**Clinical Commentary Review Article *“******Food allergen immunotherapy in preschool children: do we have the evidence?”***

**Authors and affiliations**

Paxton Loke, PhD, Murdoch Children’s Research Institute, Melbourne, Australia; Department of Paediatrics, University of Melbourne, Melbourne, Australia; Monash Children’s Hospital, Melbourne, Australia; Department of Allergy and Immunology, Royal Children’s Hospital, Melbourne, Australia

Brian P. Vickery, MD, Department of Pediatrics, Emory University and Children’s Healthcare of Atlanta, Atlanta GA

Stacie M. Jones, MD, Department of Pediatrics, Allergy and Immunology, University of Arkansas for Medical Sciences and Arkansas Children’s Hospital, Little Rock, AR

Rachel L Peters PhD, Murdoch Children’s Research Institute, Melbourne, Australia; Department of Paediatrics, University of Melbourne, Melbourne, Australia;

Graham Roberts, DM, Faculty of Medicine, University of Southampton, Southampton, UK; NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK; The David Hide Asthma and Allergy Centre, St Mary's Hospital, Isle of Wight, UK

Jennifer J Koplin, PhD, Murdoch Children’s Research Institute, Melbourne, Australia; Department of Paediatrics, University of Melbourne, Melbourne, Australia

**Corresponding Author:**

Paxton Loke, Murdoch Children’s Research Institute, 50 Flemington Road, Parkville 3052, Australia

Phone: +61-3-8341 6200; Email: Paxton.Loke@mcri.edu.au

**Conflict of interest disclosures**

P. Loke reports consultant fees from SPRIM Consulting, outside the submitted work. R.L. Peters and J.J. Koplin receive research support from NHMRC, outside of the submitted work. S.M. Jones reports grants to her institution from the National Institute of Allergy and Infectious Diseases and from Food Allergy Research and Education; clinical trials funding to her institution from Aimmune Therapeutics, Inc., DBV Technologies, Inc., Regeneron Pharmaceuticals, Inc., Astellas Pharma, Inc., Genentech, Inc., ALK, Inc; and personal fees from Aimmune Therapeutics, Inc. as a member of the scientific advisory board and FDA advisory consultant, from Regeneron Pharmaceuticals, Inc. as a research advisory consultant, and from Astellas Pharma, Inc. as scientific advisory consultant. B.P. Vickery reports grants from Abbott, grants and personal fees from Aimmune, grants from Alladapt, personal fees from AllerGenis, personal fees from Aravax, grants and personal fees from DBV, grants and personal fees from FARE, grants from Genentech, stock options from Moonlight Therapeutics, grants from NIH-NIAID, grants and personal fees from Novartis, personal fees from Reacta Biosciences, grants and personal fees from Regeneron, grants from Siolta, outside the submitted work. G. Roberts reports grants to his institution from National Institute of Allergy and Infectious Diseases, National Institutes of Health Research and Action Medicine Research; President of the British Society of Allergy and Clinical Immunology.

**Abstract**

Standard care for the management of food allergies previously centred upon allergen avoidance and treatment of adverse reactions following allergen exposure. An increase in the development of immunotherapy treatments for food allergy has occurred over the last two decades, with many centres now offering immunotherapy. Previous studies have mainly focused on school-aged children where food allergies are likely to be persistent. However, there is increasing evidence that delivering immunotherapy for food allergy in preschool age children may deliver higher rates of success, with peanut allergen immunotherapy leading the way. Conversely, the natural resolution of food allergies occurs primarily in these younger age groups, resulting in challenges in selecting patients who will ultimately benefit from these treatments. Both immunotherapy and natural history studies reveal the inherent plasticity of the immune system in early life, which may be more amenable to intervention, but this raises a delicate yet unknown balance between optimal timing of intervention versus waiting for natural resolution of the food allergy. Here we review the evidence for early food allergen immunotherapy in preschoolers, and present pro and con views for this approach, while acknowledging the important research gaps in this age group.

**Keywords**

Food allergy, allergen immunotherapy, oral immunotherapy, peanut, preschool, preschoolers

**Abbreviations**

DBPCFC – double-blind placebo-controlled food challenge; EPIT – epicutaneous immunotherapy; FDA – Food and Drug Administration; IgE – immunoglobulin E; OIT – oral immunotherapy; QoL – quality of life; sIgE – specific immunoglobulin E; SLIT – sublingual immunotherapy; SPT – skin prick test; SU – sustained unresponsiveness

**Introduction**

Food allergy prevalence continues to rise worldwide with significant lifestyle and economic burden to individuals affected and to society. 1, 2 Together with prevention strategies to stem the tide of this burden, food allergen immunotherapy is an emergent treatment, with three main modalities currently in various stages of development, including oral immunotherapy (OIT), epicutaneous immunotherapy (EPIT), and sublingual immunotherapy (SLIT). 3 OIT is the most studied with the majority of research and publications focused on peanut OIT. 4 The first product to be approved for a food allergy indication by the United States Food and Drug Administration (FDA) is a biologic OIT drug (Palforzia®). Palforzia® was approved in 2020 for select peanut-allergic patients, ages 4-17 years, targeting desensitization as a key clinical outcome, and it is now available in the US, UK and EU. 5-7

