Tolerance in raw egg allergy on consumption of cooked egg

Final Project Report

A report for the Australian Egg Corporation Limited

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Foreword

This project was conducted to define what proportion of raw egg allergic infants can tolerate egg in baked goods and whether introduction of baked goods containing egg into the diet of raw egg allergic children hastens the development of tolerance to raw egg.

This project was funded from industry revenue which is matched by funds provided by the Australian Government.

This report is an addition to AECL's range of peer reviewed research publications and an output of our R&D program, which aims to support improved efficiency, sustainability, product quality, education and technology transfer in the Australian egg industry.

Most of our publications are available for viewing or downloading through our website:

http://aecl.org/r-and-d/

Printed copies of this report are available for a nominal postage and handling fee and can be requested by phoning (02) 9409 6999 or emailing research@aecl.org.

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The HealthNuts study team consists of Katrina Allen, Melissa Wake, Lyle Gurrin Shyamali Dharmage, Melanie Matheson, Nicholas Osborne, Anne-Louise Ponsonby, Dean Tey, Jeeva Sanjeevan, Helen Czech, Leone Thiele, Deborah Anderson, Terry Dwyer, Adrian Lowe, Mimi Tang and David Hill.

We thank the children and parents who participated in the HealthNuts Study as well as the staff of Melbourne's Local Government Areas for access to community Immunization Clinics. We thank ALK Abello, S.A. Madrid, Spain for supplying the skin prick testing reagents and the HealthNuts safety committee: Associate Professor Noel Cranswick (Australian Paediatric Pharmacology Research Unit, Murdoch Childrens Research Institute), Dr Jo Smart (Department of Allergy and Immunology, Royal Children's Hospital, Melbourne, Australia), and Associate Professor Jo Douglass (Director, Department of Allergy and Immunology, Royal Melbourne Hospital, Melbourne, Australia).

The Australian Egg Corporation Limited provided the funds which supported this project.

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Abbreviations

ACTH	Adrenocorticotropic hormone
NHMRC	National Health and Medical Research Council
OFC	Oral Food Challenge
OR	Odds Ratio
SD	Standard Deviation
SPT	Skin Prick Test

1 Executive Summary

1.1 Objectives

To address the hypothesis that regular ingestion of egg in baked goods is able to induce tolerance to raw egg in children with egg allergy. Specifically, we aimed to:

1. Define what proportion of raw egg allergic 12 month old infants can tolerate egg in baked goods
2. Determine whether introduction of baked goods containing egg into the diet of raw egg allergic children hastens the development of tolerance to raw egg at age two years

1.2 Background

Increasing numbers of children are being diagnosed with food allergies including egg allergy. Australia has one of the highest rates of infantile food allergy worldwide, with 9% of one year old infants shown to have raw egg allergy. These children may benefit from being able to introduce baked goods containing small amounts of egg into their diet.

1.3 Research methods

This project was nested within the HealthNuts study, a large population-based study of 5,300 one year old infants. As part of the HealthNuts study, all infants underwent a screening test (skin prick testing) to determine whether they were sensitised to egg white. Those who tested positive on this screening test underwent a formal hospital based food challenge involving ingestion of increasing doses of raw egg to determine whether they were egg allergic or tolerant.

Within the HealthNuts study, this project involved recruiting infants for a formal baked egg challenge at a follow up clinic within one month of the initial raw egg challenge. Those who were able to tolerate baked egg were encouraged to eat egg in baked egg products (to the equivalent of less than a two-egg baked cake) at least three times per week but to avoid raw and semi-cooked eggs, as they have not passed a raw egg challenge. Those who did not pass the baked egg challenge were asked to exclude all egg (both raw and baked) from their diets. All children were offered a raw egg challenge one year later (at age two years).

1.4 Outcomes

As part of this study, 161 raw egg allergic infants underwent an oral food challenge to baked egg. Of these, 124 (77%) were tolerant to baked egg and 27 (16.8%) were allergic to baked egg. The remaining 10 (6.2%) challenges were inconclusive.

Of those 151 infants with conclusive baked egg challenge results at age one year, 111 have completed an oral food challenge to raw egg at age two years, with 58.6% of infants still allergic to raw egg and the remainder having outgrown their egg allergy.

