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Overview of oral tolerance induction for prevention of food allergy - where are we now?

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Abstract

Oral tolerance induction through early introduction of allergenic food has proven effective in randomized controlled trials. This new approach to weaning has been incorporated into many national and

international infants' feeding guidelines. However, there are questions that require further discussion, such as, which foods should be introduced early, should the intervention be targeted to infants at high risk or to the general population, and what is the ideal timing for early food introduction. This review examines the extent to which recent trials address these critical questions and highlights areas where further research is required.

Key words: prevention, immune tolerance, food allergy

Abbreviations

BEAT, Beating Egg Allergy Trial

EAT, Enquiring About Tolerance Study

EIG, early introduction group in the EAT Study

FLG, filaggrin gene

HEAP, Hen's Egg Allergy Prevention Study

ITT, intention to treat

LEAP, Learning Early About Peanut Study

OTI, oral tolerance induction

PP, per protocol

RCT, randomized controlled trial

SCORAD – SCORing Atopic Dermatitis scale

SIG, standard introduction group in the EAT Study

STAR, Solids Timing for Allergy Research Study

STEP, Starting Time of Egg Protein Study

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Introduction

Due to high prevalence and limited options for treating food allergy, prevention is particularly important.¹ Among investigated preventative methods, oral tolerance induction (OTI) achieved through early introduction of allergenic foods into the infant's diet has proven the most promising.²

The phenomenon of OTI has long been recognised in animal models.^{3,4} Extensive murine research highlights that tolerance occurs orally following antigen transfer across the epithelial barrier of the small intestine, antigen presentation in mesenteric lymph nodes by dendritic cells, the expansion of Tregs and homing of Tregs towards tissues where disease prevention may occur.⁵ Animal models also show that an impaired skin barrier, particularly in the absence of prior oral tolerance induction, promotes IgE food sensitisation.⁶ These findings have led to formulation of the dual allergen exposure hypothesis which posits that immunological tolerance to a food depends on early exposure through the gastrointestinal tract and that the development of allergic sensitization occurs by exposure to foods through an impaired skin barrier.⁷ The hypothesis has been supported by findings from clinical studies; infants and children with an impaired skin barrier due to eczema are at increased risk of food allergy.^{8,9} High environmental exposure also increases clinical risk of food allergy, with the median household peanut exposure in high risk children who developed peanut allergy being 10-fold higher than in high risk children with no peanut allergy. The relationship is not apparent in children who are consuming peanut in the first year of life.¹⁰ Furthermore, there is a dose response effect between environmental exposure and severity of eczema on the development of peanut allergy--children with severe eczema having an almost 2.5 times (OR, 2.34; 95% CI, 1.31-4.18; $P < 0.01$) greater likelihood of developing peanut allergy compared to children without eczema exposed to the similar amount of peanut protein.¹¹ The association between early-life environmental peanut exposure and peanut sensitization and allergy is even stronger in children who carry a filaggrin (FLG) mutation. This further substantiates the hypothesis that peanut allergy develops through transcutaneous sensitization in children with an impaired skin barrier and provides a good example of gene-environment interactions leading to the development of peanut allergy in young

infants.¹² The milestone discoveries in the formulation of the dual allergen exposure hypothesis and resulting clinical findings are presented in Figure 1.

Promising data from animal studies and observational clinical studies have formed the basis for the investigation of OTI in infants through the randomized controlled trials (RCT). These trials discussed within this paper have demonstrated that, under RCT conditions, consumption of peanut and egg by young infants reduces the risk of allergy to these foods. The level of evidence for peanut allergy prevention is stronger than for egg allergy prevention. In the last five years, RCTs have been used to inform governmental and societal changes to infant weaning guidelines around the world¹³⁻¹⁷ (Table 1). They have already been translated into changes in infant weaning behaviours, with countries such as Australia seeing a high uptake; 9 in 10 Australian infants now eat peanut protein in their first year of life.¹⁸ However, there are questions which require further investigation. Should OTI be advised at the general population level or in high-risk populations only?¹⁹ What is the ideal timing of food introduction?²⁰ Should high risk infants be pre-screened with allergy testing before introducing allergenic foods for OTI to be safe?²¹ Finally, which foods should be introduced early and if more than one food is to be introduced, how can adherence to this long-term dietary intervention be achieved?²² This review examines the extent to which recent trials address these critical questions and highlight areas where further research is required.

Summarising OTI RCTs

To date there are seven published randomized clinical trials of OTI (Table 2). Five studies²³⁻²⁷ trialled early introduction of egg, the LEAP Study focused on peanut introduction.²⁸ The EAT Study remains the only published RCT examining the early introduction of multiple common food allergens (egg, peanut, milk, fish, sesame and wheat).²⁹ Publication of the food allergy findings of the PreventADALL Study [NCT02449850], a 2x2 factorial RCT that examined prevention of cow's milk, egg, peanut and wheat allergy through OTI, alongside eczema management, is forthcoming.

A recent systematic review and meta-analysis of the early introduction RCTs was undertaken and the pooled risk ratio for peanut introduction was 0.29 (0.11-0.74) and for egg 0.56 (0.36-0.87). The review concluded that the current body of evidence supports the early introduction of peanut and egg for allergy prevention.³⁰ More recently, Palmer et al also highlighted that the outcomes of most studies were in favour of early introduction of egg and peanut.³¹ However, in the latest systematic review undertaken by de Silva et al to inform EAACI guidelines on food allergy prevention, the authors are more cautious with their conclusions. The review concludes that introducing well-cooked egg into infants diet between 4 to 6

months probably reduces the risk of hen's egg allergy. The authors also underscore that the evidence of large peanut allergy reduction through peanut introduction between 4 and 11 months of age comes from the population with high prevalence of peanut allergy.³² The methodology of the studies, which were conducted independently in different populations, was not uniform and the review could not investigate subgroups such as infants with eczema of varying severity, ethnicity and sensitisation. In the following sections, we examine the study findings in more detail in order to answer important clinical questions.

In whom to intervene?

