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Cost-Utility Analysis of Daily Versus Intermittent Inhaled Corticosteroids in Mild-Persistent Asthma

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Summary

Introduction—Despite the many benefits that have been demonstrated by the continuous administration of inhaled corticosteroids (ICS) in persistent asthma, a new strategy for mild-asthma is emerging, consisting of using intermittent or as-needed ICS treatment in conjunction with short-acting beta2 agonists in response to symptoms. However, no previous studies have reported an economic evaluation comparing these two therapeutic strategies.

Methods—A Markov-type model was developed in order to estimate costs and health outcomes of a simulated cohort of pediatric patients with persistent asthma treated over a 12-month period. Effectiveness parameters were obtained from a systematic review of the literature. Cost data were obtained from official databases provided by the Colombian Ministry of Health. The main outcome was the variable “quality-adjusted life-years” (QALYs).

Results—For the base-case analysis, the model showed that compared to intermittent ICS, daily therapy with ICS had lower costs (US \$437.02 vs. 585.03 and US\$704.62 vs. 749.81 average cost per patient over 12 months for school children and preschoolers, respectively), and the greatest gain in QALYs (0.9629 vs. 0.9392 QALYs and 0.9238 vs. 0.9130 QALYS for school children and preschoolers, respectively), resulting in daily therapy being considered dominant.

Conclusions—The present analysis shows that compared to intermittent therapy, daily therapy with ICS for treating pediatric patients with recurrent wheezing and mild persistent asthma is a

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dominant strategy (more cost effective), because it showed a greater gain in QALYs with lower total treatment costs. *Pediatr Pulmonol*.

Keywords

asthma; cost-effectiveness; developing countries; inhaled corticosteroids; quality-adjusted life years

INTRODUCTION

The economic burden of asthma is great in terms of both direct medical and indirect costs for patients, for their families, and for healthcare systems and governments, especially when the disease is inadequately controlled.¹ Inhaled corticosteroids (ICS) are the mainstay anti-inflammatory treatment for asthma and their continuous administration has been shown to reduce the severity of symptoms, the frequency of emergency department visits, hospitalizations due to exacerbations of the disease,² airway hyperresponsiveness,³ accelerated loss of pulmonary function,⁴ and rates of mortality from the disease.⁵

Despite the many benefits that have been demonstrated by the continuous administration of ICS, there are many reasons why they are used intermittently instead of continuously. First, steroid “phobia,” or excess concern over the systemic effects of ICS by both parents/caregivers and even physicians is the principal argument that convinces them to avoid daily controller therapy.⁶ Second, intermittent use of ICS has been proposed as a potentially useful strategy for reducing the cumulative levels of exposure to corticosteroids, thus minimizing the risk of adverse events.^{7,8} Third, in part due to a lack of appropriate educational interventions, many patients, families, and even physicians still consider asthma to be an episodic disease, and so the disease is managed exclusively based on the symptomatic periods or exacerbations, instead of treating inter-critical periods.⁹ Fourth, besides the well-known effect of prolonged treatment with ICS, a rapid, topical anti-inflammatory action of ICS has been reported, by a nongenomic mechanism of action that remains unknown.¹⁰ Fifth, one of the main problems for accomplishing asthma control is the lack of adherence to inhaler drugs; therefore, having an alternative strategy of intermittent ICS gives rise to the possibility of assuring more adherence than does using daily inhalers.¹¹ Lastly, the high cost and lack of availability of essential medications for the treatment of asthma have been reported as key barriers to the effective treatment of the disease in some low- and middle-income countries (LMIC).¹²

The above-mentioned situations might have been responsible, at least in part, for the emergence of a new strategy for control of recurrent wheezing and mild to moderate asthma, consisting of using intermittent or as-needed ICS treatment in conjunction with short-acting beta2 agonists in response to symptoms, either as a step-down strategy after asthma control is achieved, or as an alternative step 2 therapeutic option for mild persistent asthma.^{7,8,13,14} In this context, this therapeutic dilemma can be approached from the pharmacoeconomic point of view, in which the clinical consequences and costs attributed to the use of pharmaceutical products and services are considered simultaneously. However, to the best of

our knowledge, no previous studies have reported both the clinical consequences and the costs attributed to these two therapeutic strategies.

The aim of the present study was to compare the cost-utility of daily versus intermittent therapy with ICS for treating pediatric patients with recurrent wheezing and mild persistent asthma.

