

An Economic Analysis of a Peanut Oral Immunotherapy Study in Children



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What is already known about this topic? The anxiety and fear of repeat peanut exposures in children with peanut allergy impairs quality of life.

What does this article add to our knowledge? Peanut oral immunotherapy may be cost-effective but will cause more anaphylaxis than it prevents unless the annual rate of therapy-associated anaphylaxis is less than 6% or the probability of therapy-induced tolerance is 68% or greater.

How does this study impact current management guidelines? Application of peanut oral immunotherapy will involve patient preference—sensitive trade-offs. A greater understanding of longer-term risks and benefits is needed before it can be adopted into routine clinical practice.

BACKGROUND: Peanut oral immunotherapy (POIT) decreases the probability of accidental recurrent systemic reactions but reactions from the therapy itself are frequent.

OBJECTIVE: The purpose of this economic analysis was to characterize the potential cost-effectiveness of POIT.

METHODS: Cohort simulations were used to evaluate the effect of POIT for children with peanut allergy. A POIT with probiotic was used in the base-case simulation and long-term survival was modeled using age-adjusted mortality together with the risk of food allergy-associated mortality.

RESULTS: The incremental POIT cost-effectiveness ratio was \$2142 per quality-adjusted life-year. A mean number of 12.3 (95% CI, 12.0–12.5) and 2.0 (95% CI, 1.9–2.1) allergic reactions occurred in the POIT and avoidance groups over 20 years of simulation, with 2.3 (95% CI, 2.2–2.3) episodes of anaphylaxis treated with intramuscular epinephrine per subject in the POIT group and 1.1 (95% CI, 1.0–1.2) episodes per subject in the avoidance group. In sensitivity analyses, POIT was associated with lower rates of anaphylaxis than strict avoidance when the annual rate of accidental allergic reactions in the peanut avoidance group exceeded 25%, the annual rate of anaphylaxis in the POIT group dropped below 6%, or the probability of sustained unresponsiveness after 4 years of POIT was 68% or greater.

CONCLUSIONS: POIT may be cost-effective in a long-term economic model. However, treated patients may experience a greater rate of peanut-associated allergic reactions and anaphylaxis. The analysis was sensitive to rates of accidental allergic reactions, therapy-associated adverse events, and likelihood of therapy-induced tolerance. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:1707–16)

Key words: Peanut oral immunotherapy; Cost-effectiveness analysis

Peanut allergy affects 2% of children younger than 18 years or 1.5 million children.^{1,2} Because peanut allergen is difficult to avoid, approximately 12% of peanut-allergic children experience repeated allergic reactions each year and most of these reactions are potentially life threatening.^{3,4} Once a systemic reaction has occurred, the threat of a repeated or progressive reaction may be a source of great anxiety for patients and caregivers. Quality-of-life (QOL) considerations are significant in patients with food allergy and impairments in health-related QOL have been found for food-allergic patients and their families, affecting family and social activities, emotional issues, and family budgets.^{5–11}

Oral immunotherapy (OIT) involves a process of gradual ingestion of increasing allergen doses and has been recently reviewed.¹² Peanut oral immunotherapy (POIT) has demonstrated potential effectiveness in inducing a state of desensitization as demonstrated in open-label, randomized open-label, and randomized placebo-controlled studies.^{13–21} Subjects have aged from 9 months to 18 years with the ability to consume increasing amounts of peanut protein, seen in up to 93% of subjects in the most successful OIT studies.

Tang et al²⁰ performed a double-blind placebo-controlled randomized trial to investigate POIT with a probiotic over a period of 18 months in children aged 1 to 10 years.²⁰ The primary outcome was sustained unresponsiveness to peanut challenge 2 to 5 weeks after the discontinuation of treatment. In

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Abbreviations used

FAQL-PF- Food Allergy Quality of Life-Parent Form
ICER- Incremental cost-effectiveness ratio
OIT- Oral immunotherapy
POIT- Peanut oral immunotherapy
QALY- Quality-adjusted life-year
QOL- Quality of life

Glossary

Cost-effective analysis- An economic analysis that compares costs and benefits of therapies, which may be expressed in quality-adjusted life-years. Therapies can be contrasted within and across disease states from a societal perspective using this methodology that provides a common metric for comparison. In the United States, medical interventions costing less than \$50,000/quality-adjusted life-year have been considered cost-effective.

Health state utility- A metric that provides an economically quantifiable patient-reported, preference-sensitive trade-off of health states under conditions of risk. More than just an estimate of health quality, it provides a standardized and comparable measure central to the derivation of a quality-adjusted life-year. Common techniques used to measure health state utility include the standard gamble and time trade-off techniques.

Incremental cost-effectiveness ratio- The economic difference between 2 contrasting therapies expressed in terms of quality-adjusted life-years.

Markov model- An economic decision tree that involves recurrent probabilistic risk and allows transitions between defined health states over a linear time frame and a specified time horizon.

Quality-adjusted life-year- A quality-of-life measure that is economically quantitative and health state utility derived.

Sensitivity analysis- A method of incorporating uncertainty into economic analyses across a range of input probabilities to provide a plausible estimate range in a cost-effectiveness analysis.

the trial 62 children were randomized, with successful desensitization found in 89.7% of subjects receiving therapy.

Given that health care expenditures are rising faster than the gross domestic product in most developed countries, economic analyses of the value of new medical therapies are warranted.²² Cost-effectiveness analyses are useful because they allow comparisons of therapies across a wide range of health care delivery systems and circumstances.²³ In an effort to maximize health care delivery in environments in which resources are limited, it is important to weigh different therapies against their respective opportunity costs. Decision analysis provides a common metric to compare the costs of therapies used in different medical conditions.²⁴ The purpose of this economic analysis was to characterize the potential cost-effectiveness of POIT.

