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Food Allergy (M Fernández-Rivas, Section Editor)

The Economic Burden of Food Allergy: What We Know and What We Need to Learn

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Abstract

Purpose of Review Food allergy management and treatment require dietary modification, are associated with significant burdens, and affect food choices and behaviours. Emerging therapies, such as oral immunotherapy (OIT), provide a glimmer of hope for those living with the condition. Some burdens have received substantial focus, whereas many knowledge gaps on the significance of other impacts, including economic burden, remain.

Recent Findings Evidence from many countries, but disproportionately from the United States, supports that food allergy carries significant healthcare and societal costs. Early introduction for the prevention of food allergies is theoretically cost-effective, but remains largely undescribed. Unique considerations, such as those to cow's milk protein allergy, which affects a substantial proportion of infants, and adrenaline autoinjectors, which have a high cost-per-use, require a balance between cost-effectiveness to the healthcare system and adverse outcomes. Household costs have largely been explored in two countries, but owing to different healthcare structures and costs of living, comparisons are difficult, as are generalisations to other countries. Stock epinephrine in schools may present a cost-effective strategy, particularly in economically disadvantaged areas. Costs relating to OIT must be examined within both immediate benefits, such as protection from anaphylaxis, and long-term benefits, such as sustained unresponsiveness.
Summary Although the absolute costs differ by region/country and type of food allergy, a consistent pattern persists: food allergy is a costly condition, to those who live with it, and the multiple stakeholders with which they interact.

Abbreviations

AAI	Adrenaline autoinjector (epinephrine autoinjector)
AAF	Amino acid formula
CMPA	Cow's milk protein allergy
EcoQ	Food Allergy Economic Questionnaire
EPIT	Epicutaneous peanut immunotherapy
eHF	Extensively hydrolysed formula
GP	General practitioner
ICER	Incremental cost-effectiveness ratio
LEAP	Learning Early About Peanut Allergy
LGG	*Lactobacillus rhamnosus GG*
NMB	Net monetary benefit
PAL	Precautionary allergen labeling
POIT	Peanut oral immunotherapy
PRISMA-ScR	Preferred Reporting Items for Systematic reviews and Meta-Analyses Extension for Scoping Reviews
QALY	Quality-adjusted life-year
QoL	Quality of life
UK	United Kingdom
US	United States
WTP	Willingness-to-pay

Introduction

Food allergy, defined as "a potentially life-threatening immunological response that occurs reproducibly upon ingestion of the allergen," [1] is a public health concern that directly affects 4–10% of the population [2]. The condition also affects their families, communities, and society at large. Whereas the pathogenesis and natural history of food allergy [2], and most recently, methods to induce clinical tolerance [3–8], have been extensively studied, the associated economic burden and its drivers remain only partially

understood, yet food allergy requires dietary modifications, avoidance of the allergenic foods in most forms, and constant possession of adrenaline autoinjectors (AAI). The costs associated with the management of food allergy are widely considered to be substantial, albeit highly variable by country and, occasionally, by jurisdiction.

The pivotal findings from "Learning Early About Peanut Allergy" (LEAP) [9] in the United Kingdom (UK) and HealthNuts in Australia [10] shifted primary prevention guidelines worldwide from avoidance to early introduction [11, 12]. Ongoing immunotherapy research includes an ultimate goal of achieving sustained unresponsiveness [3]. Few studies, to date, have considered the overall economic benefits and willingness-to-pay (WTP) by health systems and end users, yet many individuals with food allergy continue to bare psychological and financial consequences of the condition. Recent reviews have elegantly described the former [13–16]; however, fewer studies have focused on the econonomic consequences of the condition. Herein, we aimed to summarise the existing evidence on the economic burden of food allergy to both society and patients and identify what remains unknown. Guided by the PRISMA guidelines for Scoping Reviews [17], included articles were synthesized thematically, followed by a discussion on knowledge gaps. All costs reported herein have been converted to Euros (€; exchange rate 9 March 2022).

