

**Early Introduction of Allergenic Foods for the Prevention of Food Allergy from an Asian Perspective
– An APAPARI Consensus Statement**

Tham EH^{1,2}, Shek LP^{1,2}, Van Bever HP^{1,2}, Vichyanond P³, Ebisawa M⁴, Wong GWK⁵, Lee BW¹ - On behalf of the Asia Pacific Association of Pediatric Allergy, Respiratory & Immunology (APAPARI)

¹Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

²Khoo Teck Puat-National University Children's Medical Institute, National University Hospital, National University Health System, Singapore

³Division of Allergy and Immunology, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

⁴Department of Allergy, Clinical Research Center for Allergy & Rheumatology, Sagami National Hospital, Sagami, Kanagawa, Japan.

⁵Department of Pediatrics, Prince of Wales Hospital, Chinese University of Hong Kong, Sha Tin, Hong Kong, China.

Running Title : Allergenic Food Introduction in Asia

Corresponding Author : Professor Lee Bee Wah

Email Address : paeleebw@nus.edu.sg

Address : Department of Paediatrics, 1E Kent Ridge Road, NUHS Tower Block, Level 12, Singapore 119228

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pai.12820

This article is protected by copyright. All rights reserved.

Abstract page

Authors:

Tham EH, Shek LP, Van Bever HP, Vichyanond P, Ebisawa M, Wong GWK, Lee BW On behalf of the Asia Pacific Association of Pediatric Allergy, Respiriology & Immunology (APAPARI)

Title: Early Introduction of Allergenic Foods for the Prevention of Food Allergy from an Asian perspective – An APAPARI Consensus Statement

Journal: Pediatr Allergy Immunol

Abstract

Emerging evidence for the early introduction of allergenic foods for the prevention of food allergies, such as peanut allergy in Western populations, has led to the recent publication of guidelines in the US and Europe recommending early peanut introduction for high-risk infants with severe eczema or egg allergy. Peanut allergy is, however, much less prevalent in Asia compared to the West. Varying patterns of food allergy are seen even within Asian countries - such as a predominance of wheat allergy in Japan and Thailand and shellfish allergy in Singapore and the Philippines. Customs and traditions, such as diet and infant feeding practices, also differ between Asian populations. Hence, there are unique challenges in adapting guidelines on early allergenic food introduction to the Asian setting. In this paper, we review the evidence and discuss the possible approaches to guide the timely introduction of allergenic food in high-risk infants in Asia.

Key Words : Allergenic Food Introduction, Asia, Egg, Food Allergy, Food Allergy Prevention, Peanut, Shellfish

Author for offprints to be sent to: Professor Lee Bee Wah

Address : Department of Paediatrics, 1E Kent Ridge Road, NUHS Tower Block, Level 12, Singapore 119228

This article is protected by copyright. All rights reserved.

The Evolution of Guidelines on Infant Weaning

The last 40 years have seen dramatic changes in the timing of complementary food introduction to infants. In the 1960s, almost 80% of infants in the USA had been exposed to cereal by 1 month of age ¹. By the 1970s, new guidelines recommended delaying introduction of weaning foods to “4 to 6 months onwards” to increase breastfeeding rates to protect infants against malnutrition and infectious diseases ^{2, 3}. In 2000, the World Health Organization (WHO) recommended that complementary foods be introduced no earlier than 6 months of age ⁴. The American Academy of Pediatrics (AAP) further recommended maternal restriction of cow's milk, egg, fish, peanuts and tree nuts during lactation and that solid foods should not be introduced into the diet of high-risk infants until 6 months of age, with dairy products delayed until 1 year, eggs until 2 years, and peanuts, nuts, and fish until 3 years of age ⁵. However these measures not only failed to stem the rising tide of food allergies; in contrast, the prevalence of food allergies have continued to rise exponentially in many Western countries over the last two decades ⁶.

In 2008, based on the lack of evidence that delaying introduction of solids and allergenic foods had any significant protective effects on the development of atopic diseases ⁷⁻⁹, the AAP & the National Institute of Allergy and Infectious Diseases (NIAID) replaced previous guidelines with new recommendations that solid foods should not be delayed beyond 4-6 months of age ^{10, 11}.

Food allergy guidelines in Asia have been less cohesive, as summarized in Table 1¹²⁻¹⁷. Most countries recommended exclusive breastfeeding in the first 6 months of life. However recommendations on the timing of introduction of complementary foods and delaying solid introduction were not standardized.

The dual-allergen exposure hypothesis

The dual-allergen exposure hypothesis suggests that allergic sensitization to food and environmental allergens first occurs in early life in high risk infants who have a disrupted skin barrier, such as in atopic dermatitis and Filaggrin (FLG) loss-of-function mutations, while early oral exposure to food allergens promotes tolerance ¹⁸.

Evidence for food sensitization through a disrupted skin barrier

Early murine studies showed that mice with abraded skin who were exposed to ovalbumin or peanut developed strong systemic specific IgE and Th2 cytokine responses¹⁹. Another study demonstrated that topical allergen application in mice with Filaggrin loss-of-function mutations resulted in enhanced allergen priming and allergen-specific antibody responses²⁰. These studies suggested that cutaneous allergen penetration and the development of systemic Type 2 inflammation was initiated through a dysfunctional skin barrier.

In humans, observational studies also appear to support the same hypothesis. The use of peanut-oil based emollients on the inflamed skin of infants with eczema was associated with an increased risk of peanut allergy at 5 years of age²¹. Furthermore, Boussault et al. found that 32% of children with atopic dermatitis who used oat-based creams had positive patch tests to oat, compared to none in non-oat cream users²². An outbreak of wheat allergy also occurred in Japan in users of a hydrolyzed wheat protein-containing facial soap²³.

Chan et al. found that a trend towards Th2 skewing in skin-homing CLA⁺ cells of peanut allergic subjects, suggesting that allergic sensitization occurs through the skin; whereas Th1 skewing in gastrointestinal (GI) -homing $\alpha 4\beta 7^{+}$ cells of peanut-tolerant subjects suggested that allergen exposure through the GI tract promotes tolerance²⁴. A population based study in Australia showed that infants with eczema were 6 times more likely to develop egg allergy and 11 times more likely to develop peanut allergy by age 12 months, than infants without eczema²⁵.

While there is good evidence that atopic dermatitis is a strong risk factor for food allergy, there are however currently no high-quality intervention trials demonstrating that food sensitization and food allergy can be prevented through preventing sensitization through the skin.

Early introduction of allergenic food for oral tolerance induction

A number of studies have now examined the role of timing of introduction of allergenic foods for food allergy prevention. The Learning Early About Peanut Allergy (LEAP) trial enrolled 640 high risk infants (severe eczema and/or egg allergy) in the United Kingdom between the ages of 4 and 10 months who had peanut skin prick test (SPT) responses of ≤ 4 mm and randomized them to either consume 6 grams of peanut protein at least 3 times a week or to completely avoid peanut products for the first 5 years of life. In the intention-to-treat analysis, 17.2% of children in the peanut avoidance group developed challenge-positive peanut allergy by age 5 years, compared to only 3.2%

in the peanut consumption group. The risks associated with early peanut introduction were low, with only 7 of the 319 children in the consumption group reacting to peanut at the baseline food challenge²⁶.

