Original Article: A Cost-effectiveness Analysis of Epinephrine Autoinjector Risk Stratification for Patients with Food Allergy--One Epinephrine Autoinjector or Two?

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31 Monetary Benefit (NMB); Quality adjusted life years (QALY).

32

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38

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54 Annals of Allergy, Asthma, and Immunology; and is a member of the Joint Taskforce on Allergy
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56

Abstract

BACKGROUND: Food allergic patients are routinely prescribed 2 epinephrine autoinjectors (EAI). The cost-effectiveness of this strategy is unknown.

OBJECTIVE: To evaluate the cost-effectiveness of routinely prescribing all patients 2 EAI devices vs. a risk-stratified approach (2 EAI only prescribed for patients with a risk factor)

METHODS: Markov models compared universal vs. risk-stratified approaches based on either a prior medical history of anaphylaxis (PMH-ana) or anaphylaxis requiring multiple epinephrine doses (multi-epi). Cohorts of peanut allergic (PA) children were evaluated over an 80-year time horizon from both US and UK societal and healthcare perspectives. Models assumed prescribing a 2nd EIA provided a baseline 10-fold risk-reduction vs. anaphylaxis-related fatality and hospitalization. Cost-effectiveness threshold was \$100,000/QALY.

RESULTS: From a US perspective, universal prescription of 2 EAI to all PA patients was not cost-effective in the base case vs. risk-stratification by PMH-ana. Universal prescription of 2 EAI was associated with an incremental cost of \$10,696,036/QALY vs. the PMH-ana strategy, and \$17,514,558/QALY vs. the multi-epi strategy. However, the universal strategy became cost-effective vs. a multi-epi strategy when single EAI costs were <\$80, second epinephrine dose requirements >25.5%, anaphylaxis hospitalization costs >\$18,453, annual anaphylaxis risk >76.5%, or anaphylaxis hospitalization rate >74.9%. From a UK perspective, universally

prescribing 2 EAI was also not cost-effective (incremental cost of \$4,132,440/QALY vs. PMH-ana and \$6,208,227/QALY vs. multi-epi) at single device costs >\$18.

CONCLUSIONS: At current EAI prices and low rates of needing two devices, limiting second EAI's to patients with PMH-ana is more cost-effective than routinely prescribing two EAI to all patients (particularly in resource-constrained settings).

88 Highlights Box

89 **What is already known about this study:** Food-allergic individuals are routinely prescribed two
90 epinephrine autoinjectors (EAI) for use in the event of anaphylaxis, but the economic value of
91 this practice has not been determined.

92

93 **What does this article add to our knowledge:** Compared with using a risk stratified approach,
94 routinely prescribing 2 EAI devices to anyone with food allergy is only cost-effective if the cost
95 of a single unit of an EAI is < \$80 (US) or \$18 (UK), unless the probability of requiring a 2nd
96 epinephrine dose for anaphylaxis exceeds 25%.

97

98 **How does this study impact current management guidelines:** In resource-constrained settings,
99 limiting prescription of 2 EAI devices to patients with a prior history of anaphylaxis and/or those
100 who have previously required multiple doses of epinephrine to treat anaphylaxis may be
101 appropriate, unless EAI device cost is significantly reduced.

102

103 INTRODUCTION

104 Food-induced anaphylaxis is a common and potentially life-threatening emergency,(1) and
105 food-allergic patients should receive appropriate diagnosis and advice regarding necessary
106 allergen avoidance and anaphylaxis management.(1, 2) Additionally, given that accidental
107 reactions are common, patients at risk of anaphylaxis should be prescribed an epinephrine
108 autoinjector (EAI), to be available at all times.(1) The provision of EAI has evolved
109 significantly over the past 15 years. In the USA, since 2012, all EAI are exclusively dispensed as
110 twinpacks, with prescription of 2 EAI twinpacks (i.e. 4 devices) now routine and patients
111 advised to have 2 EAI devices available all times, since some patients may require a second
112 dose of epinephrine to treat anaphylaxis.(3) Over the same time, the EAI unit price has risen
113 from <\$100 per device to >\$600 per twinpack, a situation exacerbated by multiple production
114 shortages over the past 5 years. In the United Kingdom (UK), prescribers have been mandated
115 by the Medicines and Healthcare Products Regulatory Agency (MHRA) to provide 2 EAI to all
116 patients, following several recent food-induced anaphylaxis fatalities where both single and
117 even two doses failed to prevent this outcome.(4) The European supply issue has been further
118 compromised by multiple device recalls. To ensure adequate device supply to those at risk, risk-
119 stratification for EAI prescribing may become a necessary consideration. We therefore
120 undertook this cost-effectiveness analysis to evaluate the health and economic benefits of risk-
121 stratification approaches for prescribing multiple EAI devices to food-allergic patients.

122

123 METHODS

124 *Model Structure*

Using TreeAge Pro 2018 (Williamstown, MA), we constructed a Markov model comparing risk-stratification strategies for EAI device prescribing for all individuals diagnosed with peanut allergy (PA) (Figure 1). PA was chosen because it is a severe, persistent food allergy associated with anaphylaxis, and studied in previous health economic models. Markov modeling transitioned patients through health states, including: a) persisting PA, b) resolved PA, and c) PA diagnosis despite silent/unrecognized resolution (herein referred to as “pseudoallergy”). The analysis compared three EAI prescribing strategies: (i) prescribing 2 EAI (1 twinpack) to all PA patients, universally; (ii) only prescribing 2 EAI to PA patients with a history of prior anaphylaxis (PMH-ana), and otherwise prescribing just one device; (iii) only prescribing 2 EAI to PA patients previously requiring multiple epinephrine doses (multi-epi) to treat anaphylaxis, and otherwise prescribing just one device irrespective of a history of prior anaphylaxis. In US context, modeling assumed a single EAI device cost half the price of a twinpack in the low-risk scenario.

