



Challenges of managing food allergy in the developing world

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ABSTRACT

Food allergy (FA) is currently a significant health care problem in the developing world. Widely varying study populations and methodologies, the use of surrogate markers such as self report or hospitalization rates due to anaphylaxis rather than objective methods, limits robust estimation of FA prevalence in low income settings. Also, allergy is under-recognized as a clinical specialty in the developing world which compromises the chance for accurate diagnosis. In this review, most published data on food allergens from developing or low income countries are displayed. The diagnostic challenges and limitations of treatment options are discussed. It seems that FA is an under-appreciated health care issue in the developing world, and accurate determination of its burden in low-income settings represents an important unmet need. Multicenter surveillance studies, using standardized methodologies, are, therefore, needed to reveal the true extent of the problem and provide epidemiological clues for prevention. Preventive strategies should be tailored to fit local circumstances in different geographic regions. In addition, studying the gene environment interactions and impact of early life microbiota on the expression of FA in developing communities would be worthwhile. Efforts and resources should be directed toward public health education and training of health care providers dealing with food allergic patients.

Keywords: Food allergy, Developing countries, Low income, Allergens, Diagnosis, Treatment, Unmet needs

INTRODUCTION

The past few decades have witnessed food allergy (FA) as an emerging health care issue in developed as well as developing countries and emerging economies.¹ This might reflect a previous under-recognition or under-reporting of FA prevalence as well as the rising "westernized lifestyle" in those areas. However, data on FA from

most developing countries are quite limited.^{2,3} Notwithstanding, symptoms of FA may overlap with those of malnutrition and other childhood diseases, preventing proper diagnosis especially with the limited number of allergists in most developing nations. Looming food and agricultural issues in such fragile economic realities renders the management of FA particularly difficult: malnutrition is one of the main health burden problems, and the access to both food sources and emergency measures is limited. It is a health care priority to identify the main food allergens in the developing world through cutting-edge population-based research. Some major food items addressed and promoted in international food aid programs are frequently

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allergenic (e.g. milk, eggs, soybean, fish, wheat, peanuts); it is, therefore, a priority to face the diagnostic challenges and provide alternative sources of food for sensitized individuals residing in these underprivileged communities.

EPIDEMIOLOGY

A global increase in prevalence of asthma, allergic rhinitis, and atopic dermatitis, followed by a rapid rise in FA has been termed the "second wave of the allergy epidemic". Although we know of the global trend, the patterns of FA are highly variable in different parts of the world. These differences can be attributed partly to the many difficulties encountered in reaching an accurate estimation of prevalence. Self-report leads to an overestimating of prevalence by threefold to fourfold. Furthermore, widely varying study methodologies, the lack in the use of objective methods, and differences in baseline populations limit robust comparisons between populations. Nevertheless, studies using surrogate measures of FA including health service utilization and clinical history, together with allergen-specific immunoglobulin E, provide some evidence that the prevalence of FA is increasing in the developing world. Data on challenge-diagnosed FA in some countries (e.g. China and Africa) show rates that are similar to those in Western countries.⁴

Ethnicity per se may play a role in determining risk for FA. In Australia, FA prevalence was found to be threefold higher in infants with parents of East Asian ancestry as compared to those with parents of Caucasian ancestry. It was assumed that infants with East Asian ethnicity are at a higher risk of FA than infants with Caucasian ethnicity when exposed to a similar Westernized lifestyle. A rising prevalence of FA in Asia should, therefore, be expected with economic growth.⁵ Ethnic-dependent variability in FA is evident even within the same country. For instance, South African black (Xhosa) children had a significantly lower prevalence of peanut allergy than children of mixed-race origin (Caucasian and Black).⁶

Outside Europe, the USA, and Australia, the reported prevalence of challenge-proven FA is quite variable, and until recently it was perceived to be uncommon in developing countries. Asian studies based on oral food challenges revealed an

overall prevalence of FA in pre-school children of 1% in Thailand,⁷ but as high as 5.3% in Korean infants⁸ and 3.8% and 7.7% in one- and two-year-old Chinese children respectively.⁹ A questionnaire-based, cross-sectional study in South Korea conducted on 29,842 school children in 2015 reported that the prevalence of "perceived FA, ever" was 15.82%. The prevalence of current immediate-type FA was 4.06% in total being 3.15% in 6- to 7-year-olds, 4.51% in 9- to 10-year-olds, 4.01% in 12- to 13-year-olds, and 4.49% in 15- to 16-year-olds.¹⁰ Estimation of the prevalence of immediate-type FA at a younger age was found higher (5.3%) in a Korean birth cohort followed through telephone interviews at 4, 8, and 12 months of age.⁸

Regarding prevalence trends, few Asian studies evaluated the changes in prevalence of FA but revealed a more or less considerable increase in prevalence. As with the global trend, two investigations from China, 10 years apart, that used exactly the same methodology on 0-2 year old infants showed that the prevalence of challenge-proven IgE-mediated FA has doubled from 3.5% in 1999 to 7.7% in 2009.¹¹ Another symptom-based investigation of FA prevalence in Korean school children showed little change over a 5-year period being 10.9% in 1995, and 8.9% in 2000 for 6-12 year olds and 11.3% and 12.6% for 12-15 year olds.¹²

Allergic diseases were perceived to be rare in Africa; however, an ISAAC Phase III study reported comparable rates of wheezing between some high-income African urban centers and European countries. Also, FA has been found to be increasing especially in regions where populations are affected by the Westernized lifestyle.^{13,14} This observation is confirmed not only by studies combining FA symptoms and sIgE which are culprit of overestimation, as in a Ghanaian study reporting a prevalence of 11% of FA,¹⁵ but also in a recent cross-sectional South African study.¹⁶ The latter evaluated unselected 12-36 months old toddlers from urban Cape Town (1185 participants) and 398 from the rural Eastern Cape. Study methods comprised a questionnaire and skin prick tests (SPT) with egg, peanut, cow's milk, fish, soya, wheat, and hazelnut allergens. Participants with positive SPT and history of food intolerance underwent an open oral food

challenge (OFC). The prevalence of FA was 2.5% (95% CI, 1.6%–3.3%) in urban children. Sensitization to any food was significantly higher in urban (9.0%) than rural residents (2.8%). In the rural black African cohort 0.5% (95% CI, 0.1%–1.8%) of children had FA. This was significantly lower than that encountered in the urban cohort as a whole (2.5%) and urban black Africans (2.9%; 95% CI 1.5%–4.3%; $p = 0.006$). The results denote that the prevalence of FA in Cape Town is comparable to that in industrialized middle-income countries.

