

ORIGINAL ARTICLE

Asthma and Lower Airway Disease

Cost-effectiveness analysis of house dust mite allergen immunotherapy in children with allergic asthma

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Abstract

Background: Cost-effectiveness studies evaluating allergen immunotherapy (AIT) in children are limited but needed to drive clinical and policy-making decisions such as reimbursement of new interventions. In this study, we compared the cost effectiveness of subcutaneous (SCIT) and sublingual immunotherapy (SLIT) tablets to the standard of care (SOC) treatment in children with house dust mite-driven (HDM) allergic asthma.

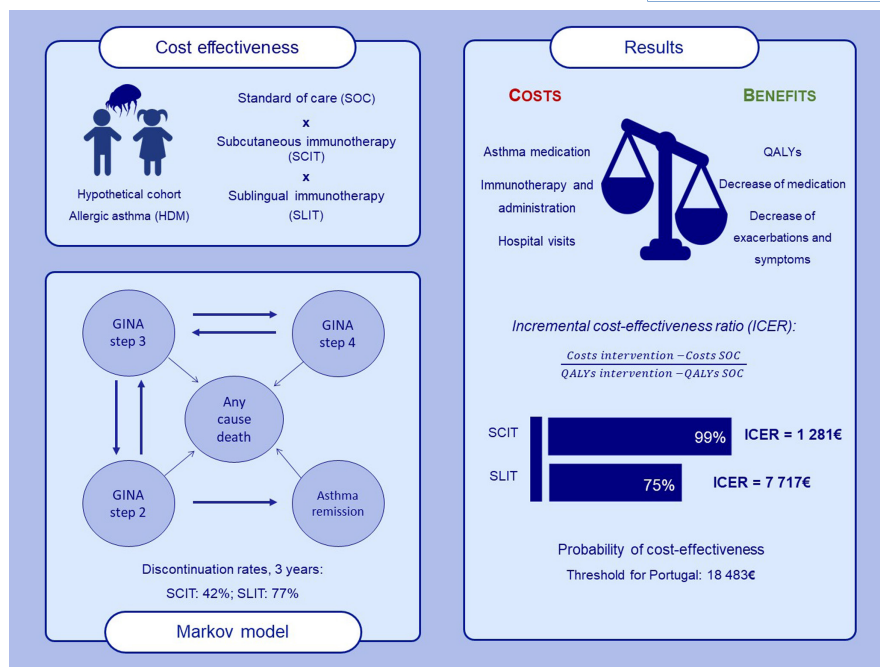
Methods: We developed a hypothetical Markov model based on the Global Initiative for Asthma (GINA) severity steps to compare the three strategies over a 10-year horizon divided by cycles of 6 months. SOC was used as a reference to calculate the incremental cost-effectiveness ratio (ICER). Deterministic and probabilistic sensitivity analyses were used to assess models' uncertainty. Other scenarios were evaluated to strengthen the presentation of results.

Results: The ICER for SCIT and SLIT tablets was 1281€ and 7717€, respectively. The cost-effectiveness threshold for Portugal was 18,482.80€; both treatment approaches were below this limit. The major contributors to these results were the AIT effects on reducing moderate and severe exacerbations and asthma controller medication. In the sensitivity analysis, SCIT revealed a higher probability of cost-effectiveness than SLIT. When including allergic rhinitis as comorbidity, ICER values reduced markedly, especially for SCIT intervention.

Conclusions: AIT was cost effective in children with HDM-driven allergic asthma, especially when given by the subcutaneous route. The high probability of cost effectiveness, especially for SCIT, may drive future policy decisions and AIT-prescribing habits. AIT adherence greatly influenced the results highlighting the value of implementing strategies to promote adherence rates.

KEYWORDS

allergen immunotherapy, asthma, children, cost effectiveness, house dust mites



GRAPHICAL ABSTRACT

We used a Markov model, based on GINA steps, to compare the cost-effectiveness of subcutaneous and sublingual tablet immunotherapy against standard of care in children with house dust mite allergic asthma. Both therapies diminished asthma medication and exacerbations while quality of life increased. Both therapies were cost effective, but SCIT showed a higher probability of cost effectiveness. Abbreviations: GINA, global initiative for asthma; HDM, house dust mite; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SOC, standard of care

1 | INTRODUCTION

Asthma is a chronic health problem that is increasing in prevalence and substantially impacting the quality of life and healthcare costs.¹⁻³ The worldwide trends in disease published by *The Lancet* in 2019 ranked asthma as 24th in the leading causes of disease burden measured as years of life lived with disability (YLD).² Both in children and adults, uncontrolled asthma has a significant effect on the quality of life, and daily activities are associated with loss of productivity at school and work.⁴ Children with asthma miss 2.5 school days each year than children without asthma.⁵ Asthma affects 224–309 million people worldwide, and its prevalence varies according to geographic region and age²; in Portugal, it is estimated to affect 5.3% of the population.⁶ In children, asthma is the most common chronic disease.² Allergen sensitization is present in up to 50% of all cases of asthma in adults and up to 80% in the pediatric population.^{7,8}