The base case was represented by a 4-year-old child with PA, representative of a common situation in which 2 EAI is prescribed. A model cycle length of 1 year with probabilities converted to annual rates and an 80-year time horizon was evaluated from the societal perspective to incorporate downstream costs of peanut allergy, with all-cause age-adjusted mortality included and sensitivity analysis from the healthcare perspective.⁽⁵⁾ Outcomes were expressed in quality-adjusted life years (QALYS), which represents the average health state utility multiplied by years of life from each strategy, and fatality risk calculated by total number of fatalities divided by patients at risk in each group. Cost-effective care was defined as costing less than \$100,000/QALY, calculated by the difference in costs between comparative strategies

divided by the incremental benefit to arrive at the incremental cost-effectiveness ratio (ICER).(6-8) Costs, probabilities, and health state utilities were derived from published literature, with costs and utilities discounted at 3% per year to account for differential future value (www.bls.gov). Microsimulations were also used (n = 100,000 patients per strategy) to allow tracker modifications to assess outcomes including total episodes of anaphylaxis and food allergy fatalities. The analysis conformed to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist and included indirect costs in the societal perspective as recommended by the Second Panel on Cost-Effectiveness in Health and Medicine.(8) This study did not involve research in human subjects and was therefore not required to undergo review by the Colorado Multiple Institutional Review Board.

Costs

Costs were reported in 2020 dollars, and included incremental grocery costs(9), nutrition, EAI costs (10), visits to healthcare professionals and alternative providers(9, 11), medical care for allergic reactions (including ambulance costs, emergency care, and hospitalizations)(11, 12), and job-related opportunity costs (societal perspective)(9). Given variability of reported EAI costs,(10) we used the lowest estimated retail price available at www.GoodRx.com (\$340, index date March 1, 2020) for an EAI twinpack (0.3mg dose), estimating the single device unit cost at \$170 (though single device units are unavailable in the USA).

Probabilities and Events

Fatal food anaphylaxis was estimated at 3.25 per million person-years for individuals aged 5-19 years, and 1.81 per million person-years for adults over 20 years (13). Rates of PA related anaphylaxis were estimated at 36%, ambulance use at 3.9%, emergency department visits at 13.2%, and hospitalizations at 2.6% over a 12 month period.(11) Rates of epinephrine use prior to emergency department arrival were estimated at 67%, and rates of admission for anaphylaxis at 35%.(11, 14)

We assumed that 12% of patients would present with a severe reaction requiring a second dose of epinephrine for treatment, objectively placing them in a higher baseline risk stratum.(15) In our model, all patients who used their EAI device then activated emergency medical services (EMS, e.g., called 911 for ambulance transport) and all patient activating EMS were transported to and evaluated in an ED in the base case (16).

For individuals less than 20 years of age, the cumulative probability of PA spontaneous resolution was 31% (95% CI, 24-40%).(17) While it is difficult to assess to number of patients with silent resolution of food allergy, Couch et al reported that 54.2% of food challenges were delayed.(2) Given variation and practice patterns, additional aspects of repeat evaluation for allergic sensitization, subject selection, and the impact of patients with true allergy reacting to OFC were not considered in the analyses because they are beyond the scope of the question evaluated, and immaterial to the strategies evaluated. The base case estimated that 46% of patients with spontaneous tolerance had this discovered and PA de-labeled through supervised oral food challenge, while 7% of this group would discover tolerance through accidental

exposure each year.(2, 18) Risk of PA recurrence was modelled at a recurrence rate of 7.9% (95% CI, 1.7-21.4%).(19)

The degree of protection provided against fatality for having an additional EAI is unknown but prior models have published a base case 10-fold protective effect against fatality (vs. not having the additional unit), and modeled sensitivity widely, out to 10,000-fold reduction.(16, 20-23) To account for the potential benefit of a 2nd dose of pre-hospital epinephrine, the base-case model assumed a 10-fold reduction in hospitalization.(14) These protective effects included both the ability to access a 2nd device in the event of malfunction as well as the ability to access a 2nd dose if required in the treatment of anaphylaxis.

Health State Utilities

Health state utilities were used to derive QALYs through the mathematical sum of the products of each health state's duration and utility for each individual patient within each strategy. Health state utilities for PA were derived from work by Carroll and Downs based on standard gamble and time trade off methods, with a mean value of 0.93 (SD, 0.17) for a moderate allergic reaction and 0.91 (SD, 0.17) for a severe allergic reaction for the standard gamble and high correspondence with the time trade off method.(24) The model used an average anaphylaxis disutility (e.g., adverse health utility state, or health detriment) of 0.09 in the base case.(24)