Infants who were allergic to baked egg at age one year were more likely to be positive on challenge to raw egg at age two (80% vs 53.8%; p=0.032). Baked egg consumption was also associated with allergy status at two years of age. Those infants who ate little or no baked egg products during the study were less likely to have recovered from their raw egg allergy at the time of the two year old challenge compared to those who ate baked egg frequently (32.5% vs 53.3%; p=0.053).

1.5 Implications

Significant numbers of children (8.9% of one year olds) have raw egg allergy. Eating baked egg products may hasten tolerance to raw egg, or alternatively it defines a group of children more likely to outgrow egg allergy. The ability to eat baked egg appears to act as a prognostic indicator of resolution of egg allergy.

2 Overall Conclusions

The majority of infants (77%) who are allergic to raw egg at 12 months of age are able to tolerate egg in baked goods. Nearly half of infants with raw egg allergy (41%) will outgrow their egg allergy at two years of age. Infants who are tolerant to baked egg and ingest baked egg products are more likely to outgrow their egg allergy, compared to infants who are allergic to baked egg at 12 months of age.

3 Introduction

3.1 Background

There is growing evidence of an epidemic of food allergy in industrialised countries. Our NHMRC-funded research project (the HealthNuts study) has shown that up to 17% of 12 month old infants are *sensitised* to raw hen's egg (i.e. have a positive skin prick test). More surprisingly however is that 9% of 12 month old children in this Melbourne population based study have a *true raw egg allergy* (i.e. cannot tolerate raw egg during a formal hospital based food challenge) (Osborne et al 2011).

The HealthNuts study has recruited 5,300 infants, all of whom have undergone skin prick testing to egg white followed by formal hospital based food challenge to raw egg for skin prick test positive individuals. The current project tested the hypothesis that although 9% of children in the population cannot tolerate raw egg the vast majority of these can tolerate egg in baked goods. A recent publication suggested that 60-70% of children with raw egg allergy can tolerate egg in baked goods (Lemon-Mule et al 2008).

Furthermore there is preliminary evidence from other studies that ingestion of egg in baked goods hastens the development of tolerance to raw egg (Lemon-Mule et al 2008). In the past, the mainstay of egg allergy management was strict dietary avoidance of egg and all egg-related products. New evidence suggests that this paradigm may be incorrect and even potentially harmful by delaying the induction of tolerance through failure to expose the immune system to egg, but further confirmatory research evidence is required.

Our pilot data has also revealed that amongst those children who are sensitised (a positive skin prick test) to raw egg but who are not allergic there appears to be a higher rate of low level egg ingestion in the form of egg in baked goods. Egg in baked goods is a less allergenic form of egg than in the semi-cooked or raw form due to the conformational change in the epitope associated with cooking at high temperatures. However it is unclear whether children who develop tolerance to egg do so because they have ingested low levels of egg in baked products or despite the fact that they have been exposed to dietary egg.

Egg allergy has an excellent prognosis with reports in the past showing that 50% of children with egg allergy have developed tolerance to egg by four years of age (Boyano-Martinex 2002). Recent reports, however, suggest that the development of tolerance to egg is now occurring less frequently (Savahe et al 2007). It has been shown that 55% of children with raw egg allergy can tolerate baked egg (Lemon-Mule et al 2008). Recent evidence also suggests that early introduction of foods to a child's diet reduces food allergy (Du Toit et al 2008).

3.2 Objectives

The aim of this research was to address the hypothesis that regular ingestion of egg in baked goods is able to induce tolerance to raw egg in children with egg allergy. Specifically, we aimed to:

1. Define what proportion of raw egg allergic 12 month old infants can tolerate egg in baked goods
2. Determine whether introduction of baked goods containing egg into the diet of raw egg allergic children hastens the development of tolerance to raw egg at age two years

4 Methods

4.1 Study methods

The HealthNuts study is an NHMRC-funded research program and has recruited 5,276 12 month old infants over a 3.5 year study period, of which 488 were diagnosed as allergic to raw egg. For this sub-study on the effect of introduction of baked egg to raw egg allergic children we aimed to recruit 130 raw egg allergic children (as assessed by formal raw egg challenge as part of the HealthNuts study). These children completed a formal baked egg challenge at a follow up clinic within one month of the initial raw egg challenge. Those who were able to tolerate baked egg were encouraged to eat egg in baked egg products (to the equivalent of less than a two-egg baked cake) at least three times per week but to avoid raw and semi-cooked eggs, as they have not passed a raw egg challenge. Those who did not pass the baked egg challenge were asked to exclude all egg (both raw and baked) from their diets. All children were offered a raw egg challenge one year later (at age two years).