MATERIALS AND METHODS

Model Structure

We developed a Markov simulation model with three mutually exclusive nonabsorbent states (regular Markov chain).^{15,16} In this model, the following three distinct health states were defined: “no symptoms,” “suboptimal control, no exacerbation,” and “asthma exacerbation,” based on the economic implications of each of these states (Fig. 1).

In the same manner as the model developed by Price and Briggs,¹⁷ and a model previously developed for our group,¹⁸ due to the chronic, episodic nature of asthma, a cycle length of 1 week was considered appropriate. Likewise, in accordance with the above-mentioned models, we did not include costs for treatment of adverse events (i.e., oropharyngeal candidiasis, dysphonia, adrenal suppression, increased cataract formation, decreased linear growth) in our cost-effectiveness model.

The main outcome of the model was the quality-adjusted life-years (QALYs), a measure of disease burden that includes both the quality and the quantity of life lived.

We developed separate models for preschool and school children, because there are differences in the therapeutic aspects of asthma between these two subgroups of patients, such as major impairment-domain disease in older children compared to young children (after considering both the impairment and risk domains), differences in adequate delivery of inhaled drugs, and dosing issues.¹⁹

SOURCES OF DATA

Disease Outcomes and Clinical Parameters

The data were obtained from a systematic review of published randomized clinical trials (RCTs). Searches of computerized databases (MEDLINE, EMBASE, and CENTRAL) and references cited in published literature identified the potentially applicable studies. The computerized search yielded 185 citations, and a total of 33 studies were examined in full text for possible inclusion. To be included in the model, the studies had to be RCTs of parallel-group design, include patients aged under 18 years with recurrent wheezing or mild persistent asthma, compare daily versus intermittent ICS (initiated for a short duration only at the onset of exacerbations), and report at least one of the following outcomes: percentage of symptom-free days, or probability of asthma exacerbation during the period of observation. After applying these criteria, data from four publications were included in the model.^{7,8,13,14} In these four studies a total of 427 preschoolers and 259 school children were analyzed.

Data Inputs: Transition Probabilities

Transition probabilities were calculated according to the following steps: first, in order to calculate transition probabilities from the “sub-optimal control, no exacerbation” to the “asthma exacerbation” state for each of the two alternatives (daily vs. intermittent therapy with ICS), we calculated a weighted average of the probability of occurrence of the outcome “time to first exacerbation” at different periods of time based on the Kaplan–Meier curves presented in the included studies. Second, in order to calculate transition probabilities from the “sub-optimal control, no exacerbation” to the “no symptoms” state for each alternative, a weighted average of the outcome “symptom-free days” was synthesized from the information provided in the included RCTs. Third, in order to calculate transition probabilities from the “no symptoms” to the “no symptoms” and to the “asthma exacerbation” states, we calculated the probability of occurrence of the outcome “symptom-free days” and the outcome “time to first exacerbation,” respectively, in patients with more than 80 percent of symptom-free days in the included studies for each alternative. Fourth, transition probabilities from the “asthma exacerbation” state to the “no symptoms” state for each alternative were derived from a previous model developed for our group.¹⁸ Fifth, in order to calculate transition probabilities from the “asthma exacerbation” to the “asthma exacerbation” state, we assumed values 10% greater than transition probabilities from the “sub-optimal control, no exacerbation” to the “asthma exacerbation” state for each alternative. Finally, in order to complete the remainder of the transitional probability matrix for each alternative, we calculated the difference of one minus the sum of the probabilities in the same row (the sum of probabilities of each row must be equal to one).

Adjustments were made for studies with different time frames. Since it is possible to convert an instantaneous rate to a probability over a particular time period if the rate is assumed to be constant over that period, we calculated 1-week probabilities of the events based on instantaneous rates derived for these events.²⁰

Data Inputs: Health Outcomes

In the same manner as was done in our previous asthma model, utility values for the three health states included in the model were based on a utility valuation survey of 76 parents of children (28 preschool children) with asthma in Colombia using standard gamble methodology.¹⁸ Parents were chosen as the most suitable patient-proxy respondents on the basis that many children with asthma would be too young to provide reliable responses. The health state description comprised three domains, based on those reported in the Pediatric Asthma Health Outcome Measure: symptoms, emotions, and activity.²¹ Descriptions for the three domains were derived largely based on this study and validated by clinical experts.