The efficacy outcomes most commonly described in clinical trials of a food allergy treatment regimen include desensitization and sustained unresponsiveness (SU). 3, 8 Desensitization is the temporary increase in reaction threshold while on treatment where allergen avoidance must be maintained and treatment may be indefinite. 3 SU is a period of non-reactivity while off treatment that allows for *ad libitum* consumption or a more liberal intake without prescriptive frequency or amount, and this may be better reflected by a newer term “remission”. 3, 8 The period of non-reactivity off treatment that defines remission is currently not standardized and it is uncertain how long remission will persist or how *ad libitum* intake influences persistence of remission. All of these treatment-induced outcome states appear to require some level and frequency of allergen exposure to maintain a lack of reactivity. 3

Food allergen immunotherapy, in particular OIT studies, have primarily been conducted in school-aged children.4, 9 Treatment in younger, preschool-aged children has been met with controversy as natural resolution of food allergy can occur, particularly in egg- and cow’s milk allergy where the majority of cases resolve in early life 10. Recent studies have explored peanut allergen immunotherapy in preschoolers due to the theoretical potential for higher rates of clinical efficacy outcomes when intervening at a younger age where the immune system is might be more dynamic or plastic, i.e. has a greater ability to undergo phenotypic and functional changes in response to the environment. Here, we review current evidence on food allergen immunotherapy in preschool children, and present both pro and con views for conducting food allergen immunotherapy in this age group.

**What is the goal of intervening with food allergen immunotherapy in preschoolers?**

Food allergy is a frightening and potentially life-threatening condition for children and their families. It is therefore not surprising that the use of immunotherapy is being assessed in young children. The clinical goals for therapy are desensitization or preferably remission, which are readily defined by food challenge and relatively objective. For the patient and family, the goals are broader but can be summarized as an improved quality of life. 11 Quality of life (QoL) has a number of different facets including the dietary and social restrictions associated with allergen avoidance, risk of accidental exposure and anxiety resulting from the broad impact of food allergy and perceived lack of control 12-14.

The benefits of earlier intervention need to outweigh any associated risks. An increased likelihood of obtaining desensitization or remission are attractive reasons, but questions remain as to whether we have the evidence to support this. Relieving families of the personal, societal and economic burdens of food allergy earlier are worthy goals. However, adverse reactions during immunotherapy in young children when feeding patterns are being established, may negatively impact feeding patterns and nutrition in the longer-term. In addition, there is limited data on QoL in food allergen immunotherapy at any age, with some studies showing a lack of benefit while others report positive benefits and others do not include patient-reported outcomes. 4, 15

**Why might early food allergen immunotherapy lead to higher remission rates?**

Early intervention immunotherapy would be expected to drive superior long-term outcomes like remission if the young child’s immune system is more receptive to, or permissive of, the immunomodulatory effects of therapy. Interventional trials in young children have been designed to assess clinical efficacy based on this theory of immunologic plasticity. 16-18 If immunologic plasticity either does not exist, or is inaccessible by current interventions, then treating an average 18-month-old with OIT would be, immunologically speaking, not much different than treating an average 18-year-old. Yet emerging evidence suggest this is not the case, rather early treatment appears to have potential for added benefit.

It is well-established that food allergies typically present with a clinical reaction in the first or second year of life, in many cases on the first known oral exposure. 19 Therefore, incipient allergic inflammation and IgE priming are likely to start during infancy or even earlier, a topic that has been examined in many birth cohorts. Yet early allergic responses seem to be immunologically disorganized, and characterized by weak T cell receptor affinity, unstable expression of GATA-3 and little IL-4 production, suggesting uncommitted TH2 differentiation programs. 20 In addition, maturation of the IgE response is delayed or immature during infancy and early life, further adding to the rationale to intervene early. Although a unified mechanistic understanding of allergic fate determination (allergy versus tolerance) remains elusive, the maturation and intensification of these initially weak signals may be required for persistence. For example, several key observational studies from around the world have linked the resolution of milk, egg, and peanut allergy with smaller quantities of allergen-specific IgE, and less diversity in IgE epitope repertoires. 21-26 Supportive data from other cohorts similarly show that persistent peanut allergy is characterized by longitudinal amplification of IgE responses during the preschool years. 27 Importantly, using challenge-proven outcomes, the longitudinal Australian HealthNuts study has shown that food allergy prognosis in later childhood is to some extent predictable by age 1. 28 Data from the BAMSE cohort extends these observations, linking peanut allergy at age 16 to preschool peanut IgE production 29. These data suggest the existence of a natural circuit or “kill switch” that regulates immune programming in the preschool years, perhaps even within the first year of life, and further suggest that the output of this programming is directly linked to allergic phenotype. Ultimately the question is: does antigen exposure influence this natural process in some way (i.e. reverse or accelerate it), and if so when is the best time to intervene?

Possible answers to these questions are derived from the secondary prevention literature, which has suggested that timely oral feedings in high-risk infants increases the probability of tolerance. 30-32 It should be clearly noted that oral exposure commenced therapeutically as a desensitization procedure, after the onset of clinical allergy, is likely to be distinct mechanistically from secondary prevention, and that inferences between these two scenarios are tenuous. Nonetheless, the explanatory power of the dual allergen exposure hypothesis depends critically on timely antigenic stimulation in the gastrointestinal tract known to create allergen tolerance in animal models via engagement of key regulatory cells and pathways.33 It should also be noted that tolerance can be induced in infants who are already manufacturing detectable amounts of allergen-specific IgE (i.e. the skin prick test-positive stratum in the LEAP study) 30, which suggests that the pathogenic process is reversible with an appropriately timed intervention. In those patients in whom the tolerance opportunity is lost, it is not difficult to imagine that standard care management advice (e.g. allergen avoidance) may further exacerbate the situation, by depriving the GI tract of the antigenic stimulation known to lead to permanent tolerance.

