

Preventing Peanut Allergy: Where Are We Now?



Helen R. Fisher, PhD^{a,b}, Corinne A. Keet, MD, PhD^c, Gideon Lack, MB, BCh, FRCPCH^{a,b,d}, and George du Toit, MB, BCh, FRCPCH^{a,b,d} *London, United Kingdom; and Baltimore, Md*

INFORMATION FOR CATEGORY 1 CME CREDIT

Credit can now be obtained, free for a limited time, by reading the review articles in this issue. Please note the following instructions.

Method of Physician Participation in Learning Process: The core material for these activities can be read in this issue of the Journal or online at the *JACI: In Practice* Web site: www.jaci-inpractice.org/. The accompanying tests may only be submitted online at www.jaci-inpractice.org/. Fax or other copies will not be accepted.

Date of Original Release: February 1, 2019. Credit may be obtained for these courses until January 31, 2020.

Copyright Statement: Copyright © 2019-2021. All rights reserved.

Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for 1.00 *AMA PRA Category 1 Credit*[™]. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: Helen R. Fisher, PhD, Corinne A. Keet, MD, PhD, Gideon Lack, MB, BCh, FRCPCH, and George du Toit, MB, BCh, FRCPCH (authors); Michael Schatz, MD, MS (editor)

Learning objectives:

1. To identify children who are at risk for the development of peanut allergy.
2. To identify interventions for the prevention of peanut allergy.
3. To understand the broader health implications of early weaning strategies.

Recognition of Commercial Support: This CME has not received external commercial support.

Disclosure of Relevant Financial Relationships with Commercial Interests: H. R. Fisher acts as a consultant for Aimmune therapeutics. C. A. Keet receives grant support from the National Institutes of Health; is on the Board of the American Board of Allergy and Immunology; and receives royalties from Up-To-Date. G. Lack reported receiving research support from the National Institute of Allergy and Infectious Diseases, Food Allergy Research and Education, MRC and Asthma UK Centre, UK Department of Health through National Institute for Health Research Biomedical Research Centre based at Guy's & St Thomas' National Health Service Foundation Trust and King's College London, National Peanut Board, Food Standards Agency, and Action Medical Research; and has stock/stock options with DBV Technologies. G. Du Toit has received research support from the National Institute of Allergy and Infectious Diseases (supporting Learning Early About Peanuts Trio Trial, covering part salary), Food Allergy Research & Education (FARE) Grant (support of EAT-On Trial), MRC and Asthma UK Centre Contribution to King's College London Division of Asthma, Allergy & Lung Biology (of which Pediatric Allergy Research is a part), Aimmune (commercial trials, CI in UK for peanut desensitization trials, Scientific Advisory Board) and DBV (commercial trial PI, UK Scientific advisor). M. Schatz declares no relevant conflicts of interest.

^aDepartment of Women and Children's Health, School of Life Course Sciences, King's College London, Guys' Hospital, London, United Kingdom

^bPeter Gorer Department of Immunobiology, School of Immunology and Microbial Sciences, King's College London, Guys' Hospital, London, United Kingdom

^cDivision of Pediatric Allergy and Immunology, Johns Hopkins University School of Medicine, Baltimore, Md

^dChildren's Allergy Service, Evelina London Children's Hospital, Guy's and St. Thomas's National Health Service Foundation Trust, London, United Kingdom
H. R. Fisher was funded/supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' National Health Service (NHS) Foundation Trust and King's College London and/or the NIHR Clinical Research Facility. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health.

Conflicts of interest: H. R. Fisher acts as a consultant for Aimmune therapeutics. C. A. Keet receives grant support from the National Institutes of Health; is on the Board of the American Board of Allergy and Immunology; and receives royalties from Up-To-Date. G. Lack reported receiving research support from the National Institute of Allergy and Infectious Diseases, Food Allergy Research and Education, MRC and Asthma UK Centre, UK Department of Health through National Institute for Health Research

Biomedical Research Centre based at Guy's & St Thomas' National Health Service Foundation Trust and King's College London, National Peanut Board, Food Standards Agency, and Action Medical Research; and has stock/stock options with DBV Technologies. G. Du Toit has received research support from the National Institute of Allergy and Infectious Diseases (supporting Learning Early About Peanuts Trio Trial, covering part salary), Food Allergy Research & Education (FARE) Grant (support of EAT-On Trial), MRC and Asthma UK Centre Contribution to King's College London Division of Asthma, Allergy & Lung Biology (of which Pediatric Allergy Research is a part), Aimmune (commercial trials, CI in UK for peanut desensitization trials, Scientific Advisory Board) and DBV (commercial trial PI, UK Scientific advisor).