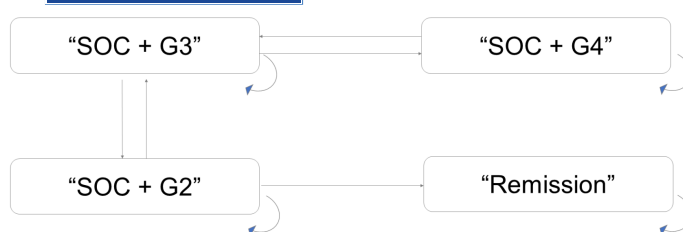
The standard of care (SOC) pharmacotherapy to achieve symptoms' control follows the Global Initiative for Asthma (GINA) guidelines.⁹ It includes the prescription of inhaled corticosteroid (ICS) plus long-acting β -agonists (LABA). Sublingual tablets of house dust mite (HDM) allergen immunotherapy (AIT) are also recommended by GINA guidelines for mild to moderate cases of patients with asthma not obtaining adequate control of the disease. HDM is a common and relevant inhalant allergen worldwide; specifically, HDM such as *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* are a vital source of indoor allergens associated with rhinitis

and asthma^{10,11} and, usually, the development of sensitization to HDM occurs before polysensitization.¹² Around 26% of people in Portugal are sensitized to HDM.¹³ AIT has a disease-modifying effect and induces allergen-specific immune tolerance. It confers prolonged benefits if administered for at least 3 years.^{11,14} Thus, it becomes decisive to evaluate the economic benefits and health gains of HDM AIT compared with SOC in respiratory allergic diseases. There are few studies investigating the cost-effectiveness of AIT, both for subcutaneous (SCIT) and sublingual (SLIT, as tablets or drops) administration routes, in children with HDM allergic asthma. Children are an essential group to assess cost-effectiveness because AIT benefits may remain long-term. Moreover, there are no studies performed within the context of the Portuguese healthcare system.

Cost-effectiveness analysis (CEA) is a recognized approach to estimate short- and long-term consequences on costs and health gains of a specific treatment.¹⁵ In Portugal, AIT is an expensive therapy that is not reimbursed, causing high nonadherence rates and health inequalities in terms of access to therapies.^{16,17} The results provided by these hypothetical models are essential to guide policy decisions, such as the reimbursement of therapies and to improve quality of life while reducing health inequalities.

We compared SCIT and SLIT tablets in children with HDM-driven allergic asthma using a mathematical modeling approach and parameters from multiple sources, including randomized controlled trials and real-world data, according to the Portuguese healthcare system.

SOC Strategy



AIT Strategy

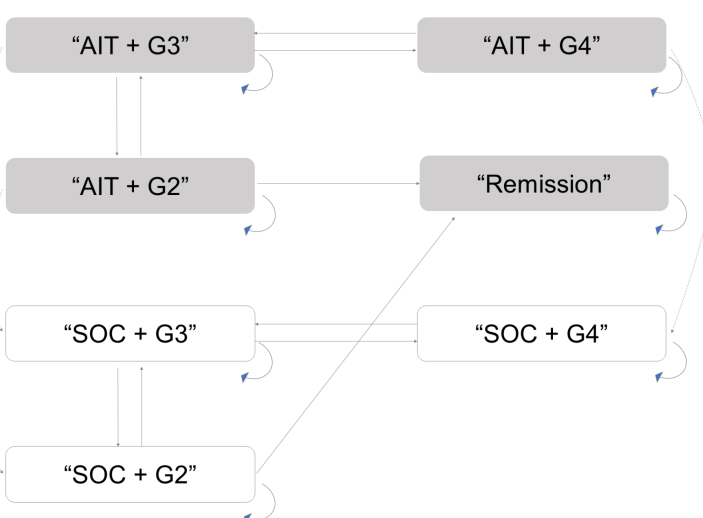


FIGURE 1 Basic structure of the Markov model. The risk of death is not shown (in order to simplify representation), but all patients, in any health state, are in risk of any-cause death. Patients under intervention (AIT administration—SCIT or SLIT) may discontinue treatment at any time (dashed arrows); at that time, patients follow the transitions and health states represented for the SOC arm. Patients achieving asthma remission do not return to any other health state (single arrow). AIT represents SCIT and SLIT strategies. All patients under the AIT strategy start, at baseline, in “AIT+G3” health state; all patients under the SOC strategy start, at baseline, in “SOC+G3” health state. AIT, allergen immunotherapy; Gx, GINA steps; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SOC, standard of care treatment

2 | METHODS

We developed a hypothetical Markov model to evaluate the costs and health outcomes of HDM allergen immunotherapy, for both SLIT tablets and SCIT, in children with allergic asthma plus pharmacotherapy compared with pharmacotherapy alone (SOC). The adopted framework used the stepwise approach of GINA (Global Strategy for Asthma Management and Prevention of the Global Initiative of Asthma) to define health states and was based on a previous cost analysis study conducted by Parra-Padilla et al.¹⁸ For the mathematical model, we simulated a hypothetical cohort of 12-year-old children, 1000 per strategy, over a 10-year horizon divided into 6-month cycles and following the Portuguese healthcare system perspective. The cycle length was defined to represent the average of medical visits scheduled in a year and allow adjustments in asthma therapy as in real-life. Each health state had an associated cost and utility value. Moderate and severe exacerbations were incorporated into the model as a relevant health outcome. Thus, the effectiveness of AIT was captured through changes in (a) health-related quality of life, quantitatively measured as utilities gained (positive scale, from zero to one); (b) asthma exacerbations, included as disutilities (negative scale, opposite of utilities); and (c) medication requirements, as patients moved along health states according to treatment-specific probabilities of step-up or step-down controller medication. The inclusion criteria of patients were a diagnosis of moderate-persistent asthma according to GINA guidelines (corresponding to Step 3) and sensitization to HDM with clinically relevant symptoms.