Data on FA prevalence from the Middle East are scant. A telephone survey in Lebanon revealed a self-reported prevalence of 4.1% in infants and children and 3.2% in adults.¹⁷ A situation that differs greatly is that of Turkey. In fact, the studies carried out in different cities, on different age groups and at different times all show lower rates than those of other Middle Eastern countries and also compared to European countries. A telephone survey was conducted both in the European and Asian sides of Istanbul. Subjects who disclosed food-related complaints underwent double-blind placebo-controlled food challenges (DBPCFCs). The lifetime prevalence of self-reported FA was found to be 9.5%, and after the clinical investigations the FA rate was only 0.1%.¹⁸ A cross-sectional study investigating 3500 children, 6–9 years old, from the eastern Black Sea region of Turkey revealed a parent-reported rate of 5.7%, a 33.1% sensitization rate by SPT and a 0.8% rate of DBPCFC confirmed IgE-mediated FA.¹⁹ Another cross-sectional survey evaluated 9096 students at the second stage of elementary schools in the Ankara province.²⁰ A questionnaire resulted in a rate of 11.2%, and this was reduced to 1.3% by phone contact with parents and down to 0.15% after SPT, serum specific IgE, and DBPCFC. Almost the same prevalence rate was found in a prospective evaluation of the ISAAC Phase II study population for FA.²¹ Parent-reported FA prevalence and skin prick sensitization rates were $20.2 \pm 0.9\%$ and $5.9 \pm 0.6\%$ respectively but OFC confirmed FA prevalence was only $0.16 \pm 0.11\%$, and the spectrum of food allergens differed from Western countries reflecting local food habits.

More robust studies using standardized methodologies are necessary to accurately define the

problem and its evolution in the developing world in order to adopt the right awareness and preventive strategies in the different countries.

FOOD ALLERGENS

Searching for studies on food allergens in developing and/or low income nations produced a low yield of cutting-edge research. In the next section, data from some nations from 3 main geographic locations namely Africa, Asia, and Latin America are displayed and discussed.

Food allergens in the African continent

Food allergy in Africa is not rare but rather under-diagnosed. The currently available data are insufficient to perform systematic reviews and/or meta-analyses due to inconsistent research methods and wide diversity of allergens. Most data are based on self-reported data or food allergen sensitization rather than oral challenge testing. Allergens reported in some publications from the African continent^{22–47} are displayed in Table 1. The available studies represent a limited number of countries from the vast continent, and the results, therefore, do not represent all African settings.

The reported prevalence of allergic disorders (including FA) in Africa range between 20% and 30%⁴⁸ suggesting that allergy represents a morbid condition in the continent which matches HIV/AIDS, malaria, and tuberculosis.² However, there are few allergy specialists in most African countries which reflects the health care infrastructure and/or the under-recognition of allergy as a clinical specialty. Also, some conflict situations and economic fragility that prevail in some African countries indirectly influence allergy management and health care delivery.¹⁴

Peanut allergy as an example of rising allergy prevalence

A study in 2007 reported a 5% rate of peanut sensitization in 151 South African Xhosa adolescents while none had proven peanut allergy.³⁶ A relevant study, on the same ethnic group, during the period from 2013 to 2014 revealed a rising trend as the rates of OFC confirmed peanut allergy and sensitization were 1.6% and 4.5%, respectively.⁴¹ In Egypt, peanut sensitization was

Country (Alphabet)	Allergens reported	Study Design	Reference
Congo	Any food (5%); crab (3.1%), wheat (1.2%), and soy (0.5%).	423 patients with allergic rhinitis SPT	Nyembue et al. ²²
Egypt	Peanut (7% sensitization) and 4% OFC proven cases.	100 allergic children SPT and OFC in SPT positive cases	Hossny et al. ²³
	Fish (13.8% sensitization)	87 allergic children Self report, SPT and serum specific IgE	Hossny et al. ²⁴
	Banana (7.5% sensitization although 50%)	80 allergic children SPT, PPT, and serum specific IgE	El-Sayed et al. ²⁵
	Sesame seed (2.2%)	90 allergic children SPT and serum specific IgE	Hossny et al. ²⁶
	Hen's egg white (28.8%)	80 allergic children Self report, SPT and serum specific IgE	Reda et al. ²⁷
	Ghana	Any food (5%); mostly peanut and pine apple	1431 school children SPT (5%); Serum specific IgE (35%)
Mauritius	Any food (20%); mostly sea food	General population (150 adults) Self report	Pugo-Gunsam et al. ²⁸
Morocco	Eggs (4.2%), peanuts (2.5%) and wheat flour (0.4%)	442 allergic patients Self report	Ouahidi et al. ²⁹
	Any food (45%)	160 atopic children SPT	Ghadi et al. ³⁰
	Fish (2.5%) mostly children	200 allergic patients (90% adults) Serum specific IgE	Bouhsain et al. ³¹
Mozambique	Any food (19.1%) mostly seafood (54.8%), meat (13%) and fruit/vegetables (13%)	General population (509 adults) Self report	Lunet et al. ³²

Nigeria	Seafood (14.7%), cereals/legumes (11.4%), vegetable oil (1.1%) and pork (1.6%)	General population (972 children and adults) Self report	Achinewu ³³
	Any food (2.5%) mostly eggs, crayfish, cow milk	1019 patients with atopic dermatitis Self report	Nnoruka ³⁴
South Africa	Crustaceans (50%), mollusks (30%) and a variety of fish species (20%)	80 Seafood allergic patients Serum specific IgE	Lopata and Jeebhay ³⁵
	Peanut sensitization (5%); none proven allergic	151 South African adolescents SPT and OFC	Du Toit et al. ³⁶
	Egg white (3.3%), peanut (1.9%) and milk (1.9%).	211 urban high school black children SPT	Levin et al. ³⁷
	Peanut (26%), egg (24%), fish (3%), milk (2%), cashew nut (1%)	Children with atopic dermatitis OFC	Gray and Kung ³⁸
	Food sensitization (66%) and food allergy (40%); egg (25%) and peanut (24%) Ethnic difference in peanut allergy (15% in Black Africans; 38% in others)	100 children with atopic dermatitis (59 Black Africans; 41 mixed ethnicity) SPT, serum specific IgE and OFC	Gray et al. ³⁹ Gray et al. ⁴⁰
	Challenge-proven IgE-mediated FA to any food (2.5%); sensitization (9.6%) Peanut: proven allergy 1.6%; sensitization 4.5%	544 randomly selected children from child care education facilities SPT and OFC	Basera et al. ⁴¹
	Egg white (25%)	100 children with atopic dermatitis (59 Black Africans; 41 mixed ethnicity) SPT, serum specific IgE and OFC	Gray et al. ⁴²
	Food sensitization: Egg (42.8%), cow milk (3.5%), peanut (25%)	29 children with atopic dermatitis SPT	Mahdavinia et al. ⁴³
Urban citizens: food allergy (2.5%); raw egg white (1.9%), cooked egg (0.8%), peanut (0.8%), cow's milk (0.1%), fish (0.1%). Rural citizens: food allergy (0.5%) all to egg	1185 children from urban and 398 from rural Cape Town. SPT and OFC in SPT positive cases	Botha et al. ¹⁶	