The majority of OTI trials enrolled infants who were at high risk of developing food allergy. Inclusion criteria ranged from first degree relative with atopic disease,^{24,27} through eczema of any severity²⁶ to moderate-severe eczema^{25,28} or egg allergy.²⁸

Early egg introduction in a high-risk population has been shown to be favourable, with RCTs demonstrating a relative risk (RR) for allergy of 0.75 in the STEP Study²⁴ and 0.59 for egg white sensitization in the BEAT Study.²⁷ It has been estimated that an absolute risk reduction of 37 cases (95% CI 17–52) per 1,000 people would be achieved for a population with an egg allergy prevalence of 9.3%.³³ The LEAP Study, the only RCT to examine peanut allergy prevention in a high-risk population, showed a notable 81% relative risk reduction of peanut allergy in the early introduction arm.²⁸ A strongly favourable outcome was observed by both subpopulations of the LEAP Study: high-risk children who were sensitised to peanut at the beginning of the intervention (SPT 1–4 mm; N=98) and high-risk children with no peanut sensitization on entry (SPT 0 mm; N=542).

Although the EAT Study enrolled exclusively breastfed infants from the general population, Perkin *et al* recently published a subgroup analysis of children deemed to be at high risk of food allergy, defined, using similar criteria as other published OTI RCTs, as: sensitisation to any study food at enrolment; presence of eczema at enrolment; and/or non-white ethnicity.³⁴ In this secondary ITT analysis, the risk of any food allergy in sensitised children was significantly reduced in the early introduction group (EIG, 19.2%) compared to the standard introduction group (SIG, 34.2%; $P=0.03$). A similar effect was noted for egg allergy (SIG, 48.6%; EIG, 20.0%; $p=0.01$). In participants with any eczema at enrolment, children in the EIG had a lower prevalence of allergy to at least one food (SIG, 18.2%; EIG, 15.6%; $P=0.56$), egg allergy (SIG, 14.0%; EIG, 9.8%; $P=0.27$) and peanut allergy (SIG, 7.0%; EIG, 2.8%; $P=0.10$) at 36 months of age. When grouped by eczema severity status (SCORAD), the results showed statistically significant reduction of allergy to one or more foods (SIG, 46.7%; EIG, 22.6%; $P=0.02$) and of egg allergy (SIG, 43.3%; EIG, 16.1%; $P=0.02$) in children with moderate eczema. Although there were insufficient participants with

severe eczema for independent analysis, when children with moderate and severe eczema were combined, a similar effect to that of the moderate group was found with respect to egg allergy ($P=0.02$). A statistically significant effect was also noted for reduction of egg allergy when analysing SCORAD as a continuous variable ($P=0.028$). Children of mixed ethnicity were at increased risk of allergy to at least one food when compared with white participants, but the highest prevalence of food allergy was observed in Asian, Black or Chinese participants ($P<0.0005$). Considering only non-white participants in the EAT Study, the rates of food allergy were lower in the EIG in 8 of the 9 comparisons with SIG. Although the effect was not statistically significant for any of the foods, this indicates that OTI is likely to be effective in non-white participants.²⁹ This finding is confirmed in the LEAP Study where non-white participants had higher rates of peanut allergy and early introduction of peanut was accompanied by statistically significant reduction in peanut allergy in infants of both non-white and white ethnicity.²⁸

Whilst there is good evidence that early introduction is an efficacious allergy prevention strategy in a high-risk cohort, the evidence regarding OTI in a general population is less compelling. Neither the HEAP Study nor EAT Study found consumption of allergenic foods by young infants prevented food allergy in their intention to treat (ITT) analyses. The HEAP Study showed no benefit of early introduction of egg in the general population. Food challenges performed at the age of 12 months revealed 2.1% of egg allergy in the egg consuming group versus 0.6% in the placebo group (RR 3.3, 95% CI, 0.35-31.32; $P=0.35$).²³ This study used pasteurized raw egg white powder which is comparable in allergenicity to raw egg white, as opposed to cooked egg used in the EAT Study. Concerningly, the HEAP Study found increased risk of allergic reactions, including anaphylactic reactions, in children who were randomized to consume egg white powder. Differences in inclusion criteria, the form in which egg was consumed, and the outcome measures used may account for differences between the findings of HEAP and other egg OTI studies.

The EAT Study, which also enrolled children from the general population found a trend towards reduction in allergy to any of the study foods in the EIG, although this difference did not meet statistical significance in ITT analysis.²⁹ Food allergy to one or more of the six intervention foods developed in 7.1% of the participants in the SIG (42 of 595 participants) and in 5.6% of those in the early-introduction group (32 of 567) ($P=0.32$). However, per protocol (PP) analysis demonstrated a statistically significant reduction in the prevalence of any food allergy (2.4% vs. 7.3%, $P=0.01$). Comparison of individual foods similarly found a reduction in allergy to peanut (0% vs. 2.5%, $P=0.003$) and egg (1.4% vs. 5.5%, $P=0.009$) in the intervention group.

The differences between the ITT and PP findings in EAT deserve some consideration. When analysing ITT populations the results may be diluted by participants who did not receive the intervention. ITT analysis

could therefore be an overly conservative measure of an intervention's effect in prevention studies.³⁵ PP analysis, on the other hand, directly examines an intervention's efficacy among participants who received the treatment rather than among participants randomized to receive treatment. A disadvantage of a PP analysis is that findings may be biased since randomization is not preserved in the subgroup of compliant participants. In short, ITT analyses measure whether an intervention works under 'real world' conditions (effectiveness), whilst PP analyses examine whether an intervention is effective under 'ideal' conditions (efficacy).

In order to adjust for the potential biases of ITT and PP analyses, new statistical methods were employed which address effect estimates when compliance is poor. Complier average causal effect (CACE) model is a type of instrumental variable analysis, which corrects for potential biases arising when participants randomized to an intervention do not receive the intervention. Essentially, the method compares the allergy rate among non-compliant participants randomized to the intervention with the allergy rate in the participants randomized to no intervention; the difference in these rates gives an estimate of bias. If the non-compliant participants randomized to intervention have a similar allergy rate to those randomized to no intervention, this gives evidence of a lack of bias in the per-protocol analysis. Conversely, if the non-compliant population had a higher rate of allergy than the control arm, this would give evidence for bias in the per-protocol population (i.e. potentially unaccounted factors associated with both non-compliance and allergy cause a per-protocol analysis to look more favourable by sub setting on only the compliant participants). This model has been shown to be just as powerful, if not more powerful, than the ITT analysis.³⁶ When results of the EAT Study were analysed using this method, the unbiased CACE estimate (risk difference of 2.47%) was nearly equal to the PP effect (2.51%). This means that potentially confounding factors in the PP analysis in the EAT Study were not highly associated with allergy,³⁵ and the PP effect estimate was likely not significantly affected by bias (Box 1).