Phone reviews were conducted to record history of egg ingestion and or allergic reaction in the year following baked egg challenge. We have used this method of follow up effectively in previous allergy cohort studies. After one year all children were reassessed for raw egg allergy at clinical follow up using skin prick testing and a raw egg challenge. Exposure was defined as eating baked egg products and the outcome as tolerance to raw egg food challenge at two years of age.

4.2 Definitions

Predefined criteria for a positive OFC response were at least one of the following: three concurrent, noncontact urticarial reactions lasting at least five minutes; severe persistent vomiting; periorbital angioedema; and/or anaphylaxis (evidence of circulatory or respiratory tract involvement; i.e. wheeze, cough, change in quality of cry, or respiratory distress) within one hour of the last challenge dose. Infants were considered to have egg allergy (and thus not offered a food challenge) if a parent reported a definite reaction to egg consistent with the above OFC criteria in the previous month before the food challenge clinic plus a positive SPT response plus current avoidance of egg in the infant's diet.

Allergic status for both raw egg and baked egg allergy were categorised as binary variables during analysis, with participants having either negative (tolerant) or positive (allergic) oral food challenges.

Although some study participants completed multiple phone questionnaires, we analysed only information retrieved from each participant's first follow-up questionnaire. From the questionnaire, the information on frequency of baked egg products (cake, biscuits, cupcake, donut or muffins) eaten was analysed to address the second aim of the study. These results were amalgamated into a single variable encompassing all baked egg food consumption, classified as none, some (1-5 times per month) or frequent (>5 times per month).

4.3 Statistical analyses

Frequency of baked egg consumption and baked egg challenge results were not analysed in the same logistic regression models as we decided *a priori* that baked egg consumption does not meet the criteria for confounding as baked egg consumption may lie on the causal pathway.

Two separate univariate logistic regression models were used to examine the association between:
a) baked egg allergy status and;
b) baked egg consumption and raw egg allergy status at age two.

To assess the relationship between baked egg consumption and raw egg allergy status at age two, we initially examined trends across the three categories of baked egg consumption (none, some, frequent) by assigning numeric values to the baked egg consumption categories and assuming a linear relationship with the log odds of the prevalence of raw egg allergy in the logistic regression models. Further analysis constricted to only those children who were baked egg tolerant was completed in attempt to untangle the effects of baked egg consumption from baked egg allergy status. This was completed by condensing the baked egg consumption variable to a binary variable of no or low frequency of consumption verses high frequency consumption, as few infants in the baked egg tolerant group had no consumption of baked egg.

Stata software (version 12) was used for all statistical analyses.

5 Results

As part of this study, 161 raw egg allergic infants have undergone an oral food challenge to baked egg. The baked egg challenges were conducted an average of 1.1 (SD, 0.95) months after the raw egg OFC. Of these, 124 (77%) were tolerant to baked egg and 27 (16.8%) were allergic. The remaining 10 (6.2%) challenges were inconclusive, and excluded from further analysis.

Of the 151 infants with valid baked egg challenge results at age one year, 111 have completed a conclusive oral food challenge to raw egg at age two years. All further analysis has included only these 111 who were both eligible for the study and completed all required follow-up. Children's second year raw egg challenges occurred on average 12 (SD, 2.85) months after their initial raw egg challenge.

