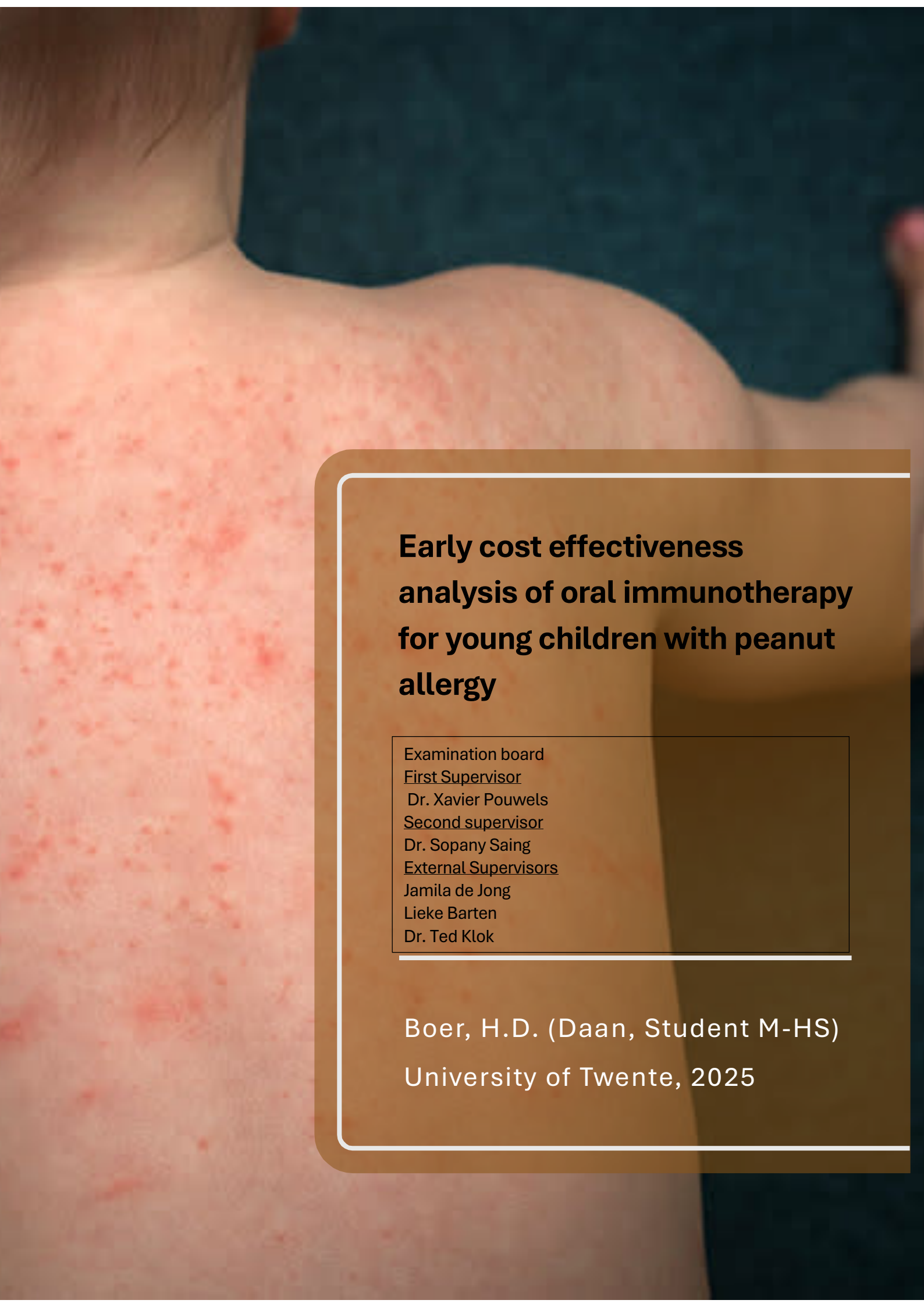

Early cost effectiveness analysis of oral immunotherapy for young children with peanut allergy

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Abstract

Peanut allergy represents a significant health and economic burden, particularly in young children, with limited treatment options currently available. This study assesses the cost-effectiveness of low-dose oral immunotherapy (OIT) compared to the standard of care (SOC) for Dutch children under 30 months. A health state transition model was developed to simulate a cohort over a 25-year horizon, incorporating treatment effects, adherence, and age-specific transitions. Costs and quality-adjusted life years (QALYs) were evaluated from patient, caregiver, and societal perspectives. Multiple scenarios were analysed to address uncertainties in key assumptions.

Results indicate that from a societal perspective OIT is both cost-saving and improves QALYs across all scenarios compared to SOC. Scenario 3, assuming sustained adherence post-desensitization, yielded the greatest QALY gain (+0.644) and cost savings (€75,030) from a societal perspective. Deterministic and probabilistic sensitivity analysis emphasized adherence as a key determinant of costs and health outcomes.

This exploratory analysis suggests that early initiation of OIT is a cost-effective strategy for managing peanut allergies in young children, with the potential to improve health outcomes and reduce societal costs. Further research is recommended to validate these results and address uncertainties related to long-term effects and adherence to regular ingestion of peanut after OIT treatment.

AI statement

"During the preparation of this work, I used chat GPT to review text and code. After using this tool/service, I thoroughly reviewed and edited the content as needed, taking full responsibility for the final outcome."

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Introduction

Peanut allergy (PA) is one of the most common food allergies, affecting approximately 2% of the population in Western countries (10, 15-17). Unlike milk and egg allergies, which are often outgrown, PA tends to persist, with only 20–25% of individuals achieving remission from now on referred to as desensitization (DES) or sustained unresponsiveness (SU) (10, 15). PA is seen as a public health challenge due to its increasing prevalence, lack of curative treatments, and a standard of care (SOC) that relies on strict avoidance of peanuts (10, 15-17). Accidental exposure can result in severe allergic reactions, such as anaphylaxis, which may require emergency interventions i.e. the use of epinephrine auto-injectors or visits to the emergency department (10). PA management imposes a burden on patients, their family and society. Food allergy burden studies, including PA, are scarce outside the United States. Studies from the U.S. found that the lack of treatment options combined with restrictions related to PA management can have an adverse impact on the experienced quality-of-life people with PA, and their informal care givers (10, 15, 16, 18). Estimate on the annual cost of managing food allergies resulted in approximately 22.8 billion euros (23.49 billion U.S. Dolars) in the U.S., with families accounting for the largest share—18.9 billion euros (19.48 billion U.S. Dolars) (17).

Oral immunotherapy for PA

Oral immunotherapy (OIT) is a treatment showing great potential in the management of peanut allergy (19, 20). OIT is designed to raise the threshold at which an allergic reaction occurs, by exposing patients to an increasing amount of the allergen, ultimately helping the immune system become less reactive (21, 22). OIT follows a structured protocol, including an escalation phase, a buildup phase, and finally a maintenance phase (23). This protocol is described in Appendix 1.

The goal of OIT is to achieve DES or SU, tested through an oral food challenge (24). DES is achieved when a patient can tolerate some amount of the allergen immediately after completing OIT (21, 24). SU, a more desirable outcome, is achieved if a patient can tolerate the allergen after a period of avoidance following OIT (21, 24). After reaching DES or SU research suggest adherence to regular peanut consumption ensures preservation of DES and SU, non-adherence could lead to losing DES or SU (3, 12, 14).

Effects of early OIT

Research on the efficacy of OIT in younger children is limited, but previous studies on older patients indicate promising results for the management of PA. Patients reached DES and SU through OIT, improved their quality of life (10, 11, 15, 25). Starting OIT at a younger age may lead to even better outcomes in terms the number of people reaching DES and SU (10, 11, 15, 25). OIT was found to be particularly effective in preschool-

aged children, significantly reducing the risk of allergic reactions following accidental peanut exposure (14).

Little is known about the long-term effects of OIT. Some studies were found to describe the long-term effects of OIT. Some studies have examined the long-term effects of OIT, conducting two-year follow-ups after treatment discontinuation. These studies concluded that OIT can be effective in the long term, while emphasizing the need for continued peanut consumption to maintain a higher threshold (3, 12, 26-28).

Cost effectiveness analysis

To assess whether the effects of an intervention are worth the costs, a cost effectiveness analysis (CEA) can be conducted. CEA is a method that evaluates the economic impact of an intervention relative to its health outcomes, comparing an intervention to the current SOC (25, 29, 30). This analysis helps determine whether a new treatment is more effective and at what possible additional cost (30). By evaluating benefits like improvement on quality-adjusted life years, a CEA aids in assessing the value of new treatments (30). It helps in ensuring that resources are allocated efficiently, balancing the potential benefits against the costs (30). This method is crucial for health care policy makers, clinicians, and organizations, as it helps to identify where more benefit can be gained for the same cost or whether lower cost can be reached for the same benefits (29).

Problem statement

There is limited evidence on the cost-effectiveness of early OIT, particularly in infants and toddlers. While studies from the U.S. and Canada have shown that OIT can be cost-effective in older children, there is a lack of similar data for children under 30 months (14, 15, 23). The increasing prevalence of peanut allergies among children underscores the urgency of addressing this knowledge gap (10, 15-17). Without robust data on the cost-effectiveness of early OIT, healthcare providers and policymakers face uncertainty in determining whether this intervention offers a viable and economically sustainable solution for children under 30 months with peanut allergies.

The ORKA-NL study (NCT05738798), a study conducted across multiple Dutch hospitals, seeks to fill this gap by investigating the cost-effectiveness of low-dose OIT for children under 30 months with established food allergies, including peanut allergies. In alignment with the ORKA-NL study, this study aims to provide early insights into the potential cost-effectiveness of OIT for children under 30 months with peanut allergies compared to SOC.

Method

A CEA was conducted using a time-dependent health state (HS) transition model to compare OIT to SOC. The model simulated the progression of PA in a cohort of 1 year old children, over 25 one-year cycles. This approach allowed for evaluation of the long-term impact of OIT compared to SOC on the development of PA and associated outcomes. This analysis incorporates treatment outcomes and long-term effects of the treatment, on quality of life and cost, considering patient, societal, and healthcare perspectives. This analysis also captures the family burden by calculating cost and treatment outcomes from the perspective of the informal care giver.