The data regarding OTI to peanut and egg in children at high risk of developing allergy are robust and it is evident that parents of infants at high risk of developing food allergy should be advised to introduce allergenic foods, alongside usual weaning foods, as soon as the infant is ready to be weaned. Whilst the data for OTI in the general population are not as strong, it is important to note that most food allergy cases come from this population with no known risk factors. O'Connor *et al* estimated that if the LEAP intervention was only applied to Irish infants with severe eczema and egg allergy, the population burden of peanut allergy would only have been reduced by 29%.³⁷ Similarly, Koplin *et al* in an Australian cohort, estimated that targeting the intervention at infants with severe eczema and/or egg allergy would have only reduced the population disease burden of peanut allergy by 6%.¹⁹ These reductions are considerably

smaller than that noted by the LEAP Study and highlight that a considerable number of children who have no known risk factors will go on to develop food allergy. Given that the EAT Study found a statistically significant effect of OTI in PP and CACE analyses and, importantly, no increased risk of food allergy in infants who were not compliant with OTI above that of the standard introduction group, parents of infants with no known risk factors for food allergy should also be advised to feed their children allergenic foods, alongside non-allergic foods once they are ready to be weaned.

There is good rationale therefore that the intervention should be applied to all infants, regardless of risk level. In the following section we examine when the intervention should be applied.

When to intervene and for how long?

If an intervention to prevent food allergy is to be recommended, it is important to understand when childhood food sensitisation and allergy develop. Studies have shown that food sensitisation is not evident at birth despite foetal production of IgE³⁸ and must therefore develop during early infancy and childhood. Of the 8344-11 month old children who were screened for the LEAP Study 302 (36.2%) already had at least one positive SPT (≥ 1 mm); children at the older age of the range being more likely to have a positive SPT than those aged 4 months. Mean age of infants with a negative SPT was 7.7 months, with SPT 1 to 4 mm – 8.1 months, and with SPT > 4 mm – 8.3 months.³⁹ Even in a general population, SPT sensitisation occurs in early infancy; 21% of children enrolled in the HealthNuts Study were found to have SPT ≥ 1 mm at 12 months of age.⁴⁰ However, EAT Study data show that OTI modifies sensitisation rates even over a nine month period; 5.1% of 3 month old infants (EIG group only) who enrolled in the EAT Study had a positive SPT result (≥ 1 mm) to at least one of the study foods. This rose to 17.3% in the SIG compared with 10.1% in the EIG at 12 months of age (PP analyses $P=0.01$). These data are further supported by a meta-analysis of OTI studies from 5 trials (1915 participants) that egg introduction at 4 to 6 months is associated with reduced egg allergy (risk ratio [RR], 0.56; 95%CI, 0.36-0.87; $I^2 = 36\%$; $P=0.009$; absolute risk reduction for a population with 5.4% incidence of egg allergy was 24 cases (95%CI, 7-35 cases) per 1000 population.⁴¹ Taken together these data highlight a critical window of opportunity at around 4-6 months, in which OTI has a substantial effect on the development of sensitisation and subsequent allergy. Commencing OTI after this age, particularly in a high-risk infant, risks missing the critical window of opportunity (Figure 2).

There are growing data that introducing allergenic foods early to all infants, at around 4 months of age once weaning commences, would potentially prevent food allergy. In the following section we consider which foods should be introduced.

In the LEAP Study children in the intervention arm continued to eat peanut for the first five years of life. We know that after five years of life they were able to stop eating peanut for one year and remained largely protected.⁴² It is indeed plausible that a shorter duration of peanut consumption (e.g. 2 to 3 years) would have conferred protection. In the EAT Study the intervention to eat peanuts and other allergenic foods was applied between 3 and 6 months of age over a 12 week period and PP efficacy of peanut consumption was demonstrated.²⁹ However, it should be noted that children in the intervention arm in the EAT Study continued to eat high levels of peanut at least until the end of the first year of life.⁴³ No studies have been carried out looking at efficacy in relation to duration of allergenic food consumption. Looking at the progression of biomarkers in the LEAP Study may provide some clues, for example, there was a very rapid rise in specific IgG4 to peanut by 12 months of age in the intervention arm. However, specific IgE to peanut and its components only started to drop significantly after 2.5 years of age.²⁸ We cannot conclude on that basis that 12 months of treatment or 2.5 years of treatment are sufficient based on the evolution of biomarkers. It is possible for example, that in an intervention that is applied early and then is withdrawn continues over time to exert immunological changes. This is indeed the case in the LEAP On Study where twelve months after cessation of peanut consumption children in the consumption arm continued to show a decrease in specific IgE to Ara h 2.⁴² The current NIAID guidelines recommend peanut consumption with the view of preventing peanut allergy for the first five years of life.¹³

Which foods to introduce early?

There are eight main allergenic foods which account for 90% of food allergy cases: milk, egg, peanut, tree nuts, soya, wheat, fish and shellfish.⁴⁴ Worldwide, egg allergy is the most common infantile food allergy.^{45,46} Sesame allergy, although less prevalent, is causing growing concern with sesame being one of the fourteen allergens under mandatory allergen labelling regulation in European Union.^{47,48} The majority of OTI studies have focused on preventing egg allergy; one addressed peanut allergy prevention²⁸ and one looked at early introduction of multiple foods, including milk, egg, peanut, wheat, fish and sesame.²⁹

The LEAP Study as well as post hoc PP analysis of the EAT Study showed that early introduction of peanut is effective in both high-risk and general risk populations. This is especially important because only about 20% of children with peanut allergy outgrow this disease.^{49,50} There is also evidence supporting early introduction of egg which was associated with reduction in egg allergy in four different studies in high risk children and proved significant in PETIT Study.³⁰⁻³²

Only one study has looked at the other foods with respect to allergy prevention, the EAT Study.²⁹ Sensitisation rates to wheat, sesame and milk were lower in the EIG in the EAT Study showing trend

towards prevention. However, the study was insufficiently powered to show significant reduction to these other foods as the prevalence of allergy to these foods was very low.³⁴

The published data regarding OTI to peanut and egg support the introduction of these two foods once weaning commences. Whilst there is limited or no evidence regarding introduction of the other allergenic foods, importantly there is also no evidence that OTI would increase rates of sensitisation or allergy, even if infants do not consume sufficient quantities of the foods, or consume them sporadically.²⁹ Neither peanut nor egg should be introduced as first solids into infant's diet. Offering other common weaning foods first, such as fruit, vegetable or grains, enables assessment of infant's readiness for weaning and prevents interpretation of gagging, vomiting or coughing as allergic reaction.¹⁷

In the following section we consider how much food infants need to consume for OTI to be effective.