There is a growing speculation, based mostly on clinical observations, that secondary prevention and early desensitization treatment may exist on a continuum. Recently an international group of authors described this as “salvage” treatment, calling for immunotherapy to be started promptly in infants after failures of preventative oral introduction 34. When reviewing the evidence supporting a “salvage” approach, it is important to consider whether the study was specifically designed to test this approach. For example, the IMPACT study 18 enrolled participants who were older and tended to have higher IgE levels, therefore phenotypically these participants were more similar to older patients with persistent peanut allergy than they were to infants receiving “salvage” OIT. One alternative consideration is that the effectiveness of the intervention in long-term outcomes may have less to do with age *per se* and more about the quality of the immune system at the time of the intervention; however this is not well understood and is likely to vary between children.

Taken together, these data suggest that there is a developmental immune program early in life –perhaps operative within the first year - that may be governed by the potency of Th2 T cell inflammation and yields IgE sensitization that is predictive of clinical disease. Allergic outcomes may be regulated by unknown factors (including allergen exposure) during this time, leading to potentially reversible persistent disease phenotypes. It has also been observed that younger children have lower allergen-specific IgE levels for environmental allergens than older children 35, 36, suggesting progression of the allergic state may occur throughout childhood. This provides indirect evidence of developmental immunological plasticity, which we generally understand to be shaped by a window of opportunity, with the outcome critically dependent on timely oral exposure (see summary Figure 1).

**Review of evidence on early food allergen immunotherapy**

Systematic reviews of food allergen immunotherapy studies, where most studies have focused on cow’s milk, egg and peanut, predominantly in children and adolescents in mixed age ranges (4-17 years) with OIT being the main modality, have demonstrated desensitization effectiveness of up to 75% in randomized and non-randomized control trials but only approximately 30-35% effectiveness for SU/remission in the few studies that have examined this outcome 4, 9. A systematic review and meta-analysis of peanut OIT studies showed that the median age across trials was 8.7 years (QR 5.9-11.2). 37 Previous cow’s milk and egg OIT studies have included young children from 1 year of age but as part of larger broad age mixed range studies (up to school-age children) rather than exclusively in preschoolers. 4, 9 An exception is one cow’s milk OIT study which enrolled children age 24-36 months which demonstrated a 90% desensitization rate after 1 year compared to 23% in the control group.38 Combining studies involving older children for cow’s milk OIT showed desensitization rates of 68% in actively-treated vs 15% in control groups respectively. 4 Overall data in preschoolers are limited.

Evidence is currently emerging from 3 recent randomized control trials (RCT) that early intervention with peanut OIT in children 1-5 years of age may increase the likelihood of achieving remission. The first randomized trial (DEVIL) to investigate efficacy and safety of peanut OIT in preschool children enrolled 40 children, ages 9-36 months, and randomized to low (300 mg) or high (3000 mg) dose of peanut protein for daily maintenance. 17 Overall high rates of desensitization of 81% were shown with no differences in the low dose (85%) versus high dose groups (76%). 17 A 4-week remission rate of 78% was demonstrated, with comparative results in the low dose (85%) versus high dose (71%) groups. 17 A caveat to this study is that there is no placebo control group.

The PPOIT-003 study was a 3-arm RCT which compared probiotic peanut OIT (PPOIT) versus peanut OIT versus placebo in 201 children age 1-10 years. Children underwent 18 months of treatment using a 2000 mg maintenance peanut OIT dose. An *a priori* decision was made to stratify the analysis by age, divided into 1-5 years (n=104) and 6-10 years (n=97). 16 There was no difference in efficacy rates in both treatment groups for desensitization (PPOIT 88% versus peanut OIT 79% versus placebo 10%) and 8-week remission (PPOIT 61% versus peanut OIT 56% vs placebo 10%) respectively. 16 Combining both treatment arms for the 1-5 year old age group demonstrated overall desensitization and 8-week remission rates of 83% and 58% respectively, compared to lower desensitizationand 8-week remission rates of 67% and 37% in the 6-10 year age group. 16 This provides some of the first evidence that OIT may be more effective in younger children compared to older.

The IMPACT trial was the first peanut OIT RCT exclusively in preschoolers, enrolling 146 children age 12-48 months.18 These children were treated for 134 weeks with a 2000 mg maintenance dose. Efficacy outcomes demonstrated desensitization rate of 71% in the peanut OIT group versus 2% in the placebo group.18 The remission rate after a 26-week avoidance period was 21% in peanut OIT versus 2% in the placebo group. A post-hoc analysis of the IMPACT trial showed highest remission rates among the youngest 2 age groups, 71% of those <24 months and 35% of those aged 24-35.9 months compared to 19% of those aged 36-47.9 months. 18 Alongside these RCTs, open-label real world peanut OIT studies in Canadian preschoolers using a 300 mg maintenance dose showed desensitization rates of 49% in infants < 12 months and 50% in preschoolers but no data on remission was available. 39, 40

Recently, a phase 3 peanut EPIT RCT (EPITOPE) conducted in 362 peanut-allergic children ages 1-3 years, released its top line results with a desensitization endpoint. 41 This study demonstrated a 67% treatment responder rate (defined as a participant with a baseline peanut eliciting dose (ED) of <10 mg who reached an ED >300 mg at month 12 or a participant with a baseline ED >10 mg who reached an ED >1000 mg at month 12) among peanut-treated participants compared to 33.5% of placebo-treated participants (p<0.001). 41 Once the EPITOPE study is published and peer-reviewed, it would be interesting to compare the results with an earlier phase 3 peanut EPIT study (PEPITES) in children age 4-11 years where a similar desensitization endpoint is used. 42 These RCTs in preschoolers are summarized in Table 1.