Sensitivity Analyses

212 Cohort deterministic sensitivity analyses were performed across wide plausible ranges for each
213 variable with tornado plots. Additional sensitivity analysis were performed comparing each
214 strategy with all patients with asthma, obesity, or rural residence prescribed 2 EAI regardless of
215 reaction history as additional risk factor estimation for requiring a second EAI. Rates of asthma
216 and obesity were obtained from the United States Centers for Disease Control and Prevention
217 National Center for Health Statics, which reports an asthma prevalence of 7.5% to 7.7% and
218 obesity in 13.9% to 39.8% of the population.(25, 26) The percentage of individuals living in rural
219 America as reported by the U.S. census is 19.3% and was used as an estimate of more remote
220 access to care.(27) For sensitivity analysis, the aggregate percentage of individuals with asthma,
221 obesity, or rural residence was estimated at 40.7 – 66.8%, realizing that in actuality this percent
222 of at-risk individuals may be lower due to individual membership in one or more categories. To
223 incorporate stochastic variation across multiple assumptions, probabilistic sensitivity analyses
224 were performed with contemporaneous sensitivity analyses of all variable simultaneously using
225 triangular distributions of modes and deterministic sensitivity ranges. Distributions were
226 validated using alternate seeding and alternative beta distributions for probabilities of
227 healthcare utilization, food allergy tolerance and relapse, and gamma distributions for costs.
228 For gamma distributions, standard deviations were set to half of the mean value, with beta
229 distributions using the observed number of events (r) as the alpha and at-risk population not
230 experiencing the event as the beta. In the base-case no disutility from carrying a 2nd EAI was
231 assumed but in sensitivity analyses a 5% disutility from carrying a 2nd device was explored. Base
232 case analyses were performed from a US perspective with additional sensitivity analyses
233 incorporating international contextual rates and costs for specific variables from the United

Kingdom (UK) (Table 1). UK costs were expressed in US dollars that represent converted rates from British pounds at an exchange rate of 1 GBP = 1.31 USD (08/17/2020).

RESULTS

Over the model horizon, a risk-stratification model for EAI device number prescription was less costly. In the base case societal cohort analysis, a universal policy of 2 EAI without risk-stratification cost \$121,965, while prescribing 2 EAI to only those with PMH-ana cost \$121,860 and to those with multi-epi \$121,082. While more expensive, the universal 2 EAI prescription strategy for all patients with food allergy had marginally greater effectiveness (26.91234) vs. the PMH-ana (26.91233) or multi-epi (26.91229) approaches (Table 2). The net monetary benefit (NMB) of a risk-stratification prescribing strategy based on history of multi-epi (\$2,570,148) was greater than for PMH-ana (\$2,569,373) or a universal approach (\$2,569,269). In the microsimulation, the average number of anaphylaxis episodes experienced per subject was 18.48 (SD 11.98). All approaches were associated with rare fatality, without differences in the rate of fatality risk per patient over the model horizon (overall model PA fatality risk, 0.00015 per subject, SD 0.012). Compared with a multi-epi approach, the universal 2 EAI prescription approach cost \$17,514,558/QALY (\$10,696,036/QALY compared with a PMH-ana approach).

Strategies were similarly distributed when considered from the healthcare perspective (e.g., non-direct medical costs considered), with a universal approach costing \$17,511,674/QALY (vs. multi-epi) and \$10,693,415/QALY compared to PMH-ana.

Sensitivity Analyses:

The differential value of prescribing strategies was highly sensitive to EAI cost. Universally prescribing 2 EAI for all PA patients became cost-effective at or below a single EAI device cost of \$93 for PMH-ana or \$80 for multi-epi (Figure 2). Risk-stratification models were also sensitive to the probability of anaphylaxis hospitalization (Figure 3). As the probability of hospitalization increased beyond 64.0% for PMH-ana or 74.9% for multi-epi, or hospitalization cost exceeded \$15,771 for PMH-ana or \$18,453 for multi-epi, a universal approach was cost-effective (WTP, \$100,000/QALY). Universal prescription of 2 EAI was also cost-effective in the base case when annual anaphylaxis rates exceeded 62.1% for PMH-ana or 76.5% for multi-epi. A universal approach also became cost-effective at higher rates of reactions needing a 2nd dose of epinephrine (21.9% for universal vs. PMH-ana and 25.5% for universal vs. multi-epi)(Figure 4). Additional deterministic sensitivity analyses did not reveal any additional levers of cost-effectiveness (Figure 5). When disutility of carrying a second EAI was considered, differences in NMB became more pronounced and risk-stratification approaches demonstrated even greater advantage.

In probability sensitivity analysis using triangular distributions, the multi-epi strategy was most optimal in 84.59% of simulations evaluated, with routine universal prescription optimal in only 7.72% of simulations, and PMH-ana alone optimal in 7.69% of simulations (Figure E1). Probability sensitivity analysis with alternative random number seeding demonstrated similar results, with 84.35% of simulations favoring the multi-epi strategy, 7.5% favoring a universal 2

EAI strategy, and 8.13% of strategies suggesting PMH-ana was optimal. Alternative probability sensitivity analysis with beta and gamma distributions also favored multi-epi in 92.3% of simulations, with PMH-ana optimal in 5.29% and a universal 2 EAI approach favored in 2.40% of simulations. In probability sensitivity analysis excluding hospital costs, universally prescribing 2 EAI was not favored in any simulation (multi-epi optimal in 88.9% of strategies and PMH-ana optimal in 11.1%).

Asthma, Obesity, and Remote Distance From Emergency Care

Assuming both a high and low prevalence of asthma, obesity, and residing at remote distance from emergency care, universal prescription of 2 EAI for patients without PMH-ana or multi-epi was not cost-effective (Table E1). Costs of PMH-ana were \$121,926 - \$121,964 (NMB, \$2,569,271 - \$2,569,307) with multi-epi costs ranging from \$121,486 - \$121,745 (NBM, \$2,569,488 - \$2,569,748).