Health states corresponding to “no symptoms,” “suboptimal control, no exacerbation,” and “asthma exacerbation” had utility values of 0.989, 0.705, and 0.275, respectively. The number of QALYs was calculated as the utility value given to a particular health state multiplied by the length of time spent in that state.

Data Inputs: Resource Utilization and Costs

Each Markov-model health state has an associated cost, which was considered from the perspective of the national healthcare system in Colombia. Unit costs of all medications were taken from the Drug Price Information System (SISMED, 2011),²² an official database provided by the Colombian Ministry of Health and Social Protection, which represents an important primary source of medication prices in the country.

In order to calculate the costs attributed to daily and intermittent therapy with ICS, we used the costs of beclomethasone dipropionate (BDP), because it was the ICS used in two of the four included studies,^{8,13} and two Cochrane systematic reviews conclude that in general all ICS at equipotent doses provide a similar level of asthma control.^{23,24} In addition, BDP is the only ICS included in the Compulsory Health Insurance Plan of Colombia. Calculation of the daily therapy with ICS was based on the estimated average daily dose appropriate for treating pediatric patients with mild persistent asthma, according to current national and international asthma guidelines,^{25,26} and the relative use of available concentrations for each medication according to current market research.

In order to determine the utilization rates of health resources and events for each of the three health states of the model, we performed a review of the literature, used the results of a previous consensus of experts consisting of a panel of ten local pediatric pulmonologists using the Delphi technique,^{25,27} and verified the results with administrative data from care providers. The data collected on health utilization were: the number of planned consultations with a general practitioner, pediatrician, or pediatric pulmonologist; the number of unscheduled medical visits; the amount of asthma medication used (reliever medications, systemic corticosteroids), and the number of pulmonary function tests.

Unit prices of health resources and events were obtained from a previously published study performed in Colombia²⁵ and previous reports based on a database provided by the Colombian Ministry of Health and Social Protection, in accordance with the Single Classification for Health Procedures (CUPS) and the International Disease Classification (ICD-10) that are relevant for asthma (ICD-10 codes J450, J451, J458, J459, or J46X). Hospital-managed exacerbations involved management of asthma either in an emergency room alone or with subsequent management as an inpatient (in an asthma inpatient ward and/or in a pediatric intensive care unit). To reflect this, the cost associated with this health state was calculated as a weighted average of the costs of exacerbations managed in the emergency room and of those managed during an inpatient stay.

Costs were calculated in Colombian pesos (COP) and converted to dollars (US\$) based on the average exchange rate for 2011 (1 US\$ = 1848.17 COP).²⁸ Given that the model duration was 1 year, costs and effects were not discounted.

Sensitivity Analyses

A series of one-way, two-way, and multi-way sensitivity analyses (using a tornado diagram) and the effect of alternative model specifications were examined. In addition, a probabilistic sensitivity analysis using second-order Monte Carlo simulation was conducted to analyze uncertainty in the data, using a cohort of 10,000 trial simulations for both alternatives. This

probabilistic sensitivity analysis allowed us to generate 95% uncertainty intervals (UI) around costs and effects. These were presented graphically on a cost-effectiveness plane to show the estimated joint distribution of incremental costs against incremental effects and evaluated using net benefit analysis.²⁹ Subsequently, a cost-effectiveness acceptability curve (CEAC) was derived from these data³⁰ to identify which alternative would be most cost-effective at various thresholds of willingness-to-pay (WTP) for QALYs. All analyses were performed with software (TreeAgePro 2012, TreeAge Software, Williamstown, MA).

RESULTS

Base-Case Analysis

While transition probabilities from all three health states to the “no symptoms” state were lower for intermittent therapy than those for daily therapy, transition probabilities from all three health states to the “asthma exacerbation” state were lower for daily therapy compared to intermittent therapy (Table 1).

As expected, the value of the unit cost of hospitalization for asthma exacerbation was greater than the cost of treatment in the emergency department and the cost of pediatrician and general practitioner consultations (Table 2). The weekly cost per patient associated with “no symptoms” and “sub-optimal” health states was lower for intermittent therapy than for daily therapy (Table 3).

