Selected, Edited, and with Issue Framing Material by:
Eileen L. Daniel, *SUNY College at Brockport*

ISSUE

Does Early Introduction of Food Reduce the Risk of Food Allergy?

YES: **Debra J. Palmer and Susan L. Prescott**, from "Early Introduction of Food Reduces Food Allergy – Pro," *Pediatric Allergy & Immunology* (2017)

NO: **Michael R. Perkin**, from "Early Introduction of Food Reduces Food Allergy – Con," *Pediatric Allergy & Immunology* (2017)

Learning Outcomes

After reading this issue, you will be able to:

- Discuss the causes of food allergies.
- Assess the health risks associated with food allergies.
- Discuss why food allergies appear to be on the rise.
- Understand the rationale for early introduction of allergenic foods to infants.

ISSUE SUMMARY

YES: Professors Debra J. Palmer and Susan L. Prescott maintain that infants should be fed "more allergenic" foods such as peanuts to help prevent the development of food allergies.

NO: Researcher Michael R. Perkin disagrees and claims that the research on benefits of early introduction of allergenic foods is limited and inconclusive.

With some schools and airlines banning nuts, especially peanuts, it seems as if food and other allergies are rising. Hay fever, which is pollen **allergy**, was first described in 1870, but **allergies** were rare until the mid-20th century. Childhood asthma, in which allergens or irritants cause the airways to tighten and become inflamed started increasing and between 1960 and 1990, it rose to epidemic proportions in developed nations, followed by an increase in hay fever. By 1991, the number of family doctor consultations for asthma in the developed countries had quadrupled in only 20 years, and appointments for conditions such as pollen and dust **allergy** more than doubled. Peanut **allergies**, for example, which can be extremely severe, appear to be increasing. It is unclear what caused this rise in **allergies**, but it is obvious how much Western lifestyles changed in the 20th century and that change may have contributed to the increase in allergies.

Allergies are caused by the immune system mistakenly reacting to certain innocuous molecules such as animal dander, plant pollen, or certain foods. Allergens are any molecule capable of causing this reaction. Although most allergens pose no real danger, their structures can be recognized as a threat by some people's antibodies—immune proteins on the lookout for harmful invaders. Allergies involve a special class of antibodies called immunoglobulin E (IgE). Different IgE antibodies detect different allergens. When this happens, the antibodies trigger immune cells to release histamine and other inflammatory chemicals, leading to symptoms, which under normal circumstances would be a useful defense against invading organisms.

One explanation for the sensitivity of the IgE arm of our immune system is that it evolved to detect and eject what was once a common, highly aggressive threat: large, invading organisms burrowing into our skin, airways, or guts. In the absence of such parasites in modern, sanitary Western lifestyles, the IgE system seems to have begun misfiring, targeting harmless chemical structures instead. It is possible that people who are more prone to **allergies** would have been better at detecting and ejecting parasites back in the human evolutionary past.

While many allergies are uncomfortable or inconvenient, some can produce a severe potentially life-threatening allergic reaction or anaphylaxis. This type of reaction causes the immune system to release chemicals that can cause a rapid drop in blood pressure and a narrowing of the airways which can block breathing. Other signs include nausea, vomiting, rapid and weak pulse, and skin rashes. These symptoms typically occur within minutes of contact with the allergen. The most common causes of anaphylaxis in children include foods such as peanuts, tree nuts, fish, shellfish, and milk products. Unfortunately, a peanut allergy does not tend to improve as children get older, and the allergy may be lifelong. Among adults, in addition to peanuts, nuts, fish, and shellfish, other allergens include insect stings, particularly bees, latex, and certain drugs such as antibiotics and aspirin. While rare, some individuals may develop anaphylaxis from exercise, particularly aerobic exercise. Exercising during weather extremes—very hot, cold, or humid—has also been linked to anaphylaxis.

