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ROSTRUM

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A pragmatic approach to infant feeding for food allergy prevention

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Abstract

Early introduction of allergenic foods into an infant's diet is currently the most promising strategy to prevent food allergy, with infant guidelines around the world shifting from promoting avoidance to actively encourage the introduction of allergenic foods in the infant diet. Infant feeding guidelines vary according to regional public health priorities, and knowledge gaps remain, resulting in ongoing challenges for clinicians and families to translate guidelines into practical strategies for the introduction of complementary foods for food allergy prevention. Evidence from Australia demonstrates high community support and uptake of revised guidelines with most parents introducing allergenic foods in the first year of life, although this has not had the expected impact on substantially reducing food allergy prevalence. To uptake of guidelines from other countries is less clear, and several barriers have been noted in infant feeding RCTs, which may warrant intervention strategies. Further research is needed to understand additional strategies for food allergy prevention, particularly in infants who develop food allergy prior to when they are developmentally ready to commence solids. Several RCTs are underway investigating preventative strategies that target the window before allergen ingestion, such as vitamin D supplementation, emollient use, and immunizations that prime the immune response away from a Th2-driven allergic phenotype. Further research is also needed to understand the role of the environment and the host environment in the development of tolerance to foods.

KEYWORDS
food allergy, guidelines, infant feeding, prevention

1 | INTRODUCTION

Early introduction of allergenic foods into the infant's diet in the first year of life is currently the most promising strategy to prevent food allergy. Around 2015, the publication of the Learning Early About Peanut Allergy (LEAP) randomized controlled trial (RCT) led to a paradigm shift in infant feeding practices, moving away from delayed introduction to deliberate early introduction of common allergenic foods, especially peanut. LEAP showed early and regular consumption of peanut in high-risk infants resulted in an 81% relative risk

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reduction in peanut allergy at age 5 years, compared with infants who delayed introduction of peanuts until after 5 years.[1] Further evidence for the early introduction of peanut in a non-high-risk cohort for the prevention of peanut allergy was reported in the Enquiring About Tolerance (EAT) study.[2] Together, a meta-analysis of these trials (1550 participants) provided evidence that peanut introduction at age 4–11 months was associated with a lower risk of peanut allergy (RR, 0.29; 95% CI 0.11–0.74; $p = .009$). For other allergenic foods, a meta-analysis of 5 trials (1915 participants) found that egg introduction (in varying forms, e.g., pasteurized raw whole egg powder, cooked egg) at 4–6 months of age was associated with a lower risk of egg allergy compared with later egg introduction (RR 0.56; 95% CI 0.36–0.87; $p = .009$).[3] Early introduction of fish (in cohort studies) was associated with reduced fish sensitization with very low certainty evidence. No consistent evidence of reduced cow's milk allergy risk was found for early cow's milk introduction[3] with later studies showing conflicting findings related to the timing of cow's milk introduction, highlighting the need for further research.[4,5]

Subsequently, infant feeding guidelines around the world have been revised to actively encourage the introduction of peanut and not delay the introduction of other allergenic foods into the infant's diet.[6–10] However, there are inconsistencies with some guidelines recommending different approaches, eg, screening for sensitization prior to allergenic food introduction based on various risk scenarios for food allergy, advice limited to particular allergens, or a universal approach for all allergenic foods and all infants. The purpose of this rostrum is to review the current state of play of infant feeding guidelines and uptake of these guidelines internationally, consider the evidence for a universal approach to infant feeding, discuss practical considerations and identify knowledge gaps that future research should address.

Highlights and future research needs

- Early introduction of allergenic solids into an infant's diet is currently the most promising strategy to prevent food allergy, however regional recommendations around infant feeding vary.
- Evidence from Australia demonstrates high community uptake of guidelines recommending introduction of allergic solids in the first year of life, although this has not had the anticipated impact on food allergy prevalence. Uptake of infant feeding guidelines in other regions has not been well documented.
- Several barriers to the regular incorporation of allergenic foods into the infant's diet have been noted in infant feeding trials; these likely warrant intervention strategies.
- Further research is needed to understand additional strategies for food allergy prevention, particularly in infants who develop food allergy prior to when they are developmentally ready to commence solids.

