

# Food Allergy Prevention: More Than Peanut



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

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**List of Design Committee Members:** Michael R. Perkin, PhD, Alkis Togias, MD, Jennifer Koplin, PhD, and Scott Sicherer, MD (authors); Robert S. Zeiger, MD, PhD (editor)

### Learning objectives:

1. To advise parents on current food allergy prevention strategies
2. To discuss the rationale of prevention approaches that address diet and skin barrier
3. To discuss limitations of what is known about current food allergy prevention approaches

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Given an apparent increase in food allergies worldwide, the focus on prevention strategies has intensified. Following the Learning Early About Peanut study, there is now a widespread acceptance that peanut should be introduced promptly into the diet of high-risk infants. However, most food allergies are caused by triggers other than peanut and additional prevention strategies are being evaluated. The appreciation of the role of an impaired skin barrier in the process of food sensitization and subsequent

allergy has led to a spectrum of dermatologically orientated studies. Other prevention strategies address the role of the microbiome, dietary components, and other modifiable risk factors. With regard to early introduction of foods other than peanut, studies are heterogeneous in design and governmental and professional society response to the early introduction trials has varied, ranging from new guidelines confining advice specifically to peanut, to ones recommending prompt

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*Abbreviations used*

|                                                                     |
|---------------------------------------------------------------------|
| AD-Atopic dermatitis                                                |
| aOR-Adjusted odds ratio                                             |
| BEEP-Barrier Enhancement for Eczema Prevention                      |
| CI-Confidence interval                                              |
| EAT-Enquiring About Tolerance                                       |
| EP-Expert panel                                                     |
| LEAP-Learning Early About Peanut                                    |
| NIAID-National Institute of Allergy and Infectious Diseases         |
| PACI-Prevention of Allergy via Cutaneous Intervention               |
| PreventADALL-Preventing Atopic Dermatitis and ALLergies in Children |
| RCT-Randomized controlled trial                                     |
| RR-Risk ratio                                                       |
| TEWL-Transepidermal water loss                                      |

**introduction of a broad spectrum of allergenic foods. Much remains to be determined with regard to the acceptability and uptake of the new guidelines and their impact on infant feeding behavior and food allergy outcomes. This review discusses the panoply of prevention approaches, their promise, and limitations.** © 2019 American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2020;8:1-13)

**Key words:** Food allergy; Allergy prevention; Children; Eczema; Microbiome

In the UK Infant Feeding Survey of 2010, mothers of 8- to 10-month-old babies were asked whether there were any particular ingredients they avoided giving their baby. Nearly half (45%) mentioned at least 1 ingredient.<sup>1</sup> Peanut induces a singularly prominent sense of fear in mothers of young infants, and amongst the allergenic foods recorded in those mentioning an ingredient, nuts were dominant (41%), with much smaller numbers avoiding eggs (12%) and dairy produce (11%).<sup>1</sup> These avoidance figures all far exceed the true rate of allergy to these foods. In the Standard Introduction Group of the Enquiring About Tolerance (EAT) study, the percentage developing an individual food allergy by 3 years of age (confirmed by double blind food challenge where possible) was as follows: egg 5.4%, peanut 2.5%, milk 0.7%, sesame 0.5%, fish 0.2%, and wheat 0%.<sup>2</sup> In 6-year-old children, tree nut allergy has a similar prevalence to peanut allergy.<sup>3</sup> These results along with similar results from other studies around the world<sup>4-6</sup> also emphasize another key fact: peanut allergy accounts for less than half of children with food allergy, with egg allergy being over twice as prevalent.

The Learning Early About Peanut (LEAP) study was remarkable for many reasons.<sup>7</sup> First, it represented a paradigm shift in philosophy with regard to early sustained consumption of a food that, until 2008, was advised to be avoided in infancy and early childhood. It was in that year that the American Academy of Pediatrics rescinded their recommendations that infants at high risk of developing allergy (having a first-degree relative with an allergic disease) avoid solids until 6 months of age, cow's milk until 1 year of age, egg to 2 years, and peanuts, tree nuts, and fish to 3 years of age.<sup>8</sup> Secondly, it achieved an exceptional follow-up rate and high sustained adherence to the consumption regimen, which collectively delivered a highly significant 81% reduction

( $P < .0005$ ) in peanut allergy, answering incontrovertibly the scientific question of the benefit of active peanut introduction in high-risk infants with absent or low peanut sensitization at enrollment in the first year of life. The issues of how the findings of LEAP in the rarefied setting of a multimillion dollar randomized controlled clinical trial apply to the real world of pragmatic peanut allergy prevention have been previously reviewed in this journal by the LEAP study team.<sup>9</sup> The outstanding, and more pertinent, issue regarding the burden of food allergy in childhood is exploring where we have reached with the prevention of food allergies beyond peanut.

## ETIOLOGY OF FOOD ALLERGY

Understanding the etiology of food allergy is the essential prerequisite to have any chance of preventing its development. The association between food allergy and eczema has long been established, with increasing severity of eczema being associated with food sensitization and allergy.<sup>10,11</sup> The discovery that transepidermal water loss (TEWL) is elevated in filaggrin loss-of-function mutation carriers unaffected by eczema at 3 months of age suggests that skin barrier impairment precedes clinical eczema.<sup>12</sup> The pivotal role the skin barrier appears to play as the portal through which sensitization to food allergens occurs was encapsulated in the "dual-allergen-exposure hypothesis."<sup>13</sup> This proposed that sensitization to food allergen occurs through environmental exposure to allergen through the skin and that oral consumption of food allergen induces immune tolerance. This hypothesis provides a possible explanation for the close link between eczema and the development of food allergies. Gideon Lack suggested 3 novel interventional strategies to prevent the development of food allergies. The first was that the prompt intensive treatment of eczema in early infancy would decrease inflammation in the skin, reduce skin permeability, and prevent allergic sensitization to foods. The second was that a reduction of food allergens in the child's environment would lead to a reduction in sensitization. The third was that the early introduction of allergenic foods to the infant's diet (in the first 6 months of life) could reduce the development of food allergies through oral tolerance induction.