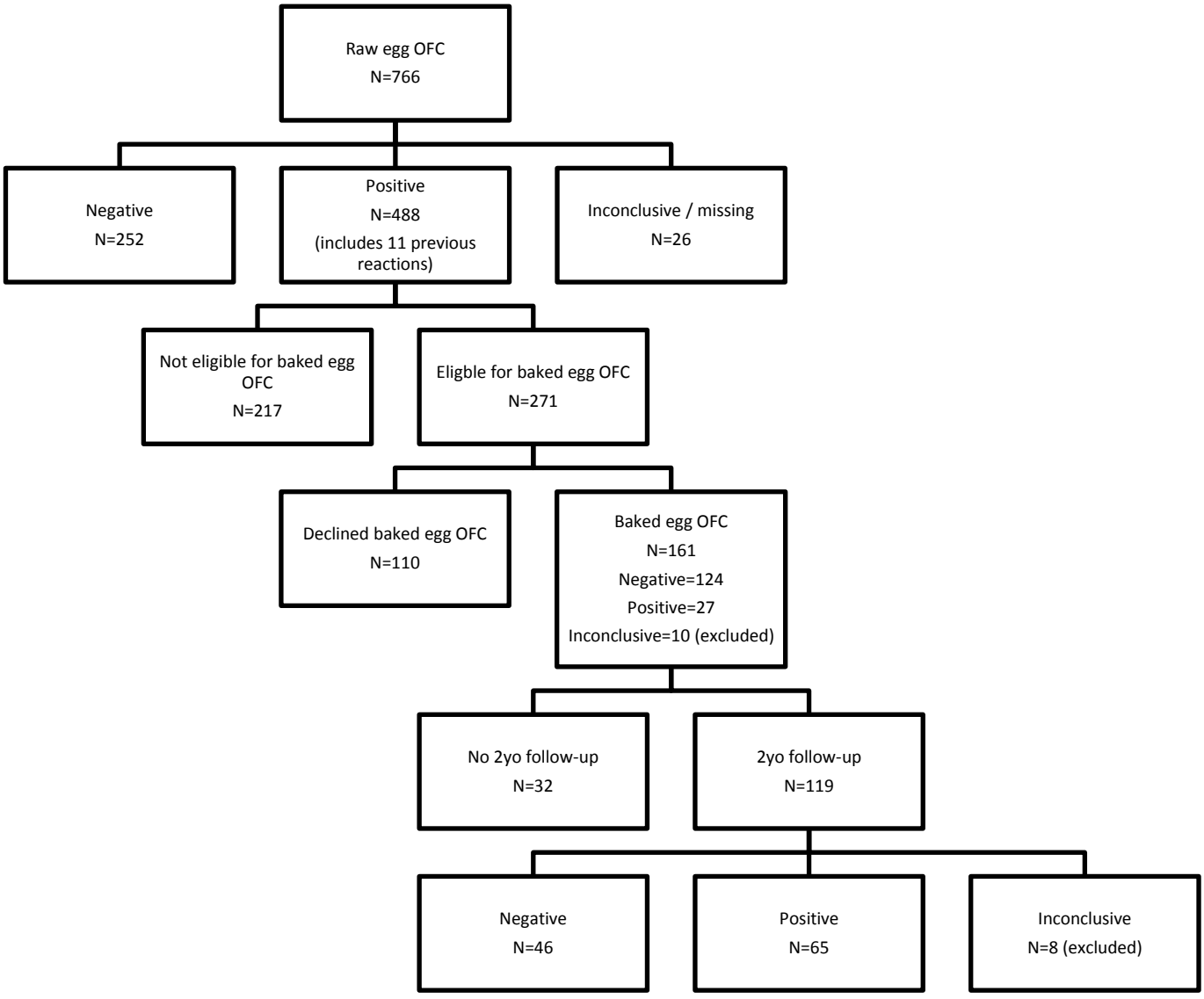

Figure 5-1 - Study flowchart

5.1 Relationship between baked egg allergy and resolution of raw egg allergy

Approximately 82% of raw egg allergic infants who completed a baked egg challenge at age one and a raw egg challenge at age two were tolerant to baked egg. While almost half of those who were baked egg tolerant outgrew their raw egg allergy by age two years, only twenty per cent of those who were both raw and baked egg allergic outgrew their raw egg allergy by age two (Table 3-1). Infants who were baked egg tolerant at age one were more likely to outgrow their raw egg allergy (p=0.032).