Received for publication July 18, 2018; revised November 7, 2018; accepted for publication November 8, 2018.

Corresponding author: George du Toit, MB, BCh, Paediatric Allergy, Block B South Wing, St Thomas' Hospital, London, SE1 7EH, United Kingdom. E-mail: George.dutoit@kcl.ac.uk.

2213-2198

© 2018 American Academy of Allergy, Asthma & Immunology
<https://doi.org/10.1016/j.jaip.2018.11.005>

Abbreviations used

AD- Atopic dermatitis
 CI- Confidence interval
 EAT- Enquiring About Tolerance
 EIG- Early introduction group
 EPE- Environmental peanut exposure
 FA- Food allergy
 LEAP- Learning Early About Peanuts
 NASEM- The National Academies of Science, Engineering and Medicine
 NIAID- National Institutes of Allergy and Infectious Disease
 OFC- Oral food challenge
 RCT- Randomized controlled trial
 SIG- Standard introduction group
 SPT- Skin prick test

Peanut allergy affects 1% to 3% of the Western world, usually begins in early childhood, is rarely outgrown, and has no currently approved treatment. The identification and application of prevention strategies is therefore essential. In 2015, the Learning Early About Peanuts study findings found that early consumption of peanut protein was effective in preventing peanut allergy in high-risk children as compared with peanut avoidance. These findings resulted in changes to allergy prevention guidelines and policy across the world. There are country-specific variations to guidelines, but, within these variations, feeding peanut to children in infancy is a common theme. There are numerous logistical challenges surrounding the implementation of contemporary guidelines at a population level. In the United States, guidelines advise according to risk level with prescreening recommended for high-risk children (mod/severe eczema, egg allergy). Even though high-risk children represent the minority of the childhood population, there are still significant challenges associated with identifying and screening such infants. The need for conducting allergy testing before first giving peanut protein to high-risk infants is debated; although adopting this approach promotes safety, it is financially and logistically challenging. Clinical trials that explore the real-life application of these guidelines are needed as is an assessment of guidelines (Australia, for example) that do not adopt the approach of screening. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:367-73)

Key words: Peanut allergy; Food allergy; Allergy prevention; Children

Peanut allergy is a potentially life-threatening condition that affects 1% to 3% of the Western world.^{1,2} Peanut allergy often develops in early life, and children may experience allergic symptoms during their first known exposure to peanut.^{3,4} It is rarely outgrown, has no currently approved treatment, and is the most common cause of food-related fatal anaphylaxis.⁵ Peanut allergy significantly influences quality of life of both peanut allergy sufferers and their families^{6,7}; developing effective prevention strategies is thus essential.

ROUTES OF SENSITIZATION

Understanding how peanut sensitization occurs is key to preventing peanut allergy. The National Academies of Science, Engineering and Medicine (NASEM) convened an expert committee to examine critical issues in food allergy (FA). The committee considered many routes of sensitization and published a comprehensive report.⁸ NASEM found limited evidence of a link between nutritional factors such as vitamin D, maternal omega-3 fatty acid intake, and folate supplementation with food allergic sensitization.⁸ Environmental factors clearly influence food sensitization and allergy.⁸ This is illustrated in the HealthNuts study, which found that children who were born to Asian (defined as East Asia or India) mothers in Asia and subsequently moved to Australia were 2 to 3 times less likely to have nut allergy at age 5 than those born to Asian mothers in Australia.⁹ Furthermore, children born to Asian mothers who later migrated to Australia from the United Kingdom or New Zealand had no difference in risk.⁹

Skin barrier dysfunction also plays a role in allergic sensitization. Because early work identified that atopic dermatitis (AD) was associated with FA,¹⁰⁻¹² many studies have examined this relationship and there is now consistent evidence that skin barrier dysfunction significantly increases the risk of FA.¹³⁻¹⁵ Environmental peanut exposure (EPE) also increases the risk of peanut sensitization and allergy.¹⁶ This risk intensifies with increasing levels of EPE, is greater in children with AD, and is further augmented in those with severe AD.¹⁷ There is now clear evidence of a causal relationship between AD and FA.¹⁸ Research examining whether early life interventions to improve skin barrier function can prevent peanut and other allergies is now underway.¹⁹

The “dual allergen exposure hypothesis” proposes that, although allergic sensitization may occur through the skin, tolerance may be induced via the gut.²⁰ In the preceding paragraphs, we have demonstrated that there is good evidence to support the first aspect of the hypothesis. In the remainder of the paper, we describe the evidence for oral tolerance induction in the prevention of peanut allergy and discuss the current guidance and concerns regarding peanut allergy prevention in clinical practice.