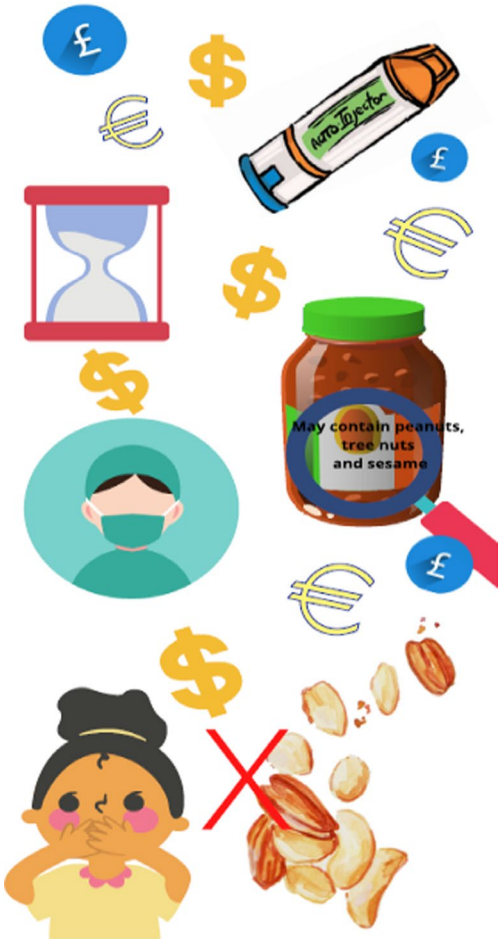
Healthcare Costs

Healthcare costs (18; Fig. 1) were the focus of 17 studies, including 9 from the United States (US), 2 from the UK, 1 from France, and 5 from international populations.

A 2013 cross-sectional survey examined the economic impact of childhood food allergy in the US and determined a caregivers' WTP for food allergy treatment generally. The total US cost was estimated at €22.8 billion annually (€3,849/year/child) [19]. Costs to the medical system accounted for €4.0 billion of the total cost, while the cost borne by families (i.e., direct out-of-pocket and opportunity costs) amounted to €18.9 billion. Of the direct-out-of-pocket costs borne by families, 31% were related to the additional cost of foods. Caregivers reported a WTP (i.e. the maximum amount willing to be paid for a product or service) of €3,224/year/child for food allergy treatment [19].

Scott et al. (2019) also examined the healthcare costs of food allergy but limited their focus to patients with peanut allergy [20]. In this study, patients were matched to two control cohorts: one based on age and sex (i.e., simple-matched) and the other based on the presence of an atopic comorbidity. Using this method, Scott and colleagues found the total annual incremental healthcare costs associated with peanut allergy were €304 (atopy-matched) and €400 (age/sex-matched) per person. Patients with a history of anaphylaxis and those prescribed an AAI had additional incremental costs of €794 (vs. no anaphylaxis) and €470 (vs. no AAI), respectively. When extrapolated to the UK population, total excess costs of peanut allergy ranged from €40–53 million/year [20].

In France, the economic costs of anaphylaxis from a healthcare and societal perspective were estimated at a mean of €1,895 for food- and drug-related anaphylaxis, and €5,610 for the most severe near-fatal cases [21]. In the UK, following an episode of anaphylaxis, referral to specialist



Healthcare costs: "The costs organisations, or a society directly or indirectly incurred by the provision of health-care goods and services, aimed at maintaining or recovering the health of a person or of a population" [18; adapted]

Household costs, include consideration to regional/country differences, as well as ethnicity and socio-economic status, costs associated with a financial cost (e.g. direct and indirect costs, qualitative descriptions of costs), but do not include any data on indirect costs, such as quality of life or perceived life status [62,63].

Fig. 1 The economic burden of food allergy

allergy clinics is evidenced as a cost-effective healthcare strategy compared to GP consultation only [22].

In the US, low socio-economic food-allergic groups not only cost the healthcare system less for specialist visits but also spent less out-of-pocket on medication [23]. However, healthcare system costs for food allergy-related emergency department visits and hospitalizations were 2.5 × greater amongst those in the lowest socio-economic group relative to those with higher incomes [23].

