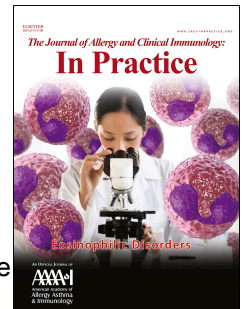


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The Cost-Effectiveness of Pre-school Peanut Oral Immunotherapy in the Real World Setting

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Original Article: The Cost-Effectiveness of Pre-school Peanut Oral Immunotherapy in the Real World Setting

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Abbreviations: Epinephrine autoinjector (EAI); incremental cost-effectiveness ratio (ICER); Net Monetary Benefit (NMB); Quality adjusted life years (QALY).

Conflicts of Interest:

MS: participates in research supported by DBV Technologies, is a member of the Joint Taskforce on Allergy Practice Parameters, and serves as a member of the editorial boards of the Journal of Allergy and Clinical Immunology In Practice, the Annals of Allergy, Asthma, and Immunology, and the Journal of Food Allergy.

EC: has received research support from DBV Technologies; has been a member of advisory boards for Pfizer, Pediapharm, Leo Pharma, Kaleo, DBV, AllerGenis, Sanofi Genzyme, Bausch Health, Avir Pharma; is a member of the healthcare advisory board for Food Allergy Canada; and was co-lead of the CSACI oral immunotherapy guidelines.

JP: COI: Steering Committee, National Food Allergy Action Plan, Canada; Section Head, Allied Health, Canadian Society of Allergy and Clinical Immunology; Steering Committee Member, Bra Mat för Alla [Good Food for All], Sweden.

LS participates in research supported by DBV Technologies.

EA: Speaker/moderator fees: GSK, AstraZeneca, Sanofi; Healthcare Advisory Board: Food Allergy Canada; Contributor: Institute for Health Metrics and Evaluation (Global Burden of Disease Unit)

MG: is an expert panel and coordinating committee member of the NIAID-sponsored Guidelines for Peanut Allergy Prevention; has served as a consultant for the Canadian Transportation Agency, Thermo Fisher, Intrommune, and Aimmune Therapeutics; is a member of physician/medical advisory boards for Aimmune Therapeutics, DBV Technologies, Nutricia, Kaleo Pharmaceutical, Nestle, and Monsanto; is a member of the scientific advisory council for the National Peanut Board; has received honorarium for lectures from Thermo Fisher, Before Brands, multiple state allergy societies, the ACAAI, the EAACI; is an associate editor for the Annals of Allergy, Asthma, and Immunology; and is a member of the Joint Taskforce on Allergy Practice Parameters.

ABSTRACT:

Background: Across North America, 1.4-4.5% of children and families live with peanut allergy. Pre-school peanut oral immunotherapy (POIT) has been shown to be safe and effective in the real world setting.

Objective: Evaluate the cost-effectiveness of pre-school POIT in North America.

Methods: Markov cohort analyses and microsimulation was used to evaluate simulated pre-school children with peanut allergy over an 80-year time horizon. Models incorporated the natural history of peanut allergy, comparing children treated with pre-school POIT with those not receiving immunotherapy. Costs were expressed in US and Canadian dollars.

Results: A pre-school POIT strategy was associated with cost-savings while improving quality-adjusted life years, dominating a non-immunotherapy approach. Over the model horizon, when all costs (and effectiveness) of peanut allergy were included from a societal perspective, a POIT vs non-POIT approach cost \$82,514 (18.51 QALY) vs \$84,367 (17.75 QALY) in the US, and \$40,111 (18.83 QALY) vs \$53,848 (18.26 QALY) in Canada. In microsimulations, systemic reactions to POIT were less frequent than anaphylaxis from accidental exposure without POIT (US: 3.59, SD 3.49 vs 19.53, SD 11.71; Canada: 3.63, SD 3.54 vs 4.56, SD 3.30), epinephrine use was reduced with POIT (US: 5.85, SD 5.73 vs 9.76, SD 5.85; Canada: 0.34, SD 0.36 vs 0.53, SD 0.38), and fatalities were rare but lower in the POIT strategy (US: 0.00005, SD 0.0071 vs 0.00015, SD 0.012; Canada: 0.00005, SD 0.0071 vs 0.00009, SD 0.0095).

Conclusions: Pre-school POIT in a real-world setting improved health and economic outcomes in the US and Canada.

Highlights Box:

What Is Known About this Subject? POIT may be cost-effective in contexts where therapy cost is low and response rate is high; however, health and economic outcomes of real world POIT have not been evaluated in real-world, geographically diverse economies.

What Does This Article Add to Our Knowledge? Compared to no therapy, starting pre-school aged children on POIT is associated with superior health and economic outcomes in both the US and Canada, with cost-savings reaching \$12.3 to \$47 billion in the US and \$10.4 to \$13.6 billion in Canada.

How Does This Study Impact Current Management Guidelines? Pre-school POIT is safe, effective, and implementable in real-world settings, associated with significant cost savings and QALY gain vs. peanut avoidance, showing it to be a feasible option to consider for interested families.

98 INTRODUCTION:

99 Peanut allergy (PA) affects between 1.4%-4.5% of children in North America and Europe, and is
100 considered to be a severe and generally lifelong allergy for nearly 2/3 of all affected children.¹⁻³
101 For years, there was no prospect for PA treatment, but in the past decade, oral immunotherapy
102 (OIT) has proven safe and effective at desensitizing children to varying doses of peanut.^{4,5}
103 Recently, the United States Food and Drug Administration (FDA) approved a commercialized
104 peanut OIT (POIT) product for use in 4-17 year-old children, and multiple practices across the
105 United States (US), Canada, and Europe have been using non-commercial peanut-containing
106 foodstuff (e.g., 12% light roast peanut flour, Bamba™, smooth peanut butter, whole/crushed
107 peanut, peanut-containing candy, etc.) for OIT in real-world clinical setting.⁵⁻⁹ There are limited
108 published reports of POIT specifically in pre-school aged children, but available data from
109 academic centers and a recently published multi-centered Canadian pragmatic study suggest
110 POIT is safe and effective in this age group.⁹⁻¹¹ The recent study from Soller, Abrams, et al
111 showed one year of a 300 mg daily maintenance dose of POIT administered in a real-world
112 community setting resulted in 78.6% of pre-school aged children tolerating a 4,000mg peanut
113 protein cumulative dose, and >98% able to tolerate a 1,000mg cumulative dose.⁹ These data
114 expand upon a smaller trial reported by Vickery et al, showing that either a 300mg or 3000mg
115 daily maintenance POIT dose may promote desensitization to 5000mg.¹¹

