Introduction

Food allergy and anaphylaxis are an increasing public health burden in developed countries. Prevalence is greatest in young children, but recent evidence indicates it is also becoming more common in adolescents and young adults, and in developing nations as well. It is uncertain whether rising rates are due to an increase in the number of new cases arising (incidence) or to changes in the natural history of food allergy, with persistence of allergy that might otherwise have resolved. This clinical perspectives article provides an update on current knowledge of time trends in food allergy prevalence. We will confine our discussion to IgE mediated food allergy, for which there is the greatest evidence of increase.

Definitions: Incidence vs prevalence

Incidence of disease refers to the number of newly diagnosed cases per population over a specified time period (eg. 1 new case/100,000/year). Prevalence refers to the proportion of the population that currently has the disease (e.g. 4/100,000 population aged 0-4 years). Prevalence is determined by the balance between incidence and disease duration/resolution rates. If there is rapid recovery in all or most affected individuals, disease prevalence will closely reflect incidence and will remain stable over time. If the disease does not resolve in all cases, then there will be a gradual accumulation of non-resolved cases with age, leading to higher overall population prevalence rates.
In the absence of a cure for food allergy, prevalence will increase steadily even if incidence remains stable. If incidence also increases, then the rates of increase in prevalence will likely accelerate exponentially. Thus, based on the current natural history of disease, food allergy prevalence might only stabilize if an effective cure becomes available allowing the rate of disease resolution to equal the rate of new cases, and only reduce when a greater number of cases are cured than new cases emerge. Given that a proportion of food allergy cases will persist throughout life (eg the majority of peanut, tree nut, fish, shellfish allergies and a minority of egg and milk allergies), prevalence is unlikely to stabilize or reduce by focusing solely on prevention strategies. As health service demand is largely determined by prevalence, it will be vital to identify effective strategies for both treatment and prevention of food allergy.

Measuring the prevalence of food allergy: methodological hurdles

Accurate assessment of food allergy prevalence is plagued by a variety of difficulties including a lack of reliable, population-based data using objective methods of assessment - few studies have used the current “gold standard” of oral food challenge to identify food allergy. Most prevalence studies have utilized surrogate markers such as food allergy or anaphylaxis hospitalization rates, outpatient presentations for food allergy, or population cohorts evaluated by clinical history together with allergen-specific IgE (sIgE) and/or challenge. These data are potentially biased by variable access to medical services, cohorts not representative of the general population (e.g. specialist clinics or hospitals), diagnostic errors or differences in health seeking behavior. Patient/parent self-report of
food allergy \textsuperscript{13,14} is similarly problematic, generally \textit{overestimating} prevalence by 3-4 fold \textsuperscript{15}, because patients (or their carers) may mistake coincidence, toxic reactions, food poisoning, enzyme deficiencies (lactase or sucrase deficiency), irritant contact reactions (e.g. citrus or tomato), food aversion or so-called “food intolerance” for \textit{food allergy}.

Studies extrapolating the results of skin or blood allergy testing to detect food-specific IgE (sIgE) offer some degree of objectivity, yet the presence of sIgE (sensitization) does not always indicate clinical allergy \textsuperscript{1}. In this regard, it is important to highlight that the majority (~50%-70%) of individuals who have detectable allergen-specific IgE (sensitized) are not food allergic and are able to tolerate the food without reaction \textsuperscript{1}. Furthermore, the wide geographical ranges reported for food allergy prevalence may represent (in part) different prevalence, different food triggers in different populations, different ethnic groups in the same geographical location, differential prevalence in the same country related to latitude, rural vs city location of residence or socio-economic status, different methodologies employed to identify food allergy, and perhaps more importantly (if prevalence has changed over time), the era in which the study was conducted. Oral food challenge (double blind, single blind, or open) is the gold standard for diagnosis of food allergy, however is resource intensive and places the affected individual at potential risk of life-threatening reactions.