EARLY CONSUMPTION OF PEANUT PREVENTS PEANUT ALLERGY

There is evidence that infants who consume peanut in early life have a lower risk of peanut allergy than those who avoid peanut. An observational study compared the early diets and allergic status of Israeli and UK primary school children, finding that peanut was introduced earlier, and in greater quantities, in Israeli infants' diets than in UK infants' diets (7.1 g of peanut protein per month vs 0 g $P \leq .0001$).²⁰ In the same study, UK children were almost 10 times more likely than Israeli children to be peanut allergic (1.85% vs 0.17% [$P \leq .001$]; adjusted risk ratio 9.8; 95% confidence interval [CI], 3.1-30.5).²⁰ Subsequently, a randomized controlled trial (RCT) examined whether early introduction of peanut was more effective than avoidance in preventing peanut allergy in infants with severe eczema and/or egg allergy. The Learning Early About Peanuts (LEAP) study randomized infants aged 4 to <11 months either to consume 2 g of peanut protein 3 times per week until 5 years of age, or to avoid peanut.²¹ In children with no skin prick test (SPT)

sensitization to peanut at study entry, there was an 86% relative reduction in risk of peanut allergy for children who consumed peanut compared with those who avoided peanut during the study (1.9% vs 13.7%).²¹ Children who were peanut sensitized (SPT 1–4 mm) at study enrolment also had a reduced risk of peanut allergy if they were assigned to the consumption arm; 10.6% of the consumption group were allergic compared with 35.3% of the avoidance arm, representing a 70.0% relative reduction in peanut allergy.²¹

The longevity of the effects of the intervention was tested in the LEAP-On study. LEAP study participants (n = 556; 88.5% retention rate from LEAP) were asked to avoid peanut protein for 12 months regardless of their assigned group in LEAP. Rates of oral food challenge (OFC) proven allergy at the end of this period were similar to those from LEAP (18.6% vs 4.8%); 3 participants in each arm developed *de novo* allergy during the 12-month period of avoidance.²² The cohort is now being followed up at age 12, after a period of *ad libitum* peanut consumption, to establish whether the early consumption of peanut achieved permanent tolerance or transient desensitization (ClinicalTrials.gov Identifier: NCT03546413).

One other study has examined the effect of peanut introduction in early infancy. The Enquiring About Tolerance (EAT) study enrolled 1303 exclusively breastfed infants at 3 months of age and randomized half to follow UK Department of Health guidance to exclusively breastfeed until approximately 6 months of age after which time they introduced solid foods according to parental preference (standard introduction group [SIG]); the other half consumed 6 allergenic foods (peanut, cow's milk, egg, wheat, fish, and sesame) twice weekly from study enrolment (early introduction group [EIG]). Adherence rates were lower in the EIG than SIG, but per protocol analysis found the prevalence of peanut allergy at 3 years of age to be significantly lower in the EIG than the SIG (0% vs 2.5%, $P = .003$) and there was a trend toward an effect in the intention to treat analysis.²³ The cohort is being followed up at 8 years of age to establish whether the early intervention affects allergic outcomes in later childhood, and to examine the effect of early weaning diet on child health more broadly (ClinicalTrials.gov Identifier: NCT03495583).

TRANSLATING THE TRIALS INTO PRACTICE

In the past 2 decades, there has been a change in the guidance regarding peanut consumption in infancy. In 2000, peanut prevention strategies were based on identifying children who were at risk of developing the disease and recommending the elimination of all peanut products from the diets of pregnant and breastfeeding mothers and children up to 3 years of age.²⁴ In the mid-2000s, many countries withdrew advice to avoid feeding peanut protein to young children, replacing this with less didactic guidance that parents may introduce peanut containing products during weaning if they wished.

There is now high-quality evidence that peanut allergy may be prevented by consumption of peanut protein in infancy, but the translation of this evidence into clinical practice is garnering significant debate. For example, a meta-analysis examining the timing of solid food introduction and FA concluded that, as only one RCT that has proven early introduction of peanut is an effective strategy for the prevention of peanut allergy in an intention-to-treat analysis, with another showing an effect only in per protocol analysis, there is still insufficient evidence to

make automatic changes to recommendations.²⁵ Despite these limitations, in 2015, a consensus statement was published by 8 national/international allergy academies that referenced the LEAP study findings. The statement recommended that “high risk” infants (defined according to the LEAP criteria of severe eczema and/or egg allergy) be given peanut protein in early life (around 4–11 months of age).²⁶ The health authorities or societies of several countries have subsequently updated their guidelines on the prevention of peanut allergy (examples shown in Table I).