116
117 Recently, two models have been published that support that POIT in older children age 4-17
118 years, using a proprietary and now FDA approved commercial product (Palforzia - Peanut
119 (Arachis hypogaea) Allergen Powder-dnfp, Aimmune Therapeutics, Brisbane, CA), which can be

cost-effective under selected contexts.^{12,13} Both the Institute for Clinical and Economic Review and Shaker and Greenhawt independently evaluated Palforzia's cost-effectiveness, using distinct models with respect to treatment of health state utility (HSU), adverse event modeling, and price. Each group concluded that POIT could be cost-effective, based on the assumptions and key levers--product price, shifts in HSU for Palforzia's benefit and detriment, reduced rate of severe reactions attributed to POIT protection, and achieving sustained unresponsiveness whereby ongoing POIT (and expense) was discontinued (because of success).^{12,13} Shaker previously demonstrated non-proprietary OIT with probiotic to also be cost-effective in school-aged children over a 20-year time horizon.¹⁴ However, no evaluations have been performed for real-world implementation of POIT in pre-school children. Therefore, the purpose of this study is to provide a cost-effectiveness model exploring the health and economic benefits of real-world POT implementation in the pre-school aged child, in US and Canadian economies.

METHODS:

Model Structure

TreeAge Pro (Williamstown, MA) was used to simulate pre-school children with PA randomized to POIT in US and Canadian contexts. Markov cohorts incorporated recurrent probabilistic risks and transitions between defined health states (Figure 1). The base case was represented by a 2-year-old child with PA. The model cycle length was one year, with an 80-year time horizon to evaluate a societal perspective of downstream costs and consequences of PA and POIT initiated in pre-school aged children. All-cause mortality was incorporated using US and Canadian life tables compiled by Centers for Disease Control and Prevention and Statistics Canada.^{15,16} The

primary outcome measure was the incremental cost-effectiveness ratio (ICER) expressed in cost per quality-adjusted life-year (QALY, the value of a perfect year of health relative to the condition of interest) and net monetary benefit (NMB, which represents the value of an intervention in monetary terms, when a willingness to pay threshold for a unit of benefit such as QALY is known). Microsimulations (n=100,000 per strategy) incorporated tracker modifications to evaluate anaphylaxis for accidental peanut exposure, systemic reactions from POIT, and anaphylaxis fatalities from either accidental exposure or POIT in each group. Base case analyses were performed from the US and Canadian societal perspectives. The analysis conformed to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist and included both the societal and healthcare perspectives as recommended by the Second Panel on Cost-Effectiveness in Health and Medicine.^{17,18} The study did not involve human subjects research and was not required to undergo review by the Colorado Multiple Institutional Review Board.

Costs

Within the US and Canadian models, costs were expressed in 2020 US and Canadian dollars to reflect differences in two distinct healthcare systems and economies, using an exchange rate of 1 USD=1.32 Canadian dollar (October 22, 2020).^{19,20} The PA model incorporated incremental grocery costs, epinephrine autoinjector costs, routine healthcare and alternative provider visits, supervised oral food challenges(OFC) to assess for peanut tolerance, acute visits for accidental reactions and anaphylaxis, and hospitalizations (Table 1).²¹⁻²⁴ After the first year, PA costs were identical between subjects receiving POIT, except grocery costs were excluded from patients

tolerating 4,000 mg of peanut protein at the 1-year OFC, given the higher threshold could potentially somewhat liberate dietary choices. In the base case, patients were assumed to be dispensed 4 epinephrine devices (2 twinpacks) until age 18 years after which time 2 epinephrine devices were dispensed.

Probabilities and Events

The model incorporated published risks of accidental peanut exposures and anaphylaxis, subsequent healthcare utilization rates including ambulance transport, emergency visits, and hospitalizations, and fatal peanut anaphylaxis (Table E1). Cohorts experienced the natural history of PA inclusive of accidental exposures and reactions, discovery of natural tolerance through OFC or inadvertent exposure to peanut, and PA recurrence.

The cumulative probability of PA spontaneous resolution was estimated from Peters et al.² The base case estimated that 46% of patients with spontaneous tolerance were de-labeled through supervised OFC based on work by Couch et al.²⁵ The rate of tolerance through accidental exposure was estimated at 8% per year.²⁵⁻²⁷ PA recurrence was estimated at 8% (95% confidence interval [95% CI], 2-21%) and patients with recurrent PA did not receive subsequent pre-school aged POIT.²⁸ Given variation in practice, additional aspects of repeat evaluation for allergic sensitization and OFCs for non-POIT related evaluation were not considered in the analyses because they are beyond the scope of the question evaluated.

Real-world POIT safety and effectiveness was estimated based on reports by Soller et al., where 78.6% tolerated cumulative doses $\geq 4,000$ mg protein (and 98.3% tolerated $\geq 1,000$ mg protein) without symptoms at the follow-up OFC after 1 year on maintenance.⁹ In the model, patients unable to tolerate $\geq 1,000$ mg of peanut protein after 1 year were followed in the food allergy natural history health state and 13% discontinued therapy within the first year.⁹ During the follow-up OFC, 0.9% of patients were transferred to the emergency department.⁹ Apart from OFC, 1.6% of patients received epinephrine for a maintenance dose reaction, and 4.1% of patients receiving epinephrine during buildup.^{5 9} Grade 1-4 reaction rates were modeled as published, incorporating systemic reactions of all grades, with anaphylaxis disutility applied to all systemic reaction grades although many systemic reactions did not fulfill anaphylaxis criteria.⁹ POIT recipients tolerating $\geq 1,000$ mg of peanut protein were assumed to have a 10-fold reduction in the rate of anaphylaxis from accidental peanut ingestion.