How much food?

Observational data from Israel, where rates of peanut allergy are low, show that children were estimated to consume on average 1.7g of peanut protein per week.⁵¹ The BEAT Study used a similar dose of 2.45g of whole egg protein²⁷ and dose response analysis of EAT Study data showed that a mean weekly dose of 2g of peanut or egg protein was highly protective (more than 80 per cent reduction) against peanut or egg allergy.²⁹ Whilst studies have included larger doses of peanut protein, for example 6g per week (as three 2g doses) in the LEAP Study, 2g seems to be sufficiently protective to promote OTI whilst also being a manageable quantity for young children to consume, particularly if multiple foods are to be consumed.

Challenges of OTI

There are now good data that OTI is an effective intervention for primary and secondary prevention of food allergy, particularly with respect to peanut and egg, concerns have been raised about the widespread adoption of the intervention at a population level. In the following section we discuss some of these concerns.

Safety of OTI

Safety of any intervention applied in wider population is of paramount importance. Even rare adverse events, when applied at the general population level constitute a significant number of cases. The safety profiles of OTI warrant investigation and, in the context of OTI, there are two types of risk which should be taken into consideration: allergic reactions and the impact of intervention on general health.

OTI has an excellent safety profile. The LEAP Study enrolled a high risk, atopic population and all subjects in the consumption arm had their first peanut containing meal under medical supervision. Seven of the 319 children who underwent a challenge, experienced an allergic reaction: six children with SPT 1 to 4 mm (6/47, 12.8%) and one child with a negative SPT (1/272, 0.04%). Notably, none of these reactions were severe and none required adrenaline.²⁸ Although the LEAP Study excluded children with skin prick test > 4 mm at enrolment, the EAT Study did not exclude any participants based on SPT positivity at enrolment.²⁹ Thirty three participants from the EIG with a positive SPT result to one or more study foods at study enrolment underwent food challenges to the appropriate food at 3 months of age. Seven of the challenges (21.2%) were positive, but no children required treatment with adrenaline or overnight admission to hospital. Severe allergic reactions have occurred during OTI, including at first introduction of the study food. In the HEAP Study, 17/23 sensitised children underwent OFC to pasteurized raw egg at screening; 16 were confirmed as egg allergic with 11 experiencing an anaphylactic reaction during their first consumption, fortunately under medical supervision where appropriate treatment could be administered. Reasons for the difference in safety profile during first food consumption between HEAP and other OTI studies may reflect differences in the form and quantity of food that was given and the risk profile of participants. EAT and PETIT Studies which used well-cooked egg experienced no serious reactions.

Safety profiles of ongoing OTI are also excellent. LEAP found no significance difference between the number of hospitalizations and severe adverse events including anaphylaxis and wheezing in the avoidance and consumption groups. Mild and moderate urticaria were noted more frequently in the consumption group than avoidance group (22.6% vs 12.5%, $P=0.001$) but the remaining adverse events which were significantly more common in the consumption group, such as upper respiratory tract infections, viral infections of the skin, gastroenteritis and conjunctivitis, were not allergic in their character.²⁸ Similarly, no children in the EAT EIG required an adrenaline injector either at home or in the hospital setting due to the study intervention. The number of IgE related symptoms during the study was similar between EIG and SIG (EIG, 19.8%; SIG, 19.4%; $P=0.89$).²⁹ Importantly, early introduction of allergenic foods in non-high risk population in the EAT Study was not associated with increased risk of allergy.³⁴

OTI has also been shown to be safe with respect to broader child health conditions. Between group comparisons in LEAP and EAT found that introduction of allergenic foods alongside established breastfeeding had no impact on duration or cessation of breastfeeding.^{29,52} Regular peanut consumption did result in differences in dietary intakes. LEAP children in the intervention group had higher

intakes of fat whilst children in the avoidance group had higher carbohydrate intakes; differences were greatest at the upper quartiles of peanut consumption. However, protein intakes remained consistent between groups and, importantly, there were no significant differences in anthropometric measurements or energy intake between the groups at any stage of the study. These findings remain true even when considering participants in the highest quartile of peanut consumption.⁵² Similarly, in EAT, there were no significant nutritional differences between the EIG and SIG.²⁹ Additionally, in EAT, the EIG reported longer sleep duration, less frequent waking at night, and a reduction in reported very serious sleep problems compared with the SIG.⁵³ There were no episodes of choking associated with the introduction of study foods in LEAP and EAT, consuming study foods as directed, i.e. avoiding whole peanut as a weaning food.

The safety profile of OTI with respect both to allergy and child health is excellent. Changes to governmental advice two decades ago, recommending infants avoid allergenic foods to prevent food allergy may have been causally related to the increasing rates of food allergy that followed this guidance and promoted the medicalisation of infant feeding. In reversing the avoidance 'intervention' and encouraging dietary diversity, the focus of public health strategies in countries where food allergy is prevalent needs to be the normalization of the inclusion of healthy allergenic foods during weaning for the general population. Screening of high risk children, as advised by NIAID guidelines, may additionally reduce the number of allergic events. However, it puts an extra pressure on health care systems and may actually contribute to delay in weaning.

Implementation of OTI at a population level

The ease with which an intervention can be carried out in countries with high prevalence of food allergy and its acceptability to the relevant population is critical to its success (Figure 3). In an RCT setting, adherence is a marker of an intervention's acceptability; interventions that are too complex or have significant side effects are likely to have low rates of adherence.³⁵

Rates of adherence to OTI are variable. Rates of adherence in LEAP were impressive with over 90% of children adhering to the randomized intervention; however, this adherence was achieved within the context of close monitoring and support, something that is not feasible in a public health intervention. Rates of adherence in EAT were lower at 42% and a dose effectiveness analysis demonstrated that adherence to the treatment regimen is necessary for prevention to be effective;⁵⁴ however, the quantity of food required for effective OTI is about 50% of that which EAT EIG children were asked to consume.