UK Perspective:

We also evaluated the model in an alternative economy and socialized healthcare system. As EAI acquisition costs are lower in the UK, additional analyses were performed in the context of UK utilization. In the UK, a universal policy of 2 EAI cost \$137,614, a PMH-ana cost \$137,557, and multi-epi cost \$137,283. Associated effectiveness of each strategy was 27.12663 (universal approach), 26.12661 (PMH-ana), and 27.12657 (multi-epi). The ICER in the UK context was \$6,208,227 for universal 2 EAI prescription vs multi-epi, and \$4,132,440 for PMH-ana. Due to the lower hospitalization costs in the UK, universal prescription of 2 EAI did not become cost-

effective until device cost fell below \$18 when compared to multi-epi (\$20 for PMH-ana)
(Figure E2).

DISCUSSION

Routinely prescribing all patients with PA 2 EAI devices is not cost-effective at current EAI costs vs. a risk-stratified approach, unless the need for a 2nd epinephrine dose with anaphylaxis exceeds 25%. This implies wastefulness of only dispensing EAI's as twinpacks, given limited value beyond very specific risk-stratified contexts. EAI are expensive and beset by supply issues in recent years, prompting the FDA to extend expiration dates on certain devices, and approve additional devices to improve epinephrine access. Limiting availability of EAI to double-packs and requiring universal prescription of 2 devices hampers effective stewardship of a limited resource critical to the treatment of community anaphylaxis, and suggests single EAI device dispensing should return as a preference-sensitive option (at the very least).

In the US analysis, universally prescribing 2 EAI to all PA patients costs \$10,696,036/QALY vs. risk stratification by PMH-ana. Universal prescription of 2 EAI vs. an multi-epi risk stratified approach was even less cost effective (\$17,514,558/QALY). Universal 2 EAI prescription remained cost-ineffective in the UK even at lower device price, because downstream costs in the UK economy are also lower. It is notable that in Australia, national practice is to prescribe a single EAI in the absence of additional risk factors that would increase the likelihood of requiring a second device. Indeed, the case fatality rate for anaphylaxis in Australia is actually lower than in the USA and UK.(28)

322

323 While the disutility of carrying a second EAI was excluded in the base-case, requiring two
324 devices be carried at all times may have unanticipated consequences. Devices are bulky and
325 can be difficult to carry outside of a supplemental bag or purse. Carrying one device is
326 challenging for many patients, and carrying two may be impractical for some, potentially
327 influencing non-carriage of any EAI in some ages though this is mainly anecdotal. It is possible a
328 universal requirement for a second device could actually decrease adherence for carrying any
329 epinephrine at all, and result in harm for some vulnerable populations.

330

331 Our findings are consistent with prior health economic analyses evaluating routine allergy
332 practices aimed at preventing fatality with blanket strategies. When considering only fatality as
333 an outcome (without impacts on quality of life or hospitalization costs), the value-based price
334 for EAI is between \$24-31.(23) The present analysis further exemplifies the overestimated
335 value attributed to prescribing personal EAI against fatal anaphylaxis, an exceedingly rare
336 event.(13) While the cost-ineffectiveness of universal 2 EAI prescription was noted in a
337 cost/QALY metric, evaluating the ICER of cost per death prevented was also beyond \$10 million
338 dollars/death prevented.(29) Similar cost-ineffectiveness has been noted for routine activation
339 of EMS for treated and resolved anaphylaxis(16), pre-emptive epinephrine use for accidental
340 peanut ingestion in the absence of symptoms (30), and routine prolonged observation of
341 resolved anaphylaxis in the emergency department.(31) While EAI cost is a clear lever, this is
342 another analysis suggesting many “routine” anaphylaxis management practices actually have

differential and potentially patient preference-sensitive value, and need more contextualized approaches.

Our analysis has several limitations. First, this was a computer simulation limited by parameter assumptions and its population health perspective. Individual patient management must be contextual, which we attempted to emulate, and informed by specific circumstances unique to each encounter. Second, device market prices are still expensive and well beyond ranges considered cost-effective. Updated prescribing advice coupled with single EAI unit availability may paradoxically increase uptake of EAI within all socioeconomic classes, potentially improving compliance and patient safety. Moreover, such a strategy combined with the use of community-based device sharing technology may provide more benefit than the status quo of two devices.(32, 33) In this respect, we did not consider additional risk reduction from existing shared community epinephrine resources (e.g., schools, commercial aircraft) (21, 22) making a universal approach even less cost-effective. Third, in the base case, we assumed a 12% rate of needing a 2nd dose of epinephrine based on history; however, sensitivity analyses of rising rates showed a universal strategy becomes more cost-effective. (34) Patients may require a 2nd device for either device failure (a rare but recognized occurrence), incorrect use of device during administration or for anaphylaxis that is not responsive to a first dose of epinephrine, and our model accounted for a fatality risk reduction of up to 10,000-fold. Fourth, we did not explicitly consider the effect of epinephrine device shortages in the model though this impact is lessened by a risk-stratified approach. Fifth, while the base case was modeled for PA, the findings of this analysis are likely to be relevant to all food allergens (and perhaps even more