While there are many causes of allergies, it seems as if peanuts and other food allergies are getting much attention. In the United States, approximately 0.6 percent of the population has a peanut allergy and it is a common cause of fatal and near-fatal food-related reactions. Individuals with a peanut allergy may also have allergies to closely related foods such as tree nuts, soybeans, peas, and lentils. These foods have similar protein structures which can trigger the same responses as peanuts to susceptible people. Interestingly, peanut allergies are rare among children in less developed countries. This may be a result of exposure to a variety of foods in early life, while children's diet in rich nations tends to be more narrow.

YES

Debra J. Palmer and Susan L. Prescott

Early Introduction of Food Reduces Food Allergy – Pro

Changing Appearance of Baby Foods

Since the dawn of humanity, infants have been introduced to foods locally available and eaten by their families. Masticated versions of all foods were fed to infants to supplement their breastmilk intake and prepare them to transition to eating family foods. Only in recent history have we had specially prepared and commercially available baby foods. Furthermore, it was not until the beginning of this century that restricting certain foods in infant diets as an allergy prevention strategy had been recommended (1). In the year 2000, the American Academy of Pediatrics recommended that infants at higher risk of allergy (based on family history) should delay the introduction of 'more allergenic' foods in their diet, including avoidance of eggs until 2 years and fish and nuts until 3 years of age. This flowed through to be incorporated in many countries into infant feeding guidelines and practices. Amplified by rising rates of food allergies in young children, many parents, caregivers and health professionals followed this advice to delay the introduction of the 'potentially more allergenic' foods. We will now summarize the current evidence to support the 'Pro' argument that, early, as opposed to delayed, introduction of food does reduce food allergy.

Sitting Up Ready to Eat

By 'early' we are not suggesting prior to infant developmental readiness to eat solid foods. This is indicated when an infant has good head and neck control and can sit upright when supported; when an infant shows an interest in family members eating, by watching them eat and reaching out for their food; and when an infant opens their mouth when offered food on a spoon. These indications of developmental readiness occur at different ages for individual infants, generally around 4–6 months of age is a good guide to look for these signs as an indication that an infant is ready to commence complementary feeding.

Same Foods Every Day, Please Give Us Diet Diversity

Once complementary feeding has commenced, an infant needs to be introduced to a large number of different solid foods during infancy. Diet diversity is critical for nutritional benefit, as well as exposure to many taste and texture variations that our food can offer. Diet diversity is an important consideration that is often overlooked, especially in infancy. The World Health Organization has guidelines on complementary feeding and minimum dietary diversity. These include that infants have at least four of the following food groups: grains, roots and tubers; legumes and nuts; dairy products (milk, yogurt, cheese); flesh foods (meat, fish, poultry and liver/organ meats); eggs; vitamin A-rich fruits and vegetables; and other fruits and vegetables. So, we need to highlight that if infants have delayed introduction of the 'potentially more allergenic' foods such as dairy products, eggs, fish and nuts, then their intake of four of the seven above diet diversity food groups could be comprised. There is also emerging evidence regarding the importance of infant dietary diversity and prevention of allergy (2). Roduit et al. (2) found an interesting association between an increased diversity of food within the first year of life and reduced allergic disease outcomes. They also found that increased infant food diversity was associated with increased expression of a marker for regulatory T cells (2). Infant solids introduction with high diet diversity will benefit nutritional and feeding development outcomes, as well as have a possible allergy prevention effect. However, the principle of encouraging infant diet diversity is more difficult to achieve if certain foods have delayed introduction in infancy.

Palmer, Debra J and Susan L. Prescott. "Early Introduction of Food Reduces Food Allergy - Pro," Pediatric Allergy & Immunology, 2017. Used by permission of Wiley.