METHODS

A computer-based mathematical model (TreeAge Pro, Williamstown, Mass) was used to perform Markov modeling of transitional health states to compare POIT with the natural history of peanut allergy in children. Markov modeling is a decision-analytic model useful in clinical circumstances characterized by recurring probabilistic risk because it can describe transitions experienced by

hypothetical cohorts of patients between defined health states over a linear time frame.²³ Markov modeling allows hypothetical patients to re-experience risks of anaphylaxis and all-cause mortality each year. With this technique risk-reduction can be evaluated in terms of costs of anaphylaxis preparedness.

The model included clinical and market assumptions. Health states were based on the natural history of peanut allergy. Long-term survival was modeled using age-adjusted mortality²⁵ in tandem with probabilities of subsequent peanut exposures³ and spontaneous peanut allergy resolution.²⁶ Vander Leek et al³ described 31 of 53 subjects who experienced an accidental reaction over 5 years. Most (31 of 60) of the subsequent reactions involved potentially life-threatening symptoms. Yu et al⁴ described similar rates of allergic reactions in children practicing strict avoidance, with 35 exposures in 29 children over 244 patient-years for an annual incidence rate of 14.3% per year (95% CI, 10%-19.9%). With similar rates as described in Vander Leek et al, 20 of 35 reactions were characterized as moderate to severe.⁴ Skolnik et al²⁶ described a 21.5% probability of peanut resolution, which was modeled over a 20-year time horizon.

Health states are depicted in Figure 1. Health states were defined to incorporate probabilities, costs, benefits, and risks associated with POIT and strict avoidance. Hypothetical subjects were randomized to POIT or avoidance of peanut. The natural history of peanut allergy was used to estimate risks of future reactions and progression from the incident case for hypothetical cohorts of patients receiving immunotherapy and those choosing not to begin therapy. Model parameters are presented in Table I. Costs were represented from a societal perspective and future costs were discounted equally at 3% per annum to reflect the average annual consumer price index for all goods and services.²⁷

The initial simulation was modeled using the study described by Tang et al.²⁰ Market costs of oral desensitization included costs of *Lactobacillus rhamnosus*²⁸ (monthly cost \$33.98 based on \$16.99 per 30 count Culturelle 1 × 10¹⁰), peanut flour²⁹ (annual cost \$18.65 based on 5 lb peanut flour light, 28%), and supervised challenge visits (cpt 95076, \$117.80 per initial 120 minutes and cpt 95079, \$83.78 per additional 60 minutes for a total cost of \$285.36).³⁰ Costs of treating allergic reactions were modeled using commercial costs of epinephrine (\$268.63 direct cost for 1 epinephrine autoinjector based on \$537.26 per twinpack³¹) and costs of hospitalization³² (\$4719.00), emergency department visits³² (\$553.00), outpatient visits³² (\$193.00), and ambulance runs³² (\$469.50). For the analysis, costs were converted to 2016 dollars using the US Department of Labor Bureau of Labor Statistics inflation calculator.²⁷

Probability of response to oral desensitization was modeled on the basis of results from Tang et al²⁰ who reported that 26 of 29 subjects receiving POIT were desensitized, so base-case probability of response was modeled at 89.7%. In this study, 3 of 31 patients randomized to therapy withdrew; therefore, a rate of 9.7% was used over the time horizon of the model. Fourteen of 31 subjects experienced a severe adverse event over 18 months (with similar rates reported between buildup and maintenance phases); 1 subject had 13 events, 1 had 4 events, 1 had 3 events, 3 had 2 events, and 8 had 1 event, for a total of 34 events in 31 subjects over 18 months. To account for the probability that a patient may experience multiple allergic reactions in a given year, these data were used to model a 73% probability that a patient may experience a significant allergic reaction to POIT in any given year. These allergic reactions consisted of local oropharyngeal symptoms in 2.9% of subjects, rhinoconjunctivitis in 2.9%, urticaria in 20.6%, abdominal pain in 8.8%, diarrhea in 2.9%, cough with urticaria in 17.7%, asthma in 26.5%, and eczema in 2.9% of subjects.²⁰ Of 31 subjects, 3 experienced

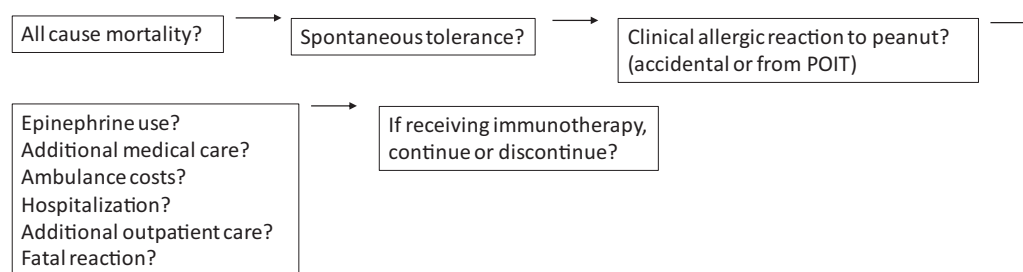


FIGURE 1. Decision-analytic model. Health states were defined to incorporate probabilities, costs, benefits, and risks associated with POIT. Hypothetical subjects were randomized to POIT or avoidance of peanut. Each cohort experienced probabilities associated with parameters with attendant benefits, risks, and costs.