An international survey of food allergy prevalence highlighted the lack of quality data available \textsuperscript{16}. Of 89 members of the World Allergy Organisation (or neighboring countries) responding to the survey,
more than half (n=52) had no data on food allergy prevalence, around a quarter (n=23) had only patient/parent reported data, and only 10% (n=9) had reliable data based on the results of oral food challenges.

**Prevalence of food allergy**

Studies based on oral food challenges indicate that the prevalence of food allergy amongst preschool children is currently between 5% - 10% in some Western countries (e.g. UK, Australia) and 7% in China, with similar prevalence reported for Korea based upon a combination of clinical history and measurement of sIgE. The highest quality evidence for food allergy prevalence is provided by the Melbourne-based HealthNuts study that reported challenge proven food allergy in over 10% of 12-month-old infants (egg allergy 8.8%; peanut allergy 3%; sesame seed allergy 0.8%). The estimated prevalence of cow's milk allergy at 2.7% was based on history and positive skin prick test alone as challenges were not undertaken.

Less is known about prevalence of food allergy in older children or adults. Most studies of food allergy prevalence in adults have been surveys undertaken at a single point in time. No studies have used food challenge to examine prevalence in these age groups. The only Australian study of food allergy in adults (published 2002) estimated that 1.3% of those aged 20-45 years suffered from food allergy, most commonly to peanut (0.4%) and prawn (0.9%), based on a combination of medical history and diagnostic allergy testing, but without food challenge. More recent survey data as part of the 2014

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Australian Health Survey 19 (which likely overestimates prevalence) suggest higher rates of self-reported food allergy amongst adults (~4-5%) (Table 1). Furthermore, increased food allergy prevalence in adults is suggested by: increasing food-related anaphylaxis hospital admission rates in adults as well as children 4, structured patient surveys at different time points 14,20 and recent acceleration in childhood incidence of allergies to peanut, tree nuts and seafood which mostly persist lifelong.

Is food allergy prevalence increasing in western countries?

Change in prevalence over time can be determined by applying the same methodology to measure prevalence in the same population at sequential times. In the absence of repeated measures of challenge proven food allergy, the next most robust evidence is provided by changes in hospital anaphylaxis admission rates derived from national government databases in westernized countries (UK, USA and Australia). Despite acknowledged caveats (potential for coding errors or changing health-seeking behavior), consistent increases reported over the last two decades are difficult to ignore. For example, between 1998 and 2012 in the UK, food anaphylaxis admission rates rose from 1.2 to 2.4/10^5 population with the highest rates observed in those aged 0-4 years 5. In the USA, food anaphylaxis admissions as a proportion of all hospital admissions more than doubled in those aged 0-18 years between 2000 and 2009 7, with emergency hospital presentations (without admission) also increasing between 2006 and 2009 21. In New Zealand, food anaphylaxis admissions increased from 3.3 to 5.8/10^5 population between 2002 and 2011 in individuals aged 15 years or greater 22. By far the
highest rates of food anaphylaxis admissions are observed in Australia, with a four-fold increase from 2 to 8.2/10^5 population between 1998/99 and 2011/12^4. As in other studies, the most prominent increases were observed in very young children aged 0-4 years where admission rates increased from 7.3 to 30.2/10^5 population between 1998/99 and 2011/12, consistent with this young group driving higher incidence rates. Importantly, although time-related increases were linear in most age groups, an exponential increase in both the prevalence and the year-on-year rate of increase in prevalence were seen in older children and teenagers aged between 5 and 14 years^4. This finding may be driven by higher incidence rates of persistent food allergy in younger children resulting in a cohort effect and/or a higher risk of more serious reactions in older individuals. While there is no available published data on outpatient food allergy presentations for Australia/New Zealand at this time, an examination of outpatient food allergy presentations in the USA (emergency departments, outpatient clinics and physician offices) found a three-fold increase in food allergy-related presentations for individuals aged less than 18 years between 1993 and 2006^9, consistent with other admissions data described above.