In the wake of the LEAP study²⁶, a joint consensus communication was released by several Allergy associations, including the American Academy of Allergy, Asthma & Immunology (AAAAI), American Academy of Pediatrics (AAP), Australasian Society of Clinical Immunology and Allergy (ASCIA), European Academy of Allergy and Clinical Immunology (EAACI) and the World Health Organization (WHO), which contained interim guidelines which recommended “introducing peanut-containing products into the diets of “high-risk” infants early on in life (between 4 and 11 months of age) in countries where peanut allergy is prevalent because delaying the introduction of peanut can be associated with an increased risk of peanut allergy”²⁷. US addendum guidelines released in January 2017 further provided three risk-stratified recommendations for peanut introduction²⁸:

- 1) Infants with severe eczema, egg allergy or both – to strongly consider evaluation by sIgE measurement and/or SPT and, if necessary, an OFC. Based on test results, introduce peanut-containing foods.
- 2) Infants with mild to moderate eczema – to introduce peanut-containing foods around 6 months of age
- 3) Infants without eczema or food allergy – to introduce peanut-containing foods in an age-appropriate manner and in accordance with family preferences and cultural practices

Since then, several other trials on the early introduction of allergenic foods have been published (Table 2)^{26, 29-33}. The earlier trials did not show convincing evidence that the early introduction of egg or other allergenic foods, apart from peanut, was able to reduce the risk of food allergy in normal or high risk infants. Tan et al. observed a significant reduction in egg sensitization at 1 year of age in infants in the early egg introduction group but this did not translate to a reduced risk of symptomatic allergy³³. A recent systematic review and meta-analysis on all the intervention trials indicated that there was “moderate-certainty evidence that introduction of egg to the infant diet at age 4-6 months was associated with reduced egg allergy and introduction of peanut at age 4 to 10 months was associated with reduced peanut allergy compared with later introduction of these foods”³⁴. However, the authors cautioned that imprecise effect estimates, indirectness and inconclusive trial sequential analyses from these trials limit the generalizability of these findings to general clinical practice at this moment.

Asian epidemiology on food allergy and timing of introduction of complementary foods

Asia is the largest and most populous region on earth and is home to more than 4.4 billion people comprising a rich diversity of cultures, traditions and lifestyles. Varying dietary practices and environmental influences in turn impact upon food allergy patterns in this region.

The epidemiology of food allergy in Asia appears to follow a latitude-dependent gradient. The highest prevalence of food allergy was reported in northern Asian countries such as Japan (5-10%) and Korea (5.3%). Countries further south such as Hong Kong, China, Philippines and Singapore, however, reported rates of less than 5% (Table 3)³⁵⁻⁴⁷. Postulated reasons for these observed inter-regional differences include meteorological factors such as lower solar radiation exposure, temperature and humidity in temperate climates, which may modulate Vitamin D status and the risk of eczema development – possible risk factors for food allergy development^{48, 49}.

While milk and egg allergies are universally common worldwide including Asia in early childhood⁵⁰, other food allergens in Asia differ from that seen in western countries. Wheat now appears to be one of the most common food allergens, after egg and milk, in Thailand⁵¹ as well as in Japan⁵² but large epidemiological studies are needed to confirm this observation. Shellfish allergy is also common in late childhood and adolescence in Singapore and the Philippines (Table 1)⁴². In contrast, egg allergy prevalence is as high as 10% in Australian children below 2 years of age⁵³. Peanut allergy predominates in older children with prevalence of up to 3% in the UK, USA and Australia⁵⁴⁻⁵⁸. Apart from Japan, peanut allergy is relatively uncommon in most of Asia⁵².

Dietary differences such as cooking methods, cultural preferences, infant weaning practices and volume of allergen consumption might partially explain the differences in food allergy prevalence between East and West. Peanuts in Asian cuisine are typically boiled or fried, which induce lower allergenicity compared to roasting, which is more common in Western diets⁵⁹⁻⁶¹. In South Asia, where the majority of the population consumes a diet rich in rice, legumes, grains, vegetables and spices – unusual allergies to foods such as fenugreek, chickpea, mango, eggplant and grains have been reported⁶².

A study on infant weaning practices found that infants in Vietnam and China were introduced to solid foods earlier than Australian infants and that rice porridge and cereal were used as the infants' first foods in most Asia-Pacific countries though it is still unclear whether these differences contribute to food allergy risk ⁶³. The average shellfish consumption in Malaysian adults was around 100g/person/day ⁶⁴, which is much higher than reported in US adults (22g/person/day) ⁶⁵ although there is currently no clear evidence linking volume of shellfish allergen consumption to the development of shellfish allergy.

Interestingly, the Asian environment appears to exert a protective influence against food allergy in early life. The Australian HealthNuts study showed that rates of peanut and egg allergies were three times higher in Australian-born infants of ethnic Asian parents compared to infants of parents who were born in the UK or Europe ⁶⁶. Panjari et al also observed that children born in Australia to Asian mothers had a 3-fold higher risk of parental-reported peanut allergy (OR 2.9, 95% CI 2.17 – 3.89) compared to Australian-born white children. Birth in Asia and postnatal migration to Australia was protective against nut allergy in this cohort ⁶⁷. This suggested that first generation Australian-born children of Asian heritage might in fact have a higher risk of food allergy while living in a Western environment. As this difference was observed in one generation alone, genetic factors are unlikely to be solely responsible and environmental influences in early life, such as breastfeeding, infant weaning practices and other environmental exposures might instead play a major role.

Infant weaning practices vary considerably according to the different customs and traditions across Asia ⁶³. The majority of infants in China, Hong Kong and Japan were introduced to solids before 6 months of age, with a significant proportion exposed even before 4 months of age ⁶⁸⁻⁷². In contrast, most Singaporean and Taiwanese infants were introduced to solid foods after 4-6 months of age ⁷³⁻⁷⁷. These epidemiological studies, however, did not specifically address subgroups such as infants with eczema, which may have demonstrated clearer links between timing of allergenic food introduction and food allergies. Apart from differences in study methodologies, significant genetic or environmental heterogeneity between populations may also account for the observed disparity in infant weaning practices and rates of food allergy between countries.

There is a paucity of data in Asia on the association between timing of introduction of allergenic foods and the development of food allergy, and the few existing studies show conflicting observations. A case-control study of cow's milk allergic infants by Onizawa et al.⁷⁸ observed a lower incidence of cow's milk allergy in infants in whom cow's milk had been introduced within the first month of life. However, the Growing Up in Singapore Towards healthy Outcomes (GUSTO) study found low rates of food allergy (the highest being only 2.9% at 12 months of age) despite late introduction of egg, peanut and shellfish into infants' diets (>10 months of age), and there were no significant associations between delayed introduction of these foods and food allergies, even within the eczema subcohort⁴³.

The first randomized controlled trial in Asia on the early introduction of heated egg in high risk infants with atopic dermatitis was very recently published by Natsume et al.⁷⁹. The study design involved a 2-step protocol, beginning with 50mg of heated whole egg powder (equivalent to 0.2g whole boiled egg), mixed with squash and glucose, daily in 6-9 month old Japanese infants in the intervention group; then increasing to 250mg heated whole egg powder (equivalent to 1.1g whole boiled egg) daily from 9-12 months of age. The placebo group received an equivalent volume of squash powder and glucose only. Eczema was also aggressively controlled in both groups. Both groups were instructed to avoid eggs and egg products until the primary outcome of hen's egg allergy was assessed at 12 months of age through an open food challenge. The trial was terminated early because the interim analysis of the first 100 participants showed a significant difference in the two groups, thus only 60 participants in each group were included in the final analysis.