Health state	Definition	Age group	Utility (SD)
Allergic	Patients that are allergic to peanut. These patients did not develop Sustained Unresponsivenes, OIT- Desensitized or OIT-Sustained Unresponsiveness.	Infant and child:	0.796 (0.02)
		Adolescent and adult:	0.796 (0.042)
		Informal care giver child:	0.855 (0.012)
		Informal care giver adolescent:	0.799 (0.038)
Lost Desensitisation	Patients who have lost their OIT-Desensitized or OIT-Sustained Unresponsiveness due to non-adherence to OIT treatment. Can only be accesed through the OIT-Desensitized or OIT-Sustained Unresponsiveness health states.	Infant and child:	0.796 (0.02)
		Adolescent and adult:	0.796 (0.042)
		Informal care giver child:	0.855 (0.012)
		Informal care giver adolescent:	0.799 (0.038)
Sustained Unresponsiveness	Allergic patients who have developed sustained	Infant and child:	0.859 (0.016)
	unresponsiveness without OIT treatment.	Adolescent and adult:	0.863 (0.036)
		Informal care giver child:	0.884 (0.011)
		Informal care giver adolescent:	0.857 (0.031)
OIT – Desensitized	Allergic patients who achieved DES through OIT	Infant and child:	0.821 (0.016)
	treatment.	Adolescent and adult:	0.845 (0.032)
		Informal care giver child:	0.849 (0.012)
		Informal care giver adolescent:	0.805 (0.032)
OIT – Sustained Unresponsiveness	Allergic patients who achieved sustained unresponsiveness	Infant and child:	0.859 (0.016)
	through OIT	Adolescent and adult:	0.863 (0.036)
		Informal care giver child:	0.884 (0.011
		Informal care giver adolescent:	0.857 (0.031)
Dead	Absorbing state representing mortality from all causes.	0	

Table 1: Health state definitions and utility values

Model structure

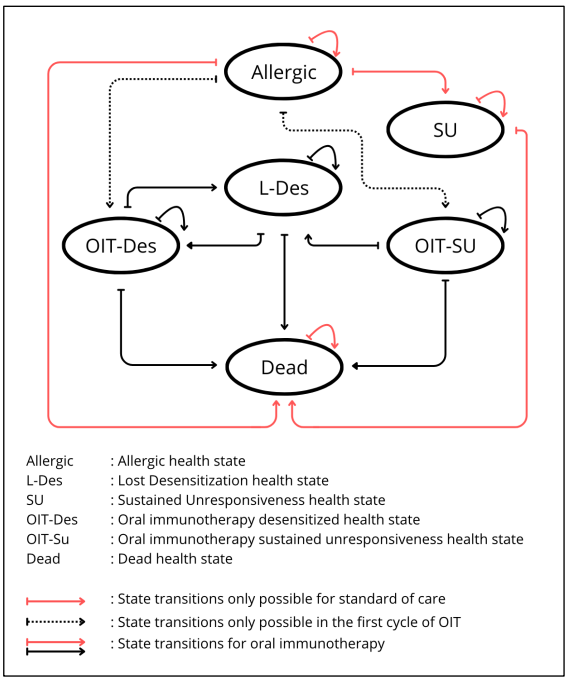
The model consists of six HS. Three of these HS are relevant for SOC and all six are relevant for OIT. The relevant HS for SOC are Allergic, SU and Dead. For OIT Lost Desensitisation (L-Des), OIT-Desensitized (OIT-Des) and OIT-Sustained unresponsiveness (OIT-SU) are relevant too. Table 1: Health state definitions and utility values shows the definition of each HS.

Health state transitions

All patients start in the Allergic HS in both strategies. It's possible for every HS in every cycle to either remain in this HS or transition to the dead HS.

In the first 10 cycles, patients can transition from the Allergic HS to the SU HS, simulating the natural development of SU in both the SOC and OIT. These transitions are the only possible HS transitions for the SOC strategy and are depicted with red arrows in Table 1: Health state definitions and utility values.

Figure 1: Model structure



Health state transitions: Oral immunotherapy

The model assumes that OIT treatment is given in the first cycle of the OIT strategy. Only in this cycle patients transition from the allergic HS to the OIT-Des, or OIT-SU HS. In the OIT-Des and OIT-SU HS, when patients are not adherent to treatment they transition to the L-Des HS. In the L-Des HS, transitioning is possible to the OIT-Des HS.

Transition Probabilities

Yearly transition probabilities (TP) were derived through a systematic review of the literature, following PRISMA guidelines (31). PubMed, Science Direct, and Cochrane Library were searched using terms including "Peanut allergy, "Oral Immunotherapy" and "Placebo".

Studies were included based on relevance to age-specific and treatment-related probabilities for SOC and OIT. Multiple random effects model meta-analysis were performed using the identified studies to estimate yearly TP. TP were calculated for different age groups, treatment effect, adherence rates, and the natural course of PA. These methods reflect the varying efficacy and adherence to regular peanut consumption for different age groups. The TP are presented in Table 2: Transition probabilities, with further methodological details provided in Appendix 3.

Description	Parameter name in the model	Mean (SE)	Source
Allergic to sustained unresponsiveness for infants during OIT	TP_IMMU_A_SU_INF	0.242 (0.170)	(1, 2)
Allergic to desensitized for infants during OIT	TP_IMMU_A_DES_INF	0.319 (0.172)	(1-3)
Allergic to OIT-desensitized for children during OIT	TP_IMMU_A_DES_CH	0.628 (0.097)	(2, 4-8)
Allergic to OIT-desensitized for adolesents and adults during OIT	TP_IMMU_A_DES_ADU	0.321 (0.078)	(9, 10)
Allergic to sustained unresponsiveness for standard of care	TP_SOC_A_SU	0.015 (0.013)	(1, 2)
Adherence to treatment for OIT-desensitized	TP_ADH_DES	0.064 (0.021)	(11, 12)
Adherence to treatment for OIT-Sustained unresponsiveness	TP_ADH_SU	0.122 (0.052)	(4, 5)
Yearly all cause mortality rate per 100,000 persons	V_p_HDage		(13, 14)
Age: 1 year		3.44	
Age: 2-5 year		0.11	
Age: 6-10 year		0.06	
Age: 11-15 year		0.10	
Age: 16-20 year		0.17	
Age: 21-25 year		0.03	

Table 2: Transition probabilities

Two categories of adverse events (AEs) have been defined: accidental AEs, resulting from unintended allergen exposure leading to allergic reactions, and treatment-related AEs, arising as a direct consequence of OIT therapy. When an AE occurs, either no medical intervention is needed, or medical treatment is required. Medical treatment was categorized into three levels of severity: the first involves calling an ambulance, administering epinephrine, and treating the patient on-site without hospital transport; the second requires administering epinephrine, transporting the patient by ambulance to the emergency department, and providing treatment there; and the third necessitates hospital admission, where epinephrine is administered, the patient is transported by ambulance, treated in the emergency department, and subsequently admitted for one day (23).

Accidental exposure to peanuts can happen in every HS. AE's due to OIT treatment can only occur in the OIT-Des and OIT-SU HS. In these HS the patient needs to keep consuming peanut to remain in this HS. The probability of an AE and the need for medical treatment was based on previous studies on accidental exposure to peanuts, OIT, and the safety of OIT (11, 12, 23, 32-34).

The expected number of AEs requiring medical treatment was calculated by considering AE's due to accidental exposure and treatment-related AEs across HS and cycles. For non-OIT HS (Allergic, L-Des and SU), the risk was based on the yearly probability of accidental peanut exposure requiring medical treatment (32).

In the model was the risk of an AE due to accidental exposure for OIT HS (OIT-Des and OIT-SU), compared to the non-OIT HS to reflect the protective effect of OIT. Findings by Baumert et al. suggest that OIT treatment reduces the risk of AE's due to accidental exposure by 95% (CI: 94.9 - 99) (33).

The risk for an AE in OIT HS incorporated treatment-related AEs, which were calculated by multiplying the probability of an AE per dose by the number of annual doses (1, 11). Bird et al. found that the risk of treatment related AE's decreases over time (35).
The proportion of patients reporting a treatment-related AE was calculated, adjusted for, and incorporated into the final AE calculations. After the first OIT cycle, 53.3% of participants experienced treatment-related AEs; in the second cycle, this figure dropped to 25.3%; in the third cycle, to 14.3%; in the fourth cycle, to 4.9%; and from the fifth cycle onward, it stabilized at 3.2%.No literature has been identified indicating a reduction in accidental-exposure AEs for the non-OIT HS; therefore, no time-dependent adjustments were applied to the risk of AEs in the non-OIT HS.

Research suggest that chronically ill patients would reintroduce treatment when their symptoms worsened after a period of non-adherence (36). In this study an AE was defined as the worsening of symptoms. Meaning that an AE in the L-Des HS could lead to the reintroduction of OIT treatment.

Cost Estimation

Cost related to PA and OIT were obtained from national healthcare databases, published cost-effectiveness studies, standard unit cost references and the ORKA-NL study (23, 37, 38). The ORKA-NL study is ongoing, and information from the study was obtained through discussions with the researchers involved.
Cost prices are assumed to be fixed and all costs were adjusted to the cost period of January 2024 using consumer price indexes and future costs were discounted following health economic guidelines (37, 39). Costs were estimated from three perspectives. A healthcare perspective, patient perspective, and societal perspective. For the patient and informal caregiver are cost divided into two categories: personal costs, and societal costs (40). A table including all costs is shown in Appendix 4: Model inputs.

Healthcare costs are the costs made in the healthcare sector for treating a patient with PA. This includes medical costs for OIT treatment, routine care, management of AE's hospitalizations, emergency department visits, ambulance transport, general

practitioner consultations, and medicine (41). Personal costs for patients and informal caregivers are travel expenses, out of pocket costs for medicine, and household productivity loss due to PA (41). Societal costs are costs for productivity losses of work or education due to PA for patients and caregivers (41).

Healthcare cost

The cost of OIT in the first cycle were estimated at €2,924 euros. Costs were based on information from ORKA-NL and are presented in Table 3: Healthcare cost build up for OIT. Yearly healthcare cost for visits to a general practitioner (GP) are calculated by the cost of a GP consult, multiplied by the number of yearly consults.

Description	**Value**	**Cost (€)**
Cost of oral food challenge		786.96
Cost for build up day		900.5
	Proportion	
Entrance oral food challenge	1	786.96
Exit oral food challenge	1	786.96
First build up day	1	900.5
Patients that needs at least 1 additional build up day	0.5	
Proportion from patients that need atleast 1 additonal build up day		
Patients that need 1 additional build up day	0.476	214.32
Patients that need 2 additional build up day	0.276	124.27
Patients that need 3 additional build up day	0.135	60.78
Patients that need 4 additional build up day	0.056	25.21
Patients that need 5 additional build up day	0.05	22.51
Patients that need 6 additional build up day	0.006	2.7
Total cost of OIT		2924.22

Table 3: Healthcare cost build up for OIT

nb: All patients had to perform an entrance and exit oral food chalenges and at least 1 build up day. 50% of the patients needed additional build up days. Cost of additional build up days are calculted by multiplying the number of days by the costs of an build up day. The cost are multiplied by the proportion of patients that needed this numer of additional build up days.
Cost for adverse events during OFC's or build-up days are accounted for in the costs of an OFC or build-up day.

Healthcare costs for medical treatments are shown in Table 4: Healthcare costs. Values for children and adults are almost the same. The difference in cost lies in the use of an epipen, which has higher purchase cost for children than they do for adults. All treatments require the use of an epipen, which results in a new delivery of medicine to the pharmacy. An ambulance ride

Total cost of care	**Child Cost (€)**	**Adult costs (€)**	**Probability**
Ambulance ride	799.53	773.25	0.005
Emergency department visit	339.90	333.62	0.027
Hospital Admission	1514.45	1508.17	0.01

Table 4: Healthcare costs

requires an epipen and the costs of an ambulance. Hospital admission requires a combination ambulance transport and a nursing day. Exact costs of these individual treatments are shown in Appendix 3. Probability shows the probability this treatment is needed in the occurrence of an AE (23).

Personal costs of treatment

The first year of OIT treatment is estimated to result in 351 euros of personal costs. These costs are a result of travel expenses for treatment, productivity loss of the informal care givers due to build up days and medicine costs. Personal costs for AE's are a result of travel expenses to the hospital and out of pocket costs for medicine.

Productivity loss

Productivity loss was calculated using the human-capital method, drawing on a real-world survey study. The study included 102 adolescent, 153 participants with PA and 382 informal caregivers of children with PA and assessed how peanut allergy affects productivity in children, adolescents, adults, and their informal caregivers (42-44). Productivity loss was measured as weekly hours lost for work, education and household jobs. The weekly hours of productivity loss were multiplied by the hourly wages for these categories. To calculate the appropriate yearly productivity loss, weekly productivity loss for household jobs has been multiplied by 52, productivity loss for work by 48, and productivity loss for education by 40 (45).
A full overview of the hourly cost is shown in appendix 3. Yearly hours lost, and yearly costs is shown in Table 5: Weekly hours of productivity lossand Table 6: Yearly costs of productivity loss.
The total cost from the patient or caregiver perspective was the sum of their personal cost, general healthcare cost, and societal cost (40). Productivity loss and personal costs for caregivers are assumed to drop to zero when the child with PA reaches 18 years of age. At this age, it is assumed that patients become responsible for their own healthcare costs, can travel independently to appointments, and may no longer reside with their parents. Consequently, costs are borne by the allergic individual from the age of 18 onwards.

