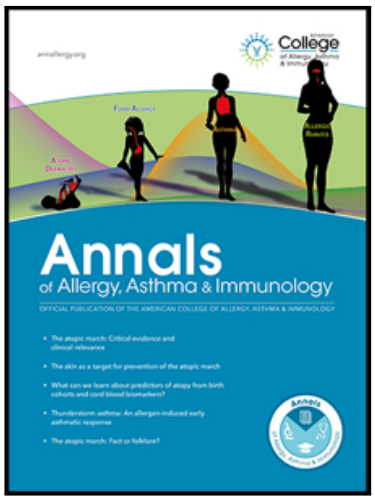
DOI:
10.1016/j.anai.2018.06.008

Document Version
Peer reviewed version



The Challenges of Preventing Food Allergy: lessons learned from LEAP and EAT

Helen Fisher PhD , George Du Toit MB, BCh ,
Henry T. Bahnson MPH , Gideon Lack MB, BCh, FRCPCH

PII: S1081-1206(18)30468-X
DOI: 10.1016/j.anai.2018.06.008
Reference: ANAI 2585

To appear in: *Annals of Allergy, Asthma Immunology*

Received date: 27 March 2018
Revised date: 7 June 2018
Accepted date: 7 June 2018

Please cite this article as: Helen Fisher PhD , George Du Toit MB, BCh , Henry T. Bahnson MPH , Gideon Lack MB, BCh, FRCPCH , The Challenges of Preventing Food Allergy: lessons learned from LEAP and EAT, *Annals of Allergy, Asthma Immunology* (2018), doi: 10.1016/j.anai.2018.06.008

Title: The Challenges of Preventing Food Allergy: lessons learned from LEAP and EAT

Authors: Helen Fisher, PhD[a,c], George Du Toit, MB, BCh[a,b,c], Henry T. Bahnson, MPH[d], Gideon Lack, MB, BCh, FRCPCH[a,b,c].

Department:

[a]Paediatric Allergy, Department of Women and Children's Heath, School of Life Course Sciences, King's College London, Guys' Hospital, London, UK

[b]Children's Allergy Service, Guy's and St. Thomas's NHS Foundation Trust, London, UK

[c]Paediatric Allergy, Peter Gorer Dept of Immunobiology, School of Immunology & Microbial Sciences, King's College London, Guys' Hospital, London, UK

[d]Immune Tolerance Network, Benaroya Research Institute, Seattle, Wash

Corresponding author details:

Professor Gideon Lack

Department of Paediatric Allergy

King's College London

St Thomas' Hospital

Westminster Bridge Road

London SE1 7EH

Tel: +44 (0)20 7188 9730

Email: gideon.lack@kcl.ac.uk

Trial Registration: Not applicable

Conflicts of Interest:

Helen Fisher: none

George Du Toit: G. Du Toit reports income from grants from the National Institute of Allergy and Infectious Diseases (NIAID, NIH), Food Allergy & Research Education (FARE), MRC & Asthma UK Centre, UK Department of Health through NIHR, National Peanut Board (NPB), and grants from UK Food Standards Agency (FSA); these grants part funded salary over period of this submitted work. PI on Aimmune-sponsored peanut allergy desensitization studies.

Henry T. Bahnson: none

Gideon Lack: G Lack has received research support from National Institute of Allergy and Infectious Diseases (NIAID, NIH), Food Allergy & Research Education (FARE), MRC and Asthma UK Centre, UK Department of Health through National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London, National Peanut Board (NPB), Food Standards Agency (FSA), Action Medical Research, and has stock/stock options with DBV Technologies.

Funding Source: None

Keywords: Oral tolerance induction; food allergy; prevention; peanut allergy; egg allergy.

Abbreviations/Acronyms:

FS – Food Allergic Sensitisation

HE - Hen’s Egg

PN – Peanut

IgE – Immunoglobulin E

WHO – World Health Organization

NIAID – National Institute of Allergy and Infectious Diseases

ASCIA – Australasian Society of Clinical and Immunology and Allergy

LEAP – Learning Early About Peanuts

EAT – Enquiring About Tolerance

HEAP – Hen's Egg Allergy Prevention

STAR – Solids Timing for Allergy Reduction

STEP – Starting Time of Egg Protein

PETIT - Prevention of Egg Allergy with Tiny Amount Intake study

BEAT – Beating Egg Allergy

RCT - Randomised Controlled Trial

OFC – Oral Food Challenge

SPT – Skin Prick Test

PP – Per Protocol

ITT – Intention to Treat

RR – Relative Risk

AR - Absolute Risk

ARR - Absolute Risk Reduction

OR – Odds Ratio

Adj RR – Adjusted Relative Risk

CI - Confidence Interval

IVA – Instrumental Variable Analysis

Key Messages

- " Allergy testing and/or supervised first introduction of the specific allergenic food is advisable for infants with eczema and/or pre-existing food allergy prior to oral tolerance induction
- " A weekly dose of 2g of peanut or egg protein appears to be protective against peanut or egg allergy
- " Oral tolerance induction is allergen specific and has only been proven to be successful in single introduction trials of peanut and egg; multiple allergen oral tolerance induction is a significant unmet need which requires investigation using novel approaches.
- " The addition of peanut, and other common food allergens (egg, fish, sesame, milk) to the infant diet has no adverse nutritional or growth effects and does not increase rates of food allergy. Breastfeeding rates are not adversely affected by these interventions in a clinical trial setting.
- " In the Western world, non-white children have the highest risk of food allergy but their families are the least likely to take up oral tolerance induction programmes; strategies to promote oral tolerance induction in non-white families are required

Introduction

Driven by both the continuing rise in food allergy prevalence[1, 2] and the lack of an effective cure, the last decade has seen an increase in clinical trials investigating the prevention of food allergy. Earlier wisdom, predominantly derived from the findings of observational studies,

considered that allergy prevention was best achieved through allergen avoidance.[3, 4] After testing under randomised controlled trial (RCT) conditions, allergen avoidance has not been deemed a suitable means of preventing food allergy.[5, 6]

As the allergy field has evolved, a view which opposes the allergen avoidance hypothesis has gained momentum: the dual allergen exposure hypothesis proposes that allergic sensitisation may occur through the skin unless oral tolerance is first induced via the GI tract.[7] The first aspect of this hypothesis, that allergic sensitisation occurs through the skin, has been explored in epidemiological studies. These studies found that atopic dermatitis precedes the development of food allergic sensitisation (FS). There is also a strong association between atopic dermatitis severity and the risk of FS and food allergy.[8, 9] RCTs examining the effect of optimal management of atopic dermatitis on FS are underway. The second aspect of the dual allergen hypothesis, whether oral tolerance may be induced via the GI tract, has been explored in recent RCTs. The majority of trials have focused on the introduction of one food only, with egg and peanut being the most commonly investigated.[2, 10-14] Only one trial, the Enquiring about Tolerance (EAT) study, has investigated oral tolerance induction to multiple foods. This trial compared the effect of early introduction (from 3 months of age) of the six most common childhood food allergens (cow's milk, hen's egg, peanut, sesame, cod fish and wheat) with exclusive breastfeeding until about 6 months of age for the prevention of childhood food allergy. [15]

The results of these early introduction trials are variable. [1, 5] The most notable results are those from the Learning Early About Peanuts (LEAP) study. This RCT randomized the introduction or avoidance of peanut in infants aged between 4-<11 months, who were at high risk of developing peanut allergy (with moderate-severe eczema and/or egg allergy), and demonstrated an 81% relative reduction in peanut allergy at 5 years of age compared with children who avoided peanut containing products for the same time period.[2] Other studies

have either failed to meet their primary outcomes or not shown such a strong effect and a meta-analysis investigating the timing of allergenic food introduction to the infant diet found moderate evidence that egg introduction at 4-6 months was associated with reduced egg allergy and that peanut introduction at 4-11 months was associated with reduced peanut allergy.[5] There is currently no evidence that early introduction of cow's milk, fish, sesame and wheat protects against the development of food allergy but, to date, few studies have investigated oral tolerance induction to these foods.[5] The dearth of clinical trials exploring multiple oral tolerance induction and the limited number of foods that have been explored in single allergen oral tolerance induction, means that the scope of oral tolerance induction in preventing food allergy is unclear. Yet in the absence of further data, introducing allergenic foods into an infants' diet appears to be the most effective means of preventing food allergy at the current disposal of the allergist. Drawing predominantly on the lessons learned from LEAP and EAT but with reference to other oral tolerance induction studies (summarised in Table 1) we now discuss some of these challenges associated with oral tolerance induction.

The window of opportunity

Choosing when to introduce a food to the infant diet presents a significant challenge: Oral tolerance induction must begin when the child is developmentally able to consume foods other than breast or formula milk but before a child has become allergic. For some infants, this window of opportunity can be narrow.

When does allergic sensitisation/allergy occur?

Allergic sensitisation and, in some cases food allergy, begins early. Data from older infants in the HealthNuts study reveal high rates of food allergy at 12 months of age with 3.1% (95% CI, 2.6% to 3.6%) of infants demonstrating oral food challenge (OFC) proven allergy to peanut, 10.1% to egg (95% CI, 9.2% to 11.0%), and 0.7% to sesame (95% CI, 0.5% to 0.9%).[16] As the prevalence of food allergy at 10-14 years of age may be as high as 4.5%[17] it

is evident that, for many children, early allergy is not transient and thus effective allergy prevention is essential.