relevant to more minor food allergens), because the rate of severe anaphylaxis of other allergens is nested within the rate for PA. Sixth, the base model assumed additional EAI units/doses would reduce hospital costs; however, it is unclear if this would do so, as opposed to a second dose being administered by paramedic staff or in hospital. In fact, recent guidance suggests anaphylaxis patients receiving more than one dose of epinephrine have extended observation, regardless if this is administered in the pre-hospital setting or emergency department.(1) Still, in the rare event of a device failure, having a 2nd device would be expected to reduce hospitalization. For example, Fleming et al reported patients with food induced anaphylaxis treated early with epinephrine had a reduced likelihood of hospitalization (17% vs 43%, $p < 0.001$), a reduction that would fall within the range of our analysis.(35) Seventh, while sensitivity analysis evaluated the impact of universal 2 EAI prescription for all patients with asthma, obesity, and rural location, it is possible the incremental benefit of a second EAI device may be even greater in this population than assumed in the base-case model, and this analysis did demonstrate a universal approach of 2 EAI prescriptions would be cost effective as the anticipated need for a second epinephrine dose increased. Eighth, since 2012, single EAI units are unavailable in the US, and it is unclear if this will change. Our model deals with the hypothetical that both single and dual device distribution is available. Ninth, and lastly, implementation of a stratified EAI approach may be challenged by societal perceptions of risk, particularly related to EAI device failure, anaphylaxis fatality, and litigation.

While a universal approach to always prescribing two EAI devices is not routinely cost-effective vs. risk-stratified approaches, our analysis shows the decision must be made contextually. As in

387 other areas of risk-based decisions, the decision to prescribe 2 EAI is appropriate for a shared-
388 decision making paradigm of healthcare delivery, informed by patient preferences and values. A
389 validated decision aid – for example to identify those with a >25% risk for requiring a second
390 device – may be of value in this setting. Our analysis suggests that when EAI devices are in
391 limited supply or potentially unaffordable to a particular patient, a risk-stratified approach is
392 reasonable, particularly in a setting where there is additional risk reduction through the use of
393 shared community epinephrine resources (e.g., schools). Finally, while carriage adherence
394 needs to improve, continued efforts to improve EAI affordability and access are particularly
395 important to patient empowerment and to ensure timely administration of epinephrine to
396 decrease anaphylaxis morbidity and mortality.

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Figures and Legends:

Figure 1: Model comparing routine prescription for two EAI vs a risk stratified approach. Arrows represent transitions between health states. In the base case, patients prescribed two EAI continue with two EAI; those with one EAI transition to two if an episode of anaphylaxis occurs. Dotted arrows represent risk of food allergy relapse. Three approaches compared a decision to prescribe “one EAI or two”: (a) a strategy to prescribe 2 EAI for all patients with food allergy, (b) a strategy to prescribe 2 EAI for all patients with food anaphylaxis (with 1 EAI for patients with food allergy but no history of anaphylaxis), PMH-ana and (c) a strategy to prescribe 2 EAI only for all patients with food anaphylaxis who previously required multiple doses of epinephrine to treat an episode of anaphylaxis (with 1 EAI prescribed for patients with food allergy and prior food anaphylaxis successfully managed with one dose), multi-epi. Dashed lines represent recurrence of food allergy.

Figure 2: Sensitivity analysis of device cost (US). Universally prescribing 2 EAI for all patients with food allergy becomes cost-effective at a cost for a single EAI device unit of \$80 when compared to an multi-epi strategy (WTP, \$100,000/QALY).

Figure 3. Sensitivity analysis of hospitalization (US). When comparing a universal approach to multi-epi, as the probability of hospitalization increases beyond 75% (panel a) or cost exceeded \$18,453 (panel b), a universal approach was cost-effective (WTP, \$100,000/QALY).

Figure 4. Two-way sensitivity analysis of the probability of anaphylaxis and the probability of requiring a 2nd epinephrine dose. In the US base-case, a universal approach becomes cost-effective at higher rates of reactions needing a 2nd dose of epinephrine. Colors indicate territories where each strategy is most cost-effective. Food allergy represents a universal approach of 2 EAI to all patients, food anaphylaxis a strategy of limiting 2 EAI to patients with anaphylaxis, and food anaphylaxis with multiple epinephrine prescription limits a second device prescription to those who have required more than one dose.

Figure 5. Tornado plot of incremental net monetary benefit. Universally prescribing 2 EAI for all patients with peanut allergy became cost-effective at or below a cost for a single EAI device unit of \$93 for PMH-ana (\$80 for multi-epi). As the probability of hospitalization increased beyond 64.0% for PMH-ana (74.9% for multi-epi) or cost exceeded \$15,771 for PMH-ana (\$18,453 for multi-epi), a universal approach was cost-effective. Universal prescription of 2 EAI was also cost-effective in the base case when the annual rate of anaphylaxis exceeded 62.10% for PMH-ana (76.6% for multi-epi). A universal approach also became cost-effective at higher rates of an eventual need for a 2nd dose of epinephrine (21.9% for PMH-ana and 25.5% for multi-epi). (panel a: multi-epi vs universal prescription of 2 EAI; panel b: PMH-ana vs universal prescription of 2 EA).