Calculation of costs

The overall cost from a societal perspective is the sum of personal cost for patients, societal cost for patients, personal cost for caregivers, societal cost for caregivers, and the total healthcare costs. Most available cost data is based on peanut-allergic patients who did not receive OIT. These costs might accurately reflect the SOC strategy but do not reflect the effects observed in OIT scenarios. To address this, AE risks were weighted relative to the baseline derived from SOC. These weights were capped between 0 and 2 to prevent for extreme values.

Category	Household (SE)	Education (SE)	Work (SE)
Child hours scheduled	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Child hours lost due to absenteeism	0.00 (0.00)	2.00 (0.00)	0.00 (0.00)
Child hours lost due to presenteeism	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Child total hours lost	0.00 (0.00)	2.00 (0.00)	0.00 (0.00)
Adolescent hours scheduled	6.40 (6.40)	17.00 (15.60)	0.00 (0.00)
Adolescent hours lost due to absenteeism	0.34 (0.34)	0.87 (0.80)	0.00 (0.00)
Adolescent hours lost due to presenteeism	0.22 (0.22)	0.52 (0.48)	0.00 (0.00)
Adolescent total hours lost	0.56 (0.40)	1.39 (0.93)	0.00 (0.00)
Adult hours scheduled	11.30 (10.70)	6.70 (16.40)	37.20 (34.20)
Adult hours lost due to absenteeism	0.67 (0.63)	0.58 (1.43)	0.82 (0.75)
Adult hours lost due to presenteeism	0.26 (0.25)	0.28 (0.68)	0.97 (0.89)
Adult total hours lost	0.93 (0.68)	0.86 (1.58)	1.78 (1.17)
Caregiver hours scheduled	13.60 (13.20)	0.00 (0.00)	36.00 (26.30)
Caregiver hours lost due to absenteeism	0.90 (0.87)	0.00 (0.00)	1.91 (1.39)
Caregiver hours lost due to presenteeism	0.33 (0.32)	0.00 (0.00)	1.17 (0.85)
Caregiver total hours lost	1.23 (0.93)	0.00 (0.00)	3.08 (1.64)

Table 5: Weekly hours of productivity loss

Absenteeism: hours being absent
Presenteeism as hours being present but not able to fully participate.

Category	Household (SE)	Education (SE)	Work (SE)
Child cost due to absenteeism	0.00 (0.00)	837.60 (0.00)	0.00 (0.00)
Child cost due to presenteeism	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Child total cost	0.00 (0.00)	837.60 (0.00)	0.00 (0.00)
Adolescent cost due to absenteeism	331.60 (331.60)	529.22 (485.63)	485.63 (0.00)
Adolescent cost due to presenteeism	213.35 (213.35)	319.60 (293.29)	293.29 (0.00)
Adolescent total cost	544.95 (394.31)	848.82 (567.32)	567.32 (0.00)
Adult cost due to absenteeism	651.77 (617.16)	566.81 (566.81)	1387.42 (1440.27)
Adult cost due to presenteeism	252.97 (239.54)	271.68 (271.68)	665.04 (1708.69)
Adult total cost	904.74 (662.02)	838.49 (838.49)	1538.56 (2234.73)
Care giver cost due to absenteeism	877.49 (851.69)	0.00 (0.00)	3652.37 (2668.26)
Care giver cost due to presenteeism	325.74 (316.16)	0.00 (0.00)	2239.66 (1636.20)
Care giver total cost	1203.23 (908.47)	0.00 (0.00)	5892.03 (3129.98)

Table 6: Yearly costs of productivity loss

Absenteeism: hours being absent
Presenteeism as hours being present but not able to fully participate.

Health Outcomes

Health outcomes were measured in quality-adjusted life years (QALYs) (46). Utility values, representing the health-related quality of life on a scale from 0 (death) to 1 (perfect health), were assigned to each HS for both patients and informal caregivers to capture the family burden of managing PA (42, 46). Utility values are shown in Table 1: Health state definitions and utility values. The values are based on a utility proxy study researching the health-related quality-of-life for PA as real-world values were not available (42). T Because this study did not include utility scores for infants or allergic adults, we used the utility values for children and adolescents, respectively, as proxies for these populations.

SU shows the highest utility followed by Des, Allergic shows the lowest utility value for all age groups.

Key model assumptions

Due to the lack of long-term evidence on the effect of OIT on PA, several assumptions were necessary for the model. Primary assumptions are detailed below.

Adherence

Patients in the OIT-Des and OIT-SU HS may lose their DES or SU when not adherent to regular peanut ingestion. Non-adherence can lead to a transition to the L-Des HS. This assumption is critical, as adherence significantly influences the effectiveness of OIT.

Reinitiation

Patients who lose DES due to non-adherence have the option to reinitiate OIT and transition back to the OIT-Des HS. However, reinitiation is assumed to occur only after an AE (36). This assumption underscores the importance of adherence, and the potential challenges associated with reinitiating therapy.

Mortality

Mortality due to PA is considered negligible compared to all-cause mortality and is not explicitly modelled. This assumption aligns with existing literature indicating that fatal outcomes from PA are rare and do not influence the life expectancy or cost effectiveness outcomes (47-49).

Analysis and Outcomes

Primary outcome measures in this study were total and incremental costs, and QALYs, of OIT compared to SOC. Analytical methods included probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis (DSA). The PSA evaluated uncertainty by varying model parameters probabilistically, while the DSA systematically examined the impact of changes in all parameters. The findings from the DSA provided insights into parameters that most affected the outcomes.

Scenario analysis

To evaluate the impact of key assumptions on model outcomes, multiple scenarios were analysed. An overview of each scenario and the assumptions is provided in Table 7: Model Scenario's.

Scenario	Name	Discription
Scenario 1 (S1)	Base Scenario	Scenario as described in state transitions
Scenario 2 (S2)	No OIT reinitiation	Patients do not reinitiate OIT after they have transitioned from OIT-Des or OIT-SU to L-Des In the model, they are not able to transition from Lost Desensitisation to OIT-Des.
Scenario 3 (S3)	Long term adherence	Patients from the age of 10 stay adherent to treatment for the full duration of the model. In the model, the transition from OIT-Des and OIT-SU to L-Des is not possible anymore after the 10th cycle.
Scenario 4 (S4)	No OIT reinitiation combined with long term adherence	A combination of scenario 2 and 3. Patients do not reinitiate OIT after they have transitioned from OIT-Des or OIT-SU to L-Desand patients from the age of 10 stay adherent to treatment.

Table 7: Model Scenario's

Probabilistic Sensitivity Analysis

To assess the impact of the uncertainty of multiple parameters on the model outcomes a PSA was performed using Monte Carlo simulation with 10,000 iterations (50). All model parameters are presented in appendix 3. Probability distributions were assigned to all model inputs to account for parameter uncertainty. Beta distributions were chosen for utility values and productivity loss percentages, because they are constrained between 0 and 1. Dirichlet distributions were used for multinomial transition probabilities when patients could transition to multiple HS from a single HS. If not, beta distribution was applied. Values assumed fixed, such as costs, were consistently applied across all iterations. Each iteration of the PSA, parameters were randomly sampled from their respective distributions, and model outcomes were recalculated to produce distributions of costs and QALYs for each treatment strategy. The PSA results allowed for the estimation of the expected mean and 95% confidence intervals around the outcomes for each strategy.

Deterministic Sensitivity Analysis

A DSA was performed to evaluate the impact of individual parameters on model outcomes. This approach helps identify key drivers of cost and effectiveness differences between treatment strategies. The DSA employed a univariate method, where each parameter was varied independently while holding other parameters constant at their mean values. Parameters were varied over their plausible ranges, which included the 2.5th and 97.5th percentiles of their respective distributions. Parameters with statistically significant effects (p-value ≤ 0.05) were included in tornado diagrams, which visually represent the magnitude of parameter effects. This method helps showing which model inputs have the greatest effect on the results, highlighting the critical areas for further research. The use of tornado diagrams provides a visual summary of the relative importance of each parameter.

Software and Computational Tools

All analyses were performed using R statistical software (R version 4.4.1 (2024-06-14). The AI tool ChatGPT (version 1.2024.339) was used for code and text review.

Ethical Considerations

This study utilized publicly available data and did not involve human subjects or personal health information. The study has been approved by the ethical committee of the University of Twente (Allocation nr. 240967).

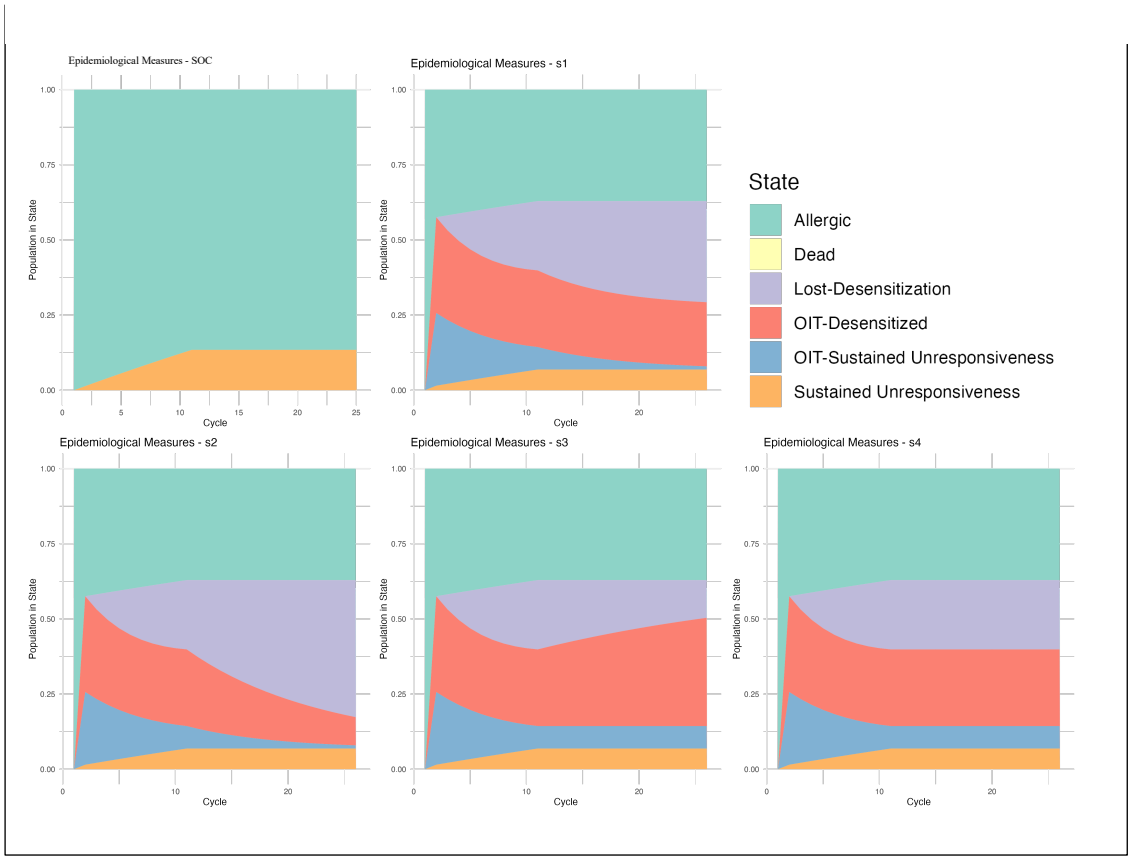
Results

This chapter presents the findings of the PSA and DSA. The PSA results are presented and analysed according to three main factors: HS occupation, AEs, and cost-effectiveness outcomes. The DSA findings are summarized using a tornado diagram to illustrate the impact of key parameters on the results.