The healthcare costs of food allergy have largely been explored in the US, a country with both private and public healthcare, rendering it difficult to extrapolate to international contexts, yet the nature of localised studies with localised cost inputs cannot be ignored owing to inter-jurisdictional (and occasionally intra-jurisdictional) diversity in healthcare funding and delivery.

Early Allergen Introduction and Screening

The health and economic benefits of early peanut introduction strategies of US/Canada, Australia/New Zealand, and the UK were compared and analysed [24•]. A Markov model was used to compare the cost-effectiveness of various approaches of introducing peanut (i.e., early introduction of peanut without screening; screening with allergist referral and peanut SPT; and primary care peanut-specific serum IgE screening with referral for positive cases) amongst high-risk (classified as severe eczema and/or egg allergy) and low-risk children. A strategy of early introduction of peanut without screening in both high and low-risk groups was economically preferable, providing both clinical and cost benefits compared to screening methods. Significant cost-effectiveness was also shown with any strategy compared to delayed peanut introduction. For high-risk children, when compared to no-screening, the incremental cost to prevent a single peanut-allergic reaction was €18,762 by SPT and €65,338 by sIgE screening. Furthermore, the cost of preventing a single peanut-allergic reaction beyond exclusively urticaria was €95,646 by SPT. SPT screening led to a false-positive result in approximately 3.4% of all identified peanut allergy cases [24•]. Further sensitivity analysis showed that the cost-effectiveness of this approach is unlikely but plausible if the negative quality of life (QoL) impact of an at-home vs. in-clinic reaction was high, or when peanut allergy prevalence was as high as 36% [25]. Even in cases of infants with a peanut-allergic sibling, an approach of at-home peanut introduction without screening was more cost-effective than a SPT screening strategy [26].

A no-screen approach was similarly more economically viable for early egg introduction in the first 6 months of life for high-risk infants (with early-onset eczema) when modeled in the US and Canada [27]. The incremental cost of identifying a positive egg allergy patient through SPT was €2,005 (€6,034, including indirect costs). Of note, primary care screening through egg sIgE (followed by avoidance in infants testing positive) was the most expensive strategy and resulted in the most incremental cases of egg allergy. When using raw pasteurized egg for early egg introduction, the preferred cost-effective strategy shifted to delayed introduction. This was due to the high reaction rate reported in at-risk infants to early introduction of raw egg. However, with the use of cooked egg, modelling of Canadian and European data also demonstrated a no-screening approach prior to early introduction was the most cost-effective [27].

Even when OFCs are indicated, significant delays may exist. Couch et al. analysed 319 challenges to peanut, egg, and milk following corresponding sIgE < 2kUA/L (50% NPV) to assess the economic effect of delaying OFCs

[28]. Within this population, 54% of OFC were delayed > 12 months, with the mean time of delay of 35.5 months. OFC delays were associated with an estimated mean economic cost of €11,227/patient/allergen.

The acute shift from delayed, to early introduction without screening may indeed prevent food allergy for other allergens. Economically, it is not viable to screen all infants for food allergens prior to early introduction. In theory, early introduction ought to, in fact, reduce costs, yet the benefits of early introduction remain largely undescribed [29]. Future research is warranted in terms of barriers and knowledge translation (particularly for groups with lower health literacy and language barriers) and perhaps most importantly, if early introduction does, in fact, decrease food allergy prevalence. Moreover, food challenges and the cost of avoidance must consider the shared decision-making process of parents/guardians, patients, and physicians. Further research is required to understand these perspectives and their impact on QoL.

Specific Cost Considerations

Cow's Milk Protein Allergy

CMPA commonly presents in infancy and early childhood, with an estimated prevalence of 2–3% [2, 30]. Current guidelines include recommendations of substituting for a hypoallergenic formula such as extensively hydrolysed formulas (eHF) or amino acid formulas (AAF) [31]. Several studies have specifically addressed the economic burdens of CMPA [32–43].