Understanding the reasons for reduced adherence in a clinical trial helps to identify strategies to improve the acceptability and efficacy of the intervention. In a recently published analysis, Perkin *et al* identified

both enrolment and post-enrolment factors related to non-adherence.⁵⁵ Older maternal age was associated with delayed introduction of study foods in both EIG and SIG. The difference in time of solid food introduction when comparing a 20 year old mother and a 45 year old mother amounted to 12.5 days in the SIG and 7.5 days in the EIG. One possible explanation is that older mothers reported allergic symptoms more frequently, leading to lower rates of adherence.

Ethnic origin has also been shown to influence adherence in OTI studies. Non-white race was the strongest predictor of non-adherence in the EAT Study, although the cause for this is unknown; difference in adherence in non-white children could not be explained by any demographic factors²⁹. Similarly, the BEAT Study found that children who were lost to follow up, withdrawn, or had no primary outcome were more likely to have a parent born outside Australasia ($P < 0.01$ for father and $P < 0.02$ for mother) than those who had complete data.

Eczema severity is significantly associated with overall nonadherence, whilst presence of any visible eczema at enrolment was of borderline significance ($P = 0.07$).⁵⁵ In the high-risk population of the EAT Study, adherence was negatively affected by presence of eczema with an inverse trend between severity of eczema and adherence level (test for trend, $P = 0.01$).³⁴

Whilst analysis of demographic and clinical data provide some information about non-adherence, these data do not provide insight into the factors that parents consider to be relevant to the acceptability of OTI, or the difficulties that may be faced by families if the intervention is implemented at a population level. The EAT Study found that food aversion and parental report of IgE-mediated type symptoms were related to reduced adherence in the EIG group but there was no significant correlation between parental report of IgE-type specific symptoms and sensitization to a particular food.²⁹ The most commonly reported issues within food aversion at this early stage was 'infant struggling to swallow' at the age of 4 months (17%) and 'infant dislikes the taste' at the age of 5 months (26%) and 6 months (38%).⁵⁶ Voorheiset *al* also looked at the challenges of OTI from the caregiver's perspective, using free text responses provided by parents in their monthly FFQ questionnaires.⁵⁶ They identified three main challenges to allergenic food consumption. First, some children refused the allergenic food, causing a sense of defeat among caregivers. Second, caregivers were concerned that allergenic foods might be causing a reaction, triggering a need for reassurance. Third, practical problems associated with the regimen compromised caregivers' capacity to persist. Their bubble chart highlights how challenges in OTI change as infants age and move through different developmental milestones; for example, dislike of taste increases with age, whilst difficulties with swallowing decreases.

Decisions about which weaning foods to provide are strongly determined by culture. Ingestion of 2g of wheat or milk protein a week by an infant would be considered acceptable within most European cultures, however the same was not true of peanut or sesame, although this may be changing. In a study conducted before the LEAP Study, Du Toit *et al* found the average weekly consumption of peanut protein by Israeli Jewish infants was 1.7g, whilst Jewish infants in the UK consumed 0g of peanut protein per week.⁵¹ It is reassuring that cultural weaning practices can be modified following guideline changes. For example, 88% of Australian infants who were recruited to a population-based cross-sectional study between 2016 and 2018 had consumed peanut protein in the first year of life compared with 28.4% of infants recruited to a similar study between 2007 and 2011.¹⁸ This dramatic shift may have been the result of significant involvement from Maternal and Child Health Nurses who provide education on infant feeding to Australian families. Nevertheless, this demonstrates the profound effect that the change of public health guidelines can have on infants' weaning over a relatively short period of time.

These data highlight that population level implementation of OTI is achievable for most infants without the need for the intensive support and education provided to LEAP families. An awareness of local cultural weaning practices in the population in which OTI is to be implemented as a prevention strategy, alongside an understanding of common barriers to successful uptake, will facilitate successful implementation of the intervention.

Summary

There is strong evidence for efficacy of early introduction of peanut and moderate evidence for egg in the diet of infants at risk of food allergy. There is also strong rationale to target the general population for intervention in order to obtain significant food allergy reduction at the population level. The safety profile of OTI is excellent which is reassuring for families and health care practitioners. However, further changes in public health policy will be critical to successfully implement the strategy of oral tolerance induction.

Table 1. Examples of modified weaning guidelines supporting OTI.¹⁶

Country	Organization	Year	Guidance	Recommends testing prior to

				peanut introduction in high risk infants?
USA/Canada ¹⁷	American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma, and Immunology; Canadian Society of Allergy and Clinical Immunology	2021	Both peanut and egg as well as other allergens should be introduced around 6 months of life, but not before 4 months. Infants should be fed diverse diet upon introducing complementary foods.	Not required but may be preferred by some families
USA/Canada ⁵⁷	National Institute of Allergy and Infectious Diseases	2017	Introduce peanut containing foods at 4-6 months in children with severe eczema, egg allergy or both. Introduce peanut containing foods around 6 months in children with mild to moderate eczema. Introduce peanut containing foods according to	In children with severe eczema, egg allergy or both, strongly consider evaluation with skin prick test, and/or sIgE and proceed to oral food challenge if necessary

			family preference and cultural practices in children with no eczema or food allergy.	
UK ^{58,59}	Scientific Advisory Committee on Nutrition/Committee on Toxicity British Society for Allergy and Clinical Immunology	2017 2018	Weaning at around 6 months, peanut need not be differentiated from other solid foods. Deliberate exclusion of peanut beyond 12 months may increase the risk of allergy	In children at high-risk of allergy referral for testing should be considered against the potential for delayed introduction as a result of the referral
Japan ¹⁴	Committee for Japanese Pediatric Guideline for Food Allergy, The Japanese Society of Pediatric Allergy and Clinical Immunology, The Japanese Society of Allergology	2016	Weaning at 5-6 months of age; no foods should be excluded	No recommendations
Australia ¹⁵	Australia Society of Clinical Immunology and Allergy	2017	For all children, introduce peanut with other solid foods around 6 months, not	No guidance regarding testing but ASCIA recommendations suggest all infants

			before 4 months and in the first 12 months	are fed peanut first in a graded manner stopping and treating allergic reactions as appropriate: Initially infants should have peanut butter rubbed on the inside of their lip, then a few minutes later feed ¼ of a teaspoon and 30 minutes later ½ teaspoon of peanut butter. This may be performed at home or under medical supervision.
Europe ⁶⁰	European Academy of Allergy and Clinical Immunology	2014* (NB these guidelines predate the WAO recommendations but are currently being updated.	There is no need to avoid introducing complementary foods beyond 4 months, and currently, the evidence does not justify	No recommendations

			recommendations about either withholding or encouraging exposure to potentially allergenic foods after 4 months once weaning has commenced, irrespective of atopic heredity.	
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Table 2. Overview of randomized controlled studies on OTI (adapted from^{30,54}).

