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Cost-utility of azithromycin in patients with severe asthma

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ABSTRACT

Background: An important proportion of asthma patients remain uncontrolled despite the use of inhaled corticosteroids and long-acting beta-agonists. Some add-on therapies, like azithromycin, have been recommended for this subgroup of patients. The purpose of this study was to assess the cost-effectiveness of azithromycin as an add-on therapy to ICS + LABA for patients with severe asthma.

Methods: A probabilistic Markov model was created to estimate the cost and quality-adjusted life-years (QALYs) of patients with severe asthma in Colombia. The total costs and QALYs of two interventions, including standard therapy (ICS + LABA), and add-on therapy with azithromycin, were calculated over a lifetime horizon. Multiple sensitivity analyses were conducted. Cost-effectiveness was evaluated at a willingness-to-pay value of \$19,000.

Results: The model suggests a potential gain of 0.037 QALYs per patient per year on azithromycin, with a difference of US \$718 in favor of azithromycin, showing dominance with respect to SOC. A position of dominance negates the need to calculate an incremental cost-effectiveness ratio. In the deterministic sensitivity analyses, our base-case results were robust to variations in all assumptions and parameters.

Conclusion: Add-on therapy with azithromycin was found to be cost-effective when added to usual care in patients who remain uncontrolled despite treatment with medium or high-dose ICS/LABA.

Abbreviations: ICS: Corticosteroids inhaled; LABA: Long-acting beta2-agonist; OCS: Oral corticosteroids; LAMA: Long-acting muscarinic antagonists; QALYs: quality-adjusted life-years; SOC: Standard therapy; WTP: willingness to pay; RR: Relative risk; CHEERS: Consolidated Health Economic Evaluation Reporting Standards; SABA: Short-Acting Beta-Agonists; ICER: Incremental cost-effectiveness rate; AMR: Antimicrobial resistance

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Background

Asthma is a disease that affects more than 300 million people worldwide (1). Trends suggest increasing asthma prevalence globally, with an anticipated 100 million new cases in the next decade, principally in developing countries (2). Around 50 million people are estimated to have moderate to severe uncontrolled asthma worldwide (3). This patient requires high doses of inhaled corticosteroids (ICS)-long-acting beta2-agonist (LABA) or ICS-LABA or oral corticosteroids (OCS) (4). Indeed, despite these drugs, almost 70% of these patients do not achieve total control of their symptoms (4). Severe asthma is a serious problem for health systems. In the US, Yaghoubi and colleagues calculate there will be 175 million person-years

with uncontrolled asthma and if all those people with uncontrolled asthma in the United States could achieve and maintain asthma control, the saving would be about \$300 billion in direct costs and \$660 billion in indirect costs, recovering 15 462 quality-adjusted life-years (5).

Administration of intermittent, low-dose administration of azithromycin in patients with mild asthma reduces the severity of bronchial hyperresponsiveness (6). Azithromycin has the potential to be a novel and potent bronchodilator, lowering cytosolic Ca²⁺ levels and causing muscle relaxation (7). Azithromycin was associated with a reduced rate of oral corticosteroid courses due to worsening asthma, antibiotic use for lower respiratory tract infection, hospitalization, and

emergency room visits in the non-eosinophilic, eosinophilic subgroups (8). Recent clinical guidelines recommend the use of add-on azithromycin for treatment with ICS-LABA in severe asthma (9). However, this recommendation raises concerns about if the extra benefit offered by this drug outweighs the additional cost compared to therapy with only ICS-LABA. This question is even more relevant in developing countries with an increasing prevalence of asthma and constrained healthcare. An economic evaluation of these new drugs could provide evidence to optimize the efficiency of the use of economic resources in these countries. The purpose of this study is to evaluate the health and economic consequences of three strategies for treating severe asthma in Colombia: continuation of standard therapy, add-on therapy with Azithromycin, and a combination of the two.