Country (Alphabet)	Allergens reported	Study Design	Reference
Tanzania	Any food (16.7%)	400 Children and adults (general population) Self report	Justin-Temu et al. ⁴⁴
Togo	Any food (4.5%)	220 outpatients with pruritus Self report	Pitche et al. ⁴⁵
Tunisia	Whole egg (38%)	5 out of 13 children with atopic dermatitis SPT	Masmoudi et al. ⁴⁶
Zimbabwe	Apple (24%), tomato (24%), soy (22%), crab (22%), peanut (20%)	40 allergic patients Serum specific IgE	Westritschnig et al. ⁴⁷

Table 1. (Continued) Some published data on food allergens from the African Continent. *PPT*: prick-prick test; *SPT*: skin prick test; *OFC*: open food challenge. The percentage in brackets refers to the positivity in the studied sample

reported in 7 out of 100 asthmatic children, and positive oral challenge was found in 3 of them.²³ The reported rate of challenge-proven peanut allergy from a group of atopic dermatitis patients from South Africa was particularly high (26%); being comparable to rates reported in relevant studies from the USA and Switzerland 10-20 years ago.¹³ It was assumed that severe allergic reactions to peanut are rare in Africans despite the high consumption rates due to some sort of natural clinical tolerance.⁴⁹ However, this may not be true as the populations may be changing, and exposure to more allergenic forms of peanuts (roasted versus boiled) is increasing.

Common food allergens

Cow milk allergy (CMA) is as important in the African continent as in many Western countries.^{37,38,43,50,51} However, it is sometimes over-diagnosed in some locations being based on self-report rather than elimination-challenge testing. Moreover, some physicians would eliminate cow's milk from the diet of infants and nursing mothers based solely on IgE sensitization to cow milk protein. Food allergic children who are put on unnecessary elimination diets are at risk of failure to thrive especially those with cow's milk allergy and other non-IgE mediated food allergies.⁵²

Some food sensitizations are particularly reported from some African countries such as potato, rice, and carrot in Zimbabwe. Other regional food allergens include pineapple, pawpaw, and oranges (Ghana), and okra (Nigeria).¹³ The gastrointestinal adverse effects to cowpea, an important source of protein in rural Nigeria, were investigated, and infants were labeled as allergic to cowpea, although they were actually never investigated to determine whether or not they were truly allergic.^{13,53} This illustrates how allergens vary widely by region and shows the importance of accurately diagnosing FA, educating families, and being able to provide an adequate source of protein substitute. Other exotic foods such as the mopane worm, consumed in some African countries including Botswana caused allergic reactions in several individuals^{54,55} Palm dates, which are very popular in the

Middle East and North Africa region, were found to be sensitizing allergens in a big sector of atopic individuals.⁵⁶

Allergy to edible insects

People in some African communities consume some insects as an alternative to other expensive protein food. Food allergy was reported from silkworm, mealworm, caterpillars, *Bruchus lentis*, sago worm, locust, grasshopper, cicada, bee, *Clanis bilineata*, and the food additive carmine, which is derived from female *Dactylopius coccus* insects. Although cockroaches are also edible insects, allergy was only reported from inhalation of its antigens. Various insect pan-allergens, Tropomyosin and arginine kinase, are insect pan-allergens that cross-react with HDM and crustaceans such as shrimps. Although purified natural insect allergens are scarce, recombinant allergens from cockroach, silkworm, and Indian mealmoth are currently available for research and investigation.^{57,58} It is not clear whether thermal processing or digestion would alter insect protein allergenicity. However, a recent study revealed that cross-reactivity and allergenicity on SPT to migratory locust (*Locusta migratoria*) can be deleted by processing steps, such as hydrolysis with different enzymes or heat, during the preparation of protein concentrates.⁵⁹

Emerging forms of food allergy in Africa

Some food allergies such as galactose-alpha-1,3-galactose allergy, food-protein induced enterocolitis and eosinophilic esophagitis (EoE) are being more frequently reported from South Africa.⁶⁰ Levin and Motala⁶¹ reported 8 children (mean age 7 years) with EoE who were mostly sensitized (SPT) to peas, wheat, milk, egg white, and banana. The children underwent patch testing and the most common allergens recorded were beef, peanut, lamb, chicken, soy, and ham.

Oral mite allergy and anaphylaxis is increasingly detected in some African nations. *Blot 5*, which is a major *Blomia tropicalis* mite allergen was detected in several raw and processed food samples collected from retail stores in the Nile Delta of Egypt including wheat, corn, rice, bean, wheat and corn flour, cake, and rusk.⁶²

The influence of residential classification and immigration

A recent cross-sectional study that involved oral food challenge compared 1185 children in urban Cape Town to 398 in the rural Eastern Cape. FA was proven in 2.5% of urban children, most commonly to raw egg white (1.9%), followed by cooked egg (0.8%), peanut (0.8%), cow's milk (0.1%), and fish (0.1%). In the rural black African children, only 0.5% had FA, all to egg.¹⁶

The risk of developing FA was found higher in children of African ancestry born in Western countries compared to children of Caucasian ancestry, and this was particularly observed among children of African ancestry in the USA.⁶³ This finding may reflect genome-environment interactions and anticipate future increase of food allergies in African countries with growing economy.⁴ On the other hand, a study from Italy explored the rates of FA among immigrant children including those from Saharan and Sub-Saharan Africa, Northern Africa, and Middle East. All children acquired Italian dietary habits, rather than those of their native countries. However, the rates of FA and cow milk protein intolerance were not higher than those of the children native to Italy.⁵⁰

Helminth infestation and allergy

Helminth infestation is common in many African countries. Deworming efforts may enhance the risk of allergy based on the theoretical assumption that some host immune responses to helminths would dampen atopic responses.¹⁴ Such controversial relationship may depend on the intensity of infestation. For instance, the intensity of Schistosome infestation was negatively correlated to SPT reactivity, mite specific IgE levels, and IgE/IgG4 ratios in an area of high transmission in Zimbabwe.⁶⁴ A recent study revealed antigenic cross reactivity between *Schistosoma mansoni* egg antigens, a common flatworm parasite in Egypt, and the peanut allergen Ara h1 and other allergic plants bearing cross-reactive carbohydrate determinants. The authors suggested that Schistosome-induced IgG antibodies that are cross-reactive with allergens such as Ara h1 may block some of its hypersensitivity reactions.⁶⁵

Allergy management and prevention concerns

Efforts to prevent allergy in low income communities within Africa should be tailored to the existing health care priorities. For instance, the preventive benefits of early introduction of solids in infants' diet should be weighed against the risk of shortening the duration of exclusive breast feeding on maternal and child health.⁶⁶ Clinical trials do suggest that early introduction of food in infants is likely to be successful, at least for peanut, but the broader effectiveness at a population level needs further validation.⁶⁷

Food allergens in Asia

The prevalence and pattern of specific food allergies are quite distinct in Asia compared to that of the Western world. Although large studies are lacking, there are sufficient data to suggest that the overall prevalence of FA, and in particular egg, peanut, and tree nut allergies in infants and schoolchildren are generally lower than in Western countries. Shellfish allergy is the only FA that is more common among the Asian populations. In addition, wheat is emerging as an important cause of FA in Thailand, Korea, Japan, and Pakistan, and it is a common cause of anaphylaxis in these countries. [Table 2](#) displays some selected data on food allergens in the Asian continent.⁶⁸⁻⁸⁵