Eating Up Delayed Introduction Then Spiting It Out

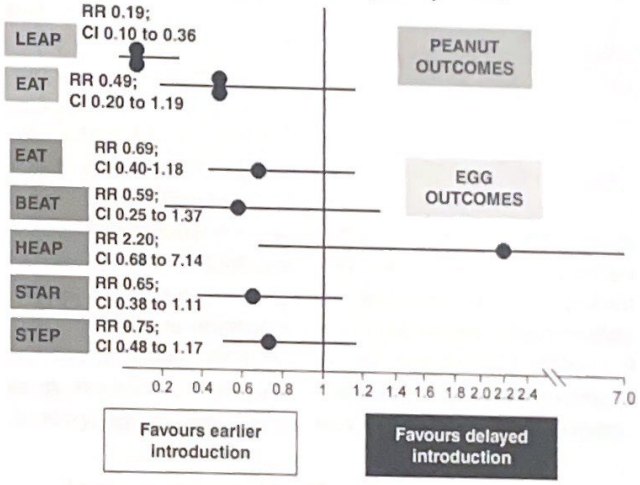
After the American Academy of Pediatrics recommended delayed introduction of 'more allergenic' foods in children's diets in the year 2000, new evidence emerged. Several observational cohorts began to publish results from 2004 to 2010 to suggest that delayed introduction, beyond 6–10 months of age, of some specific solid foods (oats, wheat, dairy foods, fish and egg) was associated with increased risk of allergic disease (3–11). Of specific relevance to our argument in this debate, with regard to food allergy, one cohort study (12) found that delaying the introduction of egg until 10–12 months (adjusted odds ratio, 1.6, 95% confidence interval (CI) 1.0–2.6) was associated with higher risk of egg allergy compared with earlier introduction at 4–6 months. For peanut, it was observed that infants in the United Kingdom have higher rates of peanut allergy and typically do not consume peanut-containing foods during infancy, compared to infants in Israel where the common age of introduction of peanut is around 7 months (13).

Confidence to Swallow with Better Tasting Evidence

This new observational evidence initiated the commencement of several randomized controlled trials (RCTs) investigating the timing of introduction of the 'more allergenic foods' into infant diets with food allergy outcomes. While most of these RCTs targeted one specific food, the Enquiring about Tolerance (EAT) Trial (14) was unique in investigating the sequential introduction of cow's milk protein (yoghurt), cooked hen's egg, peanut, white fish, sesame and wheat from 3 months, compared to exclusive breastfeeding until around 6 months of age. The EAT Trial participants did experience difficulties with protocol compliance, only 32% of the intervention group adhering to the trial protocol and having the primary outcome measured, compared to 80% of the control group (14). This poor compliance included difficulties in introduction of some of the solid foods, in particular cooked egg, between 3 and 6 months of age, and highlights the need to ensure infant developmental readiness to eat solid foods. However, in support of our case in this debate, the EAT Trial per-protocol results did find a beneficial effect of reduced food allergy of 2.4% (5/208) in the intervention group starting food introduction from 3 months of age compared to 7.3% (38/524) in the control group of solid food introduction at 6 months of age (relative risk 0.33;

Figure 1

This figure summarizes the findings from randomized controlled trials investigating the timing of commencement of regular inclusion of peanut and/or egg in infant diets on food allergy outcomes: Enquiring About Tolerance (EAT), Learning Early About Peanut Allergy (LEAP), Beating Egg Allergy Trial (BEAT), Hen's Egg Allergy Prevention (HEAP), Solids Timing for Allergy Reduction (STAR) and Starting Time of Egg Protein (STEP) trials.



95% CI: 0.13–0.83; p = 0.01) (14). Thus, the per-protocol evidence from the EAT Trial supports our 'Pro' argument that early introduction of food reduces food allergy.

Another interesting finding from the EAT trial (14) was that the consumption of 2 g per week of peanut or egg-white protein was associated with a significantly lower prevalence of these respective food allergies than was associated with less consumption. Hence, this raises the concept that induction of oral tolerance to food allergens in infancy may be dose-dependent. Many children take 10–15 exposures to new foods before they will accept eating the food. Hence, to achieve higher doses of foods into infant diets, it would seem logical that exposure to these foods needs to start early from 4 to 6 months of age and these foods be given on a regular basis multiple times per week.