Materials and methods

We conducted a probabilistic Markov model to estimate the cost and quality-adjusted life-years (QALYs) of patients with severe asthma treated with azithromycin combined with medium-dose ICS/LAB in Colombia. The choice of time horizon was 5 years. Two interventions were modeled: standard of care or SOC (high dose ICS+LABA), add-on therapy with azithromycin. In this mathematical model, the patients could transition between four mutually exclusive health states (symptom-free state or asthma controlled by azithromycin and SOC and death). During each cycle, patients in non-death health states could transit to any of three levels of asthma exacerbations: OCS

burst (which was defined as relatively major symptoms during the week and needed the use of oral corticosteroids to achieve the control of symptoms), emergency department (patients that request treatment with systemic corticosteroids) and hospitalization. Asthma-related mortality following an exacerbation or all-cause mortality could also occur (Figure 1). We did this analysis from a societal perspective (including direct and indirect costs), using a cycle length of 2 weeks. A half-cycle correction and an annual discounting rate of 5% were applied to both costs and QALYs. Treatment was considered cost-effective if the incremental cost-utility ratio was below \$19,000 per QALY gained, using the World Health Organization (WHO) recommendation of three times the GDP per capita to define the willingness to pay (WTP) in Colombia.

Parameters of the Markov model

Multiple parameters were derived from published research and local data, which are presented in Table 1. A recent individual participant data meta-analysis of azithromycin in patients with severe asthma (15) was used to extract data on the relative risk (RR) of exacerbation rate. In this study, the relative risk of asthma exacerbations was 0.61 (CI 95% 0.49–0.78). Asthma exacerbations in this meta-analysis were defined as the use of systemic corticosteroid burst, (or SCS, outpatient visits with at least three days of high-dose oral corticosteroids (OCS), or a single SCS injection) emergency department (ED) or hospitalization. Two studies, AZISAST (16) and AMAZES

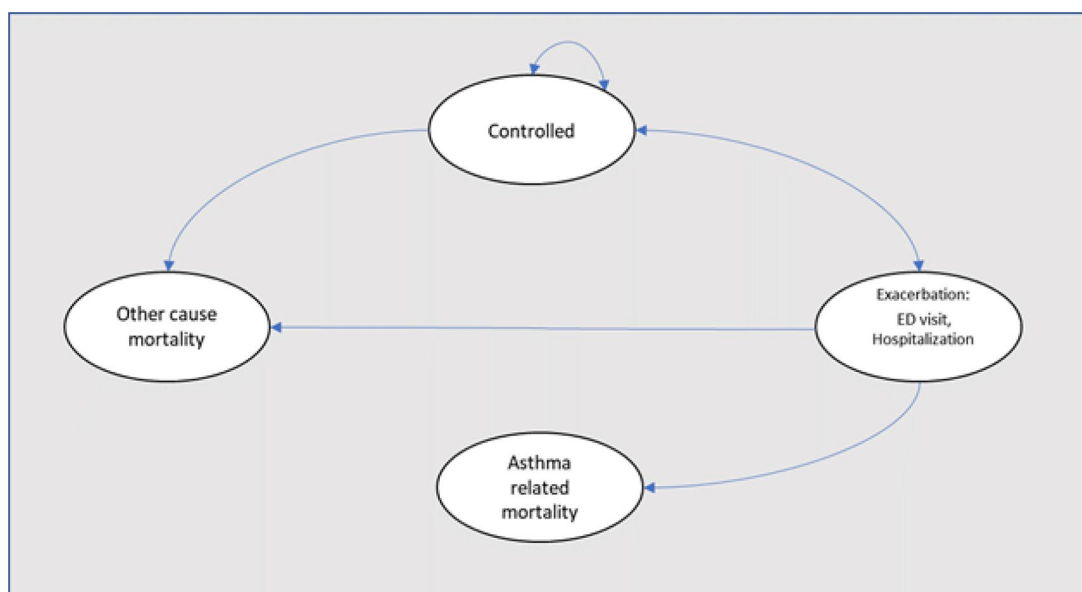


Figure 1. Markov model.

Table 1. Base case.