## Prompt intensive treatment of eczema in early infancy

Lack's dual-allergen-exposure hypothesis was published in 2008. Ten years later, the protocol for the first randomized controlled trial (RCT) investigating this strategy was published.<sup>14</sup> The Prevention of Allergy via Cutaneous Intervention (PACI) study (UMIN000028043) is investigating the early aggressive treatment of eczema that has emerged in infants aged 7 to 13 weeks within the previous 28 days, using topical steroid creams, to prevent the emergence of food allergy. The primary outcome for the study is challenge-proven IgE-mediated hen's egg allergy at the age of 28 weeks. This early age has been chosen because of the efficacy of early egg introduction observed in the Prevention of Egg allergy with Tiny amount InTake study, and participants in the PACI study will be recommended to introduce egg from 6 months of age.<sup>15</sup>

Interestingly, what Lack did not envisage was the concept of moving from restoring an actively impaired skin barrier, to attempting to prevent the skin barrier becoming impaired in the first place. The hypothesis here would be that prompt intensive moisturization from birth would help the evolution and maintenance of an intact skin barrier. This in turn would prevent, first, eczema from developing, and secondly, potentially prevent

food sensitization and subsequent food allergy. Evidence to support the former emerged, with the most promising results being seen in the Barrier Enhancement for Eczema Prevention (BEEP) pilot study, where a 50% reduction in atopic dermatitis (AD) was observed at 6 months of age in 124 infants born in the United Kingdom and United States.<sup>16</sup> A similar level of reduction was seen in a Japanese study of 118 high-risk infants with 32% developing eczema after an emulsion-type moisturizer was applied in the first 32 weeks of life in the intervention group, compared with 47% in the control group (hazard ratio, 0.48).<sup>17</sup> This pilot study also assessed allergic sensitization at 32 weeks of age, but found no statistically significant difference for egg white or ovomucoid at either a  $\geq 0.35$  or a  $\geq 0.7$  kU/L threshold.

While the BEEP pilot study and the Japanese study mentioned above used standard emollients, the Prevention of Eczema by a Barrier Lipid Equilibrium Strategy pilot study in Australia used a ceramide-rich tri-lipid emollient, EpiCeram, as it was felt to potentially provide greater preventive effects. The pilot study of 80 high-risk infants found that twice-daily application of EpiCeram for the first 6 months of life showed a trend toward reduced risk of AD and food sensitization at 6 and 12 months of age.<sup>18</sup> The per protocol analyses (only including infants who received  $\geq 5$  days per week of study treatment) revealed a significant reduction in food sensitization at 12 months in the treatment group (0%, 0 of 21 vs 19%, 7 of 36,  $P = .04$ ). The full RCT aiming to recruit 760 high-risk infants is now underway (NCT03667651).

In the United States, Simpson et al used a moisturizer, Cetaphil, containing a synthetic ceramide precursor, as well as filaggrin breakdown products (components of natural moisturizing factors) and niacinamide (vitamin B3, which is important in ceramides synthesis) applied once daily, in a small study of high-risk infants less than 3 weeks of age (NCT01375205). There was a nonsignificant reduction in the primary outcome of the cumulative incidence of AD at 1 year: 13.2% (5/38) of the intervention arm compared with 25.0% (8/32) in the control arm ( $P = .20$ ).<sup>19</sup>

Another study just about to commence is the Short-term Topical Application to Prevent Atopic Dermatitis (NCT03871998). This will investigate the effect of short-term (from birth to 2 months) neonatal skin barrier protection on the prevention of AD and food allergy in high-risk infants.

The 2 largest RCTs involving an early emollient intervention regimen, the BEEP main trial<sup>20</sup> and the Preventing Atopic Dermatitis and ALLergies in Children (PreventADALL) study,<sup>21</sup> which presented their results at the 2019 European Academy of Allergy and Clinical Immunology meeting in Lisbon, yielded disappointing results with no significant difference in eczema prevalence between the intervention and control groups in both studies. The BEEP main trial recruited newborn infants with a family history of atopic disease. In the intervention arm, families applied a daily emollient (Diprobase cream or DoubleBase gel at parental choice) in the first year of life plus standard skin-care advice, compared with standard skin-care advice in the control arm only. The primary outcome was eczema at 2 years of age diagnosed using the UK working party criteria. The PreventADALL study is a  $2 \times 2$  factorial design study testing 2 primary prevention strategies: skin care and early food introduction. The latter aspect of the study is considered below, in the section "Early introduction of allergenic foods to the infant's diet...." Women were recruited in pregnancy and the skin care

intervention was an oil bath and application of a moisturizer to the infant's face (Ceridal cream) at least 5 days per week from 0.5 to 9 months of age. The negative results of both BEEP and PreventADALL contrasted with the BEEP pilot results mentioned above<sup>16</sup> and the PreventADALL pilot data,<sup>22</sup> which showed a reduction in probable atopic eczema from 19% to 4% ( $P = .10$ ) at 6 months of age in children with dry skin subjected to skin care from 2 weeks. One could postulate that the lack of efficacy in the BEEP study may be related to somewhat reduced adherence (80% adherence rate with the intervention in the first 6 months of life, dropping to 74% for months 6-12); that emollient might need to be applied multiple times per day; or applied for longer than the study intervention period (the first year of life); or that a more complex emollient formulation, such as one containing ingredients such as ceramides and pH modulators, might be required.<sup>23</sup> For the PreventADALL, potential reasons for the negative finding include the fact that the emollient intervention was facial application of moisturizer, not to the whole body. Furthermore, a recent trial found no evidence that bath additives helped with eczema treatment, raising questions about their use for eczema prevention.<sup>24</sup> Given these concerns, we believe additional studies will be needed and that, perhaps, strategies that combine skin barrier protection and clinical management of AD should be considered.

## Reduction of food allergens in the child's environment

In a seminal interventional trial published in 2004, the Manchester Asthma and Allergy Study found that a stringent environmental intervention to reduce house dust mite exposure resulted in *increased* aeroallergen sensitization in the intervention group (sensitization to at least 1 allergen by skin tests: risk ratio [RR], 1.61; 95% confidence interval [CI], 1.02-2.55;  $P = .04$ ; house dust mite IgE: RR, 2.85; 95% CI, 1.02-7.97;  $P = .05$ ).<sup>25</sup> Although this was a trial of reducing exposure to an airborne inhalant allergen, it emphasizes that environmental manipulation studies can achieve unexpected and unwanted results.