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Table 2: Comparison of the Health and Economic Outcomes of Single vs. Multiple Epinephrine Unit Prescription

Strategy	Cost	QALY	Net Monetary Benefit	ICER of a Non Risk-Stratified Approach vs Prior Medical History of Anaphylaxis (cost/QALY)	ICER of a Non Risk-Stratified Approach vs Anaphylaxis Requiring Multiple Epinephrine Doses (cost/QALY)	Anaphylaxis Per Patient Over Model Horizon	Food Allergy Fatality Per Patient Over Model Horizon
<u>US Societal Perspective</u>				<u>Cohort Analysis</u>		<u>Microsimulation</u>	
No Risk Stratification	\$121,965	26.91234	\$2,569,269	\$10,696,036	\$17,514,558	18.48 (SD, 11.98)	0.00015 (SD 0.012)
Risk Stratify By Prior Medical History of Anaphylaxis	\$121,860	26.91233	\$2,569,373				
Risk Stratify By Anaphylaxis Requiring Multiple Epinephrine Doses	\$121,082	26.91229	\$2,570,148				
<u>US Healthcare Perspective</u>							
No Risk Stratification	\$54,310	26.91234	\$2,636,924	\$10,693,415	\$17,511,674	18.47 (SD, 12.00)	0.00012 (SD, 0.011)
Risk Stratify By Prior Medical History of Anaphylaxis	\$54,205	26.91233	\$2,637,028			18.46 (SD, 12.00)	0.00012 (SD, 0.011)
Risk Stratify By Anaphylaxis Requiring Multiple Epinephrine Doses	\$53,427	26.91229	\$2,637,802			18.46 (SD, 12.00)	0.00013 (SD, 0.0114)
<u>UK Societal Perspective</u>							
No Risk Stratification	\$137,614	27.12663	\$2,575,049	\$4,132,440	\$6,208,227	12.90 (SD, 8.67)	0.00010 (SD, 0.010)
Risk Stratify By Prior Medical History of Anaphylaxis	\$137,557	27.12661	\$2,575,104				
Risk Stratify By Anaphylaxis Requiring Multiple Epinephrine Doses	\$137,283	22.12657	\$2,575,375				
<u>UK Healthcare Perspective</u>							
No Risk Stratification	\$41,207	27.12663	\$2,671,456	\$4,128,686	\$6,204,095	12.88 (SD, 8.70)	0.00009 (SD, 0.009)
Risk Stratify By Prior Medical History of Anaphylaxis	\$41,150	27.12661	\$2,671,511			12.89 (SD, 8.70)	0.00009 (SD, 0.009)
Risk Stratify By Anaphylaxis Requiring Multiple Epinephrine Doses	\$40,876	22.12657	\$2,671,782			12.89 (SD, 8.70)	0.00010 (SD, 0.010)

Abbreviations: SD=standard deviation; ICER=incremental cost-effectiveness ratio; QALY=quality adjusted life years

Table 1: Model Inputs

Variable*	Model Reference (sensitivity range)	Supplemental UK Model (if assumption unique)	Primary Source	Supplemental Source (UK)
US Life Table (in model)	National Vital Statistics Reports, April 2018	--	Arias E, Xu J. United States Life Tables, 2015. National Vital Statistics Reports 2018; 67(7): 1- 63.	--
Food allergy fatality (in model)	5-19 years: 3.25 per million person years (0.3 – 30) 20 years and older: 1.81 per million person years (1.81-18.1)	--	Umasunthar T. Leonardi-Bee, Hodes M, et al. Incidence of fatal food anaphylaxis in people with food allergy: a systematic review and meta-analysis. Clinical & Experimental Allergy. 2013; 43: 1333-1341.	--
Rate of anaphylaxis	36% per year (0.5-90%)	25.3% per year	Shaker MS, Chaliil J, Tran O, et al. Commercial claims costs related to health care resource use associated with a diagnosis of peanut allergy. Ann Allergy Asthma Immunol. 2020. Doi 1.016/j.anai.2020.01.004	L. Noimark, J. Wales, G. Du Toit, C. Pastacaldi, D. Haddad, J. Gardner, W. Hyer, G. Vance, C. Townshend, M. Alfaham, P. D. Arkwright, R. Rao, S. Kapoor, A. Summerfield, J. O. Warner and G. Roberts, Clinical & Experimental Allergy, 2012 (42) 284–292.
Pre-EMS use of EAI for anaphylaxis	67% (25%-100%)	--	Robinson M, Greenhawt M, Stukus DR. Factors associated with epinephrine administration for anaphylaxis in children before arrival to the emergency department. Ann Allergy Asthma Immunol. 2017;119(2):164-9.	--
Hospitalization for anaphylaxis	35% (10% - 60%)	49%	Shaker MS, Chaliil J, Tran O, et al. Commercial claims costs related to health care resource use associated with a diagnosis of peanut allergy. Ann Allergy Asthma Immunol. 2020. Doi 1.016/j.anai.2020.01.004	Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review. (2010) J Allergy Clin Immunol. May;125(5):1098-1104.