The authors found a significantly reduced risk of hen's egg allergy at 12 months in the intervention group (8%, 5/60) compared to the placebo group (38%, 23/61) with a risk difference of 29.4% (95% CI 15.3 – 43.4) and a number needed to treat of 3.40 (2.30 – 6.52). There were, however, significant differences between the intervention and placebo groups at baseline which may have biased the results. The mean SCORAD in the placebo group was higher than that in the intervention group [42.0 vs 27.5, $p=0.030$]. The egg white-specific IgE concentration was also higher at baseline in the placebo group compared to the intervention group [4.46 vs 0.73, $p=0.0051$], as was the total IgE [41.2 vs 16.5, $p=0.00024$].

Summary of existing evidence

Emerging evidence suggests that *delaying* the introduction of allergenic foods might increase the risk of food allergies in high-risk infants with pre-existing severe eczema who may become food sensitized early in life through environmental exposures, and in whom the induction of oral tolerance is delayed.

Current Grade 1 evidence has also shown that the early introduction of peanut in a predominantly Western high-risk infant population with pre-existing severe atopic dermatitis or egg allergy reduces the risk of peanut allergy²⁶. There is now also some evidence that the early introduction of heated egg from 6 months onwards in Japanese infants with atopic dermatitis might reduce the risk of egg allergy at 12 months of age⁷⁹. Apart from peanut and egg, there is however currently no evidence to suggest that early introduction of all other allergenic foods, such as milk, wheat, soy, shellfish and tree nuts, in high-risk infants reduces the risk of food allergy development.

There is also no evidence to suggest that early introduction of any type of allergenic foods in a general, normal-risk population is efficacious. In the intention-to-treat analysis, the Enquiring About Tolerance (EAT) study failed to demonstrate any protective effect of early introduction of 6 allergenic foods – cow's milk, egg, peanut, wheat, sesame and fish to normal risk, fully breastfed infants from the UK general population²⁹. Bellach et al. likewise did not find any significant reduction of egg sensitization or egg allergy in normal risk infants who were introduced to egg white powder from 4 months of age³².

Adaptation of the new guidelines from USA and Europe, which focus primarily on peanut allergy and early introduction of peanut to high-risk infants, in the Asian context is both challenging and confusing for clinicians and parents. Current evidence indicates that there are distinct differences in food allergy epidemiology and contrasting dietary practices between Asia and the West. Hence, it would be unclear whether these new guidelines on infant feeding practices and food allergy prevention strategies would be applicable to the Asian context. It is questionable as to whether any changes to current infant feeding practices in Asia, such as the timing of introduction of peanut, are warranted given that the prevalence of peanut allergy is very low in Asia. Furthermore, the effect of

any changes to existing infant feeding practices on the already low peanut allergy prevalence in Asia is unknown.

The question of screening for sensitization at baseline before allergenic food introduction also remains uncertain and raises further questions about feasibility for implementation into general Asian populations. The LEAP trial's findings could not be extrapolated to 9.1% of the infants who already had positive SPTs >4mm at screening and were thus excluded even before the baseline food challenge. The BEAT study, likewise, excluded 13/332 (3.9%) of infants who had egg SPT $\geq$ 2mm at screening³³ and Bellach et al also excluded 23/406 (5.7%) of screened infants with hen's egg-specific IgE levels $\geq$ 0.35kU/L from participation in the early introduction trial³².

Studies on 95% positive predictive values (PPV) for skin prick tests and specific serum IgE for predicting positive oral food challenges have also been done mostly in non-Asian populations and there is very little data available in the Asian population. Predictive values however vary substantially between studies due to differences in the study populations such as age, atopic risk as well as assay techniques.

Sampson et al described threshold values of 7 kU_A/L for egg sIgE and 15 kU_A/L for milk sIgE as 95% positive predictive values for failing oral challenges in US children aged 3 months to 14 years referred for suspected food hypersensitivity⁸⁰. However, other studies have suggested different thresholds in their respective populations:

- 1.5 kU_A/L (95% PPV for egg) in Danish children younger than 2 years and 1.3 kU_A/L in those older than 2 years, referred for suspected egg allergy⁸¹
- 11 kU_A/L (95% PPV for egg) and 26 kU_A/L (90% PPV for milk) in high-risk German children below 1 year of age⁸²
- >0.35 kU_A/L (90% PPV for egg) in Spanish children under 2 years of age with suspected egg allergy⁸³.

Within Asia, Komata et al found 95% PPVs for failing egg challenges were 13 kU_A/L, 23 kU_A/L and 30 kU_A/L in Japanese children less than 1 year, 1 year of age and above 2 years respectively. 95% PPVs for milk were 5.8 kU_A/L, 38.6 kU_A/L and 57.3 kU_A/L for the corresponding age groups⁸⁴.

Predictive thresholds for skin prick tests are also highly variable and have also mostly been performed in populations referred for suspicious symptoms of food allergy, giving rise to high pre-test probabilities and corresponding PPVs⁸⁵. Only a few studies have examined predictive thresholds

in infants with only atopic dermatitis or in a general population. Monti et al defined an egg SPT cut-off of 4mm as predictive of a positive challenge to partially cooked egg with 95% probability in 107 Italian children aged 1-19 months (median 5 months with atopic dermatitis without prior egg exposure⁸⁶). The Australian HealthNuts cohort found an SPT cut-off of 4mm to have 95% PPV of a positive raw egg white challenge in their population-based study⁸⁷. Pre-test probabilities in these populations were however likely to be high as the Italian cohort comprised of infants with known atopic dermatitis and the HealthNuts cohort, albeit a population-based cohort, had a very high overall prevalence of challenge-proven egg allergy (11%)⁵⁸. There are currently no studies on skin prick test predictive thresholds for challenge-proven food allergy in the Asian population and it is unlikely that thresholds from other populations can be extrapolated to the Asian population. Healthcare infrastructure, timely access to trained allergists and availability of gold standard allergy investigations also vary considerably across Asian countries.

The risks of early allergenic food introduction in the high-risk group of infants with atopic dermatitis and/or known food allergies without prior screening is significant. This is evident in many of the randomized controlled trials, where between 4.7% to 21% of infants were already allergic at 4-6 months of age and reacted to the study intervention at commencement^{30, 31, 33}. Yet intervention, if any, should be focused on this group because the risks of early cutaneous sensitization culminating in food allergy might be justified by the potential benefits of achieving early oral tolerance induction through early introduction to allergenic foods. Early allergenic food introduction should be approached with caution in these high-risk infants and supported by expert supervision. Specific and timely allergy assessments are needed to guide the timing and order of allergenic food introduction in this group of infants.