The evidence for reducing environmental exposure as a means to reduce food allergy is supported by several studies regarding peanut. Fox et al<sup>26</sup> demonstrated a dose-response relationship between environmental (nonoral) peanut exposure based on peanut consumption questionnaires and the development of peanut allergy. However, environmental peanut exposure was measured by household food frequency questionnaire, rather than directly. Subsequently, Brough et al<sup>27</sup> measured peanut in household dust and confirmed the association, finding a strong and significant interaction between peanut dust levels and filaggrin mutations on peanut sensitization and peanut allergy. Furthermore, Brough et al<sup>28</sup> found that the impact of environmental peanut exposure on sensitization and likely allergy was augmented by the severity of AD in infants.

Exposure to food allergens is ubiquitous. Subsequent work by Brough demonstrated that in 87 dust samples from 18 schools, 100% had detectable peanut protein.<sup>29</sup> Peanut protein was widely detectable in dust samples obtained from both classrooms and cafeterias of schools, with peanut levels in school dust higher than levels in students' homes. Although this might infer that a strategy of reducing exposure to food allergens in the child's domestic environment is unlikely to be successful, given the potential for significant exposure outside the house, the age during which the skin is exposed to high levels of a food protein

**TABLE I.** Trials of early food introduction other than peanut alone (adapted from Ierodiakonou et al<sup>36</sup>)

| Study                                                                                                                | Population                                                                                                                  | Intervention                                                                                                                                                                                                                               | Age at assessment | Outcome                                                                                                                                       | Risk ratio (95% CI)                                                                        |
|----------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| <b>Egg only</b>                                                                                                      |                                                                                                                             |                                                                                                                                                                                                                                            |                   |                                                                                                                                               |                                                                                            |
| STAR (n = 86)<br>(Solids Timing for Allergy Reduction)<br>Australia<br>Palmer et al, 2013 <sup>31</sup>              | “High-risk” singleton-term infants with moderate or severe eczema (SCORAD $\geq 15$ ) and no prior egg or solid food intake | Pasteurized spray-dried raw whole egg powder daily (1 tsp = 0.9 g egg protein or 1/6th egg) vs rice flour powder from age 4 to 8 mo                                                                                                        | 1 y               | Egg allergy diagnosed by oral food challenge to pasteurized raw whole egg (30 mL LR or 38 mL HR $\sim 1/2$ egg) plus positive skin prick test | 0.65 (0.38-1.11)                                                                           |
| BEAT (n = 319)<br>(Beating Egg Allergy Trial)<br>Australia<br>Wei-Liang Tan et al, 2016 <sup>32</sup>                | “High-risk” infants with first-degree relative with allergic disease and egg skin prick test $< 2$ mm at age 4 mo           | Pasteurized freeze-dried raw whole egg powder daily (350 mg egg protein) vs rice powder daily from the time of solid food introduction to age 8 mo                                                                                         | 1 y               | Egg allergy diagnosed by oral food challenge to lightly cooked whole egg (scrambled) 6 g egg protein ( $\sim 1$ egg)                          | 0.59 (0.25-1.37)                                                                           |
| PETIT (n = 147)<br>(Prevention of Egg allergy with Tiny amount InTake)<br>Japan<br>Natsume et al, 2016 <sup>15</sup> | “High-risk” infants with eczema by age 4-5 mo                                                                               | Heated whole egg powder, 50 mg/d (25 mg egg protein approx. equivalent to 0.2 g of whole egg boiled for 15 min), from age 6-9 mo; 250 mg/d (125 mg egg protein $\sim 1.1$ g whole egg boiled) from age 9-12 mo vs placebo from age 6-12 mo | 1 y               | Egg allergy diagnosed by oral food challenge to 7 g ( $\sim 32$ g of boiled egg) of the heated whole egg powder used as the intervention      | 0.22 (0.09-0.54)                                                                           |
| HEAP (n = 383)<br>(Hen’s Egg Allergy Prevention)<br>Germany<br>Bellach et al, 2017 <sup>33</sup>                     | “Normal-risk” infants aged 4-6 mo with specific IgE to egg $< 0.35$ kU/L                                                    | Pasteurized raw egg white powder (2.5 g egg protein) vs rice powder 3 times/wk from age 4-6 to 12 mo                                                                                                                                       | 1 y               | Egg allergy diagnosed by oral food challenge to pasteurized liquid whole egg ( $\sim 7.16$ g egg protein)                                     | 2.20 (0.20-24.0)                                                                           |
| STEP (n = 820)<br>(Starting Time of Egg Protein)<br>Australia<br>Palmer et al, 2017 <sup>34</sup>                    | “High-risk” infants with an atopic mother, no prior egg ingestion, and no prior allergic disease                            | Pasteurized spray-dried raw whole egg powder daily (0.9 g egg powder = 0.4 g egg protein) vs rice powder daily from age 4-6 to 10 mo                                                                                                       | 1 y               | Egg allergy diagnosed by oral food challenge to pasteurized raw whole egg (30 mL LR or 38 mL HR $\sim 1/2$ egg) plus positive skin prick test | 0.75 (0.48-1.17)                                                                           |
| <b>Milk only</b>                                                                                                     |                                                                                                                             |                                                                                                                                                                                                                                            |                   |                                                                                                                                               |                                                                                            |
| MACS (n = 620)<br>(Melbourne Atopy Cohort Study)<br>Australia<br>Lowe et al, 2011 <sup>35</sup>                      | “High-risk” infants with a first-degree relative with eczema, asthma, allergic rhinitis, or food allergy                    | Cow’s milk vs soya formula, as needed from birth. Introduced at median 4 mo                                                                                                                                                                | 7 y               | Physician assessment of food allergy                                                                                                          | 0.74 (0.26-2.10)                                                                           |
| <b>Multiple foods</b>                                                                                                |                                                                                                                             |                                                                                                                                                                                                                                            |                   |                                                                                                                                               |                                                                                            |
| EAT (n = 1303)<br>(Enquiring About Tolerance)<br>UK<br>Perkin et al, 2016 <sup>2</sup>                               | “Normal-risk” singleton term infants exclusively breastfed for 3 mo                                                         | Sequential introduction of 6 allergenic foods aiming for 4 g protein/wk for each food, cow’s milk (yogurt), then peanut, boiled egg, sesame, fish, and wheat from age 3 mo, vs avoidance to age $\geq 6$ mo                                | 1 and 3 y         | Egg allergy and peanut allergy diagnosed by oral food challenge                                                                               | E 0.69 (0.40-1.18)<br>M 0.79 (0.18-3.50)<br>S 1.04 (0.21-5.14)<br>F 1.05 (0.07-16.7)<br>W* |