Taking the above RCTs together, the overall peanut OIT desensitization rates for preschoolers ranges from 71%-83% but there is a broader 21%-78% range for remission rates, depending on the definition of remission used and the duration of the avoidance period. 16-18 While the desensitization rates in preschoolers are comparable with those seen in other OIT studies involving older children and adolescents (up to 75% ) 4, 9, there appears to be a greater effect for remission rates in the younger age group. Strengths of these RCTs include study entry challenges (either open or DBPCFC) to determine that the subject is allergic, and end-of-treatment DBPCFC to determine desensitization and remission, however there is much heterogeneity with regards to study entry criteria (e.g. challenge eliciting dose), up-dosing, maintenance dose regimen, treatment length and duration of remission measured (ranging from 4 to 26 weeks). For example, the differences in the rates of remission in IMPACT as compared to PPOIT-003 subgroup may be related to the eliciting dose for study entry or the amount of peanut protein required at OFC for treatment “success”, and a longer time off treatment to measure remission. 16, 18 There is also no head-to-head data comparing younger preschool children vs older children in the IMPACT or DEVIL studies with the PPOIT-003 subgroup data limited to efficacy rates. Nevertheless, these findings encouragingly suggest that early intervention with OIT may substantially increase desensitization and remission as compared to placebo or standard allergen avoidance.

Mechanistic studies in the IMPACT trial showed early and sustained immune changes in all active treatment groups, including decreased peanut- and Ara h2-specific IgE, basophil activation and skin prick tests and increased peanut- and Ara h2-specific IgG4 in the OIT group, which contrasted sharply to the early and progressive increase in peanut- and AraH2-specific IgE for those on placebo that occurred throughout the 160 week study period. 18 Peanut IgE and screening age were predictive of remission in peanut OIT treated children where the odds of remission decreases by 88% (95% CI, 54-97%) for every 10-fold increase in baseline peanut sIgE and by 7% (95%CI, 1-12%) for each increase in month at screening age. In contrast, older participants in the IMPACT trial already had high titer IgEs at baseline, suggesting that they more closely resemble older patients with persistent allergy 18. Similarly, in the DEVIL trial, a lower baseline peanut sIgE and peanut sIgE/total IgE ratio was associated with achieving remission. Overall, treatment of young children with peanut OIT appears to have added efficacy benefits with evidence of ongoing immune modulation, again highlighting the window of opportunity for early intervention immunotherapy.

**Pro for food allergen immunotherapy in preschoolers**

OIT studies over the last two decades have focused primarily on school-aged children with limited inclusion of children <4 years, with EPIT and SLIT studies following a similar pattern 4. Researchers were initially cautious about extending studies into preschool ages with concerns for potentially higher adverse event rates and unwarranted anaphylaxis in this age group of peanut-allergic children where there may be higher risks of accidental ingestion and potential for poor reporting capacity of exposures and/or symptom progression.

It is encouraging that increasing remission rates are demonstrated with decreasing age, in particular those less than 24 months of age. While the evidence remains limited and remission rates vary between studies, the 2 larger RCTs IMPACT and PPOIT-003 point towards higher rates of desensitization and remission in a preschool age group versus an older age group. Furthermore, 57% of peanut-treated children in the IMPACT study versus only 1 on placebo, could safely consume 1750 mg of peanut, which is a child-size serving portion. 18 Similarly, the earlier DEVIL study also demonstrated that children treated with peanut OIT had a 19-fold increased ability to incorporate peanut in the diet compared to standard care controls 17. One caveat is that a simple comparison of OIT outcomes in younger verses older children does not control for a higher rate of natural resolution in the younger age groups, thus we do not know how much of the improved outcomes are due to differences in natural resolution, yet the RCT presented do not support natural tolerance as a viable explanation for the beneficial efficacy outcomes documented.

Furthermore, mechanistic findings described above suggest and supports the existence of an early window of opportunity, likely due to young age, lower IgE and immune plasticity, that allows for a robust treatment response that may be prolonged.

**Con for food allergen immunotherapy in preschoolers**

The natural course of egg and milk allergy without intervention is largely favourable, with at least 80% of egg and cow’s milk allergy expected to naturally resolve by school-age. 24, 43, 44 Although peanut and tree nut allergies are more often persistent, studies suggest that at least 10%-20% are expected to resolve 10, 28, 45, 46 Recent evidence suggests that the prognosis may be even more favourable than previously thought, with 90% of raw egg and 30% of peanut allergy resolving by 6 years of age in the Australian HealthNuts study.47 If food allergy is going to resolve, it is more likely to do so at a younger age, therefore there is an argument for reserving food allergy treatments for older children who have not naturally developed tolerance. 10 Higher efficacy rates for open-label preschooler studies in peanut OIT 39, 40 need to be interpreted with caution as some preschoolers may have achieved natural resolution without intervention. Hence the importance of having a contemporaneous placebo- control group to assess for natural resolution in OIT studies cannot be overstated, as the estimate of effectiveness should be compared to a comparable untreated group.