In contrast to these studies, two reports suggest stable prevalence for peanut allergy using a combination of history and peanut sIgE (serum or skin testing) with or without double-blind placebo-controlled challenge. Ben-Shoshan and colleagues^11 estimated that the prevalence of peanut allergy in Canadian children enrolled in kindergarten to year 3 remained relatively stable between 2000-2002 (est. prevalence 1.3%: 95% CI -0.38% - 0.63%) and 2005-07 (est. prevalence 1.6%: 95% CI 1.31 –
1.98%). In a study from the Isle of Wight, Venter and colleagues \(^{12}\) reported stable peanut allergy prevalence in 3 to 4 year olds between 1993 and 2005 using a combination of history, skin prick testing and challenge in three birth cohorts. The divergent findings from these Canadian and UK studies compared to the previously discussed studies may relate to differences in methodologies used to identify food allergy. Indeed, Kotz and colleagues reported a doubling in prevalence of GP-recorded diagnosis of peanut allergy in England from 0.24 per 1000 patients (95% CI, 0.22-0.26) in 2001 to 0.51 per 1000 (95% CI, 0.49-0.54) in 2005, using a large national database (QRESEARCH) \(^{10}\). Overall, the available data would suggest there has been a real increase in food allergy prevalence, with increased health service presentations or hospital admissions over the past 2 decades, at least in the UK, US and Australasia.

**Is food allergy increasing in regions outside of the UK, US and Australia?**

Few studies have examined time trends in food allergy prevalence in other regions. One study examined prevalence of food allergy in Chinese children aged 0-24 months when presenting for a routine well-baby check to Children’s Hospital, Chongqing Medical University between 1999 and 2009 \(^{23}\). Children underwent skin testing with a panel of 10 food allergens, and those with positive tests underwent challenge. Food sensitization increased from 9.9% to 18% (p=0.002) and food allergy doubled from 3.5% to 7.7% (p=0.02) over the 10 years.

There is also preliminary evidence that ethnicity per se plays an important role in determining risk for
food allergy. In Australia, food allergy prevalence is 3-fold higher in 1 year old infants with parents of East Asian ethnicity compared to those with Caucasian parents. This suggests that infants with East Asian ethnicity have a higher risk of food allergy than Caucasian infants when exposed to a similar western environment in early life. If this is correct, food allergy prevalence in Asian countries may increase with economic growth and adoption of a westernized lifestyle. Differences in food allergy prevalence related to ethnicity have also been reported in New Zealand (higher anaphylaxis admission rates in Pacific Islanders than other ethnic groups) and in the United States (higher rates of food allergy in African American children). These findings may similarly predict increased rates of food allergy in Africa with increasing urbanization. Notwithstanding the potential influence of Asian or African ancestry to the risk of food allergy development, individuals of Asian and African birth comprise a relatively minor proportion of the current Australian and immigrant population; hence migration effects are insufficient to explain recent increases in food allergy prevalence in Australia (ref. http://www.abs.gov.au/ausstats/abs@.nsf/mf/3412.0/).

**Counting the economic cost**

Food allergy imposes a personal and public health burden, impacting on quality of life, health-related costs and service demand. In 2007 alone, estimated direct medical costs related to food allergy/anaphylaxis in the USA were $225 million, plus indirect costs of $115 million. The annual *additional cost* of caring for a child with food allergy in the USA is estimated to be $4184 (e.g. purchasing special food, direct and indirect medical costs and time off work) translating to $21.8
billion/year for the USA alone. A questionnaire-based European study estimated that total household costs were higher by €3961 for children with confirmed food allergy and €4792 for adolescents compared to controls, with higher costs associated with a diagnosis of anaphylaxis. The EuroPrevall study examined the additional cost of care in those diagnosed with self-reported food allergy in 9 European countries, estimating an additional cost of International $927 per adult per year, with higher costs in those with more severe disease.

