, but epidemiological knowledge about causes and determinants is still limited (8). At global level, the foods commonly associated with Ig-E mediated reactions in children <5 years are milk, egg, peanuts and seafood even though there are regional variations in their frequency (9).

Table 2.1: Reported allergenic foods in various geographical regions

Adapted from Boye (10) and Prescott et al. (9).

GEOGRAPHICAL REGION	COUNTRIES	ALLERGENS REPORTED IN THE UNDER 5 YEARS POPULATION	REFERENCE
Asia	China, Hong Kong, Korea, Japan, Singapore, Thailand, Philippines, Taiwan, Indonesia and Malaysia	Shellfish, egg, peanut, beef, cow's milk, fruit, treenuts, soy, shrimp, wheat, fish, rice, crab, sesame, pork, seafood, peach, crustacean, prawn and buckwheat.	(11-18)
Middle East	Saudi Arabia, Israel, Lebanon, Iran	Peanut, egg, cow's milk, wheat, banana, fish and sesame.	(19,20)
Africa	South Africa	Peanut, egg and cow's milk	(21)
Oceania	Australia	Dairy, egg, peanuts, cashew nut, tree nuts, cow's milk, fish, seafood and mango/lemon drink.	(22,23)
North America	Canada and USA	Seafood, nuts, tree nuts, strawberry, wheat, soy, cow's milk, shellfish and peanuts.	(24-26)
Central & South America	Mexico, Colombia and Brazil	Dairy, egg, fish, shrimp, beans, soy, milk, seafood, orange, chilli, beans, mango, cacao, corn, vegetables, wheat, and shellfish	(27-29)
Nordic Countries	Denmark, Norway, Iceland, Sweden and Finland	Egg, cow's milk, peanut, fruits, vegetables, fish, nuts, cereals, wheat, soy and tree nuts,	(30-35)
Western Europe	UK, Germany, Switzerland, Greece, Poland, France, Spain	Egg, cow's milk, peanut, tree nuts, fish, wheat, soy, hazelnut, potato, fruits, meats and legumes	(35-38)
Central Europe	Turkey, Lithuania and Slovenia	Cow's milk, egg, wheat, beef and peanut	(35,39)

2.2 Global food allergy prevalence

There appears to be a gradual increase in the prevalence of allergic diseases globally in both developed and developing countries with 30-40% being affected by one or more allergic diseases. Of those affected by allergic diseases, almost 10% are estimated to be food allergic. In Europe, about 11 -26 million people suffer from FA (40). When projecting this estimate onto the world population of 6.6 billion, it translates to 220-250 million people suffering from FA (41). Besides the increasing incidence, the severity and complexity of FA is also increasing (Figure 2.2) (42).

FIGURE 2.2: Country specific cases of fatal food induced anaphylaxis (42)

The use of extrapolation to determine FA prevalence poses challenges because self-reported symptoms of food reactions are far more perceived (20–30%) than proven (2–8%) (33,43). A meta-analysis by Rona et al found self-reported FA to range between 3% and 35% for any food. When the studies were analysed under sensitisation and clinical symptoms, and food challenge categories, the prevalence was lower at 2-5% and 1-10.8% respectively, showing that self-reported reactions are not true FA (44).

It is difficult to estimate worldwide prevalence because of deficiency in data at regional/country level. Factors making comparison of existing regional/country data difficult include:

- Selection bias: studies either include selected or unselected populations.
- Differential attrition levels across studies: low participation/response rates.
- Frequency of evaluations: allergy may resolve or develop in-between.
- Inconsistent definitions of FA: self-reported symptoms, sensitisation, sensitisation with a positive history, sensitisation with a convincing history or food challenge proven (and different types of challenges).
- Data analysis: handling of missing data and no sensitivity analysis.
- Foods targeted have different natural history.
- FA severity: whether to include the responses (mild, moderate or severe).
- Study design and size: costs and accuracy (45).

Despite these methodological/measurement challenges the prevalence in children and adults varies between 4-6% and 1-3% respectively showing a greater burden in children (36,46).

3. Literature search strategy

This review focuses on the prevalence of Ig-E mediated FA or FS in different regions worldwide and the potential risk factors. To identify the relevant manuscripts to be included, Pubmed, Scopus (Embase), Ebsco Host and Google Scholar searches were undertaken for studies conducted since 1993.

The keywords used included “prevalence or incidence”, “epidemiology”, “food allergy” or “food sensitisation” or “food hypersensitivity”, “infants” and “children”, “skin prick tests” and “oral food challenges” and “risk factors” or “predictors”.

After screening with the keywords and the abstract or the text, the article was examined to determine inclusion into the literature review. Included articles were published between the years 1993 and 2014. The reference lists of these articles were also reviewed for additional studies.

For global prevalence data the following inclusion criteria was used:

- Large population based studies in unselected children populations.
- Ig-E mediated FA/FS prevalence rates based on the report of either self-reports/expert screening + evidence of confirmatory tests – sensitisation i.e. specific food Ig-E/SPT, clinical symptoms + oral food challenge (OFC) or double blind placebo-controlled food challenges (DBPCFC).

Because of paucity of high quality data in unselected populations in Sub-Saharan Africa, criteria were relaxed to include selected and unselected populations of any size that had confirmatory tests. For the risk factors general associations that have been observed in literature were reported.

4. Prevalence in the developed countries

The prevalence of challenge-proven FA in developed countries is estimated to affect from 1-2% to 10% of the population, with cumulative incidences of 3-6% (45,47,48). There appears to be evidence for FA escalation in these countries such as an almost four-fold increase in peanut allergy over the past decade in USA children (49) with similar rates being observed also in UK and Australian children (50-52). However, stabilisation in prevalence rates like the plateauing peanut sensitisation and reported allergy in the Isle of Wight (UK) have also been reported from these regions (53).

4.1 United States of America

It is believed that 3.5-4% of the population has Ig-E mediated FA (54). In 2005–2006, the National Health and Nutrition Examination Survey (NHNES) reported the overall prevalence of clinical FA to be 2.5% based on specific serum Ig-E levels (sIgE) with the highest prevalence of 4.2% being observed in those 1-5 years (55). A survey in 2007 reported that 3.9% of those less than 18 years were food allergic based on food sIgE levels (56).

Table 2.2: Summary of food allergy prevalence from population-based studies

Adapted from Prescott et al. (9) and Kung (57).

LOCATION (PUBLICATION YEAR)	STUDY SIZE	METHODOLOGY	AGE OF PARTICIPANTS	OVERALL (%)	REFERENCE
USA (2010)	8203	food specific serum Ig-E	children and adults	2.50 3.9 in children	(55)
USA (2011)	38480	convincing (symptoms based) /confirmed (SPT/sIgE/OFC)	0-17 years	8 0-2 years: 6.3 3-5 years: 9.2	(24)
Europe (2007)	Meta-analysis (51 studies)	multiple	Infants and adults	1-10.8	(44)
Europe (2014)	Meta-analysis (30 studies)	multiple	Infants and adults	SPT: 2.7 proven: 0.9	(58)
UK (1994)	7500 households	self-report & DBPCFC	Infants and adults	self-report: 20.4 proven: 1.4-1.8 6-8 children	(43)
UK (2006 & 2008)	969	OFC	1 and 2 years	2.8 & 2.5	(36,59)
Denmark (2009)	562	OFC	<5 years	1.2-3.6	(30)
Sweden (2001)	273	SPT & sIgE	2 years	7	(60)
Sweden (2008)	2563	sIgE	4 years	15	(34)
Norway (2009)	512	SPT & DBPCFC	0-2 years	6.8	(61)
Norway (2012)	353	SPT & sIgE	2 yeas	18.7	(62)
Iceland (2011)	1341	SPT & DBPCFC	0-1 years	2	(31)
Australia (1997)	620	OFC	2 years	1.18	(63)
Australia (2011)	2848	Food challenges	1 year	10	(23)
China (2011)	497	Food challenges	0-1 year	3.8	(11)
China (2012)	1604	Food challenges	0-2 years	5.5-7.3	(64)
Taiwan (2012)	30018	self-report & SPT/IgE	children and adults	<3 years: 3.44	(13)
Thailand (2012)	546	SPT & Food Challenges	2-7 years	1	(12)
Thailand (2005)	656	SPT & Food Challenges	6 months - 6 years	0.45	(65)

.....continued

.....continued

LOCATION (PUBLICATION YEAR)	STUDY SIZE	METHODOLOGY	AGE OF PARTICIPANTS	OVERALL (%)	REFERENCE
Israel (2002)	9070	food serum IgE + clinical symptoms	0-2 years	1.2	(19)
Zimbabwe (2003)	14000 & 50 for Sub-study	expert screening & SPT & ImmunoCAP	1-63 years	10	(66,67)
Ghana (2010)	1431	self-report & SPT	5-16 years	5	(68)
Botswana (2009)	55	history & SPT	Children and Adults	14.5	(69)
South Africa Cape Town (2008)	220	SPT	Teenagers	5.4	(70)
South Africa Pretoria (2007)	100	SPT	2months - 20 years	9/7	(71)
South Africa Bloemfontein (2002)	771	sIgE	3 months - 15 years	24.4/9.5	(72)
South Africa Cape Town (2008)	400	SPT & sIgE	children	13	(73)
South Africa Johannesburg (1997)	468	SPT	1 month - 18 years	30.4/18.2	(74)
South Africa (2009)	161	sIgE	12 - 24 months	47/28.4	(75)
South Africa Cape Town (2012)	100	multiple	children	42	(21)

4.2 Europe

In a review by Nwaru et al, the overall pooled point prevalence (higher in children than adults) and the lifetime prevalence (similar in children and adults) of self-reported FA were 5.9% (95% CI: 5.7–6.1) and 17.3% (95% CI: 17.0–17.6) respectively. The point prevalence of sensitisation (higher in children than adults) to ≥1 food as assessed by sIgE levels and SPT was 10.1% (95% CI: 9.4–10.8) and 2.7% (95% CI: 2.4–3.0) respectively. OFC/DBPCFC positivity (similar in children and adults) was 0.9% (95% CI: 0.8–1.1).The incidence of FA appears to be consistent over time, however there is evidence suggesting that the prevalence may be increasing (53,58).

4.3 Australia

A cohort study by Hill et al reviewed FA development in 620 infants at risk of developing atopic disease and extrapolated to a random community population. At 2 years follow-up the overall prevalence of challenge-proven allergy was 1.2%. Particular food specific sensitisation rates were; 3.2% egg, 2.0% cow's milk, 1.9% peanut, 0.2% wheat, 0.1% soya, 0.2% hazelnut and 0.1% fish (63).

The Australian HealthNuts Study (AHNS) assessed the prevalence of common Ig-E mediated FA in 2848 infants aged 12-months and overall, over 10% of the infants had challenge-proven IgE-mediated FA to one of the common allergenic foods of infancy. High levels of sensitisation to peanuts 8.9%, raw egg white 16.5%, cow's milk 5.6%, sesame 2.5% and shellfish 0.9% were reported. Challenge proven allergy prevalence was 3.0% (95% CI: 2.4-3.8) for peanut, 8.9% (95% CI: 7.8-10) for raw egg and 0.8% (95% CI: 0.5-1.1) for sesame (23).

5. Prevalence in developing and emerging economies

In many developing countries and emerging economies (like China, India and Brazil) there continues to be little epidemiological data on FA and FS. Currently it is assumed that the prevalence rates are low but this raises uncertainties about the potential health impacts should these assumptions not be supported by evidence (10).

5.1 China

In Chongqing, mainland China, an unselected population of 497 infants <12 months reported 11.3% of the participants as sensitised to one of the 10 foods tested. The overall prevalence of challenge-proven FA was 3.8% with 2.5% having egg allergy and 1.3% cow's milk allergy (11).

An unselected population of 1604 infants in Chongqing, Zhuhai and Hangzhou aged between 0-2 years reported the prevalence of challenge-proven FA from the three cities to be 7.3%, 5.8% and 5.5% respectively (64).

5.2 Taiwan and Thailand

A Taiwanese survey on 30018 participants estimated the overall self-reported and expert-screened (convincing history ± SPT/IgE/OFC) FA prevalence to be 7.0% and 3.4% in children <3 years (13). A prevalence rate of 6.3% based on self-reported FA and a challenge-proven rate of 0.5% were observed in a Thai survey involving 656 children (3 months-6 years) in Bangkok (65).

5.3 Israel

An unselected population of 9070 Israeli infants aged 0-2 years showed a 1.2% prevalence of clinically relevant IgE mediated FA. 61.5% infants were allergic to 1 food, 27% to 2 foods, and 11.5% to ≥ 3 foods (19).

5.4 Food allergy in Africa

Africa is characterised by a scarcity in epidemiological data for FA in the paediatric population. It is debatable or whether this is due to lack of research or the prevalence of FAs is really low (76). The accepted notion is that FA disorders are not a major public health issue, however, there is increasing acknowledgement that the prevalence of FA is on the increase (77).

5.4.1 Zimbabwe

In Harare, the 5 year (1997-2002) period prevalence of FA was 10% in a cohort of 14 000 patients of all ages referred to the specialist allergy clinic (67). A sub-study on this cohort on 50 allergic patients showed FS rates based on specific Ig-E antibodies to be 24%, 24%, 22%, 22%, 18% for apple, tomato, soy, crab and peanut respectively (66).

5.4.2 Ghana

In a questionnaire based survey of 1431 school children (5-16 years), 11% reported adverse food reactions. Overall, 5% had a positive SPT with FS rates of 2% each for peanuts and pineapple. 0.8% had a history of an adverse food reaction and a positive SPT (68).

5.4.3 Botswana

In Gaborone, atopic patients (3 months-51 years) with a suggestive allergic history or moderate to severe AD were screened by clinicians for FA and had SPTs performed. Overall, 14.5% were sensitised and the FS rates were; 9% egg, 8% peanut and 1.6% cow's milk. The patients with FA were children aged 11 months–8 years, with AD and their positive tests for egg and milk were above the 95 % PPVs for sIgE (69).

5.4.4 South Africa

The largest body of literature on FA in Africa comes from South Africa. Most studies are from selected populations and one is from an unselected population. In an unselected Cape Town sample of 212 Xhosa high school students, 5.4% had positive SPTs. The common allergens were; egg 3.3%, peanut 1.9% and milk 1.9%, however all participants tolerated the foods (70). A case-control study in Pretoria checking for co-morbid conditions in 100 asthmatic children showed the following FS rates; 9% peanut, 7% egg, 4% wheat, 4% fish and 3% milk (71).

In Bloemfontein, Mercer et al assessed 771 patients (3 months-15 years) with hayfever for sensitisation by performing SPT and sIgE to certain foods. In 275 children, sensitisation by SPT was mainly towards milk 30.6%, wheat 30.6% and fish 26.2%. sIgE (ImmunoCAP) on 761 patients showed positivity to wheat 24.4%, milk 9.9% and fish 5.9% (72).

Another Cape Town study recruited 400 allergic children and reported an overall sensitisation rate using immunoCAP to be 13% with most sensitisation occurring in eczematous children. The implicated foods were; peanut 35%, egg white 30%, milk 17%, fish 4%, tree nuts 3% and potato 3% (73).

In Johannesburg, 468 Caucasian asthmatics were evaluated and had SPT performed on 12% of the patients >4 years. The levels of sensitisation were; 30.4% wheat, 18.2% peanut, 15.1% fish, 12.7% soy, 6.9% egg and 5.4% milk (74).

A heterogeneous group of 161 South African infants with AD aged 12-24 months were analysed as a part of the multi-centre Early Prevention of Asthma in Atopic Children (EPAAC^{TM}). The sensitisation pattern using immunoCAP showed slightly higher levels of sensitisation in South African estimates compared to the global estimates; 47.1% vs 41.9% egg, 28.4% vs 27.4 cow's milk and 26.8% vs 24.4% peanut respectively (75).

Recent findings from a study involving children with AD at the Red Cross War Memorial Children's Hospital (RCWMCH) showed relatively high FS and challenge-proven Ig-E mediated FA rates in the mixed race and black African participants. Overall, 66% were sensitised, 42% had confirmed allergies to at least one of the foods and 12% had multiple FAs. Amongst the black African participants, 17% were challenge positive for peanut allergy (21).

6. Risk factors for food allergy

The natural course of FA is a dynamic process that is different with each food allergen. The reason why some individuals are allergic to particular foods while others are not is unknown. But like other diseases the development of FA is multifactorial and can be caused by one or a clustering of the following risk factors: genetic susceptibility, environmental, or nutritional factors (5). Numerous prenatal and postnatal factors fall under these overarching themes (Figure 2.3).

The focus for possible interventions includes prenatal and postnatal environmental influences (78) and there is belief that environmental factors are the main drivers of the increasing FA prevalence globally (79).