Health state occupation

Figure 2: Health state occupancy illustrates the HS occupancy plots for the SOC and four OIT scenarios, based on the PSA. All scenarios were modelled using the same set of parameters. SOC shows that after 10 cycles about 12.5% of the participants have developed and stay sustained unresponsive without treatment.
In S1, approximately 65% of patients are in the OIT-Des, OIT-SU, or SU HS after the first cycle. However, this decreases to around 30% by cycle 25, indicating a loss of DES or SU over time. S2 demonstrates a more rapid decline, with fewer than 20% of patients remaining in DES or SU HS after 25 cycles, suggesting poorer long-term outcomes. In contrast, S3 and S4 show more favourable trends, with approximately 40% to 50% of patients maintaining DES or SU by the end of 25 cycles. These results reflect the potential impact of adherence and successful reinitiation of OIT after non-adherence.

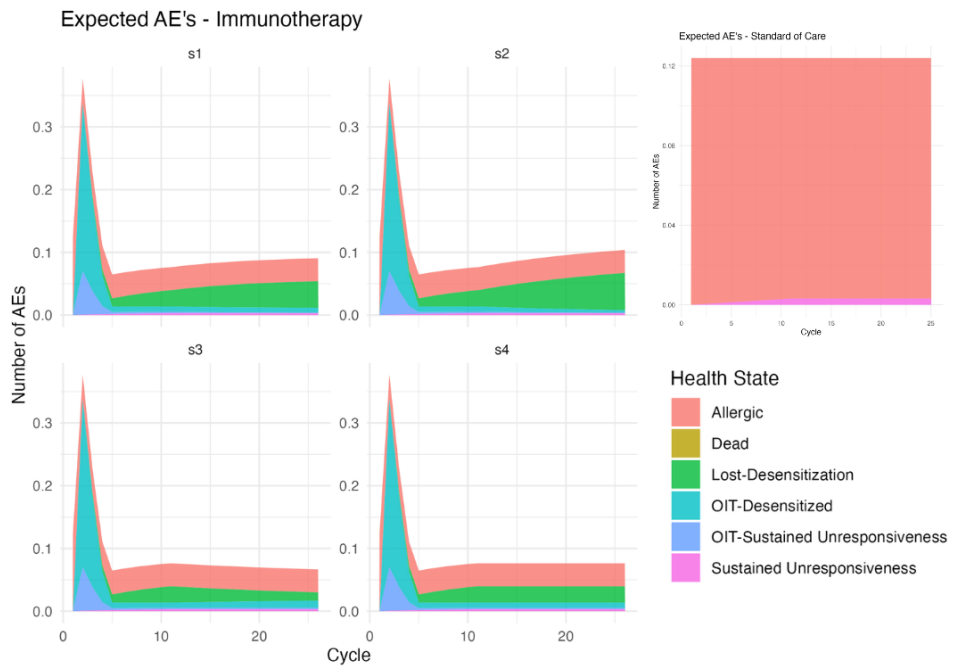
Figure 2: Health state occupancy



Expected adverse events

Followed by HS occupation, the expected number of AE's were calculated for every cycle in every HS based on the PSA results. The expected AEs are visualized in Figure 3: Adverse events for SOC and OIT. Expected AEs are the highest in the beginning of the model. Especially in the OIT-Des HS. In this HS, patients experience the highest level of peanut exposure, and it also represents the most populated HS. The risk for an AE reduces in the OIT-DES and the OIT-SU HS showing positive effects of OIT on the risk of an AE. This is also shown in the total number of AE's. For the model duration, a total of 3.22 AEs per person are expected in SOC, in S1, S2, S3 and S4 2.62, 2.73, 2.39 and 2.38 AEs are expected.

Figure 3: Adverse events for SOC and OIT



S1: Base Scenario, *S2:* No OIT reinitiation *2, S3:* Long term adherence *3, S4:* No OIT reinitiation combined with long term adherence.

Cost-effectiveness outcomes

Table 8: PSA Cost and effects shows the cost-effectiveness outcomes for all scenarios showing OIT is both cost-saving and more effective compared to SOC from a societal perspective. S3 showed the largest QALY gain for both patients (0.495) and informal care givers (0.149) compared to SOC. For informal caregivers, QALY differences across scenarios were minimal, suggesting that OIT primarily impacts the patient. S3 showed the largest cost savings of €75,030. Only the healthcare costs for all OIT scenarios were higher than SOC._OIT showed only from a healthcare perspective to not be cost saving.

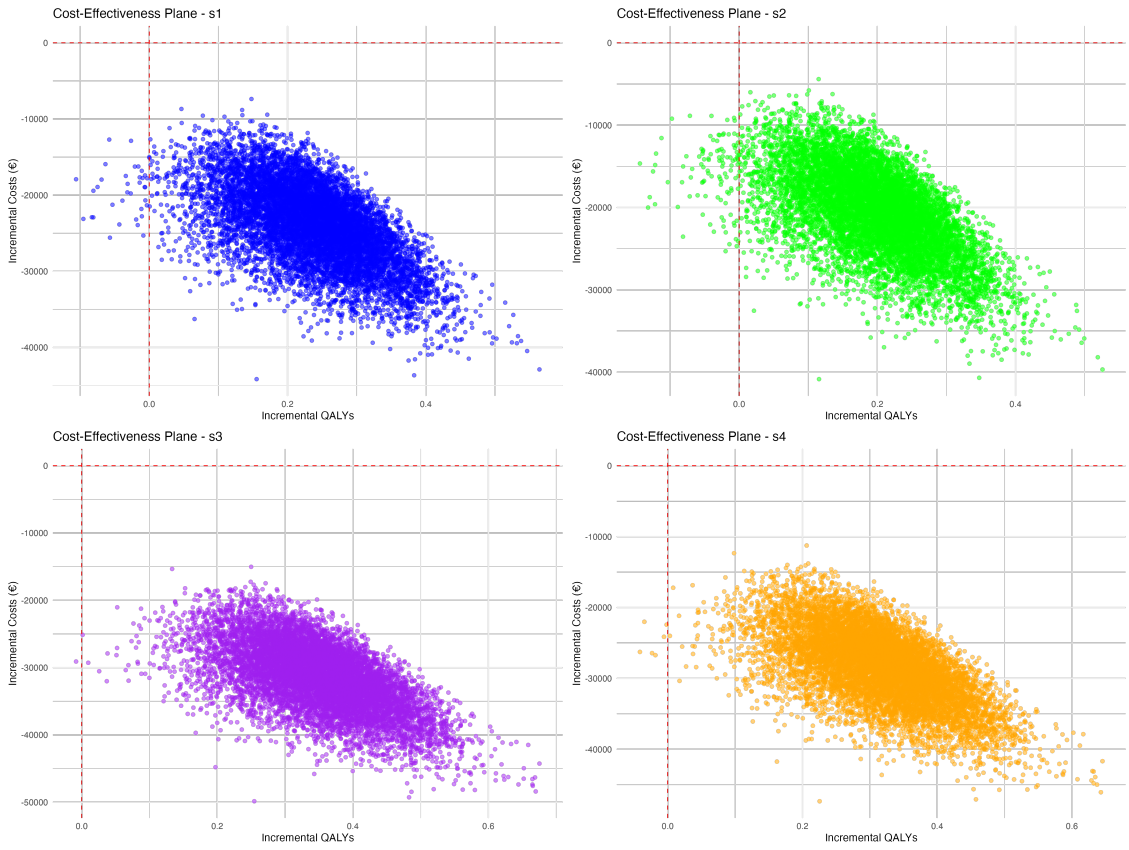
Figure 4: Cost effectiveness planesshows the combined cost-effectiveness plane. From a societal perspective all scenarios are in the cost-saving quadrants. S1 shows 99.6% of the simulations to result in higher QALY's, for S2 this is 98,9%, S3 99,9% and S4 99,9%.

	Utility			Personal cost			Societal Cost			Healthcare Cost			Total Cost		
	Patient	Caregiver	Total	Patient	Caregiver	Total	Patient	Caregiver	Total	Patient	Caregiver	Total	Patient	Caregiver	Total
SOC	17.102	17.713	34.815	€ 6,195	€ 21,676	€ 27,871	€ 29,150	€ 106,052	€ 135,202	€ 5,592	€ 5,592	€ 11,184	€ 40,956	€ 135,946	€ 176,932
S1	17.504	17.813	35.317	€ 4,304	€ 16,622	€ 20,925	€ 21,543	€ 79,602	€ 101,145	€ 7,058	€ 7,058	€ 7,058	€ 32,912	€ 105,168	€ 138,091
Δ S1	0.402	0.100	0.502	-€ 1,891	-€ 5,055	-€ 6,945	-€ 7,606	-€ 26,451	-€ 34,057	€ 1,466	€ 1,466	-€ 4,127	-€ 8,044	-€ 30,779	-€ 38,840
ICER				-€ 4,704	-€ 50,399	-€ 13,828	-€ 18,922	-€ 263,744	-€ 67,806	€ 3,646	€ 14,613	-€ 8,216	-€ 20,010	-€ 306,895	-€ 77,330
S2	17.463	17.808	35.271	€ 4,683	€ 16,868	€ 20,641	€ 23,109	€ 80,810	€ 103,919	€ 7,209	€ 7,209	€ 7,209	€ 35,009	€ 106,905	€ 141,926
Δ S2	0.361	0.095	0.457	-€ 1,511	-€ 4,808	-€ 7,229	-€ 6,041	-€ 25,243	-€ 31,283	€ 1,617	€ 1,617	-€ 3,976	-€ 5,947	-€ 29,042	-€ 35,006
ICER				-€ 4,182	-€ 50,436	-€ 15,830	-€ 16,717	-€ 264,819	-€ 68,502	€ 4,474	€ 16,960	-€ 8,705	-€ 16,458	-€ 304,675	-€ 76,653
S3	17.597	17.862	35.459	€ 3,517	€ 15,998	€ 18,561	€ 18,398	€ 76,550	€ 94,948	€ 6,735	€ 6,735	€ 6,735	€ 28,657	€ 97,585	€ 100,902
Δ S3	0.495	0.149	0.644	-€ 2,678	-€ 5,678	-€ 9,309	-€ 10,752	-€ 29,502	-€ 40,254	€ 1,143	€ 1,143	-€ 4,449	-€ 12,299	-€ 38,361	-€ 76,030
ICER				-€ 5,409	-€ 38,045	-€ 14,448	-€ 21,717	-€ 197,669	-€ 62,475	€ 2,309	€ 7,660	-€ 6,905	-€ 24,843	-€ 257,028	-€ 118,000
S4	17.565	17.858	35.423	€ 3,815	€ 16,215	€ 20,030	€ 19,608	€ 77,612	€ 97,220	€ 6,856	€ 6,856	€ 6,856	€ 30,286	€ 102,403	€ 132,700
Δ S4	0.463	0.145	0.608	-€ 2,380	-€ 5,461	-€ 7,841	-€ 9,542	-€ 28,440	-€ 37,982	€ 1,264	€ 1,264	-€ 4,329	-€ 10,670	-€ 33,543	-€ 44,232
ICER				-€ 5,141	-€ 37,582	-€ 12,893	-€ 20,615	-€ 195,720	-€ 62,454	€ 2,730	€ 8,696	-€ 7,118	-€ 23,053	-€ 230,838	-€ 72,732

Table 8: PSA Cost and effects

Soc: Standard of care, S1: Base Scenario, *S2:* No OIT reinitiation *2, S3:* Long term adherence *3, S4:* No OIT reinitiation combined with long term adherence.
Δ S1-S4 present the difference in value between this scenario and the standard of care

Figure 4: Cost effectiveness planes



S1: Base Scenario, *S2:* No OIT reinitiation *2, S3:* Long term adherence *3, S4:* No OIT reinitiation combined with long term adherence.