OTI studies in high risk population							
Source	Country	Population	Intervention	No of participants	Outcome reported	Age at outcome assessment	Outcome
Du Toit <i>et al</i> , 2015 (LEAP Study) ²⁸	United Kingdom	Infants aged 4 to 11 mon with moderate or severe eczema or egg allergy and peanut SPT between 1 and 4 mm	6 g peanut protein/wk divided between ≥ 3 meals vs peanut avoidance from randomization to age 5 y	98	Peanut allergy diagnosed by OFC	5 y	95% CI, 4.9 to 43.3; P = 0.004) RRR 70.0%
Du Toit <i>et al</i> , 2015 (LEAP Study) ²⁸	United Kingdom	Infants aged 4 to 11 mon with moderate or severe eczema or egg allergy	6 g peanut protein/wk divided between ≥ 3 meals vs	542	Peanut allergy diagnosed by OFC	5 y	95% confidence interval [CI], 3.4 to 20.3; P<0.001)

		and peanut SPT 0 mm	peanut avoidance from randomization to age 5 y				RRR 86.1%
Natsume <i>et al</i> , 2016 (PETIT Study) ²⁶	Japan	Infants with eczema by age 4-5 mo	Heated egg powder, 50 mg/d, from age 6-9 mo; 250 mg/d from age 9-12 mo vs placebo from age 6-12 mo	121	Egg allergy confirmed by OFC	1 y	RR, 0.222; 95% CI, 0.08-0.61 (P = .0012) RRR 0.78
Palmer <i>et al</i> , 2013 (STAR Study) ²⁵	Australia	Singleton term infants aged 4 to 8 mo with moderate or severe eczema (SCORAD $\geq$ 15) and no prior egg or solid food intake	One tsp pasteurized whole egg powder daily (0.9 g protein) vs rice flour powder from age 4 to 8 mo	86	Egg allergy diagnosed by OFC to pasteurised egg plus positive SPT	1 y	RR, 0.65; 95% CI, 0.38-1.11 (P = .11) RRR 0.35
Palmer <i>et al</i> , 2017 (STEP Study) ²⁴	Australia	Infants 4 to 6 mo old with an atopic mother, no prior egg ingestion, and no prior allergy disease	Pasteurized whole egg powder daily (0.9 g protein) vs rice powder daily from age 4-6 mo to 10 mo	820	Egg allergy diagnosed by OFC to pasteurised egg plus positive SPT	1 y	Adjusted RR, 0.75; 95% CI, 0.48-1.17 (P = .20) RRR 0.25
Wei-Liang Tan <i>et al</i> , 2017 (BEAT Study) ²⁷	Australia	Infants 4 to 6 mo old with first- degree relative with allergic disease and egg SPT < 2 mm at age 4 mo	Pasteurized whole egg powder daily (350 mg egg protein) vs rice powder daily from the time of solid	319	Sensitization to egg $\geq$ 3 mm Probable egg allergy defined as reaction to egg or	1 y	OR, 0.46; 95% CI, 0.22-0.95 (P = .03)

			food introduction to age 8 mo		SPT $\geq$ 5mm	1 y	6.2% in intervention group vs 10.48% in placebo group, RRR 0.41 (P=0.20); significant reduction in PP analysis (P=0.013)
Perkin <i>et al</i> , 2020 (EAT Study, high risk population analysis) ³⁴	United Kingdom	3 mo oldexclusively breastfed infants with visible eczema, non-white ethnicity and/or sensitized to food	Sequential introduction of 6 allergenic foods aiming for 4 g protein/wk for each food, cow's milk (yoghurt), then peanut, boiled egg, sesame, fish, and wheat from age 3 mo, vs avoidance to age $\geq$ 6 mo	464	Food allergy diagnosed by OFC	1 y and 3 y	Sensitized: EIG 19.2% vs SIG 34.2% (p<0.05) developed any food allergy; EIG 20.0% vs SIG 48.6% (p<0.05) developed an egg allergy Visible eczema: EIG 22.6% vs SIG 46.7% (p<0.05) developed any food allergy; EIG 16.1% vs SIG 43.3% (p<0.05) developed an egg allergy Non-white ethnicity: Nonsignificant reduction in

							food allergy between EIG and SIG
OTI studies in general population							
Source	Country	Population	Intervention	No of participants	Outcome reported	Age at outcome assessment	Outcome
Bellachet <i>et al</i> , 2017 (HEAP Study) ²³	Germany	Infants aged 4-6 mo with sIgE to egg<0.35 kUA/L	Pasteurised egg white powder (2.5 g protein) vs rice powder 3 times/wk from age 4-6 mo to 12 mo	383	Egg allergy diagnosed by OFC plus sIgE to egg≥0.35 kUA/L	1 y	RR, 2.20;95%CI, 0.68-7.14 (P = .24)
Perkin <i>et al</i> , 2016 (EAT Study) ²⁹	United Kingdom	3 mo exclusively breastfed infants	Sequential introduction of 6 allergenic foods aiming for 4 g protein/wk for each food, cow's milk (yoghurt), then peanut, boiled egg, sesame, fish, and wheat from age 3 mo, vs avoidance to age ≥ 6 mo	1303	Food allergy diagnosed by OFC	1 y and 3 y	20% reduction in food allergy in EIG (P=0.32); 67% reduction in PP analysis, P=0.01. For HE allergy:ITT analysis: RR,0.69;95%CI, 0.40-1.18 (P = .17); PP analysis:1.4% vs. 5.5%, P=0.009 For PA:RR 0.49, 95%CI 0.20-1.19 (P=0.11); in PP analysis, 0%vs.2.5%, P=0.003

							No significant effect with sesame, fish, wheat or milk.
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Abbreviations: EIG, early introduction group in the EAT Study; HE, hen's egg; mo, months old; OFC, oral food challenge; SIG, standard introduction group in the EAT Study; PA, peanut allergy; PP, per protocol analysis; RR, relative risk; RRR, relative risk reduction; SPT, skin prick tests; y, year

Box 1. Why is the outcome of the EAT Study PP analysis reliable? ^{29,35,36}

Background

- Children enrolled at 3 months of age, randomized either to consume 6 allergenic foods including peanut from 4 months of age or to avoid allergenic food consumption until 6 months of age.
- 51% reduction in peanut allergy prevalence was observed.
- Not statistically significant in the intention-to-treat analysis.