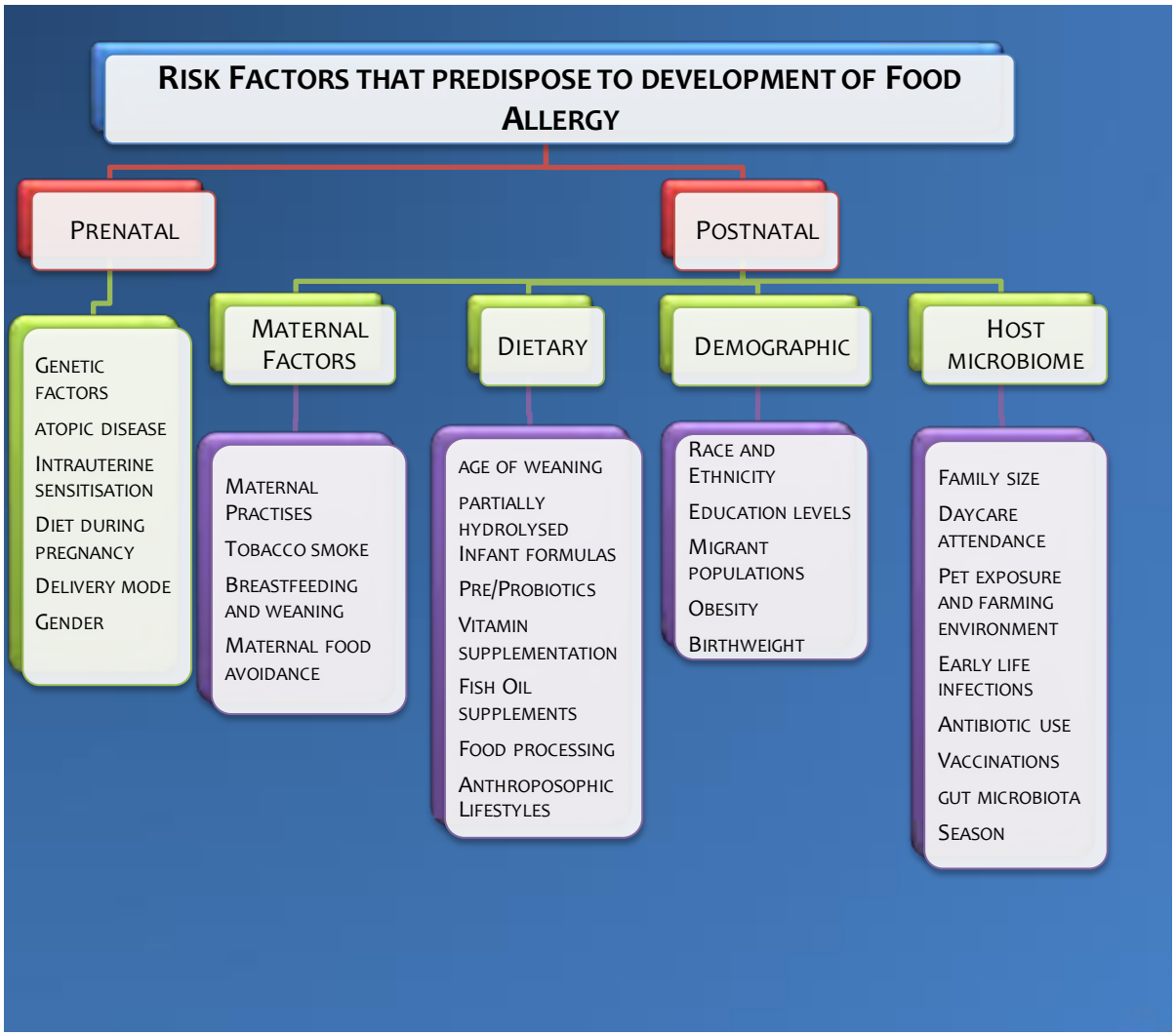
6.1 Prenatal factors

6.1.1 Family allergic disposition

Generally, the presence of concomitant allergy or allergic sensitisation in the individuals, the parents or the siblings is believed to be strongly associated with the risk of developing FA (78,80,81).

FIGURE 2.3: Risk factors for food allergy.

Adapted from Hidalgo-Castro et al. (82) and Ezendam et al. (83).



6.1.2 Age and Sex

It is believed that children <3 years have the lifetime peak prevalence of FA (21) with most sensitisation/allergy happening in the first year of life (84,85). Amongst children, being male is believed to be associated with an increased FA risk (80,86), however other studies reported no association (87).

6.1.3 Delivery Mode

It is hypothesised that caesarean delivered infants are not exposed to commensal vaginal microflora leading to gut colonisation by bacteria that further skew the T-helper 2 immune response increasing FA risk (88). Studies suggesting an increased FA risk (89,90) in caesarean delivered infants and no such association (91) have been reported.

6.2 Postnatal factors

6.2.1 Maternal practices

In a Swedish study, children whose parents cleaned pacifiers by sucking them were less likely to have asthma, eczema and FS (OR: 0.37) at 18 months than children whose parents did not (92). A Germany study reported an increased risk (OR: 2.3) of sensitisation in infants whose mothers smoked up to the end of pregnancy and continued after birth compared to infants whose parents did not (93).

6.2.2 Breastfeeding

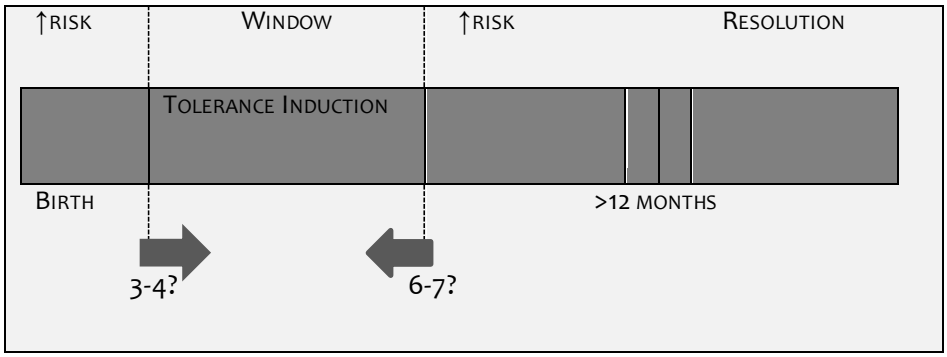
Breastfeeding exclusively and delaying solid food introduction for the first 4 months of life have been reported to decrease FA risk (94,95). However, there are reports of no difference in FS rates between children exclusively breastfed for at least 4 months and those formula-fed (96).

6.2.3 Timing of complementary feeding

Previously, feeding guidelines for prevention of FA recommended the delay of solid foods, however the manipulation of the diet during pregnancy and early infancy remains highly controversial (97,98). It has more recently been proposed that there is a window of opportunity in timing of oral food exposure to induce tolerance (Figure 2.4) (99,100). The type (form or processing) of food first introduced may also be of importance.

The studies of good quality found no benefit of delaying the introduction of solid foods for longer than 4 months in high risk populations (101) and in normal risk populations (102). Decrease in FA risk was actually observed in an unselected cohort that introduced solids earlier than 4 months (103).

Figure 2.4: Possible window of tolerance for introduction of complementary foods (99).



6.2.4 Maternal and infant food avoidance

There is increasing global acceptance that introducing food during the critical window of immune tolerance development, could possibly prevent allergy development (104,105). A trial reported a higher prevalence of atopy at 8 years in the mothers who avoided particular foods in the first 9-months of life while breastfeeding compared to mothers who did not (106). There are numerous studies underway assessing earlier introduction of solids as an intervention measure against FA like EAT (107) and LEAP (108).

6.3 Dietary factors

6.3.1 Anthroposophic lifestyles

The keys features of this lifestyle are the restricted use of antibiotics, antipyretics, vaccinations and strict dietary habits (109). In a Swedish study, the FS rates based on sIgE levels was lower (9%) in children from anthroposophic families compared to children from other families (16%) (110).

6.3.2 Pro/Prebiotics

The addition of pre/probiotics to infant formulas is intended to modify the infants gut microbiota thereby reducing the risk of developing allergies. Probiotic research data currently is relatively inconclusive with the same formula showing different effects in different countries. Prebiotic data is mainly limited to company sponsored studies. The studies that have looked at infant pre/probiotic supplementation have either yielded insufficient evidence or found no evidence of benefit (111-115).

6.3.3 Vitamin levels

Specific vitamins have been shown to skew influence of T-cells towards the helper sub-classes implying that vitamins may be involved in modulating allergic reactions (116). A German study by Weisse et al measuring Vitamin D levels in maternal and cord blood found a positive correlation with the infants' risk of FA within the first 2 years of life (117). Contrary findings have also been observed, a cohort study found possible protective effects of taking vitamins before the age of 5 years (118).

6.3.4 Partially hydrolysed infant formulas

When breastfeeding fails or is insufficient, breast milk is replaced by modified cow milk formulas. Certain partially and extensively hydrolysed formulas have been shown to be effective in the prevention of allergic diseases in high risk individuals (83,119). In the German Infant Nutritional Intervention study (GINI) and its follow-up at 6 years, the hydrolysed formulas had significant lower incidences of allergic disease compared to cow milk formula. The estimates were; extensively hydrolysed whey-based (OR: 0.86 & 0.90), partially hydrolysed whey-based (OR: 0.65 & 0.82) and extensively hydrolysed casein based (OR: 0.51 & 0.80) respectively (120,121).

6.3.5 Fish oil supplements

Increasing n-6 polyunsaturated fatty acid (PUFA) intake (implying reduced n-3 fatty acids consumption) may be one of the triggering factors for the increasing sensitisation to food allergens (122). A systematic review looking at n-3 PUFA supplementation during pregnancy/lactation found significant protective effects against egg sensitisation at 12 months (OR:0.33).(123). Conversely, findings of no benefit from fish oil supplementation have also been reported (124).

6.4 Demographic factors

6.4.1 Race and ethnicity

Findings seem to suggest that race influences sensitisation and/or FA rates. Black children were more likely to be sensitised to foods (OR: 2.34) and were sensitised to more foods (OR: 3.76) compared to Hispanics based on self-identified race (125). Studies have also shown higher FS rates in black participants and it is suggested that there could be a gene or other environmental factors making black children more sensitised or sensitisation is just more prevalent in the ethnic group (126,127).

6.4.2 Socio-economic factors

A higher socio-economic status (SES) and living in affluent societies are believed to increase FA risk. A survey in USA showed significantly decreased odds of FA in those of a lower SES (<$50000 vs ≥$50000: OR: 0.5) (24) Contrary findings of a higher SES being protective (OR: 0.65) against sensitisation have also been reported (128).

Another survey in USA reported that children in families that had someone with > high school education were more likely (OR: 1.27) to have FA as reported by a health professional compared to those with < high school education (129).

6.4.3 Migrant populations

Rapid urbanisation, the adoption of westernised lifestyles and the nutritional transition are believed to be associated with increased FA rates. The Cape Town, South Africa population grew by 1.4% in the past decade and the majority of immigration occurred from rural Black Africans from the Eastern Cape settling in urban informal settlements (130). This population is exposed to a low socio-economic environment that may contain many of the factors that affect foetal programming and skew subjects towards allergy, including a high prevalence of cigarette smoke exposure, changes in viral, bacterial and parasitic exposures, changes in allergen and pollutant profiles and dietary modifications. These changes in the environment may affect gene expression with the loss of protective factors and acquisition of risk factors leading to manifestation of allergies (21).

6.4.4 Childhood obesity

Obesity may be a contributor to the increasing prevalence of FA in children. Systemic inflammation might play a role in the development of allergic disease (131). In the USA NHANES of 2005-2006, significantly increased rates of FS were observed in obese children compared to normal weight children (aOR: 1.59) (132).

6.5 Host microbiome

6.5.1 Family size and day-care attendance

With increasing household size/day-care attendance it is believed that the rates of FA decrease because of high exposure to infections. When screened for peanut, sesame and egg allergy, infants in the AHNS demonstrated a significant 30% reduction in challenge-proven FA associated with having siblings (133).

Similarly, significantly reduced likelihoods of challenge-proven egg, sesame and peanut allergy were observed amongst children attending childcare in the first 6 months of life (aOR:0.5) when compared with those cared for at home (133).

6.5.2 Pet exposure and farming environment

High microbial exposure from pet ownership or a farming environment, either through contact with farm animals or consumption of unpasteurised milk, promotes the development of the non-allergic phenotype (134) The AHNS demonstrated a significantly reduced risk of challenge-proven egg, sesame and peanut allergy amongst infants living with a dog during the first year of life (aOR:0.6) (133).

6.5.3 Early life infections and antibiotic use

Infections in early life are thought to reduce FA risk later in life while on the other hand taking antibiotics increases FA risk via increased risk of eczema (135,136). German adults who self-reported infection with any disease in childhood had a significantly reduced risk of sensitisation (aOR: 0.8) compared to those who did not report (137). Conversely, a systematic review on antibiotic use in the first year of life and FA risk found no association (79).

6.5.4 Childhood vaccinations

It is speculated that vaccinations increase FA risk either because of modulation of the immune system or because certain immunisations contain proteins such as gelatin, casein (milk), eggs and yeast (138,139). In a survey of school children, parent-reported rubella infection amongst unvaccinated children appeared to be protective against FA (aOR: 0.2) (140). However, a systematic review found no protective benefit of the BCG vaccination against FA (141).

6.5.5 Gut microbiota

The infantile gut flora shapes the immune response and is perceived to influence allergic outcomes (142,143). Differences in the gut microbial composition between infants who later developed or those who did not develop allergy were demonstrable before any clinical manifestations of atopy in the first 2 years of life in the Estonian and Swedish cohorts (143).

6.5.6 Season

Studies suggest that FA is more common in infants born in winter or autumn. The cause could be the UV-B exposure and subsequent lower vitamin-D levels during critical periods of immune development. In Boston, increased odds (1.53) of FA in children <5 years born in the winter were reported (15,144,145).

7 Gaps in knowledge

FA has grown to be an important public health problem in western countries affecting millions of people. The challenges of an increasing FA prevalence have led to large epidemiological studies in unselected populations such as EuroPrevall in Europe (146) and the AHNS (147). However, studies undertaken locally have been mostly in selected populations (e.g. eczematous and AD infants) and only one study in unselected black African teenagers.

It was widely accepted that FA is rare in South African children, particularly the black South Africans. This perception is changing since higher than anticipated FS rates are being observed in this ethnic group in studies from selected populations (70). Migrant populations of indigenous black Africans moving to urban areas and assuming westernised diets may be influencing the increase in FA prevalence rates (21). On this premise this study aims to determine the prevalence of FS and challenge-proven Ig-E mediated FA in an un-selected population of children aged 12-36 months in Cape Town. The study is the first phase of the South African FS and FA study (SAFFA) that seeks to examine inter-ethnic differences in sensitisation and challenge-proven allergy in the Cape Town cohort and rural Eastern Cape cohort.

Determining the prevalence in a random urban sample is important towards ascertaining the possible public health burden of Ig-E mediated FAs. Findings may be used to influence advocacy and policy regarding health service provision for both children and their families (6). Subsequent study findings will compare the 95% PPVs for a positive food challenge using SPTs in South Africa compared to international cohorts and will attempt to describe the prevalence of modifiable and non-modifiable risk factors.

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STRUCTURED LITERATURE REVIEW: 4011 WORDS

Part C

JOURNAL READY MANUSCRIPT

CURRENT ALLERGY AND CLINICAL IMMUNOLOGY

A cross-sectional study of Ig-E mediated food allergy and sensitisation in South African children aged 12-36 months.

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Disclosure of conflict of interest: The authors have declared they have no conflict of interest.

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Running Title: Food allergy in South African children.

Word count: 3412

Abstract: 283

Tables: 4

Figures: 2

Abstract

Basera W

A cross-sectional study of Ig-E mediated food sensitisation and food allergy in an unselected population of South African children aged 12-36 months.

Curr Allergy Clin Immunol

Background: The recent increase in food allergy (FA) prevalence (the 'second wave' of allergy epidemic) has been inadequately studied in developing countries. In South Africa, the prevalence of Ig-E mediated FA and food sensitisation (FS) is unknown. The study aimed to determine the point-prevalence of FS and Ig-E mediated FA in an unselected population of South African children of various ethnic backgrounds.

Methodology: A sampling frame was used to randomly select children aged 12-36 months attending crèche in the Cape Town Metropolis. Parents of the children completed a questionnaire and their children underwent skin prick testing to 7 foods, viz cow's milk, egg, fish, hazelnut, peanut, soya and wheat (flour). Those with SPT≥1mm > the negative control and not clearly tolerant (on history) to 1 or more foods underwent oral food challenges (OFCs). Parents who chose not to participate completed a non-participant questionnaire.

Results: Study design was acceptable and feasible in this setting with a good response rate of 66% (141/213), participation rate of 92% (129/141) and completion rate of 94% (121/129) with 213 participants in the sampling frame. The completed participant sample consisted of 39% black African, 20% Caucasian and 41% mixed race participants, with a median age 26 months (IQR 22; 31). The prevalence of SPT≥1mm to any food was 16%, SPT≥3mm 12%, SPT≥7mm 4% and OFC confirmed Ig-E mediated FA was 1.7%. Challenge-proven Ig-E mediated egg allergy prevalence was 1.7% and peanut allergy 0.8%. Black African participants had higher FS rates when compared to Caucasian and mixed race participants but the trends did not reach statistical significance.