2 | INFANT FEEDING GUIDELINES—AN INTERNATIONAL PERSPECTIVE

The World Health Organization recommends the "introduction of nutritionally adequate and safe complementary (solid) foods at 6 months together with continued breastfeeding up to 2 years of age or beyond."[11] Specific advice regarding the introduction of allergenic foods and food allergy prevention does not feature in the WHO recommendations.[12] Around half of infant feeding guidelines from 187 countries, as reported in a recent systematic review, were consistent with the WHO recommendations, with guidelines from upper-middle to high incomes nations more likely to deviate from WHO guidelines compared with low or lower-middle income nations (79% and 21%, respectively).[13] This likely reflects different national population health priorities, with lower-income countries prioritizing a need to prevent infant mortality, infection, and malnutrition due to inadequate feeding practices; data on the prevalence of food allergy in some lower-income countries are lacking. In higher-income countries, infant feeding guidelines additionally target the prevention of noncommunicable diseases including food allergy, which presents a growing public health burden.

Earlier guidelines recommended the deliberate delayed introduction of allergenic foods;[14,15] however, since 2008, guidelines have shifted away from a deliberate delay approach to the active introduction in the first year of life. Nevertheless, recommendations remain somewhat divergent from one another between countries; infant feeding guidelines from around the world have recently been summarized in several sources.[16,17] In general, they recommend the introduction of solids at "4–6 months," "from 6 months," or "around 6 months but not before 4 months." All guidelines published between 2016 and 2019 (as reported in the systematic review) recommended not to delay the introduction of common allergens, and these sentiments featured in most guidelines published from 2006.[17,18]

In 2016, the Australasian guidelines were updated to recommend that peanut, cooked egg, and other common food allergens should be introduced in the first year of life.[19] However in other regions, such as the US, a risk stratification approach was recommended, with NIAID advising screening with peanut SPT or specific immunoglobulin E (sIgE) prior to peanut introduction in high-risk infants (severe eczema and/or egg allergy).[6] Because early exposure to allergenic foods has been associated with a reduction of food allergy in the general population in both RCT and observational settings,[2,20] questions have been raised over the merits of a public health policy targeting only high-risk infants.[21] Modeling in the Australian population-based HealthNuts cohort found that an early intervention strategy targeting high-risk infants would require screening 16% of the population with sIgE tests, which would be challenging to achieve given limited access to testing in all geographical regions,

yet would still miss 23% of peanut allergy cases that presented in low-risk infants.[22]

Concerns were raised that the guidelines advocating for screening prior to allergen introduction may lead to burgeoning demand and increased wait time for screening tests, which inadvertently may lead to delayed introduction of peanut in high-risk infants. Some have also argued that LEAP only showed that early peanut introduction was feasible and successful in a screened high-risk population, not that a screened population was necessary or safer for successful introduction.[23] US administrative health claims data from 2010 to 2018 observed an increase in allergy testing and peanut diagnosis following the release of the addendum guidelines. Most allergy testing occurred after 6 months of age, and the potential window of opportunity for peanut introduction between 4 and 6 months may therefore be missed; consequently, screening may have had an unintended consequence of delaying peanut introduction. Furthermore, increased allergy testing was observed for non-high-risk infants and for foods other than peanuts (the median number of allergens tested in this study was 9 skin tests and 10 serologic IgE tests), with neither practice being recommended by the guidelines.[24] Data from US allergists responding to an AAAAI/ACAAI survey noted that 37% (n = 451) reported an increase in referrals for early introduction assessment, and 36% (n = 431) were not willing to offer high-risk infants an in-office feeding despite guidelines.[25] Furthermore, this approach also relies on primary care physicians and families correctly identifying infants at high risk of food allergy. Attitudes and practices may change over time as further evidence emerges, and early allergen introduction becomes more widely practiced.

The EAACI guidelines were updated in 2020. Their earlier advice in 2014 did not provide specific recommendations for either withholding or encouraging exposure to allergenic foods after 4 months of age.[7] In the 2020 guidelines, EAACI specifically recommends introducing well-cooked egg into the infant diet as part of complementary feeding. The advice regarding peanut was dependent on peanut allergy prevalence in the region. In countries where there is a high prevalence of peanut allergy, peanut should be introduced as part of complementary feeding however in countries with a low prevalence of peanut allergy, no specific recommendations were made although they advocated the inclusion of peanut in the diet according to normal eating habits and local recommendations. Finally, the EAACI Task Force suggests avoiding supplementing breastfed infants with cow's milk formula in the first week of life as a very early partial introduction, and subsequent discontinuation may increase later development of cow's milk allergy, although this recommendation was made with low certainty of evidence based on one Japanese study.[4,26] A second Japanese study reported early cow's milk supplementation in breastfed infants between 1 and 3 months of life was associated with a small but significant absolute risk reduction in cow's milk sensitization and allergy, compared with avoidance.[5]