anaphylaxis over 18 months: a total of 6 episodes of anaphylaxis (1 subject experienced 3 events, 1 experienced 2 events, and 1 experienced 1 event). The model incorporated the risk of anaphylaxis from POIT, resulting in epinephrine use at 13% per year for the base-case analysis based on these data.²⁰ Probability of inadvertent accidental exposure was modeled from Vander Leek et al,³ who demonstrated that 31 of 53 subjects experienced an accidental reaction over 5 years, so an annual rate of 11.7% per year was used in the model. Most reactions (31 of 60) were potentially life threatening, so the probability of a moderate to severe reaction following accidental peanut ingestion was assumed to be 52%. The risk of hospitalization following an allergic reaction was calculated at 0.18%, using data from Patel et al³² who described 11,000 visits in 2006–2007 in an at-risk food-allergic population. To calculate the at-risk population, the 11.7% annual reaction rate from Vander Leek et al³ was combined with an 8% rate of food allergy described by Gupta et al¹ and the US population (323,360,976 persons)³³ to reach an estimated probability of 0.18% reflective of the risk of hospitalization following an allergic reaction. Using similar methods, probabilities of emergency department visits, outpatient visits, and ambulance runs were 2.7%, 20.4%, and 0.5% per year following an allergic reaction. The mortality associated with food anaphylaxis is uncertain, but it has been estimated that 150 to 200 deaths occur each year in the United States from allergic reactions to foods.³² Mortality statistics obtained from the Centers for Disease Control and Prevention³⁴ demonstrated 232 fatalities in an at-risk general population of 1,005,422,330 persons by searching the cause of mortality between 1999 and 2014 up to age 24 years by *International Classification of Diseases, Tenth Revision* codes L27.2 (dermatitis due to ingested food) and R57 (shock, not elsewhere classified). The annual death rate in children and young adults from food allergy was calculated at 5.77×10^{-7} , assuming an 8% risk of food allergy.¹ This represents a risk of 1 death in 1.7 million at-risk individuals per year, which is consistent with the food allergy fatality incident rate of 1.81 per million person-years reported by Uma-sunthar et al.³⁵ In this study, the fatality incident rate between age 0 and 19 years was 3.25 per million person-years. The baseline health state utility of food allergy was modeled at 0.85 using data from Mittmann et al,³⁶ who reported baseline health state utility scores for food allergy in the community. This is similar to health state utility data reported by Carroll and Downs,³⁷ who described a utility of 0.91 by standard gamble and time trade-off for a severe food allergy in a child reported by parents and guardians. The improvement in health state utility improvement with POIT was estimated to be 7.9%, using a –0.2 difference in the FAQL-PF questionnaire reported by Anagnostou et al¹⁹ and a baseline

FAQL-PF of 2.54 reported by Venter et al.⁹ Future costs and years were discounted at an equal rate of 3% per year to account for variance between future and present value of resources.²⁷ To allow for a parsimonious model, patients receiving POIT were assumed to have complete protection from accidental or inadvertent peanut ingestion. A 2016 review by Wood¹² summarized representative peanut OIT trials published by Jones et al,¹⁵ Blumchen et al,¹⁶ Varshney et al,¹³ Anagnostou et al,^{18,19} Vickery et al,¹⁴ Narisety et al,¹⁷ and Wasserman et al.³⁸ More recently, Vickery et al²¹ published an analysis of peanut OIT in preschool children. These studies were used to model sensitivity analyses on response rates and rates of allergic reactions and anaphylaxis. Across these studies, rates of desensitization ranged from 31% to 93%. Allergic symptoms during POIT were universal and potentially more severe symptoms, though not always clearly depicted, were common and within the range of the base-case estimates.

In 2013, Gupta et al³⁹ estimated the economic cost of food allergy to be \$4184 per year per child with food allergy. Costs included physician visits, emergency care, overnight stays, travel, medication costs, and special diets. The authors reported an average cost of \$285 per child for special diets in children with food allergy. Additional annual costs included \$92.00 for pediatrician visits, \$138.00 for allergist visits, \$16.00 for nutritionist visits, \$23.00 for alternative provider care, and \$2,399.00 in lost opportunity job-related costs. Opportunity costs included restricted career choice, job loss, or job change. These costs were converted to 2016 dollars²⁷ and incorporated into base-health states of children living with peanut allergy (strict avoidance); however, for children receiving POIT, ongoing grocery costs were excluded. Costs associated with treated food allergy (provider care, opportunity costs) were applied to both cohorts in the base model. The incremental cost-effectiveness ratio (ICER) was calculated by dividing the incremental cost of the POIT strategy by the differences in effectiveness between subjects receiving therapy and those who were not.

$$\frac{\text{Cost(POIT)} - \text{Cost(no POIT)}}{\text{Effectiveness(POIT)} - \text{Effectiveness(no POIT)}}$$

RESULTS

Base model

Markov modeling demonstrated an ICER of \$2,142 per quality-adjusted life-year (QALY) when POIT was compared with simple avoidance. POIT led to incremental improvements of 1.15 QALYs while costing \$2,463 more over the 20-year