Since these policy changes, many countries are now proactively encouraging parents to feed their children peanut during infancy. The universality of these changes has been questioned by Levin et al,³³ who point out that, to date, all studies have been conducted in developed countries where the risk of malnutrition and HIV is low. They caution against universal changes to weaning guidelines and recommend that advice be both country and family specific.³³ Some reassurance may be offered with respect to concerns regarding the effect of early weaning on breastfeeding; in LEAP and EAT, the introduction of peanut/other allergenic foods was not deleterious to breastfeeding rates or duration.^{23,34}

In countries where allergy prevention guidelines have been updated, the practicalities of translating these changes into practice are now being discussed with debates including “is testing before peanut introduction either necessary or practicable?” and “who should be tested?”

IDENTIFYING CHILDREN “AT RISK” OF PEANUT ALLERGY

The LEAP intervention targeted children who were “at risk” of developing peanut allergy (defined as having severe eczema and/or egg allergy). However, it is estimated that approximately 25% infants with peanut allergy do not meet these criteria,³⁵ and previous attempts at targeting public health allergy interventions at allergic high-risk groups have failed.³⁶ Whether to aim public health messages at allergic high-risk infants, and how to identify that group, remains controversial and does not take into account the substantial proportion of children who develop peanut allergy despite not meeting the allergic high-risk criteria. The arguments for broad-based introduction of peanut in infancy include evidence that early peanut introduction may help prevent peanut allergy in unselected populations (the EAT study); findings from both the EAT and LEAP studies that the early introduction of peanut did not have negative effects on overall nutritional status or the duration of breastfeeding; and the concept that broad-based public health messages are more effective than targeted messages. On the other hand, arguments against universal recommendations for early peanut introduction include the lack of evidence in other populations that early peanut introduction is effective, and questions regarding the cultural and other unintended impacts of such recommendations.³⁷ In arguing for caution against prioritizing allergy prevention over broader health concerns, especially malnutrition, Levin et al³³ call for a unified protocol that addresses allergy prevention in the context of wider causes of child mortality, particularly within resource constrained settings. Although the cost-benefit analysis of universal early peanut introduction has also been questioned, health and economic benefit modeling found that early peanut introduction is cost effective when compared with delaying peanut introduction beyond 12 months of age.³⁸

TABLE I. Specific country guidelines for peanut allergy prevention

Country	Organization	Year	Guidance	Recommends testing before peanut introduction in high-risk infants?
USA/Canada ²⁷	National Institute of Allergy and Infectious Diseases	2017	Introduce peanut containing foods at 4-6 mo in children with severe eczema, egg allergy or both Introduce peanut containing foods around 6 mo in children with mild-to-moderate eczema Introduce peanut containing foods according to family preference and cultural practices in children with no eczema or food allergy	In children with severe eczema, egg allergy, or both, strongly consider evaluation with skin prick test, and/or sptIgE and proceed to oral food challenge if necessary
United Kingdom ^{28,29}	Scientific Advisory Committee on Nutrition/ Committee on Toxicity British Society for Allergy and Clinical Immunology	2017 2018	Weaning at around 6 mo, peanut need not be differentiated from other solid foods. Deliberate exclusion of peanut beyond 12 mo may increase the risk of allergy	In children at high risk of allergy referral for testing should be considered against the potential for delayed introduction as a result of the referral ²⁹
Japan ³⁰	Committee for Japanese Pediatric Guideline for Food Allergy, The Japanese Society of Pediatric Allergy and Clinical Immunology, The Japanese Society of Allergology	2016	Weaning at 5-6 mo of age; no foods should be excluded	No recommendation
Australia ³¹	Australia Society of Clinical Immunology and Allergy (ASCIa)	2017	For all children, introduce peanut with other solid foods around 6 mo, not before 4 mo and in the first 12 mo	No guidance regarding testing but ASCIA recommendations suggest all infants are fed peanut first in a graded manner stopping and treating allergic reactions as appropriate: Initially infants should have peanut butter rubbed on the inside of their lip, then a few minutes later feed 1/4 of a teaspoon and 30 min later 1/2 teaspoon of peanut butter. This may be performed at home or under medical supervision
Europe ³²	European Academy of Allergy and Clinical Immunology	2014*	There is no need to avoid introducing complementary foods beyond 4 mo, and currently, the evidence does not justify recommendations about either withholding or encouraging exposure to potentially allergenic foods after 4 mo once weaning has commenced, irrespective of atopic heredity	No recommendations

*These guidelines predate the WAO recommendations but are currently being updated.

The emerging guidelines reflect the current debates: the US guidelines on peanut introduction differ depending on risk status of the infant, whereas all other guidelines published thus far give uniform recommendations for the whole population. All guidelines caution against the intake of whole nuts in young children due to the risk of choking and aspiration.