Between 10-20% of children in Asia suffer from atopic dermatitis and up to 10% of these are severe⁸⁸⁻⁹¹. The prevalence of food allergy in most Asian populations is generally low and egg is the commonest food allergen in the majority of Asian countries⁵⁰. Deviation from existing cultural dietary practices is thus recommended only in high-risk infants with severe eczema and with a focus on prevention of egg allergy. These guidelines differ from the US and European guidelines, which focus mainly on prevention of peanut allergy, as the prevalence of peanut allergy in Asia (with the exception of Japan) is low. In Asian countries, such as Japan, where egg allergy is more prevalent (approximately 3.8%), the early introduction of heated egg may be considered, alongside

appropriate allergy consultation, in infants with severe atopic dermatitis. Early peanut introduction should only be recommended in countries where the prevalence of peanut allergy is high.

Taking into consideration the current evidence and the characteristics of our populations in Asia, APAPARI proposes the following recommendations on the introduction of allergenic foods in infants for the prevention of food allergy in Asia, which are also summarized in Table 4.

1) *Healthy infants*

No changes in feeding guidelines are recommended.

Infant feeding should follow existing WHO guidelines – to introduce complementary foods at 6 months of age and breastfeeding to continue alongside complementary food introduction up to 2 years if possible⁹², according to each country's cultural practices.

2) *Infants with non-severe eczema or a family history of atopy (At risk)*

There should be no delay in the introduction of allergenic foods (including egg, cow's milk, peanut, soy, wheat and shellfish). These should be introduced in a sensible manner once weaning has successfully commenced, similar to all other foods being introduced.

3) *Infants with Severe Eczema (High risk)*

Undiagnosed food allergies may exist in this group of infants even before introduction of allergenic food. Timely recognition of allergic reactions is also challenging and the complications of severe allergic reactions are particularly significant because of their young age. Infants in most Asian countries undergo frequent compulsory well baby visits between the ages of 3-6 months for assessment of growth, development and administration of vaccinations. Infants who fit the above-mentioned high-risk criteria are typically first seen by general practitioners, paediatricians and dermatologists in the community who may then refer them on to allergy specialists for evaluation. Ease of access to allergy specialists varies between Asian countries, thus this guideline recommends separate approaches depending on each country's healthcare infrastructure.

Referral to allergy specialists is strongly recommended in countries with ready access to allergy expertise if early introduction of egg (and/or peanut in countries where the prevalence of peanut allergy is high) is desired by the family, in accordance with cultural dietary practices, for the prevention of food allergy. Families should be made aware that the current evidence only supports early egg introduction from 5-6 months of age (and early peanut introduction between 4-10 months of age, only in countries with high peanut allergy prevalence) for the prevention of the respective food allergies.

A) Countries with ready access to allergy expertise

Infants with severe eczema whose families, after appropriate counselling, are keen for early dietary interventions for prevention of egg and/or peanut allergy should undergo clinical evaluation by trained allergy specialists beginning at 4 months of age but ideally not later than 10 months of age.

Allergy evaluation should include a detailed clinical history, skin prick tests and/or specific serum IgE testing to common food allergens in the country such as egg, based on existing cultural dietary practices. Peanut should also be screened for if the prevalence of peanut allergy is high in that country and parents are keen to introduce peanut early.

Supervised oral food challenges should be performed in infants who are found to be sensitized if parents are still keen to introduce the food early. Sensitization cut-offs will be determined by each centre's existing clinical practice, as there are no validated population based predictive thresholds for sensitization in Asia. Introduction of the allergenic food into the infant's regular diet should be commenced as soon as possible after passing a food challenge.

B) Countries with limited access to allergy expertise

In areas where allergy expertise is not readily accessible and parents are keen for intervention, careful oral challenges to egg, and to peanut in countries where peanut allergy is prevalent, are recommended to be performed in the office of a doctor trained in recognition and management of allergic reactions before the introduction of allergenic food.

Regardless of parental decision regarding early introduction, the clinician should recommend that there is no necessity to delay allergenic food introduction. Parents should also be advised that

should any symptoms of allergy occur at home subsequently, introduction of the food item should be stopped and the child should be re-evaluated as soon as possible.

Concomitant aggressive control of eczema is also strongly recommended.

Conclusions

Evidence to significantly support the early introduction of allergenic foods is currently limited to only two randomized controlled trials, one of cooked egg introduction in Japan and one of peanut introduction in the United Kingdom. However evidence suggests that delaying allergenic food introduction might increase the risk of food allergy and is not necessary. Further epidemiological and prospective studies are needed to determine the factors that explain the differences in the patterns of food allergies between Asian populations and the western world.

Acknowledgements

The APAPARI Standing Committee:

Hong Kong:	Gary Wong
	Ting Fan Leung
	Alfred Tam
Indonesia:	Sjawitri P. Siregar
	Sumadiono
	Zakiudin Munasir
Japan:	Motohiro Ebisawa
	Akihiro Morikawa
Malaysia:	Jessie de Bruyne
New Zealand:	Allen Y.L Liang
People's Republic of China:	Yuzhi Chen
	Jing Zhao

Philippines:

Shen Kunling

Maria Carmela Kasala

Milagros Salvani-Bautista

Madeleine Sumpaico

Singapore:

Lee Bee Wah

Hugo van Bever

Lynette Shek Pei-Chi

Anne Goh Eng Neo

South Korea:

Hae-Ran Lee

Bok Yang Pyun

Thailand:

Pakit Vichyanond

Wasu Kamchaisatian

Suwat Benjaponpitak

Taiwan:

Huang Jing Long

Wang Jiu-Yao

References

1. Harris LE, Chan JC. Infant Feeding Practices. *Am J Dis Child*. 1969;117(4):483-92.
2. Jelliffe DB. World Trends in Infant Feeding. *Am J Clin Nutr*. 1976;29(11):1227-37.
3. Woodruff CW. The Science of Infant Nutrition and the Art of Infant Feeding. *JAMA*. 1978;240(7):657-61.
4. World H, Organization, UNICEF. Global Strategy for Infant and Young Child Feeding: World Health Organization; 2003.
5. American Academy of Pediatrics. Committee on Nutrition. Hypoallergenic Infant Formulas. *Pediatrics*. 2000;106(2 Pt 1):346-9.
6. Prescott S, Allen KJ. Food Allergy: Riding the Second Wave of the Allergy Epidemic. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology*. 2011;22(2):155-60.
7. Zeiger RS, Heller S. The Development and Prediction of Atopy in High-Risk Children: Follow-up at Age Seven Years in a Prospective Randomized Study of Combined Maternal and Infant Food Allergen Avoidance. *The Journal of allergy and clinical immunology*. 1995;95(6):1179-90.
8. Kajosaari M. Atopy Prophylaxis in High-Risk Infants. Prospective 5-Year Follow-up Study of Children with Six Months Exclusive Breastfeeding and Solid Food Elimination. *Adv Exp Med Biol*. 1991;310:453-8.
9. Zutavern A, Brockow I, Schaaf B, Bolte G, von Berg A, Diez U, et al. Timing of Solid Food Introduction in Relation to Atopic Dermatitis and Atopic Sensitization: Results from a Prospective Birth Cohort Study. *Pediatrics*. 2006;117(2):401-11.
10. Greer FR, Sicherer SH, Burks AW, American Academy of Pediatrics Committee on N, American Academy of Pediatrics Section on A, Immunology. Effects of Early Nutritional Interventions on the Development of Atopic Disease in Infants and Children: The Role of Maternal Dietary Restriction, Breastfeeding, Timing of Introduction of Complementary Foods, and Hydrolyzed Formulas. *Pediatrics*. 2008;121(1):183-91.
11. Boyce JA, Assa'a A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the Diagnosis and Management of Food Allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report. *Nutrition*. 2011;27(2):253-67.
12. Lee BW, Aw MM, Chiang WC, Daniel M, George GM, Goh EN, et al. Academy of Medicine, Singapore-Ministry of Health Clinical Practice Guidelines: Management of Food Allergy. *Singapore medical journal*. 2010;51(7):599-607.
13. Malaysian Dietary Guidelines for Children and Adolescents 2013. National Coordinating Committee on Food and Nutrition, Ministry of Health Malaysia. http://Nutrition.Moh.Gov.My/Wp-Content/Uploads/Penerbitan/Buku/Mdg_Children_Adolescent_2014.Pdf. 2013