TABLE I. Decision analytic model base-case assumptions

Variable	Value
Cost of peanut immunotherapy	
<i>Lactobacillus rhamnosus</i> ^{20,28}	\$33.98 per month
Peanut flour (4 g/d maintenance dosing) ^{20,29}	\$18.65 per year
Supervised graded oral challenge test, 240 min cpt 95076 & 95079 (national rate) ³⁰	\$285.36
Follow-up visits for dose increases (99212) ³⁰	\$698.88
Costs of food allergy	
Epinephrine autoinjector (cost per injector) ³¹	\$268.63 per year
Hospitalization-2007 dollars ³² (mean cost per patient per year in 2016 dollars)*	\$4719 (\$5,474.04)
ED visits-2007 dollars ³² (mean cost per patient per year in 2016 dollars)*	\$553.00 (\$641.48)
Outpatient visits-2007 dollars ³² (mean cost per patient per year in 2016 dollars)*	\$193.00 (\$223.88)
Ambulance runs-2007 dollars ³² (mean cost per patient per year in 2016 dollars)*	\$469.50 (\$544.62)
Pediatrician visits for food allergy-2013 dollars ³⁹ (mean cost per patient per year in 2016 dollars)*	\$92.00 (\$94.76)
Allergist visits for food allergy-2013 dollars ³⁹ (mean cost per patient per year in 2016 dollars)*	\$138.00 (\$142.14)
Nutritionist visits for food allergy-2013 dollars ³⁹ (mean cost per patient per year in 2016 dollars)*	\$16.00 (\$16.48)
Alternative provider visits for food allergy-2013 dollars ³⁹ (mean cost per patient per year in 2016 dollars)*	\$23.00 (\$23.69)
Grocery costs alone-2013 dollars ³⁹ (mean cost per patient per year in 2016 dollars)*	\$285.00 (\$295.00)
Job-related opportunity costs-2013 dollars ³⁹ (mean cost per patient per year in 2016 dollars)*	\$2,399.00 (\$2,470.09)
Probability of desensitization	
Probiotic and peanut immunotherapy ²⁰	89.7%
Nonadherence (discontinuation rate) ²⁰	9.7% for model horizon
Spontaneous tolerance ²⁶	1.1% per year
Probability of accidental exposures, reactions, and treatments	
Risk of peanut allergy/food allergy ¹	2%/8%
US population — total (and <18 years) ^{2,33}	323,360,976 (74,181,467) persons
Accidental exposure with allergic reaction (baseline, no OIT) ³	11.7% per year
Moderate to severe reaction following exposure (baseline, no OIT) ³	52%
Allergic reactions from therapy (OIT) ²⁰	73% per year
Anaphylaxis during OIT (with epinephrine use) ²⁰	13% per year
Hospitalization following allergic reaction ^{1,32,33}	0.18% per year following reaction
ED visit following allergic reaction ^{1,32,33}	2.7% per year following reaction
Outpatient visits for food allergy ^{1,32,33}	20.4% per year following reaction
Ambulance run for allergic reaction ^{1,32,33}	0.5% per year following reaction
Fatality following reaction ³⁴	5.77×10^{-7}
QOL	
Baseline health state utility (food allergy) ³⁶	0.85
Health state utility with peanut allergy and OIT ^{9,19}	0.92
Additional model variables	
Annual discount rate ²⁷	0.03
Start age of cohort	6 y

*Costs converted to 2016 dollars.

TABLE II. Cost-effectiveness and cost-benefit analysis of POIT vs strict avoidance strategies

Strategy	Cost per subject (\$)	Effectiveness (QALY per subject)	Incremental cost-effectiveness ratio	Allergic reactions per subject	Anaphylaxis per subject
POIT	\$44,148 (95% CI, \$43,448-\$44,848)	18.26 (95% CI, 18.17-18.35)	\$2142/QALY	12.3 (95% CI, 12.0-12.5)	2.3 (95% CI, 2.2-2.3)
Avoidance	\$41,685 (95% CI, \$41,033-\$42,337)	17.11 (95% CI, 17.03-17.23)		2.0 (95% CI, 1.9-2.1)	1.1 (95% CI, 1.0-1.2)

model time horizon. Microsimulation of 1,000 subjects randomized to each arm of the model revealed a mean cost of \$44,148 (95% CI, \$43,448-\$44,848) versus \$41,685 (95% CI,

\$41,033-\$42,337), with effectiveness differences of 18.26 QALYs (95% CI, 18.17-18.35) versus 17.11 (95% CI, 17.03-17.23), for the POIT group versus the avoidance group. A

TABLE III. Sensitivity analyses

Variable	Range	Cost (\$)	Effectiveness (QALY)	ICER (\$/QALY)	Allergic reactions (n)	Anaphylaxis (n)
Spontaneous tolerance	1.1%-3% per year					
POIT		44,148-37,542	18.26-18.53	\$2,142-\$2,264	12.3-10.3	2.3-1.9
Simple avoidance		41,685-35,369	17.11-17.57		2.0-1.7	1.1-0.9
Probiotic costs excluded	\$0-\$33.98/mo					
POIT		38,794-44,148	18.26	Dominated- \$2,142	NA	NA
Simple avoidance		41,685	17.11			
Accidental reactions	5%-30% accidental exposures per year					
POIT		44,105-44,126	18.26	2,259-1,832	12.4-12.6	2.2-2.3
Simple avoidance		41,507-42,019	17.11		0.9-5.3	0.5-2.8
Baseline health state	0.85-0.91			0.89-0.91		
POIT		44,148	18.26-19.34	\$2,142-\$2,161	NA	NA
Simple avoidance		41,685	17.11-18.20			
Health state utility change	1%-15% improvement					
POIT		\$44,148	17.30-19.34	\$12,963-\$1,104	NA	NA
Simple avoidance		\$41,685	17.11			
Reaction rate from POIT	Reaction rate: 25%-89%; Anaphylaxis rate: 5%-25%					
POIT		43,809-\$44,565	18.26	\$1,847-\$2,504	4.32-15.15	0.89-4.28
Simple avoidance		\$41,685	17.11		2.0	1.1
Discontinuation rate of POIT	4.5%-38% over model horizon					
POIT		44,158-\$43,895	18.30-18.13	\$2,078-\$2,167	12.68-11.24	2.27-2.11
Simple avoidance		\$41,685	17.11		2.0	1.1
Job-related office desensitization costs included	4-8 h per visit					
POIT		\$45,342-\$46,573	18.26	\$3,180-\$4,250	NA	NA
Simple avoidance		\$41,685	17.11			
Grocery costs	Grocery costs excluded/ included: \$0-\$295/y					
POIT		43,943-44,148	18.26	\$5,490-\$2,142	NA	NA
Simple avoidance		37,629-41,685	17.11			
Job-related opportunity costs of peanut allergy excluded	Opportunity costs: \$0-\$2,470.09/y					
POIT		10,493-44,148	18.26	\$2,146-\$2,142	NA	NA
Simple avoidance		8,025-41,85	17.11			
Health care utilization for allergic reactions	Hospitalization: 0.18%-0.8%; ED visit: 2.7%-11.8%; Outpatient visit: 20.4%-85% Ambulance runs: 0.5%-2.1%			Low to high utilization		
POIT		44,148-44,640	18.26	\$2,142-\$2,385	NA	NA
Simple avoidance		41,685-41,897	17.11			
Sustained unresponsiveness	50%-82% after 4 y					
POIT		27,862-17,463	18.87-19.25	Dominated	7.65-4.58	1.38-0.83
Simple avoidance		41,685	17.11		2.0	1.1