Whilst it is clear that FS begins in infancy, to date no studies have utilised sequential testing to discover the natural history of the onset of FS in very early childhood. Oral tolerance induction studies, including LEAP and EAT, shed some light on this biological process. Children were enrolled into the LEAP study between the ages of 4 and <11 months with a mean age of 7.8 months. All children underwent skin prick testing (SPT) to peanut at their screening visit and 9.1% (76/834) were excluded from LEAP as they were assumed to already be allergic with a SPT >4mm.

[18] Of those who were eligible for LEAP participation 15.3% (98/640) were sensitised (1-4mm) to peanut and 12.8% (6/47) of the sensitised group who were randomised to the intervention were found to be allergic during their baseline OFC.[2] Similar findings were evident in the Beating Egg Allergy Trial (BEAT) of egg oral tolerance induction in infants at high risk of allergic disease[11]; 3.9% of infants had an SPT of >2mm by 4 months of age and 10% (14/165) of infants were deemed to be egg allergic during the study entry OFC despite having SPT<2mm.

LEAP and BEAT both enrolled infants who already had, or were at risk of, atopic disease and were thus at high risk of demonstrating FS or allergy; however the EAT Study enrolled infants from the general population. Despite being a 'lower risk' population, infants who took part in EAT also demonstrated FS or allergy from an early age;[15] 5.1% (33/652) of 3 month old infants had a positive SPT to at least one of the study foods (SPT range 1mm-16mm). Of these, 2.9% (19/652) had an SPT of ≥ 5mm. Any infant with a positive SPT underwent an OFC and 1% (7/652) were deemed allergic to at least one of the six study foods at 3 months of age.

These data highlight that the window of opportunity to prevent allergy may be narrow and, unless oral tolerance induction begins in infancy, the window may be closed for those infants at most risk of food allergy. As we now discuss, the practicalities of intervening in early infancy also presents challenges.

Access to services

Recent updates to the allergy prevention guidance issued by the US (NIAID) and Australia (ASCIA) encourage the early introduction of peanut protein into infant diets. The specifics of this guidance varies, with ASCIA recommending this approach for all infants, regardless of atopic risk[19], whilst NIAID emphasizes this approach for high risk children who have eczema or egg allergy.[20]

Which infants should undergo allergy testing prior to commencing oral tolerance induction is still under debate. Infants who took part in LEAP underwent SPT, spIgE and OFC prior to the introduction of the study foods. Unexpectedly, in LEAP, 17% children who showed no SPT sensitisation at enrolment had peanut-specific IgE sensitization ≥0.35 kU/L. Moreover, 56% of children with SPT sensitisation of 1-4mm and 91% with SPT ≥5mm (not eligible for LEAP participation) had peanut-specific IgE sensitization ≥0.35 kU/L.[18] Of children who already demonstrated SPT sensitivity (1-4mm) at LEAP enrolment, 12.8% (6/47) of those randomised to the intervention were found to be allergic during their baseline OFC.[2]

In the Healthnuts study, SPT of eczematous infants (16% of the population) was able to identify 77% of all children who subsequently developed peanut allergy.[21] This highlights the potential effectiveness of screening prior to commencing oral tolerance induction. While the issues of National Screening Programmes to prevent food allergy are controversial,[21-23] testing is likely to be beneficial in high risk groups, namely children with severe eczema or egg allergy in the first 11 months of life, as in the LEAP study. The approach proposed by

NIAID seems to balance logistical and safety concerns by adopting a three tiered approach: i) children with severe eczema, egg allergy or both should aim to introduce peanut at about 4-6 months after undergoing SPT and/or IgE testing and, depending on the results, an OFC; ii) children with mild to moderate eczema should introduce peanut at around 4-6 months; iii) children with no eczema should introduce peanut containing foods according to family preferences.[20]

If testing and/or OFC are to be utilised prior to commencing oral tolerance induction then, to maximise effectiveness , high risk infants should attend specialist allergy services in early infancy or when risk factors for food allergy are first demonstrated. However, in many countries, where access to specialist services are limited, this will be difficult to achieve. Improving access to specialist services by increasing the number of training places for physicians, specialist nurses and dietitians is essential in order to facilitate early intervention. Developing rapid access oral tolerance induction clinics would also ensure the infants who are at the highest risk of developing allergy are able to safely introduce allergenic foods into their diets. Such clinics will allow identification and introduction of the highest priority allergens both with respect to allergens which are most likely to persist in later childhood, allergens to which the child is already sensitised and allergens which form a regular part of the familial diet.