Patients were allowed to move across five health states according to the intervention prescribed (SOC or AIT—SCIT or SLIT

tablets): GINA Step 3 (“AIT+G3” or “SOC+G3”), all patients started at this health state in the first Markov cycle defined as a low dose of inhaled corticosteroid plus long-acting beta-agonists (ICS/LABA); GINA Step 4 (“AIT+G4” or “SOC+G4”), characterized as an increase in asthma severity requiring a medium dose of ICS/LABA; GINA Step 2 (“AIT+G2” or “SOC+G2”), described an improvement of asthma by ICS step-down protocol (low dose of ICS); remission of asthma (“AIT+R” or “SOC+R”), defined as the withdrawal of asthma therapy for the remaining time horizon; and any-cause death (“death”), every participant was at risk for death during all the time horizon independently of the health state taken in the model (Figure 1). In both SLIT and SCIT strategies, patients were allowed to discontinue AIT as in real-life,¹⁷ maintaining the standard of care treatment for the remaining time horizon; after treatment discontinuation, patients were not allowed to return to any AIT health state. For those patients, AIT effects on medication, exacerbations, and utilities were not considered when treatment was discontinued, and SOC values were considered instead. AIT was ideally administered for 3 years, as recommended,¹¹ and patients completing AIT intervention then continued pharmacotherapy alone for the remaining cycles; the effectiveness of AIT on medication, exacerbations, and utilities remained the same for the remaining years. When completing 3 years of AIT, the probability of asthma remission for these patients increased.^{19,20} For all strategies, patients achieving asthma remission continued in that state until the end of the 10-year time horizon.²¹

Each health state reflected a specific asthma severity level or disease remission. In each Markov cycle, costs and utilities were accumulated according to the re-distribution of participants until the end

TABLE 1 Parameters included in the Markov model (base case analysis) for the three strategies (SOC, SCIT, and SLIT)

Parameter	SOC	SCIT and SLIT	DSA parameters range		Distribution	Ref.
			Lower	Higher		
Time horizon	10 years					
Age at baseline	12 years					
Initial Health State (t0)	"SOC+G3" (N = 1000)	"SCIT+G3" (N = 1000); "SLIT+G3" (N = 1000)	-	-	-	-
Annual discount rate (costs/QALYs)	3% (range 0%–6%)					
Duration of a Markov cycle	6 months					
Transition probabilities (6 months)						
Disease progression (SOC+G3 -> SOC+G4) ^a	0.048160		0	0.159762	Binomial	29
Disease progression (AIT+G3 -> AIT+G4)	-	SCIT: 0.030979 SLIT: 0.040833	SCIT: 0 SLIT: 0	SCIT: 0.140348 SLIT: 0.151472	Binomial	29,30
Disease progression (SOC+G2 -> SOC+G3) ^a	0.133975		0.025321	0.258380	Binomial	29
Disease progression (AIT+G2 -> AIT+G3)	-	SCIT/SLIT: 0.105572	SCIT/SLIT: 0	SCIT/SLIT: 0.175985	Binomial	29
Disease Improvement (SOC+G3 -> SOC+G2) ^a	0.133975		0.025321	0.258380	Binomial	29
Disease Improvement (SOC+G4 -> SOC+G3) ^a	0.056602		0	0.169338	Binomial	31
Disease Improvement (AIT+G3 -> AIT+G2)	-	SCIT: 0.183299 SLIT: 0.169337	SCIT: 0.068872 SLIT: 0.056602	SCIT: 0.316626 SLIT: 0.300000	Binomial	29,32
Disease Improvement (AIT+G4 -> AIT+G3)	-	SCIT/SLIT: 0.056602	SCIT/SLIT: 0	SCIT/SLIT: 0.169338	Binomial	31
AIT discontinuation (for any AIT health state during the first 3 years of SCIT or SLIT)	-	SCIT: 0.086788 SLIT: 0.217253	SCIT: 0.040564 SLIT: 0.131216	SCIT: 0.148932 SLIT: 0.400000	Binomial	17
Remission (SOC+G2 ->R) ^{b,c}	0.012468		0.002575	0.025348	Binomial	33
Remission (point estimate for AIT completion—3 years) (AIT+G2 ->R) ^c	-	SCIT: 0.500000 SLIT: 0.340000	SCIT: 0.300000 SLIT: 0.140000	SCIT: 0.700000 SLIT: 0.540000	Binomial	19,30
Annual mortality						
All-cause mortality	0.000061					34

(Continues)

TABLE 1 (Continued)

Parameter	SOC	SCIT and SLIT	DSA parameters range		Distribution	Ref.
			Lower	Higher		
Costs (6 months)						
AIT acquisition price	-	SCIT: 127.28€ SLIT: 450.00€	SCIT: 101.82€ SLIT: 360.00€	SCIT: 152.74€ SLIT: 540.00€	-	Market price
Administration of SCIT	-	126€	100.8€	151.2€	-	35
Scheduled visits+ additional tests	75.00€		60.00€	90.00€	-	35
Medication Gina 4	108.66€		74.10€	128.37€	-	36
Medication Gina 3	102.57€		89.43€	118.11€	-	36
Medication Gina 2	23.88€		14.70€	29.76€	-	36
Moderate exacerbation (ED visit)	127.67€		102.14€	153.20€	-	35
Severe exacerbation (hospitalization)	2759.00€		2207.20€	3310.80€	-	35
Utilities						
Step Gina 3	0.789		0.631	0.947	Beta	37,38
Step Gina 2	0.781		0.625	0.937	Beta	37,38
Step Gina 4	0.725		0.580	0.870	Beta	37,38
Remission	0.812		0.650	0.974	Beta	37,38
Disutilities						
Moderate exacerbations	-0.117		-0.114 ^o	-0.121 ^o	LogNormal	39
Severe exacerbations	-0.179		-0.153 ^o	-0.217 ^o	LogNormal	39
Exacerbations (6 months probabilities)						
Moderate exacerbations (ED visits)	0.206275	SCIT: 0.0536315 SLIT: 0.072196	SOC: 0.145510 ^o SCIT: 0.037832 ^o SLIT: 0.050928 ^o	SOC: 0.278890 ^o SCIT: 0.072511 ^o SLIT: 0.097611 ^o	Binomial	40-42
Severe exacerbations (Hospitalization)	0.007025	SCIT: 0.001826 SLIT: 0.002458	0	SOC: 0.035635 ^o SCIT: 0.009265 ^o SLIT: 0.012472 ^o	Binomial	40-42

Note: DSA range defined according to a margin error of $\pm 20\%$, unless otherwise stated. ^o95% confidence interval.