NA, Not applicable/available.

mean number of 12.3 (95% CI, 12.0-12.5) and 2.0 (95% CI, 1.9-2.1) allergic reactions occurred in the POIT and avoidance groups over 20 years of simulation, with 2.3 (95% CI, 2.2-2.3) episodes of anaphylaxis treated with intramuscular epinephrine per subject in the POIT group and 1.1 (95% CI, 1.0-1.2) episodes in the avoidance group (Table II).

Sensitivity analyses

Sensitivity analyses were performed on specified inputs (Table III). Evaluation of the model along rates of increased spontaneous tolerance to peanut revealed cost-effectiveness of POIT of \$37,542/18.53 QALYs compared with the simple avoidance strategy costing \$35,369/17.57 QALYs. As one would

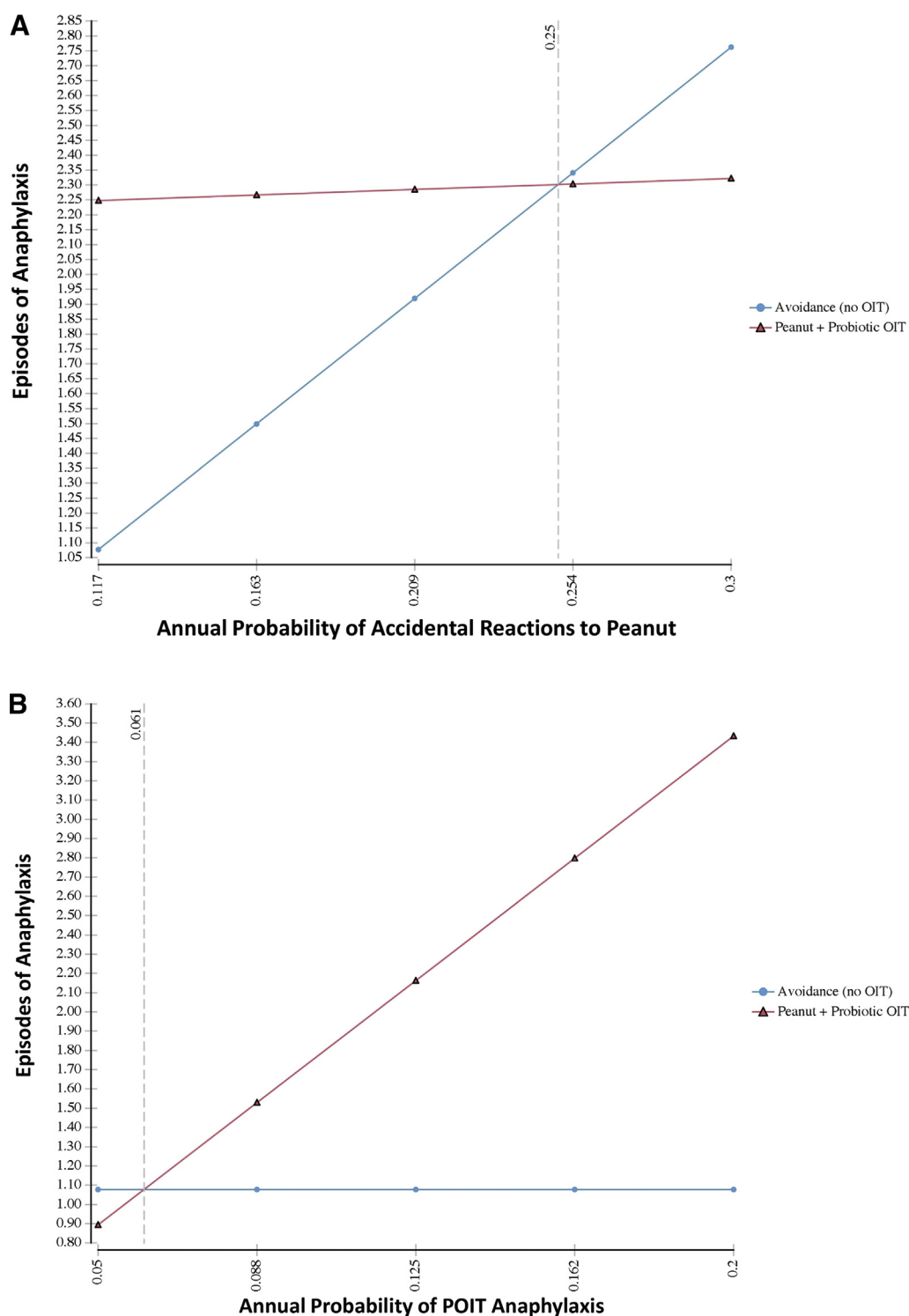


FIGURE 2. Sensitivity analyses. **A**, The annual probability of accidental allergic reaction to peanut in the strict avoidance cohort by rates of anaphylaxis over a 20-year time horizon. **B**, The annual rate of POIT anaphylaxis by total episodes of anaphylaxis over the modeling period. **C**, The probability of prolonged sustained unresponsiveness by total episodes of anaphylaxis over the modeling period.