WHO advice regarding exclusive breastfeeding versus oral tolerance induction

The World Health Organisation (WHO) advocates exclusive breastfeeding for the first six months of life;[24] this advice is also promoted by the health departments of many countries, including the United Kingdom's Department of Health. At least in developed countries, few mothers adhere to this advice with 44.3% of UK mothers breastfeeding when their infant is 6-8 weeks old,[25] and only 3.6% of mothers exclusively breastfeeding until 6 months of age.[26] Rates of exclusive breastfeeding to 6 months are higher in the USA, approximating 25%,[27]

but still fall short of the expectations of the WHO. Introduction of solid food before 6 months of age is also common, with 30% of UK infants having solid foods introduced by 4 months of age and 75% by 5 months of age.[26]

The WHO guidelines for infant feeding are appropriate for many children but do not appear to be suitable for infants with risk factors for the development of food allergy. Such infants may benefit from introduction of specific allergenic foods, alongside breastfeeding, before this time.[28] International guidelines for allergy prevention now encourage active introduction of peanut protein into the diet of high risk infants at 4-6 months of age (US NIAID[20]) and all allergenic foods to all infants from 4 months of age (Australia ASCIA[19]).

Further studies which consider the effect of early introduction of allergenic foods on breastfeeding rates, and which explore the long term effects of both on child health are required. Until such data are published, reassurance is provided from the EAT findings in which introduction of solid food from 3 months of age had no effect on (already established) breastfeeding rates--over 97% of infants were still being breastfed at 6 months of age.[15] Furthermore, between group comparisons in LEAP and EAT show early introduction of one or more allergenic (and thus energy dense) food had no deleterious nutritional or growth outcomes at 72 and 36 months (respectively).[15, 29]

Developmental ability of the child

Beginning to wean an infant to food substances alongside breast or formula milk feeding, requires that an infant expresses interest, can hold their head up, can sit with support and has lost the tongue thrust reflex which prevents food from passing to the back of the mouth. These developmental milestones tend to occur between 4 and 6 months but atopic children may already be sensitised or allergic by this age.

Additionally, introduction of allergenic foods before 6 months of age in specific quantities is discordant with baby led weaning (BLW) and responsive feeding; weaning principles which are gaining in popularity. Studies exploring how to apply oral tolerance induction to very young infants and alongside responsive weaning methods are required.

The challenges of intervening to prevent allergy during the window of opportunity are compounded by a lack of evidence regarding the most appropriate oral tolerance induction regime. In the following section we discuss some of these challenges.

Dose and adherence in early introduction regimes

Choosing the quantity, frequency and type of the early introduction regime poses additional challenges, not only in ensuring the regime is effective but also in balancing an effective regime with one that is not so onerous as to be unachievable.

Varying types of allergenic food introduction

Studies examining oral tolerance induction to egg have differed in the type of egg protein used. Three studies (HEAP[12], STEP[14] and STAR[13]) used raw egg protein whilst two (EAT,[15] PETIT[10]) used cooked egg. None of the studies using raw egg protein showed a difference in effect (see Table 1). In all three of the studies using raw egg protein, a high proportion of infants experienced allergic reactions either during the entry OFC or during home consumption. Two studies were discontinued early: in the HEAP study 10/16 (62.5%) of children with egg allergy experienced anaphylaxis during OFC[12], whilst in the STAR study recruitment was paused to allow the independent data safety monitoring committee to examine the rates of allergic reaction and anaphylaxis to study powder. The committee found that the study could continue but was subsequently discontinued for logistical reasons[13].

The safety profile of oral tolerance induction using raw egg powder contrasts with the EAT and PETIT studies, which utilised cooked egg protein. PETIT found oral tolerance induction

to be effective, and EAT also found an effect to egg in the PP group. Both studies demonstrated the safety of cooked egg oral tolerance induction with no cases of anaphylaxis either at home or during OFC.

Dose

The dose of protein consumed by children in the oral tolerance induction studies published to date has been somewhat varied. In one study, PETIT, substantially smaller doses of protein were found to be effective in preventing hen's egg allergy; however, there are several differences between PETIT and LEAP, EAT and BEAT (see Table 1). Children in PETIT were already sensitised to egg white at enrolment with a mean sIgE of 0.73kUA/l (range 0.17-5.55kUA/l). Subgroup analysis of the 36 children with an egg sIgE of <0.35kUA/l found no risk difference between the groups (2/24 active versus 3/12 placebo; risk difference 16.7% [95% CI –10.2 to 43.5] p=0.31).[10] This finding suggests that PETIT is predominantly a secondary prevention, rather than a primary prevention study. Similarly, for a subgroup of participants, the LEAP intervention acted as a secondary prevention strategy. Whilst the majority (542) of infants in the LEAP study had a negative peanut SPT at enrolment - and thus for them the intervention was preventative - 98 children were sensitised (SPT 1-4mm) at enrolment[2]. However, unlike PETIT, the LEAP the intervention was effective in both groups. The difference in findings between the non-sensitised infants who were enrolled in LEAP and PETIT suggest that very small quantities of protein may not be sufficient for primary oral tolerance induction.