Deterministic sensitivity analysis

The results of the DSA, visualized in Figure 5: Parameter effect, show the impact of varying parameters within their confidence intervals on the cost and health related outcomes. Across all scenarios, the parameter representing the natural progression towards SU under SOC (TP_SOC_A_SU) has the greatest influence on health outcomes. Adherence parameters—TP_ADH_DES and TP_ADH_SU—affects both cost and effectiveness, aligning with the trends observed in HS occupancy. The probability of an AE following accidental exposure in health states not receiving OIT (v_ae_nooit) influences the cost outcomes of OIT, but its effects are relatively minor compared to those of adherence parameters. The effectiveness of reintroducing OIT after an AE, represented by TP_IMMU_A_DES_CH and TP_IMMU_A_ADU for children and adults, respectively, plays a crucial role in shaping outcomes. Lastly, the parameters TP_IMMU_A_DES_INF and TP_IMMU_A_SU_INF, reflecting OIT efficacy in infants, underscore the importance of treatment effectiveness in determining cost and health outcomes.

Figure 5: Parameter effect

Upper bound: outcomes when a parameter is set to its upper confidence limit
Lower bound: outcomes when the parameter is set to its lower confidence limit.

S1: Base Scenario, *S2:* No OIT reinitiation *2, S3:* Long term adherence *3, S4:* No OIT reinitiation combined with long term adherence.

Discussion

This CEA provides an early indication of the cost-effectiveness of early low-dose OIT for PA in Dutch children under 30 months, suggesting that OIT is a promising alternative to SOC. All scenarios involving OIT are cost-saving and for the larger part more effective than SOC from a societal perspective. Scenario 3, the most optimistic scenario simulating the possibility to reinitiate OIT, showed the most favourable outcomes, saving €75,030 euros and gaining 0.644 QALY's. These results support the potential of OIT to improve QALYs while reducing costs.

The findings that OIT may be cost-effective align with previous cost-effectiveness studies (14, 25, 38). Shaker et al. demonstrated that OIT could improve health and economic outcomes for young children in real-world settings (14, 23). In their 80-year simulation, OIT treatment showed a cost reduction of $1,853 dollars and a QALY gain of 0.75 from a societal U.S. perspective compared to no OIT (14). From a Canadian societal perspective OIT showed a cost reduction of $13,737 dollars and a QALY gain of 0.57 (14). The use of epinephrine was per person reduced from 9.76 (5.85) to 5.85 (SD 5.73) with OIT in the US, and in Canada from 0.53, (SD 0.38) to 0.34 (SD 0.36).

Although that Shaker et al. arrived at similar conclusions regarding OIT's cost-effectiveness there are notable differences in the outcomes between the current study and the work by Shaker et al. The reason for these different outcomes could come from the time horizon, perspective, HS and transitions, cost construction and utility values that were used by Shaker et al.

Shaker et al. simulated outcomes over 80 years, whereas the current study used a 25-years. Additionally, Shaker et al. adopted an US and Canadian societal perspective, which involved different cost inputs and excluded the utility of informal caregivers.

Regarding the HS did Shaker et al. distinguish two HS that could tolerate different amount of peanut and tow HS for resolved PA. In their model after receiving OIT there is no possibility to transition from an allergic HS to an HS that tolerates peanut.

By constructing the costs do Shaker et al. take cost for groceries into account but they do not account for productivity loss due to PA. Regarding utility values does the current study incorporated utility values from a proxy study by Gallop et al., offering a broader view of informal caregiver impact (51). Shaker et al. relied on utility values from studies that did not specifically measure health-related quality of life for PA, potentially limiting their real-world applicability (14, 23, 51). The model assumed 0.91 utility for the allergic HS and subtracted 0.09 (SD 0.06 to 0.11) disutility in case of an AE. Although utility values for the other HS were unclear. This utility calculation results in a relatively high

utility compared to the utility values used in this model where the highest utility value is 0.884 (0.011).

To the author's knowledge, only Huang et al. incorporated real-world data into a CEA (52). Their study consisted of a prospective CEA conducted alongside a randomized controlled trial at the Royal Children's Hospital in Melbourne, Australia, involving 56 children aged 1–10 years with peanut allergy. Among patients who achieved SU following probiotic OIT, the mean utility increased from 0.86 (SD 0.9) at baseline to 0.95 (SD 0.04) at the four-year post-treatment follow-up. In comparison, the placebo group's mean utility changed from 0.82 (SD 0.11) at baseline to 0.86 (SD 0.13) over the same period. Comparing the utility values reported by Huang et al. with those used in this model by McCann et al. indicates that, for infants and children, the utility values for both the allergic and SU health states are relatively similar.

The importance of adherence was mentioned in previous research by Uhl et al. and Vickery et al. Both underscored that it would be essential to keep consuming peanuts after reaching DES or SU to keep a higher tolerance to peanut (3, 28). The HS occupation analysis and deterministic analysis of this research confirm that adherence is a critical factor in achieving optimal outcomes.

Strengths and limitations

To the knowledge of the author, this cost-effectiveness study is the first to include the perspective of the informal care giver in researching the cost-effectiveness of OIT for PA. In addition, this study is the first to clearly distinguish the personal, societal and healthcare costs providing a comprehensive perspective where cost savings are made when providing OIT. This approach shows that despite OIT has minimal effect on quality of life of the informal care givers, costs reductions are mostly observed in their perspective. While the findings of this study are promising, several limitations must be acknowledged. The model relies on assumptions regarding adherence rates, treatment efficacy, the natural progression of the allergy, and age-specific transitions. Although the simulation spans 25 years, evidence supporting the long-term efficacy and safety of OIT remains scarce (12, 34). However, by incorporating multiple scenarios, the analysis provides valuable insights into potential outcomes under different assumptions, helping in the understanding of how OIT might perform.

Utility values used in the model were based on a study focusing on adolescents, and caregivers, as real-world data was unavailable. The study used a cross-sectional design with data collected through an online survey and structured interviews, involving 100 caregivers and 38 adolescents who were treatment-naïve, and 7 caregivers and 2

adolescents with experience of OIT for PA (51). The use of these results could possible over or underestimate the effects of OIT on the health-related quality of life.

The model excludes mortality directly related to PA, assuming that anaphylaxis-related deaths and their reduction are negligible compared to other causes. This assumption aligns with similar models and systematic reviews indicating that food allergy mortality has minimal impact on costs, outcomes, or life expectancy (48, 49, 53). Nagendran et al. even suggested that it is extremely unlikely that OIT would reduce food allergy mortality (47). This limitation is a conservative assumption, as it potentially underestimates the benefits of OIT by excluding any reduction in mortality risk associated with anaphylaxis. By assuming no significant impact on mortality, the model focuses on quality-of-life improvements and cost savings, avoiding overestimation of OIT's overall effectiveness. However, if OIT does reduce mortality risks, the model may underestimate its benefits.

Given the exploratory nature of this study, further research is needed to validate the findings and refine model inputs, especially the long-term effects of OIT, quality of life, and adherence. Large cohort studies are crucial to comprehensively assess the benefits and limitations of early OIT.

Conclusion

This study shows that early OIT is a cost-effective strategy for managing peanut allergy in young children, improving both patient and caregiver quality of life while reducing societal costs compared with standard of care. Nonetheless, uncertainties remain regarding the long-term effects of OIT and the extent of treatment adherence, underscoring the need for continued research.

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Appendix

Appendix 1: Oral Immunotherapy Protocol

The treatment follows a protocol that consists of three phases, the initial dose escalation, buildup, and maintenance phase (24). The initial dose escalation phase lasts one day and starts with a very small, subthreshold dose of the allergen, which is increased over time until the goal dose for that day, or the highest dose tolerated without symptoms is reached (24).

The initial dose phase is followed by the up-dosing phase (24). In this phase, patients consume the highest dose they achieved during the initial phase at home once a day until their next appointment (24). The number of appointments can vary, between 1 and 6 appointments, depending on the height of the threshold (54). At each appointment, the dose is increased, and the patient is observed for reactions. This process continues at two-week intervals until the goal dose, or the highest tolerated dose is reached(24).

Next is the maintenance phase of oral immunotherapy, this phase involves the patient continuing to take the established maintenance dose daily, which can last for months to years (24). For the peanut-allergen product, the recommended dosage is 300 mg/day (24). This phase ensures that the patient maintains DES and hypo responsiveness to the allergen (24).

When the patient has been in the maintenance phase for a long time and is doing well, a food DES challenge, called an oral food challenge, may be performed(24). This challenge involves ingesting a full serving of food to test for tolerance (24). This challenge can be performed directly after discontinuation of the daily treatment, but also after a period of avoidance of the peanut allergen after discontinuation of the treatment (24). If performed directly after discontinuation of daily treatment, DES is tested. If performed after a period of avoidance, SU is tested.

If the patient can ingest the food without an adverse reaction after a period of avoidance, SU has been achieved, meaning the desensitized state is maintained without the need for daily allergen ingestion (21, 24). Some patients experience symptoms of a hypersensitivity reaction during the food challenge: egg, they had been tolerating the controlled doses of the allergen but reacted to a full meal. These patients are often deemed “bite-proof,” or desensitized meaning they are unlikely to have an allergic reaction to 1 bite of a peanut product or a product contaminated by peanut, but unlike patients who have SU, they need to continue their maintenance dosing to sustain their hypo responsiveness (24). Despite that there are not any generally accepted definitions for these outcomes, these definitions seem to be commonly used (21).

Threshold level	0.001g = 1mg	0.003g = 3mg	0.010g = 10mg	0.030g = 30mg	0.1g = 100mg	0.3g = 300mg	1g = 1000mg	3g = 3000mg
Step 1	0.3 mg	1 mg	3.3 mg	10 mg	33 mg	100 mg	300 mg	300 mg
Step 2	0.6 mg	2 mg	6.6 mg	20 mg	66 mg	125 mg		
Step 3	1.2 mg	4 mg	13.2 mg	40 mg	75 mg	160 mg		
Step 4	2.4 mg	8 mg	26.4 mg	75 mg	100 mg	200 mg		
Step 5	4.8 mg	16 mg	52.8 mg	100 mg	125 mg	250 mg		
Step 6	9.6 mg	32 mg	75 mg	125 mg	160 mg	300 mg		
Step 7	19.2 mg	64 mg	100 mg	160 mg	200 mg			
Step 8	38 mg	75 mg	125 mg	200 mg	250 mg			
Step 9	75 mg	100 mg	160 mg	250 mg	300 mg			
Step 10	100 mg	125 mg	200 mg	300 mg				
Step 11	125 mg	160 mg	250 mg					
Step 12	160 mg	200 mg	300 mg					
Step 13	200 mg	250 mg						
Step 14	250 mg	300 mg						
Step 15	300 mg							

Afigure 1: Example of a build-up scheme, dependent on threshold levels

Appendix 2: Methods for Deriving Transition Probabilities

Search Strategy

To identify relevant literature on transition probabilities for peanut allergy, a systematic review was conducted in the following databases:

PubMed: Focused on clinical studies and epidemiological data.

Cochrane Library: To incorporate systematic reviews and meta-analyses.

Science Direct: Peer reviewed health literature

The search was conducted on in the period of 1-7-2024 and 11-11-2025 and included studies published between 2011–2024. The following search terms and Boolean operators were used:

("Food Allergy" or "Peanut Allergy") AND ("Oral immunotherapy" OR "OIT") AND "Placebo"

Inclusion criteria:

Peer-reviewed studies reporting the effectiveness as desensitization, sustained unresponsiveness, adherence to treatment, and adverse events. Health related quality of life and personal, societal and health care cost outcomes for oral immunotherapy to peanut allergy.