The Learning Early About Peanut Allergy (LEAP) study (15) commenced in 2006 and examined the regular inclusion of peanut in the child's diet commencing in infancy compared to peanut avoidance until 5 years of age. Four RCTs, Beating Egg Allergy Trial (BEAT) (16), Hen's Egg Allergy Prevention (HEAP) (17), Solids Timing for Allergy Reduction (STAR) (18) and Starting Time of

Egg Protein (STEP) (19), all focussed on earlier regular egg inclusion in infant diets commencing at 4–6.5 months of age compared to the more common age of introduction in these countries at 8–10 months of age.

By 2015, we had the first conclusive randomized controlled trial evidence to know that the introduction of peanut-containing foods should commence during infancy and not be delayed until 5 years of age (15). Now in 2016, we have systematic review and meta-analysis evidence which concluded that early egg introduction at 4–6 months was associated with reduced egg allergy (risk ratio 0.56; 95% CI: 0.36–0.87; I^2 = 36%; p = 0.009) (20). In addition to this systematic review publication, the largest double-blinded RCT (n = 820 infants) investigating the timing of commencement of regular egg inclusion in infant diets was also recently published (19). The STEP RCT found a 25% risk reduction in egg allergy with early regular egg intake from 4 to 6.5 months compared with egg avoidance to 10 months of age, although this did not achieve statistical significance. Figure 1 illustrates the findings from RCTs investigating the timing of commencement of regular inclusion of peanut and/or egg in infant diets on food allergy outcomes. Thus, it appears that all but one (17) of these trials favour the earlier, compared to delayed, introduction of the two most common food allergens in early childhood, egg and peanut.

Are Some of Us Still Chewing and Not Yet Ready to Swallow?

So why not introduce potentially allergenic foods to infants along with a variety of other healthy nutritious solid foods? The worry remains that some infants will have allergic reactions as observed in two of the RCTs where infants had anaphylactic reactions to egg (17, 18). It is likely that these infants would have had allergic reactions to egg ingestion regardless of which age it was introduced. In the STAR Trial (18), three infants had anaphylaxis to egg, one upon initial ingestion of the study powder of pasteurized raw egg at 4 months of age (intervention group), but another infant also had anaphylaxis to hard-boiled egg first eaten at 8 months of age (control group) and a third infant (also in the control group) had an anaphylactic reaction to a pasteurized raw egg challenge at 12 months of age. Hence, severe reactions in this STAR trial were not just limited to the intervention early egg introduction group. Of particular interest is our finding that upon investigation of the early T-cell responses to egg proteins in these infants in relation to patterns of egg exposure and subsequent IgE-mediated egg allergy, those 4-month-old infants, who subsequently developed egg allergy already, had significantly higher Th2 cytokine responses to multiple egg allergens, particularly elevated IL-13 responses to ovalbumin (p = 0.004), ovomucoid (p = 0.012) and lysozyme (p = 0.003), and elevated IL-5 to the same antigens (p = 0.031, 0.04 and 0.003, respectively) (21). IL-13 responses to ovalbumin and lysozyme, and IL-5 responses to lysozyme at 4 months significantly predicted egg allergy at 12 months, and this did not appear to be modified by timing of introduction of egg (21). Hence, these infants appear to be already on the pathway to egg allergy before 4 months of age, even prior to commencement of egg in solid foods.

What Is the Rest of the Family Eating?

Future research still needs to investigate intervention strategies to reduce food allergy development in early life prior to the commencement of complementary feeding. For some infants, this 'critical time' may be *in utero* and/or the first few post-natal months of life. We need more high-quality evidence on effects of food allergens in maternal diets during pregnancy and lactation, as well as the effects of food allergen environmental exposures in early life.

Conclusion

Overall, the evidence has become clearer in the past few years. When an infant is developmentally ready, it is far better to introduce a variety of nutritious foods to ensure high diet diversity, including the 'more allergenic' foods during infancy, than to avoid them.