The 2017 Asia Pacific Association of Pediatric Allergy, Respirology & Immunology consensus statement also differentiated between high and low peanut allergy prevalence countries, with early peanut introduction recommended only for high prevalence countries and high-risk infants.[8] Interestingly, some countries, such as Singapore, have a low prevalence of peanut allergy despite the delayed introduction of peanut into the infant diet,[27] suggesting that there is regional variation in drivers of food allergy, and therefore, regional variations in recommendations may be warranted given potential differences in disease etiology and public health priorities.

In 2021, a consensus guidance and approach for the prevention of food allergy were reached between allergy professional societies in the US and Canada (American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma and Immunology, and the Canadian Society for Allergy and Clinical Immunology). This recommended that all infants, irrespective of risk, should be introduced to cooked egg and peanut at around age 6 months but not before 4 months of life, when the infant is developmentally ready. These recommendations also state that screening is not required but can be an option for hesitant families at the clinician's and family's preference. Further recommendations include that, other allergens should be introduced around this time, infants should be fed a diverse diet, hydrolyzed milk formulas should not be used for prevention, and that no allergen should be deliberately avoided (or given) during pregnancy or breastfeeding for prevention purposes.[9] Infant feeding guidelines that promote the introduction of solids at 4–6 months of age contradict the WHO guidelines to exclusively breastfeed for 6 months. Reassuringly, the EAT study did not find that the early introduction protocol impacted breastfeeding rates.[2] Current infant feeding recommendations for allergy prevention are summarized in Table 1.

3 | INFANT FEEDING FOR ALLERGY PREVENTION FROM AN ECONOMIC PERSPECTIVE

Discussions surrounding the necessity of screening high-risk infants prior to allergen introduction, with common sensitization tests, eg, serum-specific IgE, have raised concerns about timely access and costs. Cost-effectiveness analyses have demonstrated that universal early introduction, to all infants irrespective of risk and without prescreening (using any test, including Ara h 2)/medicalized introduction, prevented most cases of peanut or egg allergy with the lowest societal costs compared to screening with medicalized introduction or delayed introduction.[28,29] Sensitivity analyses have suggested that the only way a screening policy could be cost-effective was at a high pretesting prevalence of peanut allergy (33%) or a significant health disutility equivalent to a trade-off of 76–148 days of life to avoid the risk of an allergic reaction at home from introduction, neither of which applies in the real world.[30] Canadian and US survey data have noted poor physician and caregiver support for highly medicalized processes involving in-office introduction and screening tests, and confusion regarding the precise definition of "high risk."[24] The value of the cost-effectiveness analysis is that policy was simulated at a population level, with multiple sensitivity assumptions tested representing plausible outcomes from trials. The results were

TABLE 1 Summary of current infant feeding recommendations for food allergy prevention

Guideline	Timing	Egg	Peanut	Other common allergens	References
World Health Organization (WHO)	From 6 months of age with continued breastfeeding to 2 years	No specific allergen advice			11
American and Canadian Consensus, 2021	At around 6 months not before 4 months	For all infants, cooked egg at around months and not before 4 months	All infants, at around 6 months not before 4 months	Once the infant has tolerated other foods, **cows milk, soy, wheat, tree nuts, sesame, fish, and shellfish** to be introduced if part of the family diet with ongoing ingestion	9
European Academy of Allergy and Clinical Immunology (EAACI), 2020	From 4 to 6 months	Well-cooked but not raw or unpasteurized egg from 4 to 6 months	For countries with high prevalence from 4 to 6 months	**Milk**-avoid supplementing breastfed infants with cow's milk-based formula in the first week of life	7,10
ASCIA, 2020	When your infant is ready, at around 6 mths but not before 4 months, preferably while still breastfeeding	Cooked egg in the first year **High risk:** from 8 months	First year, including infants at **high risk** of food allergy	**Wheat, fish, and other nuts** that are part of the family diet before 12 months and only introduce one new common food allergen at each meal	
British Society of Clinical Immunology and Allergy (BSACI), 2018	From around 6 months of age (not before 4 months), alongside continued breastfeeding	Before 1 year and continue as part of a usual diet **High risk** (eczema or PHx food allergy)—cooked egg from 4 months	Before 1 year and continue as part of a usual diet **High risk** (eczema or PHx food allergy)—from 4 months	Single allergen introduction for foods part of the normal family diet	40
Asia Pacific Association of Pediatric Allergy, Respirology & Immunology (APAPARI), 2017	6 months with continued breastfeeding alongside complementary food up to 2 years if possible, according to cultural practice	5–6 months for high-risk infants (severe eczema)	4–10 months for those high prevalence countries and high-risk infants (severe eczema)	To be introduced in a sensible manner once weaning has commenced	8