LEAP, EAT and BEAT all utilised larger quantities of protein than PETIT. LEAP study children consumed 6g of peanut protein per week, divided into 3 doses of 2 g and EAT study children consumed 4g of each of the six study foods per week divided into 2 doses of 2g. The LEAP regime was successful, achieving an 86.1% reduction in peanut allergy in the SPT-Negative Stratum.[2] The EAT ITT analyses showed no effect but, although the absolute

numbers were small, PP analyses reveal a 75% reduction in egg allergy and a 100% reduction in peanut allergy.[15] These quantities concur with the upper quartiles of peanut consumption in Israeli infants who appeared to be protected against peanut allergy in an ecological study exploring prevention of peanut allergy.[30]

A dose that sits somewhere between the PETIT and LEAP/EAT doses has also been shown to be effective. Weekly consumption of 2g of protein promoted oral tolerance induction in the BEAT study which achieved a 47.8% relative reduction in the frequency of IgE sensitisation to egg white using a weekly quantity of 2.45g protein which was consumed in 0.35g daily aliquots, although no effect was noted on rates of clinical allergy to egg.[11] Dose response analyses of EAT study data reveal similar findings to the BEAT study; a mean weekly dose of 2g of peanut or egg protein was protective against peanut or egg allergy.[15] Furthermore, an ecological study of Israeli children who consumed peanut in early life found that consumption of 1.7g of peanut protein per week was protective against peanut allergy.[30] It is notable that comparable doses of protein were required for prevention of egg and peanut allergy, and the evidence therefore suggests that a weekly dose of approximately 2g of egg or peanut protein is likely to be sufficient to prevent egg or peanut allergy in the majority of children. This dose, which represents 1 teaspoon of peanut butter or 1 hardboiled egg per week, is also likely to be achievable for the majority of infants. This is particularly important given the challenges associated with adherence to oral tolerance regimes, which we now discuss.

Adherence

The EAT study demonstrates that adherence to the treatment regime is necessary for oral tolerance to be effective. Specifically, a per-protocol analysis showed a 67.1% (p=0.01) relative reduction in allergy, compared to a 21.1% (p=0.32) relative reduction in the intention to treat analysis.[15] Moreover, it is reassuring that EIG infants who were non-adherent to the intervention had similar rates of allergy compared to the control group. This implies, although it does not prove, that the presence of allergy was not responsible for non-adherence in the intervention group.[15] Potential bias in the PP analysis resulting from poor adherence was examined in the EAT study using an instrument variable (IV) analysis. Specifically, the complier average causal effect (CACE) method projects the rate of allergy observed in the non-adherent intervention group, onto the control arm. Using the assumption that randomization balances all factors, the CACE method estimates the effect of confounding potentially caused by non-compliance and removes it from the PP intervention effect. In the EAT study the unbiased CACE estimate was almost identical to that of the PP analysis (risk difference 2.47% versus 2.51%). This indicates that non-adherence was likely not due to reverse causality (i.e. that children did not adhere because they were allergic and thus unable to consume the foods).[31]

Rates of adherence in oral tolerance studies are variable (see Table 1) however consumption of 2g of peanut protein three times a week did not pose significant problems in LEAP with 92% of participating families adhering to the intervention.[2] In EAT, for which six study foods were investigated, adherence (defined as consumption of 2 g or more per week of allergenic protein for 4 or more weeks) was much lower at 31.9%. Adherence in BEAT and PETIT, for which lower overall quantities of egg protein were consumed, was also good with BEAT achieving 85% adherence[11] and PETIT achieving 79%.[10]

To date, single oral tolerance induction trials have enjoyed high level of adherence whilst the EAT Study had low adherence to the intervention (adherence in the control arm was 92.9%[2]). It is easy to assume that the clear difference in rates of adherence in the single oral tolerance induction studies and (to date) the only published multiple oral tolerance induction study are the result of the number of foods being introduced; however other factors are also likely to be relevant. For example palatability, texture, overall portion size and ease of preparation by parents of young infants, are likely to be relevant to adherence. This is evidenced by data from the EAT study showing specific foods were associated with lower adherence. Adherence to wheat was low but this was, at least in part, due to the study design; wheat was the last of the foods to be introduced making it more difficult to meet the protocol definition of adherence. With respect to the other study foods, those that were easy to prepare and palatable to an infant e.g. cow's milk and peanut, achieved the highest levels of adherence; those that required more preparation and/or had a taste or texture which was unfamiliar or unpleasant to an infant, e.g. egg, sesame, and fish, had the lowest adherence.

The factors that influenced adherence in LEAP and PETIT could not be investigated as adherence was high. However, adherence was lower in the EAT study affording the opportunity for investigation. A dominance analysis of non-adherence in the EAT study found that 78% of the variance could be accounted for by four main factors: nonwhite race (odds ratio, 2.21; 95% CI, 1.18 to 4.14), parent perception that the child experienced symptoms to one of the study foods (odds ratio, 1.70; 95% CI, 1.02 to 2.86), reduced maternal quality of life (psychological domain) (odds ratio, 0.69; 95% CI, 0.47 to 1.00), and the child having eczema at enrolment to EAT (odds ratio, 1.38; 95% CI, 0.87 to 2.19).