Variable	Base case	Valor High	Valor Low	Reference
Cost Azitromycin (per cycle)	\$ 3	\$ 4	\$ 2	
Cost controlled (anual)	\$ 2.244	\$ 2.805	\$ 1.683	
Cost OCS burst (per episode)	\$ 195	\$ 244	\$ 146	
Cost ED visit (per episode)	\$ 228	\$ 285	\$ 171	(10)
Cost hospitalization (per episode)	\$ 4.635	\$ 5.794	\$ 3.477	
Antimicrobial Resistance costs	\$ 3	\$ 5	\$ 2	(11)
Utilities (anual)				
Utility of controlled state	0,740	0,93	0,56	(12)
Utility decrement				
Exacerbations requiring OCS burst	0,1	0,13	0,08	(13)
Exacerbations requiring ED visit	0,15	0,19	0,11	
Exacerbations requiring hospitalization	0,2	0,25	0,15	
Azitromycin effect				
Relative risk on exacerbation rate	0,61	0,49	0,78	(8)
Exacerbations				
Exacerbation anual rate	1,1	4	1	(10)
# Hospitalization anual	2,6	5	1	
Azitromycin discontinuation due to AE	7%	9%	5%	(14)
Antimicrobial Resistance	49%	61%	37%	(14)
Annual discount rate	5%	6%	0%	

(14), contributed data to the IPD meta-analyses of the primary exacerbation endpoint. In AZISAST, 70 patients (65%) were classified as non-eosinophilic and 38 (35%) as eosinophilic; all were using ICS. In AMAZES, 224 (53%) were non-eosinophilic (99.6% using ICS) and 196 (47%) were eosinophilic (100% using ICS).

The transition probabilities for moving between different health states for standard therapy and add-on therapy were derived from clinical trials and economic evaluations of azithromycin (14,17). Data on the utilities of each Markov state was extracted from a systematic review of utilities in asthma (12,13), Table 1. This systematic review identifies a total of four studies in asthma that report utility in different severity states of asthma. Within these four studies ($n=330$ patients) show a median utility of 0.74 ± 0.029 for severe asthma, all estimated using time tradeoff or standard gamble or Asthma symptom utility index in the US and UK population. Because none of these data (RR, transition probabilities, and utilities) are from the Colombian population, they were subjected to a probabilistic sensitivity analysis, as detailed below and as recommended by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement (18). In this sensitivity analysis, to build the range of RR to be used in this analysis, we used the CI of 95% of RR published by clinical trials (8). In the case of utilities and transition probabilities, the upper and lower ranges were estimated by adding or subtracting 25% of the value from the central value defined for the base case. The risk of mortality from other causes was estimated using age- and gender-specific Colombian life tables for all-cause mortality over 5 years (2016 to 2020) (19).

For azithromycin, we assumed a discontinuation rate due to adverse events of 7% (14). Patients who discontinued (non-adherents) treatment had the same costs and clinical outcome values as the SOC group. Sensitivity analyses of the percentage of non-adherents and response rate were made, estimating the upper and lower range of each value by adding or subtracting 25% of the value defined previously. To take account of broader costs that may arise due to therapy, costs related to antimicrobial resistance (AMR) were estimated. Following the same methodology as the previous cost-effectiveness study of azithromycin in asthma (17), AMR for azithromycin was estimated at the midpoint of the range (0–5 US \$) for the cost of AMR per course associated with azithromycin reported by Shresta (11).

All costs of each health state defined in the Markov model were extracted from a previously published Colombian-based study (10). Briefly, this study identified the asthma-related direct and indirect costs of 1131 patients with severe asthma from January 1, 2004, through December 31, 2014, in Colombia. Asthma severity classification was mainly based on the paper of Jacob et al (20). Severe persistent asthma was required to have more than six Short-Acting Beta-Agonists (SABA) fills per year, and the number of OCS fills per year was greater than or equal to two or 4 or more exacerbations. Moreover, zero to six SABA and three or more SABA per year also constitute severe asthma. This criterion related to the use of rescue medication per year may be more accurate than the use of LABA + ICS given the high frequency of underuse and prescription of controller medications in Latin American countries (21). This group of patients with severe asthma had an average

of 1.4 ED visits per year, and 2.5 hospitalizations per year, rates that are comparable to those reported in clinical trials and observational studies in patients with severe asthma (14,22). Unit costs of azithromycin were taken from the National Drug Price Information System (SISMED, 2020). Using Colombia's official inflation data, all costs were converted to 2020 costs. We use US dollars (currency rate: US \$1 = COP) to express all costs in the study.