clear each time in that the "one size fits all" universal approach was preferred in each iteration.

4 | UPTAKE OF INFANT FEEDING GUIDELINES

Successful implementation of infant feeding guidelines will need to overcome some challenges, and given the rapidly changing advice, it would not be surprising if some parents were confused and therefore reluctant to adhere to the new advice. Given that the early introduction of allergenic foods is the only evidence-based food allergy prevention strategy, it is essential to measure whether the new guidelines have resulted in changes to infant feeding practices and subsequently food allergy prevalence. This has recently been evaluated in Australia.

Two population-based studies using the same sampling frame and study methodology have been conducted in Melbourne, Australia, 10 years apart, that is, before and after infant feeding guidelines were changed. From 2007 to 2011 (HealthNuts), only 28% of infants had peanut introduced in the first year of life; however, following guideline changes in 2016 that recommended introduction in the first year of life, a striking shift was observed. In 2018–2019 (EarlyNuts), 89% of infants were introduced to peanut in the first year, and the median age of introduction was 6 months. Most infants (75%) had eaten peanut more than 4 times and around a quarter were consuming peanut more than once per week. However, a proportion of infants were consuming peanut infrequently (5.5% only consumed peanut once and 18% consumed them 2–4 times), and nearly half were consuming only small amounts of peanut (eg <1 teaspoon).[31] A national survey of 1940 Australian parents showed similarly high rates of peanut introduction in infants by age 12 months (86%).[13]

While the dramatic shift in infant feeding practices is promising, the more pressing question is whether this has had an impact on peanut allergy prevalence. In HealthNuts, the prevalence of peanut allergy was 3.1%, and this reduced to 2.6% in EarlyNuts after adjustment for changes in population demographics; however, this difference did not meet statistical significance. There was a higher proportion of infants with East Asian ancestry in EarlyNuts compared with HealthNuts, a risk factor for peanut allergy in this population; however, peanut allergy prevalence did not increase in the later EarlyNuts study. This suggests that the widespread early introduction of peanut in infancy attenuated a rise in peanut allergy that could have otherwise occurred. The prevalence of peanut allergy was still high despite the majority of infants consuming peanut within the first year and suggests that timely introduction is necessary to prevent some peanut allergy but not sufficient to prevent all peanut allergy.[32] Similarly, a national survey of food anaphylaxis admissions in Australia over a 20-year period spanning updated allergy prevention and infant feeding recommendations showed attenuation of year-on-year increases coinciding with the introduction of updated guidelines in 2008 to 'not delay' and in 2015 to 'introduce early'. Nevertheless, the absolute rates of anaphylaxis admissions have continued to increase, suggesting that other environmental factors continue to play a role in driving food allergy prevalence.[33] Given that not all infants in EarlyNuts who introduced peanut continued to eat it regularly or in large quantities, further research is needed to provide clarity on the frequency and quantity of peanut ingestion needed to induce and maintain tolerance, and how this can be supported at the population level. Few studies have examined the efficacy of allergen introduction in relation to the duration of allergen consumption. However, the LEAP study continued ongoing ingestion for the first 5 years of life, and children were then able to stop eating peanut for 1 year and the majority remained tolerant.[34]