Adherence

- Among participants with adherence information available, 61.9% of participants randomized to the EAT intervention group were PP adherent to early consumption of peanut and 43.1% to early consumption of egg.

Disadvantages of ITT analyses

- ITT analyses estimate the effect of treatment assignment, not the actual treatment received. When adherence is poor, ITT analyses may exhibit biases common to observational studies.
- Effective interventions, diluted by non-adherence, can appear to be ineffective using ITT analyses and lead to Type II error (false negative trial outcomes).
- Ineffective or unsafe interventions may appear to be effective using ITT analyses if discontinuation of treatment and lost-to-follow-up is associated with the worse outcome; the retained study population after dropout is disproportionately enriched with treatment successes and a biased safety profile.

- Higher rates of noncompliance are often observed in primary allergy prevention studies in normal populations with a low prevalence of allergy due to a perceived lack of benefit among healthy participants who have not yet developed disease. The long observation periods, which are required for the intervention effect to be detectable with adequate statistical power, also contribute to noncompliance and are exacerbated in ITT analyses.
- Healthcare professionals and families with infants may be most interested in bias adjusted estimates of the effectiveness of early introduction of peanut when adhered to, as opposed to the average overall effect in a partially non-adherent population.

Disadvantages of PP analyses

- Bias can result in subgroup PP analyses of compliant participants because randomization is not preserved.
- PP populations may not be representative of the target population enrolled.
- The smaller sample sizes inherent in PP populations lead to decreased power and can therefore produce Type II error.
- PP analyses are only unbiased if the probability of taking the treatment is random with respect to all predictors of the study's outcome.

Causal inference methods

- Causal inference methods estimate the causal effect of treatment received rather than treatment offered. They mitigate PP bias by using propensity scores, regression adjustment, and instrumental variable analysis to recreate randomized experiments from observational studies or from RCTs with non-compliance.
- They use the entire study population to give unbiased estimates of the causal effect of treatment and often have greater statistical power.

Instrumental variable analyses and EAT outcomes

- Instrumental variable analyses of the EAT Study showed that noncompliant allergy rate in the intervention arm is approximately equal to the allergy rate in the control arm (PP effect, 2.51%; unbiased CACE effect, 2.47%). This shows that potentially confounding factors in PP analysis in the EAT Study likely did not produce biased estimates.

Figure 1. Milestones in OTI approach.⁶¹

1992: *In vitro* study on murine T-cells shows that low dose exposure to allergens (rather than high dose exposure) favors production of IgE⁶²

1994: The first report of epicutaneous sensitization leading to IgE-mediated FA⁶³

1996: The dual-allergen exposure hypothesis is first proposed⁶⁴

2003: ALSPAC birth cohort shows an association between peanut oil containing creams applied on the skin of children with AD and the development of PA⁹

2004: Animal models show that an impaired skin barrier, particularly in the absence of prior oral tolerance induction, promotes IgE food sensitisation⁶ and that the lymphocytes in Peyer patches play a role in development of tolerance to food⁶⁵

2006: FLG loss-of-function mutations are confirmed to be major predisposing factor for AD, thus arguing that AD is a disease resulting from a defective skin barrier⁶⁶

2008: Prevalence of PA in infants in the UK is found to be ten times higher compared with infants in Israel while peanut is being introduced at an earlier age and consumed in larger quantities in the Israeli infant.⁵¹ This leads to hypothesis that early introduction of peanut prevents PA.

2009: High household peanut consumption is associated with the development of PA¹⁰

2011: FLG loss of function is shown to be associated with challenge-proven IgE-mediated PA, even after adjusting for AD⁶⁷

2012: *In vitro* evidence shows that PA correlates with peanut-specific proliferation in the skin-homing memory T-cell subset, suggesting that sensitization occurs through the skin⁶⁸

2013: HealthNut Study shows that by 12 months of age, 3.1% of children have challenge-proven FA and 9% were egg-allergic. There is therefore a narrow window of opportunity to induce tolerance⁶⁹

2013-2017: Early introduction of egg is associated with reduction in egg allergy in four different studies in high risk children and proves significant in one study which used heated egg.²⁴⁻²⁷ HEAP Study shows no evidence for prevention of egg allergy through early introduction of egg in general population²³

2015: High environmental exposure to peanut measured in dust is shown to increase the risk of peanut sensitization and likely allergy in children with mutation of in the FLG gene or with AD¹¹

2015: The LEAP randomized controlled trial demonstrates that oral peanut ingestion from 4 to 11 months of age prevents PA in high-risk infants²⁸

2016: LEAP-On Study shows that the early introduction of peanut induced unresponsiveness to peanut that persisted after 12 months of avoidance⁴²

2016: Early introduction of peanut proves feasible in infants at high risk of peanut allergy and does not affect the duration of breast-feeding nor impacts negatively on growth or nutrition⁵²

2016: ITT analysis of the EAT Study does not show statistically significant reduction in allergy to six tested foods in a general population of infants aged three to six months. Low adherence to the study intervention is noted. Statistically significant reduction of PA and egg allergy is present in PP analysis.²⁹ Early introduction of at least some amount of multiple allergenic foods appears achievable and did not affect breastfeeding⁴³

2018: The effect of early consumption of peanut in infants at high risk of peanut allergy is allergen specific and does not prevent the development of other allergic disease, sensitization to other food allergens and aeroallergens, or reported allergic reactions to tree nuts and sesame. Peanut consumption does not hasten the resolution of eczema or egg allergy⁷⁰

2019: Secondary analysis of the EAT Study results shows early introduction was effective in preventing the development of food allergy in specific groups of infants at high risk of developing food allergy, such as children with sensitization to food or eczema.³⁴ Increased maternal age, non-white ethnicity, and lower maternal quality of life at enrolment were independently and significantly associated with overall nonadherence.⁵⁵

2019: Genetic testing within the LEAP Study participants shows that MALT1 carriers from the peanut avoidance group have the highest risk for peanut allergy, thus supporting a genotype-phenotype relationship that implicates the MALT1 pathway in the allergic immune pathogenesis of peanut allergy.⁷¹

Abbreviations: AD, atopic dermatitis; ALSPAC, Avon Longitudinal Study of Parents and Children; FA, food allergy; FLG, filaggrin; ITT, intention-to-treat; PA, peanut allergy; PP, per protocol

Figure 2. Timing of OTI.