The cost of dealing with food allergy and anaphylaxis in Australia has not been specifically examined. Some insights may be obtained from data pertaining to the number and cost of hospital admissions (The Independent Hospital Pricing Authority) and the cost of allergy-related medication (Australian Government, Department of Human Services, Pharmaceutical Benefits Scheme Item Reports) summarized in Table 2. These minimum estimates of $42 million/year do not take into account non-admission hospital treatment costs, additional patient contributions to medication (including privately purchased adrenaline auto-injectors or infant hypoallergenic formula or other direct/indirect medical costs). Furthermore in New Zealand, adrenaline auto-injectors do not receive government subsidy and thus all costs are patient funded.

**What can be done to address the rising burden of food allergy?**

For many individuals, food allergy will be a lifelong chronic burden for which there is currently no cure. The personal burden can only be addressed by development of an effective cure, while disease
incidence can only be reduced by identification of risk factors and effective prevention strategies. Population prevalence will only stabilize when the rate of disease resolution/death is equal to the incidence and can only fall when the rate of resolution of existing cases exceeds the incidence.

Prevention of food allergy: reducing childhood incidence

International allergy prevention guidelines (US, Canada, UK, Europe, Australia) recommend breastfeeding for at least 6 months and introduction of solid foods from 4 to 6 months of age preferably while still breastfeeding. The recently published LEAP, LEAP-ON and EAT studies offer level 1 evidence supporting the recommendation to introduce solids, in particular the allergenic solids such as egg and peanut, from 4-6 months and represent a major step forwards for preventing food allergy, at least in children. In Australia, the Australasian Society of Clinical Immunology and Allergy have recently updated their allergy prevention and infant feeding advice to incorporate these recent developments and recommends introduction of solid foods (including the allergenic foods) from around 6 months but not before 4 months of age (ASCIA Guidelines for Allergy Prevention and Infant Feeding; www.allergy.org.au). One other important change that was included in the updated ASCIA guidelines is removal of the recommendation to use hydrolyzed formula when mothers are unable or choose not to breastfeed; this change is based on a recent meta-analysis that concluded there is no consistent evidence to support the use of hydrolyzed formula for the prevention of allergic disease.29

Reducing prevalence: finding a cure
There is an urgent need to develop a safe, effective and feasible long-term treatment for IgE-mediated food allergies. Recent studies have focused on oral immunotherapy as a means of inducing tolerance. There are two main outcomes when evaluating potential food allergy treatments - ‘desensitization’ and ‘tolerance’. Desensitization is the ability to eat a food without reaction while continuing on regular doses of that food (eg continuing oral immunotherapy), however the underlying allergy persists. Tolerance (also known as sustained unresponsiveness) is the ability to eat a food without reaction once regular consumption ceases, and is considered to result from reprogramming of the immune response.

Individual studies and a meta-analysis of randomized trials indicate that oral immunotherapy is very effective at inducing desensitization in the majority of patients 30. The ability for OIT to induce tolerance / sustained unresponsiveness remains less certain, with rates of up to 30% reported in randomized trials. Addition of an immune modifying adjuvant may enhance tolerance induction and our recent randomized trial of probiotic and peanut OIT (PPOIT) reported sustained unresponsiveness in 82% of children with peanut allergy as compared to 4% in those treated with placebo 31. PPOIT was associated with changes in immune responses with reduced peanut sIgE and SPT as well as increased peanut sIgG4. A follow up study is underway to clarify whether PPOIT offers additional benefit over peanut OIT alone and to determine if PPOIT can induce longer lasting sustained unresponsiveness (after 3 months peanut elimination). OIT is associated with frequent adverse reactions in the majority of treated participants, with anaphylaxis in 10-15% of participants and eosinophilic esophagitis in
~3%. Use of concurrent immunomodulatory medication (eg. Omalizumab or Ketotifen) may enhance effectiveness and reduce the risk of adverse reactions. Novel methods of immunotherapy (such as application of epicutaneous food patches) are also in phase III trials and show promising results.32