Cost-effective analyses and initial comparisons between eHF and AAF vary across countries as a result of differing management guidelines and the relative costs of these clinical nutrition preparation formulas. Using published clinical outcomes and resource utilisation estimates, Guest and Valovirta estimated the economic impact of tightening of public reimbursement guidelines for eHF and AAF in Finland. Through their modelling, they predicted a significant increase in healthcare resource use, including a 10% increase in the number of specialist visits over 6 months and a 12% increase in public health spending (i.e., €889,389 to €992,761) [32]. Of this cost, only 3–5% was associated with formulas. Australian researchers focused on CMPA management and its associated costs, finding variability in the formula prescribing practices of paediatricians, paediatric gastroenterologists, and paediatric allergists, including divergence from existing guidelines [33]. The authors also estimated that prescribed formulas account for 62% of the total 6 monthly cost to the healthcare system, with clinician visits accounting for 28%. Furthermore, despite additional costs of €4.4 million to €4.7 million (over 6 months), using AAF as the initial treatment for CMPA would reduce clinician consultations from approximately 10,400 to 6,100–7,100 and potentially release limited paediatric specialist resources for alternative use [33].

In contrast, CMPA is predominantly managed by general practitioners (GP) in the UK [34]. Sladkevicius et al. noted the 12 monthly public healthcare cost following initial presentation to a GP to be €1,657/patient. GP

visits were the primary cost driver, accounting for 44% of the total cost, with formulas accounting for up to 38%. Fifty-two of the "diagnosis cost" was accounted for by an average seven GP visits/patient. The cost of managing the estimated 18,350 infants with CMPA in the UK over the initial 12 months was estimated to be €30.8 million and resulted in 336,575 GP visits [34]. Studies in Brazil, Netherlands, and Turkey showed formulas to be the primary cost drivers in CMPA management accounting for 95%, 89–92%, and 91% of the total costs, respectively [35–37].

In 2013, Berni et al. observed the addition of the probiotic Lactobacillus rhamnosus GG (LGG) to the eHF accelerated the development of tolerance to cow's milk in infants with CMPA (78.9%) compared with those receiving eHF alone (43.6%) or an AAF (18.2%) [44]. Subsequent cost-effectiveness studies in Italy, Spain, Poland, and the US showed that the initial management of CMPA with eHF + LGG to be the preferred strategy in terms of costs and use of healthcare resources [38–41]. From a US perspective, the initial management of an IgE-mediated allergic infant with eHF + LGG rather than eHF alone or an AAF would reduce insurer costs by €460 and €3,864/infant, respectively, and parent costs by €28 and €46 per infant, respectively, over the 18 months following the start of a formula. These savings were greater for non-IgE-mediated allergic infants. Furthermore, eHF alone for first-line management was more cost-effective than AAF in Brazil, Italy, Spain, Poland, the UK, and the US [37–42].

For IgE-mediated CMPA children, a further study by Berni et al. showed that those who were fed eHF + LGG had a relative risk reduction of 49% for the occurrence of at least one allergic manifestation (urticaria, eczema, asthma, or rhinoconjunctivitis) compared with those fed an eHF alone [45]. Beyond the benefits of being symptom-free, decreasing the development of asthma and an increased tolerance to cow's milk, Guest and Singh estimated the total healthcare cost over 5 years in the UK of initially feeding CMPA infants with eHF + LGG was €5,075/patient compared to €6,163 for eHF alone [43].

Adrenaline Autoinjectors

Internationally, prescribing practices for AAI vary widely [46–49]. In the US, since 2012, all AAIs are exclusively dispensed as twin-packs, whereas in the UK, 2 AAIs are prescribed to all patients [50•, 51]. Shaker et al. (2017) noted significant variation in costs of AAIs throughout US pharmacies, with prices between brands ranging from €143 to €682 per twin-pack [52]. If two twin-packs were prescribed a year, the additional expenditure between AAIs could amount to €11,570/reaction treated over a 2-year period. Shaker and Greenhawt (2018) undertook a cost-effectiveness model to define a value-based pricing of stock AAIs [53]. Costs were evaluated from a societal perspective comparing children with peanut allergy prescribed AAIs vs. those without prescribed adrenaline. Over the 80-year modelling, the total cost of anaphylaxis preparedness and treatment in those with vs. without prescribed AAIs was €23,440 vs. €602, respectively. The average