predict with higher rate of spontaneous tolerance there was a decrease in the number of allergic reactions (from 12.3 to 10.3 in the POIT group and 2.0 to 1.7 in the simple avoidance group) and anaphylaxis (from 2.3 to 1.9 in the POIT group and 1.1 to

0.89 in the simple avoidance group). When evaluating rates of accidental reactions ranging from 5% to 30%, ICERs ranged from \$2,259 to \$1,832 per QALY. However, as rates of accidental reactions increased and exceeded 25% per year, the POIT

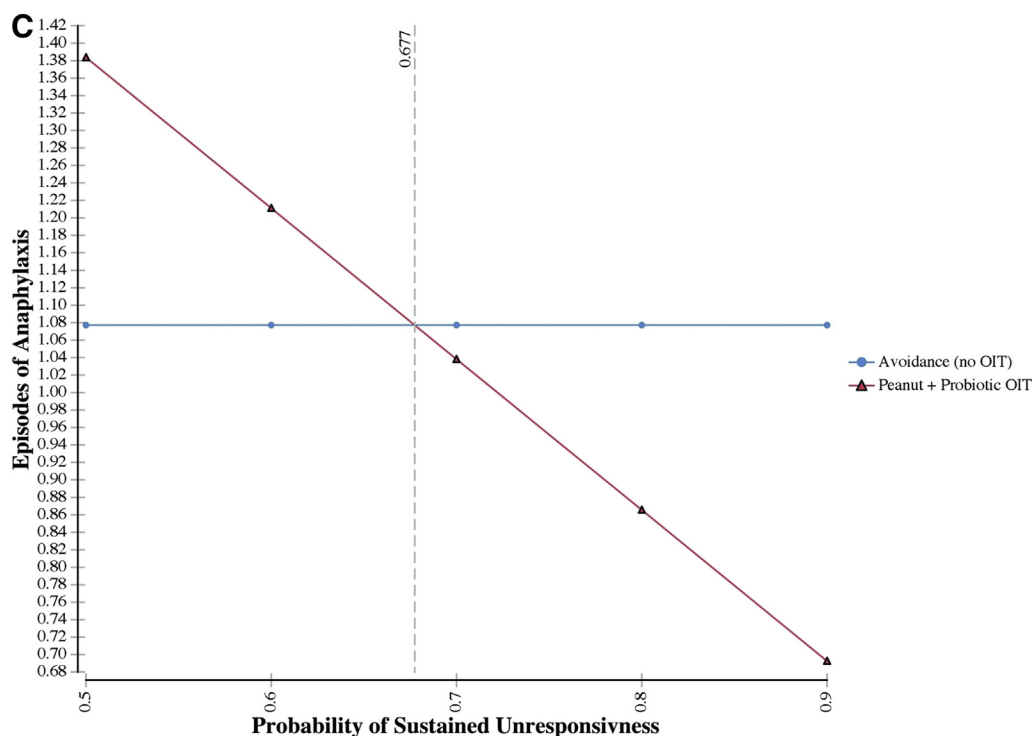


FIGURE 2. (CONTINUED).

strategy became favored over the avoidance strategy in its ability to prevent anaphylaxis (Figure 2). POIT remained cost-effective when the higher health state utility reported by Carrol and Downs³⁷ of 0.91 was modeled with an ICER of \$2161 per QALY. As health state utility improvement reached 15%, POIT subjects gained 2.23 QALYs compared with avoidance.

An important determinant in the cost-effectiveness of POIT would be expected to be the rate of reactions experienced by subjects receiving the therapy. The base-case model assumed that 73% of patients would experience an allergic adverse event each year.²⁰ In a retrospective review performed in 5 clinical allergy practices, Wasserman et al³⁸ reported on 352 patients who received 240,351 doses of peanut, peanut butter, or peanut flour at 5 clinics across the United States. Epinephrine was used to treat 95 reactions in this population. In the populations studied, mild reactions variably involved urticaria, rash, mild itch, mild abdominal pain, and “any reaction that does not involve throat closing or chest tightness or loss of consciousness.” Criteria for administering epinephrine variably included angioedema, generalized urticaria, respiratory tract symptoms, vomiting, coughing, wheezing, throat tightness, and hoarseness. Overall, 12% of patients received epinephrine during escalation and 6% of patients received epinephrine during maintenance. Indications for treatment were multisystem reactions in 202 of 352 patients (57% of patients) and 89% of patients experienced at least 1 “IgE-mediated symptom.” In this context, sensitivity analyses evaluated rates of allergic reactions from POIT ranging from 25% per year to 89% per year, with rates of anaphylaxis modeled from 5% to 25% per year. Across these ranges, POIT remained cost-effective (\$1,847–\$2,504 per QALY), while allergic reactions and anaphylaxis from POIT ranged from 4.32 to 15.15 and 0.89 to 4.28 per patient over the 20-year time

horizon, respectively. As expected, the model was sensitive to rates of allergic reactions and anaphylaxis associated with therapy, with POIT producing fewer cases of anaphylaxis than strict avoidance at the lowest range of the sensitivity analysis. POIT was more favorable in terms of reducing anaphylaxis when rates of anaphylaxis associated with the therapy itself were 6% per year or less (Figure 2).