Health State Utilities

HSU were used to estimate QALY values, ranging from 0 to 1 to reflect the values of death (0) to a perfect year of health (1) without quality of life (QoL) impairment.²⁹ The baseline impairment of PA was estimated at an HSU of 0.91 using data reported by Carrol and Downs, with a transient disutility of an episode of anaphylaxis of 0.09.³⁰ PA QoL improvements were taken from published estimates by Venter et al and Anagnostou et al. The POIT-associated HSU gain was derived from a median 1.61-point improvement in the Food Allergy Quality of Life -Parent Form (FAQLQ-PF) shown with an 800mg POIT maintenance dose³¹ divided by a global 3.0 FAQLQ-PF impairment for PA³², representing a 54% QoL improvement for POIT recipients, with

a residual 1.39 point impairment for PA with POIT. This residual impairment was used to derive the POIT HSU disutility difference per 100mg of peanut protein buffer allowed in the diet of treated individuals, with a maximum POIT disutility improvement of 0.08 in the base case, as previously published for POIT.¹²

Sensitivity Analyses:

Deterministic sensitivity analyses were performed on all variables across plausible ranges shown in Table E1. Additional sensitivity analyses were performed excluding EAI costs for patients tolerating $\geq 4,000$ mg of peanut, limiting systemic reaction rates to grade 2 reactions and above, and evaluating a virtual/telehealth POIT buildup strategy which excluded in-person visits. For this sensitivity analysis, risk of non-supervised POIT buildup was incorporated with a 10-fold increase in anaphylaxis fatality and 2-fold hospital cost increase for this phase.

Additional probabilistic sensitivity analyses (PSA) were performed using triangular modal distributions bounded by sensitivity ranges for each variable to incorporate stochastic variation and interaction of multiple variables simultaneously. PSA distributions were validated with alternate number seeding and use of alternate beta distributions for probabilities of healthcare utilization, tolerance, and relapse, and gamma distributions for costs. Standard deviations reflected half of each mean variable value for gamma distributions, with beta distributions incorporating the observed number of events (r) as the alpha and at-risk population not experiencing the variable event as the beta.

RESULTS

Pre-school POIT was the dominant strategy across both US and Canadian economies (Table 1). In the cohort analysis from the societal perspective, US and Canadian costs per patient of the POIT strategy (US: \$82,514; Canada: \$40,111) were lower than a non-POIT approach (US: \$84,367; Canada: \$53,848). In each country, POIT was associated with greater benefit in terms of QALY and NMB (US: 18.51 QALY, NMB \$1,768,578; Canada: 18.83 QALY, NMB \$1,843,362). Outcomes were similar when evaluated in the healthcare perspective cohort analyses (Table 1). In microsimulation (n=100,000 subjects per strategy), POIT was associated with fewer episodes of anaphylaxis per patient vs. a non-POIT strategy over the model horizon (US: 12.63, SD 10.94 vs 19.53, SD 11.71; Canada: 2.97, SD 2.96 vs 4.56, SD 3.30), excluding POIT-related systemic reactions (US: 3.59, SD 3.49; Canada: 3.63, SD 3.54). In each country, POIT was associated with fewer episodes of community epinephrine use (US: 5.85, SD 5.73 vs 9.76, SD 5.85; Canada: 0.34, SD 0.36 vs 0.53, SD 0.38). Although PA fatality was a rare outcome, POIT offered a protective effect in both countries (per patient fatality rate in the US: 0.00005, SD 0.0071 vs 0.00015, SD 0.012; Canada: 0.00005, SD 0.0071 vs 0.00009, SD 0.0095).

In the base case, POIT resulted in a cost-savings of \$1,853 per patient in the US (\$13,737 per patient in Canada). At current population estimates of 330,616,991 (US) and 38,005,238 (Canada) persons, population-level cost savings were pronounced.^{33,34} Assuming a 2% PA prevalence in each country³⁵ the POIT-associated cost-savings over the model horizon were \$12.3 billion in the US and \$10.4 billion in Canada.

Sensitivity Analyses:

The cost-effectiveness of pre-school POIT without requiring dose-escalation visit varied based on regional costs. When costs exceeded \$151 (US) or \$30 (Canada), this strategy was cost effective (WTP, \$100,000/QALY). In the US base case model, POIT without clinic visits could also be cost-effective at incremental fatality risk increases < 62-fold (holding hospital costs constant) or if hospital costs increased < 30% (holding fatality risks constant) (Figure 2). In Canada, if the incremental fatality risk increased >162-fold (with fixed hospital costs) or hospital costs were inflated above a 6.4-fold increase (without change in fatality risk), POIT with clinic buildup was preferred over home up dosing (Figure 3). Additional one-way deterministic sensitivity analyses in each country did not reveal any additional levers favoring peanut avoidance over pre-school POIT (Figure 4).

When EAI costs were excluded in children tolerating $\geq 4,000$ mg of peanut protein, cost savings were even more dramatic in both the US and Canada. In the US, cohort analysis excluding EAI costs in this population resulted in a cost saving of \$7,104 per subject over the model horizon (POIT strategy, \$77,263 vs avoidance, \$84,367). In Canada savings were even more pronounced, reaching \$17,947 per subject (POIT strategy, \$35,901 vs avoidance, \$53,848). When considered from a population perspective³³⁻³⁵ the cost-savings of pre-school POIT excluding EAI costs reached \$47 billion in the US and \$13.6 billion in Canada. When considering only systemic reactions grade 2 or higher (Table E2), pre-school POIT demonstrated greater NMB (POIT vs avoidance US: \$1,783,346 vs \$1,690,578; Canada: \$1,856,604 vs \$1,772,192). Per subject POIT grade 2 or higher systemic reaction rates were 0.977 (SD 1.16) in the US and 0.987 (SD, 1.17) in Canada.

Probabilistic sensitivity analyses (n=10,000 simulation in each country) revealed POIT to be the most cost-effective strategy in 98.15% (US) and 98.40% (Canada) simulations (WTP = \$100,000/QALY). With alternate random number seeding, POIT remained cost-effective in 98.16% of US simulations and 98.56% of simulations in Canada, and remained preferred in the majority of simulations using alternate distributions in both countries (US 75.73%; Canada 71.97%).