References

1. American Academy of Pediatrics Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics* 2000: **106**: 346–9.
2. Roduit C, Frei R, Depner M, et al. Increased food diversity in the first year of life is inversely associated with allergic diseases. *J Allergy Clin Immunol* 2014: **133**: 1056–64.
3. Alm B, Aberg N, Erdes L, et al. Early introduction of fish decreases the risk of eczema in infants. *Arch Dis Child* 2009: **94**: 11–5.
4. Filipiak B, Zutavern A, Koletzko S, et al. Solid food introduction in relation to eczema: results from a

Michael R. Perkin

NO

Early Introduction of Food Reduces Food Allergy – Con

Only one study of the early introduction of allergenic food or foods into an infant's diet has produced truly compelling results—the LEAP study (1, 2). The EAT study showed no effect in the intention to treat analysis (3), neither did the STAR study (4) nor did the HEAP study (5). And the LEAP study truly did work—an 81% reduction in the primary outcome of peanut allergy in the intention to treat (ITT) analysis. An ITT analysis 'avoids overoptimistic estimates of the efficacy of an intervention resulting from the removal of non-compliers by accepting that non-compliance and protocol deviations are likely to occur in actual ... practice' (6).

And here is the rub—the LEAP study did not allow participating families the option of non-compliance. LEAP families received weekly phone calls from 4 to 11 months of age monitoring compliance and exhorting families in the consumption group to keep eating and the avoidance group to avoid, and these calls continued fortnightly from 12 to 30 months of age, and monthly from 30 to 60 months of age. Thus, a family enrolling a 4-month old onto the LEAP study were telephoned 104 times to remind them to eat or avoid peanut. Hence, the overall rate of adherence to the two assigned interventions was 92.0%. This is about as divorced from 'actual practice' as is possible. The LEAP team have rebuffed this by stating that mothers achieved the recommended consumption level after only three phone calls, the implication being that they were not being cajoled into adherence. However, those same mothers were fully aware that they were going to be phoned again and again and again about their adherence, so an independent perspective might be to say that resistance was futile.

What about the Real World?

So, in essence, the LEAP study is a scientific proof of principle, it says nothing about what would happen if you asked the same high-risk participants to undertake the same intervention in actual practice. Let us assume that, miraculously, the same level of adherence was achieved, and hence, the results could be extrapolated into the real world, would it make much of a difference to the burden of peanut allergy that a country experiences? The answer is a difference, but not the seismic shift that one might be hoping to see.

Two centres have extrapolated the LEAP results to their paediatric populations: Ireland and Australia. O'Connor and colleagues calculated that there would be a substantial effect on the incidence of PA in Irish children who met the two most objective LEAP criteria of severe AD or egg allergy, with a relative reduction in the incidence of PA of 71% (7). However, the population-level effect is much less dramatic with only a 29% relative reduction, because LEAP-defined high-risk children only produce a minority of cases of peanut allergy in Irish children (488/1202 cases per annum).

Even the more optimistic Australian calculation, by Koplin and colleagues, would still only result in just under half of expected cases of peanut allergy (48%—20 cases of PA instead of 41 per 1000 children) being prevented when the LEAP data were extrapolated to the HealthNuts population (8).

The difference between the Irish and Australian estimates rests on the Australian's determination that 16% of their HealthNuts cohort would have met the enrolment criteria for the LEAP study through either an egg allergy or severe eczema. This compares with a figure of 4.8% of the Irish children being eligible.

The latter is a much more realistic figure as the HealthNuts egg allergy figure was based on raw egg allergy (9), and the actual number of children that would be identified as being eligible for the LEAP study intervention in real life would be much lower as very few young children are exposed to raw egg.

Perkin, Michael R. "Earlly Introduction of Food Reduces Food Allergy - Con," Pediatric Allergy & Immunology. Used by permission of Wiley.