14. Jang YA, Lee HS, Kim BH, Lee Y, Lee HJ, Moon JJ, et al. Revised Dietary Guidelines for Koreans. *Asia Pacific journal of clinical nutrition*. 2008;17 Suppl 1:55-8.
15. Tiwari S, Bharadva K, Yadav B, Malik S, Gangal P, Banapurmath CR, et al. Infant and Young Child Feeding Guidelines, 2016. *Indian pediatrics*. 2016;53(8):703-13.
16. Ebisawa M, Ito K, Fujisawa T, Committee for Japanese Pediatric Guideline for Food Allergy TJSOPA, Clinical Immunology TJSOA. Japanese Guidelines for Food Allergy 2017. *Allergology international : official journal of the Japanese Society of Allergology*. 2017;66(2):248-64.
17. Recto MST, Genuino MLG, Castor MAR, Casis-Hao RJ, Tamondong-Lachica DR, Sales MIV, et al. Dietary Primary Prevention of Allergic Diseases in Children: The Philippine Guidelines. *Asia Pacific allergy*. 2017;7(2):102-14.
18. Lack G. Update on Risk Factors for Food Allergy. *The Journal of allergy and clinical immunology*. 2012;129(5):1187-97.
19. Strid J, Hourihane J, Kimber I, Callard R, Strobel S. Disruption of the Stratum Corneum Allows Potent Epicutaneous Immunization with Protein Antigens Resulting in a Dominant Systemic Th2 Response. *European journal of immunology*. 2004;34(8):2100-9.
20. Fallon PG, Sasaki T, Sandilands A, Campbell LE, Saunders SP, Mangan NE, et al. A Homozygous Frameshift Mutation in the Mouse Flg Gene Facilitates Enhanced Percutaneous Allergen Priming. *Nature genetics*. 2009;41(5):602-8.
21. Lack G, Fox D, Northstone K, Golding J, Avon Longitudinal Study of P, Children Study T. Factors Associated with the Development of Peanut Allergy in Childhood. *N Engl J Med*. 2003;348(11):977-85.
22. Boussault P, Leaute-Labreze C, Saubusse E, Maurice-Tison S, Perromat M, Roul S, et al. Oat Sensitization in Children with Atopic Dermatitis: Prevalence, Risks and Associated Factors. *Allergy*. 2007;62(11):1251-6.
23. Yagami A, Aihara M, Ikezawa Z, Hide M, Kishikawa R, Morita E, et al. Outbreak of Immediate-Type Hydrolyzed Wheat Protein Allergy Due to a Facial Soap in Japan. *The Journal of allergy and clinical immunology*. 2017;10.1016/j.jaci.2017.03.019.
24. Chan SM, Turcanu V, Stephens AC, Fox AT, Grieve AP, Lack G. Cutaneous Lymphocyte Antigen and Alpha4beta7 T-Lymphocyte Responses Are Associated with Peanut Allergy and Tolerance in Children. *Allergy*. 2012;67(3):336-42.
25. Martin PE, Eckert JK, Koplin JJ, Lowe AJ, Gurrin LC, Dharmage SC, et al. Which Infants with Eczema Are at Risk of Food Allergy? Results from a Population-Based Cohort. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology*. 2015;45(1):255-64.
26. 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. *N Engl J Med*. 2015;372(9):803-13.

27. Fleischer DM, Sicherer S, Greenhawt M, Campbell D, Chan E, Muraro A, et al. Consensus Communication on Early Peanut Introduction and the Prevention of Peanut Allergy in High-Risk Infants. *The Journal of allergy and clinical immunology*. 2015;136(2):258-61.
28. Togias A, Cooper SF, Acebal ML, Assa'ad A, Baker JR, Jr., Beck LA, et al. Addendum Guidelines for the Prevention of Peanut Allergy in the United States: Report of the National Institute of Allergy and Infectious Diseases-Sponsored Expert Panel. *J Allergy Clin Immunol*. 2017;139(1):29-44.
29. Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, et al. Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants. *N Engl J Med*. 2016;374(18):1733-43.
30. Palmer DJ, Sullivan TR, Gold MS, Prescott SL, Makrides M. Randomized Controlled Trial of Early Regular Egg Intake to Prevent Egg Allergy. *The Journal of allergy and clinical immunology*. 2017;139(5):1600-7 e2.
31. Palmer DJ, Metcalfe J, Makrides M, Gold MS, Quinn P, West CE, et al. Early Regular Egg Exposure in Infants with Eczema: A Randomized Controlled Trial. *J Allergy Clin Immunol*. 2013;132(2):387-92.e1.
32. Bellach J, Schwarz V, Ahrens B, Trendelenburg V, Aksunger O, Kalb B, et al. Randomized Placebo-Controlled Trial of Hen's Egg Consumption for Primary Prevention in Infants. *The Journal of allergy and clinical immunology*. 2017;139(5):1591-9 e2.
33. Wei-Liang Tan J, Valerio C, Barnes EH, Turner PJ, Van Asperen PA, Kakakios AM, et al. A Randomized Trial of Egg Introduction from 4 Months of Age in Infants at Risk for Egg Allergy. *The Journal of allergy and clinical immunology*. 2017;139(5):1621-8 e8.
34. Ierodiakonou D, Garcia-Larsen V, Logan A, Groome A, Cunha S, Chivinge J, et al. Timing of Allergenic Food Introduction to the Infant Diet and Risk of Allergic or Autoimmune Disease: A Systematic Review and Meta-Analysis. *JAMA*. 2016;316(11):1181-92.
35. Chen J, Hu Y, Allen KJ, Ho MH, Li H. The Prevalence of Food Allergy in Infants in Chongqing, China. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology*. 2011;22(4):356-60.
36. Zeng GQ, Luo JY, Huang HM, Zheng PY, Luo WT, Wei NL, et al. Food Allergy and Related Risk Factors in 2540 Preschool Children: An Epidemiological Survey in Guangdong Province, Southern China. *World J Pediatr*. 2015;11(3):219-25.
37. Ho MH, Lee SL, Wong WH, Ip P, Lau YL. Prevalence of Self-Reported Food Allergy in Hong Kong Children and Teens--a Population Survey. *Asian Pacific journal of allergy and immunology*. 2012;30(4):275-84.
38. Noda R. Prevalence of Food Allergy in Nursery School (Nationwide Survey). *Jpn J Food Allergy*. 2010;10:5-9.
39. Ebisawa M. Management of Food Allergy in Japan "Food Allergy Management Guideline 2008 (Revision from 2005)" and "Guidelines for the Treatment of Allergic Diseases in Schools". *Allergology international : official journal of the Japanese Society of Allergology*. 2009;58(4):475-83.