TO TEST OR NOT TO TEST?

Whether children who are at high risk of developing peanut allergy require SPT and/or specific immunoglobulin E (spIgE) testing before eating peanut protein is strongly debated in the literature. Although some countries make no recommendation in this regard, the UK Scientific Advisory Committee on Nutrition/Committee on Toxicity and National Institutes of Allergy and Infectious Disease (NIAID) recommend that clinicians consider testing for children with severe eczema, egg allergy, or both, the entry criteria of the LEAP study. Despite this guideline, 44% (35/79) of pediatricians who responded to a survey regarding adherence to the NIAID guidelines reported not testing high-risk children before introducing peanut.³⁹ Two studies have investigated the logistics of implementing the LEAP intervention using these screening criteria at a population level. Koplin et al³⁵ used the HealthNuts study cohort to establish that, if the LEAP study criteria were to be applied to the Australian population, 16% of the population would need to be screened, of which 29% would require clinical follow-up; yet this screening program would still miss almost a quarter (23%) of peanut allergy cases. They highlight the financial and logistical challenges of such a program against the additional finding that there were no life-threatening events among either low- or high-risk infants who were fed peanut protein at home in the first year of life.³⁵ O'Connor et al⁴⁰ draw similar conclusions from their calculations of the effect of implementing the LEAP protocol in the Irish population. They found that 348 cases of peanut allergy could be prevented every year in Ireland (a 71% relative reduction in the high-risk population and 29% relative reduction at a population level), but caution that community implementation would demand huge additional resources at all levels of health care. Shaker et al³⁸ also modeled the health and economic benefits of testing before early peanut introduction finding that, when compared with no testing, testing by any method (SPT or spIgE) incurs increased costs without improvement in quality adjusted life years.

In their pro/con debate, and arguing against the need for testing, Tang et al⁴¹ point out that for most children, even high-risk children, testing is unnecessary and may actually be detrimental: 87% of high-risk children would unnecessarily delay peanut introduction while waiting for specialist review and this delay might, paradoxically, increase their risk of developing peanut allergy. Turner and Campbell⁴² point out that the risk of severe reaction to first exposure of peanut is low; there have been no known fatalities related to peanut exposure within the first year of life. Furthermore, they caution against "screening creep" where children are tested unnecessarily because of parental anxiety or overcautious health care providers.⁵

The main argument for testing high-risk infants before them consuming peanut is to ensure the safe introduction of peanut. Children with an SPT of >4 mm were excluded from LEAP and the EAT study enrolled children from the general population. The safety of peanut introduction in a whole cohort of young

high-risk infants is thus unknown, although HealthNuts data showed that 80% (95% CI, 73.0-87.4) of high-risk infants with an SPT wheal size of >4 mm had challenge confirmed peanut allergy at 12 months of age³⁵ (but these children were slightly older than the LEAP cohort who were assessed between 4 and 11 months of age). Testing may also be beneficial if a negative SPT provides reassurance for parents who would otherwise be too concerned to feed their children peanut.⁴¹ In this context testing may act as an additional tool in the prevention of peanut allergy because it gives confidence to parents who would otherwise be too fearful to give their children peanut protein, and thus potentially prevents them from developing peanut allergy. It should be noted however that it is not known whether children excluded from LEAP with SPT >4 mm were allergic or sensitized. Although approximately 80% of children with an SPT of ≥ 5 mm will be peanut allergic,³⁵ one fifth of children may still tolerate peanut and thus other factors, including whether an OFC is appropriate, should be considered before sensitized children are given an allergic diagnosis.

ADHERENCE TO GUIDELINES

The publication of evidence-based guidelines is only the first step in preventing peanut allergy. Successful implementation is also essential. There is little data regarding the use of the new peanut allergy prevention guidelines in practice, although a 2017 survey of US-based pediatricians found that only 11% adhered to the NIAID guidelines of early peanut introduction, and those who saw food allergic patients more frequently described greater guideline adherence.³⁹ Reasons for nonadherence to these specific guidelines have not been investigated, but a broad systematic meta-review found that barriers to implementation of clinical guidelines are usually multifactorial and include simplicity of the guidance, the characteristics of professionals who the guidance is targeted at, and the support, time, and financial resources available to the professionals.⁴³ Bearing this in mind, implementation of the peanut allergy prevention guidelines by health care professionals is likely to be enhanced when questions such as "should testing be conducted by allergists or trained community health care professionals?," "should testing programs prioritize SPT or spIgE testing?," and "should testing focus only on peanut or include other common food allergens?" have been answered. In all scenarios, additional resources would be required to facilitate the additional demand on health services, and, if testing on a large scale is deemed necessary, there will be a significant delay while additional allergist/specialist community practitioners are trained.