food allergy fatality per patient prescribed vs. not prescribed an AAI was 0.00056 compared to 0.00148, respectively. The value-based price for personal epinephrine based on a tenfold fatality risk increase was €22, and at a 100-fold hypothetical fatality risk was €243. If the model assumed a 100% carriage and appropriate use compliance rate for when treatment was indicated, the cost ceiling of personal adrenaline was slightly higher (€33 at tenfold fatality risk). In addition, when considering both the increased hospitalization and fatality risks, the value-based price for personal epinephrine ceiling was €30 (or €46, assuming universal carriage and appropriate use of device) [54].

From a UK perspective, Armstrong et al. (2013) showed that when combined with specialist care, an AAI prescription was cost-effective (with a WTP of at least €2160/QALY) [22]. A separate cost-effective analysis was undertaken by Shaker et al. (2021) to compare and model 3 AAI prescribing strategies in the US and UK: prescribing 2 AAIs as a twin-pack to all patients with peanut allergy; prescribing 2 AAIs only to patients with a peanut allergy and a history of previous anaphylaxis, and otherwise prescribing just one device; and prescribing 2 AAIs only to patients with peanut allergy previously requiring multiple adrenaline doses to treat anaphylaxis, and otherwise prescribing just 1 device irrespective of a history of anaphylaxis [50•]. From the US perspective, universal prescription of 2 AAIs to all patients with peanut allergy was not cost-effective compared to the alternate strategies. The universal prescription strategy could be cost-effective compared to strategy 3 when the cost of a single AAI was less than €74, the rate of second adrenaline dose required was more than 25.5%, and the cost of hospitalization for anaphylaxis was more than €16,977. From a UK perspective, universally prescribing 2 AAIs was also not cost-effective compared to both alternate strategies when single devices cost more than €17 [50•].

Whilst food allergy and anaphylaxis action plans differ internationally, Shaker and Greenhawt (2018) assessed the health and economic benefits of pre-emptive injection of adrenaline following definite peanut ingestion in the absence of symptoms [55] as advised by some US allergy action plans [56]. Pre-emptive adrenaline use, followed by emergency medical service activation and care cost an additional €1098/patient over the 20-year modeled period. The incremental cost/life-year saved was €10,746,980 for early precautionary epinephrine use without symptoms (€101,449,154/death prevented), but even at a 1000-fold increased risk of waiting for symptoms to emerge, pre-emptive costs were significantly greater than cost-effectiveness cut-offs. Rather than immediately contacting emergency services following adrenaline use, a study by Shaker et al. (2018) evaluated the cost-effectiveness of watchful waiting and only activating emergency services if initial symptoms of the reaction do not promptly resolve after treatment [57]. They assumed a tenfold increased fatality risk with delayed emergency service activation. There was a minimal change in per-patient fatality rate of 0.0000012 vs. 0.0000019 for wait and see. The incremental cost per life-year saved was €131,507,971 for early emergency service activation compared to wait and see (costing > €1 billion/death prevented). They concluded that

medical observation of a treated and promptly resolved peanut-allergic reaction is not cost-effective, with minimal benefit and excessive costs [57].

Adrenaline is the cornerstone of anaphylaxis treatment [56], yet for many, AAI remain out of reach due to cost. Out-of-pocket costs range dramatically, costs range significantly by country, as do prescribing practices. For example, in Australia, often AAIs are only prescribed to high-risk individuals or those with previous anaphylaxis. This initial prescription is limited also to emergency department physicians and allergists/immunologists. With such varied AAI prescribing, it is not possible to extrapolate the results of Shaker et al. [50•] beyond this population. These differences in prescribing practices vary by country, and may thus alter cost-effectiveness. In metropolitan areas and those with quick reliable access to emergency services, a more cost-effective approach may involve stocking of AAIs in public areas rather than multiple dispensing for every child.

While it is not cost-effective to attend the emergency department if one's symptoms resolve following use of an AAI device, from a safety perspective, our recommendation is still to seek medical attention.