40. Kim J, Chang E, Han Y, Ahn K, Lee SI. The Incidence and Risk Factors of Immediate Type Food Allergy During the First Year of Life in Korean Infants: A Birth Cohort Study. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology*. 2011;22(7):715-9.
41. Park M, Kim D, Ahn K, Kim J, Han Y. Prevalence of Immediate-Type Food Allergy in Early Childhood in Seoul. *Allergy Asthma Immunol Res*. 2014;6(2):131-6.
42. Shek LP, Cabrera-Morales EA, Soh SE, Gerez I, Ng PZ, Yi FC, et al. A Population-Based Questionnaire Survey on the Prevalence of Peanut, Tree Nut, and Shellfish Allergy in 2 Asian Populations. *J Allergy Clin Immunol*. 2010;126(2):324-31, 31.e1-7.
43. Tham EH, Lee BW, Chan YH, Loo EXL, Toh JY, Goh A, et al. Low Food Allergy Prevalence Despite Delayed Introduction of Allergenic Foods-Data from the Gusto Cohort. *The journal of allergy and clinical immunology In practice*. 2017;10.1016/j.jaip.2017.06.001.
44. Lee AJ, Shek LP. Food Allergy in Singapore: Opening a New Chapter. *Singapore medical journal*. 2014;55(5):244-7.
45. Wu TC, Tsai TC, Huang CF, Chang FY, Lin CC, Huang IF, et al. Prevalence of Food Allergy in Taiwan: A Questionnaire-Based Survey. *Intern Med J*. 2012;42(12):1310-5.
46. Lao-araya M, Trakultivakorn M. Prevalence of Food Allergy among Preschool Children in Northern Thailand. *Pediatrics international : official journal of the Japan Pediatric Society*. 2012;54(2):238-43.
47. Santadusit S, Atthapaisalsarudee S, Vichyanond P. Prevalence of Adverse Food Reactions and Food Allergy among Thai Children. *J Med Assoc Thai*. 2005;88 Suppl 8:S27-32.
48. Matsui T, Tanaka K, Nakagawa T, Sasaki K, Nakata J, Sugiura S, et al. Sun Exposure Inversely Related to Food Sensitization During Infancy. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology*. 2015;26(7):628-33.
49. Tanaka K, Matsui T, Sato A, Sasaki K, Nakata J, Nakagawa T, et al. The Relationship between the Season of Birth and Early-Onset Food Allergies in Children. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology*. 2015;26(7):607-13.
50. Lee AJ, Thalayasingam M, Lee BW. Food Allergy in Asia: How Does It Compare? *Asia Pacific allergy*. 2013;3(1):3-14.
51. Jirapongsananuruk O, Bunsawansong W, Piyaphanee N, Visitsunthorn N, Thongngarm T, Vichyanond P. Features of Patients with Anaphylaxis Admitted to a University Hospital. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology*. 2007;98(2):157-62.
52. Akiyama H, Imai T, Ebisawa M. Japan Food Allergen Labeling Regulation--History and Evaluation. *Advances in food and nutrition research*. 2011;62:139-71.

53. Prescott SL, Pawankar R, Allen KJ, Campbell DE, Sinn J, Fiocchi A, et al. A Global Survey of Changing Patterns of Food Allergy Burden in Children. *The World Allergy Organization journal*. 2013;6(1):21.
54. Bunyavanich S, Rifas-Shiman SL, Platts-Mills TA, Workman L, Sordillo JE, Gillman MW, et al. Peanut Allergy Prevalence among School-Age Children in a Us Cohort Not Selected for Any Disease. *J Allergy Clin Immunol*. 2014;134(3):753-5.
55. Sicherer SH, Munoz-Furlong A, Godbold JH, Sampson HA. Us Prevalence of Self-Reported Peanut, Tree Nut, and Sesame Allergy: 11-Year Follow-Up. *J Allergy Clin Immunol*. 2010;125(6):1322-6.
56. Venter C, Maslin K, Patil V, Kurukulaaratchy R, Grundy J, Glasbey G, et al. The Prevalence, Natural History and Time Trends of Peanut Allergy over the First 10 Years of Life in Two Cohorts Born in the Same Geographical Location 12 Years Apart. *Pediatr Allergy Immunol*. 2016;27(8):804-11.
57. Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, et al. Prevalence of Challenge-Proven Ige-Mediated Food Allergy Using Population-Based Sampling and Predetermined Challenge Criteria in Infants. *The Journal of allergy and clinical immunology*. 2011;127(3):668-76.e1-2.
58. Peters RL, Koplin JJ, Gurrin LC, Dharmage SC, Wake M, Ponsonby AL, et al. The Prevalence of Food Allergy and Other Allergic Diseases in Early Childhood in a Population-Based Study: Healthnuts Age 4-Year Follow-Up. *The Journal of allergy and clinical immunology*. 2017;140(1):145-53 e8.
59. Beyer K, Morrow E, Li XM, Bardina L, Bannon GA, Burks AW, et al. Effects of Cooking Methods on Peanut Allergenicity. *The Journal of allergy and clinical immunology*. 2001;107(6):1077-81.
60. Kim J, Lee JY, Han Y, Ahn K. Significance of Ara H 2 in Clinical Reactivity and Effect of Cooking Methods on Allergenicity. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology*. 2013;110(1):34-8.
61. Mondoulet L, Paty E, Drumare MF, Ah-Leung S, Scheinmann P, Willemot RM, et al. Influence of Thermal Processing on the Allergenicity of Peanut Proteins. *Journal of agricultural and food chemistry*. 2005;53(11):4547-53.
62. Arakali SR, Green TD, Dinakar C. Prevalence of Food Allergies in South Asia. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology*. 2017;118(1):16-20.
63. Inoue M, Binns CW. Introducing Solid Foods to Infants in the Asia Pacific Region. *Nutrients*. 2014;6(1):276-88.
64. Ahmad NI, Wan Mahiyuddin WR, Tengku Mohamad TR, Ling CY, Daud SF, Hussein NC, et al. Fish Consumption Pattern among Adults of Different Ethnicities in Peninsular Malaysia. *Food & nutrition research*. 2016;60:32697.