Cow's milk and egg are two of the most common food allergens in young children across Asia. Population-based studies on FA in Singapore, Indonesia, and Malaysia demonstrated that cow's milk and egg allergies were most prevalent in infants less than 2 years of age.^{70,81} The prevalence of self-reported cow's milk and egg allergies in 1-year-old infants in Singapore was 0.4% and 1.8% respectively. The prevalence of egg allergies in Singapore appears to be significantly lower than that reported in Western populations. For example, the prevalence of challenge-proven egg allergy in 5276 1-year old Australian infants was 9.5%.^{86,87} Population-based studies from Thailand revealed that cow's milk, egg, and shrimp allergies were commonly reported in the pediatric age group.^{7,82} The situation is not different in more developed communities in Asia. In a wide-scale epidemiological survey in Japan, the most frequent food allergies in children were toward hen's egg, cow's milk, and wheat, accounting for

72.5% of all food allergies.^{88,89} The 3 major causative foods in the below 1-year-olds were hen's egg, cow's milk, and wheat, while crustaceans, wheat, fruits, and peanut allergies were seen in the older age groups.⁹⁰

Shellfish/crustacean allergy is important in most Asian populations. Similar to Japan, it is more prevalent in older children and adults in the developing nations of South-East Asia such as Singapore, Philippines, and Vietnam. The prevalence of self-reported shellfish allergy in Singapore was 1.19% in the 4-6-year olds compared to 5.23% in 14-16-year-old children.⁷⁴ In Singapore, it is also the most common food allergen in adults.⁷⁷ Mirroring the situation in Singapore, a population-based survey in the Philippines reported that shellfish allergy (5.12%) was the most common self-reported FA in 14-16 year-old school children.⁷⁴ In a population-based survey in Vietnam, shellfish allergy (2.6%) was the most common FA reported in adults, followed by beef allergy (0.8%), milk (0.2-0.7%), and egg (0.4%).⁸⁵

A survey using the random cluster-sampling method investigated children from 24 kindergartens of 12 cities in Guangdong, China. A questionnaire on FA diagnosis or symptoms in the children and their first degree relatives, that was completed by the parents or guardians, revealed a prevalence rate of 4%.⁶⁸ Major causative foods were shrimp, crab, mango, cow's milk and dairy products, and eggs. In Taiwan, the major causative foods across all age groups were seafood (67.5%), fish (6.2%), and fruits (4.3%). In the pediatric age group, the 3 most common allergens were seafood (66.4%), fish (4.9%), and fruits (3.3%), followed by egg, nuts, milk, wheat, vegetables, and meat. The 3 most common food triggers in adults were seafood (68%), fish (6.9%), and fruits (4.9%), followed by milk, meat, vegetables, egg, and nuts.⁹¹

Wheat allergy is particularly prominent in Japan, Korea, Thailand, and Pakistan.¹² It is an allergen that is important in developed communities in Asia. In Japanese school children,⁹⁰ wheat allergy is more common than shellfish and nuts, and it is the main cause of food-induced anaphylaxis in Japan and Korea.⁹² In Japan, the prevalence of wheat allergy confirmed by SPT and raised serum ω -5 gliadin-specific IgE was

Country (alphabet)	Allergens	Study Design	Reference
China	Shrimp; crab; mango; cow's milk; dairy products; egg	Population-based survey	Zeng et al. ⁶⁸
Hong Kong	Peanut; seafood; eggs; milk	Emergency Department visits for anaphylaxis	Wang et al. ⁶⁹
Indonesia (no published population data)	<5 years Cow's milk and egg >5 years Seafood, eggs, nuts	WAO global survey	Prescott et al. ⁷⁰
Korea	Overall: Peanut (0.22%); hen's egg (0.21%); cow's milk (0.18%); buckwheat (0.13%) 6-7 year olds: Hen's egg (0.25%); peanut (0.22%); cow's milk (0.16%); sesame (0.15%) 9-10 year olds: Peanut (0.34%); hen's egg (0.32%); cow's milk (0.24%); buckwheat (0.1%) 12-13 year olds: Cow's milk (0.26%); peanut (0.23%); hen's egg (0.19%); buckwheat (0.17%) 15-16 year olds: Buckwheat (0.18%); pork (0.17%); hen's egg (0.13%); peanut (0.13%) Food-induced anaphylaxis: Peanut (0.08%); cow's milk (0.07%); buckwheat (0.06%); hen's egg (0.06%)	Population-based survey	Kim et al. ¹⁰
	Milk; egg white; walnut; wheat; buckwheat	Anaphylaxis cases at 23 hospitals	Lee et al. ⁷¹
Malaysia (no published population data)	<5 years Cow's milk, egg, peanut, tree nuts, sea food >5 years Sea food, chicken, peanut, egg	WAO global survey	Prescott et al. ⁷⁰
Pakistan	Wheat; egg; corn; chicken	Adult allergic patients at two allergy centres	Inam et al. ⁷²
	Seafood; dry fruits (peanut etc), egg	Anaphylaxis cases at a tertiary hospital	Khan et al. ⁷³

Country (alphabet)	Allergens	Study Design	Reference
Philippines	14-16 years Shellfish (5.12%); peanut (0.43%); treenuts (0.3%)	Population-based (survey)	Shek et al. ⁷⁴
	14-16 years Fish (2.29%)	Population-based (survey)	Connett et al. ⁷⁵
Singapore	1. Bird's nest; seafood; egg/milk	Hospital database (anaphylaxis)	Goh D et al. ⁷⁶
	2. Shellfish; molluscs; bird's nest	Outpatient allergy referrals in adults	Thong et al. ⁷⁷
	0-2 years 1. Egg; seafood; cow's milk; peanut 2-5 years 1. Peanut; treenuts; cow's milk; seafood; egg 5-10 years 1. Seafood; peanut; treenuts; cow's milk; egg 10-16 years 1. Seafood; peanut; treenuts; egg; cow's milk	Emergency Department Visits for anaphylaxis	Ganapathy et al. ⁷⁸
	0-18 years Shellfish; peanut; milk; fish; egg >18 years 1. Shellfish; peanut; egg	Emergency Department Visits for anaphylaxis	Goh SH et al. ⁷⁹
	Peanut; egg; shellfish; bird's nest	Emergency Department Visits for anaphylaxis	Liew et al. ⁸⁰
	<2 years (GUSTO) 1. Egg (0.7-1.8%); milk (0.1-0.4%); peanut (0.2-0.3%) 3-4 years 1. Shellfish (0.6-0.9%); peanut (0.1-0.2%)	Population-based (birth cohort study)	Tham et al. ⁸¹
	4-6 years - Shellfish (1.19%); peanut (0.64%); tree nuts (0.28%) - 14-16 years - Shellfish (5.23%); peanut (0.47%); tree nuts (0.33%)	Population-based (survey)	Shek et al. ⁷⁴
	14-16 years - Fish (0.26%)	Population-based (survey)	Connett et al. ⁷⁵