Sensitivity analyses included a range of nonadherence rates reported in controlled studies of POIT,^{13–21} with cost-effectiveness maintained from a 4.5% to a 38% rate of discontinuation over the model horizon (\$2,078–\$2,167 per QALY). The model remained cost-effective when job-related opportunity costs were excluded (\$2,146–\$2,142 per QALY). Given variation in wage earnings, opportunity costs of initial office desensitization were not modeled in the base case; however, sensitivity analyses evaluated these costs using the average hourly wage from September 2015 reported by the Bureau of Labor Statistics (\$25.14; modeled in 2016 dollars at \$25.64).²⁷ Assuming 24 visits²⁰ and 4 hours of lost work time per visit, the therapy remained cost-effective (ICER \$3180 per QALY). Even extending each visit to include 8 hours of lost work time, cost-effectiveness remained reasonable, with an ICER of \$4,250 per QALY. Excluding all incremental grocery costs, strict avoidance cost \$37,629 compared with POIT costing \$43,943 over the 20-year time horizon. However, even after excluding incremental grocery costs POIT remained cost-effective, with an ICER of \$5,490 per QALY. Costs of probiotic were included in the Tang et al²⁰ study and in the base simulation; however, POIT remained cost-effective when probiotic costs were excluded. In fact when costs of probiotic were removed, OIT dominated avoidance in terms of cost and QOL (\$38,794 for immunotherapy vs \$41,685 for avoidance).

TABLE IV. Desensitization and reaction rates among POIT studies

Reference	Year	Desensitization in active group	Allergic symptoms during treatment (active)	Potentially more severe adverse events (active)
Tang et al ²⁰	2015	26 of 29 (89%)	34 events/31 subjects/18 mo; modeled at a rate of 73% per year	6 events/31 subjects/18 mo; modeled at a rate of 13% per year
Jones et al ¹⁵	2009	27 of 29 (93%)	All patients experienced allergic symptoms, typically minor, during the protocol; during initial escalation 69% experienced sneezing/itching and mild laryngeal symptoms	4 of 39 required epinephrine during initial day escalation (10%)
Blumchen et al ¹⁶	2010	14 of 23 (61%)	185 events/23 subjects	88 respiratory symptoms and 64 gastrointestinal symptoms in 23 patients
Varshney et al ¹³	2011	16 of 19 (84%)	9 of 19 (47%)	2 of 19 subjects required epinephrine (11%)
Anagnostou et al ¹⁸	2011	19 of 22 (86%)	19 of 22 (86%)	28 episodes of wheezing in 22 patients; 19 episodes of vomiting, 146 episodes of abdominal pain, 8 episodes of angioedema, 14 episodes of sore throat
Anagnostou et al ¹⁹	2014	24 of 39 (62%)	Symptoms included mouth itch (81% of subjects), abdominal pain (57% of subjects), vomiting (33%), angioedema (19%), wheezing (22%), and others	21 episodes of wheezing in 39 patients; 1 subject treated with epinephrine
Vickery et al ¹⁴	2014	12 of 39 (31%)	See Jones et al ¹⁵	See Jones et al ¹⁵
Narisety et al ¹⁷	2015	5 of 11 (45%)	1,732 doses with symptoms in 11 of 11 subjects	282 respiratory symptoms, 369 gastrointestinal symptoms, 139 symptoms rated moderate severity in 11 patients
Wasserman et al ³⁸	2014	298 of 352 (85%)	89% of 352 patients	95 doses of epinephrine in 352 patients
Vickery et al ²¹	2016	29 of 37 (78%)	35 of 37 (95%)	36 of 211 adverse events of moderate severity (17%); no severe adverse events reported

Analyses were performed assuming higher probabilities of hospitalization, emergency department visits, outpatient visits, and ambulance runs for allergic reactions³⁰ by applying US census estimates for the population younger than 18 years (74,181,467 individuals).² Using this approach, the probability of hospitalization following an allergic reaction was 0.8%, with probabilities of emergency department visits, outpatient visits, and ambulance runs modeled at 11.8%, 85%, and 2.1% per year following an allergic reaction. Using higher rates of medical utilization increased costs of POIT to \$44,640 and costs of avoidance to \$41,897.

In the Tang et al²⁰ study, possible sustained unresponsiveness assessed 2 to 5 weeks after treatment discontinuation was described in 82% of subjects receiving therapy. In the 2014 Vickery et al¹⁴ report, 24 of 39 subjects enrolled were evaluated 1 month after dose interruption for sustained unresponsiveness. Twelve (50%) subjects met this definition and added peanut to their diets.¹⁴ In the more recent 2016 report of POIT in preschool children aged 9 to 36 months, 4-week sustained unresponsiveness was reported in 29 of 37 (78%) subjects.²¹ Whether or not sustained unresponsiveness translates into longer-term tolerance or cure is unknown and so was not included in the base-case simulation; however, sensitivity analyses were performed to evaluate outcomes on the basis of prolonged sustained unresponsiveness after 4 years of therapy, with probabilities ranging from 50% to 82% of subjects achieving POIT-induced tolerance. In these sensitivity analyses, subjects achieving tolerance discontinued therapy and were considered peanut nonallergic for the remainder of the simulation. Assuming a 50% probability of POIT-induced tolerance, the cost-effectiveness of

POIT was \$27,862/18.87 QALYs with 7.65 allergic reactions and 1.38 episodes of anaphylaxis over 20 years. When the rate of POIT-induced tolerance after 4 years was 82%, POIT's cost-effectiveness was \$17,423/19.25 QALYs with 4.58 allergic reactions with only 0.83 episodes of anaphylaxis. When the probability of POIT-induced tolerance reached 68%, POIT resulted in lower rates of anaphylaxis compared with strict avoidance.