Conclusion: This study was acceptable and feasible in this population. The prevalence of FS is high in this sample and there are ethnic differences that require further investigation.

Key Words: Africa, children, cow's milk, egg, food allergy, food sensitisation, Ig-E mediated, Incremental food challenge, peanut, skin prick testing

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Key Messages

- This is the first South African food allergy study in an unselected population.
- The study was acceptable and feasible in this population assumed to be representative of the Cape Town population.
- The prevalence of food sensitisation is high (16%) in a sample of children aged 12-36 months.
- Most sensitisation in decreasing frequency was towards egg, peanut and soya.
- The prevalence of challenge-proven Ig-E mediated food allergy was 1.7% for raw egg and 0.8% for peanut butter.
- Black African participants are more likely to be sensitised and allergic compared to Caucasian and mixed race participants.

Abbreviations

Ig-E : Immunoglobulin E

SPT: Skin Prick Test

OFC: Oral Food Challenge

FA: Food Allergy

FS: Food Sensitisation

The article meets the requirements set out in the Instructions for Authors for the Current Allergy and Clinical Immunology Journal, an extract of these instructions is included in Appendix D of the dissertation. For readability purposes, figures and tables are inserted in the text of the manuscript rather than appended. Instead of the stipulated 3 figures and 3 tables, the manuscript has 4 tables and 2 figures via permission granted by the Editorial Co-ordinator through personal communication (Basera W 2014, personal email, April 11). No co-authors are listed here. The contribution of collaborators and supervisors is listed in the acknowledgements section of the dissertation.

1 Introduction

Epidemiological data on FA is predominantly situated in the developed world (1). Evidence suggests that there may be a 'second wave' of the allergy epidemic with FAs increasing in a similar fashion, albeit a few decades later, to other allergic diseases (allergic rhinitis, eczema and asthma) (2). There is very little data on FS and challenge-proven Ig-E mediated FA in unselected population based studies in the developing world.

The potential increase in FAs impacts at multiple levels, including the food industry, health care professionals and the wellbeing of nations at large. However, prevalence estimates vary widely and studies have a high degree of heterogeneity because of small sample size studies, selection bias, different response rates, differential report of FA, inconsistent FA definitions and variations in data analysis (3).

Many studies base FA on self-reports and few have utilised objective measures to diagnose FA (4-6). This leads to an overestimation of FA with estimates varying from 20-35% (7-9). However, recent findings in children under-five years report the prevalence to be 1-2% to over 10% based on OFC confirmed Ig-E mediated FA (10,11).

In South Africa, research shows an increase in respiratory allergies similar to that in the westernised countries but following it by several years (12). In South Africa there are differences in prevalence of respiratory allergy, eczema and aeroallergen sensitisation according to ethnicity and socio-economic class which may reflect diverse environmental exposures, genetic influences or epigenetic phenomena (13). Studies performed in Africa have reported FS rates or allergies based on questionnaire surveys mostly in selected populations (14,15). There is no data on the point-prevalence of FS and challenge-proven Ig-E mediated FA in unselected African populations.

It is believed that FA is rare in South Africa especially in the black African population however, the rise in respiratory allergy in rural and the black African population thought to be associated with changes in living environment (urbanisation) may precede a similar increase in FS and Ig-E mediated FA. There is therefore a need to determine prevalence, particularly at the age that FAs are likely to peak and compare the local FA burden to global estimates using similar objective measures (16).

The aim of the study was to determine the prevalence of FS and challenge-proven Ig-E mediated FA in an unselected sample of 12-36 months children in Cape Town, South Africa. This study is the first phase of the broader SAFFA (South African FS and FA) study which aims to increase understanding on the prevalence, the possible risk factors and diagnosis of common Ig-E mediated FAs in the local context.

2 Methodology

2.1 Design and setting

This was a cross-sectional study from February 2013-October 2013 conducted in crèches in the Cape Town Metropolis. Participants were recruited from crèches using an allergy questionnaire and SPTs, and if they qualified, were invited to the Red Cross Hospital Paediatric Allergy Clinic (RCHPAC) for further investigations.

2.2 Population and sampling frame

From an online database of Cape Town registered crèches maintained by the provincial Department of Social Development (DSD) a random sequence of numbers was generated using Microsoft excel and we selected 20 crèches. Once a crèche agreed to participate from this list we approached all eligible children (213 children) between the ages 12-36 months to participate and we stopped (at 8 crèches) once we had achieved the sufficient study numbers after considering all the non-completion.

Selection of participants was based on equal probability of selection method, were eligible children (source population) from different ethnic backgrounds attending crèches in Cape Town had an equal chance of being part of the study population. The study population was therefore a random sample that was assumed to be representative of children who are 12-36 months in the Cape Town urban population.

2.3 Recruitment and assessment

All participants were assessed by the team with an allergy questionnaire and a general physical exam for signs of eczema, hayfever and asthma. Non-participants completed a non-participant questionnaire which had questions on demographics and allergy information to assess for participant selection bias.

2.3.1 Skin prick testing

SPTs were done using standardised solutions from ALK Abelo (Thermo Fisher™) and ALK lancets, to egg white extract, peanut, cow's milk, wheat (flour), soy, hazelnut, fish (cod), positive (10mg/mL histamine) and negative (saline) controls. In addition, modified SPTs for egg, milk and peanut were performed using raw egg white, fresh cow's milk and fresh peanut butter. The skin on the forearm was pricked through a drop of the extract. SPT results were read at 15 minutes and recorded as average wheal diameter size in millimetres.

2.3.2 Indications for oral food challenges

All participants with any sensitisation (SPT≥1mm > the negative control) to the foods tested, but for whom tolerance was not clearly reported on clinical history were eligible for a food challenge unless there was a history of a recent anaphylactic reaction (<6 months for peanut and <2 months for all other allergens) with high SPTs greater than previously published 95% PPVs (>24 months old: milk ≥8mm, egg ≥7mm & peanut ≥8mm and <24 months old milk ≥6mm, egg ≥5mm & peanut ≥4mm) (17).

Participants who recorded any SPT≥1mm > the negative control who were not tolerating the normal age appropriate serving of the food or not yet exposed to that food were invited for an OFC. Those with a SPT≥1mm but were currently tolerating the food with no history of any reaction to that food were not eligible for an OFC.

2.3.3 Oral food challenges

Challenges were performed as open incremental oral challenges at the RCHPAC using a standardised protocol adapted from the Australian HealthNuts study (AHNS). In completing an OFC, the general target dose recommendations are 8-10g protein for dry foods, 16-20g for meats and 100 ml for wet food. OFCs were initiated with 0.1-1% of the total challenge food however the European Academy of Allergy and Clinical Immunology (EAACI) proposes lower initial doses for OFCs to the following common food allergens: peanut 0.1mg, milk 0.1ml, egg 1mg, fish (cod) 5mg, wheat 100mg, soy 1mg, shrimp 5mg and hazelnut 0.1mg.

Following the initial dose, the challenge food was then given in gradually increments every 15 minutes (18,19). The doses and the incremental times for the different challenge foods are documented in Appendix 5. Food challenges were stopped if they met pre-set standardised positive criteria (Appendix 5) (20) and the participant was treated according to protocol. Participants were observed for a minimum of 2 hours after a negative challenge and 2-4 hours after a positive challenge.

After a negative challenge parents were encouraged to include the food in the diet regularly and to report any unforeseen reactions on subsequent consumption. We contacted the participant's family via telephone 48-72 hours after the challenge to enquire about delayed symptoms.

2.4 Definitions of sensitisation and allergy

Any food (Low level) food sensitisation – 1 or more SPT with a wheal size ≥1mm > the negative control.

Moderate level food sensitisation – 1 or more SPT with a wheal size ≥3mm > the negative control.

High level food sensitisation – 1 or more SPT with a wheal size ≥7mm > the negative control.

Ig-E mediated FA – a positive SPT and a positive food challenge or history of anaphylactic reaction with high SPT greater than the previously published 95% PPV.

2.5 Ethics

This study was approved by the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee (reference number: HREC REF: 497/2013) (Appendix 1). Informed consent was obtained from the parent/guardian for participation and food challenges (Appendix 2).

2.6 Data entry and Statistical analysis

The data was entered into a Microsoft Access database by the investigators and cleaned using pivot tables before being exported to STATA version 11.1 (Stata Corp. College Station Texas) for analysis. Statistical tests were done according to whether the variable was continuous or categorical. Since most of our data was categorical the Chi-square test/Fisher's exact and the Z-test were used to test for statistical difference between variables and proportions respectively. A p-value of <0.05 was considered statistically significant.

3 Results

From a total of 213 eligible children the response rate was 66% (141/213). We had a high participation rate of 92% (129/141) and 9% (12/141) completed the non-participant questionnaire. Of those who participated, the completion rate was 94% (121/129) and those that did not complete the SPTs because of time constraints of the caregiver (8/129) were considered as non-participants.

The competed study population consisted of 121 participants with a median age of 26 months (IQR 22; 31 months). The proportion of males, 62/121 (51%; 95% CI: 42-60) and females, 59/121 (49%; 95% CI: 40-58) were similar (p=0.7). There was no significant difference between the participants and the non-participants regarding history of a first-degree relative (i.e. mother, father and siblings) with asthma (28/121 vs. 5/20: p=0.86), hayfever (68/121 vs. 8/20: p=0.18), eczema (32/121 vs. 3/20: p=0.27) and FA (8/121 vs. 1/20: p=0.78).

The study comprised of participants from different parts of Cape Town with varying ethnicity. The proportion of black African participants was 47/121 (39%), mixed race 50/121 (41%) and Caucasian 24/121 (20%). The proportion of Caucasian participants in the study sample was statistically different from the Caucasian 0-4 year old population in the most recent Cape Town census (33) of 2011 (20% vs. 8%: p=<0.0001 respectively). The proportion of black African (39% vs. 46%: p=0.10) and mixed race (41% vs. 45%: p=0.37) participants were not statistically different.

3.1 Food sensitisation prevalence

Nineteen participants were sensitised to one or more foods, and 102 were negative to all foods. Table 3.1 shows the prevalence of FS amongst the participants in categories of degree of sensitisation viz, SPT≥1mm, ≥3mm and ≥7mm. Overall, 16%, 12% and 4% had a SPT≥1mm, ≥3mm and ≥7mm respectively to 1 or more of the 7 foods tested. One participant had a high level of FS with SPT≥7mm to more than 1 food, however they are yet to be challenged to the 4 foods. Of the whole group, 7/121 (6%) were polysensitised with 5/121 (4%) sensitised to 2 foods and 1/121 (1%) sensitised to 3 and 4 foods each. Of those sensitised, 12/19 (63%) were tolerant to the foods on history and 7/19 (37%) underwent OFCs.

3.2 Spectrum of food sensitisation

SPT≥1mm was detectable in decreasing frequency to egg, peanut, soya, wheat, cow's milk, fish and hazelnut. SPT≥3mm was detectable in decreasing frequency to egg, peanut, fresh cow's milk, soya and hazelnut. Only three foods; fresh hen's egg, fresh peanut and hazelnut were detectable at SPT≥7mm in decreasing frequency (Table 3.1).

3.3 Perceived food allergy

The rate of perceived FA was 12% as 14/121 participants reported having had a prior reaction to 1 of the foods. There was no significant difference between the rate of perceived FA in participants and non-participants (14/121 vs. 3/20: p=0.66). 5/121 (4%) participants reported having an itchy rash, diarrhoea and flushing towards cow's milk. 4/121 (3%) and 3/121 (3%) participants reported having predominantly an itchy rash towards fish and egg respectively. Lastly, 1/121 (1%) and 1/121 (1%) participants reported vomiting and diarrhoea towards soya and wheat. No reactions conformed to the World Allergy Organisation definition of anaphylaxis (21). For most of the reported reactions, the participants also reported that a doctor confirmed the diagnosis (10/14, 71%).

Table 3.1: Ig-E mediated food allergy and food sensitisation patterns

FOOD TESTED	*PREVALENCE SENSITISATION SPT*	*PREVALENCE SENSITISATION SPT*	*PREVALENCE SENSITISATION SPT*	*POSITIVE OFC (N)*	*IG-E MEDIATED FOOD ALLERGY PREVALENCE*
	ANY SENSITISATION (≥1 MM) N % 95% CI	≥3MM N % 95% CI	≥7MM N % 95% CI		(%) 95% CI
OVERALL	19 (16) 10-23	15 (12) 7-20	5 (4) 1-9	2	2 0-6
EGG WHITE	13 (11) 6-18	7 (6) 2-12	0	-	
FRESH HEN'S EGG	14 (12) 7-19	12 (10) 5-17	5 (4) 1-9	2	2 0-6
PEANUT	4 (3) 1-8	4 (3) 1-8	1 (1) 0-5	-	
FRESH PEANUT	4 (3) 1-8	4 (3) 1-8	2 (2) 0-6	1	1 0-5
COW'S MILK	1 (1) 0-5	0	0	-	
FRESH COW'S MILK	1 (1) 0-5	1 (1) 0-5	0	0	
SOYA	3 (3) 1-7	1 (1) 0-5	0	0	
WHEAT	2 (2) 0-6	0	0	-	
FISH	1 (1) 0-5	0	0	-	
HAZELNUT	1 (1) 0-5	1 (1) 0-5	1 (1) 0-5	-	

3.4 Prevalence of Ig-E mediated food allergy

All the participants save for one who were sensitised (7/19) and either not tolerant or who never knowingly ingested the food had an OFC. Challenge-proven Ig-E mediated FA to raw egg was present in 2/121 (1.7%; 95% CI: 0.2-5.8) and peanut butter in 1/121 (0.8%; 95% CI: 0.02-4.5) of the participants. Challenge-proven Ig-E mediated FA by sex category was 1.7% (2/121) for males and 0% (0/121) for females. No participants were classified food allergic based on recent severe reactions with SPT greater that previously described 95% PPVs (17).

3.5 Food sensitisation and ethnicity

Black African participants exhibited higher rates of sensitisation compared to mixed race and Caucasian participants. This was shown for low level, medium level and high level sensitisation to any food. Similar higher prevalence in black African participants was shown for sensitisation to egg and peanut. However, these differences in sensitisation between the ethnic groups did not reach statistical significance (Table 3.2). Overall, a higher proportion of black African participants had a cumulative SPT wheal size ≥1mm when compared to other ethnic groups (Figure 3.1). There was no significant difference between the median cumulative SPT sizes of the ethnic groups (Kruskal wallis: p=0.15). Upon analysing for inter-ethnic group differences, there was no difference between Caucasian and mixed race participants (Mann Whitney: p=0.72). Differences between black African vs. Caucasian and mixed race participants were observed but were not statistically significant (Mann Whitney: p=0.27 and 0.07 respectively).

Figure 3.1: Cumulative wheal size distribution by ethnicity

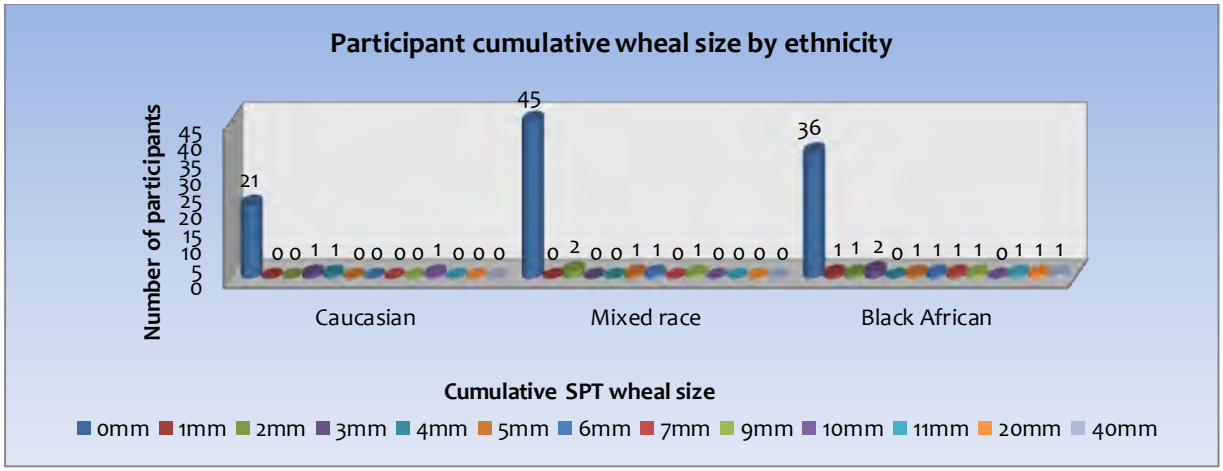


Table 3.2: Sensitisation patterns using SPT categories and ethnicity

ETHNICITY	ANY FOOD N %	EGG N %	FRESH EGG N %	PEANUT N %	FRESH PEANUT N %	COW'S MILK N %	FRESH COW'S MILK N %	SOYA N %	WHEAT N %	FISH N %	HAZELNUT N %
	≥1 MM	≥1 MM	≥1 MM	≥1 MM	≥1 MM	≥1 MM	≥1 MM	≥1 MM	≥1 MM	≥1 MM	≥1 MM
	≥3MM	≥3MM	≥3MM	≥3MM	≥3MM	≥3MM	≥3MM	≥3MM	≥3MM	≥3MM	≥3MM
	≥7MM	≥7MM	≥7MM	≥7MM	≥7MM	≥7MM	≥7MM	≥7MM	≥7MM	≥7MM	≥7MM
BLACK AFRICAN	11 (23)	8 (17)	9 (19)	4 (9)	4 (9)	1 (2)	0	2 (4)	0	0	1 (2)
(47)	9 (19)	4 (9)	8 (17)	4 (9)	4 (9)	0	0	1 (2)	0	0	1 (2)
	3 (6)	0	3 (6)	1 (2)	2 (4)	0	0	0	0	0	1 (2)
MIXED RACE	5 (10)	2 (4)	3 (6)	0	0	0	1 (2)	1 (2)	2 (4)	1 (2)	0
(50)	3 (6)	2 (4)	2 (4)	0	0	0	1 (2)	0	0	0	0
	1 (2)	0	1 (2)	0	0	0	0	0	0	0	0
CAUCASIAN	3 (13)	3 (13)	2 (8)	0	0	0	0	0	0	0	0
(24)	3 (13)	1 (4)	2 (8)	0	0	0	0	0	0	0	0
	1 (4)	0	1 (4)	0	0	0	0	0	0	0	0
DIFFERENCE BETWEEN THE ETHNIC GROUPS BY SPT CATEGORY	PR=0.17[†] 0.15[†] 0.52[§]	0.11[†] 0.61[§] EQUAL	0.11[†] 0.10[§] 0.52[§]								

[†] Difference non-significant by Chi-square

[‡] Difference non-significant by Fischer's exact

3.6 Sex category and prevalence of food sensitisation

A greater proportion of sensitised participants was male (14/62, 23%) than female (5/59, 8.5%) and the difference was statistically significant using the Pearson's Chi-square test (p=0.03).