DISCUSSION:

In real world settings, POIT in pre-school aged children is safe and effective, complementing other published data suggesting similar POIT efficacy in children of all ages.^{4,5,9} While POIT safety data has noted an increased risk of both treatment-associated anaphylaxis and increased epinephrine use in older children³⁶, the FDA approved a commercialized POIT product for children age 4-17 years.⁶ This decision reflects, to some degree, that such risks should be incorporated into a shared decision-making discussion, where the choice to engage in OIT incorporating known safety data is preference-sensitive.³⁷ Notably, rates of anaphylaxis and epinephrine use appear comparatively lower in the pre-school population.^{5,11,38}

We show that real-world pre-school POIT is highly cost-effective and a dominant therapy (e.g., the option with the greatest health and economic benefits) vs. peanut avoidance, in both US and Canadian economies from societal and healthcare perspectives (cost-savings per preschooler of \$1,853 - \$7,104 in the US and \$13,737 - \$17,947 in Canada). Assuming a 2% PA

prevalence at current population estimates, the cost-savings of pre-school POIT over a lifetime is staggering--\$12.3 to \$47.0 billion in the US and \$10.4 to \$13.6 billion in Canada.^{33,34} POIT is associated with higher up-front risks of therapy-associated reactions (rarely severe), but is also associated with lower long-term rates of accidental reactions.⁵ Of note, a significant factor in this analysis is the low acquisition cost of peanut flour from non-commercial sources, for which a year supply costs 42 times less than the monthly wholesale acquisition cost of Palforzia, a highly similar 12% fat light-roasted peanut flour. Furthermore, many US companies selling peanut flour actually buy their 12% light roast peanut flour from Golden Peanut Company (which supplies the flour in Palforzia) which is then re-branded for sale in grocery stores and on-line retailers. Other leveraging factors making the analysis dominated include the high rate of effectiveness that translates to large HSU/QoL gains, as evidenced by the large QALY and NMB gains for successful therapy. Both the low product cost and the significantly higher QALY gain differentiate this POIT analysis from a previously published analysis showing Palforzia was not cost-effective in the base case (ICER~\$256,000 vs. avoidance), had a value-based ceiling base case price of just under \$1300 per year, and a much lower QALY gain.¹²

Importantly, this analysis demonstrates a considerable long-term safety advantage in a pre-school POIT strategy vs. avoidance via decreasing the risk for anaphylaxis triggered by unintentional exposure over the model horizon, despite initially elevated rates of systemic reactions during buildup. This is the central trade-off that hinges on parents accepting higher rates of therapy-associated reactions (many not even constituting anaphylaxis) up front for lower accidental rates later on.⁵ It is challenging to compare pre-school POIT adverse event

rates to those in older children, but a higher proportion of older children aged 4-17 years received epinephrine in the PALISADE trial (results from the companion trial (POSEIDON) evaluating Palforzia in children ages 1-3 years old are not yet available).⁶ This analysis can inform the potential cost-effectiveness of Palforzia in this age, in terms of setting the margins for key parameters to achieve value. However, the commercialized product will have a firm daily maintenance limit of 300mg, and a maximal efficacy of 600mg protection, which is several fold lower than the one year target protective 4000mg cumulative dose shown to be effective in a real-world setting.^{5,9}

An additional unique feature of this model are the sensitivity analyses investigating potential home-dosing. Pre-COVID-19 pandemic, home up dosing would have been an unlikely consideration, but the pandemic has shifted thinking regarding how we deliver care, especially the potential feasibility of home up dosing of OIT given constraints on care.³⁹ The possibility of home up dosing for pre-school aged children adds crucial flexibility, enabling children to be started and progressed through POIT despite a pandemic, or increase access to those living far from an allergist.⁴⁰ Provided incremental fatality risk increases are <62-fold or if hospital costs increase <30% (US); or incremental fatality risks are <162-fold or hospital costs do not exceed a 6.4-fold increase (Canada), a home buildup strategy is cost-effective. This is a distinct advantage over a commercialized product requiring stringent regulatory compliance and in-office dosing. It is important to note that home up dosing relies on caregiver's ability to recognize treat reactions, similar to the requirement of daily dosing without up dosing.

This study has several limitations. First, this is a microsimulation and cost-effectiveness analysis, which is reliant on the quality of the data inputs. Where possible we used previously published assumptions but also used data from a single large real-world effectiveness and safety study.^{5,9} We used wide sensitivity ranges as well as multiple distributions and seedings to ensure robustness of the model assumptions and findings. Second, while \$100,000/QALY is a well-referenced WTP threshold, there is no universally accepted threshold in the US or Canada, and other thresholds could be presumed.⁴¹ Third, there is no defined HSU change that has been established for food therapy, nor known data regarding POIT-attributable QoL change in this age group. This is somewhat better known for older children undergoing both commercial and non-commercial POIT, and we assumed similar QoL gains would occur. While there is no published mapping algorithm translating FAQLQ score to HSU, we used a previously published calculation for this, though true HSU may differ if measured vs. being calculated from QoL. This is a knowledge gap requiring future research to address. Fourth, the decision to enter into POIT at any age is preference-sensitive, and while trade-offs and goals have been studied for caregivers of older children, these are undescribed for pre-school aged children. The risk-tolerance for certain safety to efficacy trade-offs needs further study. Fifth, this study details use of regular foodstuff for therapeutic process, an OIT practice long used in clinical practice in the US, Canada, and Europe for the past 15 years. Both the European Academy of Allergy and Clinical Immunology (EAACI) and the Canadian Society of Allergy and Clinical Immunology (CSACI) have recently published guidelines endorsing this practice, though such practice has not yet been formally endorsed by the American Academy of Allergy, Asthma and Immunology (AAAAI) or the American College of Allergy, Asthma and Immunology (ACAAI).^{4,42} Sixth, all

systemic reactions from POIT assumed the disutility of anaphylaxis; however, in reality it is likely that not all systemic reactions would be considered anaphylaxis per se. Still, such a reality would only make pre-school POIT more dominant. Similarly, patients only tolerating 1,000 mg of peanut protein did not transition to the 4,000 mg health state because the probability of this event is not known; however, this again would only lead to pre-school POIT being more dominant.

In conclusion, this study shows that vs. peanut avoidance, pre-school POIT is a highly cost-effective therapy in both US and Canadian economies in real-world settings, at both the healthcare and societal perspectives, and is the first study to additionally show cost-savings. Pre-school POIT is associated with a substantial QALY gain and reduced long-term risk of severe reactions attributable to unintended peanut exposure, and can be done with a low annual product acquisition cost. Furthermore, under certain contexts, up dosing at home is cost-effective, which, in light of a pandemic that disrupted healthcare delivery, may prove advantageous for certain families.