Meta analysis, Systematic review, Randomized Controlled trails, Clinical trials, cohort studies.

Exclusion criteria:

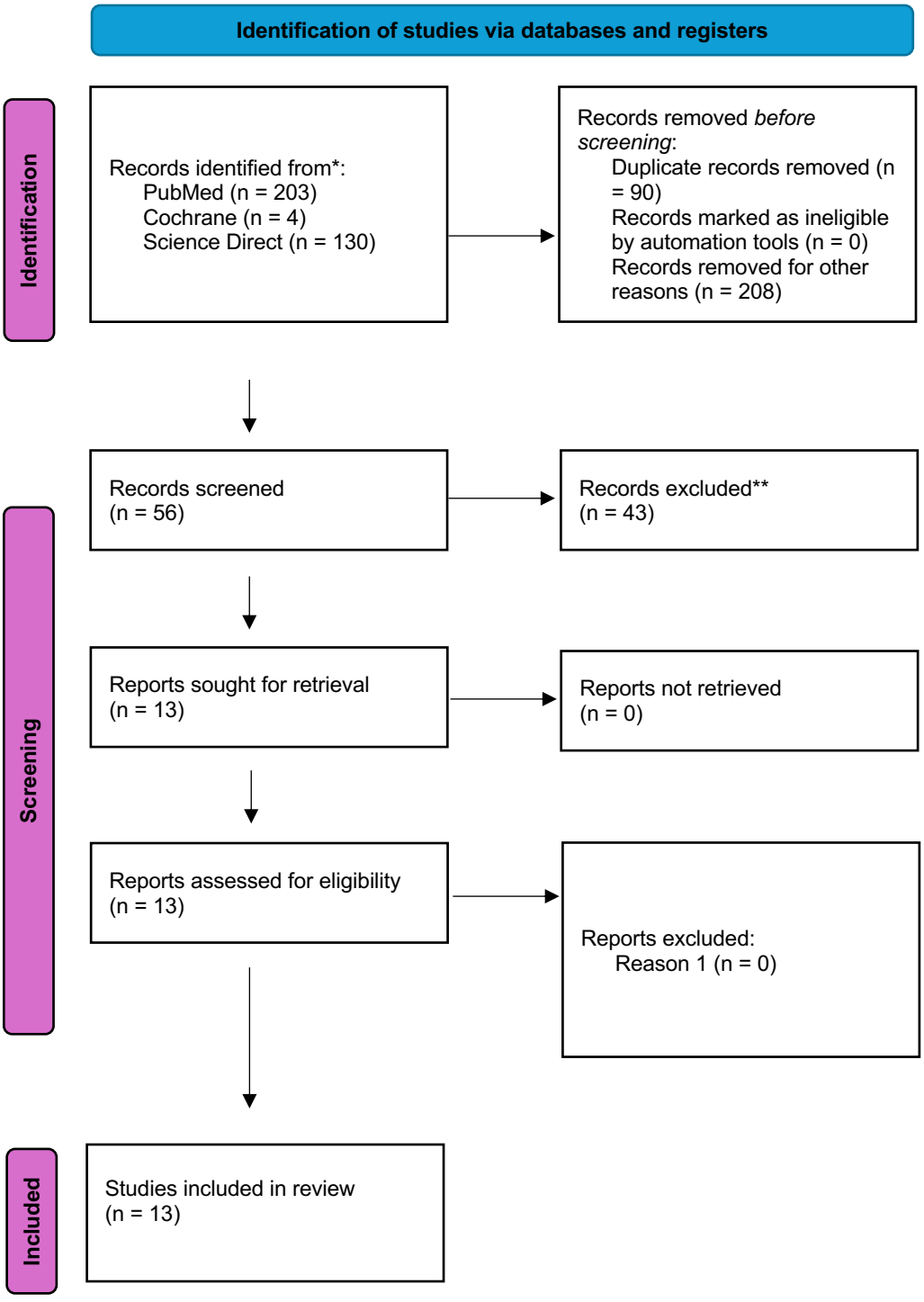
Single case reports, reviews without quantitative data, or studies with unclear methodologies.

Studies not conducted in populations comparable to the target cohort.

Studies including sublingual immunotherapy or epicutaneous immunotherapy

Study Selection

The initial search identified 337 studies. After removing duplicates, 247 studies were screened based on title and abstract. Full-text reviews were performed for 56 studies, of which 13 met the inclusion criteria. A PRISMA flow diagram summarizing the selection process is provided below (Figure A1).



Afigure 2: PRISMA Flow Diagram for Study Selection

Meta-Analysis Methods

To aggregate transition probabilities across studies, a random effects meta-analysis was conducted using R version 4.4.1 (2024-06-14). The random effects model was chosen due to expected heterogeneity across studies in population demographics, treatment regimens, and study designs.

Data Extraction: For each included study, the following data were extracted:

- Transition probabilities or rates for each health state.
- Population characteristics
- If available: Confidence intervals or standard errors of reported estimates.

Transformation of Rates: weekly transition probabilities were derived from the rates using the formula: wp = 1 - e^(-r/t)

where wp is the weekly probability, and r is the rate and t is the duration in weeks

Yearly transition probabilities were calculated by

Yp = 1 – (1-wp) ^ 52

where yp is the yearly probability

Integration into the Model

The derived transition probabilities were stratified by age.

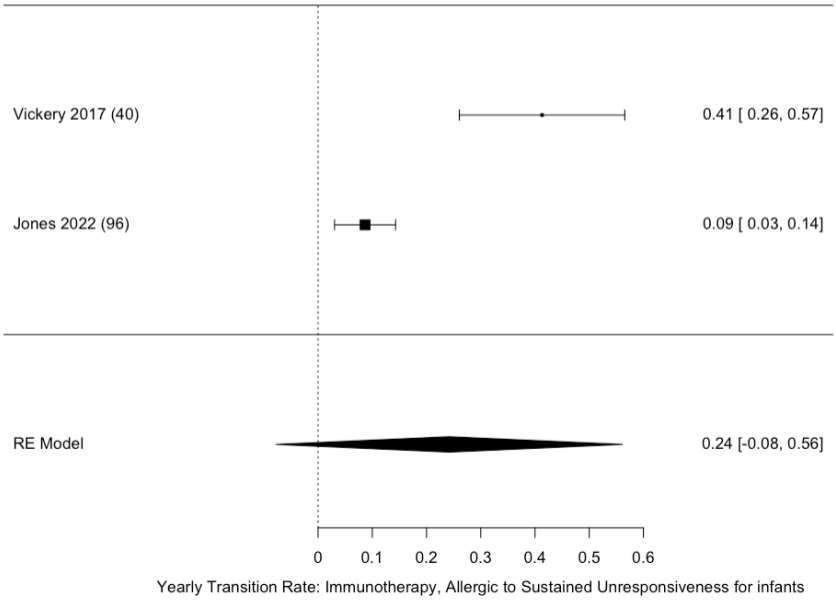
Infants: 1 to 4 years old.

Children and adolescents: 5 to 18 years old

Adults: 7 to 55 years old

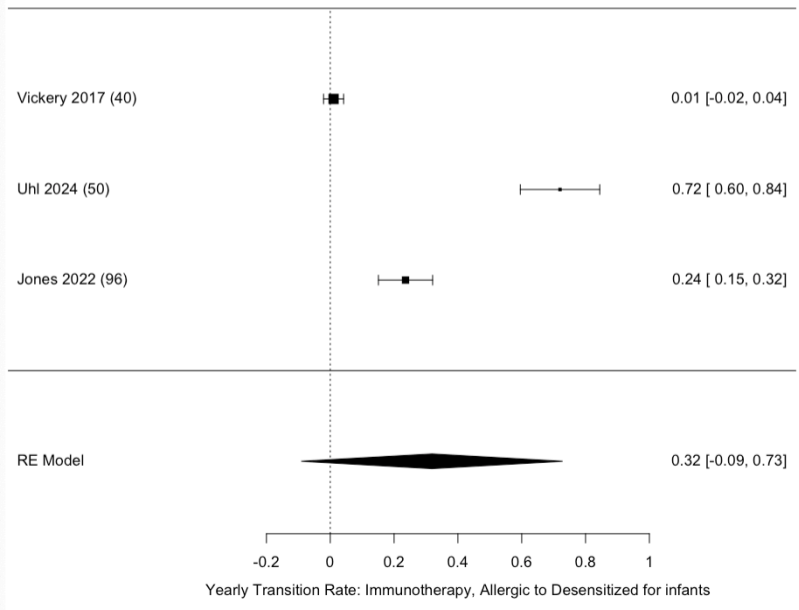
Treatment-specific probabilities were applied for the intervention and comparator arms of the model, reflecting observed differences in efficacy and adherence.

Results of the meta-analysis



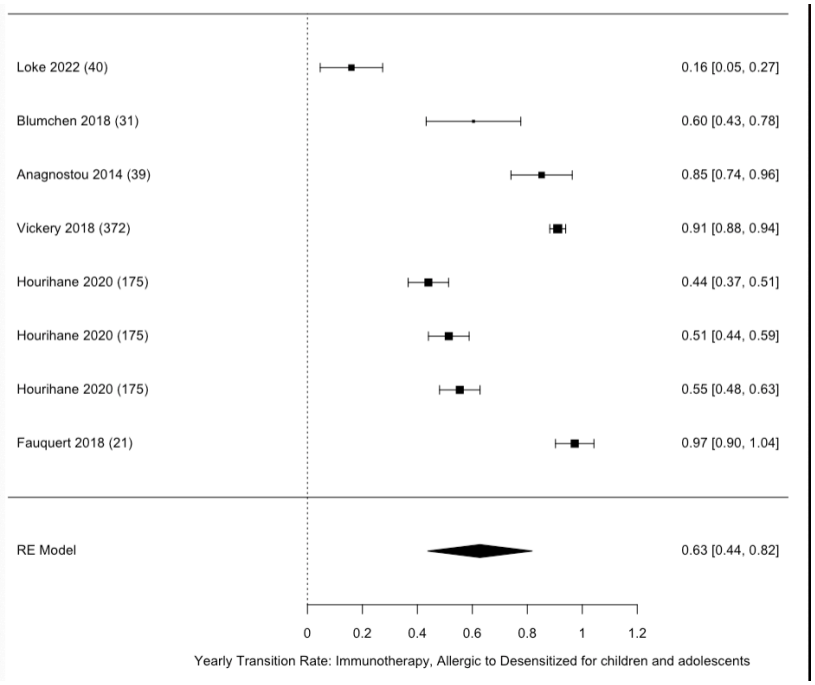
Afigure 3: OIT - Transition from Allergic to SU for infants

This figure illustrates the estimated yearly transition probability of individuals receiving OIT moving from an allergic state to SU. According to the RE model, the probability of transitioning is 0.25 (-0.08, 0.58).



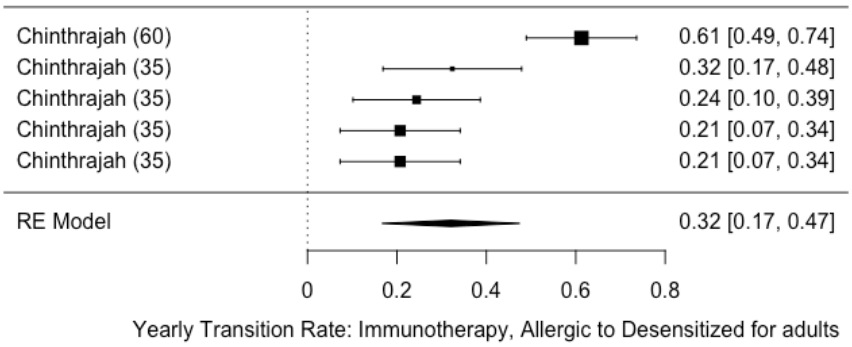
Afigure 4: OIT - Transition from Allergic to Desensitized in Infants

This figure presents the estimated yearly probability of infants undergoing OIT transitioning from an allergic state to a desensitized state. The RE model estimates this probability at 0.37 (0.03, 0.71).