Parental willingness to feed peanut protein to their infant is also critical to the successful implementation of the peanut allergy prevention guidelines, and 2 studies have examined parental knowledge and behaviors after changes to infant feeding guidelines for peanut introduction. HealthNuts study data were used to examine the history of peanut consumption before and after the changes to Australian infant feeding guidelines in 2008, which removed previous advice to delay the introduction of allergenic foods. The study found that mothers who were born outside Australia were more likely to adhere to the changed guidelines than those born inside Australia.⁴⁴ Perhaps counter-intuitively, families with a history of FA were less likely to adopt the new guidelines and were more likely to delay introducing allergenic foods compared with those with no family history of

FA.⁴⁴ More recently, US caregivers' response to the publication of NIAID's recommendation that infants at risk of peanut allergy should be given peanut protein in early infancy has been explored. A study (conducted only a few months after implementation of the new guidelines) showed that 31% of expectant mothers or parents of young infants were willing to introduce peanut before or around 6 months of age.⁴⁵

To date, no study has investigated the reasons why parents did not wish to give peanut protein to young infants. Studies are needed that explore these attitudes, particularly with respect to the views of groups who may be harder to reach and less likely to engage with health promotion guidance such as those from lower socioeconomic groups and ethnic minorities.^{44,46,47} In developed countries at least, recent changes to guidelines may mean that, rather than following previous advice to avoid peanut in early childhood, feeding peanut to young infants will become part of the natural weaning process. Health care providers should consider health promotion strategies that promote this. Such campaigns would empower parents and primary caregivers to view peanut as food that can be safely fed to most children at home. This would further assist in the prevention of peanut allergy.

PROVIDING SUPPORT TO PARENTS WHO FEED THEIR CHILDREN PEANUT IN INFANCY

Families who took part in the LEAP study received a high level of dietetic support throughout the intervention (weekly telephone calls until 12 months of age; fortnightly until 30 months; and monthly until 60 months of age). The need for, and feasibility of, providing this level of input to high-risk infants has been highlighted as both essential for efficacy and difficult to replicate at a population level.⁴⁸ The differing levels of dietetic support and rates of adherence in the LEAP and EAT studies have been cited as evidence for this,⁴⁸ but this argument overlooks differences in the designs of the study (1 food compared with 6 foods, high-risk vs general population) and definitions of adherence between the studies. These differences suggest that prevention of peanut allergy may not be dependent on intensive dietetic support; *post hoc* analysis of LEAP data shows that participating families required an average of only 3 phone calls before they were able to feed their children peanut 3 times per week.³⁴ Studies that explore the amount and type of support required by families who feed peanut protein to their high-risk infant are required. Until these data are available, clinicians may be reassured that, in the EAT study, children who were nonadherent in the early introduction arm did not have an increased risk of peanut allergy compared with those in the standard introduction arm.²³ Encouraging families to feed their high-risk infant peanut in infancy, without intensive dietetic follow-up, is thus unlikely to increase the child's risk of peanut allergy.

CONCLUSION

Since late 1990s/early 2000s guidance that peanut allergy was best prevented through avoidance of peanut,²⁴ the field of allergy has seen a paradigm shift. There is now good evidence that peanut sensitization occurs through the skin, that feeding peanut protein to young children reduces the risk of peanut allergy in high-risk children, and that, in the general population, noncompliance with regular consumption of peanut in early

infancy presents no greater risk than the previous guidance of peanut avoidance.

How the early introduction of peanut can be achieved at a population level is the subject of debate and requires more research. Although national and international bodies have produced guidelines, the effective dissemination and implementation of these guidelines requires considerable work. Convening country- and/or region-specific committees made up of stakeholders from all relevant professional groups, from both community and hospital settings, and from patient advocacy groups to agree the most appropriate method of implementation will be critical if peanut allergy prevention is to be achieved at a population level. Until additional data and consensus are available, the strategic use of testing in children with the greatest risk of developing peanut allergy is a safe approach but the practicalities and costs of testing should also be considered. Furthermore, strategies and campaigns that seek to destigmatize peanut may also be beneficial in the prevention of peanut allergy.