3.7 Concomitant allergy and prevalence of sensitisation

69/121 (57%) participants self-reported any one or more of the allergic conditions. 18/121 (15%), 44/121 (36%) and 40/121 (33%) reported any asthma, any hayfever and any eczema respectively. There was no significant difference between participants and non-participants regarding their self-report of asthma (18/121 vs. 6/20: p=0.10), hayfever (44/121 vs. 7/20: p=0.91) and eczema (40/121 vs. 4/20: p=0.24).

From those with SPT≥1mm, 15/19 had a co-morbid allergy diagnosis based on self-report, 10/19 by a clinical confirmed diagnosis while 4/19 had no co-morbid condition. There was a significant difference in the rates of co-morbid allergic conditions regardless of the mode of diagnosis between those with SPT≥1mm and those not sensitised. Higher levels of sensitisation were observed in those with co-morbid allergies based on self-report compared to those with a clinically confirmed diagnosis. Participants with co-morbid allergy based on either diagnosis had a higher proportion of participants with increasing degrees of sensitisation compared to those without co-morbid allergies. However, not all the differences reached statistical significance (Table 3.3).

3.8 Sensitisation pattern by SPT levels and tertile age groups

A higher proportion of participants in the youngest tertile were sensitised compared to those in the older age tertiles. However, the decrease in sensitisation rate with increasing age did not reach statistical significance (Table 3.4).

Table 3.4: Sensitisation pattern by SPT category and tertile age group

	12-24 MONTHS	25-29 MONTHS	30-36 MONTHS	P VALUE †
SPT≥1MM (19)	9 (47%)	5 (26%)	5 (26%)	0.76
SPT≥3MM (15)	7 (47%)	5 (33%)	3 (20%)	0.74
SPT≥7MM (5)	3 (60%)	0	2 (40%)	0.33

† Difference between the age groups non-significant by Fisher's exact/Chi-square tests

Table 3.3: Sensitisation pattern and method of concomitant allergy diagnosis

	CO-MORBID ALLERGY (SELF-REPORTED)	CO-MORBID ALLERGY (CLINICAL DIAGNOSIS)	NO CO-MORBID ALLERGY	DIFFERENCE BETWEEN CO-MORBID ALLERGY CATEGORIES	DIFFERENCE BETWEEN CO-MORBID ALLERGY CATEGORIES AND NO CO-MORBID ALLERGY §
NOT SENSITISED (102)	54 (52.9%)	19 (18.6%)	48 (47.1%)	<0.0001	0.58 & <0.0001
SPT≥1MM (19)	15 (78.9%)	10 (52.6%)	4 (21.1%)	0.09	0.0004 & 0.04
SPT≥3MM (15)	12 (85.7%)	7 (50%)	3 (21.4%)	0.04	0.0006 & 0.11
SPT≥7MM (5)	4 (80%)	2 (40%)	1 (20%)	0.02	0.06 & 0.49
DIFFERENCE BY SENSITISATION STATUS†	0.04	0.001			

† Difference significant by 2-sided test of proportions

§ By 2-sided test of proportions.

4 Discussion

SAFFA is the first study in Africa to investigate the prevalence of FS and challenge-proven Ig-E mediated FA in an unselected sample. We randomly sampled from an unselected population of children attending crèches and the approach yielded a good overall participation rate of 66%. The study was feasible and acceptable in the target population. This is despite the significant obstacles in this setting viz inability to contact parents directly for consent, unavailability of a caregiver able to give consent and the time constraints of caregivers to complete the allergy tests. We found appreciable rates of FS with inter-ethnic differences and a considerable burden of Ig-E mediated FA in the study population.

To assess for selection bias in individual study participation we administered a non-participant questionnaire that was answered by a small proportion of the eligible population (12/213, 6%). Those who chose not to participate did not have time to come for SPTs. The similar prevalence history of FA and concomitant atopy in participants and non-participants means that it is unlikely that selection bias has had a large effect on the allergy prevalence rates.

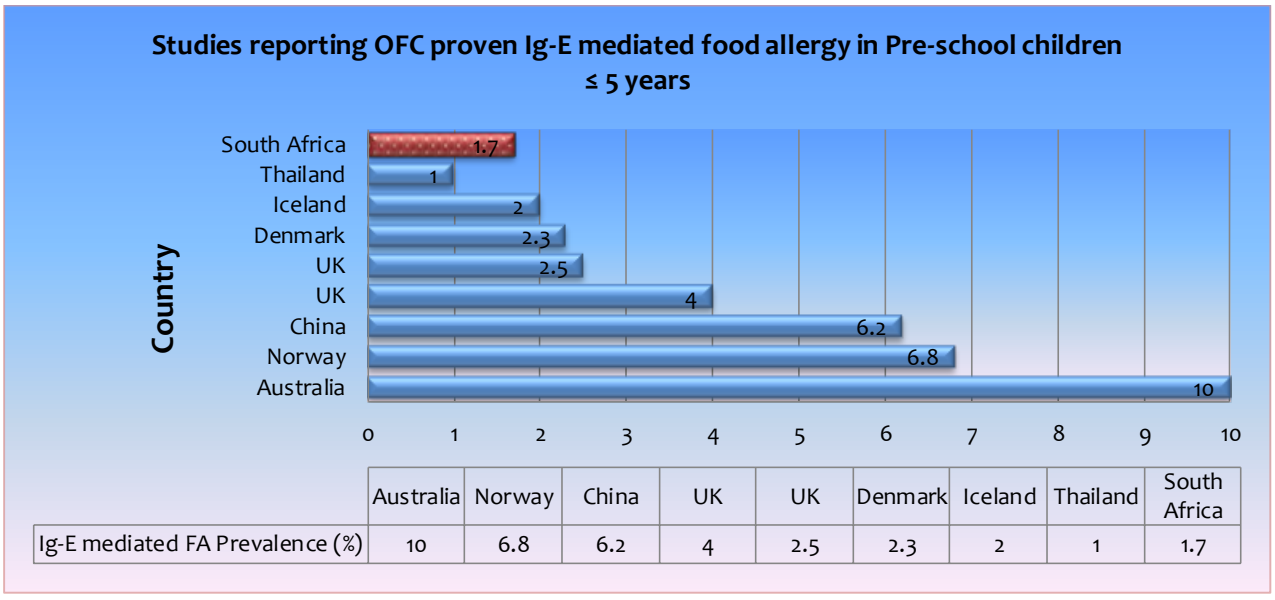
When the ethnic distribution in our sample was compared to the most recent results of the 0-4 year's population in the Cape Town census of 2011, it showed an over-representation of the Caucasian group. This may be because the online crèche list we sampled from has more contact details for crèches in the more affluent areas than the less affluent areas thereby skewing the study population. This is possible because the crèches from higher socio-economic (SE) settings are more likely to be registered than those from lower SE settings because of the stringent requirements. As a result the source population may reflect a skewed population with less representation from the lower SE settings and furthermore the crèches accessed from these areas were more difficult to organise study logistics with.

We have demonstrated high levels of FS comparable to that of previous findings from highly selected populations in South Africa and much higher than what has been previously observed in an unselected population of older high-school children with a mean age of 17 years (22). We observed high rates of FS in the black African vs. mixed race and Caucasian participants similar to the pattern of higher rates of food and aeroallergen sensitisation observed in this sub-group in other studies (23,24).

South Africa appears to have among the low levels of Ig-E mediated FA compared with data from unselected populations confirmed by food challenges in the range of 1%-10% (11). However, the rate of challenge-proven Ig-E mediated FA in our setting is similar to that reported in unselected cohorts in Thailand (1%) (25) and the Nordic countries; Denmark (2.3%) (26) and Iceland (2%) (27) (Figure 3.2).

The prevalence of any sensitisation to any one or more of the common allergic foods was 16%; highest for egg, peanut and soya. FA prevalence was 1.7%; highest to raw egg (1.7%) and peanut butter (0.8%). There is high likelihood that the prevalence could have been higher because the 1 participant that was not challenged had a high level of sensitisation and was not tolerating the food on clinical history.

Figure 3.2: Summary of OFC proven Ig-E mediated FA from studies that have data for children aged 5 years or less (3,11,25-29).(11)



	Australia	Norway	China	UK	UK	Denmark	Iceland	Thailand	South Africa
Ig-E mediated FA Prevalence (%)	10	6.8	6.2	4	2.5	2.3	2	1	1.7

Associations between FA and risk factors could not be assessed because of a lack of statistical power. However we explored the effect of ethnicity, age, sex and presence of co-morbid conditions on FA. Ethnic differences in sensitisation were evident between, the black African, mixed race and Caucasian participants. Sensitisation was higher in the black African compared with the Caucasian and mixed race participants. Although our numbers are still very small, the proven-allergy rate was 1.7% in the black African, 0.8% in the Caucasian and 0% in mixed race participants.

It was previously thought that Ig-E mediated FA and FS are rare in the black African population but there is a suggestion of a recent emergence of allergies in this group as reported by a recent study in a selected population (24) . This cohort appears to be sensitised to common foods implying that they may have genetic predisposition for FA. The cohort also had an appreciable prevalence of Ig-E mediated FA. It is known that not all patients with sensitisation have food allergy, however this tendency may be accentuated in our setting. This may be because of environmental protection via unknown mechanisms of epigenetic regulation.

The Black African cohort had higher rates of both sensitisation and allergy although this did not reach statistical significance. It may be postulated that a black African cohort that migrates from rural areas adopt westernised lifestyles and acquire new risk factors. At the same time they may discard traditional lifestyles and remove of protective factors. This may have caused both sensitisation and allergy rates to increase, perhaps not to the same degree.

In this study, sensitisation to any food was higher in the younger age group compared to the older age groups. This is similar to the findings from selected populations in our recent study of children with AD (24) and the EPAAC^{TM} study (30) that appears to suggest that most FS is completed by the first birthday. A greater proportion of male participants compared to female participants was sensitised and had challenged-proven Ig-E mediated FA confirming findings in literature that the male sex is associated with an increased FA risk (31,32).

The presence of concomitant allergy associated with Ig-E mediated FA is shown via a higher proportion of participants with SPT≥3mm and SPT≥7mm when compared to those with no diagnosis of concomitant allergy. With documented increases in the prevalence of other allergic conditions (allergic rhinitis, eczema and asthma) in the South African context mimicking the global trend of the first wave of allergy (12), there is potential for an increase in the complexity and severity of FA as the allergy epidemic advances.

The study reflects the community prevalence of Ig-E mediated FA in South African children aged between 12-36 months. However, the risk factors influencing the prevalence and the differences between the ethnic groups could not be explored because of a lack of precision. The second phase of the study will focus of determining the inter-ethnic differences and rural-urban differences in the prevalence of FS and FA in South Africa. The study will further explore whether the 95% PPVs for a positive food challenge using SPT are the same in South African children as international cohorts, and will attempt to describe the modifiable and non-modifiable risk factors.

5 Conclusion

Ig-E mediated FA and FS rates in this unselected South African sample were higher than expected since they were comparable with rates from local studies in selected cohorts and were equivalent to unselected cohorts in Denmark, Iceland and Thailand. There are ethnic differences, with the black African participants having higher levels of sensitisation and proven allergy than Caucasian and Mixed race participants. Further investigations should explore the prevalence of FS and FA in both urban and rural South African populations.

6 Author's Contribution

Wisdom Basera was involved in the SAFFA study in the following capacities; data collection process (recruiting of participants), data entry into the database, data cleaning, performed the statistical analysis and drafted the manuscript.

7 Author's Information

Wisdom Basera is a Masters student in the School of Public Health and Family Medicine at the University of Cape Town

8 Acknowledgements

Financial and other support. This study was supported by the Medical Research Council, Nestle, Mylan, Adcock Ingram, Akacia, Aspen, Atellas, Beiersdorf, Cipla, Pharmadynamics, Takeda Nycomed and Thermofisher. We thank staff at the Institute of Child Health, UCT and the Red Cross Hospital Paediatric Allergy Clinic.

Potential conflicts of interest The authors declare that they have no competing interests.

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PART D

APPENDIX

1. Ethics Approval Letter

Letter of approval from the UCT Human Research Ethics Committee

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences

Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/research/humanethics/forms

29 November 2013

HREC REF: 497/2013

Prof M Levin
Paediatric, Allergy
Red Cross War Memorial Children's Hospital

Dear Prof Levin

PROJECT TITLE: A CROSS SECTIONAL STUDY OF IgE MEDIATED FOOD SENSITIZATION AND FOOD ALLERGY IN AN UNSELECTED POPULATION OF SOUTH AFRICAN CHILDREN AGED 12-36 MONTHS

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has formally approved the above-mentioned study. We acknowledge that the student Wisdom Basera is also involved as a Master's student on this project.

Approval is granted for one year until the 30th November 2014

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period. (Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC reference no in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and312.

2. Parent Information Sheet and Consent

This Information Sheet has been written to help you decide if you would like you and your child to participate in the SAFFA Study. Please read this Information Sheet carefully and feel free to ask questions to any of the staff members or contact Dr Maresa Botha on 021 658 5779 or 0762540860.

By signing the *Consent Form*, you indicate that you have read and understood this Information Sheet and that you give consent for your child to take part in the SAFFA Study on the terms set out in this Information Sheet. You will be given a copy of this Information Sheet to keep as well as a copy of the consent you've signed.

Before you decide you need to understand why the research is being done and how you will be involved. Please read all the sections carefully and feel free to ask questions to members of staff if you wish. Your participation in the study is entirely voluntary and your child's care will not be affected if you decide not to take part.

Why is this study being performed?

Studies in other parts of the world, especially in Europe and the USA, have found that many children have allergies to certain foods. Food allergies are very common especially in children between 1-3 years. In some children food allergies may cause problems such as an itchy rash, breathing difficulties or even collapse soon after they eat the food they are allergic to. This can be a medical emergency. In other children, eating the food they are allergic to may cause their eczema to get worse many hours to days after eating the food. It is important to know about such food allergies so that the child can get the right feeding advice.

Previously we had thought that food allergies were *not* very common in the South African children and especially rare in black South African children. We are trying to find out how many South African children have food allergies, to see whether it is as common as in the overseas studies, or whether it is perhaps not common here, and what the factors are that may be associated with food allergy in this country.

Why has your child been invited to take part?

We are inviting 1200 children between 12 months and 36 months who attend crèches in Cape Town and Bulungula (Eastern Cape) to take part in the study.

Do you have to take part?

You are not in any way obligated to take part in our study. Taking part is entirely voluntary. Your child will only be entered with your permission and signed consent. Your child's medical care will not be affected in any way whatever you decide to do. If you say yes to be part of the study and later change your mind, you can do this without any consequences to your child or his/her medical care.

What will happen if you decide to take part?

1. We will describe the study to you and answer any questions you may have. We will ask you to sign a consent form if you decide to take part.

2. Your child will be seen by one of the study team members and you will be asked questions about the child's medical history and diet. We will also ask you about any allergies you may know of and some questions about allergies in your family. If there is anything from what you tell us that makes us think that your child might have had a reaction to food in the past, we will ask you to come to Red Cross Children's Hospital where your child will have a Skin Prick Test, some blood tests and an Oral Food Challenge done. We will explain these to you should it be necessary. If there is no concern from what you tell us about food allergies, we will do a Skin Prick Test here in the Clinic. If the skin prick test shows no reaction, your child will have no further test performed.