Figure 3. Elements of successful implementation of OTI strategy, where applicable.^{28,29,42,52,55,56,72,73}

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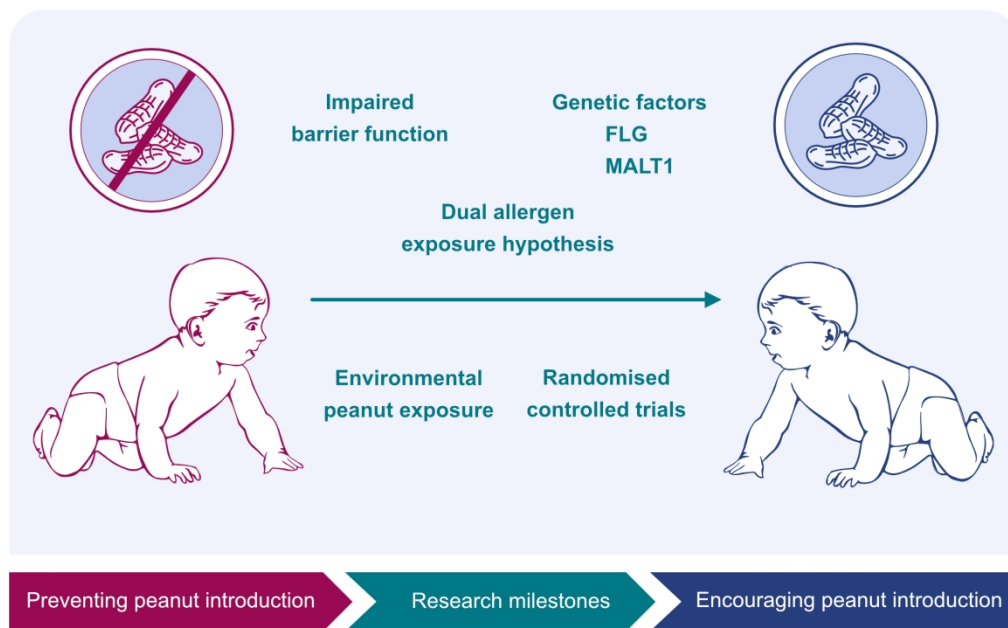


Figure 1_Krawiec et al.

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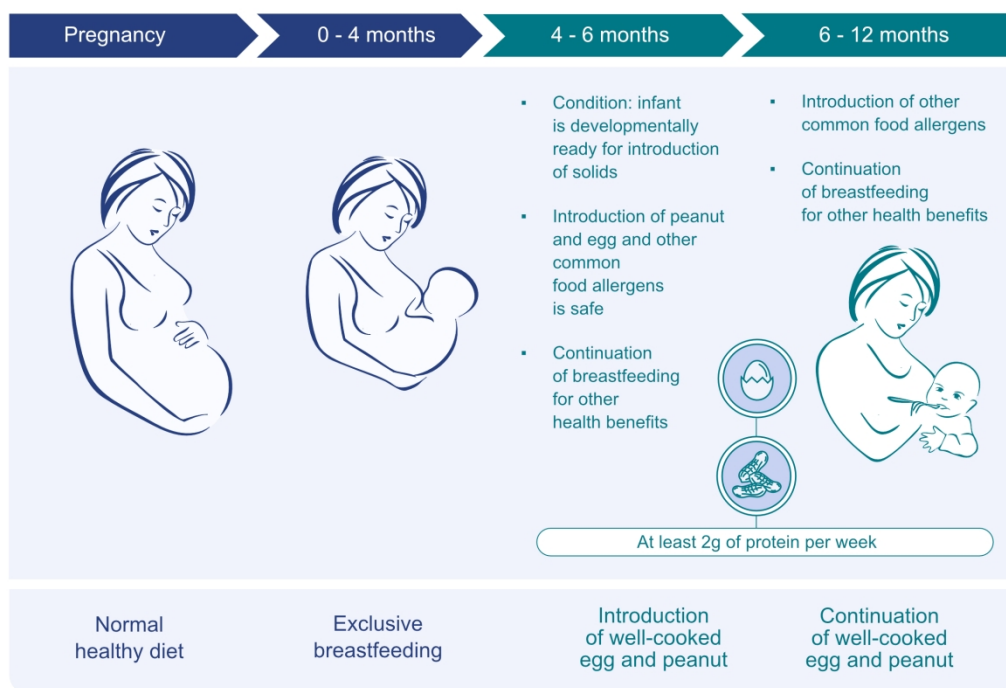


Figure 2_Krawiec et al.

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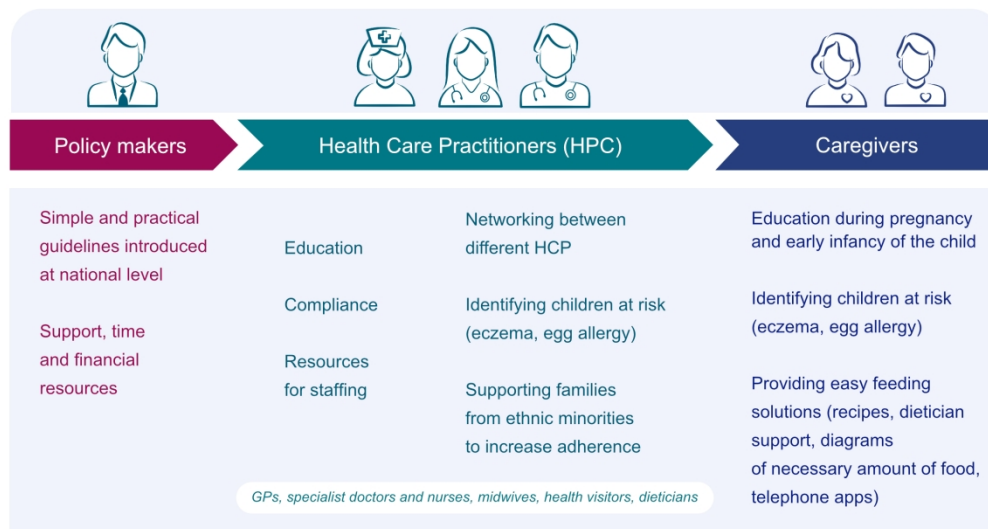


Figure 3_Krawiec et al.

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