65. Jahns L, Raatz SK, Johnson LK, Kranz S, Silverstein JT, Picklo MJ. Intake of Seafood in the Us Varies by Age, Income, and Education Level but Not by Race-Ethnicity. *Nutrients*. 2014;6(12):6060-75.
66. Koplin JJ, Peters RL, Ponsonby AL, Gurrin LC, Hill D, Tang ML, et al. Increased Risk of Peanut Allergy in Infants of Asian-Born Parents Compared to Those of Australian-Born Parents. *Allergy*. 2014;69(12):1639-47.
67. Panjari M, Koplin JJ, Dharmage SC, Peters RL, Gurrin LC, Sawyer SM, et al. Nut Allergy Prevalence and Differences between Asian-Born Children and Australian-Born Children of Asian Descent: A State-Wide Survey of Children at Primary School Entry in Victoria, Australia. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology*. 2016;46(4):602-9.
68. Wang X, Wang Y, Kang C. Feeding Practices in 105 Counties of Rural China. *Child Care Health Dev*. 2005;31(4):417-23.
69. Xu F, Binns C, Lee A, Wang Y, Xu B. Introduction of Complementary Foods to Infants within the First Six Months Postpartum in Xinjiang, Pr China. *Asia Pac J Clin Nutr*. 2007;16 Suppl 1:462-6.
70. Li L, Li S, Ali M, Ushijima H. Feeding Practice of Infants and Their Correlates in Urban Areas of Beijing, China. *Pediatr Int*. 2003;45(4):400-6.
71. Hong Kong Department of Health. Family Health Service. Breastfeeding Survey, Hong Kong Sar.:. 2012.
72. Okubo H, Miyake Y, Sasaki S, Tanaka K, Hirota Y. Feeding Practices in Early Life and Later Intake of Fruit and Vegetables among Japanese Toddlers: The Osaka Maternal and Child Health Study. *Public Health Nutr*. 2016;19(4):650-7.
73. Pang WW, Aris IM, Fok D, Soh SE, Chua MC, Lim SB, et al. Determinants of Breastfeeding Practices and Success in a Multi-Ethnic Asian Population. *Birth*. 2016;43(1):68-77.
74. Toh JY, Yip G, Han WM, Fok D, Low YL, Lee YS, et al. Infant Feeding Practices in a Multi-Ethnic Asian Cohort: The Gusto Study. *Nutrients*. 2016;8(5).
75. Chuang CH, Hsieh WS, Chen YC, Chang PJ, Hurng BS, Lin SJ, et al. Infant Feeding Practices and Physician Diagnosed Atopic Dermatitis: A Prospective Cohort Study in Taiwan. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology*. 2011;22(1 Pt 1):43-9.
76. Chiu CY, Liao SL, Su KW, Tsai MH, Hua MC, Lai SH, et al. Exclusive or Partial Breastfeeding for 6 Months Is Associated with Reduced Milk Sensitization and Risk of Eczema in Early Childhood: The Patch Birth Cohort Study. *Medicine (Baltimore)*. 2016;95(15):e3391.
77. Lin JR, Tzeng MS, Kao MD, Yang YH, Pan WH. Practice to Introduce Complementary Foods to Infants in Taiwan--Changes from 1997 to 2008. *Asia Pac J Clin Nutr*. 2011;20(2):337-45.

78. Onizawa Y, Noguchi E, Okada M, Sumazaki R, Hayashi D. The Association of the Delayed Introduction of Cow's Milk with IgE-Mediated Cow's Milk Allergies. *The journal of allergy and clinical immunology In practice*. 2016;4(3):481-8 e2.
79. Natsume O, Kabashima S, Nakazato J, Yamamoto-Hanada K, Narita M, Kondo M, et al. Two-Step Egg Introduction for Prevention of Egg Allergy in High-Risk Infants with Eczema (Petit): A Randomised, Double-Blind, Placebo-Controlled Trial. *Lancet*. 2017;389(10066):276-86.
80. Sampson HA. Utility of Food-Specific IgE Concentrations in Predicting Symptomatic Food Allergy. *The Journal of allergy and clinical immunology*. 2001;107(5):891-6.
81. Osterballe M, Bindslev-Jensen C. Threshold Levels in Food Challenge and Specific IgE in Patients with Egg Allergy: Is There a Relationship? *The Journal of allergy and clinical immunology*. 2003;112(1):196-201.
82. Celik-Bilgili S, Mehl A, Verstege A, Staden U, Nocon M, Beyer K, et al. The Predictive Value of Specific Immunoglobulin E Levels in Serum for the Outcome of Oral Food Challenges. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology*. 2005;35(3):268-73.
83. Boyano Martinez T, Garcia-Ara C, Diaz-Pena JM, Munoz FM, Garcia Sanchez G, Esteban MM. Validity of Specific IgE Antibodies in Children with Egg Allergy. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology*. 2001;31(9):1464-9.
84. Komata T, Soderstrom L, Borres MP, Tachimoto H, Ebisawa M. The Predictive Relationship of Food-Specific Serum IgE Concentrations to Challenge Outcomes for Egg and Milk Varies by Patient Age. *The Journal of allergy and clinical immunology*. 2007;119(5):1272-4.
85. Peters RL, Gurrin LC, Allen KJ. The Predictive Value of Skin Prick Testing for Challenge-Proven Food Allergy: A Systematic Review. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology*. 2012;23(4):347-52.
86. Monti G, Muratore MC, Peltran A, Bonfante G, Silvestro L, Oggero R, et al. High Incidence of Adverse Reactions to Egg Challenge on First Known Exposure in Young Atopic Dermatitis Children: Predictive Value of Skin Prick Test and Radioallergosorbent Test to Egg Proteins. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology*. 2002;32(10):1515-9.
87. Peters RL, Allen KJ, Dharmage SC, Tang ML, Koplin JJ, Ponsonby AL, et al. Skin Prick Test Responses and Allergen-Specific IgE Levels as Predictors of Peanut, Egg, and Sesame Allergy in Infants. *The Journal of allergy and clinical immunology*. 2013;132(4):874-80.
88. Wananukul S, Chatproedprai S, Tempark T, Phuthongkamt W, Chatchatee P. The Natural Course of Childhood Atopic Dermatitis: A Retrospective Cohort Study. *Asian Pacific journal of allergy and immunology*. 2015;33(2):161-8.
89. Wang XS, Tan TN, Shek LP, Chng SY, Hia CP, Ong NB, et al. The Prevalence of Asthma and Allergies in Singapore; Data from Two Isaac Surveys Seven Years Apart. *Archives of disease in childhood*. 2004;89(5):423-6.

- Accepted Article
90. Wang IJ, Guo YL, Hwang KC, Hsieh WS, Chuang YL, Lin SJ, et al. Genetic and Environmental Predictors for Pediatric Atopic Dermatitis. *Acta paediatrica Taiwanica* = *Taiwan er ke yi xue hui za zhi*. 2006;47(5):238-42.
 91. Loo EX, Shek LP, Goh A, Teoh OH, Chan YH, Soh SE, et al. Atopic Dermatitis in Early Life: Evidence for at Least Three Phenotypes? Results from the Gusto Study. *International archives of allergy and immunology*. 2015;166(4):273-9.
 92. Brown KH. Who/Unicef Review on Complementary Feeding and Suggestions for Future Research: Who/Unicef Guidelines on Complementary Feeding. *Pediatrics*. 2000;106(5):1290.