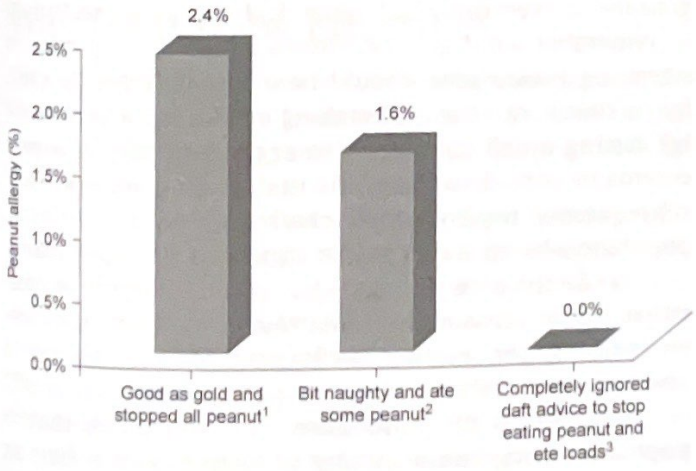
Need to Do It for Ever

In the LEAP-On study, there were three new cases of peanut allergy in the LEAP consumers who had been asked to avoid peanut for 12 months. There were also three new cases of peanut allergy in the avoidance group, and hence, there was no statistical significance, but this belies an interesting observation hidden in a supplementary table of the LEAP-On publication (2). Not surprisingly, LEAP consumers were more circumspect about stopping peanut consumption and per-protocol adherence with stopping was only 69.3% in this group. Closer inspection of the spectrum of adherence to the request to stop eating peanut reveals a dose–response relationship between the degree to which a mother listened to this advice and the likelihood of her child having a peanut allergy (Fig. 1).

The question is—would these three cases have emerged if the families had carried on feeding their child peanut? The answer would seem obvious—it would not. Hence, far from the conclusion of the LEAP-On publication that sustained tolerance has been achieved, I believe lifelong consumption is the reality of what has to be recommended.

Figure 1

Adherence to LEAP-On recommendation to stop eating peanut in LEAP consumers. This figure is based on the data given in table S3 of the LEAP-On study publication (2). The column headings in my figure are adulterations of the originals in the table, namely [1]complete avoidance of peanut—per protocol (3 cases of peanut allergy of 127 LEAP consumers); [2]consumption of some peanut—per protocol (1/63); and [3]consumption of some peanut—not per protocol (0/65). Per-protocol consumption was defined as: no more than 2 g of peanut protein on six occasions over a period of 12 months with a maximum of 1 event per month AND no more than 1 g of peanut consumption on 12 occasions over a period of 12 months with a maximum of two events per month.



Why Just Peanut? What about All the Tree Nuts? And What about All the Other Principal Allergenic Foods?

Allergy to egg (10) and milk (11) is likely to be outgrown, so there is an argument for saying why make wholesale changes to the age at which these foods are introduced into the diet, when allergy to these foods has such a good prognosis? Even 20% or so of children outgrow peanut allergy (12). However, clearly the majority of children with allergy to peanuts, tree nuts, fish or sesame are unlikely to outgrow these problems. Hence, the logical extension of LEAP is leading to families I see in clinic already asking why should they not be actively introducing all the other tree nuts into their infant's. Presumably when they are 4–6 months of age. And then eat them *ad infinitum*. Along with all the other principal allergenic foods.

Nutritional Implications of Extrapolating LEAP to Other Nuts

However, such an intervention is likely to have significant nutritional consequences, the long-term impact of which is unknown. Helen Brough has been leading the Pronuts study, looking at the efficacy of introducing multiple nuts into a child's diet to induce tolerance. In the Pronuts study for child 11 years of age or older, consumption of 10 nuts/seeds at 13 g per portion of each nut twice weekly results in 260 g of nuts being consumed per week. This means that 14.1% (240/1700 kcals) of the child's calories come from nuts alone. However, for this precise reason, Pronuts has already had to be a significant compromise compared with what the LEAP children ate. Pronuts 1- to 4-year-olds ate 10 g of each nut per week. LEAP infants ate the equivalent of 24 g of peanut per week. Consuming the LEAP quantity of 10 nuts/seeds would mean 240 grams of nuts per week, which would be 22% of a 1- to 4-year-olds' 1000 kcal requirement.