(continued)

TABLE I. (Continued)

| Study                                                                                                                                                | Population                                               | Intervention                                                                                                                                                                                                                                                                      | Age at assessment              | Outcome                                  | Risk ratio (95% CI) |
|------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|------------------------------------------|---------------------|
| PreventADALL (n = 2397)<br>(Preventing Atopic Dermatitis and ALLergies in Children)<br>Norway and Sweden<br>Lødrup Carlsen et al, 2018 <sup>21</sup> | “Normal-risk” singleton or twin ≥35 wk gestation infants | Factorial design of 2 interventions: (1) skin care (oil bath and Ceridal face cream at least 5 d/wk from 0.5 to 9 mo of age); (2) consecutive introduction, between 3 and 4 mo of age, of tastes of peanut, milk, wheat, and egg, at least 4 d/wk, complementary to breastfeeding | 1 y (AD)<br>3 y (food allergy) | Food allergy confirmed by food challenge | Ongoing             |

E, egg; F, fish; HR, high risk; LR, low risk; M, milk; S, sesame; SCORAD, SCORing Atopic Dermatitis; W, wheat.

\*EAT study wheat intention to treat results: standard introduction group 0% (0/597), early introduction group 0.2% (1/572),  $P = .49$ , RR not calculable.

is likely to also be critical. Kelleher et al<sup>30</sup> showed that 75% of children who developed food allergy at 2 years of age in the Babies After SCOPE: Evaluating the Longitudinal Impact on Neurological and Nutritional Endpoints study had a TEWL measurement, measured at 2 days of age, in the upper quartile of the distribution, and that this association was present even in those without AD.

Although families might be amenable to reducing household peanut consumption, it would be much harder to maintain sustained reductions in domestic environmental exposure to more common food allergens such as cow's milk or egg, where removing the allergen from the family's diet would impose a much greater burden in terms of change of household diet.

### Early introduction of allergenic foods to the infant's diet (in the first 6 months of life) to reduce the development of food allergies through oral tolerance induction

**Randomized controlled trials.** Of studies involving early introduction of an allergenic food other than peanut that have been completed and published, all but 2 have introduced a single food: 5 studies using egg<sup>15,31-34</sup> and 1 study using milk.<sup>35</sup> The 2 studies that have introduced multiple foods are the EAT study: peanut, egg, milk, sesame, fish, and wheat<sup>2</sup>; and the PreventADALL study: peanut, milk, wheat, and egg.<sup>21</sup> The studies are summarized in Table I.

Given the acceptance of the premise that early food allergen exposure is tolerance inducing, much interest has remained in the situation specifically with cow's milk and the fact that so many infants are exposed to cow's milk—based formula very early in infancy. This is given either exclusively in formula-fed infants or as supplements in mixed-fed infants. Exposure in the latter group ranges from negligible (eg, the milk-based formula supplemented on the postnatal ward for an infant of a first-time mother while her milk comes in) versus regular mixed-feeding with both formula and breast milk. In a large prospective study of 13,019 infants in Israel, those infants who developed an IgE-mediated cow's milk allergy were introduced to cow's milk significantly later (116 days) than those who were healthy (62 days) and only 0.05% of the infants who were started on regular cow's milk protein formula within the first 14 days versus 1.75%

who were started on formula between the ages of 105 and 194 days had IgE-mediated cow's milk allergy ( $P < .001$ ).<sup>37</sup> The authors proposed that early exposure to cow's milk protein as a supplement to breastfeeding might promote tolerance. A subsequent trial to explore this further was proposed and registered but does not appear to have been initiated (NCT02785679).

### Systematic review of early food introduction trials.

In their meta-analysis of the early introduction studies,<sup>36</sup> Boyle et al found moderate-certainty evidence from the 5 available trials at the time (1915 participants) that early egg introduction at 4 to 6 months was associated with reduced egg allergy (RR, 0.56; 95% CI, 0.36-0.87;  $I^2 = 36\%$ ;  $P = .009$ ). The absolute risk reduction for a population with 5.4% incidence of egg allergy was 24 cases (95% CI, 7-35 cases) per 1000 population. This contrasts with peanut for which there are still only 2 published studies, EAT and LEAP (1550 participants), with early peanut introduction at 4 to 10 months being associated with a greater proportional reduction in peanut allergy (RR, 0.29; 95% CI, 0.11-0.74;  $I^2 = 66\%$ ;  $P = .009$ ). However, because the population prevalence of peanut allergy (2.5%) is significantly lower than that of egg allergy, the absolute risk reduction of peanut allergy was 18 cases (95% CI, 6-22 cases) per 1000 population, less than for egg. These considerations suggest that there may be significantly more public health benefits from a program recommending early egg introduction than from one recommending early peanut introduction.

The systematic review also found that there was no evidence for a relationship between the introduction of any other allergenic foods and food allergy, or between the introduction of one allergenic food and allergy to a different food.

### Pragmatic trials and food introduction guidelines.

When clinical efficacy has been demonstrated in trials such as EAT and particularly LEAP, and confirmed in a systematic review, translating this into a public health intervention is complex and the results are likely to be subject to effect modification in different populations.<sup>38</sup> Both the internal and external validity of RCT findings can be greatly enhanced by observational studies using adequacy or plausibility designs. Such trials serve to identify the barriers and facilitators of the intervention in the real world.