Abbreviations: AIT, allergen immunotherapy; DSA, deterministic sensitivity analysis; ED, emergency department; SCIT, subcutaneous immunotherapy; SLIT, sublingual (tablets) immunotherapy; SOC, standard of care.

^aProbabilities from the SOC arm were also used for patients in AIT strategies that discontinued SLIT tablets or SCIT earlier.

^bRemission in AIT strategies assumed the value as in SOC arm for all the time horizon; however, those patients completing 3 years of AIT, at that point, had a higher probability of asthma remission corresponding to the values presented in this table.

^cPatients achieving remission remained in this state until the end of the analysis.

of the analysis. The distribution of participants according to specific probabilities was different for each strategy, representing the real-life flow of patients taking AIT or SOC alone. Transition probabilities followed some assumptions: patients started in the "SOC+G3" or "AIT+G3" health state; step-down or step-up of treatment was gradual; for example, patients in GINA step 4 were not allowed to transit directly to GINA step 2 or remission but were allowed to decrease to GINA step 3, while in step 3 they could move again to step 4 or improve to step 2; when a patient achieved remission was not allowed to move into other health states; the probability of moderate and severe exacerbations was determined according to the probability of emergency department (ED) visits and hospitalizations due to asthma, respectively, and were possible to occur in all health states except in GINA Step 2 in which was allowed only ED visits (moderate exacerbations); AIT discontinuation was considered in SLIT tablets and SCIT strategies, the parameters of therapy effectiveness for these patients was equal to those in the SOC arm from the time of discontinuation; death was an absorbing state.

TABLE 2 Base case results of costs and health gains for SOC, SLIT, and SCIT strategies at the end of the model calculation (10-year horizon)

Variables base case scenario	SOC	SCIT	SLIT
Asthma medication+ scheduled visits	2,915,378€	2,476,179€	2,760,857€
Intervention costs (SLIT or SCIT+ administration)	0€	1,176,098€	1,327,165€
Moderate exacerbations costs	506,673€	264,369€	409,105€
Number of moderate exacerbations	3969	2071	3205
Severe exacerbations costs	243,756€	118,214€	189,383€
Number of severe exacerbations	88	43	69
Total cost	3,665,807€	4 034 859€	4,686,510€
Total cost (discount rate)	3,209,552€	3 647 624€	4,231,070€
Utilities	17,785	17,949	17,842
Disutilities	480	250	387
QALYs	17,305	17,699	17,455
QALYs (discount rate)	15,096	15,438	15,228
Cost difference	Reference	438€	1021€
Effect difference	Reference	0.342	0.132
ICER	Reference	1281€	7717€

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SOC, standard of care.

The input data used in our model are presented in [Table 1](#) and are explained in detail in the [Supporting Information](#) of this article. All data were retrieved from literature and discussed with medical specialists. We extensively described the sensitivity analysis and other scenarios taken into account to strengthen the base case results presented in this work (see the [Supporting Information](#) for these details).

2.1 | Model calculation

Cost-effectiveness was established by calculating the incremental cost-effectiveness ratio (ICER) as incremental costs divided by incremental quality-adjusted life-years (QALYs), assuming SOC strategy as the reference. Costs and QALYs were discounted at 3% per year as performed in previous studies.^{18,22} The cost-effectiveness threshold (CE threshold) was based on WHO recommendations as one to three times the gross domestic product (GDP) per capita of the country.²³ We considered the value corresponding to the lowest category suggested by WHO—thus, up to one time the GDP per capita.^{23,24} Therefore, in Portugal, the GDP per capita in 2020 was set at 22,488,62USD (18,482,80€; conversion on June 7th, 2021). All the analyses were performed in RStudio Software version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria) using the *Heemod* package.²⁵

3 | RESULTS

3.1 | Base case results

The base case results of this economic analysis indicate an ICER of 1281€ and 7717€, per QALY, gained, for SCIT and SLIT tablets compared with the SOC strategy, respectively. The base case results are presented in [Table 2](#). For SCIT and SLIT tablets, per patient, we observed an incremental cost of 438€ and 1021€ and an incremental QALY of 0.342 and 0.132. As we expect a CE threshold for Portugal of 18,482.80€, both treatment strategies are below this limit. The major contributor to these results was AIT effects on health outcomes by reducing moderate and severe exacerbations and asthma controller medication. For the SCIT strategy, we expected a reduction of 1898 moderate exacerbations and 45 severe exacerbations, corresponding to cost differences of 242,304€ and 125,542€, respectively. We anticipated a less optimistic scenario for the SLIT tablet strategy. A reduction of 764 moderate exacerbations and 19 severe exacerbations; still, the impact on asthma-related costs was relevant. The reduction in asthma medication and scheduled medical visits (for patients in remission) led to savings of 439,199€ and 154,521€ in SCIT and SLIT tablets strategies, respectively.