Sri Lanka	0-18 years Shellfish; peanut; milk; fish; egg >18 years 2. Shellfish; peanut; egg	Emergency Department Visits for anaphylaxis	Goh SH et al. ⁷⁷
Taiwan	Peanut; egg; shellfish; bird's nest	Emergency Department Visits for anaphylaxis	Liew et al. ⁸⁰
Thailand	Challenge proven estimate: Shrimp (0.88%) Current Food Allergy (self-reported): shrimp; milk; egg Ever food allergy: milk; shrimp; egg	Population-based (survey)	Lao-Araya et al. ⁷
	<5 years (self-reported) 1. Cow's milk; Egg >5 years - Shellfish	Population-based (survey)	Santadusit et al. ⁸²
	<3 years - wheat >3 years - shellfish	Oral food challenges in an allergy clinic	Srisuwachari et al. ⁸³
	1. Seafood; wheat; egg; milk	Anaphylaxis admissions at a tertiary hospital	Manuyakorn et al. ⁸⁴
	14-16 years - Fish (0.29%)	Population-based (survey)	Connett et al. ⁷⁵
Vietnam	Seafood (2.6%); beef (0.8%); milk (0.2-0.7%); egg (0.4%); peanut (0.1-0.3%); soy (0.2-0.3%); treenuts (0.2-0.3%)	Population-based (survey) in adults	Le et al. ⁸⁵

Table 2. (Continued) Some published data on food allergens from Asia. *Figures in parentheses refer to population prevalence*

0.21% in adults.⁹³ An outbreak of IgE-mediated wheat allergy and wheat-dependent exercise-induced anaphylaxis was recently reported in previously healthy Japanese adults after exposure to hydrolyzed wheat protein in facial soap on intact facial skin,⁹⁴⁻⁹⁶ highlighting the role of epicutaneous sensitization in the pathogenesis of FA.

Wheat is also emerging as an important allergen in some developing parts of Asia. Challenge-proven wheat allergy (1.6%) followed by egg (1.3%), corn (1%), chicken (1%), rice (0.87%), and beef (0.97%) were reported in Pakistani adults.⁷² The prevalence of wheat allergy in Thailand has been on the rise recently, and wheat-induced anaphylaxis in Bangkok was reported in a few children.⁹⁷ The variation in prevalence of wheat allergy in the Asian communities may be related to cooking methods and patterns of household exposure to wheat. For instance, dry wheat flour is used more often in some Japanese and Korean dishes such as tempura.⁹⁸

A population-based survey in Korea revealed that peanut was the leading cause of immediate-type FA in children (0.22%) followed by hen's egg (0.21%), cow's milk (0.18%), and buckwheat (0.13%). The prevalence of these allergens varied with age (Table 2). Hen's egg sensitivity was most common in younger children, whereas peanut, egg, cow's milk, and buckwheat allergies were more expressed in the older age groups.¹⁰ In Japanese children, peanut and tree nut allergies were less common than egg, milk, and wheat allergies.^{90,93}

Peanut and fish allergies are relatively uncommon in South East Asia including Singapore (fish 0.26%⁷⁴ and peanut 0.1-0.6%^{74,81}) and Vietnam (peanut 0.1-0.3% and tree nut 0.2-0.3%).¹² Likewise, peanut (0.43%) and tree nut allergies (0.3%) were infrequently reported in Philippine schoolchildren,⁷⁴ but the prevalence of fish allergy was relatively higher (2.29%).⁷⁵ Peanut allergy was also rarely observed in South Asian countries such as Sri Lanka, Bangladesh, and India.^{99,100}

The relative low prevalence of peanut allergy in Asia (less than 0.5%) contrasts with the high prevalence in the Western world. For instance, peanut allergy is highly prevalent in US (3%)¹⁰¹ as well as

Australian children at 4 years (1.9%)⁸⁷ and 10-14 years (2.7%) of age.¹⁰² Peanut was also the most commonly reported allergen in Australian adults.¹⁰³ Interestingly, children of Asian ancestry living in Australia appear to be more prone to FA as compared to those of Caucasian ancestry. The HealthNuts study showed increased risk of challenge-proven peanut allergy in infants born to parents who were born in East Asia compared to those whose parents were born in the UK or Europe.¹⁰⁴ A similar observation was noted by Panjari et al. in school-age children of Asian mothers compared to Australian-born Caucasian children.¹⁰⁵

Food allergens triggering anaphylaxis in Asia

Data on the prevalence of food-induced anaphylaxis are scarce in South East Asia. A hospital based Singapore study estimated rates of all-cause anaphylaxis in children to be around 2.5 per 100,000 population per year, of which food was responsible for 63% of cases.⁸⁰ The incidence of pediatric anaphylaxis was reported to be 42.93 per 100,000 hospital admissions in Thailand.¹⁰⁶ Studies from Singapore have noted changing patterns of food allergens triggering anaphylaxis. Two decades ago, bird's nest was the most common trigger of food-induced anaphylaxis in children in Singapore.^{76,107} More recently, egg and seafood allergy were reported to be the leading triggers in Singaporean children below 2 years of age.⁷⁸ Although the prevalence of peanut allergy in Singapore is generally low, it is an important cause of food-induced anaphylaxis up to 18 years of age.⁸⁰

Shellfish is the leading cause of anaphylaxis in adolescents and adults in Singapore, Hong Kong, and Pakistan.^{69,73,78-80} It is also one of the most common triggers of food-induced anaphylaxis in Thai children and adults.^{83,84,106} Wheat allergy is the leading cause of food-dependent exercise-induced anaphylaxis (FDEIA) in Japan¹⁰⁸ and Korea⁹² and is currently replacing shellfish as a prominent trigger of FDEIA¹⁰⁹ in Thailand¹¹⁰ and Singapore.¹¹¹

Food-induced anaphylaxis was reported in 0.97% of schoolchildren in Korea. The most prevalent trigger was peanut (0.08%), followed by cow's milk (0.07%), buckwheat (0.06%), and hen's egg (0.06%) in one study. Generally, fruits

constituted 0.28% of triggers followed by crustaceans (0.18%), tree nuts (0.12%), and fish (0.09%).¹⁰ Other investigators, reported that walnut allergy was more prevalent than that of peanut as a cause of nut-induced anaphylaxis in Korean children.^{71,112,113}

Food allergen particularities in Asia

Some unique food allergies in the Asian continent arise in part from the distinctive cultural food practices of the region and environmental exposure.