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Figures Legends:

Figure 1. State Transition Diagram: Health states of preschool POIT (panel A) and non-POIT (panel B). Children beginning POIT assume probabilities of success in the first year of tolerating 4,000 mg or 1,000 mg. Subjects also experience the probability of spontaneously outgrowing peanut allergy (known or unknown). Subjects experience age-adjusted all-cause mortality and patients with peanut allergy experience risk of a fatal peanut reaction.

Figure 2. US Sensitivity Analysis on Home Build Risk: In the US context, home POIT without requiring clinic build-up visits was the optimal strategy when incremental fatality risk increased less than 62-fold excluding hospital cost increases (a) or hospital costs increased less than 30% excluding fatality risk increases (b). The interaction between these two variables is depicted in (c).

Figure 3. Canada Sensitivity Analysis on Home Build Risk: If home build-up POIT incremental fatality risk rose beyond 162-fold excluding hospital cost increases (a) or hospital costs inflated above a 6.4-fold increase (excluding increased fatality risk) this strategy was not cost-effective compared to POIT with clinic buildup (b). The interaction between these two variables is depicted in (c).

Figure 4. Tornado Plots: Deterministic one-way sensitivity analyses in the US (a) and Canada (b) did not reveal any conditions under which POIT was not the optimal strategy. Strategies are compared across individual variable sensitivity ranges below (blue) and above (red) shown, with

514 incremental net monetary benefit (INMB) depicted. Positive INMB values reflect incremental

515 cost-effectiveness of POIT over a non-POIT strategy.

516

Table 1. Preschool POIT cost-effectiveness

Strategy	Cost	QALY	Net Monetary Benefit	ICER (cost/QALY)	Anaphylaxis from Accidental Exposure*	Systemic Reaction from POIT*	Epinephrine Use*	Food Allergy Fatality*
<u>US Perspective (USD)</u>	<u>Cohort Analysis</u>				<u>Microsimulation</u>			
Preschool POIT	\$82,514 (\$33,569)	18.51	\$1,768,578 (\$1,817,656)	Dominant	12.63 (SD 10.94)	3.59 (SD 3.49)	5.85 (SD 5.73)	0.00005 (SD 0.0071)
Food Allergy Without POIT	\$84,367 (\$35,361)	17.75	\$1,690,578 (\$1,739,313)	Dominated	19.53 (SD 11.71)	--	9.76 (SD 5.85)	0.00015 (SD 0.012)
<u>Canadian Perspective (CAN)</u>								
Preschool POIT	\$40,111 (\$14,157)	18.83	\$1,843,362 (\$1,811,883)	Dominant	2.97 (SD 2.96)	3.63 (SD 3.54)	0.34 (SD 0.36)	0.00005 (SD 0.0071)
Food Allergy Without POIT	\$53,848 (\$18,299)	18.26	\$1,772,192 (\$1,865,174)	Dominated	4.56 (SD 3.30)	--	0.53 (SD 0.38)	0.00009 (SD 0.0095)

Societal perspective costs shown (with healthcare perspective costs excluding grocery and job-related costs) in US (USD) and Canadian (CAN) dollars.

*Per patient over model horizon. Epinephrine use represents the per patient utilization of epinephrine for community anaphylaxis before EMS access and the epinephrine utilization for POIT systemic reactions.

Table 2. Preschool POIT cost-effectiveness

Strategy	Cost	QALY	Net Monetary Benefit	ICER (cost/QALY)	Anaphylaxis from Accidental Exposure*	Systemic Reaction from POIT*	Epinephrine Use*	Food Allergy Fatality*
<u>US Perspective (USD)</u>	<u>Cohort Analysis</u>				<u>Microsimulation</u>			
Preschool POIT	\$82,514 (\$33,569)	18.51	\$1,768,578 (\$1,817,656)	Dominant	12.63 (SD 10.94)	3.59 (SD 3.49)	5.85 (SD 5.73)	0.00005 (SD 0.0071)
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*Per patient over model horizon. Epinephrine use represents the per patient utilization of epinephrine for community anaphylaxis before EMS access and the epinephrine utilization for POIT systemic reactions.