3. We will examine your child to see if we can find any evidence of eczema, hay fever or asthma.

4. You will be seen by a nurse who will do skin prick tests for 7 common foods to look for signs of possible allergies (egg, milk, peanut, hazelnuts, wheat, soya and fish). For the Skin Prick test we will put small drops of special mixtures containing food proteins on to the child's arm or back, and gently scratch the skin with a sharp lancet and wait for 15 minutes to see if there is a reaction on the skin. Skin prick tests are not very painful – they feel a bit like a mosquito bite.

   The arm may become itchy, and if this happens we will give your child a cream to put on or medicine to drink (both antihistamines). Very rarely do children get more serious reactions like a wheeze or a more serious allergic reaction. Even though these reactions are extremely rare (about one in a 1000 children will have a more severe reaction) we are experienced to recognise any problems and will have emergency medicine with us to give immediately should your child have any signs of a more serious reaction. After the Skin Prick test is done you will need to wait for 15 minutes to see what the result is. If there is any reaction it may indicate that your child is sensitive or maybe even allergic to that particular food. We will then arrange for your child to have further tests (an oral food challenge and blood and stool tests) done at Red Cross Children's Hospital.

5. If your child has a history or a skin prick test result that makes it likely that he/she has a food allergy, we will also do some blood tests. Some of these bloods are part of the routine care of a child with a possible food allergy. Other blood tests are for the purposes of our research study and will help us to look for risk factors that might cause food allergies. These risk factors include genetic information.

   Part of our research study includes genetic analysis of the blood of some of our participants. This analysis will only be of factors related to allergic diseases and not of any other illnesses that can be investigated through genetic testing.

Some of the bloods will be stored for future testing but once again only for research related to allergy diseases. The blood samples and the information they contain will stay the property of the University of Cape Town and will not be sold for profit and will only be used for research that has been approved by the Human Research Ethics Committee of the University of Cape Town.

6. If there are any positive results for allergy tests your child may be asked to come to a hospital another day for a "food challenge." A food challenge involves coming in to hospital for the morning, and your child will be given very small amounts of the food to which they had a positive allergy test. This will be given under medical supervision to check for a reaction. We will then give bigger and bigger amounts of the food as long as there is no reaction. We will explain this in detail to you if your child needs a food challenge.

7. If we find that your child has a food allergy, we will arrange for you to see a dietician to give advice on avoiding the food; and we will give you a treatment plan and medications for an accidental allergic reaction. We will also arrange for you to be seen in the allergy clinic or the local hospital along with the history, results of your investigations and the challenge test.

How much time will you have to spend on the study?

We are hoping to perform all of the tests (questions and skin tests) on the same day over about ½ hour. If your child has taken antihistamine medicines in the previous few days we will need to arrange the skin tests for another day.

If your child needs a food challenge, this will be arranged for another day and will involve a half day visit to the hospital. If your child has a reaction during the food challenge they will need to stay a few hours longer so that we can watch them carefully. Very rarely children may need to be observed in hospital overnight if they have had a more severe reaction.

What about expenses and payment for the study?

You will not be paid for taking part in the study, but if you need to make any trips to the hospital for the study, we will pay travel expenses of R150 per day (or actual expenses should they be more than this).

What are the possible benefits of taking part?

The information from this study may help to improve our understanding of food allergies in South African children. It will be helpful to know if your child has food allergies so that we can try and avoid reactions to certain foods and refer you for follow up. It will also be helpful to know if your child is *not* allergic to foods as you can then use the food in the child's diet without worrying about it.

What are the possible disadvantages of taking part?

There is a very small risk of a reaction to skin tests but these will be performed in a safe environment by trained individuals.

For those having blood tests there is a chance of temporary bruising and pain where the blood was taken. We will put a special local pain-numbing cream on the skin to numb where the needle goes in.

If your child needs a food challenge, there is a risk of an allergic reaction. If there is an allergic reaction, it is usually mild, such as a rash. In a small proportion of children having a food challenge (about one in ten) there may be a more severe reaction such as breathing difficulties, which we will treat immediately. We will give the foods starting in very small amounts, and the child will be closely watched between each dose to make sure we recognise any reactions early on. Your child will be in the hospital setting where all emergency treatment is available, so it is much safer than giving the food at home.

What if there is a problem?

You may at any stage decide to withdraw from the study. This will not affect any treatment your child is receiving. If you have any concerns about any aspects of the study, please speak to the researcher who will try and help you.

Should anything go wrong with your child during the study, you will be covered by the no-fault insurance offered by the University of Cape Town.

Confidentiality

Any information on your child will be kept strictly private, and if the information is published, we will not use any names. Thus you and your child will never be able to be identified by anyone except study staff. If your child has food allergy we will, however, refer you by name to the local health service for follow up.

Who has reviewed the study?

This study has been reviewed and approved by the University of Cape Town's research ethics committee.

Further information and contact details

If you need any further information at any stage, you can contact:

Prof Mike Levin: 021 6585111

Dr Claudia Gray: 021 6585111

Dr Maresa Botha: 0216585779

UCT Research Ethics Committee: Tel 021 406 6338 Fax 021 406 6411

Consent Form for Participation in the Study

I (name of parent or legal guardian)……..
Have been fully informed about the above study with its risks and benefits, and hereby permit my child (Name, Date of birth)……..
to take part in the study.

This consent includes the following study procedures:	
Asking some health-related questions	YES/NO
Examining the child	YES/NO
Skin prick tests	YES/NO
Blood and stool tests if needed	YES/NO
Dust samples from the home if needed.	YES/NO
Food challenge if needed	YES/NO
Blood to be stored for genetic analysis related to allergy research	YES/NO
Using the health information gathered from the study in a confidential manner	YES/NO

I understand that my participation is voluntary. If I refuse to permit my child to participate, or choose to withdraw my child at any anytime, I understand there will be no prejudice against me or my child by the doctors or hospital.

I have been given a copy of this form.

To enter into the above study (sign)……..

Date ……

For illiterate parents only:

Signature substitute (cross or finger print)…….

Witness (name)……...

(Sign)…… Date……..

I (study personnel name)…….
have fully explained the nature and purpose of the above described study with its risks and benefits. I have answered all the questions to the best of my ability. I will inform the participant of any changes in the procedures or the risks and benefits should they change during the course of the study. I have given a copy of the consent form to the parents/guardian.

(Sign)……..Date…….

3. Participant Questionnaire

Participant details

Q1	Participant ID	0000/XX	
Q2	Enrolment date	DD/MM/YYYY	
Q3	Study site	1 = Urban	2= Rural
Q4	Date of birth	DD/MM/YYYY	
Q5	Age at enrolment	XX months	
Q6	Sex	1= Male	2=Female
Q7	Weight	XXX kg	
Q8	Height/Length	XXX cm	

Q9 Immunisations

			Yes	No				Yes	No
Birth	**9.1**	BCG			14 weeks	**9.10**	RV(2)		
	9.2	OPV (0)				**9.11**	DTaPIPV/HiB(3)		
6 weeks	**9.3**	OPV (1)				**9.12**	HepB(3)		
	9.4	RV (1)				**9.13**	PCV7 or 13 (2)		
	9.5	DTaPIPV/HiB (1)			9 months	**9.14**	Measles vaccine		
	9.6	HepB (1)				**9.15**	PCV 7 or 13 (3)		
	9.7	PCV7 or 13(1)			18 months	**9.16**	DTaPIPV/HiB (4)		
10 weeks	**9.8**	DTaPIPV/HiB (2)				**9.17**	Measles Vaccine		
	9.9	HepB (2)							

Q10 Vaccination Status

1 = Complete		2 = Incomplete	

Q11 Paracetamol Exposure

Q11.1	Did your child have paracetemol or medicines containing paracetamol in the first year of life? (Panado, Calpol, Paramed)		1 = Yes	0 = No
Q11.2	If Yes, How old was your child when they first had paracetamol?	XXXX	months	
Q11.3	If Yes, How often did your child have paracetamol on the first year of life?	**1 =** 1-10 days	**2 =** 10-20 days	**3 =** More than 20 days

Q12 Childhood infections

Has your child had any of the following childhood infections?									
		1 = Yes	**0 = No**	**999 = don' t know**			**1 = Yes**	**0 = No**	**999 = don't know**
12.1	Measles				**12.5**	Glandular Fever			
12.2	Mumps				**12.6**	Tuberculosis			
12.3	Rubella				**12.7**	Hepatitis			
12.4	Chickenpox				**12.8**	Other (please specify)			

Q13 Antibiotic exposure and anti-helminthic exposure

13.1	Did your child have any antibiotics in the first year of life?	**1** = Yes	**0** = No	**999** = Don't know	
13.2	If Yes, how old were they with the first course??	XXXX		Months	
13.3	How many courses did your child have in the first year of life?	**1 =** None	**2** = 1 to 2 Courses	**3** = 3 to 5 courses	**4** = > 5 courses
13.4	Did your child have any antibiotics in the last 2 months?	**1** = Yes	**0** = No	**999** = Don't know	

13.5	Has your child ever had medicines for worms?	0= No	1 = Yes	999=Don't Know
13.6	If Yes, at what age were they dewormed?			months
13.7	If Yes, at what age did they last take anti worm medicines?			months
13.8	Has your child had regular (yearly) medicine for worms?	0 = No	1 = Yes	999 = Don't know

Q14 Probiotic Exposure and Amasi exposure (CHILD)

14.1	Did this **child** have probiotics in food or supplements in the first year of life?	**1** = Yes	**0** = No	**999** = Don't know
14.2	**If Yes,** how old was this child when they first had probiotics?	XXXXX		Months
14.3	**If Yes,** How often did this child have probiotics in the first year of life?	**1 =** 1-10 days	**2 =** 10-20 days	**3 =** >20 days
14.4	**If Yes,** which probiotic product were they given?			
14.5	Has your **child** ever have **amasi** ?	**0 = No**	**1 = Yes**	**999** = Don't know
14.6	**If Yes,** how old was this child when they first had **amasi**?			Months
14.7	**If Yes,** how often does your child take amasi?	**1 =** Less than once a month	**2 =** 1-4 times per month	**3 =** more than 4 times per month

Q14 Probiotic exposure and Amasi exposure (MOTHER)

14.8	Did this child's mother have probiotics during pregnancy?	**0** = No	**1** = Yes	**999** =Don't know
14.9	If Yes, How often did she use probiotics?	**1** = 1-10 days	**2** = 10-20 days	**3** = >20 days
14.10	Which yes, which products did she use?			

14.11	Did this child's mother regularly have amasi during pregnancy? (more than once a month)	**0** = No	**1** =Yes	**999** = Don't know

Q15 Delivery mode

Q15	How was this child born?	**1** = Normal vaginal delivery	**2** = Caesarean section	**999** = Don't Know

Q16 Sunlight Exposure

How much time does your child spend outdoors on an average day? *(add crèche daily average X5, to weekend total hours and divide by 7. Report to nearest 0.1)*	
Q16.1 Winter	**Q16.2 Summer**
00.0 hours	00.0 hours
999 = Don't Know	**999 =** Don't Know

Q17 Peanut exposure in pregnancy

17.1	Did this child's mother eat peanuts regularly (every week) during pregnancy?	**1**=Yes	**0** = No	**999** = Don't know
17.2	Did this child's mother completely avoid peanuts during pregnancy?	**1**=Yes	**0** = No	**999** = Don't know

Q18 Breastfeeding information

Q18.1	Was this child ever breastfed?	**1** = Yes	**0** = No	**999** = Don't know
Q18.2	If Yes, up to what age was this child exclusively breastfed (i.e. no milk or other fluids via bottle nor given any solids)	XXXXXX	months	**999** = Don't know
Q18.3	At what age did you completely stop breastfeeding this child?	XXXXXX	months	**999** = Don't know
Q18.4	At what age did you first introduce any other milk (other than breast milk)	XXXXXX	months	**999** = Don't know

Q19 Weaning foods

Q19.1	When did you first introduce solids into your child's diet?			months
Q19.2	Which three types of foods did you introduce first**?** *(see coding chart for food categories)*	Free Text	Free text	Free text

Q20 Exposure to Pasteurised milk

Q20	Has this child ever had non-pasteurised (Fresh farm) milk?	**1** = Yes	**0** = No	**999** = Don't know

Q21 Food exposure

Foods Eaten		Ever Eaten			Age first eaten				Still eating regularly *(once a month or more)*		
21.1	**Peanut** e.g. peanut butter, peanut oil, peanuts in cookies or chocolates	**21.1.1**	0 = No	1 = Yes	**21.1.2**		months	999 = don't know	**21.1.3**	0 = No	1 = Yes **If yes please continue with 21.1.4**

If yes to 21.1.4 **Please try an remember how many times your child ate the following peanut containing foods in the last day and *week***	**Type of peanuts consumed**	**Number of times per day**	**Number of times per week**	**Usual amount**			**Total amount in grams**
	Peanut butter on bread				Thin slices	**21.1.4**	
					Thick slices	**21.1.5**	
	Peanut butter in porridge				Teaspoons	**21.1.6**	
	Raw/boiled peanuts				Handfuls	**21.1.7**	
	Roasted peanuts				Handfuls	**21.1.8**	
	Peanuts in chocolate or biscuits					**21.1.9**	
	Total amount of peanut consumed in the last week					**21.1.10**	

21.2	**Other nuts** e.g. Cashew, hazelnut, brazil nut, almonds, walnuts, pistachio, macadamia in chocolate and cookies or cakes and breads	**21.2.1**	0 = No	1 = Yes	**21.2.2**		months	999 = don't know	**21.2.3**	0 = No	1 = Yes
21.3	**Cow's milk products** e.g. fresh milk, cheese, yoghurt, cream	**21.3.1**	0 = No	1 = Yes	**21.3.2**		months	999 = don't know	**21.3.3**	0 = No	1 = Yes
21.4	**Cow's milk formula** e.g. Nan, Lactogen, Novolac, S26, Infacare, Pelargon	**21.4.1**	0 = No	1 = Yes	**21.4.2**		Months	999 = don't know	**21.4.3**	0 = No	1 = Yes
21.5	**Soya products** e.g. soya mince, soya sauce, tofu, baby foods, soya in bread	**21.5.1**	0 = No	1 = Yes	**21.5.2**		Months	999 = don't know	**21.5.3**	0 = No	1 = Yes
21.6	**Soya milk products** e.g. Infasoy, Isomil, Infacare	**21.6.1**	0 = No	1 = Yes	**21.6.2**		Months	999 = don't know	**21.6.3**	0 = No	1 = Yes
21.7	**Hen's egg** e.g. boiled, scrambles eggs, omelettes, quiches(souttert), cakes, cookies, rusks	**21.7.1**	0 = No	1 = Yes	**21.7.2**		Months	999 = don't know	**21.7.3**	0 = No	1 = Yes
21.8	**Wheat** e.g. cereal (Wheetabix, All Bran, Tasty Wheat), bread or pasta, cakes, rusks, couscous, semolina	**21.8.1**	0 = No	1 = Yes	**21.8.2**		Months	999 = don't know	**21.8.3**	0 = No	1 = Yes
21.9	**Fish (excluding shellfish)** Hake, snoek, sardines,pilchards, tuna, kingklip, salmon etc and fish products: Fish paste(Redro), Worcester sauce, fish sauce	**21.9.1**	0 = No	1 = Yes	**21.9.2**		months	999 = don't know	**21.9.3**	0 = No	1 = Yes

Q22 Food Reactions

22.1 PEANUTS					
22.1.1	Has your child ever had any of these reactions below to peanuts or food containing peanuts			**1** = yes	**0** = no
22.1.2	If yes, which of the following reactions has this child had? (you can circle more than one)				
	1= none	**6**= tight throat	**11**=shock/low blood pressure		
	2= itchy Rash	**7**= wheeze	**12**= collapse/loss of consciousness		
	3=swelling(face/lips/eyes)	**8**= vomiting	**13** = worsening of eczema		
	4= flushing	**9**= diarrhoea			
	5= itchy mouth/throat	**10**= blue lips			
22.1.3	If Yes, how old was this child when he/she had the first reaction?		XXXXX	months	
22.1.4	If yes, how long after the eating the food did the reaction occur?		**1** = < 1 hour	**2** = 1-24 hours	**3** = >24 hours
22.1.5	If yes, was this reaction confimed by a doctor?		**1** = yes	**0** = no	

22.2 OTHER NUTS					
22.2.1	Has your child ever had any of these reactions below to other nuts or food containing nuts other than peanuts			**1** = yes	**0** = no
22.2.2	If yes, which of the following reactions has this child had? (you can circle more than one)				
	1 = none	**6** = tight throat	**11** =shock/low blood pressure		
	2 = itchy Rash	**7** = wheeze	**12** = collapse/loss of consciousness		
	3 =swelling(face/lips/eyes)	**8** = vomiting	**13** = worsening of eczema		
	4 = flushing	**9** = diarrhoea			
	5 = itchy mouth/throat	**10** = blue lips			
22.2.3	If Yes, how old was this child when he/she had the first reaction?		XXXXX	months	
22.2.4	If yes, how long after the eating the food did the reaction occur?		**1** = < 1 hour	**2** = 1-24 hours	**3** = >24 hours
22.2.5	If yes, was this reaction confimed by a doctor?		**1** = Yes	**0** = No	