Table 5-1 - Relationship between baked egg oral food challenge results at 1 year and raw egg oral food challenge at two years

	Raw egg OFC at two yrs of age		**Chi2 P value**
	Tolerant (%)	**Allergic (%)**	
Baked egg tolerant 1yr	42 (46.1)	49 (53.9)	
Baked egg allergic 1yr	4 (2)	16 (80)	0.032

A logistic regression model comparing odds of allergy at age two between baked egg tolerant and allergic infants found a strong association (p=0.039). The estimated odds of being allergic to raw egg at age two for those who were allergic to baked egg at age one was 3.4 fold higher than those infants who were baked egg tolerant at age one. Therefore it is evident that having a raw and baked egg allergy at a young age significantly reduces one's odds of outgrowing his or her raw egg allergy.

Table 5-2 - Logistic regression modeling raw egg allergy at age two years against baked egg OFC status at age 1 year (n=111)

Conditions	**Odds Ratio for egg allergy at age two years**	**95% Confidence Interval**	**P-value**
Baked egg tolerant 1 yr	1.0	Reference	-
Baked egg allergic 1 yr	3.4	1.1-11.1	0.039

5.2 Frequency of bakeg egg ingestion and the resolution of egg allergy

Table 5-3 - Resolution of egg allergy stratified by frequency of baked egg ingestion

Baked egg consumption	Raw egg OFC at two yrs of age		Chi2 P value
	Tolerant (%)	Allergic (%)	
None	1 (12.5)	7 (87.5)	
1-5 times per month	12 (37.5)	20 (62.5)	
5 or more times per month	24 (53.3)	21 (42.7)	0.068

A logistic regression model was completed including raw egg challenge results at age two and frequency of baked egg consumption using no consumption of baked egg as the reference category. A moderate association was found revealing that as frequency of baked egg consumption increased, the odds of outgrowing raw egg allergy at age two also increased.

The estimated odds of being raw egg tolerant at age two for those who consumed baked egg between one and five times in the month was 4.2 times when compared to those who ate none. A stronger association was found when comparing those who consumed baked egg foods five or more times in the month with those who had eaten no baked egg products, with the estimated odds of raw egg tolerance at age two being 8.0 fold for those that ate large amounts of baked egg compared to those who ate none. Increased baked egg consumption thus increases a raw egg allergic one year-olds' odds of outgrowing his or her raw egg allergy (p=0.026 for trend).

Table 5-4 - Logistic regression modeling the odds of becoming tolerant to raw egg at age 2 against frequency of baked egg consumption (n=85)

Frequency of baked egg consumption	Odds Ratio for outgrowing raw egg allergy by two years	95% Confidence Interval	P-value, trend
None	1.0	Reference	
1-5 times during month prior	4.2	0.5-38.4	
5 or more times	8.0	0.9-70.5	0.026

In order to analyse how baked egg consumption and raw egg allergy at age two were associated, independently of baked egg allergy status at age one, the baked egg consumption variable was re-categorised to be low frequency (those infants who ate no baked egg or ate it between one and five times) and high frequency (those infants who ate baked egg five or more times). The analysis was then restricted to only those infants who

were baked egg tolerant at age one (Table 3-5). In this analysis, there was only weak evidence of an association between low and high frequency baked egg consumption and raw egg allergy status at age two (p=0.124).

Table 5-5 - Logistic regression modeling the odds of the resolution of egg allergy at 2 years for those who have no or low, versus high exposure to baked egg products amongst those who were tolerant to baked egg at age one

Conditions	Baked egg exposure	Odds ratio for outgrowing raw egg allergy at age two	95% Confidence Interval	P-value
Tolerant to baked egg	None/Low	1.0	Reference	-
	High	2.1	0.8-5.3	0.124

6 Conclusions and Recommendations

A significant number of children in the Australian population (8.9% of one year olds) have raw egg allergy. The majority of infants allergic to raw egg are able to tolerate egg in baked foods, for example, muffins and biscuits. Infants who were tolerant to baked egg at age one were significantly more likely to outgrow their egg allergy by two years of age. Eating baked egg products may hasten tolerance to raw egg, or alternatively it defines a group of children more likely to outgrow it. The ability to tolerate baked egg appears to act as a prognostic indicator of resolution of egg allergy.

Baked egg challenges should be undertaken in raw egg allergic infants as a majority are expected to tolerate baked egg. Knowledge of baked egg tolerance may ease the burden of dietary restrictions among infants with egg allergy. Baked egg tolerant infants should be encouraged to incorporate baked egg into their diet as this will not hinder, and may in fact hasten, the development of tolerance to raw egg.