Food Industry Concerns

Consumers managing food allergy rely heavily on ingredient lists when making food choices, but vary more often on their reliance on precautionary allergen labeling (PAL) [58]. Gupta et al. (2017) surveyed 50 food industry professionals (predominantly in the US) to identify factors contributing to the economic impact of food allergen control practices [59]. Recalls related to food allergen cross-contamination ranked as the greatest allergen management expense. Although 96% of companies had a food allergen control plan in place, nearly half (42%) had at least one food allergen–related recall within the past 5 years [59].

Food allergy management requires strict allergen avoidance [2]. However, evidence exists to support that 95% of the peanut-allergic population will tolerate 1.5 mg of peanut protein (6 mg by package weight) [60]. In a 2018 study, strict avoidance of peanut, including avoidance of products carrying a PAL, were associated with minimal reduction in peanut-associated fatality (<0.0001 fewer patient fatalities), but an incremental cost of €3075/patient, vs. strict avoidance but use of products carrying a PAL [61]. The incremental cost/life-year saved with strict avoidance of precautionary allergen labeling was €17,779,914 (€167,839,535/death prevented). Shaker and Greenhawt determined that such a strategy of a supervised low-dose threshold challenge to exclude those who would react to trace allergens included in precautionary allergen testing, was cost-effective, with overall lower peanut allergy costs, higher QALYs, and lower peanut allergy fatality rates [61].

Household Costs

We identified 9 studies in which household costs of food allergy were addressed, of which 3 were from Sweden [62–64] and 6 were from Canada [65–69].

Swedish and Canadian researchers estimated excess household costs amongst children and adolescents with any specialist-diagnosed allergies to any food [64, 67]. In Sweden, cases had comparable total annual household costs, but higher direct (difference: €123.22) and indirect (difference: €254.35) medical-related costs, compared to age- and sex-matched non-food allergic controls [64]. Amongst children aged 0–12 years, total household costs were also comparable; however, differences in direct costs were found, which were largely driven by costs associated with medical care [64]. In contrast, in Canada, despite comparable total annual household costs, allergic cases had greater overall direct costs compared to controls (€8,845 vs. €7,156), largely due to food costs and to a lesser extent, travel to medical appointments and medications [67]. Total indirect costs were not significantly different between the groups, although cases reported lower shopping/preparation costs (€6,655 vs. €8,471).

A Canadian study of socio-economically diverse families with food allergy reported on the parent-perceived social and financial burden of the condition [68]. Three themes spanned income groups, including the increased time costs for food shopping and preparation. In contrast, themes on medication, medical appointments, and allergy-friendly food differed between economically advantaged and economically disadvantaged families. Of note, the latter group noted that occasionally medication was purchased on credit, and that dietary modifications were made only for the child with food allergy, not the entire family, due to costs.

Another Canadian group qualitatively explored the costs of medication as perceived by 10 stakeholders working with low-income families, and 13 low-income families affected by food allergy [69]. Direct costs were perceived to be impacted in multiple ways. AAI costs were often described as a barrier to anaphylaxis treatment, resulting in behaviours that may contribute to suboptimal anaphylaxis treatment: retention of AAI past expiration date, limited or lack of AAI carriage, preferential anaphylaxis treatment with antihistamine due to cost, or relying on emergency services. Perceptions of allergy-friendly food costs varied widely. Overall, few indirect costs for low-income families were described. Also in Canada, an estimated 14.3% of mothers, but no fathers, have experienced career limitations directly related to food allergy [65].

The type of food allergy also appears to influence excess costs. Compared to non-food allergic controls, Swedish adults [62], adolescents [63], and children [63] with allergies to milk, egg, and/or wheat reported significantly higher total annual costs (with differences of €8,164, €3,961, and €4,792, respectively, vs. age- and sex-matched controls). Amongst adults, this difference was largely driven by indirect costs, which were €6,424 greater amongst cases vs. controls [62]. In contrast, the difference was driven by both indirect costs and direct costs, including food, amongst children [63]. These findings

are supported by a pan-Canadian mixed-methods online study in which most (81.5%) of parents described milk as the most costly food allergy [66]. This finding was echoed in the qualitative results, as one of the themes addressed the high cost of allergy-friendly alternatives to cow's milk.