Figure 1

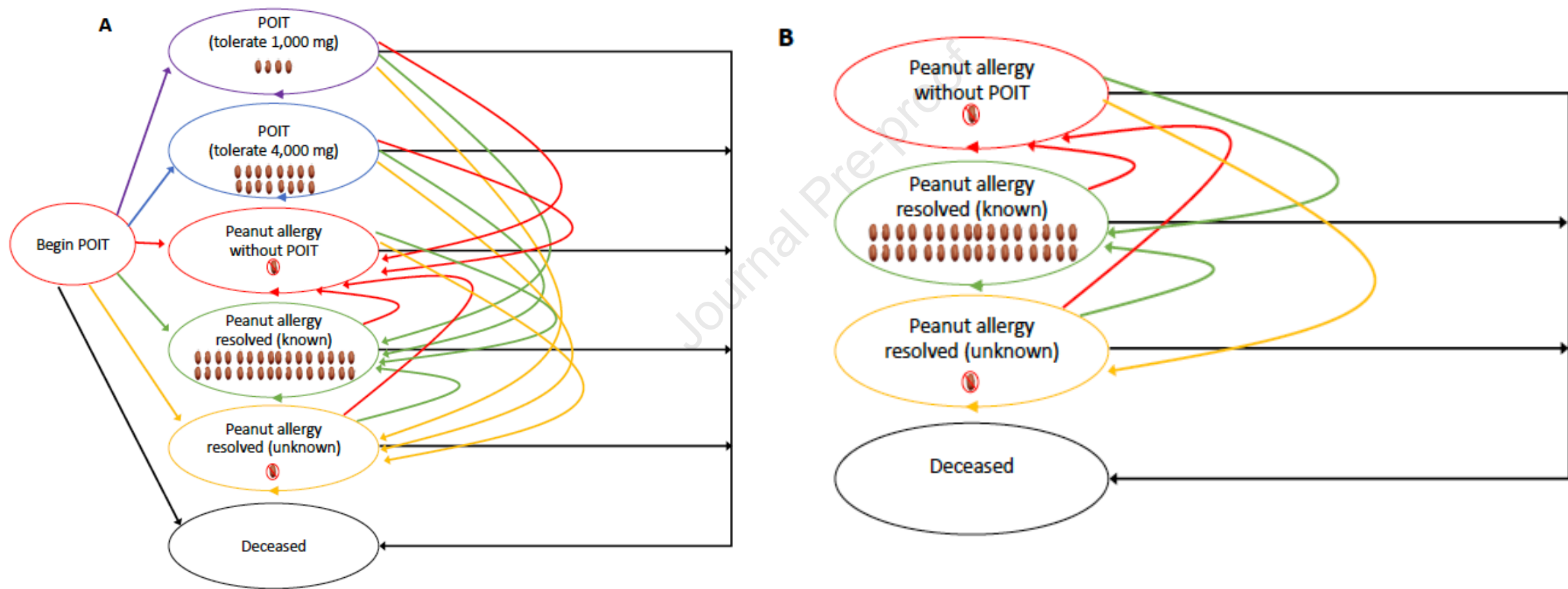
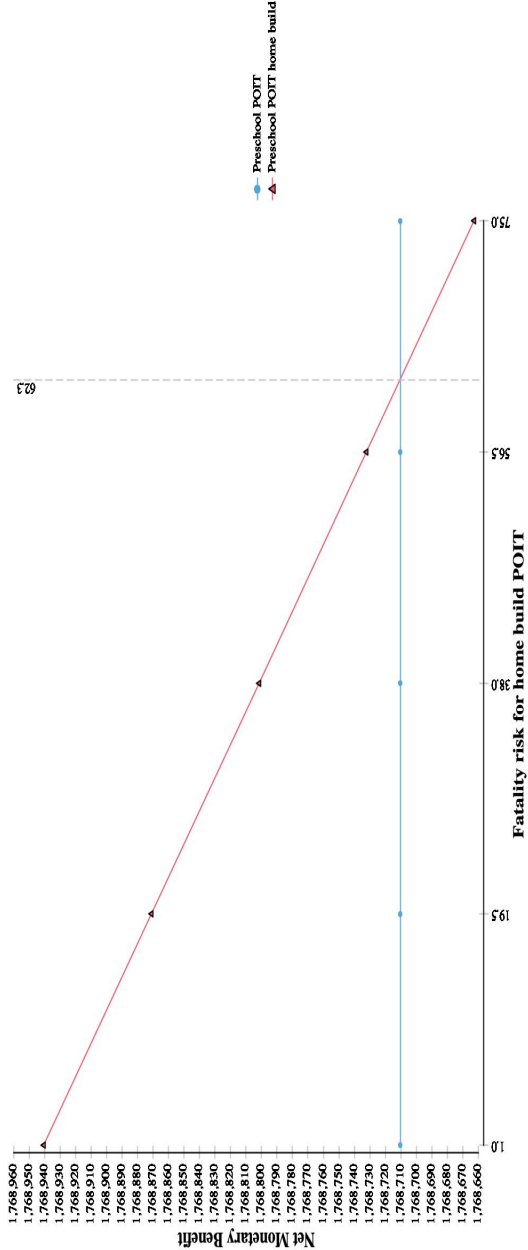