REFERENCES

- Venter C, Hasan Arshad S, Grundy J, Pereira B, Bernie Clayton C, Voigt K. Time trends in the prevalence of peanut allergy: three cohorts of children from the same geographical location in the UK. *Allergy* 2010;65:103-8.
- 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* 2010;125:1322-6.
- Sicherer SH, Furlong TJ, Muñoz-Furlong A, Burks AW, Sampson HA. A voluntary registry for peanut and tree nut allergy: characteristics of the first 5149 registrants. *J Allergy Clin Immunol* 2001;108:128-32.
- Hourihane JOB, Kilburn SA, Dean P, Warner JO. Clinical characteristics of peanut allergy. *Clin Exp Allergy* 1997;27:634-9.
- Turner PJ, Campbell DE. Implementing primary prevention for peanut allergy at a population level. *JAMA* 2017;317:1111-2.
- Avery NJ, King RM, Knight S, Hourihane JOB. Assessment of quality of life in children with peanut allergy. *Pediatr Allergy Immunol* 2003;14:378-82.
- King RM, Knibb RC, Hourihane JOB. Impact of peanut allergy on quality of life, stress and anxiety in the family. *Allergy* 2009;64:461-8.
- Sicherer SH, Allen K, Lack G, Taylor SL, Donovan SM, Oria M. Critical issues in food allergy: a national academies consensus report. *Pediatrics* 2017;140:e20170194.
- Panjari M, Koplin JJ, Dharmage SC, Peters RL, Gurrin LC, Sawyer SM, et al. Nut allergy prevalence and differences between Asian-born children and Australian-born children of Asian descent: a state-wide survey of children at primary school entry in Victoria, Australia. *Clin Exp Allergy* 2016;46:602-9.
- Hill DJ, Hosking CS. Food allergy and atopic dermatitis in infancy: an epidemiologic study. *Pediatr Allergy Immunol* 2004;15:421-7.
- Hill DJ, Sporik R, Thorburn J, Hosking CS. The association of atopic dermatitis in infancy with immunoglobulin E food sensitization. *J Pediatr* 2000;137:475-9.
- Hill DJ, Hosking CS, De Benedictis FM, Oranje AP, Diepgen TL, Bauchau V. Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: an international study. *Clin Exp Allergy* 2008;38:161-8.
- Lack G, Fox D, Northstone K, Golding J. Factors associated with the development of peanut allergy in childhood. *N Engl J Med* 2003;348:977-85.
- Martin PE, Eckert JK, Koplin JJ, Lowe AJ, Gurrin LC, Dharmage S, et al. Which infants with eczema are at risk of food allergy? Results from a population-based cohort. *Clin Exp Allergy* 2015;45:255-64.
- Matsumoto K, Mori R, Miyazaki C, Ohya Y, Saito H. Are both early egg introduction and eczema treatment necessary for primary prevention of egg allergy? *J Allergy Clin Immunol* 2018;141:1997-2001.e1993.
- Fox AT, Sasieni P, du Toit G, Syed H, Lack G. Household peanut consumption as a risk factor for the development of peanut allergy. *J Allergy Clin Immunol* 2009;123:417-23.
- Brough HA, Liu AH, Sicherer S, Makinson K, Douiri A, Brown SJ, et al. Atopic dermatitis increases the effect of exposure to peanut antigen in dust on peanut sensitization and likely peanut allergy. *J Allergy Clin Immunol* 2015;135:164-170.e164.
- Tsakok T, Marrs T, Mohsin M, Baron S, du Toit G, Till S, et al. Does atopic dermatitis cause food allergy? A systematic review. *J Allergy Clin Immunol* 2016;137:1071-8.