**TABLE II.** Specific country guidelines for food allergy prevention beyond peanut

| Country       | Organization                                                                                                               | Year | Food                                             | Guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Recommends testing before food introduction in high-risk infants?                                                                           |
|---------------|----------------------------------------------------------------------------------------------------------------------------|------|--------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| United States | American Academy of Pediatrics (Committee on Nutrition, Section on Allergy and Immunology) <sup>43</sup>                   | 2019 | Peanut, egg, and fish                            | There is no evidence that delaying the introduction of allergenic foods, including peanuts, eggs, and fish, beyond 4-6 mo prevents atopic disease<br>There is now evidence that the early introduction of infant-safe forms of peanuts reduces the risk for peanut allergies. Data are less clear for timing of introduction of eggs                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Not for any food other than peanut                                                                                                          |
| Europe        | European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on Nutrition <sup>44</sup> | 2017 | Cow's milk, egg, fish, gluten, peanut, and seeds | There may be an increased risk of allergy if solids are introduced before 3-4 mo. There is, however, no evidence that delaying the introduction of allergenic foods (cow's milk, egg, fish, gluten, peanut, and seeds) beyond 4 mo reduces the risk of allergy, either for infants in the general population or for those with a family history of atopy<br>Infants at high risk of peanut allergy (those with severe eczema, egg allergy, or both as defined in the LEAP study) should have peanut introduced between 4 and 11 mo; after evaluation by an appropriately trained professional                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | No<br>Infants with severe eczema and or egg allergy should be evaluated by an appropriately trained professional before peanut introduction |
|               | European Food Safety Authority (EFSA) Panel on Nutrition, Novel Foods and Food Allergens (NDA) <sup>45</sup>               | 2019 | Egg, cereals, fish, and peanut                   | Specific allergenic foods<br>In relation to the "delayed" introduction of allergenic foods (egg, cereals, fish, and peanuts) into an infant's diet, the Panel finds no evidence that their "early" introduction increases the risk of developing atopic diseases. The Panel considers that, as far as the chance/risk of allergy is concerned, these foods can be introduced when other complementary foods are introduced<br>Hen's egg and egg allergy<br>With respect to egg introduction, the data pointed toward a favorable effect of its introduction between around 3 and 4 mo compared with 6 mo of age on the risk of developing egg allergy. However, the confidence in the evidence is low to moderate and is, therefore, insufficient to support introducing egg at around 3-4 mo of age in all infants for the prevention of egg allergy. In the available studies, no serious adverse reactions occurred with consumption of cooked egg, whereas anaphylactic reactions were observed when the intervention consisted of pasteurized raw egg powder. As far as the chance/risk of allergy is concerned, cooked egg can be introduced into the diet of infants when other complementary foods are introduced.<br>Peanuts and peanut allergy<br>There is evidence that peanut introduction during the first year of life (either at 4-10 mo or at 4-6 mo) compared with peanut avoidance up to 5 yr of age reduces the risk of peanut allergy. However, the evidence is insufficient to conclude whether a similar effect occurs when comparing infants introduced to peanuts <6 mo of age compared with those introduced >6 mo, but still within the first year of life, which is the subject of this mandate | No                                                                                                                                          |

|                |                                                                                                                                                              |      |                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                           |
|----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|------|---------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
|                | European Academy of Allergy and Clinical Immunology (EAACI <sup>46</sup> ) Food Allergy and Anaphylaxis Guidelines Group <sup>46</sup>                       | 2014 | Cow's milk, egg, and peanut                                   | <p>Introduction of complementary foods after the age of 4 mo according to normal standard weaning practices and nutrition recommendations, for all children irrespective of atopic heredity</p> <p>No special dietary restrictions after the age of 4 mo for infants with high risk for development of allergic disease</p> <p>No withholding or encouraging exposure to "highly allergenic" foods such as cow's milk, hen's egg, and peanuts irrespective of atopic heredity, once weaning has commenced</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | No                                                                                                                                                        |
| United Kingdom | Scientific Advisory Committee on Nutrition (SACN)/ Committee on Toxicology of Chemicals in food, Consumer products and the Environment (COT) <sup>47</sup>   | 2017 | Peanut and egg                                                | <p>The benefit-risk assessment indicated that there were insufficient data to support the existence of a "window of opportunity" for the introduction of peanut before 6 mo of age. Evidence that the introduction of hen's egg before 6 mo might be beneficial was limited and derived from RCTs where participants were not representative of the general population</p> <p>The benefit-risk assessment indicated that there were insufficient data to demonstrate that the introduction of peanut or hen's egg into the infant diet between 4 and 6 mo of age reduced the risk of developing food allergy to any greater extent than introduction from around 6 mo</p> <p>Reasonable data exist to demonstrate that the deliberate exclusion or delayed introduction of peanut or hen's egg beyond 6-12 mo of age may increase the risk of allergy to the same foods</p> <p>The government should continue to recommend exclusive breastfeeding for around the first 6 mo of life. Advice on complementary feeding should state that foods containing peanut and hen's egg need not be differentiated from other complementary foods. Complementary foods should be introduced in an age-appropriate form from around 6 mo of age, alongside continued breastfeeding, at a time and in a manner to suit both the family and individual child</p> <p>The deliberate exclusion of peanut or hen's egg beyond 6-12 mo of age may increase the risk of allergy to the same foods. Once introduced, and where tolerated, these foods should be part of the infant's usual diet, to suit both the individual child and family. If initial exposure is not continued as part of the infant's usual diet, then this may increase the risk of sensitization and subsequent food allergy</p> | No<br>Families of infants with a history of early-onset eczema or suspected food allergy may wish to seek medical advice before introducing peanut or egg |
|                | British Society for allergy and Clinical Immunology (BSACI) and Food Allergy Specialist Group (FASG) of the British Dietetic Association (BDA) <sup>48</sup> | 2018 | Egg, peanut, other nuts, dairy foods, fish/seafood, and wheat | <p>Infants with eczema and/or existing food allergy</p> <p>These children may benefit from the earlier introduction of cooked egg (and then peanut), alongside other solids. When the baby is ready, consider introducing solid foods—including cooked egg and then peanut—from age 4 mo, followed by other allergenic foods (other nuts, dairy foods, fish/seafood, and wheat)</p> <p>All other infants</p> <p>When the baby is ready, introduce solid foods at around 6 mo of age (but not before 4 mo). Include peanut, egg, and other foods (other nuts, dairy foods, fish/seafood, and wheat) that are eaten as part of the family's normal diet</p> <p>It may be beneficial to introduce egg before peanut, as the available data indicate that egg allergy may have an earlier onset than peanut. The impact of earlier introduction of egg in higher risk infants may be greater than that for peanut. However, peanut allergy is more likely to persist into adulthood, so the longer-term benefits with earlier introduction of peanut are likely to be greater</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | No<br>Screening is not routinely recommended                                                                                                              |