22.3 COW'S MILK					
22.3.1	Has your child ever had any of these reactions below to cow's milk or food containing cow's milk			**1** = Yes	**0** = No
22.3.2	If yes, which of the following reactions has this child had? (you can circle more than one)				
	1 = none	**6** = tight throat	**11** = shock/low blood pressure		
	2 = itchy Rash	**7** = wheeze	**12** = collapse/loss of consciousness		
	3 =swelling(face/lips/eyes)	**8** = vomiting	**13** = worsening of eczema		
	4 = flushing	**9** = diarrhoea			
	5 = itchy mouth/throat	10 = blue lips			
22.3.3	If Yes, how old was this child when he/she had the first reaction?		XXXXX	months	
22.3.4	If yes, how long after the eating the food did the reaction occur?		**1** = < 1 hour	**2** = 1-24 hours	**3** = >24 hours
22.3.5	If yes, was this reaction confirmed by a doctor?		**1** = Yes	**0** = No	

22.4 SOYA					
22.4.1	Has your child ever had any of these reactions below to soya or food containing soya			**1** = Yes	**0** = No
22.4.2	If yes, which of the following reactions has this child had? (you can circle more than one)				
	1 = none	6= tight throat	11=shock/low blood pressure		
	2 = itchy Rash	7= wheeze	12= collapse/loss of consciousness		
	3 =swelling(face/lips/eyes)	8= vomiting	13 = worsening of eczema		
	4 = flushing	9= diarrhoea			
	5 = itchy mouth/throat	10= blue lips			
22.4.3	If Yes, how old was this child when he/she had the first reaction?		XXXXX	months	
22.4.4	If yes, how long after the eating the food did the reaction occur?		**1 =** < 1 hour	**2 =** 1-24 hours	**3 =** >24 hours
22.4.5	If yes, was this reaction confirmed by a doctor?		**1** = Yes	**0** = No	

22.5 HEN'S EGG					
22.5.1	Has your child ever had any of these reactions below to hen's egg or food containing egg			**1** = Yes	**0** = No
22.5.2	If yes, which of the following reactions has this child had? (you can circle more than one)				
	1 = none	6 = tight throat	11 =shock/low blood pressure		
	2 = itchy Rash	7 = wheeze	12 = collapse/loss of consciousness		
	3 =swelling(face/lips/eyes)	8 = vomiting	13 = worsening of eczema		
	4 = flushing	9 = diarrhoea			
	5 = itchy mouth/throat	10= blue lips			
22.5.3	If Yes, how old was this child when he/she had the first reaction?		XXXXX	months	
22.5.4	If yes, how long after the eating the food did the reaction occur?		1= < 1 hour	**2=** 1-24 hours	**3=** >24 hours
22.5.5	If yes, was this reaction confirmed by a doctor?		**1** = Yes	**0** = No	

22.6 WHEAT					
22.6.1	Has your child ever had any of these reactions below to wheat or food containing wheat			**1** = Yes	**0** = No
22.6.2	If yes, which of the following reactions has this child had? (you can circle more than one)				
	1= none	6= tight throat	11=shock/low blood pressure		
	2= itchy Rash	7= wheeze	12= collapse/loss of consciousness		
	3=swelling(face/lips/eyes)	8= vomiting	13 = worsening of eczema		
	4= flushing	9= diarrhoea			
	5= itchy mouth/throat	10= blue lips			
22.6.3	If Yes, how old was this child when he/she had the first reaction?		XXXXX	months	
22.6.4	If yes, how long after the eating the food did the reaction occur?		**1=** < 1 hour	**2=** 1-24 hours	**3=** >24 hours
22.6.5	If yes, was this reaction confirmed by a doctor?		**1** = Yes	**0** = No	

22.7 FISH (excluding shellfish)					
22.7.1	Has your child ever had any of these reactions below to fish or food containing fish			**1** = Yes	**0** = No
22.7.2	If yes, which of the following reactions has this child had? (you can circle more than one)				
	1 = none	6 = tight throat	11 =shock/low blood pressure		
	2 = itchy Rash	7 = wheeze	12 = collapse/loss of consciousness		
	3 =swelling(face/lips/eyes)	8 = vomiting	13 = worsening of eczema		
	4 = flushing	9 = diarrhoea			
	5 = itchy mouth/throat	10 = blue lips			
22.7.3	If Yes, how old was this child when he/she had the first reaction?		XXXXX	Months	
22.7.4	If yes, how long after the eating the food did the reaction occur?		**1=** < 1 hour	**2=** 1-24 hours	**3=** >24 hours
22.7.5	If yes, was this reaction confirmed by a doctor?		**1** = Yes	**0** = No	

Q23 Asthma

Q23.1	Has your child ever had symptoms of asthma? (e.g. wheeze, persistent cough at night or when exercising, shortness of breath)	**1** = Yes		**0** = No
Q23.2	If Yes, how old was he/she?	XXX		Months
Q23.3	If yes, who diagnosed the asthma?	**1** = Self	**2** = Nurse	**3** = Doctor

Q24 Hay fever

Q24.1	Has your child ever had symptoms of hay fever (e.g. itchy runny eyes, itchy runny nose, blocked nose, frequent sneezing) without having a "cold" or upper respiratory tract infection?	**1** = Yes		**0** = No
Q24.2	If Yes, how old was he/she?	XXX		Months
Q24.2	If yes, who diagnosed the hay fever?	**1** = Self	**2** = Nurse	**3** = Doctor

Q25 Eczema

Q25.1	Has your child ever had symptoms of eczema (e.g. an itchy rash especially in the folds of the elbows, behinds the knees, in front of the ankles, under the buttocks or around the neck, ears or eyes?)	**1** = Yes		**0** = No
Q25.2	If yes, how old was your child then?	XXX		Months
Q25.3	If yes, who diagnosed the eczema?	**1** = Self	**2** = Nurse	**3** = Doctor

Q26 Medication use

Q26.1	Is your child on any of the following medication? (see NAEP Chart)							
26.1.1	INHALERS	Relievers (blue) e.g. Asthavent	1 = yes	0 = no	**25.1.5**	Nasal corticosteroid spray e.g. Beclate	1 = yes	0 = no
26.1.2		Controllers (brown/cream) e.g. Budeflam	1 = yes	0 = no	**25.1.6**	Antihistamines **(If yes, please complete Q26.4 below)**	1 = yes	0 = no
26.1.3		Other (please specify below)	1 = yes	0 = no	**25.1.7**	Steroid creams	1 = yes	0 = no
26.1.4		Home nebuliser	1 = yes	0 = no	**25.1.8**	Adrenalin auto injector or pen e.g. Epipen	1 = yes	0 = no
Q26.2	If your child is on any other oral medication (pills or syrups) for asthma, please **specify each one.** (e.g. oral steroids or leukotriene receptor antagonists)				Free text			
Q26.3	If your child is on antihistamines, **please specify** which type/brand?				Free text			
Q26.4	If your child is on antihistamines, how many days since they were last taken?				**1 =** <2 days	**2 =** 2-5 days	**3 =** >5 days	
Q27.5	If your child is on any other medication for other illnesses, please specify each one.				Free text			

Q27 Family history of allergic disease

	Does anyone in your family have allergic diseases? Please circle. (you can choose more than one option)					
	Family member	None	Asthma	Hay fever	Eczema	Food allergy
Q27.1	Mother	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy
Q27.2	Father	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy
Q27.3	Full Sibling 1	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy
Q26.4	Full Sibling 2	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy
Q27.5	Full Sibling 3	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy
Q27.6	Full Sibling 4	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy

Q28 Child's Medical history

Q28.1	Does your child have any other significant medical problems? (e.g. heart or lung problems, kidney or liver disease, epilepsy, diabetes)	**1** = Yes	**0** = No
Q28.2	If yes, please specify		

Q29 Home Language and Migration

Q29.1	What language do you mainly speak at home? (Please choose only one)			
	1 = IsiXhosa	**2** = English	**3** = Afrikaans	
	4 = IsiZulu	**5** = Sesotho	**6** = Setswana	
	7 = SiSwati	**8** = IsiNdebele	**9**=Xitsonga	
	10 = Sepedi	**11**=Tshivenda	**12** = Other	
Q29.1.2	If Xhosa speaking, was this child born in Cape Town?		**1** = Yes	**0** = No

29.2.1	If no, where was this child born?	Province			
		1 = Western Cape 2 = Eastern Cape 3 = Northern Cape 4 = Free state 5 = Gauteng		6 = Kwazulu Natal 7 = Mpumalanga 8 = Limpopo 9 = North West Province 10 = Other	
		Town (specify)		Free text	
29.2.2	When did this child move to Cape Town?	XXX	Year	XXX	Month

Q29.3	Was this child's mother born in Cape Town?			0 = No	1 = Yes
29.3.1	**If No,** where was she born?	Province (please circle)			
		1 = Western Cape 2 = Eastern Cape 3 = Northern Cape 4 = Free state 5 = Gauteng		6 = Kwazulu Natal 7 = Mpumalanga 8 = Limpopo 9 = North West Province 10 = Other	
		Town (specify)		Free text	
29.3.2	**If no** when did she move to Cape Town?		Year		Month
29.3.3	Was this Child's father born in Cape Town?			0 = No	1 = Yes
	If No, where was he born?	Province			
		1 = Western Cape 2 = Eastern Cape 3 = Northern Cape 4 = Free state 5 = Gauteng		6 = Kwazulu Natal 7 = Mpumalanga 8 = Limpopo 9 = North West Province 10 = Other	
		Town(specify)			

Q30 Ethnicity

Q30	What is your child's ethnic origin? (circle as appropriate)	**1** = White/Caucasian	**2** = Coloured / Mixed race
		3 = Black African	**4** = Asian/Indian
		5 = Other (Specify)	

Q31 Household information

Q31.1	How many people live together in your house?	
Q31.2	How many children (12 years or less) that are OLDER than this child live in the same household?	
Q31.3	How many children that are YOUNGER than this child live in the same household?	

Q32 Parental Education level

1 = None	**11** = Grade 9 / Std 7
2 = Grade R / preschool	**12** = Grade 10 / Std 8
3 = Grade 1 / SubA	**13** = Grade 11 / Std 9
4 = Grade 2 / Sub B	**14** = Grade 12 / Matric
5 = Grade 3 / Std 1	**15** = Grade 9,10,11 (Std 7,8,9) & diploma
6 = Grade 4 / Std 2	**16** = Grade 12 (Std 10) & Certificate or Diploma
7 = Grade 5 / Std 3	**17** = Grade 12 (Std 10) & Degree
8 = Grade 6 / Std 4	**18** = Grade 12 (Std 10) & Degree plus Diploma
9 = Grade 7 / Std 5	**19** = Grade 12 (Std 10) & PhD
10 = Grade 8 / Std 6	Other (**Specify**) : Free text

Q33 Household income

Q33.1	What job does this child's mother/female guardian do?		
Q33.2	What job does this child's father/male guardian do?		
Q33.3	How much money or income does your household receive every month after tax? (incl. money from work, pensions, informal business etc.)	R	999 = Don't know

Q34 Contact with pets and animals

Q34.1	Do you own a cat or have a cat in your home?		**1** = Yes	**0** = No
Q34.2	Do you own a dog or have a dog in your home?		**1**= Yes	**0** = No
Q34.3	Does your child have regular (at least once a week) contact with farm animals (e.g. cattle, pigs, goats, sheep or poultry)?	**1** = Yes	**0** = No	**999** = Don't know
Q34.4	Has this child's mother had regular (at least once a week) contact with farm animals (e.g. cattle, pigs, goats, sheep or poultry) while being pregnant with this child?	**1** = Yes	**0** = No	**999** = Don't know

Q35 Fuel exposure

Q35.1	At your house, what fuel is used for cooking?	
	1 = Electricity/Gas	**4** = Open fires outside the house
	2 = Paraffin Stove	**5** = Other (specify)
	3 = Open fires in the house	
Q35.2	At your house, what fuel is used for heating?	
	1 = Electricity	**4** = Wood/coal
	2 =Gas	**5** = Other (specify)
	3 =Kerosene/Paraffin	

Q36 Cigarette smoke exposure

Q36.1	Does this child's mother (or female guardian) currently smoke cigarettes?	**1** = Yes	**0** = No	**3** = Don't know
36.1.1	If **YES**, about how many cigarettes does the child's mother (or female guardian) smoke each day?	number of cigarettes:		
Q36.2	Does this child's father (or male guardian) currently smoke cigarettes?	**1** = Yes	**0** = No	**3** = Don't know
36.2.1	If **YES**, about how many cigarettes does the child's father (or male guardian) smoke each day?	number of cigarettes:		
Q36.3	How many people living in the house currently smoke cigarettes, including parents?	No of people:		
Q36.4	Did this child's mother smoke cigarettes while being pregnant with this child?	**1** = Yes	**0** = No	**3** = Don't know

4. Non-Participant Questionnaire and Consent

We would be very grateful if you could take the time to complete a short survey which will help us to improve the quality of our study findings. These questions will be about your child's diet, history of allergies and also some questions regarding your family's history of allergy and where you and your child were born.

This information will be anonymous and we will not keep any record of you or your child's name. It will therefore not be possible to identify you or your child from the information you give us.

The SAFFA study was approved by the Human Research Ethics Committee of the University of Cape Town.

Consent for my anonymous information to be used in the SAFFA study.

I (name of parent or legal guardian)…….. have been fully informed about the above study with its risks and benefits, and hereby consent for the information I share in this non-participant questionnaire to be used in the study.

This consent includes the following study procedures:

- Asking some health-related questions about my child and my family
- Using the health information gathered from the study in a confidential manner

Signature: …….

For illiterate parents only:

Signature substitute (cross or finger print)…….

Witness (name)……...

(Sign)……. Date……..

I (study personnel name)……,
have fully explained the nature and purpose of the above described study with its risks and benefits. I have answered all the questions to the best of my ability. I will inform the participant of any changes in the procedures or the risks and benefits should they change during the course of the study. I have given a copy of the consent form to the parents/guardian.

Non-Participant's details

Q1	NPID number	00000	
Q2	Questionnaire date	DD/MM/YYYY	
Q3	Study site	1 = Urban	2= Rural
Q4	Date of birth	DD/MM/YYYY	
Q5	Age at survey	XX months	
Q6	Sex	1= Male	2=Female
Q7	You have chosen not to take part in our SAFFA study. Could you please tell us what your reasons are?		
	1 = I don't have enough time		
	2 = I am not concerned about food allergies in my child		
	3 = I do not wish my child to undergo a skin prick test		
	4 = I do not wish my child to undergo any blood tests		
	5 = I am not the parent or guardian and the parent is not available		
	6 = Other reasons (please specify):		

Q21 Food exposure

Foods Eaten		Ever Eaten			Age first eaten				Still eating regularly (once a week or more)		
21.1	**Peanut** e.g. peanut butter, peanut oil, peanuts in cookies or chocolates	**21.1.1**	1 = Yes	0 = No	**21.1.2**	XX	months	999 = don't know	**21.1.3**	1 = Yes	0 = No
21.2	**Other nuts** e.g. Cashew, hazelnut, brazil nut, almonds, walnuts, pistachio, macadamia in chocolate and cookies or cakes and breads	**21.2.1**	1 = yes	0 = no	**21.2.2**	XX	months	999 = don't know	**21.2.3**	1 = Yes	0 = No
21.3	**Cow's milk products** e.g. fresh milk, cheese, yoghurt, cream	**21.3.1**	1 = yes	0 = no	**21.3.2**	XX	months	999 = don't know	**21.3.3**	1 = Yes	0 = No
21.4	**Cow's milk formula** e.g. Nan, Lactogen, Novolac, S26, Infacare, Pelargon	**21.4.1**	1 = yes	0 = no	**21.4.2**	XX	Months	999 = don't know	**21.4.3**	1 = Yes	0 = No
21.5	**Soya products** e.g. soya mince, soya sauce, tofu	**21.5.1**	1 = yes	0 = no	**21.5.2**	XX	Months	999 = don't know	**21.5.3**	1 = Yes	0 = No
21.6	**Soya milk products** e.g. Infasoy, Isomil, Infacare	**21.6.1**	1 = yes	0 = no	**21.6.2**	XX	Months	999 = don't know	**21.6.3**	1 = Yes	0 = No
21.7	**Hen's egg** e.g. boiled, scrambles eggs, omelettes, quiches(souttert), cakes, cookies, rusks	**21.7.1**	1 = yes	0 = no	**21.7.2**	XX	Months	999 = don't know	**21.7.3**	1 = Yes	0 = No
21.8	**Wheat** e.g. cereal (Wheetabix, All Bran, Tasty Wheat), bread or pasta, cakes, rusks, couscous, semolina	**21.8.1**	1 = yes	0 = no	**21.8.2**	XX	Months	999 = don't know	**21.8.3**	1 = Yes	0 = No
21.9	**Fish (excluding shellfish)** Hake, snoek, sardines, tuna, kingklip, salmon etc and fish products: Fish paste(Redro), Worcester sauce, fish sauce	**21.9.1**	1 = yes	02 = no	**21.9.2**	XX	months	999 = don't know	**21.9.3**	1 = Yes	0 = No