We have included AIT discontinuation rates to simulate what happens in the real world; 570 children completed 3 years of subcutaneous immunotherapy compared with 227 children in the sublingual strategy. Over the 10-year time horizon, the numbers of patients experiencing remission of asthma medication were estimated to be 79, 233, and 128, corresponding to SOC, SCIT, and SLIT strategies. At the end of the time horizon, SOC, SCIT, and SLIT led to

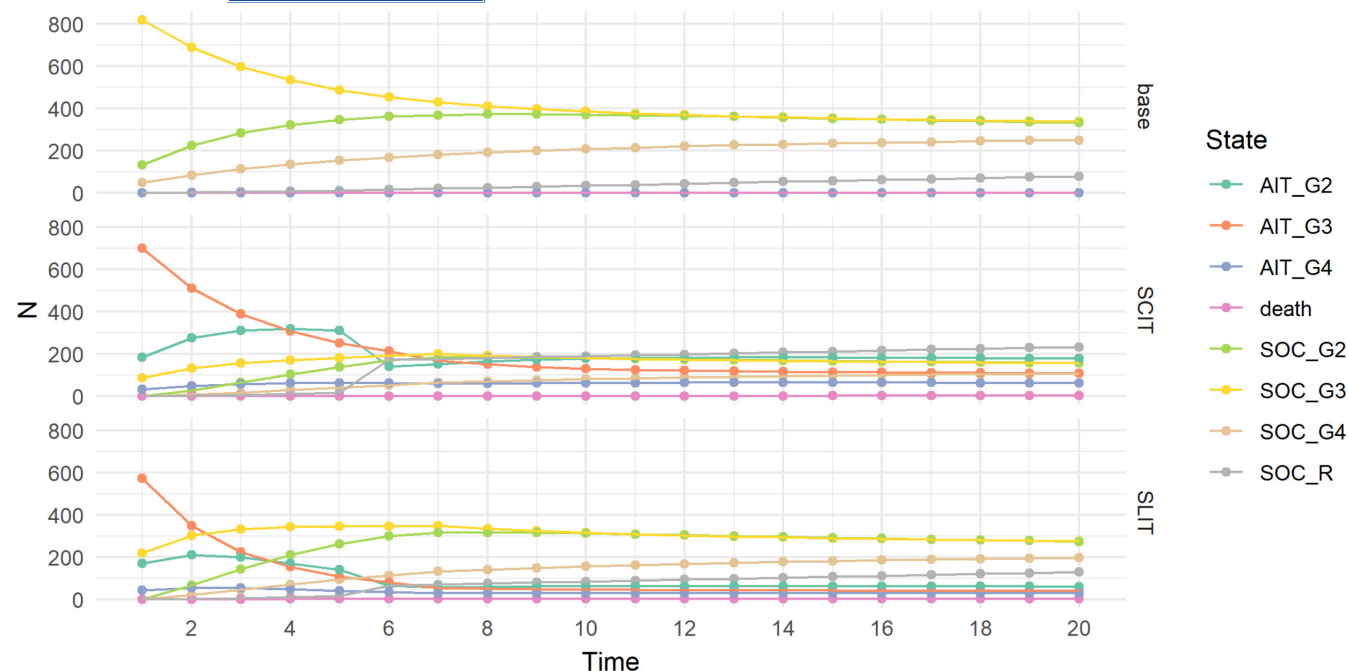


FIGURE 2 Number of participants in each health-state over a 10-year time horizon, corresponding to 20 Markov cycles, per strategy; namely, base (standard of care treatment), SCIT (subcutaneous immunotherapy), and SLIT (sublingual immunotherapy)

an increase in asthma medication (Gina Step 4) in 250, 170, and 225 children, respectively (Figure 2 and Table S1).

3.2 | Sensitivity analysis

The robustness of the model was assessed through deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA). The DSA (Figure 3) showed which parameters contributed to cost differences between the AIT and SOC strategies. Differences in utilities due to parameters uncertainty are shown in the (Figure S1). These variations caused differences in ICER results (Figure S2 and Table S2). Considering the lowest and highest boundaries for each parameter uncertainty, ICER values ranged between 138€ and 6628€ for SCIT, and 3273€ and 46,710€ for SLIT tablets (Table S2). Additionally, one of the analyses of the SCIT strategy led to a scenario of cost savings meaning that the new treatment dominated the old one resulting in a negative ICER (Table S2). On the other hand, one of the analyses of the SLIT strategy led to a scenario of no health gains (negative effect difference), and consequently, a negative ICER; meaning that the intervention was not cost-effective when considering an increase in the probability of moving from “SLIT GINA step 3” into “SLIT GINA step 4”.