To date, most household costs studies have been conducted in two countries. In these countries, the same instrument (adapted for local context) was used, thereby facilitating comparison, yet as both countries have a unique healthcare structure and consequently, fee structure, even comparisons using the same instruments have limited utility.

Unique Considerations at Schools

As part of the 10-year National Allergy Programme in Finland (2008–2018), Palmu et al. (2018) evaluated the prevalence of parent-reported, doctor-diagnosed food allergies requiring avoidance diets. The annual costs of these diets represented 4.2–9.5% of the total costs of student meals with an additional incremental cost of approximately €230/food allergy student [70].

Approximately half (48%) of children at risk for anaphylaxis may not possess/carry a designated AAI device [71], highlighting a need for stock AAI at schools. A 2019 cost-effectiveness study compared two school epinephrine supply strategies and demonstrated that stocking two unprescribed twin-pack units in addition to student's individual AAI is cost-effective when total school adrenaline acquisition expenses do not exceed €311/school/year [72]. However, a universal (school stock only) model, without requiring student-prescribed units, provided superior value, at €6,825 per student at risk.

Economic Evaluation of Peanut Immunotherapy

Three studies have evaluated the economic and health benefits of peanut immunotherapies regimes [54, 73, 74••, 75••]. An initial cost-effectiveness study on peanut oral immunotherapy (POIT) was modeled based on a study by Tang et al. [76], randomising hypothetical subjects to POIT with a probiotic or avoidance of peanut [73]. From a US perspective, costs were comprised of desensitisation materials, supervised challenge visits, and costs of healthcare visits and treatment. Overall, POIT was shown to be cost-effective when compared to simple avoidance with an incremental cost-effective ratio (ICER) of €1,971/QALY. POIT resulted in an improvement of 1.15 QALYs with an additional cost of €2,266 over the 20-year modeled time horizon. A mean number of 12.3 and 2.0 allergic reactions occurred in the POIT groups and avoidance groups, respectively, over the 20 years, with 2.3 episodes of anaphylaxis treated with intramuscular adrenaline per subject in the POIT group compared to 1.1 episodes in the avoidance group. This cost-effectiveness was maintained following sensitivity analysis including, with or without grocery costs, with increased rates of spontaneous tolerance, accounting for

accidental peanut exposure rates of 5–30%/year, changing QoL improvement and higher reaction rates from peanut oral immunotherapy. Although overall QoL improved with POIT, allergic symptoms and episodes of anaphylaxis were higher [54, 74••].

Shaker and Greenhawt's 2019 study [74••] examined both oral and epicutaneous forms of POIT modeled from phase 3 studies of a commercial POIT treatment (AR101 (*Palforzia*); Aimmune Therapeutics) [76] and a commercial epicutaneous peanut immunotherapy (EPIT) patch (*Viaskin peanut*; DBV Technologies) [77]. The authors used Markov modelling and a cost-effectiveness analysis to compare these two proposed therapies to no immunotherapy. Over the 80-year modelling, EPIT was associated with lower costs compared to POIT (mean €142,289 vs. €150,442) with fewer total episodes of anaphylaxis (mean 1.33 vs. 3.83) and fewer episodes of therapy-associated anaphylaxis (mean 0.62 vs. 3.10). Assuming an annual cost of therapy of €3,532 for caregivers' WTP [19], neither therapy was cost-effective (EPIT ICER of €198,776 and POIT ICER of €234,997). When evaluating a value-based cost analysis (WTP of US$100,000/QALY), the annual cost of each therapy could not exceed €1,443 (EPIT) and €1,136 (POIT) inclusive of clinician visits to be cost-effective. Using sensitivity analysis and if health-related QoL reached 98% with therapy, the maximum value-based therapy costs would be €6,043 (EPIT) and €4,816 (POIT). The three largest determinants of cost-effectiveness and value of each peanut therapy were improving health-related QoL with therapy, reducing the risk of anaphylaxis, and increasing the likelihood of achieving sustained unresponsiveness.