Immunomodulatory treatments for food allergy usually involve burdensome regimes and are associated with a number of risks, including adverse events (AE). A meta-analysis of peanut OIT reported a three-fold increased risk of anaphylaxis, a two-fold increase in epinephrine use, and an increased risk of non-anaphylactic reactions compared to placebo or standard care. 37 There was also little improvement in QoL observed in those who underwent treatment compared to the standard care group, although this was measured in older children. 37 Treatment-related AEs were higher among peanut OIT-treated children (98%) compared to placebo-treated (80%) in the preschooler IMPACT study, including 21 peanut OIT-treated children who received epinephrine during 35 peanut OIT-associated episodes. 18 Open label preschool peanut OIT studies also showed high rates of treatment related reactions (68%) with ~4% receiving epinephrine.39 Even the EPITOPE study was not devoid of AE, with mild to moderate skin reactions at the patch site (22.5% active versus 8.5% placebo), one treatment-related serious AE and 4 anaphylaxis events. 41

Several clinical factors are associated with prognosis of food allergy. History of severe reactions, lower eliciting doses and presence of co-morbid allergic disease are associated with the persistence of food allergy. 10, 45, 46, 48 However, caveats of these retrospective clinical audits includes a bias towards persistent allergic disease. Data from the prospective population-based HealthNuts study showed that infants with early-onset eczema and multiple food sensitisations had an increased risk of persistent food allergy at age 6 years. Among infants allergic to raw egg, baked egg allergy was the strongest predictor of persistent egg allergy, associated with 6-fold increased odds of persistent egg allergy.47 However, even among those with baked egg allergy, 60% were no longer allergic to raw egg by age 6, thus more precise predictors of persistence are needed before early interventions can be targeted appropriately.

OIT conduct requires specialized allergy services. Resources for allergy services vary by region, with some countries reporting lengthy wait-times to access an allergy specialist for the diagnosis of food allergy. 49 Incorporating OIT into clinical practice would require substantial resources that some health settings cannot currently facilitate. Hence, initiating a resource-intensive treatment in young children who may naturally acquire tolerance may not be the best use of resources in settings where healthcare funding and access is limited.

Until we can accurately predict who would benefit from immunotherapy in the preschool years, questions remain as to whether it is in the best interests of the young child to subject them to intensive immunotherapy regimens. This need to be balanced against the proposed benefits of intervening early when the immune system has greater plasticity and early evidence suggesting that treatment may be safer and more effective when initiated early. 16-18 Given the significant commitment, lifestyle impacts and the risk of AEs during food immunotherapy treatments, it may be more relevant for those who are unlikely to naturally outgrow their food allergies.

**Knowledge gaps**

There are limited studies of immunotherapy in preschoolers using allergens other than peanut. Currently no evidence on the impact of immunotherapy on QoL is available for this age group, and hence it is unknown whether treatment is associated with better QoL. A recent paper suggested that preschool peanut OIT in the real world setting may be cost-effective in North America 50; however is still unknown if it is cost-effective to implement this therapy across all health services. Thus it remains uncertain if personal and/or economic burdens of food allergy for families can be alleviated through OIT. Further understanding of risk assessment and mitigation is critical to widescale implementation in very young children. This includes better knowledge in the assessment of AEs in pre-schoolers where the means of communicating allergic symptoms may be different from school-age children and ensuring child assent when they continue with therapy although the minimal age of assent varies greatly from 5-13 years.51 Identifying prognostic biomarkers that can accurately predict the prognosis of food allergy, and which patients may benefit most from treatment, requires further research. Numerous studies have found that higher SPT and sIgE at diagnosis are associated with an increased likelihood of persistent food allergy. 10, 21, 28, 43, 45-48, 52-54 However, predictive thresholds with high specificity for persistent food allergy vary widely in the literature, likely related to heterogeneity in study settings, participants and methods.55

Current debates also exist on whether early treatment could accelerate the onset of tolerance among children destined to outgrow their allergy independent of intervention. Furthermore, as the frequency and amount of consumption required to maintain tolerance following natural resolution are not known, for example in peanut allergy where a risk of recurrence have been described 45, 56, more evidence regarding the need for maintaining ingestion following treatment induced or natural resolution is required. Additionally, information is missing on identifying the “optimal” window of opportunity, whether based on age, IgE level or other factors that contribute to an enhanced response without sacrificing safety. Increasingly, some countries are using milk and egg ladders for IgE-mediated food allergies and it remains unclear whether this is a form of tolerance acceleration versus pseudo-OIT.57, 58 Furthermore, ongoing studies in the US (CAFETERIA study) 59 and Germany 60 which aim to investigate ingestion of sub-threshold amounts of allergen in the diet of children with peanut and/or tree nut allergy versus standard care of strict avoidance to enhance tolerance may assist in contributing to this knowledge gap. Using threshold information from food challenges to design tailored subthreshold feeding regimens that could be an easier, more family friendly, and less burdensome approach as compared to OIT, particularly in low resource settings, is also being debated 61.

**Conclusion**

Emerging evidence suggests that food allergen immunotherapy-induced desensitization and remission rates are higher in the preschool age group as compared to older children. These findings suggest that early treatment in young children is feasible and has potential to be a life-changing therapy for many young food-allergic children. However, it is not clear how much of this improvement is due to natural remission and evidence is insufficient in patient-important outcome measures, such as QoL, impact on diet patterns and nutrition, and on cost-effectiveness which limits implementation in health resource settings (see summary Figure 2). Despite compelling evidence from several well-designed randomized trials, more work is needed to definitively address the important knowledge gaps that remain. Several ongoing or recently completed Phase 3 trials in preschool children 41, 62, 63 will deliver important new data that will inform implementation of scalable interventions in this vulnerable population.

**References**

1. Gupta R, Holdford D, Bilaver L, Dyer A, Holl JL, Meltzer D. The economic impact of childhood food allergy in the United States. JAMA Pediatr. 2013;167(11):1026-31.