Figure 2

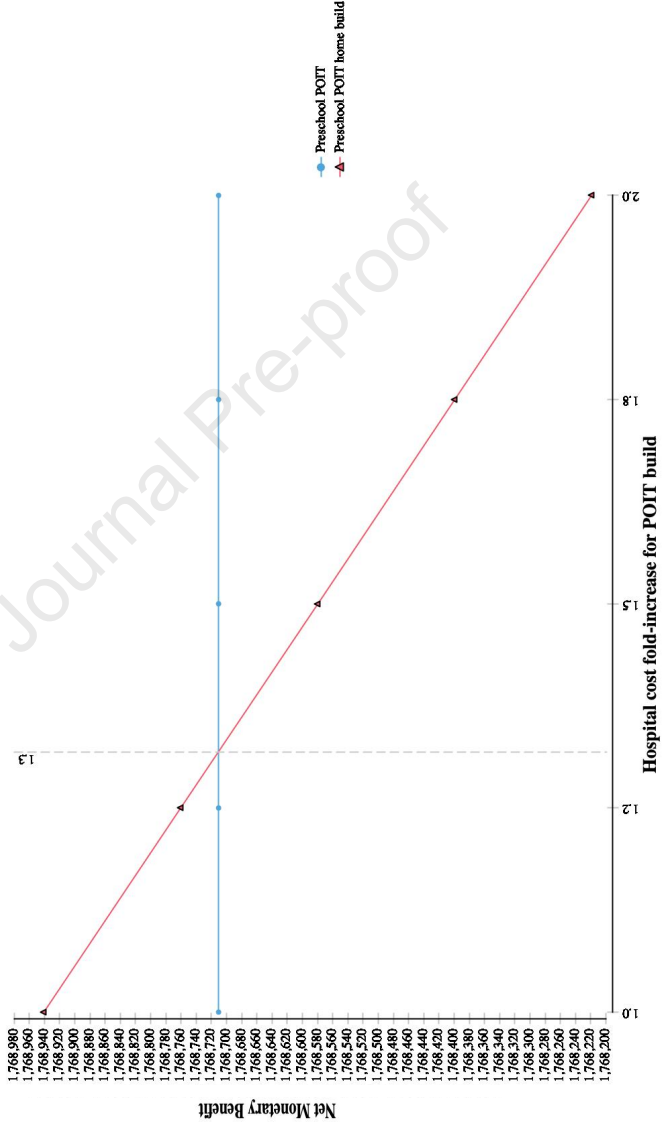
A

US Sensitivity Analysis on Home Build Fatality Risk



B

US Sensitivity Analysis on Home Build Hospital Cost



C

US Sensitivity Analysis on Home Build Risk

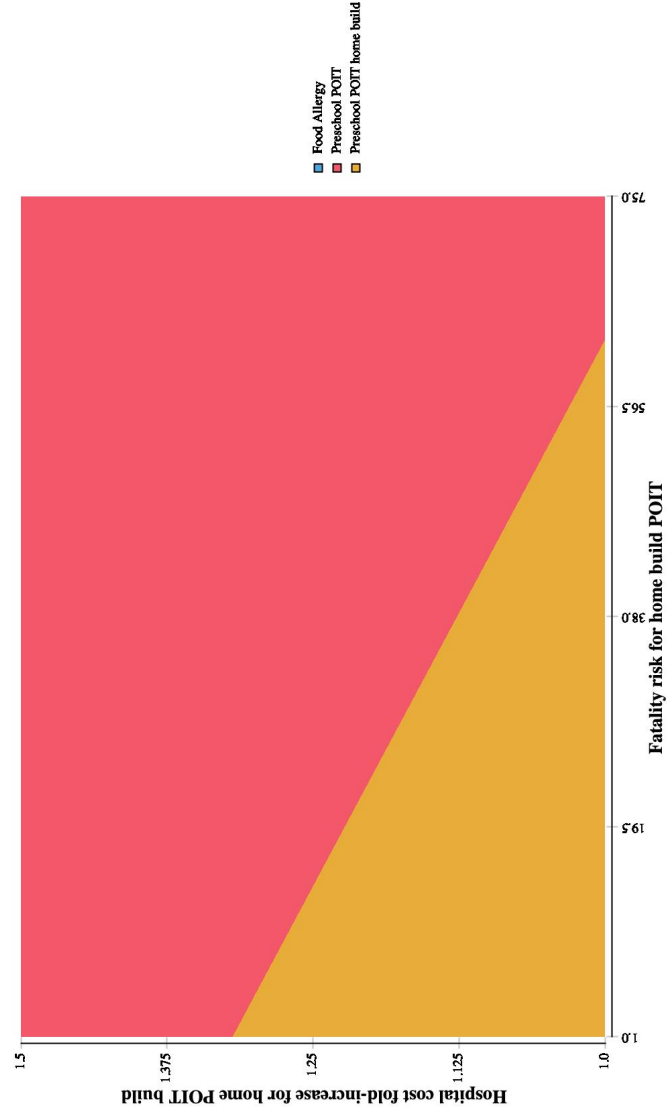


Figure 3

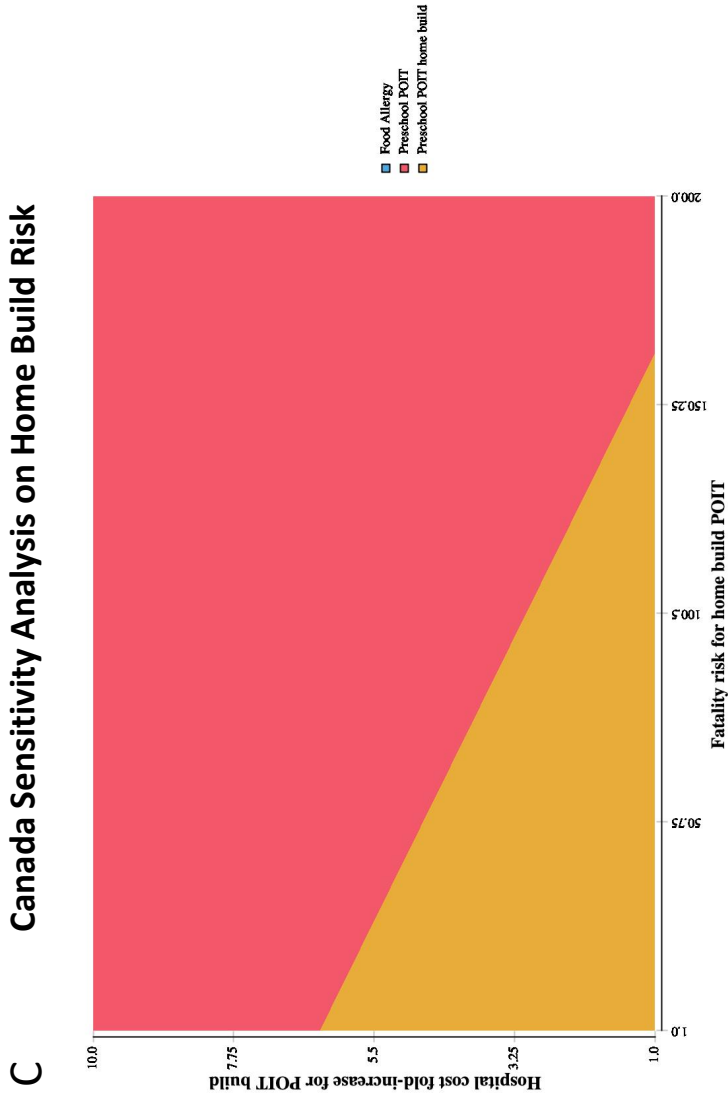