Sensitivity analyses

To explore the parameter uncertainty of the model inputs, we conducted a probabilistic sensitivity analysis by randomly sampling from each of the parameter distributions (beta distribution in the case of relative risk and utilities, Dirichlet distribution for multinomial data in the case of transition probabilities, and gamma distribution in the case of costs). The expected costs and expected QALYs for each treatment strategy were calculated using a combination of parameter values in the model. This process was replicated one thousand times (i.e. second-order Monte Carlo simulation) for each treatment option, resulting in the expected cost-utility. All analyses were made in Microsoft Excel®.

Results

The main results are presented in Table 2. For a patient with severe asthma, the base-case analysis showed that, compared to SOC, treatment with the combination of SOC and azithromycin was associated with a lower treatment cost and a higher QALY. The total discounted 5-year cost per person for SOC and azithromycin was US \$2961 (CI 95% US \$2890 to US\$3032) and US \$2244 (CI 95% US\$2196 to US\$2291), respectively. The QALYs per person estimated in the model for those treatments were 0.59 (CI 95% 0.58 to 0.61), and 0.63 (CI 95% 0.62 to 0.65) respectively.

In the analysis of the Markov cohort model, we estimated a median probability of surviving free of exacerbation of 0.60 in SOC and 0.71 of add-on therapy with azithromycin. The model suggests a potential gain of 0.037 QALYs per patient per year on

azithromycin, with a difference of US \$718 in favor of azithromycin, showing dominance with respect to SOC. A position of dominance negates the need to calculate an incremental cost-effectiveness ratio.

Sensitivity analyses

In the deterministic sensitivity analyses, our base-case results were robust to variations in all assumptions and parameters. For none of the variables evaluated, variations within the established ranges led to the incremental cost-effectiveness ratio being higher than the WTP, Figure 2. The results of probabilistic sensitivity analysis are graphically represented on the cost-effectiveness plane in Figure 3. This scatter plot shows that, compared with SOC, treatment with azithromycin tends to be associated with lower costs and higher QALYs. Indeed, 62% of simulations were graphed in quadrant 2 (lower cost, high QALYs), 15% in quadrant 1 (high cost, high QALYs), 13% in quadrant 3 (lower cost, lower QALYs), and 8% in quadrant 4 (high cost, lower QALYs). The cost-effectiveness acceptability curve shows that azithromycin becomes cost-effective at 100% for all willingness-to-pay thresholds (Figure 4).

Discussion

This cost-effectiveness study estimates cost and QALY outcomes over a five-year horizon for a hypothetical cohort of patients with severe asthma who had azithromycin added to their usual controller therapy. Our findings suggest that add-on therapy with azithromycin achieves better outcomes at a lower cost compared to standard treatment.

Our results are in line with previous studies. O'Neill et al. evaluated the cost-effectiveness of add-on azithromycin in terms of healthcare and societal costs during the AMAZES trial. In this trial, 420 participants were randomly assigned to either azithromycin or a placebo, and clinical outcomes were measured during the treatment period. Add-on azithromycin resulted in a reduction in healthcare costs (mean (95% CI)) (AUD 433.70 (95% CI AUD 48.59–818.81) $p < 0.05$). The net monetary benefit of add-on

Table 2. Cost- effectiveness of azithromycin versus standard of care.

Strategy	Cost	Marginal difference	QALYs	Marginal difference	C/E	ICER
Azithromycin	\$ 2244	\$ -718	0,631	0,037	\$ 3556	Dominated
SOC	\$ 2961		0.594		\$ 4988	

ICER=Incremental cost effectiveness ratio.

SOC=standard of care.