2. Sampath V, Abrams EM, Adlou B, Akdis C, Akdis M, Brough HA, et al. Food allergy across the globe. J Allergy Clin Immunol. 2021;148(6):1347-64.

3. Burks AW, Sampson HA, Plaut M, Lack G, Akdis CA. Treatment for food allergy. J Allergy Clin Immunol. 2018;141(1):1-9.

4. de Silva D, Rodríguez Del Río P, de Jong NW, Khaleva E, Singh C, Nowak-Wegrzyn A, et al. Allergen immunotherapy and/or biologicals for IgE-mediated food allergy: A systematic review and meta-analysis. Allergy. 2022;77(6):1852-62.

5. Hong TS, Hu A, Fahim G, Hermes-DeSantis ER. Emerging Therapies for Peanut Allergy. J Pharm Pract. 2022;35(2):289-97.

6. Smith SS, Hilas O. Peanut (Arachis hypogaea) Allergen Powder-dnfp: The First FDA-approved Oral Immunotherapy for Desensitization of Peanut Allergy in Children. J Pediatr Pharmacol Ther. 2021;26(7):669-74.

7. National Institute for Health and Care Excellence. Palforzia for treating peanut allergy in children and young people Technology appraisal guidance [TA769]. 2022.

8. Sampson HA, O'Mahony L, Burks AW, Plaut M, Lack G, Akdis CA. Mechanisms of food allergy. J Allergy Clin Immunol. 2018;141(1):11-9.

9. Nurmatov U, Dhami S, Arasi S, Pajno GB, Fernandez-Rivas M, Muraro A, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. Allergy. 2017;72(8):1133-47.

10. Savage J, Sicherer S, Wood R. The Natural History of Food Allergy. The journal of allergy and clinical immunology In practice. 2016;4(2):196-203; quiz 4.

11. Muraro A, De Silva D, Halken S, Worm M, Khaleva E, Arasi S, et al. Managing food allergy: GA2LEN guideline 2022. World Allergy Organization Journal. 2022;15(9):100687.

12. Flokstra-de Blok BMJ. Food Allergy Quality of Life Questionnaires (FAQLQ). In: Michalos AC, editor. Encyclopedia of Quality of Life and Well-Being Research. Dordrecht: Springer Netherlands; 2014. p. 2319-22.

13. DunnGalvin A, Roberts G, Schnadt S, Astley S, Austin M, Blom WM, et al. Evidence-based approaches to the application of precautionary allergen labelling: Report from two iFAAM workshops. Clin Exp Allergy. 2019;49(9):1191-200.

14. DunnGalvin A, Roberts G, Regent L, Austin M, Kenna F, Schnadt S, et al. Understanding how consumers with food allergies make decisions based on precautionary labelling. Clin Exp Allergy. 2019;49(11):1446-54.

15. Lloyd M DA, Tang M. Measuring the Impact of Food Immunotherapy on Health-Related Quality of Life in Clinical Trials. Frontier Allergy. 2022;3:941020.

16. Loke P, Orsini F, Lozinsky AC, Gold M, O'Sullivan MD, Quinn P, et al. Probiotic peanut oral immunotherapy versus oral immunotherapy and placebo in children with peanut allergy in Australia (PPOIT-003): a multicentre, randomised, phase 2b trial. Lancet Child Adolesc Health. 2022;6(3):171-84.

17. Vickery BP, Berglund JP, Burk CM, Fine JP, Kim EH, Kim JI, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. J Allergy Clin Immunol. 2017;139(1):173-81.e8.

18. Jones SM, Kim EH, Nadeau KC, Nowak-Wegrzyn A, Wood RA, Sampson HA, et al. Efficacy and safety of oral immunotherapy in children aged 1-3 years with peanut allergy (the Immune Tolerance Network IMPACT trial): a randomised placebo-controlled study. Lancet (London, England). 2022;399(10322):359-71.

19. Green TD, LaBelle VS, Steele PH, Kim EH, Lee LA, Mankad VS, et al. Clinical characteristics of peanut-allergic children: recent changes. Pediatrics. 2007;120(6):1304-10.

20. Sicherer SH, Wood RA, Stablein D, Burks AW, Liu AH, Jones SM, et al. Immunologic features of infants with milk or egg allergy enrolled in an observational study (Consortium of Food Allergy Research) of food allergy. J Allergy Clin Immunol. 2010;125(5):1077-83.e8.

21. Peters RL, Dharmage SC, Gurrin LC, Koplin JJ, Ponsonby AL, Lowe AJ, et al. The natural history and clinical predictors of egg allergy in the first 2 years of life: a prospective, population-based cohort study. The Journal of allergy and clinical immunology. 2014;133(2):485-91.

22. Ho MH, Wong WH, Heine RG, Hosking CS, Hill DJ, Allen KJ. Early clinical predictors of remission of peanut allergy in children. J Allergy Clin Immunol. 2008;121(3):731-6.

23. Sicherer SH, Wood RA, Vickery BP, Jones SM, Liu AH, Fleischer DM, et al. The natural history of egg allergy in an observational cohort. J Allergy Clin Immunol. 2014;133(2):492-9.

24. Wood RA, Sicherer SH, Vickery BP, Jones SM, Liu AH, Fleischer DM, et al. The natural history of milk allergy in an observational cohort. J Allergy Clin Immunol. 2013;131(3):805-12.

25. Dang TD, Peters RL, Koplin JJ, Dharmage SC, Gurrin LC, Ponsonby AL, et al. Egg allergen specific IgE diversity predicts resolution of egg allergy in the population cohort HealthNuts. Allergy. 2019;74(2):318-26.