Galacto-oligosaccharide (GOS) allergy

Galacto-oligosaccharides (GOS) are carbohydrates added to commercially available food products and beverages as prebiotics for the promotion of gut health. Allergic reactions were first reported in Japanese oyster shuckers who developed anaphylaxis after consumption of GOS-supplemented lactic acid beverages.¹¹⁴ This was later shown to result from cross-reactivity of GOS with the Hoya antigen derived from sea squirts present on oyster shells.¹¹⁵ Similar reactions were also reported in cow's milk-tolerant children in Vietnam and Singapore after consumption of GOS-containing milk formula.^{116,117} Chiang et al. demonstrated that these patients were sensitized to short chain (sc) GOS rather than to cow's milk or long-chain fructo-oligosaccharides.¹¹⁶ These reactions occur more commonly in atopic individuals, and GOS allergy was estimated to occur in about 3.6% of the atopic Singaporean population.¹¹⁸ The primary sensitizer for GOS allergy in South East Asia currently remains unknown, but it is postulated to be a trigger that is specific to Asia.

Bird's nest allergy

Bird's nest is a Chinese delicacy derived from the edible nests of swiftlets (*Collocalia spp.*) and is widely consumed in many parts of Asia, in particular Hong Kong, China, and Singapore, and it is acclaimed for its nutritious and medicinal properties. It has been considered the most common cause of food-induced anaphylaxis in Singaporean children in the 1990s.⁷⁶ Its putative major allergen is a 66-kDa protein.¹⁰⁷ In a more recent cross-sectional study on anaphylaxis admissions in a Singaporean tertiary pediatric hospital, it was the fifth most common trigger of food-induced

anaphylaxis after seafood, peanuts, tree nuts, and hen's egg.⁷⁸

Oral mite anaphylaxis/pancake syndrome

Oral mite anaphylaxis (OMA) is reported in Asian tropical and subtropical climates with high temperatures and humidity such as Singapore,¹¹⁹ Japan,^{120,121} and Taiwan,¹²² as well as South America.¹²³ Reactions to group 2 thermoresistant mite allergens are likely involved in these reactions.¹²⁴ An association with salicylate intolerance has also been observed,¹²⁵ although the pathophysiological mechanism behind this is still unknown.

Ant's egg anaphylaxis

Weaver ants (*Oecophylla smaragdina*) are arboreal ants found in tropical Asia and Australia. Weaver ant eggs are an expensive Thai delicacy consumed mainly in the northern and northeastern regions of Thailand. Anaphylactic reactions have been reported after ingestion of these eggs.^{7,126}

Legumes and seeds

Perilla seed (*Perilla frutescens*) is a plant traditionally grown in the Korean peninsula, Japan, and China and is a common spice used in Korean cuisine. Anaphylaxis to perilla seeds was reported in Korean subjects with strongly positive SPT to perilla extracts (10 mg/ml) and elevated serum IgE levels to perilla. Immunoblot analysis demonstrated the putative allergen to be a 21kDa protein.¹²⁷

In India, chickpea was reported to trigger IgE mediated hypersensitivity reactions ranging from rhinitis up to anaphylaxis. In a study on 1,400 randomly selected patients from allergy clinics, those reporting an allergic reaction every time after eating chickpea were subjected to a modified SPT and double-blind, placebo-controlled food challenges using chickpea and other members of the legume family. Out of the studied sample, 41 patients were SPT positive and 31 were challenge-positive to chickpea.¹²⁸ Another study showed fenugreek as a cause of FA.¹²⁹

Beef allergy

Beef allergy was the most common anaphylaxis trigger in children and adults seen in an immunology clinic in Colombo, Sri Lanka.¹⁰⁰

Sensitization to galactose- α -1,3-galactose (α -Gal) typically manifests with delayed onset allergic reactions upon exposure to all red-meats with raised α -Gal IgE and low specific IgE to beef. However, in this cohort, reactions were immediate-type, occurring within 1 hour of exposure, and no delayed-onset reactions were seen. Positive SPT and specific IgE to beef were observed in the beef-allergic subjects suggesting that α -Gal sensitization was not the underlying etiology.

Food allergens in Latin America

Data regarding FA prevalence in Latin America are scarce. There are multiple potential contributing factors to this paucity of information including poor availability and affordability of testing and lack of well-trained healthcare workers, as well as inadequate labeling of food products and cultural and language issues.^{2,3} In Table 3, some published data on FA from Latin American countries are displayed.^{124,130-140} Challenge proven publications seem to be missing and most available data rely on self-report or surrogate markers such as SPT or serum specific IgE assay. In general, the most common sensitizing foods are not different from other geographic locations, and this includes cow milk proteins, seafood, hen's egg, and peanut.^{130,132,136-140} Sensitization to vegetables and tropical fruits is commonly reported from Colombia,¹³⁵ Costa Rica,¹³⁶ and Mexico.¹³⁸ Also, beans including soya bean seem to be prevalent sensitizing allergens in South America.^{131,135,136,138}

Oral mite allergy

Oral mite anaphylaxis (OMA) has been described to occur within minutes of ingestion of dust mite contaminated flour. Most cases of OMA from Latin America have been residents in tropical locations, where higher temperatures and humidity facilitate dust mite proliferation. The foods most commonly implicated were pancakes, sponge cake, pizza, pasta, steak parmigiana, corn cake (mixed corn and wheat flour), wheat bread, Tequeños (wheat flour and cheese appetizer), Alfajor (wheat and milk sweet), and white sauce. There is no sex predominance in this syndrome, and it is more common in young adults and adolescents.¹²⁴ Sanchez-Borges et al. noted that the

diagnosis requires fulfillment of criteria including symptoms that occur after eating food containing wheat flour containing, previous history of atopy, positive *in vivo* or *in vitro* specific IgE tests to dust mites, positive skin SPT to samples of the suspected contaminated flour, and negative SPT to commercial wheat extract and uncontaminated flour as well as absence of allergic reactions on ingestion of uncontaminated wheat flour, microscopic identification of mites, and the detection of mite allergens (by immunoassay) in the suspected flour. The diagnosis may be augmented by the presence of aspirin and/or non-steroidal anti-inflammatory drug (NSAID) hypersensitivity. The authors stated that it is very important to hold preventive measures such as keeping flour in low temperatures in sealed plastic or glass containers and following environmental control measures to diminish dust mite proliferation. In addition, health care providers must be capable of diagnosing and treating the life-threatening condition of anaphylaxis.¹²³⁻¹²⁵

Data on food induced anaphylaxis in Latin America

Recognizing the scanty published data on anaphylaxis in Latin America, Sole et al.¹⁴¹ addressed this particular concern in 15 Latin American countries and Portugal. This information was gathered from the online Latin American Survey of Anaphylaxis (OLASA). The study included 634 patients who were treated for anaphylaxis stratified by age. The most predominant clinical manifestations were urticaria and angioedema (94%) followed by respiratory (79%), cardiovascular, and gastrointestinal symptoms, and most subjects (80.5%) received treatment for anaphylaxis in the emergency room. The triggering allergens varied according to age; food, specifically cow's milk, was the most predominant allergen in the first 4 years of life followed by insect stings and antibiotics. Above 8 years of age, the most common triggers were medications such as NSAIDs and antibiotics followed by food especially seafood. Food allergies always have been considered the most common triggering factor for anaphylaxis in children.^{142,143} It is of interest that only 33.7% of patients with anaphylaxis in the OLASA study received epinephrine and that 75% of physicians were unaware of the biphasic anaphylaxis.