Discovery of Tolerance	46% (35% - 100%)	--	Couch C, Franxman T, Greenhawt M. The economic effect and outcome of delaying oral food challenges. Ann Allergy Asthma Immunol. 2016;116(5):420-4.	--
Recurrence of food allergy	8% (0% - 22%)	--	Fleischer DM, Conover-Walker MK, Christie L, Burks AW, Wood RA. Peanut allergy: recurrence and its management. J Allergy Clin Immunol. 2004;114(5):1195-201.	--
Prescribed two EAI in risk-stratification (need for a 2nd EAI)	12% (3%-90%)	10.7%	Rudders SA, Banerji A, Corel B, Clark S, Camargo CA, Jr. Multicenter study of repeat epinephrine treatments for food-related anaphylaxis. Pediatrics. 2010;125(4):e711-8.	
EAI cost (per device)	\$170 (\$100 - \$373)	\$45	Shaker M, Bean K, Verdi M. Economic evaluation of epinephrine auto-injectors for peanut allergy. Ann Allergy Asthma Immunol. 2017;119(2):160-3. Epinephrine generic package of 2 auto-injectors of 0.3mg. GoodRx.com [Available from: https://www.goodrx.com/epinephrine-epipen]. Accessed March 1, 2020.	https://www.currency.me.uk/convert/gbp/usd
Primary care visits (mean incremental annual cost for food allergy diagnosis)	\$146 (\$90 - \$250)	Children: \$1,630; Adults: \$1,133(overall direct costs)	Shaker MS, Chalil J, Tran O, et al. Commercial claims costs related to health care resource use associated with a diagnosis of peanut allergy. Ann Allergy Asthma Immunol. 2020. Doi 1.016/j.anai.2020.01.004; US Department of Labor, Bureau of Labor Statistics. Available from www.bls.gov . =	Fox M, Mugford M, Voordouw J, et al. Health sector costs of self-reported food allergy in Europe: a patient-based cost of illness study. Eur J Public Health. 2013 Oct;23(5):757-62. doi: 10.1093/eurpub/ckt010. https://www.bls.gov/data/inflation_calculator.htm

Allergist visits for food allergy (mean incremental annual cost for food allergy diagnosis)	\$155 (\$100 - \$200)		Gupta R, Holdford D, Bilaver L, Dyer A, Holl JL, Meltzer D. The economic impact of childhood food allergy in the United States. JAMA Pediatr 2013;167:1026-31; US Department of Labor, Bureau of Labor Statistics. Available from www.bls.gov .	
Cost of oral food challenge	\$296 (\$110 - \$1,200)	\$747	Food Allergy Challenge Testing. Healthcare Bluebook. [Available from: https://www.healthcarebluebook.com/ui/proceduredetails/932]. Accessed March 1, 2020	https://www.nice.org.uk/guidance/DG24
Nutritionist visits for food allergy (per year)	\$18 (\$15 - \$100)	Children: \$1,630; Adults: \$1,133(overall direct costs)	Gupta R, Holdford D, Bilaver L, Dyer A, Holl JL, Meltzer D. The economic impact of childhood food allergy in the United States. JAMA Pediatr 2013;167:1026-31; US Department of Labor, Bureau of Labor Statistics. Available from www.bls.gov .	Fox M, Mugford M, Voordouw J, et al. Health sector costs of self-reported food allergy in Europe: a patient-based cost of illness study.Eur J Public Health. 2013 Oct;23(5):757-62. doi: 10.1093/eurpub/ckt010.
Alternative provider visits for food allergy (per year)	\$26 (\$20 - \$110)	Children: \$1,630; Adults: \$1,133(overall direct costs)	Gupta R, Holdford D, Bilaver L, Dyer A, Holl JL, Meltzer D. The economic impact of childhood food allergy in the United States. JAMA Pediatr 2013;167:1026-31; US Department of Labor, Bureau of Labor Statistics. Available from www.bls.gov .	Fox M, Mugford M, Voordouw J, et al. Health sector costs of self-reported food allergy in Europe: a patient-based cost of illness study.Eur J Public Health. 2013 Oct;23(5):757-62. doi: 10.1093/eurpub/ckt010.
Incremental annual grocery costs (living with food allergy)	\$323 (\$250-\$500)	\$1,609	Gupta R, Holdford D, Bilaver L, Dyer A, Holl JL, Meltzer D. The economic impact of childhood food allergy in the United States. JAMA Pediatr 2013;167:1026-31; US Department of Labor, Bureau of Labor Statistics. Available from www.bls.gov .	Cerecedo I, Zamora J, Fox M, et al. The impact of double-blind placebo-controlled food challenge (DBPCFC) on the socioeconomic cost of food allergy in Europe. J Investig Allergol Clin Immunol. 2014;24(6):418-24. https://www.bls.gov/data/inflation_calculator.htm
Job-related opportunity costs from food allergy (per year)	\$2,703 (\$0 - \$5,000)	--	Gupta R, Holdford D, Bilaver L, Dyer A, Holl JL, Meltzer D. The economic impact of childhood food allergy in the United States. JAMA Pediatr 2013;167:1026-31;	--