(continued)

TABLE II. (Continued)

| Country   | Organization                                                                                                                                                                               | Year | Food                                    | Guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Recommends testing before food introduction in high-risk infants?                                                                                                          |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Australia | Australasian Society of Clinical Immunology and Allergy (ASCIA) <sup>49</sup>                                                                                                              | 2017 | Cooked eggs, peanuts, nuts, wheat, fish | <p>When your infant is ready, at around 6 mo, but not before 4 mo, start to introduce a variety of solid foods, starting with iron rich foods, while continuing breastfeeding</p> <p>All infants should be given allergenic solid foods including peanut butter, cooked egg, and dairy and wheat products in the first year of life. This includes infants at high risk of allergy</p> <p>When your infant is ready, introduce foods according to what the family usually eats, regardless of whether the food is considered to be a common food allergen. There is some evidence that the introduction of common allergenic foods (including cooked eggs as raw egg is not recommended, peanuts, nuts, wheat, fish) should not be delayed. However, further evidence is required to clarify optimal timing for each food</p> <p>There is good evidence that for infants with severe eczema and/or egg allergy, that regular peanut intake before 12 mo of age can reduce the risk of developing peanut allergy. If your child already has an egg allergy or other food allergies or severe eczema, you should discuss how to do this with your doctor</p> <p>There is moderate evidence that introducing cooked egg (raw egg is not recommended) into an infant's diet before 8 mo of age, where there is a family history of allergy, can reduce the risk of developing egg allergy</p> | No<br>For peanut only: if your child already has an egg allergy or other food allergies or severe eczema, you should discuss how to <i>introduce</i> this with your doctor |
| Japan     | Committee for Japanese Pediatric Guideline for Food Allergy, The Japanese Society of Pediatric Allergy and Clinical Immunology (JSPACI), The Japanese Society of Allergology <sup>50</sup> | 2017 | Peanut and egg                          | <p>Weaning is appropriate at 5-6 mo of age. Delaying in weaning due to concerns regarding the onset of food allergies is not recommended</p> <p>It was reported that delayed peanut consumption might increase the risk of developing peanut allergy, and in countries where peanut allergy occurs frequently, the early peanut consumption (4-10 mo after birth) is recommended</p> <p>Although it was reported that the intake of foods that may induce allergies (peanut, hen's egg) from 3 mo after birth may reduce the onset risk of food allergies in comparison with the start at 6 mo or later after birth, the amount and quality of foods to safely induce tolerance are still unknown and under study</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | No                                                                                                                                                                         |

LEAP, Learning Early About Peanut; RCT, randomized controlled trial.

Although governments and organizations ought to be undertaking pragmatic trials before offering or, for that matter, changing infant feeding advice, this is often not done. For example, between 1998<sup>39</sup> and 2009,<sup>40</sup> the United Kingdom government recommended avoidance of peanut consumption in high-risk families during pregnancy, lactation, and to the child until 3 years of age. The American Academy of Pediatrics from 2000<sup>41</sup> to 2008<sup>8</sup> also recommended high-risk infants avoid solids until 6 months of age, dairy products until 1 year of age, hen's egg to 2 years, and peanuts, tree nuts, and fish to 3 years of age.<sup>41</sup> The evidence basis for both the initiation and the revocation of these guidelines was limited.<sup>42</sup> These relatively recent changes have occurred on a background of significant shifts in infant feeding advice over the last 40 years.<sup>42</sup>

It is perhaps therefore not surprising that the integration of the results of the early allergenic food introduction studies into public health policy has varied hugely around the world (Table II). Some countries have confined their recommendations to peanut (eg, the United States) with a very literal application of the LEAP study's methodology. Others have extrapolated the early introduction recommendation to a broad array of other allergenic foods.

In the hierarchy of research evidence, a well-conducted systematic review is considered more important than any individual RCT.<sup>51</sup> One might infer that guidelines should be advocating early egg introduction with at least equal vigor to early peanut introduction, given the results of the systematic review by Boyle's group, and that within the review the  $I^2$  test for heterogeneity was greater for peanut ( $I^2 = 66\%$ ,  $P = .09$ ) than for egg ( $I^2 = 36\%$ ,  $P = .18$ ).<sup>36</sup> However, this belies significant concerns about the heterogeneity in design of the egg introduction studies and particularly the vehicle used for introduction, the varied doses and regimens that were used, and the form of egg used in the outcome determining challenge, despite the lower  $I^2$  score (Table I). All the studies introducing egg alone used egg powder as the vehicle, derived from raw and pasteurized egg. Four used whole egg powder and one used egg white powder. Pasteurized egg powder is considered to be of similar allergenicity to raw hen's egg.<sup>52-54</sup> However, there is some uncertainty about this, and in the Solids Timing for Allergy Reduction study, 2 of the intervention infants who were tolerating the 0.9 g dose of pasteurized raw whole egg powder (1/6th of an egg) for 4 months reacted to a challenge with 1/6th of an egg's worth of hard-boiled mashed egg.<sup>55</sup>

**Commercial response to the early intervention studies.** The early introduction studies have triggered the emergence of a number of companies specifically manufacturing a whole new category of baby food add-ins, with the sole purpose of exposing an infant to specific food allergens in the hope that this will induce oral tolerance. The process is only likely to gather momentum because the US Food and Drug Administration, in response to a petition for a qualified health claim by a company producing a peanut-based product with regard to its potential to prevent the development of peanut allergy, determined that the current scientific evidence supported a qualified health claim in the labeling of conventional foods that contain ground peanuts and a reduced risk of developing peanut allergy for a specific population of infants and children over a specific period of time. A whole smörgåsbord of products have appeared. Some products

have focused exclusively on peanut, aiming to allow infants to consume the requisite amount of peanut that induced tolerance in the LEAP study. Others have included a multitude of allergens. The issue with the latter is that the EAT study has clearly shown that the dose of allergen consumed is critical with doses of 4 g of whole egg per week (2 g of egg white protein) and 2 g of peanut protein per week being required to induce tolerance. Hence, products containing significantly less than this dose are unlikely to be effective.