Country (Alphabet)	Allergens reported	Study Design	Reference
Brazil	Cow milk	Preschoolers (52.8%) Infants (42.7%) Self report	Guimarães et al. ¹³⁰
	Fish (29.5% vs. 11.3%), egg (24.4% vs. 4.8%), cow milk (23.1% vs. 3.2%), wheat (20% vs. 8.1%), peanut (14% vs. 4.8%), soybean (11.8% vs. 4.8%), corn (10.6% vs. 4.8%) in patients versus control group Sensitization to milk was prevalent in children below 2 years.	457 allergic and 62 healthy children Specific IgE sensitization	Naspitz et al. ¹³¹
Chile	Cow milk	Children 8 months-15 years evaluated by SPT for 14 foods.	Martinez et al. ¹³²
	Peanuts, Walnuts	Parent reported cross sectional survey of 488 parents of school age children	Hoyos-Bachiloglu et al. ¹³³
Colombia	Fruits (14.9%), vegetables (41.8%), seafood (26.6%), meats (20.8%)	Cross-sectional study on children and adults from Cartagena Self report	Marrugo et al. ¹³⁴
	Guava, papaya, banana, passion fruit, mango, tomato, corn, yellow potato, soybean, cassava 47 (23%) children with sensitization to one food including corn (12%), banana (10%), guava (4%), yellow potato (2%), mango (1%)	160 children under 2 years from Bogota Specific IgE (Immudot)	Leal et al. ¹³⁵
Costa Rica	Sensitization in the asthmatic group: Fish (60%), mixed vegetable (58%), almond (54%), garlic (53%), yeast (51%), wheat (50%), soybean (48%), egg (48%), milk (43%), peanut (42%), corn (40%), onion (38%), orange (28%), cereal mixture (15%) In the non-asthmatic group sensitization rate was very similar to the asthmatic group, being significantly lower for wheat and eggs, but higher for peanuts (48%) and soybean (51%).	183 asthmatic and 275 healthy children from 98 schools Specific IgE for 15 food items	Soto-Quiros et al. ¹³⁶
Honduras	Milk (9.0%), egg (6.9%), peanuts (4.9%), pork (4.4%) 58.3% were poly-sensitized	365 children, 1-18 years old (average 9.8 years) SPT	Gonzales-González et al. ¹³⁷

Country (Alphabet)	Allergens reported	Study Design	Reference
Mexico	Fish (12%), cow milk (7.7%), seafood (6.5%), soybean (4.3%), beans (4.3%), orange (4.1%), onion (3.7%), tomato (3.6%), nuts (3.5%), chicken (3.5%), lettuce (2.7%), strawberry (2.0%) 442 (31%) had sensitization to one or more foods; most affected children 4–7 years old (49%); Children less than 3 years old (24%)	1,419 patients from Mexico City. SPT	Avila Castañon et al. ¹³⁸
Venezuela	Shrimp (1.3%), other shellfish (0.7%), strawberries (0.6%), chocolate (0.5%), egg (0.4%)	Children 5–13 years old from Culliacán Parent-reported questionnaire	Ontiveros et al. ¹³⁹
	Cow's milk: 45 patients of AD (80%)	56 patient with atopic dermatitis (AD) and 53 healthy children SPT to multiple food allergens	Navarro D et al. ¹⁴⁰
	Oral mites: pancakes, sponge cake, pizza, pasta, stake parmigiana, corn cake (mixed corn and wheat flour), wheat bread, Tequeños (wheat flour and cheese appetizer), Alfajor (wheat and milk sweet), and white sauce	Both in vitro and in vivo specific IgE testing performed	Sánchez-Borges et al. ¹²⁴

Table 3. (Continued) Some published data on food allergens from Latin America SPT: skin prick test

Although some patients were kept in the emergency room under observation, most of them were discharged without further prescription.¹⁴¹ Data from this study outline the urgent need to train emergency room physicians and other health care providers in Latin America and other developing communities on the proper management of anaphylaxis.

Recommended measures in Latin America

Food allergy problems in Latin America, as in many developing countries, deserve close attention. The paucity of publications on prevalent food allergens needs more elaborative research. It is imperative to develop educational programs geared toward creating awareness among the general population and medical community. In order for the entire process to be successful, there must be integrative national efforts from the scientific community, food industry, and legislative branch of government.

DIAGNOSTIC CHALLENGES IN THE DEVELOPING WORLD

Many obstacles hinder the proper diagnosis of FA in the developing world since there is evidence that knowledge about FA by parents and healthcare workers is insufficient, *in vitro* diagnostic tests are not easily accessed, and personnel capable of performing OFC are scarce.

Early diagnosis of FA is important for prognosis and proper nutritional management. However, even in developed countries, a 4-month diagnostic lag is reported especially in infants with less severe manifestations of non-IgE mediated milk allergy.¹⁴⁴ This situation is probably worse in developing countries; Aguilar-Jasso et al. found a 38-month delay in the diagnosis of FA in North Western Mexico.¹⁴⁵

Public knowledge about food allergy

The paucity and heterogeneity of reliable data on the prevalence of FA probably reflect variable diagnostic methodology and definitions of allergy. Reports from many countries are based on surrogate measures such as self-reporting and/or sensitization rather than challenge-proven FA.⁷⁰

Parent-perceived symptoms usually overestimates the real FA; and reflects, in part, the knowledge physicians deliver to their patients. It was noted that parents self-report leads to more than 8 times overestimation of FA compared to OFC.¹⁴⁶ Potential confounding elements affecting the reliability of questionnaires include local cultural factors, language barriers, knowledge, and beliefs.¹⁴⁷ Recently, Mendoza-Quispe et al. showed an overestimation of parent-perceived FA in Peru 40 times higher than FA confirmed with clinical history, FA work up, skin prick test, and OFC.¹⁴⁸

The dynamic change of the allergic response with time especially in children and the variation with races and ethnicity further complicates the interpretation of clinical manifestations of FA.¹⁴⁹ Unraveling a food allergen within a meal requires detailed knowledge on composition and manufacture of food which might not be adequate in many instances owing to the unprivileged food resources and lack of detailed food labeling.¹⁵⁰ Public education about FA, therefore, should not be ignored, and extensive mass communication campaigns of FA must also be implemented.

Skin testing issues

Certain precautions may be considered while interpreting skin-prick test results. It was assumed that racial differences in skin characteristics and histamine reactivity might influence the outcomes.¹⁵⁰ Also, standardized allergen extracts might not represent local allergens due to different food consumption patterns in different cultures. Certain countries may also have unusual foodstuff consumption like insects, causing what is called "insect food allergy". Examples include Sago worm in Malaysia, Silk worm in China, and Mopane worm in Botswana.^{55,151,152} Allergenic potential of insects by variable methods of food processing and digestion, and the cross-reactivity of insect allergens with crustaceans and HDM, make accurate diagnosis using skin testing and oral food challenge more complicated.⁵⁸ Another example of non-traditional food allergen is manioc which is a tuber consumed in some geographic

locations, mainly South America, Africa, and Asia.¹⁵³

In vitro test accessibility

Measurement of specific IgE to foods is part of a routine clinical procedure for allergy diagnosis all around the world. It represents quantitative measurement of food-specific antibody levels in patient serum. Many methods have been described; however, in Latin America and many other developing regions, RAST test without a solid phase and other semi-quantitative techniques are still being used frequently.¹⁵⁴ Also, the misinterpretation of serum specific IgE results is common in some settings; physicians may consider any detectable level as diagnostic and put their patients onto unnecessary elimination diets.