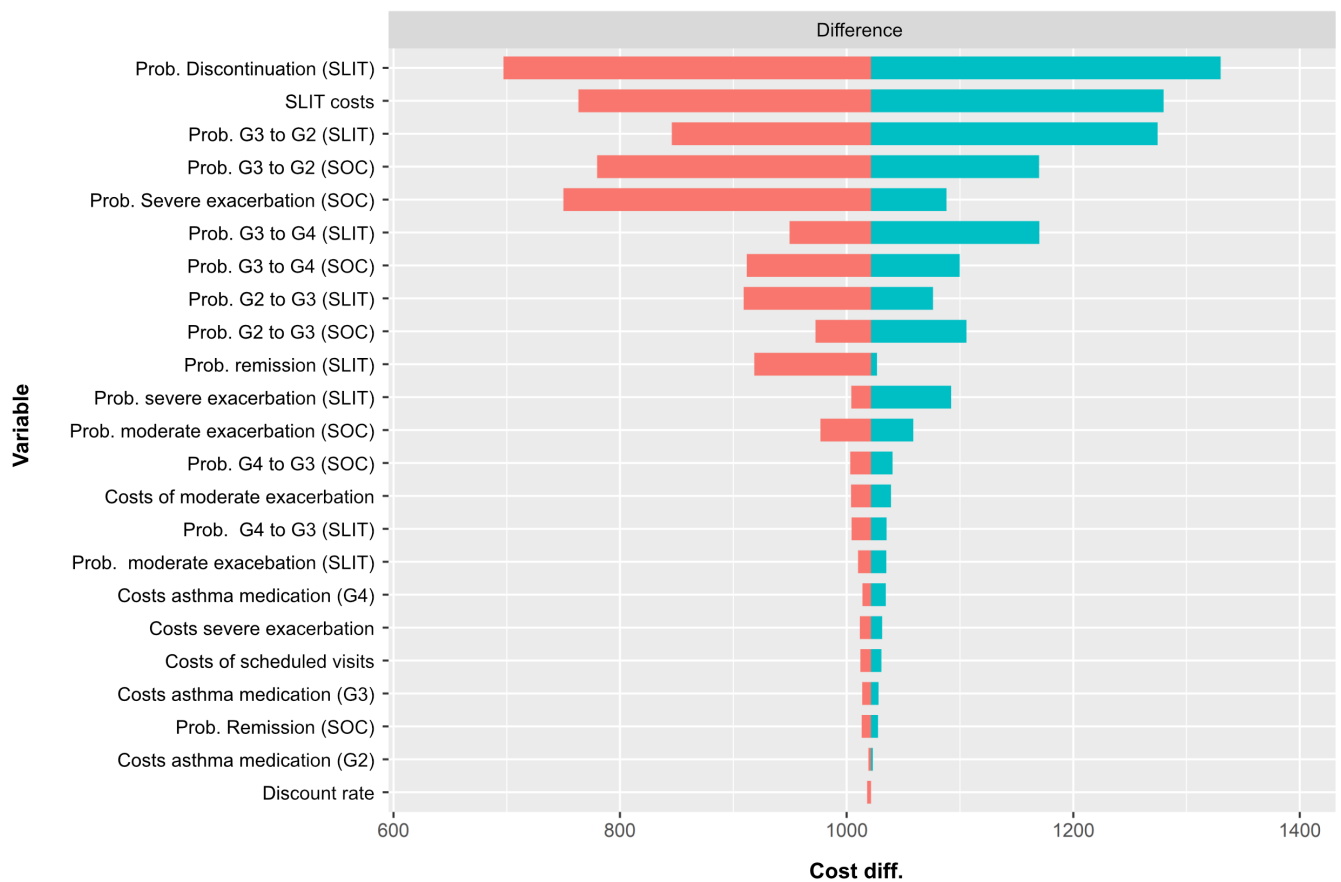
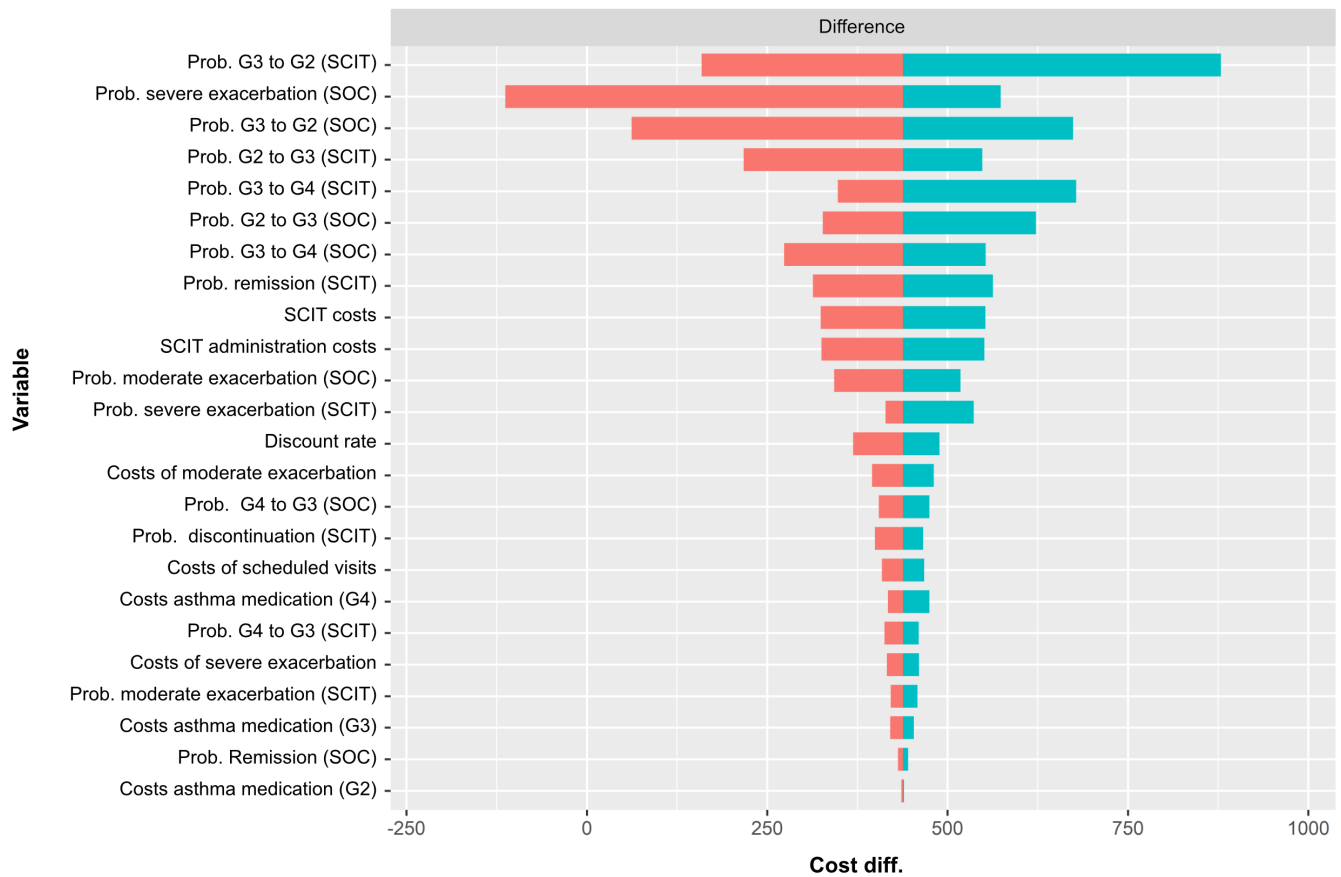
The PSA analysis (Figure 4) showed a linear correlation trend evidencing the cost-effectiveness of both interventions because as