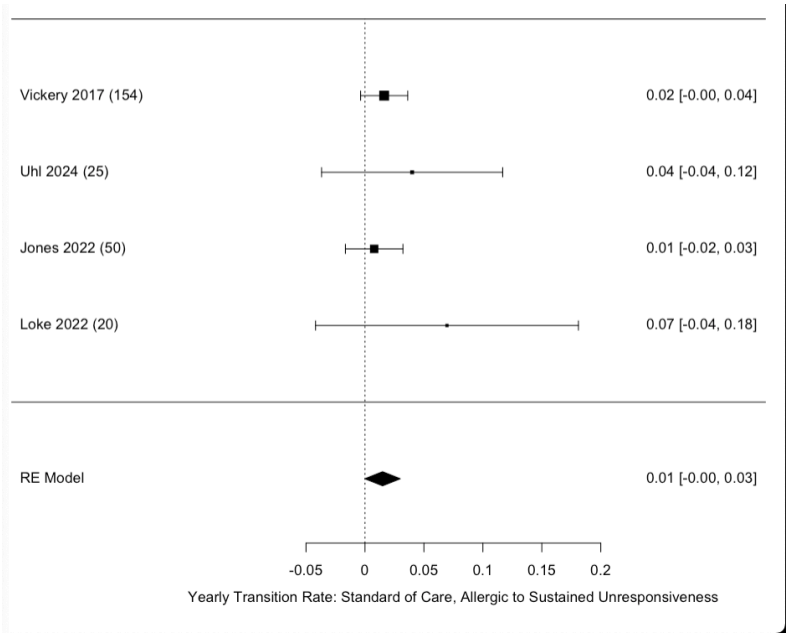
Afigure 5: OIT - Transition from Allergic to Desensitized in Children

The yearly transition probability for children receiving OIT from the allergic state to the desensitized state is shown in this figure 3. The RE model estimates a probability of [0.62 (0.44, 0.82).



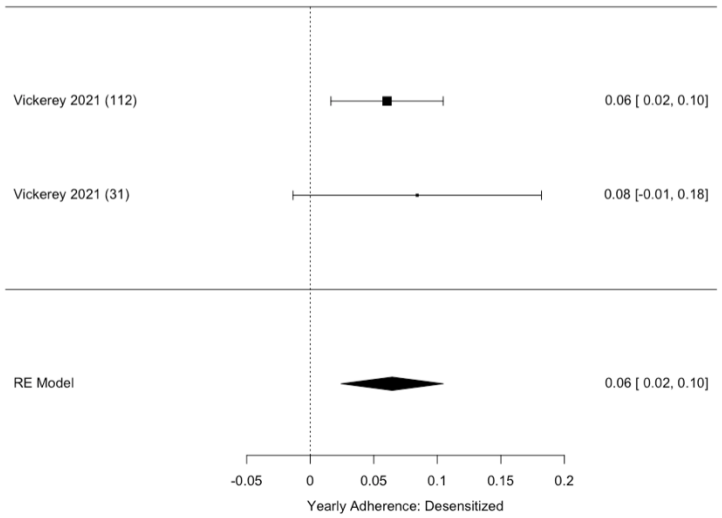
Afigure 6: OIT - Transition from Allergic to Desensitized in Adults

This figure depicts the yearly transition probability of adults undergoing OIT transitioning from the allergic state to the desensitized state. The RE model reports this probability as 0.32 (0.17, 0.47).



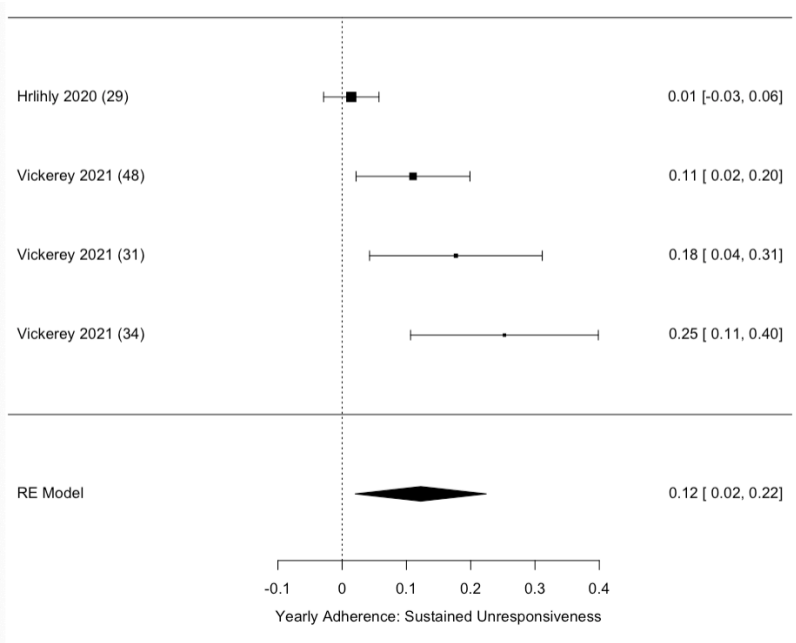
Afigure 7: SOC - Transition from Allergic to SU in SOC

The estimated yearly transition probability for individuals receiving SOC to progress from the allergic state to SU is presented here. The RE model estimates this probability at 0.01 (-0.01, 0.04).



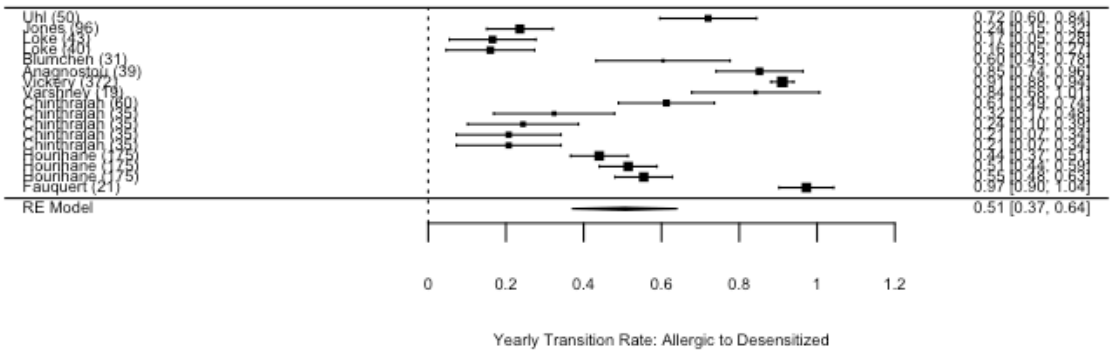
Afigure 8: Adherence in the Desensitized State

This figure illustrates adherence rates for individuals in the desensitized state following therapy. According to the RE model, the adherence probability is estimated at 0.06 (0.02,0.10)



Afigure 9: Adherence in the SU Health State

This figure shows adherence rates among individuals who achieved SU. The RE model estimates this adherence at 0.12(0.02, 0.22).



Afigure 10: SOC - Transition from Allergic to Desensitized

The probability of transitioning from an allergic state to a desensitized state under SOC is shown in this figure. The RE model estimates this probability at 0.51 (0.37, 0.64).

Appendix 3: Model inputs

Future costs and QALYs were discounted. Costs by at an annual rate of 3% and QALY by an annual rate of 1.5% reflect time preference, following health economic guidelines (37).

It was assumed that non-adherence to treatment could lead to the loss of DES in the OIT-Des and OIT-SU states resulting in a health state transition to the Lost Desensitisation health state (3, 28).

Adherence rates were based on several short-term follow-up studies (12, 34). It was assumed that non-adherence to treatment was present in every cycle.

Model inputs					
Name	**Description**	**Value**	**SD**	**Distribution**	**Source**
n_age_init	Age at the start of the simulation	1	0	-	-
n_age_max	Age at the end of the simulation	25	0	-	-
cycle_length	Cycle length	1	0	-	-
n_cycles	Number of cycles	25	0	-	-

n_part	Number of participants in the cohort	1	-	-	-
n_sim	Number of simulations for sensitivity analysis	10.000	-	-	(55)
d_c	Discounting of costs	3%	-	-	(37)
d_e	Discounting of effects	1,5%	-	-	(37)
Utility values					
Name	**Description**	**Value**	**SD**	**Distribution**	**Source**
U_C_A	Utility of an allergic child	0.4998	0.0195	Beta	(51)
U_C_DES	Utility of a desensitized child	0.4996	0.0163	Beta	(51)
U_C_SU	Utility of a sustained unresponsive child	0.4996	0.0175	Beta	(51)
U_cC_A	Utility of the caregiver of an allergic child	0.4996	0.0129	Beta	(51)
U_cC_DES	Utility of the caregiver of a desensitized child	0.5000	0.0127	Beta	(51)
U_cC_SU	Utility of the caregiver of a sustained unresponsiveness child	0.4999	0.0130	Beta	(51)
U_ADO_A	Utility of an allergic adolescent	0.4982	0.0415	Beta	(51)

U_ADO_DES	Utility of a desensitized adolescent	0.4983	0.0341	Beta	(51)
U_ADO_SU	Utility of a sustained unresponsiveness adolescent	0.4978	0.0399	Beta	(51)
U_cADO_A	Utility of the caregiver of an allergic adolescent	0.4976	0.0376	Beta	(51)
U_cADO_DES	Utility of the caregiver of a desensitized adolescent	0.4981	0.0316	Beta	(51)
U_cADO_SU	Utility of the caregiver of a sustained unresponsiveness adolescent	0.4979	0.0338	Beta	49)

Transition probabilities					
Name	**Description**	**Value**	**SD**	**Distribution**	**Source**
TP_SOC_A_SU	Transition probability in standard of care from allergic to sustained unresponsiveness	0.0142	0.0129	Dirichlet	(1-3, 11)
TP_IMMU_A_DES_INF	Transition probability in immunotherapy from allergic to desensitized for infants	0.3718	0.0474	Dirichlet	(1-3, 11)
TP_IMMU_A_SU_INF	Transition probability in immunotherapy from allergic to sustained unresponsiveness for infants	0.2499	0.0428	Dirichlet	(1, 2, 11)
TP_IMMU_A_DES_CH	Transition probability in immunotherapy from allergic to desensitized for children	0.6280	0.0483	Dirichlet	(2, 4-8)
TP_IMMU_A_DES_ADU	Transition probability in immunotherapy from allergic to desensitized for adults	0.3201	0.0458	Dirichlet	(9, 10)
TP_ADH_DES	Transition probability from desensitized to lost desensitization	0.0645	0.0242	Dirichlet	(11, 12)
TP_ADH_SU	Transition probability from sustained unresponsiveness to lost desensitization	0.1228	0.0326	Dirichlet	(4, 5)
Oral immunotherapy					
Name	**Description**	**Value**	**SD**	**Distribution**	**Source**
P_OIT	Proportion of patients that need at least 1 additional oit day	1.0	0	-	ORKA-NL
P_OIT0	Proportion of patients that need at least 1 additional oit day	0.5			ORKA-NL
P_OIT1	Proportion of patients that need 1 additional build up day	0.5	0	-	ORKA-NL
P_OIT2	Proportion of patients that need 2 additional build up day	0.3	0	-	ORKA-NL
P_OIT3	Proportion of patients that need 3 additional build up day	0.1	0	-	ORKA-NL
P_OIT4	Proportion of patients that need 4 additional build up day	0.1	0	-	ORKA-NL
P_OIT5	Proportion of patients that need 5 additional build up day	0.1	0	-	ORKA-NL