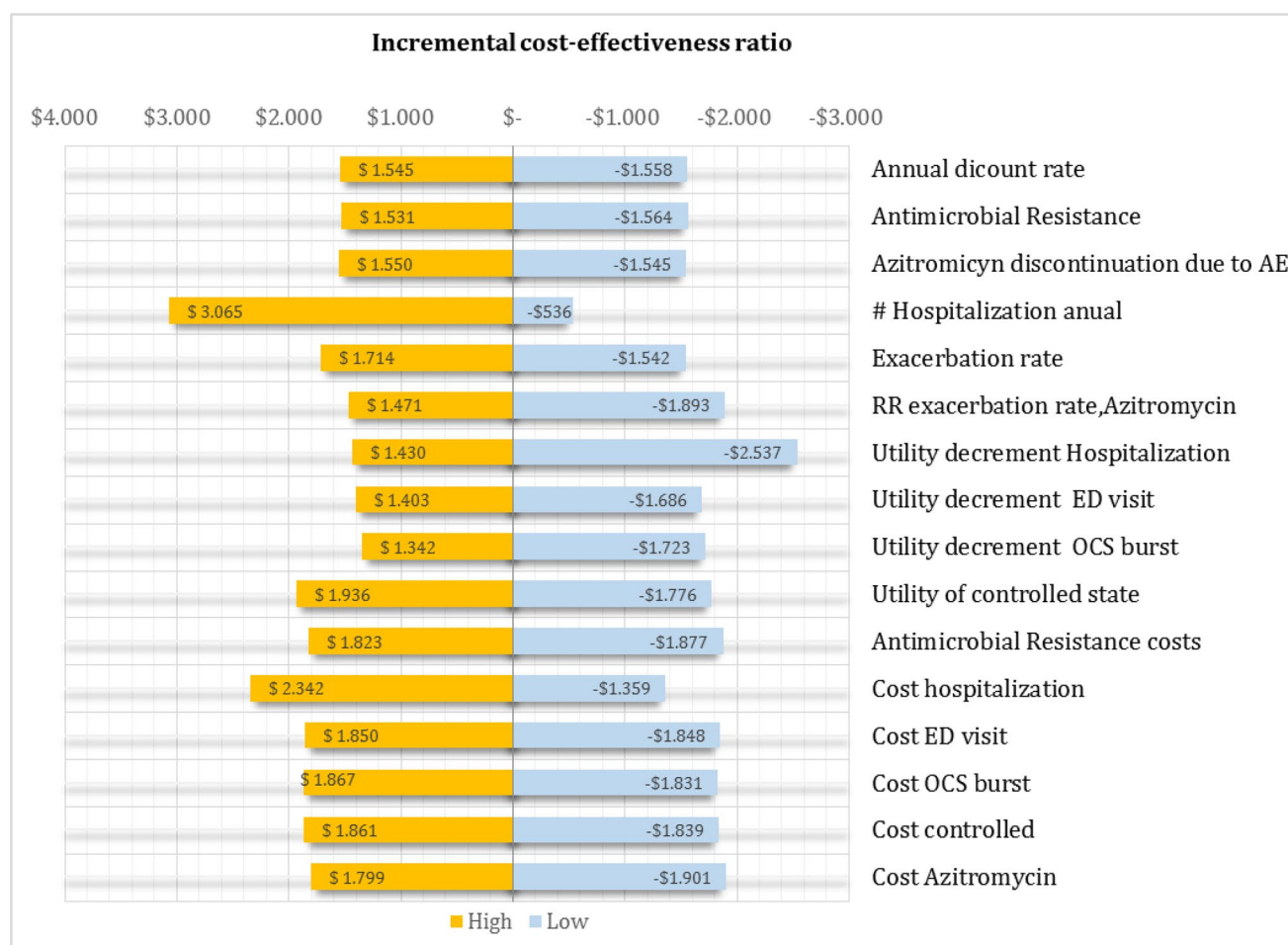


Figure 2. Tornado diagram.