			US Department of Labor, Bureau of Labor Statistics. Available from www.bls.gov .	
Hospitalization	\$8,625 (\$3,000 - \$20,000)	\$2,236	Shaker MS, Chaliil J, Tran O, et al. Commercial claims costs related to health care resource use associated with a diagnosis of peanut allergy. Ann Allergy Asthma Immunol. 2020. Doi 1.016/j.anai.2020.01.004 US Department of Labor, Bureau of Labor Statistics. CPI Inflation calculator. Accessed at https://data.bls.gov on 9/2/18.	https://improvement.nhs.uk/documents/1972/1_-_Reference_costs_201718.pdf ;
ED visit	\$1,214 (\$500 - \$3,000)	\$224	Shaker MS, Chaliil J, Tran O, et al. Commercial claims costs related to health care resource use associated with a diagnosis of peanut allergy. Ann Allergy Asthma Immunol. 2020. Doi 1.016/j.anai.2020.01.004 US Department of Labor, Bureau of Labor Statistics. CPI Inflation calculator. Accessed at https://data.bls.gov on 9/2/18.	https://improvement.nhs.uk/documents/1972/1_-_Reference_costs_201718.pdf
Ambulance	\$845 (\$500-\$3,000)	\$319	Shaker MS, Chaliil J, Tran O, et al. Commercial claims costs related to health care resource use associated with a diagnosis of peanut allergy. Ann Allergy Asthma Immunol. 2020. Doi 1.016/j.anai.2020.01.004	https://www.independent.co.uk/life-style/health-and-families/ambulance-call-outs-cost-millions-sore-throats-false-nails-a8299306.html
Start age	4 years (0 years to 8 years)	--		--
Negative health state influence for food allergy and food anaphylaxis	Food allergy: -0.08 (-0.02 - -0.11) Episode of anaphylaxis (transient): -0.09 (-0.09 - 0)	--	Carroll AE, Downs SM. Improving decision analyses: parent preferences (utility values) for pediatric health outcomes. J Pediatr 2009;155:21-5, 5 e1-5.	--
Probability of spontaneous tolerance	31% (0-40%)	--	Peters RL, Allen KJ, Dharmage SC, Koplin JJ, Dang T, Tilbrook KP, et al. Natural history of peanut allergy and predictors of resolution in the first 4 years of life: A population-based	--

			<p>assessment. J Allergy Clin Immunol. 2015;135(5):1257-66 e1-2</p> <p>Peters R, Koplin J, Ponsby AL, Perret K, Dharmage SC, Allen K. The natural history of peanut and egg allergy and predictors of persistence: the HealthNuts longitudinal study, 6-year old follow-up. J Allergy Clin Immunol 2019;143:AB421</p>	
Additional EAI device protection	10x (10x – 10,000x)	--	<p>Shaker M, Kanaoka T, Feenan L, Greenhawt M. An economic evaluation of immediate vs non-immediate activation of emergency medical services after epinephrine use for peanut-induced anaphylaxis. Ann Allergy Asthma Immunol. 2019;122(1):79-85.</p> <p>Shaker MS, Greenhawt MJ. Analysis of Value-Based Costs of Undesignated School Stock Epinephrine Policies for Peanut Anaphylaxis. JAMA Pediatr. 2019;173(2):169-75.</p> <p>Shaker M GM. Association of Fatality Risk With Value-Based Drug Pricing of Epinephrine Autoinjectors for Children With Peanut Allergy: A Cost-effectiveness Analysis. JAMA Network Open. 2018;17(1):e184728.</p> <p>Shaker M, Greenhawt M. Cost-Effectiveness of Stock Epinephrine Autoinjectors on Commercial Aircraft. J Allergy Clin Immunol Pract. 2019.</p>	--
Cycle length	1 year	--		--
Start age	4 years (0 – 20)	--		--

Time Horizon	80 years (5 years – 80 years)	--		--
Annual discount rate	0.03 (0-0.03)	--		--

* All dollars expressed in 2020 US currency.

Figure 1:

Figure 2:

Figure 3

A

B

Figure 4:

Figure 5:

A

Food Anaphylaxis with Multiple Epi Doses vs Food Allergy

B

Food Anaphylaxis vs. Food Allergy

Table E1

Strategy	Cost	QALY	Net Monetary Benefit	ICER of PHA With Universal AOR vs Without (cost/QALY)	ICER of AMED With Universal AOR vs Without (cost/QALY)
<u><i>US Societal Perspective with 66.8% AOR</i></u>				<u><i>Cohort Analysis</i></u>	
No Risk Stratification	\$121,965	26.91234	\$2,569,269	\$10,400,000	\$16,575,000
Risk Stratify By Prior History of Anaphylaxis (PHA)	\$121,964	26.91234	\$2,569,271		
Risk Stratify By Anaphylaxis Requiring Multiple Epinephrine Doses (AMED)	\$121,745	26.91233	\$2,569,488		
<u><i>US Societal Perspective with 40.7% AOR</i></u>					
No Risk Stratification	\$121,965	26.91234	\$2,569,269	\$6,600,000	\$20,200,000
Risk Stratify By Prior History of Anaphylaxis (PHA)	\$121,926	26.91234	\$2,569,307		
Risk Stratify By Anaphylaxis Requiring Multiple Epinephrine Doses (AMED)	\$121,486	26.91231	\$2,569,746		

*AOR: Universal prescription of 2 EAI for all patients with asthma, obesity, or rural location

Supplementary Online Content

Shaker MS, Turner PJ, Greenhawt M. A Cost-effectiveness Analysis of Epinephrine Autoinjector Risk Stratification for Patients with Food Allergy--One Epinephrine Autoinjector or Two?

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Figure E1: Probability Sensitivity Analysis (US).

A.

B.

Figure E1. Cost-effectiveness Acceptability Curve (panel A) and Acceptability at Willingness To Pay Threshold of \$100,000/QALY (panel B). In probability sensitivity analysis, a strategy incorporating risk-stratification based on multi-epi was the most optimal strategy in 84.59% of simulations evaluated, with routine universal prescription of 2 EAI optimal in only 7.72% of simulations, and stratification by PMH-ana optimal in 7.69% of simulations.

Figure E2: Sensitivity analysis of device cost (UK).

Figure E2. In the UK context with lower hospital costs, universally prescribing 2 EAI becomes cost-effective at a cost for a single EAI device unit of \$18 when compared to the multi-epi strategy (WTP, \$100,000/QALY).