26. Caubet JC, Lin J, Ahrens B, Gimenez G, Bardina L, Niggemann B, et al. Natural tolerance development in cow's milk allergic children: IgE and IgG4 epitope binding. Allergy. 2017;72(11):1677-85.

27. Neuman-Sunshine DL, Eckman JA, Keet CA, Matsui EC, Peng RD, Lenehan PJ, et al. The natural history of persistent peanut allergy. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2012;108(5):326-31.e3.

28. Peters RL, Allen KJ, Dharmage SC, Koplin JJ, Dang T, Tilbrook KP, et al. Natural history of peanut allergy and predictors of resolution in the first 4 years of life: A population-based assessment. J Allergy Clin Immunol. 2015;135(5):1257-66 e1-2.

29. Asarnoj A, Hamsten C, Lupinek C, Melén E, Andersson N, Anto JM, et al. Prediction of peanut allergy in adolescence by early childhood storage protein-specific IgE signatures: The BAMSE population-based birth cohort. J Allergy Clin Immunol. 2017;140(2):587-90.e7.

30. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. The New England journal of medicine. 2015;372(9):803-13.

31. Addendum Guidelines for the Prevention of Peanut Allergy in the United States.

32. Koplin JJ, Soriano VX, Peters RL. Real-World LEAP Implementation. Curr Allergy Asthma Rep. 2021;22(6):61-6.

33. Tordesillas L, Berin MC. Mechanisms of Oral Tolerance. Clin Rev Allergy Immunol. 2018;55(2):107-17.

34. Chua GT, Greenhawt M, Shaker M, Soller L, Abrams EM, Cameron SB, et al. The Case for Prompt Salvage Infant Peanut Oral Immunotherapy Following Failed Primary Prevention. The journal of allergy and clinical immunology In practice. 2022.

35. De Amici M, Ciprandi G. The Age Impact on Serum Total and Allergen-Specific IgE. Allergy Asthma Immunol Res. 2013;5(3):170-4.

36. Voloshin S, Smoldovskaya O, Feyzkhanova G, Arefieva A, Pavlushkina L, Filatova T, et al. Patterns of sensitization to inhalant and food allergens among pediatric patients from the Moscow region (Russian Federation). PLoS One. 2018;13(3):e0194775.

37. Chu DK, Wood RA, French S, Fiocchi A, Jordana M, Waserman S, et al. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. Lancet (London, England). 2019;393(10187):2222-32.

38. Martorell A, De la Hoz B, Ibáñez MD, Bone J, Terrados MS, Michavila A, et al. Oral desensitization as a useful treatment in 2-year-old children with cow's milk allergy. Clin Exp Allergy. 2011;41(9):1297-304.

39. Soller L, Abrams EM, Carr S, Kapur S, Rex GA, Leo S, et al. First Real-World Effectiveness Analysis of Preschool Peanut Oral Immunotherapy. The journal of allergy and clinical immunology In practice. 2021;9(3):1349-56.e1.

40. Soller L, Carr S, Kapur S, Rex GA, McHenry M, Cook VE, et al. Real-world peanut OIT in infants may be safer than non-infant preschool OIT and equally effective. The journal of allergy and clinical immunology In practice. 2022;10(4):1113-6.e1.

41. DBV Technologies Announces Positive Topline Results from Phase 3 EPITOPE Trial of Viaskin Peanut in PeanutAllergic Toddlers.

42. Fleischer DM, Greenhawt M, Sussman G, Begin P, Nowak-Wegrzyn A, Petroni D, et al. Effect of Epicutaneous Immunotherapy vs Placebo on Reaction to Peanut Protein Ingestion Among Children With Peanut Allergy: The PEPITES Randomized Clinical Trial. JAMA. 2019;321(10):946-55.

43. Boyano-Martinez T, Garcia-Ara C, Diaz-Pena JM, Martin-Esteban M. Prediction of tolerance on the basis of quantification of egg white-specific IgE antibodies in children with egg allergy. The Journal of allergy and clinical immunology. 2002;110(2):304-9.

44. Xepapadaki P, Fiocchi A, Grabenhenrich L, Roberts G, Grimshaw KE, Fiandor A, et al. Incidence and natural history of hen's egg allergy in the first 2 years of life-the EuroPrevall birth cohort study. Allergy. 2016;71(3):350-7.

45. Fleischer DM, Conover-Walker MK, Christie L, Burks AW, Wood RA. The natural progression of peanut allergy: Resolution and the possibility of recurrence. J Allergy Clin Immunol. 2003;112(1):183-9.

46. Fleischer DM, Conover-Walker MK, Matsui EC, Wood RA. The natural history of tree nut allergy. The Journal of allergy and clinical immunology. 2005;116(5):1087-93.

47. Peters RL, Guarnieri I, Tang MLK, Lowe AJ, Dharmage SC, Perrett KP, et al. The natural history of peanut and egg allergy in children up to age 6 years in the HealthNuts population-based longitudinal study. The Journal of allergy and clinical immunology. 2022.

48. Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA, Burks W, Wood RA. The natural history of peanut allergy. J Allergy Clin Immunol. 2001;107(2):367-74.

49. Morawetz DY, Hiscock H, Allen KJ, Davies S, Danchin MH. Management of food allergy: a survey of Australian paediatricians. J Paediatr Child Health. 2014;50(6):432-7.