azithromycin was estimated to be AUD 2072.30 (95% CI AUD 1348.55–2805.23) assuming a willingness to pay per exacerbation avoided of AUD 2651. Irrespective of the sensitivity analysis applied, the net monetary benefit for total, moderate and severe exacerbations remained positive and significant. The authors concluded add-on azithromycin therapy in poorly controlled asthma was a cost-effective therapy in Australia. Despite methodological differences such as the mathematical model, higher drug and direct costs in Australia, and benefits, our conclusion is the same. We decided to use utilities reported in a systematic review. Variations in the values of these utilities in the probabilistic sensitivity analysis did not significantly change the calculated ICER. Indeed, after 10 000 simulations in our PSA, azithromycin tends to be associated with lower costs and higher QALY; 77% of simulations were graphed in quadrant 1 and 2 of the cost-effectiveness plane.

A minor difference in our evaluation from previous studies is the fact that we have adjusted our estimates for discontinuation due to AE. Assuming 100%

adherence is unrealistic and tends to overestimate the effect of azithromycin. On the other hand, including the cost of antimicrobial resistance in the azithromycin group serves to reflect concerns around AMR costs, biasing downward the intervention's cost-effectiveness and serving to make estimates of its relative value more conservative.

A crucial methodological aspect is the discussion of willingness to pay (WTP) to declare Colombia a cost-effective technology or not. Since Colombia does not have a threshold that represents the WTP per unit of effectiveness (QALY), the ICER results per QALY were evaluated by using the reference corresponding to the World Health Organization (WHO) recommendation (three times the GDP per capita). Not having your own estimate of the WTP may be debatable. However, up to now, all the economic evaluations of health carried out in the country follow the threshold suggested by the WHO, which has also been endorsed by the national technology evaluation agency (23). The results of the probabilistic sensitivity analyses confirm the robustness of the model results. Since transition

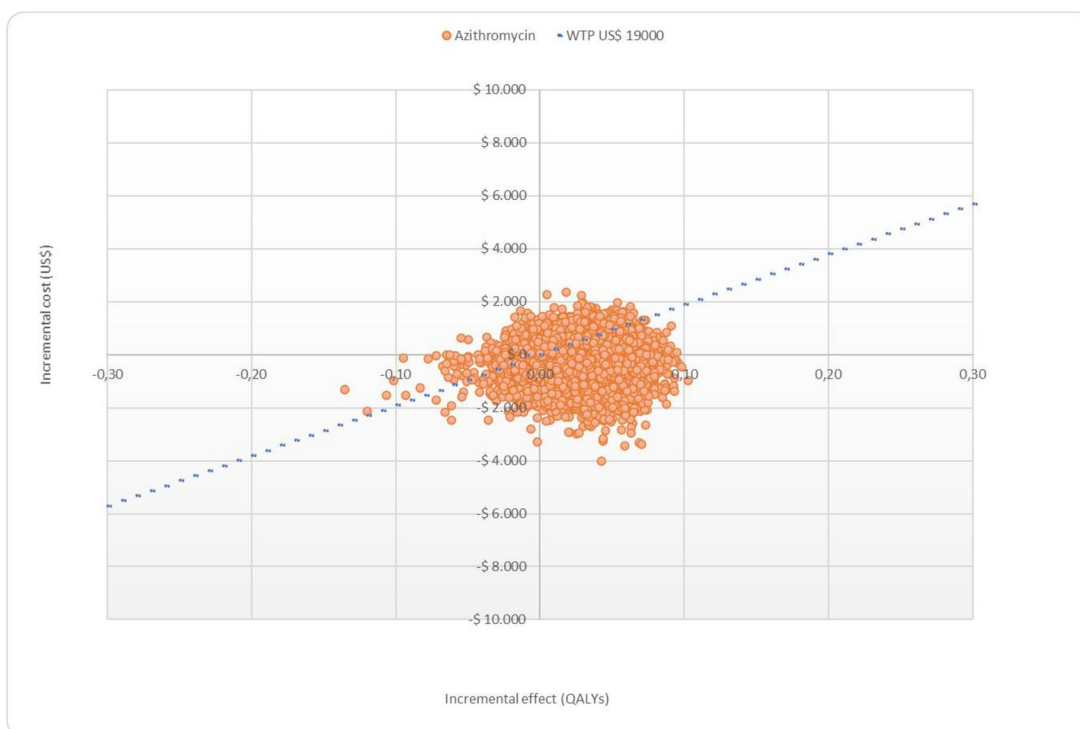


Figure 3. Cost-effectiveness diagram.