In contrast to commercially available forms of POIT, Soller et al. explored a non-commercial form of preschool POIT, which utilised store-bought peanut puffs or peanut powder/powdered peanut butter [6]. Following a period of up-dosing to a 300 mg daily dose of POIT, after 1 year of POIT, 78.6% of preschool-aged children tolerated a cumulative dose of 4,000 mg of peanut protein, and >98% were able to tolerate a 1,000 mg cumulative dose. This study was evaluated in terms of the health and economic benefits in the US and Canadian contexts [75••]. Compared to a non-POIT approach, POIT was the dominant strategy with lower costs (POIT: US: €75,913; Canada: €28,479; non-POIT: US: €77,618; Canada: €38,232) and greater benefits in terms of QALY and net monetary benefit (NMB) (US: 18.51 QALY, NMB €1,627,092; Canada: 18.83 QALY, NMB €1,308,787) in both countries. Over the 80-year modeled horizon, POIT was associated with fewer episodes of anaphylaxis and fewer episodes of AAI use compared to a non-POIT strategy; however, like previous studies, systemic reactions to POIT were noted.

Until recently, food allergy research and treatment have largely focused on disease and symptom management. OIT offers hope for those living with allergic disease, yet data on future sustained unresponsiveness and quantity of data available for further economic analysis remain limited. Consideration of discounting the negative QoL and health utility over the initial stages of the study may enhance overall QoL of therapy and hence improve measures of cost-effectiveness. Further research is required to better understand the degree of health state utility (and disutility) of epicutaneous and oral immunotherapy, the degree of protection against anaphylaxis, and the long-term benefits from sustained unresponsiveness.

Conclusions

In this scoping review of the economic burden of food allergy, we identified that food allergy contributes to significant excess direct and indirect costs, including time and opportunity costs, for patients, the healthcare system, taxpayers, and society. Much of the literature on the costs of food allergy has been published in the past 10 years. Pre-dating these increases in food prices are increases relating to the costs of AAI in certain jurisdictions, most notably in the US, where prices increased by 500% [78].

The COVID-19 pandemic caused an acute, global shift in healthcare delivery [79], including allergy care. Data from the early days of the pandemic support that virtual allergy care has been well received by families [80], but as pandemic-related restrictions relax, the appropriate balance of in-person to virtual care warrants careful consideration. While a hybrid model is likely to persist, creating opportunities for cost-savings, both to the healthcare system and to households, its benefits must be weighed with its limitations.

As we move through the COVID pandemic and beyond, a lens on how COVID-related cost increases and supply chain concerns will increase direct and indirect household costs related to food allergy is critical. Since the start of the COVID-19 pandemic, food prices broadly have increased by 10–44%, depending on the region and type of food [81, 82]. Rates of food insecurity, independent of food allergy, have similarly increased dramatically across the world [83–85], and are likely to remain high for the foreseeable future owing to increased food costs. Within the food allergy community, food insecurity is thought to be more prevalent than in the general population, yet food banks are often underequipped to accommodate medical dietary restrictions, including food allergy. Discussions about food insecurity may be warranted for some patients and families, yet only 25% of clinicians routinely screen patients [86]. Similarly, greater emphasis on the burden of direct and indirect costs by income level is warranted to most effectively allocate resources and implement policy.

Although the absolute costs differ by region/country, and type of food allergy, a consistent pattern persists: food allergy is a costly condition, to those who live with it, and the multiple stakeholders with which they interact.

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Declarations

Human and Animal Rights
All reported studies/experiments with human subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its

amendments, institutional/national research). This article does not contain any studies with animal subjects performed by any of the authors.

Conflict of Interest

AF declares that he has no conflict of interest. SA declares that he has no conflict of interest. MG declares that he has no conflict of interest. JP is a member of the Board of Directors, as well as Section Head of Allied Health, Canadian Society of Allergy and Clinical Immunology; sits on the steering committee for Canada's National Food Allergy Action Plan, and reports consultancy with Novartis and ALK Abelló.

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Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

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