Q22 Food Reactions

22.1 PEANUTS					
22.1.1	Has your child ever had any of these reactions below to peanuts or food containing peanuts			**1** = yes	**0** = no
22.1.2	If yes, which of the following reactions has this child had? (you can circle more than one)				
	1= none	**6**= tight throat	**11**=shock/low blood pressure		
	2= itchy Rash	**7**= wheeze	**12**= collapse/loss of consciousness		
	3=swelling(face/lips/eyes)	**8**= vomiting	**13** = worsening of eczema		
	4= flushing	**9**= diarrhoea			
	5= itchy mouth/throat	**10**= blue lips			
22.1.3	If Yes, how old was this child when he/she had the first reaction?			XX	months
22.1.4	If yes, how long after the eating the food did the reaction occur?			**1** = < 1 hour	**2** = 1-24 hours / **3** = >24 hours
22.1.5	If yes, was this reaction confimed by a doctor?			**1** = yes	**0** = no

22.2 OTHER NUTS					
22.2.1	Has your child ever had any of these reactions below to other nuts or food containing nuts other than peanuts			**1** = yes	**0** = no
22.2.2	If yes, which of the following reactions has this child had? (you can circle more than one)				
	1 = none	**6** = tight throat	**11** =shock/low blood pressure		
	2 = itchy Rash	**7** = wheeze	**12** = collapse/loss of consciousness		
	3 =swelling(face/lips/eyes)	**8** = vomiting	**13** = worsening of eczema		
	4 = flushing	**9** = diarrhoea			
	5 = itchy mouth/throat	**10** = blue lips			
22.2.3	If Yes, how old was this child when he/she had the first reaction?			XX	months
22.2.4	If yes, how long after the eating the food did the reaction occur?			**1** = < 1 hour	**2** = 1-24 hours / **3** = >24 hours
22.2.5	If yes, was this reaction confimed by a doctor?			**1** = Yes	**0** = No

22.3 COW'S MILK					
22.3.1	Has your child ever had any of these reactions below to cow's milk or food containing cow's milk			**1** = Yes	**0** = No
22.3.2	If yes, which of the following reactions has this child had? (you can circle more than one)				
	1 = none	**6** = tight throat	**11** = shock/low blood pressure		
	2 = itchy Rash	**7** = wheeze	**12** = collapse/loss of consciousness		
	3 =swelling(face/lips/eyes)	**8** = vomiting	**13** = worsening of eczema		
	4 = flushing	**9** = diarrhoea			
	5 = itchy mouth/throat	10 = blue lips			
22.3.3	If Yes, how old was this child when he/she had the first reaction?			XX	months
22.3.4	If yes, how long after the eating the food did the reaction occur?			**1** = < 1 hour	**2** = 1-24 hours / **3** = >24 hours
22.3.5	If yes, was this reaction confimed by a doctor?			**1** = Yes	**0** = No

22.4 SOYA					
22.4.1	Has your child ever had any of these reactions below to soya or food containing soya			**1** = Yes	**0** = No
22.4.2	If yes, which of the following reactions has this child had? (you can circle more than one)				
	1 = none	6= tight throat	11=shock/low blood pressure		
	2 = itchy Rash	7= wheeze	12= collapse/loss of consciousness		
	3 =swelling(face/lips/eyes)	8= vomiting	13 = worsening of eczema		
	4 = flushing	9= diarrhoea			
	5 = itchy mouth/throat	10= blue lips			
22.4.3	If Yes, how old was this child when he/she had the first reaction?		XX	months	
22.4.4	If yes, how long after the eating the food did the reaction occur?		**1 =** < 1 hour	**2 =** 1-24 hours	**3 =** >24 hours
22.4.5	If yes, was this reaction confirmed by a doctor?		**1** = Yes		**0** = No

22.5 HEN'S EGG					
22.5.1	Has your child ever had any of these reactions below to hen's egg or food containing egg			**1** = Yes	**0** = No
22.5.2	If yes, which of the following reactions has this child had? (you can circle more than one)				
	1 = none	6 = tight throat	11 =shock/low blood pressure		
	2 = itchy Rash	7 = wheeze	12 = collapse/loss of consciousness		
	3 =swelling(face/lips/eyes)	8 = vomiting	13 = worsening of eczema		
	4 = flushing	9 = diarrhoea			
	5 = itchy mouth/throat	10= blue lips			
22.5.3	If Yes, how old was this child when he/she had the first reaction?		XX	months	
22.5.4	If yes, how long after the eating the food did the reaction occur?		1= < 1 hour	**2=** 1-24 hours	**3=** >24 hours
22.5.5	If yes, was this reaction confirmed by a doctor?		1 = Yes		**0** = No

22.6 WHEAT					
22.6.1	Has your child ever had any of these reactions below to wheat or food containing wheat			**1** = Yes	**0** = No
22.6.2	If yes, which of the following reactions has this child had? (you can circle more than one)				
	1= none	6= tight throat	11=shock/low blood pressure		
	2= itchy Rash	7= wheeze	12= collapse/loss of consciousness		
	3=swelling(face/lips/eyes)	8= vomiting	13 = worsening of eczema		
	4= flushing	9= diarrhoea			
	5= itchy mouth/throat	10= blue lips			
22.6.3	If Yes, how old was this child when he/she had the first reaction?		XX	months	
22.6.4	If yes, how long after the eating the food did the reaction occur?		**1=** < 1 hour	**2=** 1-24 hours	**3=** >24 hours
22.6.5	If yes, was this reaction confirmed by a doctor?		**1** = Yes		**0** = No

22.7 FISH (excluding shellfish)					
22.7.1	Has your child ever had any of these reactions below to fish or food containing fish			**1** = Yes	**0** = No
22.7.2	If yes, which of the following reactions has this child had? (you can circle more than one)				
	1 = none	6 = tight throat	11 =shock/low blood pressure		
	2 = itchy Rash	7 = wheeze	12 = collapse/loss of consciousness		
	3 =swelling(face/lips/eyes)	8 = vomiting	13 = worsening of eczema		
	4 = flushing	9 = diarrhoea			
	5 = itchy mouth/throat	10 = blue lips			
22.7.3	If Yes, how old was this child when he/she had the first reaction?		XX	Months	
22.7.4	If yes, how long after the eating the food did the reaction occur?		**1=** < 1 hour	**2=** 1-24 hours	**3=** >24 hours
22.7.5	If yes, was this reaction confirmed by a doctor?		1 = Yes	**0** = No	

HISTORY OF ALLERGIC ILLNESSES

Q23 Asthma

Q23.1	Has your child ever had symptoms of asthma? (e.g. wheeze, persistent cough at night or when exercising, shortness of breath)	**1** = Yes		**0** = No
Q23.2	If Yes, how old was he/she?	XX		Months
Q23.3	If yes, who diagnosed the asthma?	**1** = Self	**2** = Nurse	**3** = Doctor

Q24 Hay fever

Q24.1	Has your child ever had symptoms of hay fever (e.g. itchy runny eyes, itchy runny nose, blocked nose, frequent sneezing) without having a "cold" or upper respiratory tract infection?	**1** = Yes		**0** = No
Q24.2	If Yes, how old was he/she?	XX		Months
Q24.3	If yes, who diagnosed the hay fever?	**1** = Self	**2** = Nurse	**3** = Doctor

Q25 Eczema

Q25.1	Has your child ever had symptoms of eczema (e.g. an itchy rash especially in the folds of the elbows, behinds the knees, in front of the ankles, under the buttocks or around the neck, ears or eyes?	**1** = Yes		**0** = No
Q25.2	If yes, how old was your child then?	XX		Months
Q25.3	If yes, who diagnosed the eczema?	**1** = Self	**2** = Nurse	**3** = Doctor

Q27 Family history of allergic disease

Does anyone in your family have allergic diseases? Please circle. (you can choose more than one option)						
	Family member	None	Asthma	Hay fever	Eczema	Food allergy
Q27.1	Mother	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy
Q27.2	Father	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy
Q27.3	Full Sibling 1	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy
Q26.4	Full Sibling 2	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy
Q27.5	Full Sibling 3	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy
Q27.6	Full Sibling 4	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy

Q28 Child's Medical history

Q28.1	Does your child have any other significant medical problems? (e.g. heart or lung problems, kidney or liver disease, epilepsy, diabetes)	**1** = Yes	**0** = No
Q28.2	If yes, please specify		

Q29 Home Language and Migration

Q29.1	**What language do you mainly speak at home? (Please choose only one)**		
	1 = IsiXhosa	2 = English	3 = Afrikaans
	4 = IsiZulu	5 = Sesotho	6 = Setswana
	7 = SiSwati	8 = IsiNdebele	9=Xitsonga
	10 = Sepedi	11=Tshivenda	12 = Other
Q29.1.2	**If Xhosa speaking, was this child born in Cape Town?**	**1 = Yes**	**0 =** No
	If No, please complete **Q 29.2** **If Yes,** please skip to **Q29.3**		

29.2.1	**Where was this child born?**	**Province**			
		1 = Western Cape 2 = Eastern Cape 3 = Northern Cape 4 = Free state 5 = Gauteng		6 = Kwazulu Natal 7 = Mpumalanga 8 = Limpopo 9 = North West Province 10 = Other	
		Town (specify)		Free text	
29.2.2	**When did this child move to Cape Town?**	XXXX	**Year**	XX	**Month**

Q29.3	**Was this child's mother born in Cape Town?**			**1 =** Yes	**0 =** No
29.3.1	**If No, where was he/she born?**	**Province (please circle)**			
		1 = Western Cape 2 = Eastern Cape 3 = Northern Cape 4 = Free state 5 = Gauteng		6 = Kwazulu Natal 7 = Mpumalanga 8 = Limpopo 9 = North West Province 10 = Other	
		Town (specify)		Free text	
29.3.2	**If no when did she move to Cape Town?**	XXXX	**Year** **Year**	XX	**Month**

Q30 Ethnicity

Q30	What is your child's ethnic origin? (circle as appropriate)	**1** = White/Caucasian	**2** = Coloured / Mixed race
		3 = Black African	**4** = Asian/Indian
		5 = Other (Specify)	

Q32 Parental Education level

What is the highest level of education obtained by any parent of this child?	
1 = None	**11** = Grade 9 / Std 7
2 = Grade R / preschool	**12** = Grade 10 / Std 8
3 = Grade 1 / SubA	**13** = Grade 11 / Std 9
4 = Grade 2 / Sub B	**14** = Grade 12 / Matric
5 = Grade 3 / Std 1	**15** = Grade 9,10,11 (Std 7,8,9) & diploma
6 = Grade 4 / Std 2	**16** = Grade 12 (Std 10) & Certificate or Diploma
7 = Grade 5 / Std 3	**17** = Grade 12 (Std 10) & Degree
8 = Grade 6 / Std 4	**18** = Grade 12 (Std 10) & Degree plus Diploma or further degree
9 = Grade 7 / Std 5	**19** = Grade 12 (Std 10) & PhD
10 = Grade 8 / Std 6	Other (**Specify) :** Free text

5. General Protocol for Open Oral Food Challenge

Note: Exact doses of individual foods to be challenged will be held in a separate study folder

Q1	Participant ID		**Q4**	Today's Date	
Q2	Date of Birth		**Q5**	Today's Weight	
Q3	Sex (please circle)	1 = Male 2 = Female	**Q6**	Food challenge being performed	

Step 1: Pre-challenge assessment	**Tick when complete**
1. Ensure that oxygen and suction are in working order	
2. Ensure that the drug box is complete and accessible	
3. Calculate the emergency drug doses for the participants weight of today	

Drug	**Recommended dose**	**Calculated dose for participant weight: ___kg**
Adrenaline 1:1000	0.01mL/kg IM	
Adrenaline neb 1:1000	0.2-0.4mL/kg adrenaline (max 5 mL) mixed with equal amounts of normal saline	
Hydrocortisone	4mg/kg IV (max 100 mg)	
Nebulised salbutamol	2.5-5 mg	
Promethazine (Phenergan)	1mg/kg IV	
Salbutamol via MDI	6-10 puffs	
Cetirizine	2.5mg/5mg	

4. Assess if this is a high risk child (and gain IV access if needed)

- Any symptoms of asthma within the last 4 years.
- Any previous severe allergic reactions i.e. cardio-respiratory symptoms regardless of the allergen
- Any child who has received adrenaline for an allergic reaction in the past.

5. Ensure that the child has not had an acute exacerbation of asthma, rhinitis or eczema in the last 2 weeks.

(If he/she has, discuss with consultant and decide whether challenge should be postponed)

6. Ensure that the child has not taken any medications that need to be stopped prior to the food challenge. *(see note below)*

Medication	**Duration to be stopped prior to the challenge**
• **Long acting antihistamines,** i.e.Cetirizine, Loratadine, Aterax • **Oral steroids**	5 days
• **Long acting β agonists,** i.e. Serevent or Formoterol (green inhalers), Seretide(purple inhaler) or Symbicord (red inhaler) • **Short acting antihistamines,** i.e.Piriton, Vallergan, Phenergan	48 hours
• **Leukotrine receptor antagonists,** i.e. Montelukast or Singulair	24 hours

7. Ensure that the child has not eaten (apart from sips of water) for 2 hours prior to the start of the challenge

8. Ensure that the child is fit for challenge on brief physical examination

Note:

- Regular preventative (steroid) inhalers, brown or orange in colour, such as Becotide should not be stopped prior to a challenge.
- Reliever inhalers may also be given, however, any child who is using their blue inhaler more frequently than normal in the two weeks prior to the challenge should discuss this with the study team before a decision is made whether or not to challenge them.
- Combined preventative and long acting relievers, i.e. Seretide and Symbicord inhalers should be stopped and the preventative part of the inhaler should be commenced instead for 72 hours prior to the challenge

Step 2: Preparation for oral food challenge	**Tick when complete**
The study nurse/doctor (and dietician if necessary) will organise both the challenge foods and any carrier foods on the day of admission. The foods should be labelled and dated and should be checked by 2 staff members prior to administration.	
The challenge food can be disguised in a food which the child eats regularly and is known to tolerate well.	
Follow the challenge protocol step by step as shown in Step 3 below	
The challenge should be discontinued at any stage when a reaction occurs, and action taken where necessary.	
At each stage, a full assessment set of observations should be performed 15-20 minutes after the dose has been given, or immediately when there are signs of a reaction.	
If there has been no reaction then observe for 2 hours with half-hourly observations	
If there has been a reaction, stop the challenge and refer to Step 4	

Criteria for a positive challenge
One or more of the following within 2 hours of the last dose within the food challenge • three or more concurrent non-contact hives (urticarial lesion) lasting for more than 5 min • Perioral or peri-orbital angioedema • Vomiting (excluding immediate post-ingestion gag/ vomits) • Circulatory compromise • Respiratory compromise (Wheezing, Inability to speak, Stridor, Dysphonia, Aphonia or signs of respiratory "distress")
Additional signs noted (but not positive challenge)
• Transient urticaria (less than three hives lasting less than 5min) • Erythematous rashes • Diarrhoea • Abdominal pain (such as abnormal stillness or doubling over) that persists for ≥ 3 minutes • Persistent rubbing of nose or eyes that lasts for ≥ 3 minutes • Persistent rhinorrhoea that lasts for ≥ 3 minutes • Persistent scratching that lasts for ≥ 3 minutes

Step 3: Oral Food Challenge						
Time	Dose number	Time into challenge (minutes)	Test Dose	Time interval	Reaction If YES stop challenge and go to step 4	Observations
	Baseline (pre-dose) observations					Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	1	0		15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	2	15		15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	3	30		15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	4	45		15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	5	60		15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	6	75		15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	7	90		15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		120	Observations only	30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		150		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		180		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		210		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____

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Step 4. Positive Reactions: Record any reactions in the table below, then follow the steps for management		
Time	Symptoms	Treatment Given
2 hour post challenge check		
3 days post challenge check		
OUTOME OF OFC:		

Mild, non-cardiorespiratory reactions (e.g. rash/angioedema)

- The child should receive chlorpheniramine and be closely observed.
- If the child is asthmatic, also give 10 puffs of their salbutamol inhaler via a spacer device and a dose of prednisone to prevent a late phase reaction.
- The patient should be observed for at least 3 hours post challenge.

Reaction involving wheeze

- Give 15 litres of oxygen via a face mask with a reservoir bag.
- Give a salbutamol nebulizer.
- If **ANY** respiratory distress occurs give IM adrenaline.
- Following administration of the adrenaline give a dose of chlorpheniramine and give hydrocortisone/prednisone to prevent late phase reaction.
- If there is no response in 5 minutes, give a second dose of IM adrenaline and another salbutamol nebulizer and contact paediatric ICU for advice.
- The patient should be observed for at least 6 hours post-reaction and admitted overnight if deemed necessary.