## Other interventions to prevent food allergies

### Maternal consumption of allergenic foods during pregnancy and lactation.

There has been a longstanding debate as to whether maternal consumption of allergenic foods during pregnancy and/or lactation has any bearing on her infant developing a food allergy, but almost all of this has focused on nut consumption in pregnancy. A systematic review included 42 studies and did not find widespread or consistent links between mothers' dietary intake and atopic outcomes in their children.<sup>56</sup> However, the PrEggNut RCT is now underway, investigating whether regular consumption in pregnancy of a high egg- and peanut-containing diet will prevent the development of challenge-proven food allergy at 12 months of age (ACTRN12618000937213). It is important to consider that trials that encourage allergen (and particularly nut) consumption in pregnancy and/or during lactation will potentially result in their being higher environmental exposure to the allergen in the infant's environment, which might then carry the risk inducing sensitization through transcutaneous exposure, especially in infants with an impaired skin barrier. Interestingly, the systematic review concluded that maternal consumption of Mediterranean dietary patterns was suggestive of benefit and required further evaluation.<sup>56</sup>

**Microbial exposure.** Lack<sup>13</sup> noted that other factors could modulate immunologic responses to a food in addition to the allergen and its route of exposure, and participate in shaping the clinical outcome. Suggested factors include high levels of vitamin D or the presence of microbial organisms being potentially also necessary for oral tolerance induction to occur.<sup>13</sup> In animal models, oral tolerance induction can only occur in the presence of normal gastrointestinal microflora and cannot be achieved in germ-free mice.<sup>57</sup> A systematic review of the association between microbial exposures and food allergy was published in 2013 identifying the many gaps in this field.<sup>58</sup> In the systematic review, results of probiotic studies were generally disappointing. One of 11 trials investigating probiotics demonstrated a quicker acquisition of milk tolerance amongst allergic infants.<sup>58</sup>

In more recent studies, Fujimura et al<sup>59</sup> and Feehley et al<sup>60</sup> respectively identified a specific neonatal gut microbiota state associated with eventual development of multisensitization that included food allergens or demonstrated that the gut microbiota of healthy infants, as opposed to infants with cow's milk allergy, protect mice from allergic reactions to cow's milk. These and other studies are bringing us closer to the design of human trials aiming at early microbiome manipulation for the prevention of food allergy, but specific interventions have yet to be tested.

The association between caesarean delivery and food allergy was investigated in 13 studies, of which 3 infant cohorts demonstrated an increase in challenge-proven food allergy (1 cohort) and food sensitization (2 cohorts), and 1 cross-sectional

study found increased reported doctor-diagnosed food allergy. The National Institute of Allergy and Infectious Diseases (NIAID)-supported Immune Tolerance Network is currently conducting a pilot, prospective, randomized trial to examine whether prompt exposure to the mother's vaginal microbiome of newborns born with C-section will influence the rate of food allergen sensitization by the end of the first year of life (NCT03567707).

**Vitamin D.** The debate about the role of vitamin D in the etiology of atopy has been going on for decades now. Both too much<sup>61</sup> and too little vitamin D<sup>62</sup> have been linked to the rise in atopic disease. With regard to the latter, numerous ecological studies have shown an increased risk of food allergy the further a child resides from the equator (associated with decreased UV exposure and vitamin D levels).<sup>63,64</sup> Allen et al<sup>62</sup> demonstrated an association between vitamin D insufficiency and increased risk of challenge-proven food allergy in 12-month-old infants in an observational study. Hence, the VITALITY RCT is investigating whether vitamin D supplementation in infants can prevent food allergy in the first year of life.<sup>65</sup>

**Pet exposure.** Two studies have now shown a reduction in food allergy with a dog being present in the household in the first year of life. In the HealthNuts study, children with a pet dog at home were less likely to develop egg allergy by 1 year of age (adjusted odds ratio [aOR], 0.72; 95% CI, 0.52, 0.99).<sup>66</sup> The effect was even stronger in the EAT study with infants who had a dog in the household at enrollment into the study at 3 months of age having a 90% reduction in the odds of developing a food allergy (aOR, 0.10; 95% CI, 0.01-0.71;  $P = .02$ ).<sup>67</sup> The microbiome may be mediating this protective effect with it having been shown that a dog's microbiome can influence the microbiome of its owner. Cohabitation with a dog resulted in dog-owning adults sharing more skin microbiota with their own dogs than with other dogs<sup>68</sup> and led to alterations in the microbiota of dust within the home.<sup>69</sup>

## PRACTICALITY AND CONTROVERSIES

The uptake and impact of the new guidelines recommending early allergenic food introduction are still being determined. A study found high physician and parent comfort levels with the US NIAID peanut introduction guidelines, but evidence of low or modified implementation.<sup>70</sup> Evidence that infant feeding behavior can be changed has been shown in Australia. The introduction of guidelines recommending allergenic food introduction before 12 months for all infants in 2016 was followed by an increase in timely allergenic food introduction in Australia, particularly for peanut. The EarlyNuts study, a population-based, cross-sectional study of 12-month-old infants in Melbourne, Australia, recruited infants in 2017-2018 using an identical sampling frame and methods to HealthNuts. Most infants (88.7%; 95% CI, 86.1-90.9) were introduced to peanut by 12 months (median age, 6 months), an increase from 28.4% (95% CI, 27.2-29.7) in HealthNuts (2007-2011). By 12 months, the majority of these (76.4%) had consumed peanut more than 4 times and 28% were eating peanut more than once per week. Egg consumption by 12 months of age was almost universal in both studies (97.6% [95% CI, 96.2-98.6] in EarlyNuts compared with 95.7% [95% CI, 95.1-96.3] in HealthNuts). Notably, in the EarlyNuts study, there was a shift toward

egg introduction by 6 months (57.9% vs 25.0%). The effect of this earlier introduction on the food allergy prevalence will be measured at the completion of the study at the end of 2019.<sup>71</sup>