Health inequalities influence access to health services, engagement with health services and adherence to treatment.[32-34] Maternal ethnic group, education and social class are also relevant to infant feeding and have been shown to influence breastfeeding[35] and infant

weaning practices.[36] Non-white race was the strongest predictor of non-adherence in the EAT study, The BEAT study similarly found that children who were lost to follow up, withdrawn or had no primary outcome data were more likely to have a parent born outside of Australasia (father $p < 0.001$ and mother $p < 0.02$) than those who had complete data. Non-white children had a greater risk of food allergy in both LEAP and EAT. Notably, children with the greatest risk of food allergy are most likely to come from families who are least likely to take up the intervention. Prevention studies and strategies must focus on such communities; patient and public involvement in these studies and strategies will be essential if oral tolerance induction is to be effective.

Allergen specificity

Single allergen oral tolerance induction studies have shown promising results, however, atopy and food allergy are rarely isolated conditions; for example, between a third and half of children with peanut allergy are allergic to at least one tree nut.[37, 38]

Early introduction of peanut did not hasten the resolution of egg or milk allergy or atopic dermatitis, nor did it prevent the development of asthma or allergic rhinitis. Despite potential cross reactivity to either T cell or B cell epitopes, early introduction of peanut did not protect against new onset tree-nut or sesame allergy.[39] Conversely, long term follow up of the LEAP cohort showed a small and inconsistent but statistically significant rise in tree nut sensitisation and parent reported allergy in children in the early introduction arm.[39] This finding is being further investigated in the LEAP *Ad-lib* study.

Given the specificity of oral tolerance induction, multiple oral tolerance induction strategies are necessary to facilitate adherence and successful oral tolerance induction.

Conclusion

Allergy prevention is beset by difficulties. Use of SPT and/or IgE testing in children at high risk of allergy (those with moderate/severe eczema and/or egg allergy) prior to commencing oral tolerance induction is desirable but may be difficult to implement. Intervening whilst the window of opportunity is open (before allergy occurs), using a programme that provides protection against multiple allergens, presents significant challenges and may not be easily achievable at such a young age. The findings of recent trials provide evidence that allergy prevention through oral tolerance induction programmes which employs a regime of protein consumption of 2g/week are effective in preventing peanut and egg allergy. However, there is currently no evidence with respect to other common food allergens and it is not clear whether this lack of evidence is simply the result of a lack of high quality studies, or reflects true differences in the underlying mechanisms of allergic sensitisation/tolerance. For example, it may be that the dual allergen exposure hypothesis only applies to specific foodsMoreover, not all allergy is IgE mediated and there is no evidence that oral tolerance induction is appropriate for non-IgE mediated allergy. Further research and consensus with regards to food preparations, target populations, dosing regimes and preparations, and clearly defined adherence are now required. [1,40, 41]

References

1. Sicherer SH, Sampson HA. Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. J Allergy Clin Immunol.2017;141:41-58.
2. Du Toit G, Roberts G, Sayre PH, et al. Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy. N Engl J Med. 2015;372:803-813.
3. Arshad SH. Food allergen avoidance in primary prevention of food allergy. Allergy. 2001;56:113-116.