QALYs increased, the costs decreased. However, for the SLIT tablets strategy, some simulations were plotted in a non-cost-effectiveness region (upper left quadrant of the graph), and costs were markedly higher for most simulations when compared to SCIT. The average ICER after 1000 simulations was 1387€ for SCIT and 8498€ for SLIT; the SLIT strategy presented a higher uncertainty compared with base case results. The Monte Carlo simulation results were used to compute cost-effectiveness acceptability curves (CEAC) according to a range of WTP thresholds. The graphs show the probability of cost-effectiveness considering different threshold values; specifically, considering a limit of 10,000€ the probability of being cost-effective was around 58% (SLIT tablets) and 98% (SCIT), but increasing this limit to 20,000€, which is a similar value to the CE threshold that we assumed for Portugal, the values increased to 75% and 99%, respectively (Figure S3).

3.3 | Other scenarios

We also considered other possible scenarios, according to circumstances that might happen in the real world, to evaluate the robustness of the model while strengthening the recommendations provided by the base case results. The results are presented in Table S3. None of the ICER values hit the CE threshold considered in our analysis in all scenarios. However, we verified which variables

FIGURE 3 Tornado plot resulting from the deterministic sensitivity analysis. Blue and red bars represent an increase or decrease in costs, respectively, according to model's parameters uncertainty (the range of values is represented in each side of the bars and also in Table 1). Subcutaneous strategy (top plot) and sublingual strategy (bottom plot). To simplify y-axis, the reference to health states according to GINA steps is G4, G3, and G2 corresponding to GINA step 4, GINA step 3, and GINA step 2. Cost diff, cost difference; Prob., probability; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SOC, standard of care



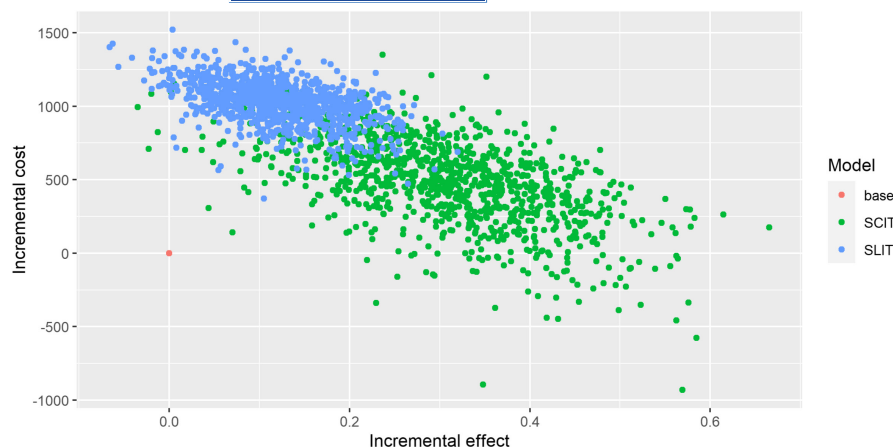


FIGURE 4 Results of the probabilistic sensitivity analysis graphically represented on a cost-effectiveness plan. Green: subcutaneous immunotherapy, Blue: sublingual immunotherapy, Orange: standard of care (reference)

had a higher impact on ICER. On the one hand, in a perfect scenario of full adherence to AIT or considering a 50% discount in AIT acquisition prices, we observed a marked reduction in the ICER.

On the other hand, if the effects of AIT in asthma remission were the same as in the SOC arm, the ICER increased. As expected, ICER values were higher when considering a short-time horizon and lower for a long-time horizon. When AR medication costs were included, the ICER decreased, particularly in the SCIT strategy because adherence rates to SCIT are higher and more children benefit from a reduction in AR drug use. If we do not take into account the effects of AIT on moderate and severe exacerbations for the entire time horizon, as expected, the ICER values increased. Still, SCIT results remained optimistic (3539€ and 17,437€ for SCIT and SLIT, respectively). For the remaining scenarios, ICER values were similar or slightly higher than the base case, evidencing the robustness of the results since these scenarios were less optimistic about the effects of AIT on asthma.

4 | DISCUSSION

Allergen immunotherapy, for both subcutaneous and sublingual administration routes, seems cost-effective in children with moderate HDM-driven allergic asthma, considering a CE threshold in Portugal of 18,482.80€. The core parameters contributing to these ICER values were the AIT effects on reducing exacerbations and asthma medication. Comparing both administration routes, SCIT was more cost effective and the sensitivity analysis demonstrated the robustness of the model. The cost-effectiveness of both strategies can be improved if AIT acquisition costs decrease and adherence rates increase.

To our knowledge, this is the first study estimating both SCIT and SLIT tablets' effects on health and costs in children with allergic asthma while addressing the limitations of previous economic analyses. Our model was adapted from a recent study conducted by Parra-Padilla and colleagues in children with asthma, but some new considerations were included to better reflect the real world.¹⁸ First, the model has been restructured to allow the flow of patients across health states representing different medication requirements as defined in GINA guidelines; thus, medication step-up was allowed instead of medication step-down only as in the previous study.