In school children, the model showed that compared to intermittent ICS, daily therapy with ICS had lower costs (US\$437.02 vs. 585.03 average cost per patient over 12 months) and the greatest gain in QALYs (0.9629 vs. 0.9392 QALYs on average per patient over 12 months), thus leading to dominance. In preschoolers, daily therapy with ICS also had lower costs (US \$704.62 vs. 749.81) and the greatest gain in QALYs (0.9238 vs. 0.9130 QALYs), also resulting in daily therapy being considered dominant. A position of dominance negates the need to calculate an incremental cost-utility ratio (Table 4).

Sensitivity Analyses

Deterministic sensitivity analyses showed that the cost of an asthma exacerbation has the highest impact on the model outcome. However, although as the cost of an asthma exacerbation decreases the intermittent therapy tends to be more cost-effective, daily therapy was the dominant strategy over all the ranges of the cost of asthma exacerbation analyzed. Parameter distributions used in the probabilistic sensitivity analysis are presented in Table 5. The results of the probabilistic sensitivity analysis are graphically represented as a scatter plot in Figure 2. This scatter plot shows that daily therapy tends to be associated with lower costs and a greater gain in QALYs. Based on the results from this simulation, for school children, the 95% UI for cost per patient treated with daily and intermittent therapy were US \$218.93 to 1079.79 and US\$315.56 to 1359.71, respectively. Likewise, these 95% UI for utilities were 0.8594–0.9844, and 0.8456–0.9618 QALYs, respectively. In 98.3% of the iterations, daily therapy was associated with a greater gain in QALYs and lower costs compared to intermittent therapy. The CEAC shows that the probability that daily therapy

provides a cost-effective use of resources compared to intermittent therapy exceeds 99% for all WTP thresholds (Fig. 3).

For preschoolers, the 95% UI for cost per patient treated with daily and intermittent therapy were US \$405.32 to 1496.13 and US\$429.97 to 1594.29, respectively. Likewise, these 95% UI for utilities were 0.8232 to 0.9537, and 0.8168 to 0.9432 QALYs, respectively. In 68.4% of the iterations, daily therapy was associated with a greater gain in QALYs and lower costs compared to intermittent therapy. In the CEAC it can be seen that the probability that daily therapy provides better value for the money compared to intermittent therapy exceeds 70% for all WTP thresholds (Fig. 3).

DISCUSSION

The present study shows that compared to intermittent therapy, daily therapy with ICS for treating pediatric patients with recurrent wheezing and mild persistent asthma is a dominant strategy because it showed a greater gain in QALYs at lower total treatment costs. This dominance of daily over intermittent ICS therapy was more marked in school-age children than in preschoolers. Although the only variable that exhibited a significant effect on these results was the cost of asthma exacerbation, daily therapy was the dominant strategy over all the ranges of the cost of asthma exacerbation analyzed.

The findings of the present study support the use of daily therapy with ICS as the most efficient therapy in pediatric patients with recurrent wheezing and mild persistent asthma in Colombia and probably in other similar LMIC. These findings are important because one of the reasons that has been given for preferring intermittent ICS over daily ICS in LMIC is the high cost of essential medications for the treatment of asthma.¹² Our results do not support this argument, because compared to daily therapy, intermittent therapy with ICS was associated with greater costs and lower health benefits, especially in school-age children.

Our results agree with those published by Rodrigo and Castro-Rodríguez,³¹ and Chauhan et al.,³² showing no significant differences between daily and intermittent ICS in reducing the incidence of asthma exacerbation, but compared to intermittent ICS, the daily ICS strategy was superior in many other outcomes with potential economic implications, such as the percent of asthma-free days, asthma control, reliever use, and lung function parameters. Due to the low cost of acquisition of BDP in our country and to the differences in clinical consequences between the two strategies, the base-case analysis resulted in daily therapy with ICS being the most cost-effective strategy. However, we consider that the fact that the only variable that exhibited a significant effect on these results was the cost of asthma exacerbation was unexpected, given that there was no significant difference in the reduction of the incidence of asthma exacerbations between the two strategies. One possible explanation for this finding is that although there was no significant difference in the pool estimate of risk ratio of asthma exacerbations for the included studies, there were differences in the point estimates of this outcome, favoring daily therapy with ICS, especially in school-age children. Due to the large variability in the cost of asthma exacerbations, because there was a proportion of children that required hospitalization in the pediatric intensive care unit, these differences in point estimates of asthma exacerbations not only favored daily ICS, but

also caused the cost of asthma exacerbation to be the only variable that exhibited a significant effect on these results. However, differences in both costs and health benefits between daily and intermittent therapy with ICS could be due to imprecision of their estimates, because their 95% UI overlap. Therefore, we cannot be at least 95% confident about which is the better strategy with regards to their economic value.