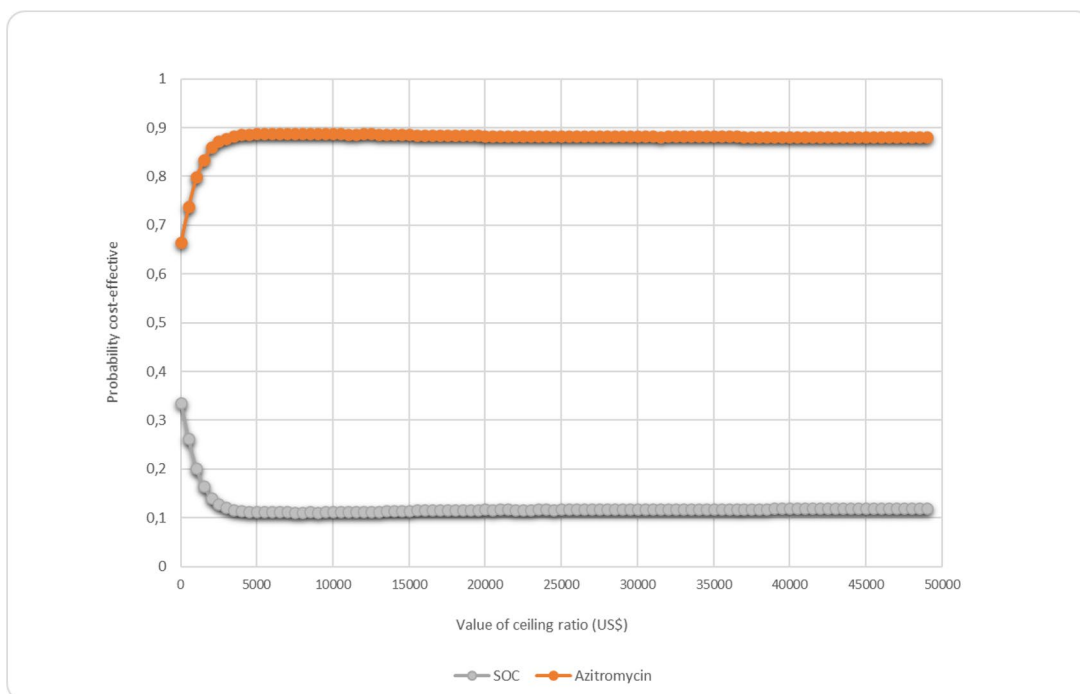


Figure 4. Cost-effectiveness acceptability curve.

probabilities and utilities do not come from the Colombian population, they were subjected to probabilistic sensitivity analysis as detailed below as recommended by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement (18).

Our study has some limitations. We use utilities extracted from the literature and not estimated directly from our population. As was mentioned previously, the reliability and robustness of the results were evaluated by sensitivity analyses. Our result only refers to a patient with severe asthma uncontrolled

by medium-dosage to high-dosage inhaled corticosteroids plus long-acting β_2 -agonists, and cannot be extrapolated to patients with the use of oral daily corticosteroids. Studies of azithromycin in asthma have recruited both allergic and non-allergic asthma patients. We assumed the same health benefits of azithromycin for allergic and non-allergic asthma patients and this assumption is supported by trials of azithromycin. Previous studies showed no difference between allergic versus non-allergic subjects (8).

Conclusion

In conclusion, add-on therapy with azithromycin was found to be cost-effective when added to usual care in patients who remain uncontrolled despite treatment with medium or high-dose ICS/LABA.

Declaration of interest

No potential conflict of interest was reported by the authors.

Authors' contributions

All authors contributed equally to designed and performed of research, analyzed data and co-wrote the paper

Declarations

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Consent for publication

All authors have given their permission for this paper to be published.

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