Second, we included AIT adherence rates since this is a major concern for clinicians, patients, and policymakers. Third, we conducted an extensive analysis considering another scenario that we believed to be relevant for interpreting the results among different contexts. Our results are in line with those obtained for SCIT in the aforementioned study¹⁸; the small differences may be due to the inclusion of compliance data and medication step-up in the model and the differences in the input data according to each country specifications. Another study evaluated the cost-effectiveness of SLIT in adults with asthma sensitized to HDM in three European countries.²² Our ICER estimate was slightly lower when compared to Czech Republic, Poland, and Slovakia (7455€, 7492€, and 8814€, respectively). However, differences in the model assumptions, WTP thresholds, lack of compliance data and population's age might have led to these differences. Our results agreed with the previous ones and highlighted the higher likelihood of cost-effectiveness for the subcutaneous route due to lower acquisition prices and greater health and quality of life improvements that were enlarged by better adherence rates than SLIT.

This study has several strengths. We have included discontinuation rates based on real-world studies to surpass previous gaps from cost-effectiveness studies. As emphasized by Parra-Padilla et al.,¹⁸ the definition of health states according to GINA steps allows its use in different contexts and captures both the complexity of the disease and the effects of interventions. Moreover, the length of each Markov cycle was chosen to represent the clinical response of patients and changes in medication requirements according to the average number of scheduled medical visits in Portugal. The base case model followed important conservative assumptions to avoid over- or underestimation of the results. First, moving across health states was gradual. Second, the probability of asthma remission was the same for all strategies and higher only for patients who completed 3 years of immunotherapy. Third, after AIT discontinuation, patients followed the odds and health states represented in the SOC strategy; thus, AIT had no effects in the subsequent years. Finally, whenever possible, input data were retrieved from real-world studies conducted in children with HDM-driven asthma. The sensitivity analyses were extensive to test the robustness of the base case model, while the alternative scenarios analyses were relevant to identify

core parameters that may contribute to improving cost-effectiveness in the real world and to drive political decisions. We considered an alternative scenario including the costs due to allergic rhinitis since this is a common comorbidity in children with asthma and an indication for AIT.⁹ The results reinforced the cost-effectiveness of AIT, especially for SCIT, and were in line with literature findings.¹⁸

We should also address limitations. This model was applied to the Portuguese context, but it can be easily applied to other settings (hospital, region, or country, for example) that need to estimate the ICER of immunotherapy for patients with asthma. In practice, this can be achieved by changing the parameter values of the model according to the available specific data for that setting, such as adherence rate and drug costs, for example. Furthermore, these results provide relevant insights for clinicians and policymakers independently of the country. The transition probabilities were calculated based on studies performed in children under HDM SLIT tablets or SCIT except for two probabilities due to lack of published data; first, the transition probability from GINA step 4 into GINA step 3 was equal in all strategies because we did not find specific data for AIT, second, transition probability from GINA step 2 into GINA step 3 in the SLIT strategy was assumed to be the same as in SCIT strategy. In the DSA analysis, the variation of those specific parameters did not affect the ICER estimates significantly. Markov models are highly dependent on the underlying assumptions and data retrieved from the literature; this was shown by the DSA analysis since some parameters, especially transition probabilities, led to considerable variations in cost and effect differences and ICER. We also lack high-quality evidence of AIT effects on moderate and severe exacerbations in the short- and long-term since these are major drivers of costs; consequently, results should be interpreted cautiously, but SCIT remained cost-effective in an alternative scenario in which AIT effects on exacerbations were not considered. This study highlights the need for high-quality studies evaluating the long-term effects of AIT in children with asthma, particularly the steroid-sparing effects and asthma progression for those whose AIT is not effective. Additionally, we were unable to estimate the cost-effectiveness of SLIT-drops due to the lack of both steroid-sparing effect data and discontinuation rates. We did not incorporate nonmedical costs, such as transportation to the hospital for SCIT administration and the management of adverse events due to AIT, which may underestimate the ICER to some extent.²⁶ We did not consider the risk of death from SCIT, but the risk exists despite being very low.²⁷ We proposed a CE threshold based on the lower limit suggested by the WHO. However, this limit should be interpreted cautiously since the Portuguese authorities may consider another willingness to pay value for the health system.²³ Another possible threshold relies on the estimates of the individuals' willingness to pay (WTP) to improve their health; this approach defines the value of health consumption from a social perspective rather than that defined by the health system.²³ Since we did not find this estimate for Portugal, due to the proximity and similarities with Spain, we decided to compare the ICER with the individuals' WTP threshold defined for that country (which ranged from 10,119€ up to 28,187€) and we verified that both SCIT and SLIT tablets were cost-effective.²⁸ Nevertheless, the

extensive presentation of the results allows the interpretation using different thresholds.

This study fills a gap in the literature in different ways. Firstly, in our model, we included adherence rates to represent what happens in the real world. Secondly, it was simulated in a pediatric population for different administrations routes of AIT. Thirdly, we applied the model considering a Portuguese context. Both strategies were cost-effective. However, SCIT showed more consistent results and seemed to have a greater impact on clinical and quality of life outcomes by reducing exacerbations leading to emergency department visits and medication requirements. The high probability of cost-effectiveness for both strategies may drive future policy decisions and AIT-prescribing habits. To perform reliable and accurate cost-effectiveness studies, AIT's long-term effects should be addressed in high-quality studies. We also conclude that AIT adherence rates significantly impact results, highlighting the value of implementing strategies to promote adherence rates.

AUTHOR CONTRIBUTIONS

AM, JCR, and MF conceptualized the study. AM, IA, and MS reviewed, discussed, and approved the clinical data included in the model as medical and scientific experts. MF conducted the literature review. MF and JCR implemented the model (data analysis). All authors interpreted, discussed the results, and finalized the manuscript.

CONFLICT OF INTEREST

None of the other authors report any conflict of interest in relation to this work.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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