## Medicalizing food introduction

The randomized trials of early allergenic food introduction involve, by their design, highly proscriptive regimens: in LEAP 3 times a week consumption of a specific amount of peanut<sup>7</sup> and in EAT twice weekly consumption of 6 allergenic foods.<sup>2</sup> There is concern that in attempting to replicate the same regimens in the real world (as exemplified in the dosing regimens of the commercial infant food products that have appeared), one runs the risk of medicalizing the process of complementary food introduction, with parents feeling pressure to comply with a regimen, or being seen to have failed their infant if they then subsequently develop a food allergy. There were children within the early introduction trials who developed food allergy despite compliance with the early introduction regimen, and this should also not be considered a failure on the part of the physician and should not discourage physicians and allergists from continuing to make recommendations for early food introduction. Conversely, it may be that as a society becomes more familiar and comfortable with early introduction of an allergenic food, that this becoming the norm will reduce anxiety levels and facilitate high levels of adherence. It will be interesting to observe what proportion of the original LEAP intervention group have maintained consumption of peanut at the level of the original recommended consumption of 6 g of peanut protein per week when the cohort is assessed at 12 years of age in the LEAP Trio Cohort Study (ClinicalTrials ID: NCT03546413).

## Historical issues in infant feeding and length of exclusive breastfeeding

Sensitization to allergenic foods emerges early, even in the general population. In the EAT study, using a  $\geq 0.1$  kU/L threshold at 3 months of age, 6.7% of participants were already sensitized to egg, 6.0% to milk, 2.0% to sesame, and 4.3% to wheat.<sup>72</sup> Furthermore, 1% of the EAT participants had a challenge-proven food allergy at enrollment. This suggests that different windows of opportunity might exist when allergenic foods might need to be introduced to prevent food allergy development. This further links to the historic debate as to what is the optimal age for the introduction of complementary foods and therefore the length of exclusive breastfeeding, a debate where food allergy only plays a partial role. With regard to the introduction of complementary foods, in the United Kingdom, there has been a significant trend since 1975 toward later introduction. The proportion of infants given solids by 8 weeks of age has decreased: 49% in 1975, 24% in 1980 and 1985, and 19% in 1990.<sup>73</sup> So clearly there have been periods of time where significantly earlier introduction of solids was deemed acceptable. However, it remains uncertain precisely at what age an allergenic food might need to be introduced to optimally induce tolerance and whether this age varies by food.

## Unknowns with amount, type, or preparation

Furthermore, there is uncertainty as to the amount of allergenic food required for the induction of tolerance. As stated previously, in the EAT study a dose of 4 g of whole egg per week (2 g of egg white protein) was required to be effective in preventing an egg allergy from emerging.<sup>2</sup> Further research on this matter is warranted.

## Screening for occult food sensitization

The NIAID-sponsored Expert Panel (EP) that produced the Addendum Guidelines for the Prevention of Peanut allergy in the United States recommended that, in high-risk infants, that is, infants with severe eczema and/or egg allergy, screening with either serum-specific IgE to peanut or a peanut skin prick test is conducted and offered an algorithm as to the way early peanut introduction should be conducted (or not). The panel explicitly indicated that food allergen panel testing or the addition of sIgE testing for foods other than peanut should not be conducted “because of poor positive predictive value, which could lead to misinterpretation, overdiagnosis of food allergy, and unnecessary dietary restrictions.”<sup>74</sup> The US panels’ recommendation reflects a conservative approach aiming at reducing the possibility of severe reactions on first introduction. However, no other guideline so far produced is recommending testing for any food (including peanut) before first introduction (Table II) as reactions at initial introduction are, in their majority, mild and the addition of a screening step may pose a barrier to or delay early peanut introduction. It is hoped that physician and parent surveys will be conducted in the next few years that will offer answers to this guideline discrepancy and will allow for appropriate adjustments.

## CONCLUSION

The NIAID EP stated that they had “no reason to believe that the mechanisms of protection of early dietary peanut differ in infants with mild-to-moderate eczema from those that lead to protection in infants at higher risk of peanut allergy.” By extension one could conclude that there is no logical reason to believe that the mechanisms of protection of early dietary food allergen exposure differ for any food. Countries and organizations adopting this logic have chosen to advocate for the timely introduction of a broad array of allergenic foods in infancy, and not just peanut and egg for which the systematic review has shown significant results. However, other organizations consider that there remains insufficient evidence to advocate early introduction of allergenic foods beyond peanut, although there is a broadly universal acceptance that delaying the introduction of specific allergenic foods is of no value.

Issues that remain include just how early consumption needs to start, and whether the starting age required differs by food. Furthermore, it remains unknown what the impact might be of consumption being commenced but then being intermittent or ceasing. Dose also remains uncertain. Although consumption of lesser quantities of food allergen in the EAT study was not associated with an increase in risk of developing food allergy, the EAT study enrolled few infants with severe eczema or pre-existing food allergy and the effects of lesser levels of consumption in such infants remains unknown.

Advice to introduce allergenic foods has to be relevant to a specific country (ie, introducing allergenic foods into the infant diet that are not widely consumed in a country seems inappropriate) and broadly consistent with a family’s cultural feeding habits. In clinical practice, a change in perception of the allergenic foods and infant complementary food introduction is palpable. Families are increasingly cognizant of a philosophy of exposure, rather than one of avoidance. It will be interesting to see whether this leads to a change in culture with regard to early allergenic food introduction, which, in itself, might facilitate adherence with active introduction and sustained consumption,

and reduce the associated tensions with, what certainly in the EAT study was seen as a proscription regimen.

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