Data from other regions are sparse. Following the 2017 addendum guidelines, a US nationally representative survey assessed 2000 expecting parents and parents of infants with less than 1 year's knowledge and preferences for early peanut introduction. The survey found that 29% had no or vague awareness of the new guidelines although half thought that the timing of food introduction was important to the development or prevention of food allergy. Concerningly, 40% of parents expressed a desire to delay peanut introduction after 11 months of age, and only 31% reported a willingness to introduce peanut around 6 months of age. These findings highlight a need for broader formal implementation planning and education strategies in the US to facilitate early allergen introduction.[35] Given that several years have passed since this survey was conducted and that guidelines have once again changed, an updated survey would be beneficial to inform current practices in the US. However, similar surveys from the perspective of the US allergist and pediatricians reflect some hesitancy regarding the concept and a need for further education even among those expected to implement the strategy.[36]

The uptake of infant feeding guidelines in Australia is impressive, but these findings cannot be easily generalized to other nations. Challenges associated with the timely introduction of allergenic foods need to be quantified and addressed to promote the uptake of infant feeding guidelines for allergy prevention. Without definitive data on infant feeding practices, earlier infant feeding trials can shed light on common barriers to compliance with infant feeding recommendations, which will enable targeting strategies to at-risk groups.

Compliance with the changes in feeding guidance remains a challenge, some of which may segment along particular sociodemographic patterns. The EAT study had a rigorous early introduction regimen that was difficult for some families to implement, evident by only 42% adherence to the protocol.[2] Maternal characteristics associated with poorer compliance were older maternal age, nonwhite ethnicity, and lower maternal quality of life, while parent-reported allergic food reactions and feeding difficulties by 4 months of age were also associated with poorer compliance.[37] Evidence of ethnic differences in food allergy prevalence within the same country has been observed, for example, within Australia, children-born to Asian-born parents have a higher risk of food allergy compared with children of Australian-born parents. Therefore, it is essential to determine where differences in infant feeding patterns contribute to the differences in prevalence related to ethnicity. The American

multisite Food Allergy Outcomes Related to White and African American Racial Differences (FORWARD) cohort examined infant feeding patterns among children with allergist-diagnosed food allergy. Based on parent-report of infant feeding patterns by the retrospective recall, White children were more than twice as likely to have been introduced to peanut and milk early (age 6 months or less) compared with Black children. No significant difference in the timing of egg introduction by race was observed.[38] In the Australian EarlyNuts study, peanut introduction in the first year of life was more frequent in infants of Australian-born mothers (93%, 95% CI 90%–95%) compared with non–Australian-born mothers (82%, 95% CI 77%–87%).[31]

Multiple drivers for these differences are possible, such as differences in the advice given to families by health professionals, identification of high-risk infants, family knowledge of and concern about food allergy, or cultural practices, which need to be determined. Given these findings, it is essential that primary and secondary food allergy prevention RCTs find the balance between rigorous conduct and pragmatism to ensure the interventions are feasible for families and readily translatable into public health policies and/or clinical care guidelines applicable to culturally diverse populations.

5 | PRAGMATIC APPLICATION OF THE CURRENT EVIDENCE AND INFANT FEEDING RECOMMENDATIONS

Given the rapidly evolving evidence yet ongoing gaps regarding the role that complementary feeding plays in allergy prevention, and the disparity in allergy prevention guidelines around the world, it can be challenging for clinicians and families to translate this information into practical strategies for the introduction of complimentary foods. The goals of complementary feeding should be to provide nutrition to meet evolving growth and development needs and to expose the infant to foods of varying flavors and textures to encourage the development of a diverse and nutritionally complete diet. It is important to approach this space considering a multitude of factors not simply with an allergy prevention lens as doing so may overlook, ignore, or at worst have detrimental impacts on other factors paramount to infant nutrition and development.

The recommendations for the timing of commencement of complementary foods for allergy prevention vary. Some allergy prevention guidelines limit recommendations to specific allergens[9,26] while others provide recommendations for the timing of any complementary foods in the window of 4–6 months, or around 6 months of age but not before 4 months.[17,39] While this is not aligned with the WHO guideline of "from 6 months of age",[11] it could be argued the slightly earlier starting age may be appropriate in countries where food allergy prevalence is higher and the need for prolonged exclusive breastfeeding as a public health measure to prevent infant mortality from infection and malnutrition is not the primary health concern. The caveat when working with individual families would be discussing cues of developmental readiness for solid foods.