International Guidelines

The LEAP study has already prompted international organizations to re-examine their allergy prevention advice. A consensus communication was produced that

was most noteworthy for its circumspection: 'Infants with early-onset atopic disease, such as severe eczema, or egg allergy in the first 4–6 months of life *might* benefit from evaluation by an allergist or physician trained in management of allergic diseases. ... Evaluation of such patients *might* consist of performing peanut skin testing, in-office observed peanut ingestion, or both. ...' (13). The Australians have adopted a simple recommendation that solids should start at around 6 months and not before 4 months and that 'all infants should be given allergenic solid foods including peanut butter, cooked egg, dairy and wheat products in the first year of life. This includes infants at high risk of allergy' (14).

So What Age Should Do You Really Need to Start at?

The USA have now gone further, producing an algorithm based guideline for preventing peanut allergy. For infants with severe eczema, egg allergy or both, one should 'strongly consider' evaluation by specific IgE and/or SPT and, if necessary, an oral food challenge and based on test results, introduce peanut-containing foods at between 4 and 6 months of age (15).

The rationale for recommending 4- to 6-month introduction of peanut in high-risk infants in the new USA guidelines is again an extrapolation arguably over and beyond what the results show. LEAP participants were enrolled between 4 and 10 months of age. In fact, a recent publication based on an analysis of the publicly available LEAP data claims that the likelihood of being peanut tolerant was significantly higher with peanut introduction between 6 and 10 months of age than at 4–6 months of age (16).

This seems counter-intuitive given that children are not born with positive skin prick tests and hence logically the earlier the introduction the better. However, in making any statements in this age range, it is worth remembering just how few infants were enrolled onto the LEAP study at this age: 24 four-month-old and 95 five-month-old infants. Thus, early age-specific recommendations are being made on the basis of just 63 pre-six-month-old consuming LEAP infants.

However, it is interesting to note if one goes back to the original paper by du Toit, which led to the LEAP study being initiated, that in the Kaplan–Meir estimate for the age at which peanut was introduced (Fig. 1 of their paper) it can be seen that virtually no Israeli child had peanut introduced under 6 months of age (17).

Furthermore, it seems very likely that there is not a panacea age at which all solids can be realistically introduced and tolerance then ensue. EAT raised many heckles by enrolling infants at 3 months, but in reality they started their first solids as they turned 4 months. However, this was already too late for seven participants who had enrolment positive food challenges, five of whom fulfilled the study primary outcome for food allergy (table S29A in the EAT results paper). Given there is no realistic prospect of commencing any earlier than the 3–4 months of EAT, particularly in breastfed infants, it seems likely that food allergy is not going to disappear entirely no matter what early introduction regimen gets recommended.

Safety

The issue of safety is paramount. Both LEAP and EAT suggested that the early introduction of peanut and other allergenic foods was safe. However, clearly the early introduction of pasteurized raw whole hen's egg powder in the STAR study was not; 31% (15/49) of 4-month-old infants in the active arm reacted to their pasteurized raw whole egg powder, 10 on first exposure, one with anaphylaxis (4) and the early introduction of pasteurized raw hen's egg white powder in the BEAT study was frankly, dangerous: 6% (23/406) of infants were already sensitized (specific IgE ≥ 0.35 kU/1) at enrolment, 17 of whom underwent double blind challenge with pasteurized raw egg white powder of whom 16 reacted, three with anaphylaxis. In the active group, 2 of 142 (1.4%) were allergic, both reacted at home on first exposure, one with anaphylaxis (5). Hence, the choice of allergen vehicle appears to be critical.