Reaction involving stridor

- Give 15 litres of oxygen via a face mask with a reservoir bag.
- Give an adrenaline nebulizer.
- If **ANY** respiratory distress occurs give IM adrenaline.
- Following administration of the adrenaline give a dose of cetirizine or Phenergan and give hydrocortisone/prednisone to prevent late phase reaction.
- If there is no response in 5 minutes, give a second dose of IM adrenaline and contact paediatric ICU.
- The patient should be observed for at least 6 hours post-reaction and admitted overnight if deemed necessary.

Reaction involving hypotension or collapse

- Give IM adrenaline.
- Gain IV access and give 20ml/kg bolus of fluid, 0.9% NaCl.
- Give Phenergan IV, and IV hydrocortisone to prevent late phase reaction.
- If no response in 5 minutes, repeat IM adrenaline and fast bleep an anaesthetist if not already present.
- The patient should be observed for at least 6 hours post-reaction and admitted overnight if deemed necessary.

Step 3: Oral Food Challenge: PEANUT

Product: Black Cat peanut butter (salt and sugar free)
(May be mixed with apple sauce, yoghurt, meat pie)

Time	Dose number	Time into challenge (minutes)	Test Dose	Time interval	Reaction If YES stop challenge and go to step 4	Observations
	Baseline (pre-dose) observations					Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	1	0	Smear inside lip	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	2	20	1/16th tsp	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	3	40	1/8th tsp	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	4	60	¼ tsp	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	5	80	½ tsp	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	6	100	1 tsp	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		120	Observations only	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		150		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		180		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		210		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		240		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____

Step 3: Oral Food Challenge: RAW EGG WHITE Raw egg white (total eqw 60g egg) (May be mixed with apple sauce, yoghurt,)						
Time	Dose number	Time into challenge (minutes)	Test Dose	Time interval	Reaction If YES stop challenge and go to step 4	Observations
	Baseline (pre-dose) observations					Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	1	0	Touch lip (use dropper or syringe)	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	2	15	0.5ml	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	3	30	1.0ml	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	4	45	2.0ml	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	5	60	5.0ml	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	6	75	10ml	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	7	90	20ml	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		105	Observation	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		120		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		150		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		180	Continue observations for another hour if any reaction occurred	30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		180		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____

Step 3: Oral Food Challenge: COW'S MILK						
Time	Dose number	Time into challenge (minutes)	Test Dose	Time interval	Reaction If YES stop challenge and go to step 4	Observations
	Baseline (pre-dose) observations					Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	1	0	1 ml	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	2	15	5 ml	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	3	30	10ml	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	4	45	20ml	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	5	60	40ml	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	6	75	100ml	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	7	90	100ml	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		105	Observations only	30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		135		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		165		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		195		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____

Step 3: Oral Food Challenge: SOYA						
Time	Dose number	Time into challenge (minutes)	Test Dose	Time interval	Reaction If YES stop challenge and go to step 4	Observations
	Baseline (pre-dose) observations					Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	1	0	1 ml	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	2	15	5 ml	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	3	30	10ml	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	4	45	20ml	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	5	60	40ml	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	6	75	100ml	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	7	90	100ml	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		105	Observations only	30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		135		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		165		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		195		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____

Step 3: Oral Food Challenge: HAZELNUT						
Time	Dose number	Time into challenge (minutes)	Test Dose	Time interval	Reaction If YES stop challenge and go to step 4	Observations
	Baseline (pre-dose) observations					Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	1	0	0.02g	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	2	15	0.07g	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	3	30	0.2g	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	4	45	0.7g	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	5	60	2.2g	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	6	75	7.3g	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	7	90	22g	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		105	Observations only	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		120		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		150		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		180		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		210		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____

Step 3: Oral Food Challenge: WHEAT (WHEATBIX)						
Time	Dose number	Time into challenge (minutes)	Test Dose	Time interval	Reaction If YES stop challenge and go to step 4	Observations
	Baseline (pre-dose) observations					Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	1	0	10mg	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	2	15	0.5g	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	3	30	1g	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	4	45	2g	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	5	60	5g	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	6	75	10g	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	7	90	20g	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		105	Observations only	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		120		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		150		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		180		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		210		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____

Step 3: Oral Food Challenge: FISH (PLAIN POACHED HAKE)						
Time	Dose number	Time into challenge (minutes)	Test Dose	Time interval	Reaction If YES stop challenge and go to step 4	Observations
	Baseline (pre-dose) observations					Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	1	0	10mg	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	2	15	0.25g	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	3	30	0.5g	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	4	45	2g	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	5	60	5g	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	6	75	10g	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	7	90	30g	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		105	Observations only	15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		120		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		150		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		180		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		210		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____

Parent Information on Food Challenge

Dear Parent

The results of the allergy tests in your child suggest that he/she may have a food allergy. However, we are not sure of this so we need to find out for sure by doing a food challenge.

What is a Food Challenge?

In a food challenge we bring the child in to hospital for the day and give them small amounts of the food to which they had a positive allergy test, to see if there is any reaction. This is done in a very controlled way and the doctors and nurses will be there with you and your child to watch them closely. That way we can notice reactions early and treat them if needed.

If the child has no reactions to a very tiny amount of the food, then we will give them a little more, step by step, until we reach the top dose. The top dose will be similar to a normal "portion" of the food, for example about 1 tablespoon of peanut butter or one cupful of milk. In between each dose we will gently examine the child to look for any reactions, and also measure the temperature, pulse rate, heart rate, blood pressure and oxygen levels.

If there are any reactions along the way, we will stop the food challenge and treat the child if necessary.

We will then give you the correct advice on the food in the child's diet according to the results of the challenge.

The doctor will also phone you at home after 2 days to make sure everything is alright and to ask if the child's eczema has got any worse.

How long will the challenge take?

You and your child will need to be in hospital for at least a whole morning. Giving the doses of food takes up to 2 hours because we leave a 20 minute gap between each dose.

After the challenge, we will keep an eye on the child for at least 2 hours if there has been no reaction. This is to be safe that the child remains well and that there are no "late reactions."

If there has been a reaction, we will keep an eye on your child for at least 4 hours until we are happy that all is well. Sometimes, if children have had a bad reaction, we may decide it is better to keep them in hospital overnight. However, this is very rare.

Will it hurt my child?

The actual food challenge is not painful in any way. Some children may be a bit frightened of having their temperature and pulse e.t.c. taken but it is not sore.

In a few children who are at higher risk of a reaction, especially those with asthma, we may consider putting a drip up before the challenge. We will only do this if absolutely necessary.

If children have a reaction during the challenge, the doctors and nurses will be right there to treat the child as quickly as possible. Most reactions are mild, such as rashes, and the child may need to take some antihistamine syrup. A few children will have more severe reactions, and these children may need an injection or even a drip.

We do not expect this in many children at all because we start off with such small doses of food and watch the children so carefully.

What do you need to do?

1. Your child will need to be off some of their regular medications for up to a week before the challenge. Your doctor will give you details of these below:

   Medication……When to stop……

   Medication……When to stop……

   Medication……When to stop……

2. If your child has been unwell in the 2 weeks before the challenge, please let the study doctor know a few days before the challenge so that we can decide whether we need to postpone the challenge. The doctor or nurse will also phone you 2 days before the challenge to make sure all is well.

3. We will ask you to come to the paediatric allergy clinic at 8.30 on the morning of the challenge. We will then ask a few questions to make sure all is well, have a quick look at the child and take their observations such as temperature and pulse. We will aim to start the actual challenge by 9 am.

4. On the morning of the challenge, your child can have their regular milk and/or a light breakfast between 6 and 7 am. After that they should not eat or drink anything (except a few sips of water) before the challenge.

5. We may ask you to bring along some of the child's favourite food or regular milk so that we can mix the test food into it for the child to eat.

6. Please dress the child in comfortable clothes that are easy to lift up for examining the child.

7. Bring along any favourite toys/dummies/blankets. It is a long morning for the children and we would like to make it as nice as possible for them!

8. We will give you travel money once you are in hospital for the challenge.

Thank you

If you have any questions or concerns at any stage about the food challenge, please contact: Dr Maresa Botha on 0216585779

6. Checklists and Data Capture Sheets

DATA CAPTURE SHEET 1

Q1	Participant ID	0000/XX		
Q2	Enrolment date	DD/MM/YYYY	Creche	
Q3	Study site	1 = Urban	2= Rural	
Q4	Date of birth	DD/MM/YYYY		
Q5	Age at enrolment	XX years XX months		
Q6	Sex	1= Male	2=Female	

Crèche visit activity checklist (please circle)		
Consent to SAFFA study	Yes/No	If No, please complete non-participant questionnaire
Consent form copy given to parents	Yes/No	
Questionnaire completed	Yes/No	
Physical examination completed	Yes/No	
Skin Prick Test completed	Yes/No	
Need further investigation/OFC?	Yes/No	If Yes, • Was appointment booked at RXH? Yes/No • Was parent given OFC information? Yes/No • Appointment Date:

Hospital Visit Activity Checklist (please circle)		
Consent form for OFC and other tests	Yes/No	
Information and consent form given to parents?	Yes/No	
Skin Prick test	Yes/No	
Blood sample	Yes/No	
Stool sample	Yes/No	
Oral Food Challenge completed and conclusive	Yes/No	If not conclusive, • Was repeat appointment booked? Yes/No • Appointment Date:

FINAL RESULT	YES	NO
Sensitised (SPT≥1mm)	a	b
Oral food challenge indicated (SPT≥1mm)	c	d

Study Complete: Yes/No

Data Entry Complete: Yes/No

Crèche Visit: Physical Examination: Date_____ Examined by _____

Question 6: Anthropometric measures

Q 6.1 Height	**cm**	**Q 6.2 Weight**	**kg**
Q 6.3 Abdominal girth	**cm**	**Q6.4 Skin fold thickness**	**cm**

Question 7: Physical examination

Q 7.1 Allergic Rhinitis Yes/No (tickV)		**Q 7.2 Eczema Yes/No (tickV)**		**Q 7.3 Asthma Yes/No (tickV)**	
Sneezing		**Facial pallor**		**Tachypnoea(>40/min)**	
Itchy nose		**Facial erythema**		**Hyperinflation**	
Transverse nasal crease		**Hypo pigmented patches**		**Prolonged Expiration**	
Allergic salute		**Infra orbital folds (Dennie-Morgan folds)**		**Wheeze**	
Rhinorrhoea/discharge		**Angular cheilitis**			
Nasal congestion		**Anterior neck folds**			
Mouth Breathing		**Flexor involvement**			
Oedematous turbinates		**Extensor patches**			
"long face syndrome"		**Darkening lesions**			
Red eyes		**Lichenification**			
Itchy eyes					
Teary eyes/discharge					
Post –nasal drip (Clicking)					

Crèche Visit: Skin Prick Test results: Date_____ Done By_____

Anti-histamine taken? Yes/No When last? _____

Batch Numbers			
Negative		**Fish(cod)**	
Egg White		**Peanut**	
Cow's Milk		**Hazelnut**	
Soy		**Positive**	
Wheat			

Question 8: Skin Prick Test Results

Reagent		**Weal**			**Comments**
		X mm	Y mm	**Mean (mm)**	
8.1	**Negative**				
8.2	**Egg White**				
8.3	**Cow's Milk**				
8.4	**Soy**				
8.5	**Wheat**				
8.6	**Fish(cod)**				
8.7	**Peanut**				
8.8	**Hazelnut**				
8.9	**Positive**				
	Fresh Agent				
8.10	**Fresh Peanut**				**Comments**
8.11	**Egg White**				
8.12	**Cow's Milk**				

DATA CAPTURE SHEET 2

Blood specimen: Sample obtained: Yes/No

Food specific IgE levels	kU/L
Egg White	
Cow's milk	
Soy	
Wheat	
Fish (cod)	
Peanut	
Hazelnut	
Ascaris specific IgE	

Serum stored: Yes/No

Stool: Sample obtained: Yes/No

Worm Ova Present: Yes: _____ No: _____ If Yes:

Type	Yes	No	Quantity (epg)	Burden of infestation (Light/moderate/heavy)
A.lumbricoides				
T. trichiuria				
Hookwurm				
S. japonicum **S. mansoni**				

Stool sample stored: Yes/no

House Dust: Sample obtained: Yes/No Date obtained_____

Macroscopic examination				
Pollen				
Mould				
House Dust mite	**Negative**	**Scanty**	**Well represented**	**Heavy infestation**
ELISA				
Dog				
Cat				
House Dust Mite DerP1				
Cockroach				
Peanut Allergen				
Endotoxin				

Dust sample stored: Yes/No

DATA CAPTURE SHEET 3

ORAL FOOD CHALLENGE:
Study no: _____
Initials_____DOB_____
Date OFC performed: _____
Weight: _____

FOOD	TESTED?	Result if tested		
		Positive	Equivocal	Negative
Hen's egg (raw)	Yes			
	No			
Hen's egg (cooked)	Yes			
	No			
Cow's milk	Yes			
	No			
Soya milk	Yes			
	No			
Peanut butter	Yes			
	No			
Hake	Yes			
	No			
Wheat	Yes			
	No			
Tree nuts	Yes			
	No			

If result equivocal, Was OFC rebooked: Yes_____ No _____

Date of new booking: _____

OFC performed by: _____ Signature: _____

7. Journal submission guidelines

Current Allergy and Clinical Immunology

Journal of the Allergy Society of South Africa

7.1 Study Summary

Title

A cross-sectional study of Ig-E mediated food sensitisation and food allergy in an unselected population of South African children aged 12-36 months.

Background

Food allergies have been described as the new allergy epidemic in recent literature from resource rich settings with a prevalence of up to 10% in the 1st year of life. In South Africa there has been documentation over the last few years of an increase in the prevalence of allergic disease in population groups believed to be protected.

Objectives

4. To determine the sensitisation levels and challenge-proven prevalence to any one or more of the 7 common allergic foods (hen's egg, cow's milk, peanut, tree nuts, soy, wheat and fish) in children aged between 12-36 months.

Methodology

A sampling frame of all crèches in Cape Town will be used to randomly select crèches. A participant questionnaire and skin prick tests will be used to collect data from children enrolled into the study. Those who qualify will be invited for food challenges.

Envisaged outcomes

To determine the true prevalence of food allergy in a rapidly urbanising context for issues of advocacy regarding health service provision, availability of safe and affordable alternative foods particularly in resource poor communities.

STUDY SUMMARY: 200 WORDS

INSTRUCTIONS FOR AUTHORS

Current Allergy & Clinical Immunology publishes articles concerned with the understanding and practice of allergic diseases or clinical immunology.

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Manuscript preparation

1. Articles may be submitted electronically by email to mail@allergysa.org. Authors should state their full name, qualifications, institutional affiliation and provide a corresponding address and email on the title page. Articles should be a maximum of 3500 words with no more than 3 figures and 3 tables. Short reports should be a maximum of 1000 words with a maximum of 2 tables or illustrations. Case reports should not exceed 2000 words, with a maximum of 3 figures, 3 tables and 10 references, and should conform to the usual structure: abstract (not more than 50 words), introduction, methods, results, discussion.

2. Each article should be accompanied by a summary of not more than 200 words (50 words for short reports). A structured abstract is required for original research papers.

3. Authors are requested to declare conflict of interest and source of funding relating to the article. Authors should disclose any relationship within the last 2 years with pharmaceutical companies in the following categories if pertinent to the article: research grants, educational support (sponsorship at conference), advisory boards, speaker, consultant or shares in companies. This must be stated at the end of the manuscript before the references. Details of ethical approval obtained must be included in all original research articles.

4. All abbreviations should be spelt out when first used in the text and thereafter used consistently.

5. Scientific measurements should be expressed in SI units.

6. Tables should be labelled with Roman numerals, thus: I, II, III, etc. and illustrations with Arabic numerals, thus: 1, 2, 3, etc. Tables should be submitted as part of the manuscript file. Please do not submit photographs in Powerpoint and MS Word format - a high-resolution jpg is required. Photographs should be submitted separately from the manuscript file and clearly labelled.

7. Where identification of a patient is possible from a photograph the author must submit a consent to publication signed by the patient, or by the parent or guardian in the case of a minor.

8. If any tables or illustrations submitted have been published elsewhere, written consent to republication should be obtained by the author from the copyright holder and the author(s).

References

1. References should be inserted in the text as superior numbers, and should be listed at the end of the article in numerical order.

2. References should be set out in the Vancouver style, and only approved abbreviations of journal titles should be used; consult the January issue of *Index Medicus* (No. 1 Part 1) for these details. Names and initials of all authors should be given unless there are more than six, in which case the first three names should be given followed by 'et al.' First and last page numbers should be given.

   Example:
   1. Khakoo G, Lack G. Recommendations for using MMR vaccine in children allergic to eggs. BMJ 2000; 320: 929-932.

3. References for books should include author, title, town, publisher and date.

   Example:
   1. Abbas AK, Lichtman AH. Basic Immunology. Philadelphia: WB Saunders, 2001.

4. 'Unpublished observations' and 'personal communications' may be cited in the text, but not in the reference list. Articles accepted but not yet published can be included as references followed by '(in press)'.

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