6.1 Dissemination strategy

At completion of this study, a manuscript detailing the results of this study will be submitted to the Journal of Allergy and Clinical Immunology. The Journal of Allergy and Clinical Immunology has a high impact factor (11.0) and is the top journal in the field of allergy. Findings will also be widely disseminated to the media. Media stories generated by our results are likely to be highly topical resulting in high levels of media interest and exposure.

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8 Plain English Summary

Project Title:	Tolerance in raw egg allergy on consumption of cooked egg.
AECL Project No	1MC091
Researchers Involved	Katrina J Allen
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Objectives	Define what proportion of raw egg allergic 12 month old infants can tolerate egg in baked goods and to determine whether introduction of baked egg into the diet of raw egg allergic children hastens the development of tolerance to raw egg at age two years
Background	Australia has one of the highest rates of infantile food allergy worldwide, with 9% of one year old infants allergic to egg. Previous research suggests that some children with egg allergy can tolerate egg in baked goods and that ingestion of baked egg may hasten the resolution of egg allergy.
Research	This project was nested within the HealthNuts study, a large population-based study of 5,276 12-month-old infants. As part of the HealthNuts study, all infants underwent a screening test (skin prick testing) to determine whether they were sensitised to egg white. Those who tested positive on this screening test underwent a formal hospital based food challenge involving ingestion of increasing doses of raw egg to determine whether they were egg allergic or tolerant. A subgroup of children with raw egg allergy were invited to participate in a formal baked egg challenge. Those who were able to tolerate baked egg were encouraged to eat egg in baked egg products (to the equivalent of less than a two-egg baked cake) at least three times per week but to avoid raw and semi-cooked eggs. Those who did not pass the baked egg challenge were asked to exclude all egg from their diets. All children were offered a raw egg challenge one year later (at age two years).
Outcomes	As part of this study, 161 raw egg allergic infants underwent an oral food challenge to baked egg. 77% were tolerant to baked egg. 111 have completed OFC to raw egg at age two years, with 41% of infants having outgrown their egg allergy. Infants who were allergic to baked egg at age one year were more likely to remain allergic to raw egg at age two (80% vs 53.8%; p=0.032). Infants who ate little or no baked egg products during the study were less likely to have recovered from their raw egg allergy at the time of the two year old challenge compared to

	those who ate baked egg frequently (32.5% vs 53.3%; p=0.053).
Implications	Significant numbers of children (8.9% of one year olds) have raw egg allergy, yet the majority of these infants are able to tolerate egg in baked foods. The ability to eat baked egg appears to act as a prognostic indicator of resolution of egg allergy. Eating baked egg products may hasten tolerance to raw egg, or alternatively it defines a group of children more likely to outgrow egg allergy.
Key Words	Raw egg allergy; baked egg allergy; tolerance
Publications	Boyano-Martínez, T., García-Ara, C., Díaz-Pena, J.M., Martín-Esteban, M. (2002) Prediction of tolerance on the basis of quantification of egg white-specific IgE antibodies in children with egg allergy. *Journal of Allergy and Clinical Immunology*.110(2):304-9. Du Toit, G., Katz, Y., Sasieni, P., Mesher, D., Maleki, S.J., Fisher, H.R., et al. (2008) Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *Journal of Allergy and Clinical Immunology.* 122(5):984-91. Lemon-Mulé, H., Sampson, H.A., Sicherer, S.H., Shreffler, W.G,, Noone, S., Nowak-Wegrzyn, A. (2008) Immunologic changes in children with egg allergy ingesting extensively heated egg. *Journal of Allergy and Clinical Immunology*.122(5):977-83. Osborne, N.J., Koplin, J.J., Martin, P.E., Gurrin, L.C., Lowe, A.J., Matheson, M.C. et al. (2011) Prevalence of challenge-proven IgE-mediated food allergy using population based sampling and predetermined challenge criteria in infants. *Journal of Allergy and Clinical Immunology*. 127(3):668-76. Savage, J.H., Matsui, E.C., Skripak, J.M., Wood, R.A. (2007) The natural history of egg allergy. *Journal of Allergy and Clinical Immunology*. 120(6):1413-7.