19. Lødrup KKC, Rehder EM, Skjerven HO, Carlson MH, Fannes TA, Fugelli P, et al. Preventing atopic dermatitis and ALLergies in children—the PreventADALL study. *Allergy* 2018;73:2063-97.
20. Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* 2008;122:984-91.
21. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015;372:803-13.
22. Du Toit G, Sayre PH, Roberts G, Sever ML, Lawson K, Bahnson HT, et al. Effect of avoidance on peanut allergy after early peanut consumption. *N Engl J Med* 2016;374:1435-43.
23. Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med* 2016;374:1733-43.
24. Sampson HA. Managing peanut allergy. *BMJ* 1996;312:1050-1.
25. Ierodiakonou D, Garcia-Larsen V, Logan A, Groome A, Cunha S, Chivinge J, 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;316:1181-92.
26. Fleischer DM, Sicherer S, Greenhawt M, Campbell D, Chan ES, Muraro A, et al. Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants. *Ann Allergy Asthma Immunol* 2015;115:87-90.
27. Togias A, Cooper SF, Acebal ML, Assa'ad A, Baker JR, Beck LA, et al. Addendum guidelines for the prevention of peanut allergy in the United States. *Pediatr Dermatol* 2017;34:5-12.
28. A Joint Statement from the Scientific Advisory Committee on Nutrition and the Committee on Toxicity of Chemicals in food CpatE. Assessing the health benefits and risks of the introduction of peanut and hen's egg into the infant diet before six months of age in the UK; 2017. Available from: <https://cot.food.gov.uk/sites/default/files/jointscacnotallergystatementfinal2.pdf>. Accessed October 15, 2018.
29. British Society for Allergy and Clinical Immunology. Preventing Allergy in Higher Risk Infants: Guidance for Health Care Professionals. 2018. Available from: <https://www.bsaci.org/pdf/Early-feeding-guidance-for-HCPs.pdf>. Accessed October 15, 2018.
30. Ebisawa M, Ito K, Fujisawa T. Japanese guidelines for food allergy 2017. *Allergol Int* 2017;66:248-64.
31. Australasian Society of Clinical Immunology and Allergy (ASCIA). ASCIA infant feeding advice. Available from: https://www.allergy.org.au/images/pcc/ASCIA_Guidelines_infant_feeding_and_allergy_prevention.pdf. Accessed April 2, 2015.
32. Muraro A, Halken S, Arshad SH, Beyer K, Dubois AE, Toit G. EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy. *Allergy* 2014;69:1008-25.
33. Levin M, Goga A, Doherty T, Coovadia H, Sanders D, Green RJ, et al. Allergy and infant feeding guidelines in the context of resource-constrained settings. *J Allergy Clin Immunol* 2017;139:455-8.
34. Feeney M, Du Toit G, Roberts G, Sayre PH, Lawson K, Bahnson HT, et al. Impact of peanut consumption in the LEAP study: feasibility, growth, and nutrition. *J Allergy Clin Immunol* 2016;138:1108-18.
35. Koplin JJ, Peters RL, Dharmage SC, Gurrin L, Tang MLK, Ponsonby A-L, et al. Understanding the feasibility and implications of implementing early peanut introduction for prevention of peanut allergy. *J Allergy Clin Immunol* 2016;138:1131-1141.e1132.
36. Hourihane JOB, Aiken R, Briggs R, Gudgeon LA, Grimshaw KEC, DunnGalvin A, et al. The impact of government advice to pregnant mothers regarding peanut avoidance on the prevalence of peanut allergy in United Kingdom children at school entry. *J Allergy Clin Immunol* 2007;119:1197-202.
37. Turner PJ, Campbell DE, Boyle RJ, Levin ME. Primary prevention of food allergy: translating evidence from clinical trials to population-based recommendations. *J Allergy Clin Immunol Pract* 2018;6:367-75.
38. Shaker M, Stukus D, Chan ES, Fleischer DM, Spergel JM, Greenhawt M. "To screen or not to screen": comparing the health and economic benefits of early peanut introduction strategies in five countries. *Allergy* 2018;73:1707-14.
39. Hoffman B, Moreno L, Gerber L, D'Angelo D, Abramson E. OR075 What pediatricians are advising on infant peanut introduction. *Ann Allergy Asthma Immunol* 2017;119:S10.
40. 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* 2016;137:1263-1264.e1262.
41. Tang MLK, Koplin JJ, Sampson HA. Is skin testing or sIgE testing necessary before early introduction of peanut for prevention of peanut allergy? *J Allergy Clin Immunol Pract* 2018;6:408-13.
42. Turner PJ, Campbell DE. Epidemiology of severe anaphylaxis: can we use population-based data to understand anaphylaxis? *Curr Opin Allergy Clin Immunol* 2016;16:441-50.
43. Francke AL, Smit MC, de Veer AJ, Mistiaen P. Factors influencing the implementation of clinical guidelines for health care professionals: a systematic meta-review. *BMC Med Inform Decis Mak* 2008;8:38.
44. Tey D, Allen KJ, Peters RL, Koplin JJ, Tang MLK, Gurrin LC, et al. Population response to change in infant feeding guidelines for allergy prevention. *J Allergy Clin Immunol* 2014;133:476-84.
45. Greenhawt M, Chan ES, Fleischer DM, Hicks A, Wilson R, Shaker M, et al. Caregiver and expecting caregiver support for early peanut introduction guidelines. *Ann Allergy Asthma Immunol* 2018;120:620-5.
46. Campbell JL, Ramsay J, Green J. Age, gender, socioeconomic, and ethnic differences in patients' assessments of primary health care. *Qual Health Care* 2001;10:90-5.
47. Lakhanpaul M, Culley L, Robertson N, Bird D, Hudson N, Johal 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.
48. Palmer DJ, Prescott SL, Perkin MR. Early introduction of food reduces food allergy—pro and con. *Pediatr Allergy Immunol* 2017;28:214-21.