4. Fiocchi A, Assa'ad A, Bahna S. Food allergy and the introduction of solid foods to infants: a consensus document. Ann Allergy Asthma Immunol.97:10-21.
5. Ierodiakonou D, Garcia-Larsen V, Logan A, et al. Timing of allergenic food introduction to the infant diet and risk of allergic or autoimmune disease: A systematic review and meta-analysis. JAMA. 2016;316:1181-1192.
6. Zeiger RS. Dietary Aspects of Food Allergy Prevention in Infants and Children. J Pediatr Gastroenterol Nutr. 2000;30:S77-S86.
7. Lack G. Epidemiologic risks for food allergy J Allergy Clin Immunol.2008;121:1331-1336.
8. Hill DJ, Hosking CS. Food allergy and atopic dermatitis in infancy: an epidemiologic study. Pediatr Allergy Immunol. 2004;15:421-427.
9. Tsakok T, Marrs T, Mohsin M, et al. Does atopic dermatitis cause food allergy? A systematic review. J Allergy Clin Immunol. 2016;137:1071-1078.
10. Natsume O, Kabashima S, Nakazato J, et al. Two-step egg introduction for prevention of egg allergy in high-risk infants with eczema (PETIT): a randomised, double-blind, placebo-controlled trial. Lancet.389:276-286.
11. Wei-Liang Tan J, Valerio C, Barnes EH, et al. A randomized trial of egg introduction from 4 months of age in infants at risk for egg allergy J Allergy Clin Immunol.139:1621-1628.e1628.
12. Bellach J, Schwarz V, Ahrens B, et al. Randomized placebo-controlled trial of hen's egg consumption for primary prevention in infants J Allergy Clin Immunol.139:1591-1599.e1592.
13. Palmer DJ, Metcalfe J, Makrides M, et al. Early regular egg exposure in infants with eczema: A randomized controlled trial J Allergy Clin Immunol.132:387-392.e381.
14. Palmer DJ, Sullivan TR, Gold MS, Prescott SL, Makrides M. Randomized controlled trial of early regular egg intake to prevent egg allergy. J Allergy Clin Immunol.139:1600-1607.e1602.
15. Perkin MR, Logan K, Tseng A, et al. Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants. New Engl J Med. 2016;374:1733-1743.
16. Osborne NJ, Koplin JJ, Martin PE, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. J Allergy Clin Immunol.127:668-676.e662.
17. Sasaki M, Koplin JJ, Dharmage SC, et al. Prevalence of clinic-defined food allergy in early adolescence: The SchoolNuts study. J Allergy Clin Immunol.141:391-398.e394.
18. Du Toit G, Roberts G, Sayre PH, et al. Identifying infants at high risk of peanut allergy: The Learning Early About Peanut Allergy (LEAP) screening study J Allergy Clin Immunol.131:135-143.e112.
19. Netting MJ, Campbell DE, Koplin JJ, et al. An Australian consensus on infant feeding guidelines to prevent food allergy: outcomes from the Australian Infant Feeding Summit J Allergy Clin Immunol Pract 2017;5:1617-24.
20. Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States. Pediatr Dermatol. 2017;34:5-12.
21. Koplin JJ, Peters RL, Dharmage SC, et al. Understanding the feasibility and implications of implementing early peanut introduction for prevention of peanut allergy. J Allergy Clin Immunol.138:1131-1141.e1132.
22. Greenhawt MJ, Fleischer DM, Atkins D, Chan ES. The Complexities of Early Peanut Introduction for the Practicing Allergist. J Allergy Clin Immunol Pract.4:221-225.
23. O'Connor C, Kelleher M, O'B Hourihane J. Calculating the effect of population-level implementation of the Learning Early About Peanut Allergy (LEAP) protocol to prevent peanut allergy. J Allergy Clin Immunol.137:1263-1264.e1262.
24. Kramer MS, Kakuma R. Optimal duration of exclusive breastfeeding. Cochrane Database Syst Rev. 2012;15.
25. Public Health England. Breastfeeding at 6 to 8 weeks after birth:2017 to 2018 quarterly data. Available at: https://www.gov.uk/government/statistics/breastfeeding-at-6-to-8-weeks-after-birth-2017-to-2018-quarterly-data . Accessed 10th March 2018

26. McAndrew F, Thompson J, Fellows L, Large A, Speed M, Renfrew MJ. Infant Feeding Survey 2010. Leeds, United Kingdon: Health and Social Care Information Centre, 2012.
27. Centers for Disease Control and Prevention. Nutrition, Physical Activity, and Obesity: Data, Trends and Maps. Available at: https://nccd.cdc.gov/dnpao_dtm/rdPage.aspx?rdReport=DNPAO_DTM.ExploreByLocation&rdRequestForwarding=Form . Accessed 10th March 2018
28. Abrams EM, Greenhawt M, Fleischer DM, Chan ES. Early Solid Food Introduction: Role in Food Allergy Prevention and Implications for Breastfeeding. J Pediatr. 2017;184:13-18
29. Feeney M, Du Toit G, Roberts G, et al. Impact of peanut consumption in the LEAP Study: Feasibility, growth, and nutrition. J Allergy Clin Immunol. 2016;138:1108-1118.
30. Du Toit G, Katz Y, Sasieni P, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. J Allergy Clin Immunol.2008;122:984-991.
31. Bahnson HT, du Toit G, Lack G. Statistical Considerations of Food Allergy Prevention Studies. J Allergy Clin Immunol Pract. 2017;5:274-282.
32. Szczepura A. Access to health care for ethnic minority populations. Postgrad Med J. 2005;81:141-147.
33. Campbell JL, Ramsay J, Green J. Age, gender, socioeconomic, and ethnic differences in patients' assessments of primary health care. Qual Health Care. 2001;10:90-95.
34. Lakhanpaul M, Culley L, Robertson N, et al. A qualitative study to identify parents' perceptions of and barriers to asthma management in children from South Asian and White British families. BMC Pulm Med. 2017;17:126.
35. Griffiths L, Tate A, Dezateux C. The contribution of parental and community ethnicity to breastfeeding practices: Evidence from the Millennium Cohort Study. Int J Epidemiol 2005;34:1378-1386.
36. Griffiths LJ, Tate AR, Dezateux C. Do early infant feeding practives vary by maternal ethnic group? Pub Health Nutr. 2007;10:957-64.
37. Sicherer SH, Muñoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. . J Allergy Clin Immunol.125:1322-1326.
38. Sicherer SH, Muñoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: A 5-year follow-up study. . J Allergy Clin Immunol. 2003;112:1203-1207.
39. du Toit G, Sayre PH, Roberts G, et al. Allergen specificity of early peanut consumption and effect on development of allergic disease in the Learning Early About Peanut Allergy study cohort. J Allergy Clin Immunol. 2017 [in press]
40. Ebisawa M, Ito K, Fujisawa T. Japanese guidelines for food allergy 2017. Allergology International. 2017;66:248-264.
41. Tham EH, Shek LP, Van Bever HPS, et al. Early introduction of allergenic foods for the prevention of food allergy from an Asian perspective-An Asia Pacific Association of Pediatric Allergy, Respirology & Immunology (APAPARI) consensus statement. Pediatric Allergy and Immunology. 2018;29:18-27.