50. Shaker M, Chan ES, Protudjer JLP, Soller L, Abrams EM, Greenhawt M. The Cost-Effectiveness of Preschool Peanut Oral Immunotherapy in the Real-World Setting. The journal of allergy and clinical immunology In practice. 2021;9(7):2876-84.e4.

51. Cayouette F, O'Hearn K, Gertsman S, Menon K. Operationalization of assent for research participation in pre-adolescent children: a scoping review. BMC Med Ethics. 2022;23(1):106.

52. Montesinos E, Martorell A, Felix R, Cerda JC. Egg white specific IgE levels in serum as clinical reactivity predictors in the course of egg allergy follow-up. Pediatr Allergy Immunol. 2010;21(4 Pt 1):634-9.

53. Nolan RC, Richmond P, Prescott SL, Mallon DF, Gong G, Franzmann AM, et al. Skin prick testing predicts peanut challenge outcome in previously allergic or sensitized children with low serum peanut-specific IgE antibody concentration. Pediatr Allergy Immunol. 2007;18(3):224-30.

54. Spergel JM, Beausoleil JL, Pawlowski NA. Resolution of childhood peanut allergy. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2000;85(6 Pt 1):473-6.

55. Peters RL, Gurrin LC, Dharmage SC, Koplin JJ, Allen KJ. The natural history of IgE-mediated food allergy: can skin prick tests and serum-specific IgE predict the resolution of food allergy? International journal of environmental research and public health. 2013;10(10):5039-61.

56. Fleischer DM, Conover-Walker MK, Christie L, Burks AW, Wood RA. Peanut allergy: recurrence and its management. J Allergy Clin Immunol. 2004;114(5):1195-201.

57. Chomyn A, Chan ES, Yeung J, Vander Leek TK, Williams BA, Soller L, et al. Canadian food ladders for dietary advancement in children with IgE-mediated allergy to milk and/or egg. Allergy, Asthma & Clinical Immunology. 2021;17(1):83.

58. Leech SC, Ewan PW, Skypala IJ, Brathwaite N, Erlewyn-Lajeunesse M, Heath S, et al. BSACI 2021 guideline for the management of egg allergy. Clin Exp Allergy. 2021;51(10):1262-78.

59. Immune and Clinical Implications of Threshold-based Phenotypes of Peanut Allergy (CAFETERIA).

60. Trendelenburg V, Dölle-Bierke S, Unterleider N, Alexiou A, Kalb B, Meixner L, et al. Tolerance induction through non-avoidance to prevent persistent food allergy (TINA) in children and adults with peanut or tree nut allergy: rationale, study design and methods of a randomized controlled trial and observational cohort study. Trials. 2022;23(1):236.

61. Garvey AA, O'Sullivan D, Hourihane JO. Home-based induction of sustained unresponsiveness in children with mild reactions to high doses of peanut. The journal of allergy and clinical immunology In practice. 2017;5(6):1757-9.

62. Wood RA, Chinthrajah RS, Rudman Spergel AK, Babineau DC, Sicherer SH, Kim EH, et al. Protocol design and synopsis: Omalizumab as Monotherapy and as Adjunct Therapy to Multiallergen OIT in Children and Adults with Food Allergy (OUtMATCH). Journal of Allergy and Clinical Immunology: Global. 2022.

63. Peanut Oral Immunotherapy Study of Early Intervention for Desensitization (POSEIDON).

Figure 1. Immune plasticity related to age may influence outcomes of early food allergen immunotherapy

Figure 2. Balance risks and benefits of starting food allergen immunotherapy (AIT) early in life

Table 1. RCT peanut OIT and EPIT in preschoolers

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Design** | **Age and sample size** | **Updosing** | **Maintenance Dose and duration****(mg peanut protein)** | **Desensitization****(ITT analysis)** | **Sustained Unresponsiveness/Remission (ITT analysis)** |
| Vickery et al., 2017 | Randomized trial with 2 doses of OIT(no placebo control) | 9-36 months, Low Dose n=20; High Dose n=17 | 42 weeks  | 300 mg (Low Dose);3000 mg (High Dose); up to 3 years | 5g peanut protein DBPCFC: Overall 81% (30/37); Low Dose 85% (17/20) vs High Dose 76% (13/17)  | 5g peanut protein DBPCFC after 4 weeks elimination: Low Dose 85% (17/20) vs High Dose 71% (12/17)  |
| Loke et al., 2022 | RCT | 1-5 years, n=104 | 16 weeks | 2000 mg, 18 months | 5g peanut protein DBPCFC: Overall 83% (70/84); PPOIT 88% (36/41) vs peanut OIT 79% (34/43) vs placebo 10% (2/20) | 5g peanut protein DBPCFC after 8 weeks elimination: Overall 58% (49/84); PPOIT 61% (25/41) vs peanut OIT 56% (24/43) vs placebo 10% (2/20) |
| Jones et al., 2022 | RCT | 1-4 years, n=146 | 30 weeks | 2000 mg, 134 weeks or 30 months | 5g peanut protein DBPCFC: Peanut OIT 71% (68/96) vs placebo 2% (1/50) | 5g peanut protein DBPCFC after 26 weeks elimination: Peanut OIT 21% (20/96) vs placebo 2% (1/50) |
| EPITOPE (EPIT) 2022 | RCT | 1-3 years, n=362 | Incremental increase in patch application time from 2 hrs to 24 hours daily during a 5-week initial dosing period | 12 months | Treatment responders: Viaskin peanut 250 mcg active group 67% vs placebo 33%  | N/A |

OIT: oral immunotherapy; DBPCFC: double-blind placebo-controlled food challenge; EPIT: epicutaenous immunotherapy; N/A = not available