There are still some concerns that complementary foods should be introduced a few days apart.[40] Allergy prevention guidelines suggested the introduction of new foods singly and several days apart to assist with the identification of trigger foods for adverse reactions[17]; however, the updated European and the US/Canadian guidelines have now omitted this recommendation,[9,26] while the current Australasian and BSACI guidelines recommend the single introduction of allergens.[10,39] The Caring for Your Baby and Young Child publication from the AAP, stated in 2019 that "in the past, pediatricians recommended starting one new food every few days so that you can see whether a reaction occurs to the particular food. New research suggests that it is safe to start multiple foods at once."[41]

In terms of what order foods should be introduced, the evidence is strongest for the early introduction of egg and peanut, mainly because these have been the primary foods studied to date.[42] However, the practicality of introducing these foods without initial acceptance of more basic (and less potentially allergenic) solids and without food to mix well-cooked egg and peanut into can be challenging. It therefore makes practical sense that a grain, fruit, or vegetable be trialed first followed by cooked egg then peanut as per the most recent US/Canadian consensus guideline.[9] To date there is a lack of efficacy data regarding frequency, quantity, and duration of allergen ingestion that supports ongoing tolerance. Peanut amounts were approximately 6 g per week in LEAP and 4 g per week in EAT.[1,43] The study dose-response data for EAT showed mean weekly dosing of 2 g of peanut or egg to be highly protective against peanut or egg allergy; however, efficacy data for lower doses have not been explored, and data for other allergens are yet to be established, and these volumes have been shown to not negatively impact growth, micronutrient intake, or breastfeeding rates in both studies.[43–45] With many guidelines now recommending ongoing exposure to maintain tolerance,[9,10,39] advice regarding other common allergens such as tree nuts and shellfish should be based on family and cultural diet considerations as an introduction without ongoing ingestion may be counterproductive. Consideration of priority allergens to encourage an early introduction may need to be tailored to the families' individual needs and preferences. Additionally, while EAT and LEAP found little impact on breastfeeding rates, growth, and micronutrient intakes,[43–45] there is a lack of data characterizing the nutritional intake of infants on "early introduction" regimens, and comparative efficacy data are not available.[46] There is a risk if we extrapolate out the doses and frequency of ingestion of allergens seen in these studies to all other common allergens, particularly each individual tree nut the diet can become very calorie dense risking displacement of meats, grains, fruits, and vegetables and negatively impacting diet diversity.

Diet diversity is a measure of the number of different foods or food groups eaten over a period of time, and there has been recent considerable interest in the effect of infant diet diversity in preventing allergic diseases. To date, several observational studies have shown increased diet diversity in the first year of life to be associated with reduced food allergy outcomes,[47–49] and diet diversity

is supported as an important factor in dietary allergen prevention strategies in an EAACI task force report[49] and the consensus statement from the US/Canada.[9]

A recent Australian study has reported the low allergen content of commercial infant foods with only 1% of 257 products tested containing egg and none containing peanut, highlighting the potential for limited exposure to allergens to prevent allergy if the diet is heavily reliant on commercial infant food products.[50] Commercial early allergen introduction products containing single or multiple allergenic proteins in a powdered or puff form have become available in some countries. These products offer measured doses of allergen in a form that is developmentally appropriate for an infant's diet. The market for such products has emerged in an environment where barriers to the early and ongoing ingestion of common allergens into an infant's diet have been identified.[37,51]

Commercial early allergen introduction foods have been shown to be a potentially convenient, well-accepted way to incorporate common allergens into the diet[52]; however, the efficacy of these products for food allergy prevention has yet to be demonstrated. When compared to the whole food form of the allergen, they are costly and do not provide the equivalent broad range of nutrients.[51] There are currently no standards for the formulation or composition of early allergen introduction products, and a recent study of 32 products reported significant variability in allergen composition, concentration, and dose with some products having no detectable allergen.[53] This may explain the observation found in a case series of 12 infants from Mt Sinai who had tolerated a commercial early allergen product but experienced allergic reactions once ingestion of the whole food occurred.[54] More research is required regarding the efficacy of such products for food allergy prevention, particularly in high-risk infants.

6 | ALTERNATIVE FOOD ALLERGY PREVENTION STRATEGIES AND IN-PROGRESS PRAGMATIC TRIALS

To date, the early introduction of allergenic solids, specifically peanut and egg, is the only evidence-based strategy proven to reduce food allergy.[1–3] Unfortunately, the enviable rates of Australian early peanut introduction (89% in the first year of life with a median age of introduction of 6 months) following changes to the infant feeding guidelines in 2016, did not translate into LEAP RCT-level-efficacy outcomes at the population level. While a 16% reduction in peanut allergy prevalence is a start, it is clear that this strategy is not the panacea for the prevention of food allergy in all infants.