Table 1: Summary of Oral Tolerance Induction studies

Name of Trial	**Type and N**	**Population**	**Screen failures due to allergy /likely allergy**	**Intervention group (protein per week)**	**Control group**	**Age at study entry (age in months)**	**Outcome assessed (age in months)**	**Per protocol Adherence rates intervention/control**	**Primary outcome**	**Outcome in ITT (p value)**
LEAP (Learning Early About Peanut), UK	RCT, open label (640)	High risk (infants with moderate/severe eczema and/or egg allergy)	76/834 SPT ≥5mm	Peanut snack or peanut butter (6g)	PN avoidance until 60 months	4-11	60	SPT-ve group I= 96%; C=93% SPT+ve group I=95% C=98%	PN allergy (OFC)	**ARR** 11.8 % (95% CI 3.4 to 20.3; P<0.001)
Enquiring About Tolerance (**EAT**), UK	RCT, open label (1303)	general population	No exclusions required per protocol	cooked **whole HE, Peanut** butter**, Cow's Milk** (yoghurt), **Fish** (white, cooked), **Sesame** (Tahini), **Wheat** (wheat based	Exclusive breastfeeding and avoidance of all 6 study foods until 6 months of age	3	12-36	I=31.9% C=92.9%	HE allergy (OFC)	**RR** 0.69 (95% CI 0.40-1.18) (p= 0.17)

				breakfast cereal) (4g of each allergen)						
Hens' Egg Allergy Prevention (**HEAP**), Germany	RCT, blinded (298)	general population	23/406 EW IgE ≥0.35KUA/L	pasteurised **raw HE white** powder (7.5g) HE free diet	placebo powder (rice) HE free diet	4-12	12	I=86.7% C=93.5%	HE sensitisation (sIgE)	**RR** 2.20 (95% CI 0.68-7.14) (p=0.24)
Solids Timing for Allergy Research (**STAR**), Australia	RCT, blinded (86)	high risk (infants with moderate/ severe eczema)	Not required per protocol	pasteurised **raw whole HE** powder (6.3g)	placebo powder (rice)	0-8	12	I=94% C=97%	raw HE allergy (OFC) and Sensitisation (SPT)	**RR** 0.65 (95% CI 0.38-1.11) (p=0.11)
Starting Time for Egg Protein (**STEP**), Australia	RCT, blinded (820)	moderate risk (atopic mothers)	Not required per protocol	pasteurised **raw whole HE** powder (2.8g)	placebo powder (rice)	4-10	12	I=84% C=85%	raw HE allergy (OFC) and Sensitisation (sIgE)	**Adj RR** 0.75 (95% CI 0.48-1.17 (p=0.20)
Beating Egg Allergy (**BEAT**),	RCT, blinded (25	moderate risk (1^{st} degree relative with	13/332 SPT≥2 mm	pasteurised **raw whole HE** powde	placebo powder (rice) HE free	4-8	12	I=81% C=89%	HE sensitisation (SPT)	**OR** 0.46 (95% CI 0.22-

Australia	4)	allergy)		r (2.45g) HE free diet	diet					0.95) (p=0.03)
Two-step egg introduction for prevention of egg allergy in high-risk infants with eczema (**PETIT**), Japan	RCT, blinded (121)	moderate risk (with atopic dermatitis)	Not required per protocol	heated **HE** powder (0.175g for 3 months then 0.875g for 3 months)	placebo powder (squash)	4-12	12	I=92% C=93%	HE allergy (OFC)	**RR** 0·222 (95% CI 0·08–0·61) (p=0·0012)

Abbreviations: ARR, absolute risk reduction; Adj RR, Adjusted risk ratio; C, control; HE, hen's egg; I, intervention; IgE, Immunoglobulin E; OFC, oral food challenge; OR, odds ratio; PN, peanut; RCT, randomised controlled trial; RR, relative risk; sIgE, specific immunoglobulin E; SPT, skin prick test.