Table 1. Infant feeding guidelines in Asia

Country	Year	Recommendations for exclusive breastfeeding	Recommended Age for introduction of complementary foods	Recommendations on delaying solid introduction	Reference
India	2016	First 6 months of life	After completion of 6 months	Not mentioned	[15]
Japan	2017	Not specifically mentioned	5-6 months of age	Delay not recommended	[16]
Korea	2008	Up to 6 months of age	Depending on infant development	Not mentioned	[14]
Malaysia	2013	Up to 6 months of age	6 months	Not mentioned	[13]
Philippines	2017	At least 3-6 months	Cooked egg: 4-6 months Wheat: less than 6 months Fish: 6-9 months Peanut: 4-11 months	Delay not recommended	[17]
Singapore	2010	At least 4-6 months	4-6 months	Delay not recommended	[12]

Table 2. Randomized controlled trials on early introduction of allergenic foods for food allergy prevention

Food	Year / Country	Study population	Intervention	Age of early intervention group	Age at outcome assessment	Food allergic outcomes				Ref
						Early introduction (%)	Late introduction (%)	Risk Ratio (95% CI)	P value	
Peanut	2015 United Kingdom	- Moderate to severe eczema or egg allergy - Peanut SPT ≤ 4mm	6g peanut protein per week	4-10 months	5 years	FA 10/312 (1.9%)	FA 54/313 (13.7%)	0.19 (0.10-0.36)	<0.001	Du Toit (LEAP) [26]
	2016 United Kingdom	- Normal risk infants - Exclusively breastfed	6 allergenic foods = 4g protein per week/food*	3 months	1 year & 3 years	FA 7/571 (1.2%)	FA 15/597 (2.5%)	0.49 (0.20 – 1.19)	0.11	Perkin (EAT) [29]
Egg	2017 Australia	- Infants of atopic mothers - No known allergic disease	Pasteurized raw whole egg powder (0.4g protein) daily	4-6 months	1 year	Sensitized 40/371 (10.8%)	Sensitized 57/377 (15.1%)	0.77 (0.54 – 1.10)	0.15	Palmer et al (STEP) [30]
						FA 26/371 (7%)	FA 39/377 (10.3%)	0.75 (0.48 – 1.17)	0.20	
	2013 Australia	Moderate to severe eczema	Pasteurized raw whole egg powder (0.9g protein) daily	4-6 months	8 months (cooked egg)	FA 6/40 (15%)	FA 6/35 (17%)	0.88 (0.31 – 2.47)	0.80	Palmer et al (STAR) [31]
					1 year (raw egg)	Sensitized 19/42 (45%)	Sensitized 22/35 (63%)	0.72 (0.47 – 1.09)	0.12	
						FA 14/42 (33%)	FA 18/35 (51%)	0.65 (0.38 – 1.11)	0.11	
	2017 Germany	Normal risk infants with egg specific IgE <0.35 kU_A/L	Pasteurized egg white powder (2.5g protein) 3 times a week	4-6 months	1 year	Sensitized 8/142 (5.6%)	Sensitized 4/156 (2.6%)	2.20 (0.68 – 7.14)	0.24	Bellach et al (HEAP) [32]
						FA 3/142 (2.1%)	FA 1/156 (0.6%)	3.30 (0.35 – 31.32)	0.35	
	2017 Australia	1st degree relative with history of atopy - Egg white SPT <2mm	Pasteurized whole egg powder (0.35g)	4 months	1 year	Sensitized 13/122 (10.7%)	Sensitized 25/122 (20.5%)	0.46 (0.22 – 0.95)	0.03	Tan et al (BEAT) [33]
						FA 13/124 (10.5)	FA 8/130 (6.2%)		0.20	
	2016 United Kingdom	- Normal risk infants - Exclusively breastfed	6 allergenic foods = 4g protein per week/food	3 months	1 year & 3 years	FA 21/569 (3.7%)	FA 32/596 (5.4%)	0.69 (0.40 – 1.18)	0.17	Perkin et al (EAT) [29]
	2016 Japan	Infants with atopic dermatitis	50mg heated egg powder (6-9mth) → 250mg heated egg powder (9-12 mth)	6 months	1 year	FA 5/60 (8%)	FA 23/61 (38%)	0.221 (0.090 – 0.543)	0.0001	Natsume et al (PETIT) [79]

* (cow's milk, peanut, egg, sesame, fish, wheat)

Table 3. Food Allergy in Asia

Year	Country	Age (yr)	Population (N)	Overall Food allergy prevalence (%)	Cow's milk (%)	Egg (%)	Peanut (%)	Shellfish (%)	Reference
2011	Chongqing, China	0-1	477	3.8	1.3	2.5	0.41	-	Chen [35]
2015	Guangdong, China	1-7	2540	4	1.9	1.4	0.4	7.7	Zeng [36]
2012	Hong Kong	0-14	7393	4.8	0.5	0.7	0.3-0.5	1.4	Ho [37]
2001	Japan	0-6	101, 322	5.1 ~10	1.4	3.8	0.3	0.1	Noda R [38] Ebisawa [39]
2011	Korea	0-1	1177	5.3	1.7	2.8	0.67 (nuts)	-	Kim J [40]
2014	Korea	0-6	16, 749	3.7	0.5	0.8	0.3	0.5	Park [41]
2012	Philippines	14-16	11,434	-	-	-	0.4	5.1	Shek [42]
2016	Singapore	0-3	1152	1.1 – 3.1	0.1 – 0.5	0.1-1.9	0.1-0.3	0.2-0.7	Tham [43]
2014 2010	Singapore	11-30mth 4-6 14-16	4115 ~4390 ~ 6450	~5	0.5	1.8	0.2 0.6 0.5	- 1.2 5.2	Lee AJ [44] Shek [42]
2012	Taiwan	0-3 4-18 >18	813 15, 169 14, 036	3.4 7.7 6.4	1.1 0.9 0.5	0.4 0.5 0.3	1.1 0.9 0.5	1.1 7.7 7.1	Wu [45]
2012	Thailand	3-7	452	1.1	-	-	-	0.9	Lao-araya [46]
2005	Thailand	3m-6yr	656	-	-	0.2	-	0.3	Santadusit [47]

Table 4. Recommendations for infant feeding and introduction of allergenic foods in infants in Asia

Recommendation 1 - Healthy Infants	
No changes to current feeding guidelines	
Introduce complementary foods at 6 months of age Breastfeeding to continue alongside complementary food introduction up to 2 years if possible, according to cultural practice	
Recommendation 2 – At risk infants (Healthy infants with a family history of atopy)	
No delay in introduction of allergenic foods - To be introduced in a sensible manner once weaning has commenced	
Recommendation 3 – High risk infants with Severe Eczema^Ψ	
Access to Allergy expertise readily available	Limited access to Allergy expertise
Allergy testing (skin prick tests and/or sIgE) to egg* [†] (+ peanut in countries with high peanut allergy prevalence) [‡]	
Supervised oral challenges in sensitized infants, followed by introduction of the allergenic food into the infant's regular diet if challenge-negative*	Supervised oral food challenges to egg* [†] (+ peanut in countries with high peanut allergy prevalence) [‡] - To be performed in the office of a doctor trained in recognition & management of allergic reactions
Introduction of all allergenic foods should not be delayed	
Aggressive control of eczema	

* In accordance with family and cultural dietary preferences

[†] beginning as early as 4 months but ideally not later than 10 months of age

[‡] current evidence supports only early egg introduction from 5-6 months of age (and peanut introduction from 4-10 months of age only in countries with high peanut allergy prevalence)

Ψ Severe eczema is defined as a persistent or frequently occurring rash with typical eczema morphology and distribution, assessed as severe by a health-care provider, which has required the application of topical corticosteroids or calcineurin inhibitors despite appropriate use of emollients.