However, the field of food allergy prevention is at an exciting stage with additional trials on infant diet interventions and the role of maternal diets during pregnancy and breastfeeding underway. In the pipeline are other approaches targeting a diverse range of interventions in addition to dietary interventions including the expansion of previous studies exploring eczema prevention through maintaining skin barrier integrity,[55–57] vitamin D supplementation, and the role of immunizations that prime the immune response away from a Th2-driven allergic phenotype may play.

Expanding on the findings of the EAT trial, two additional multiallergen introduction trials are underway. The TEFFA trial (**T**olerance induction through **E**arly **F**eeding to prevent **F**ood **A**llergy) is a randomized controlled trial in infants with eczema 4–8 months of age assessing the efficacy of introduction of egg, cows milk, peanut, and hazelnut via a rusk-like feeding powder on food allergy development in the first year of life.[58] The **S**tart **E**ating **E**arly **D**iet (SEED) study, a randomized, controlled trial in an unselected population in the US, will assess the role of multiple common allergens (milk, egg, peanut, cashew, walnut, sesame, soy, and almond) ingested in the first year of life on food allergy outcomes by 2 years of age.[59] However, the earlier window of maternal diet during pregnancy and breastfeeding may benefit those infants who develop food allergy too early for timely infant dietary introduction to be effective.[34,60] The Australian PrEggNut multicenter RCT, is testing a high peanut and egg diet compared with a standard diet from 23 weeks gestation until the breastfed infant is 4 months of age with peanut and egg allergy outcomes measured at 12 months of age.[61]

The Pebbles study is a large population-based multicenter RCT underway in Australia testing whether the application of a ceramide dominant emollient cream as a skin barrier strategy to high-risk infants from birth versus standard skin care is effective in preventing eczema, food sensitization, and challenge-confirmed food allergy at 12 months of age.[62] The Stopping Eczema and Allergy Study (SEAL) is a multicenter RCT with sites in the US and the UK targeting infants with early-onset eczema (<12 weeks of age). It compares two methods of proactive sequential skin care, 1. Twice daily tri-lipid skin barrier cream (Epiderm) or 2. Twice daily moisturizer, versus reactive standard of care with topical products to assess the occurrence and severity of eczema in early infancy and challenge-confirmed food allergy development at 1 and 3 years of age.[63] The role of vitamin D in food allergy prevention is currently contradictory,[64] and there is a need for well-designed RCTs.[65] The Vitality RCT is testing whether daily vitamin D supplementation from 3 months of age versus placebo is effective for preventing challenge-confirmed food allergy at 12 months.[66]

Furthermore, early Th1-stimulating infant vaccines (BCG vaccine versus placebo in MIS-BAIR RCT,[67] and whole-cell pertussis vaccine versus routine acellular pertussis vaccine in optimum RCT)[68] are testing the hypothesis that they will act to prime the immune response away from a Th2-driven allergic phenotype. If successful, these approaches may offer a suite of relatively simple population-level recommendations or specific strategies targeted at populations with an increased risk of food allergy.

7 | CONCLUSION

Despite exciting advances in the last several decades, there is still substantial work to be done to prevent the development of food allergy. While the timely introduction of allergenic foods into the infant's diet

is the only strategy with high-level evidence, many questions remain regarding the optimal timing, dose, and frequency of allergen ingestion to promote and maintain food tolerance. Although community uptake of parts of the infant feeding guidelines for allergy prevention has been promising in areas such as Australia, the uptake in other regions where food allergy prevalence is high as unknown, and some infants/families will need greater support with ongoing consumption. Investigating barriers to uptake is also essential to inform health promotion strategies. Evidence from Australia also highlights that while the early introduction of peanut is possible, it may not be sufficient to prevent all peanut allergy, particularly in infants who develop food allergy prior to when they are developmentally ready to commence solids. Several RCTs are underway investigating other preventative strategies. Further research is also needed to understand the role of the host–environment interface (eg microbial environment) and respiratory and gastrointestinal epithelium in the development of tolerance to foods.

AUTHOR CONTRIBUTIONS

JJK involved in conceptualization; VM, RLP, CV, MG, and KP involved in writing—original draft preparation; all authors involved in writing—review and editing.

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CONFLICT OF INTEREST

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