P_OIT6	Proportion of patients that need 6 additional build up day	0.0	0	-	ORKA-NL
Duration_ofc	Duration in hours ofc	5.0	0	-	ORKA-NL
Duration_bud0	Duration of build-up day 1 in hours	4.0	0	-	ORKA-NL
Duration_bud1	Duration of additional build up day 1 in hours	3.0	0	-	ORKA-NL
Duration_bud2	Duration of additional build up day 2 in hours	4.0	0	-	ORKA-NL
Duration_bud3	Duration of additional build up day 3 in hours	4.0	0	-	ORKA-NL
Duration_bud4	Duration of additional build up day 4 in hours	4.0	0	-	ORKA-NL
Duration_bud5	Duration of additional build up day 5 in hours	4.0	0	-	ORKA-NL

Productivity and productivity loss					
Name	**Description**	**Value**	**SD**	**Distribution**	**Source**
v_weeks_work	Number of weeks of work in a year	48	0	-	(42)
v_weeks_edu	Number of weeks of education in a year	40	0	-	(42)
v_weeks_house	Number of weeks of household in a year	52	0	-	(42)
w_absentism	Weight of cost for unproductivity due to presentism	1	0	-	(42)
w_presentism	Weight of cost for unproductivity due to absenteeism	0	0	-	(42)
v_prod_ch_house		0	0	-	(42)
v_prod_ch_edu	Scheduled education hours per week for a child	0	0	-	(42)
v_prod_ch_work	Scheduled work hours per week for a child	0	0	-	(42)
v_prod_ado_house	Scheduled household hours per week for an adolescent	6.9452	5.5893	Normal	(42)
v_prod_ado_edu	Scheduled education hours per week for an adolescent	18.2488	13.9164	Normal	(42)
v_prod_ado_work	Scheduled work hours per week for an adolescent	0.0000	0.0000		(42)
v_prod_adu_house	Scheduled household hours per week for an adult	12.1207	9.4416	Normal	(42)
v_prod_adu_edu	Scheduled Education hours per week for an adult	10.3712	11.7562	Normal	(42)
v_prod_adu_work	Scheduled work hours per week for an adult	27.0423	15.4843	Normal	(42)

v_prod_cg_house	Scheduled household hours per week for a caregiver	14.6133	11.4483	Normal	(42)
v_prod_cg_edu	Scheduled Education hours per week for a caregiver	0	0		(42)
v_prod_cg_work	Scheduled work hours per week for a caregiver	28.2735	14.1928	Normal	(42)
v_prodloss_ado_house_abs	% of Household productivity loss due to absenteeism for an adolescent	0.0526	0.1785	Normal	(42)
v_prodloss_ado_house_pres	% of Household productivity loss due to presenteeism for an adolescent	0.3391	0.3080	Normal	(42)
v_prodloss_ado_edu_abs	% of Education productivity loss due to absenteeism for an adolescent	0.0512	0.1999	Normal	(42)
v_prodloss_ado_edu_pres	% of Education productivity loss due to presenteeism for an adolescent	0.3120	0.2936		(42)
v_prodloss_ado_work_abs	% of Work productivity loss due to absenteeism for an adolescent	0	0		(42)
v_prodloss_ado_work_pres	% of Work productivity loss due to presenteeism for an adolescent	0	0		(42)
v_prodloss_adu_house_abs	% of Household productivity loss due to absenteeism for an adult	0.0602	0.1965	Normal	(42)
v_prodloss_adu_house_pres	% of Household productivity loss due to presenteeism for an adult	0.2322	0.3078	Normal	(42)
v_prodloss_adu_edu_abs	% of Education productivity loss due to absenteeism for an adult	0.0884	0.2540	Normal	(42)
v_prodloss_adu_edu_pres	% of Education productivity loss due to presenteeism for an adult	0.4210	0.3095	Normal	(42)

v_prodloss_adu_work_abs	% of Work productivity loss due to absenteeism for an adult	0.0220	0.0000		(42)
v_prodloss_adu_work_pres	% of Work productivity loss due to presenteeism for an adult	0.2610	0.0000		(42)
v_prodloss_cg_house_abs	% of Household productivity loss due to absenteeism for a caregiver	0.0672	0.1024	Normal	(42)
v_prodloss_cg_house_pres	% of Household productivity loss due to presenteeism for a caregiver	0.2428	0.2965	Normal	(42)
v_prodloss_cg_work_abs	% of Education productivity loss due to absenteeism for a caregiver	0.0531	0.1614	Normal	(42)
v_prodloss_cg_work_pres	% of Education productivity loss due to presenteeism for a caregiver	0.3258	0.3383	Normal	(42)
v_prodloss_cg_edu_abs	% of Work productivity loss due to absenteeism for a caregiver	0	0	-	(42)
v_prodloss_cg_edu_pres	% of Work productivity loss due to presenteeism for a caregiver	0	0	-	(42)

Adverse events					
Name	**Description**	**Value**	**SD**	**Distribution**	**Source**
v_ae_nooit	Yearly proportion accidental exposure and allergic reaction that leads to an adverse event during no OIT	0.1240	0.0051	Normal	(32)
v_ae_oit	Yearly proportion accidental exposure and allergic reaction that leads to an adverse event during OIT	0.0062	0.0013	Normal	(32)

AE_immu_inf	Per dose chance of an AE per for infants	0.0080	0.0028	Normal	(11)
AE_immu	Per dose chance of an AE for children, adolescents, and adults	0.0019	0.0007	Normal	(1)
v_AE_OIT_cycle1	Proportion of patients reporting treatment related adverse events in cycle 1	0.5530	0	-	(33)
v_AE_OIT_cycle2	Proportion of patients reporting treatment related adverse events in cycle 2	0.2530	0	-	(33)
v_AE_OIT_cycle3	Proportion of patients reporting treatment related adverse events in cycle 3	0.1430	0	-	(33)
v_AE_OIT_cycle4	Proportion of patients reporting treatment related adverse events in cycle 4	0.0490	0	-	(33)
v_AE_OIT_cycle5	Proportion of patients reporting treatment related adverse events in cycle 5 and further	0.0320	0	-	(33)
v_ae_hos	Yearly probability of hospitalization after an allergic reaction	0.0010	0	-	(23)
v_ae_ed	Yearly probability of an emergency department visit after an allergic reaction	0.0270	0	-	(23)
v_ae_ambu	Yearly probability of ambulance transport to the hospital after an allergic reaction	0.0050	0	-	(23)
doses_DES	Yearly number of doses of peanut allergen for desensitization	365	0	-	(12, 34)
doses_SU	Yearly number of doses of peanut allergen for SU	104	0	-	(12, 34)

Costs					
v_c_OFC1	Cost Entrance Oral food challenge	786.96	0.00	-	ORKA-NL
v_c_OFC2	Cost Exit Oral food challenge	786.96	0.00	-	ORKA-NL
v_c_OIT	Cost OIT build-up day	900.50	0.00	-	ORKA-NL
v_c_carkm	Travel costs per car per km	0.27	0.00	-	(37)
v_c_carpark	Parking costs per hospital visit	4.03	0.00	-	(37)
v_c_pp	Cost of dose of peanut protein	0.01	0.00	-	ORKA-NL
v_c_epi_pers	The personal cost of an EpiPen	16.35	0.00	-	(37)
v_c_job_unpayd	The hourly cost of unproductivity for an unpaid job	18.80	0.00	-	(37)
v_c_job_payd	The hourly cost of unproductivity for a paid job	39.88	0.00	-	(37)
v_c_education_primary	Hourly cost of unproductivity for primary education	10.47	0.00	-	(37)
v_c_education_secondary	Hourly cost of unproductivity for secondary education	15.26	0.00	-	(37)
v_c_education_vocational	Hourly cost of unproductivity for vocational education	24.31	0.00	-	(37)
doses_DES	Yearly number of doses of peanut allergen for desensitization	365.00	0.00	-	(12, 34, 35)
doses_SU	Yearly number of doses of peanut allergen for SU	104.00	0.00	-	(12, 34, 35)

Health care					
Name	**Description**	**Value**	**SD**	**Distribution**	**Source**

v_c_pharma_delivery	Cost of delivering medicine to the pharmacy	7.1619	0	-	(37)
v_d_pharma	Distance in KM to the pharmacy	1.2000	0	-	(37)
v_d_hospital	Distance in KM to the hospital	5.9500	0	-	(37)
v_c_ambu	Cost of an ambulance responding to an emergency call	723.90	0	-	(37)
v_c_nursing_day	Cost of 1 hospital nursing day	734.92	0	-	(37)
v_c_ED	Cost of a visit to the emergency department	284.27	0	-	(37)
v_c_chepi	The healthcare cost of a low dose epi pen for infants and children	48.47	0	-	(37)
v_c_epi	Healthcare cost of a normal dose EpiPen	42.19	0	-	(37)
v_c_gp	Cost of a visit to the general practitioner	47.72	0	-	(37)
v_d_gp	Travel distance for a visit to the general practitioner	1.2000	0	-	(37)
p_gp_1_cg	Caregiver: 1 yearly general practitioner visit for PA child	0.0490	0	-	(42)
p_gp_2_cg	Caregiver: 2 yearly general practitioner visits for PA child	0.0490	0	-	(42)
p_gp_3_cg	Caregiver: 3 yearly general practitioner visits for PA child	0.0490	0	-	(42)
p_gp_4_cg	Caregiver: 4 yearly general practitioner visits for PA child	0.0490	0	-	(42)
p_gp_5_cg	Caregiver: 5 yearly general practitioner visits for PA child	0.0490	0	-	(42)
p_gp_1_ado	Adolescent: 1 yearly general practitioner visit for PA	0.1370	0	-	(42)
p_gp_2_ado	Adolescent: 2 yearly general practitioner visits for PA	0.1370	0	-	(42)
p_gp_3_ado	Adolescent: 3 yearly general practitioner visits for PA	0.1370	0	-	(42)
p_gp_4_ado	Adolescent: 4 yearly general practitioner visits for PA	0.1370	0	-	(42)
p_gp_5_ado	Adolescent: 5 yearly general practitioner visits for PA	0.1370	0	-	(42)
p_gp_1_adu	Adult: 1 yearly general practitioner visit for PA	0.1700	0	-	(42)
p_gp_2_adu	Adult: 2 yearly general practitioner visits for PA	0.1700	0	-	(42)
p_gp_3_adu	Adult: 3 yearly general practitioner visits for PA	0.1700	0	-	(42)
p_gp_4_adu	Adult: 4 yearly general practitioner visits for PA	0.1700	0	-	(42)
p_gp_5_adu	Adult: 5 yearly general practitioner visits for PA	0.1700	0	-	(42)

Mortality					
Name	**Description**	**Value**	**SD**	**Distribution**	**Source**
v_HD_age	Yearly mortality for 1-year olds per 100000 persons	3.4400	0	-	(56)
	Yearly mortality for 2–5-year-olds per 100000 persons	0.1100	0	-	(56)
	Yearly mortality for 6–10-year-olds per 100000 persons	0.0600	0	-	(56)
	Yearly mortality for 11- 15-year-olds per 100000 persons	0.1000	0	-	(56)
	Yearly mortality for 16–20-year-olds per 100000 persons	0.1700	0	-	(56)
	Yearly mortality for 21–25-year-olds per 100000 persons	0.0300	0	-	(56)

Appendix 4: WTP threshold

Scenario	WTP	Proportion of cost-effective
1	20000	0.9989
1	50000	0.9955
1	80000	0.9920
2	20000	0.9976
2	50000	0.9915
2	80000	0.9877
3	20000	1.0000
3	50000	0.9998
3	80000	0.9990
4	20000	0.9998
4	50000	0.9988
4	80000	0.9977