Conclusion
Accurate assessment of changing food allergy prevalence is plagued by a lack of reliable, population-based estimates using objective methods of assessment. Undertaking oral food challenges in unselected populations may be the optimal method, but is resource intensive. Accepting these limitations, the best available evidence indicates that food allergy has increased in many westernized countries, and is starting to increase in developing countries in line with economic growth and urbanization. Of greatest concern is the apparent acceleration in prevalence in older children and teenagers, a group in which the risk of death due to food anaphylaxis is highest. Based on available evidence and statistical principles, we can expect a continuing global increase in food allergy prevalence. Even if we reduce incidence through effective prevention strategies, prevalence will continue to increase in the short to medium term since risk of developing food allergy is only reduced not abolished, early introduction of allergenic solids may be difficult to implement, and food allergy once it develops will persist in many cases. Identifying an effective treatment offers the greatest hope for stabilization or reduction in prevalence.

References


Table 1

**Food allergy in Australia: Australian Health Survey 2014 [18]**

<table>
<thead>
<tr>
<th>Food (%)</th>
<th>Age 2-18 years</th>
<th>Age 19-30 years</th>
<th>Age 31-50 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>2.9</td>
<td>1.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Tree nuts</td>
<td>1.6</td>
<td>0.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Fish</td>
<td>0.5</td>
<td>1.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Prawn</td>
<td>0.5</td>
<td>2.3</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Table 2: **Economic cost of food allergy/anaphylaxis in Australia**

- **Hospital anaphylaxis admissions**
  - $4.6 million; 4460 in 2012/13

- **Adrenaline autoinjectors**
  - $17.4 million; 108,653 prescriptions (government contribution)
  - $3.03 million patient contribution*
  - $4.67 million private purchase*

- **Infant hypoallergenic formulae**
  - $12.3 million: ~ 44,000 prescriptions

- **Other costs (no Australian data available)**

- **Emergency rooms costs**
Other medication and co-morbidity

GP/specialist visits

*Unpublished estimates supplied by Alphapharm, Australia July 2015
Abstract (223 words)

It is generally accepted that prevalence of food allergy has been increasing in recent decades, particularly in Westernised countries, yet high quality evidence that is based on challenge confirmed diagnosis of food allergy to support this assumption is lacking due to the high cost and potential risks associated with conducting food challenges in large populations. Accepting this caveat, the use of surrogate markers for diagnosis of food allergy (such as nationwide data on hospital admissions for food anaphylaxis or clinical history in combination with allergen-specific IgE (sIgE) measurement in population-based cohorts) has provided consistent evidence for increasing prevalence of food allergy at least in Western countries such as the UK, USA and Australia. Recent reports that children of East Asian or African ethnicity who are raised in a western environment (Australia and US, respectively) have an increased risk of developing food allergy compared with resident Caucasian children suggest that food allergy might also increase across Asian and African countries as their economies grow and populations adopt a more westernized lifestyle. Given that many cases of food allergy persist, mathematical principles would predict a continued increase in food allergy prevalence in the short to medium term until such time as an effective treatment is identified to allow the rate of disease resolution to be equal to or greater than the rate of new cases.
"Food allergy: is prevalence increasing?"

Mimi LK Tang\textsuperscript{1,2,3}, Raymond J Mullins\textsuperscript{4,5}

1. Allergy and Immune Disorders, Murdoch Childrens Research Institute, Melbourne, Australia
2. Department of Paediatrics, University of Melbourne, Australia.
3. Royal Children’s Hospital, Melbourne, Australia
4. John James Medical Centre, Deakin, ACT 2600, Australia
5. Australian National University, Canberra, ACT 0200, Australia

**Corresponding Author:**

Mimi LK Tang
Department of Allergy and Immunology
Royal Children’s Hospital Melbourne
Flemington Rd, Parkville
VIC 3052 Australia
Tel: (03) 9345 5911
Fax: (03) 9345 4848
Email: mimi.tang@rch.org.au

**Keywords**

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Abstract (217 words)

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Tang, MLK; Mullins, RJ

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