DISCUSSION

In the United States, medical interventions costing less than \$50,000/QALY have been considered cost-effective.⁴⁰ The base case for this analysis was a small limited study of probiotic with POIT, but when incorporated into the economic model POIT appeared cost-effective in a hypothetical cohort modeled over a prolonged time horizon. However, if future costs of ingredient for therapy escalate beyond the current market value of peanut flour used in this analysis, these conclusions could change. In the base-case simulation, the ICER was \$2,142 per QALY, and this cost-effectiveness was maintained with and without incremental grocery costs, increasing rates of spontaneous tolerance, across ranges of accidental exposure rates, QOL improvements, and POIT allergic reactions. When the model was analyzed without costs of a probiotic, cost-effectiveness was dominated by POIT. However, the therapy was associated with increased rates of allergic reactions and anaphylaxis when compared with simple avoidance in the base-case simulation. Although feelings of safety and security improve with therapy, subjects experienced more allergic reactions and anaphylaxis than with simple avoidance. As

illustrated in Figure 2, when the annual rate of accidental peanut exposure in the strict avoidance group exceeded 25% or the annual rate of anaphylaxis associated with POIT was less than 6%, POIT decreased rates of anaphylaxis.

The model used data by Skolnik et al²⁶ to model the rate of spontaneous peanut tolerance. The modeled probability derived from this study is nearly identical to the 22% rate of peanut allergy resolution described at age 4 years in the HealthNuts cohort.⁴¹ In the POIT study by Tang et al,²⁰ 89% of subjects were desensitized to peanut. Severe allergic reactions occurred at a rate of 13% per year. Although the base-case rates used in this analysis were derived from this small single study, these rates are consistent with other studies reporting peanut desensitization between 2009 and 2016 (Table IV). Across studies rates of desensitization ranged from 31% to 93%, with rates of more severe allergic reactions occurring in no less than 10% of patients. Although studies have included relatively small populations, rates appear consistent among these evaluations. Sensitivity analyses were performed in the present analysis to account for variability in rates of allergic reactions and more severe anaphylactic events with these reported ranges. It was assumed that short-term rates of adverse effects would be persistently present; however, this may not be the case and further research is needed to further clarify longer-term risks of POIT. Many studies of POIT have relatively short time horizons, so some degree of uncertainty remains as to the true rates of allergic reactions and anaphylaxis over the longer-term. It is possible that after years of therapy rates of allergic reactions and anaphylaxis may decrease. Longer-term follow-up reported by Wasserman et al³⁸ is somewhat informative in this regard. In the study by Wasserman et al, follow-up of maintenance dosing ranged from a few weeks to over 7 years, with 12% of patients receiving epinephrine during escalation and 6% receiving epinephrine during maintenance. As demonstrated in the present study, if long-term rates of anaphylaxis drop below 6% per year, POIT may prove favorable in reducing anaphylaxis when compared with strict avoidance.

Initial costs of desensitization were based on the 4-hour initial day protocol reported by Tang et al²⁰ and incorporated use of cpt 95076: ingestion challenge test (sequential and incremental ingestion of test items); initial 120 minutes of testing and cpt 95079: each additional 60 minutes of testing.³⁰ The use of cpt 96076 and 95079 could be controversial because these codes are intended for ingestion challenge testing and not desensitization. An alternative modeling approach would be use of the evaluation and management code 99212 (\$43.68).³⁰ Because food allergen OIT remains experimental and a code does not exist specific to this procedure, the true cost of office desensitization is challenging to model. However, even using codes with lower reimbursement, the cost-effectiveness of the therapy would not be expected to exceed the base-case estimate.

A potential limitation in any food allergy cost-effectiveness analysis is the uncertainty associated with health state utility change among patients with food allergy. Although Mitmann et al reported baseline health state utility associated with food allergy in community-dwelling populations,³⁶ true health state utilities representing economically quantifiable trade-offs have not been systematically evaluated or reported for OIT. However, the utility reported by Mitmann et al³⁶ is similar to that reported by Carroll and Downs³⁷ and POIT appeared

cost-effective and similar when each utility was modeled. The present model incorporated a food allergy OIT-attributable difference of 7.9% in food allergy-associated QOL using data derived from the FAQL-PF, applying the -0.2 difference in FAQL-PF reported by Anagnostou et al¹⁹ against the baseline FAQL-PF of 2.54 reported by Venter et al.⁹ This percentage improvement was applied to the reported baseline health state utility to incorporate applicable health state utility associated with POIT into the model. To account for uncertainty in this estimate, extensive sensitivity analyses were performed with health state utility improvements ranging from 1% to 15%. This range of health state utility improvement would certainly be expected to include plausible ranges of health state utility improvement. Across these ranges POIT remained cost-effective.

Gupta et al³⁹ reported that caregivers would pay \$3,504 per year for a safe and effective treatment for food allergy. The present analysis demonstrates the potential for POIT to produce not only improvements in QOL but also cost savings (if probiotic costs are excluded); however, increasing rates of allergic reactions compared with strict avoidance raise important questions about acceptable risks of the therapy. Certainly a food allergy treatment that is cost-effective while resulting in fewer episodes of anaphylaxis than strict avoidance would be preferable to one that causes more reactions than it prevents. However, when POIT-induced tolerance was incorporated into the model, POIT could lower rates of anaphylaxis. When 68% of subjects experienced therapy-induced tolerance after 4 years, POIT was cost saving, improved QOL, and resulted in fewer episodes of anaphylaxis. Further research is needed to clarify the duration of sustained unresponsiveness in POIT; however, if the benefit is durable, such a lasting benefit may outweigh early costs, inconvenience, risks, and reactions associated with therapy.

CONCLUSIONS

Although QOL improves with POIT, allergic symptoms due to therapy are experienced almost universally and episodes of more severe symptoms and anaphylaxis are more likely in patients receiving OIT than in patients simply avoiding peanut. However, if sustained unresponsiveness is durable, rates of anaphylaxis could be lower in treated subjects than in those who practice strict avoidance. Further understanding of the duration of sustained unresponsiveness and long-term therapy-associated rates of allergic reactions and anaphylaxis are needed to clarify trade-offs associated with the therapy when compared with strict avoidance.

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