Measurement of specific IgE to individual allergenic molecules or the epitopes of those allergens is a relatively recent advance in the evaluation of FA through molecular-based diagnostics. This enables the detection of specific IgE not just against mixed whole protein extracts, but can identify sensitization to specific major allergens, pan-allergens, or minor allergens. It distinguishes genuine versus cross-reactive sensitization in polysensitized patients and, in some food allergic patients, the risk of severity can be assessed.^{155,156} It is frequent to have access to methods for specific IgE measurement to single components in most developed countries; however, this is not the case in many low-income countries.

Settings and personnel for oral food challenges

Controlled OFC is considered the gold standard for the diagnosis of FA. Any OFC implies some level of risk, and health care providers should consider the potential for facing a severe reaction before undertaking the OFC. In high risk challenges, the setting to perform the test should be appropriate with availability of materials for the treatment of a severe reaction.¹⁵⁷ The challenge team should receive adequate training and periodic practice drills.¹⁵⁸ In developing-world settings, there may be an insufficient number of specialists to perform OFCs, and they may

require training to allow them to do so safely.^{159,160}

Although DBPCFC is considered the most accurate method for diagnosing FA, an open or single-blind OFC is more commonly used in clinical practice because it is less expensive and more convenient.¹⁶¹ DBPCFC may be expensive and prohibitively time- and resource-consuming in areas with suboptimal health resources.¹⁶² Moreover, open OFC is usually considered sufficient in young children.

MANAGEMENT ISSUES WITH RESPECT TO LOCAL CIRCUMSTANCES

All over the world, the standard approach for management of FA relies on eliminating culprit food(s) from the diet.¹⁶³ However, this may be difficult and frustrating, particularly for foods common in the local diet. Another problem is the challenging burden of malnutrition in developing and emerging communities. In such poor economies, it is extremely difficult to strictly avoid the food allergen and to find a substitute with adequate nutritional value to avoid malnutrition. Furthermore, proper reading of food labelling is crucial but often difficult to achieve considering inadequate labelling legislation in some countries and high levels of illiteracy in some geographic locations. Governmental authorities and food industries should implement illustrated food allergen labelling and prevent unintentional allergen contamination of food products. Clinicians should inform patients on how to deal with their food allergies. Patients and their parents must be educated on FA in terms of natural history (which is related to the type of food allergen involved), management including prevention of accidental exposure, and rescue therapy in the event of adverse reaction.^{164,165}

Breastfeeding babies with FA usually can continue breastfeeding when their mothers avoid consuming the offending food.¹⁶⁶⁻¹⁶⁸ In many instances, the level of food allergens present in maternal milk is so low that definitively allergic babies can tolerate mothers' milk. In formula fed infants, extensively hydrolyzed cow's milk formulas can be used in mild-to-moderate cow's milk allergy.¹⁶⁹ In infants who do not improve,

amino acid-based formulas would be indicated. Other indications include inadequate growth, severe symptoms, and non-IgE mediated gastrointestinal manifestations (food-protein induced enterocolitis and enteropathies, and eosinophilic gastroenteropathies).¹⁶³ Soy formulas may be considered in patients with IgE mediated symptoms who are negative to tests for sensitization to soya, especially if they cannot tolerate taste or afford cost of extensively hydrolyzed and amino acid based formulas or regions where these formulas are unavailable.¹⁷⁰ A minority of patients allergic to cow's milk also have allergy to soy, which represents a main ingredient in several traditional recipes (e.g. Asian cuisines).¹⁷¹ Exclusive feeding on rice formula is nutritionally inadequate and should not be used unless weaning onto solid foods fulfills the nutritional adequacy. Overall, hypoallergenicity and nutritional adequacy of any cow's milk substitute should be documented before being subscribed for infant's feeding. In this regard, camel milk is under investigation.¹⁷² Guidelines can sometimes shape clinical practice globally. The World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guidelines had positive effects on the international approach toward prevention of morbidity in milk allergic infants through reducing malpractices and enhancing the efficient use of limited resources.^{173,174}

The age of introduction of solid foods seems to be important, at least for peanut, and this may explain the lower prevalence of peanut allergy in relation to early introduction of peanut in the infant's diet in some locations including tropical communities.¹⁷⁵ However, this notion has not been studied enough in the developing world. Moreover, it is imperative, in low income settings, to weigh the preventive benefits of early introduction of solid foods against the risk of a shorter duration of exclusive breast feeding on maternal and child health.^{66,67}

Although avoidance remains the main stay of management of FA, some other promising strategies are in phase 2 and 3 trials, which gives hope that a better approach will be available one day.¹⁷⁶ Several trials evaluated the role of allergen-specific immunotherapy and other modes of immunotherapy, such as anti-IgE or

anti-cytokine. Food allergy immunotherapy (FA-AIT) may increase the threshold of reactivity that is the food amount that would be taken safely without clinical reaction (the so-called desensitization), and mitigate the risk of life-threatening allergic reactions upon accidental exposure.^{177,178} However, though FA-AIT currently represents the only active measure that can modify the natural history of the disease, several gaps, including safety issues, are still unmet. Biological therapeutics (alone or combined with FA-AIT) might offer a new hope in the near future for the management of FA, mainly in patients with comorbidities and/or allergies to multiple foods.^{179,180} However, these experimental therapies are burdened by high cost, and further larger well-designed studies are awaited.

CONCLUSION AND UNMET NEEDS

The available data indicate that FA is currently a significant healthcare issue in the developing world and its real magnitude is under-appreciated. It seems that sequential lifestyle changes have impacted its expression and outcome.

The accurate determination of FA burden in low-income settings represents an important unmet need. The under-recognition of allergy as a medical specialty, and the limited healthcare infrastructure, compromise the chance for definitive diagnosis of food hypersensitivity. Multicenter surveillance studies, using standardized methodologies, are needed to reveal the true extent of the problem and provide epidemiological clues to prevention. Preventive strategies should be tailored to fit local circumstances in different geographic regions. In addition, studies tackling the gene environment interactions and the impact of early life gastrointestinal microbiota on the expression of FA would be worthwhile.

In order for physicians in the developing world to address these caveats and conduct cutting-edge research in this field, they need full support from their governments as well as scientific partnership and funding from devoted global organizations. Sufficient resources should be directed toward public health education and training of health care providers in dealing with food allergy.

Ethics approval and consent to participate

Not applicable; the manuscript does not report on or involve the use of any animal or human data or tissue.

Consent for publication

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