An Algorithm Based on Measuring Sensitization Will Be Impossible to Implement

The new USA guidelines constitute a screening programme in everything but name. It therefore seems timely to remember what are the criteria by which a proposed screening programme should be assessed (Table 1) (18). By no metric can the undertaking of skin prick or specific IgE testing on all children with egg allergy and/or severe eczema be considered easy, and undertaking promptly the subsequently required food challenges on a systematic population-based scale I would argue is near impossible.

So do the Irish who stated '... community implementation would demand huge additional resources at all levels of health care. Further studies need to be performed to assess many unresolved aspects of peanut introduction' (7).

And so do the Australians who concluded that 'a population programme aiming to identify and screen all

infants at risk of peanut allergy would pose major cost and logistic challenges that need to be carefully considered'. The co-author of that paper, one Gideon Lack (8).

That the LEAP screening algorithm being proposed is so time critical has already been demonstrated with a case report of a peanut skin prick test negative infant who undertook his peanut challenge one month later and had anaphylaxis (19). As the LEAP team responded, this was much more likely to reflect the emergence of sensitization in the intervening one month than the report author's contention that it was an anaphylactic reaction in a skin prick negative child. Regardless, the LEAP team recommended that consumption of peanut or, where necessary, a supervised oral food challenge should take place immediately on the day the SPT is performed.

Table 1

Wilson & Junger criteria for a screening programme (18)

- The condition should be an important health problem
- The natural history of the condition should be understood
- There should be a recognizable latent or early symptomatic stage
- There should be a test that is easy to perform and interpret, acceptable, accurate, reliable, sensitive and specific
- There should be an accepted treatment recognized for the disease
- Treatment should be more effective if started early
- There should be a policy on who should be treated
- Diagnosis and treatment should be cost-effective
- Case-finding should be a continuous process

Is a Societal Change in Consumption the Only Realistic Way for It to Be Effective?

Such a screening regimen is never going to be successfully introduced at a society level, whether by the USA or anyone else. The question therefore is what happens with the results of the LEAP and EAT studies.

Here, I think the Australians are closer to being right. Israel, which started this whole research enterprise off, does not systematically screen its infants for latent peanut sensitization, they simply nearly universally eat peanut by 1 year of age. Surely therefore, if we are going to do anything, then we simply should follow their footsteps and encourage active early consumption. That this seems safe at a societal level is reflected in the fact; there was not a single death from peanut allergy when food allergy mortality in Israel between 2004 and 2011 was reviewed (20).

However, if what happens in Israel were universally propagated, it seems inevitable that somewhere there will be a fatality in an infant whose family will state that they were introducing peanut earlier than they previously would have done. The question is whether society will be able to acknowledge that that is a price that almost inevitably will be paid for preventing a much greater amount of food allergy morbidity and mortality in older children and adults.

References

1. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015: **372**: 803–13.
2. Du Toit G, Sayre PH, Roberts G, et al. Effect of avoidance on peanut allergy after early peanut consumption. *N Engl J Med* 2016: **374**: 1435–13.
3. Perkin MR, Logan K, Tseng A, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med* 2016: **374**: 1733–43.
4. Palmer DJ, Metcalfe J, Makrides M, et al. Early regular egg exposure in infants with eczema: a randomized controlled trial. *J Allergy Clin Immunol* 2013: **132**: 387–92.
5. Bellach J, Schwarz V, Ahrens B, et al. Randomized placebo-controlled trial of hen's egg consumption for primary prevention in infants. *J Allergy Clin Immunol* 2016: http://dx.doi.org/10.1016/j.jaci.2016.06.045 (In press).
6. Gupta SK. Intention-to-treat concept: a review. *Perspect Clin Res* 2011: **2**: 109–12.
7. 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**: 1263–4.
8. Koplin JJ, Peters RL, Dharmage SC, et al. Understanding the feasibility and implications of implementing early peanut introduction for prevention of peanut allergy. *J Allergy Clin Immunol* 2016: **138**: 1131–41.
9. Osborne NJ, Koplin JJ, Martin PE, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and