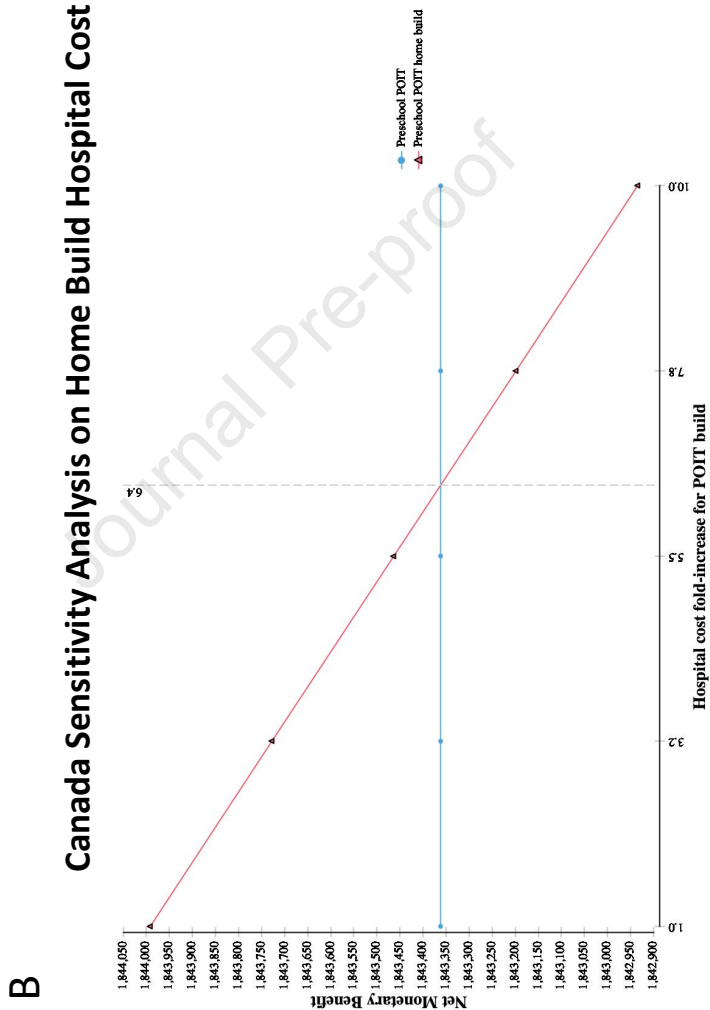
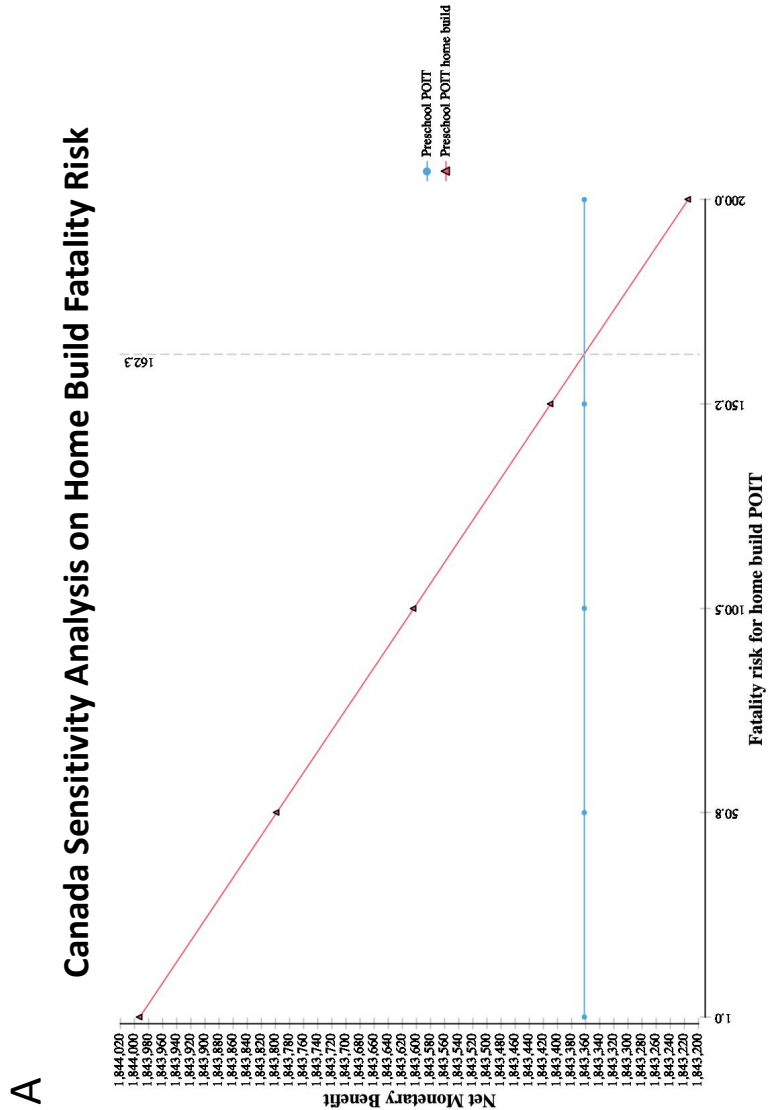
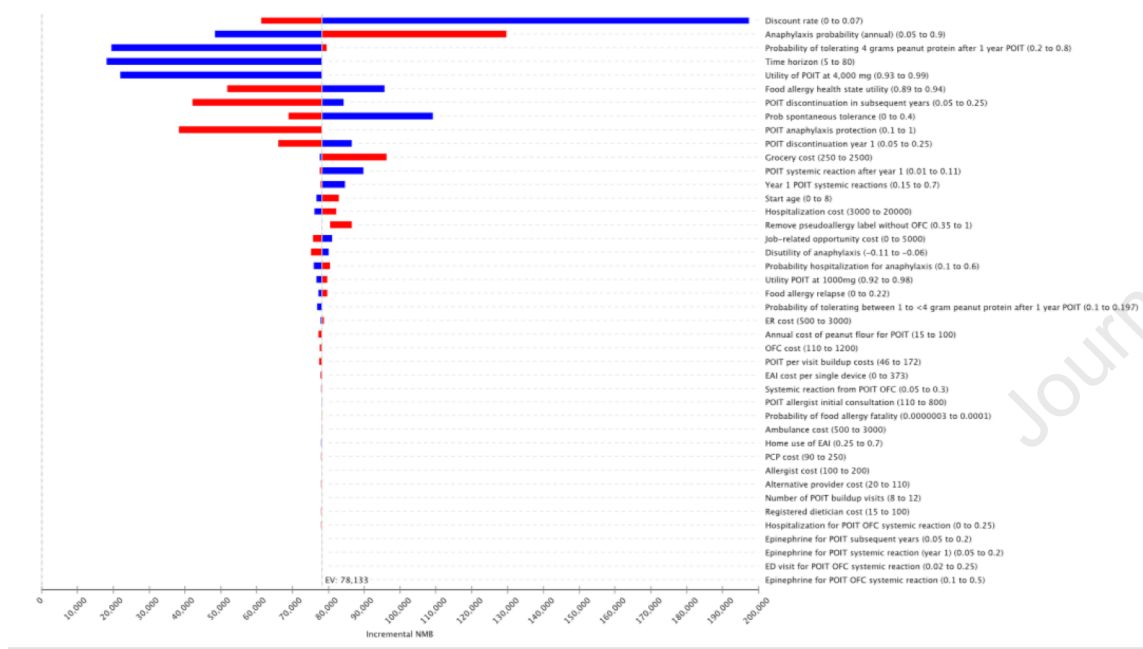


Figure 4

A

US Tornado Diagram. Preschool POIT vs Food Allergy Without POIT (WTP: \$100,000/QALY)



B

Canada Tornado Diagram. Preschool POIT vs Food Allergy Without POIT (WTP: \$100,000/QALY)