Our model also has some limitations. First, the base-case analysis was run for 12 months instead of a complete lifetime. However, we judged a 12-month period to be enough for determining the major health and economic consequences of the use of ICS in pediatric asthmatics. Second, we did not take into account the effect of incomplete and failing adherence to therapy, which typically occurs when treating chronic diseases such as asthma. However, although this adherence problem has been reported when ICS have been prescribed continuously,⁶ the literature does not convincingly show support for adherence with rescue ICS treatment in children being higher than adherence with regular daily treatment.^{33,34}

In conclusion, the present analysis shows that in Colombia, a LMIC, compared with intermittent therapy, daily therapy with ICS for treating pediatric patients with recurrent wheezing and mild persistent asthma is a dominant strategy, because it showed a greater gain in QALYs at lower total treatment costs. This dominance was more marked for school-age children than for preschoolers.

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Fig. 1.
Diagram of the Markov model for each treatment option.

Fig. 2.

A: Scatter plot of each iteration's cost and effectiveness values for each strategy in school asthmatic children*. *The X-axis shows effectiveness measured as quality-adjusted life-years (QALYs); the Y-axis shows costs measured in dollars (US\$, 2011). Each point represents one of the 10,000 trial simulations, where each input was assigned a random value according to its probability density function. B: Scatter plot of each iteration's cost and effectiveness values for each strategy in preschool asthmatic children*. *The X-axis shows effectiveness measured as quality-adjusted life-years (QALYs); the Y-axis shows costs measured in dollars (US\$, 2011). Each point represents one of the 10,000 trial simulations, where each input was assigned a random value according to its probability density function.

Fig. 3.

A: Cost-effectiveness acceptability curve with daily versus intermittent therapy with inhaled corticosteroids for school children with asthma*. *The cost-effectiveness acceptability curve shows the probability of daily therapy being cost-effective compared to intermittent therapy over a wide range of WTP thresholds. This probability exceeds 99% for all WTP thresholds.

B: Cost-effectiveness acceptability curve with daily versus intermittent therapy with inhaled corticosteroids for preschool children with asthma*. *The cost-effectiveness acceptability curve shows the probability of daily therapy being cost-effective compared to intermittent therapy over a wide range of WTP thresholds. This probability exceeds 70% for all WTP thresholds.

TABLE 1

Transition Probabilities for Pediatric Patients with Recurrent Wheezing and Mild Persistent Asthma Treated with Daily and Intermittent Inhaled Corticosteroids

Transition from	Transition to:		
	No symptoms	Sub-optimal control, no exacerbation	Asthma exacerbation
A. School patients			
No symptoms			
Daily therapy	0.933	0.058	0.009
Intermittent therapy	0.858	0.132	0.010
Sub-optimal control, no exacerbation			
Daily therapy	0.887	0.097	0.016
Intermittent therapy	0.817	0.16	0.023
Asthma exacerbation			
Daily therapy	0.255	0.733	0.012
Intermittent therapy	0.105	0.878	0.017
B. Preschool patients			
No symptoms			
Daily therapy	0.810	0.181	0.009
Intermittent therapy	0.780	0.210	0.010
Sub-optimal control, no exacerbation			
Daily therapy	0.520	0.464	0.016
Intermittent therapy	0.450	0.529	0.021
Asthma exacerbation			
Daily therapy	0.255	0.723	0.022
Intermittent therapy	0.105	0.876	0.019

TABLE 2

Values of Unit Costs (US\$, 2011)

Cost items	Unit costs	Lower value	Higher value
General practitioner consultation	17.81	12.47	23.15
Pediatrician consultation	29.21	20.45	37.97
Treatment in the emergency department	39.74	27.82	51.66
Spirometry	13.25	9.27	17.22
Albuterol via pMDI ^{a,b}	2.78	1.94	3.61
Beclomethasone dipropionate pMDI $\times$ 50 mcg ^c	4.25	3.08	5.28
Beclomethasone dipropionate pMDI $\times$ 250 mcg ^d	5.72	4.56	7.30
Prednisolone $\times$ 5 mg ^e	0.03	0.02	0.04
Hospitalization for asthma exacerbation	290.18	102.24	16585.41
Others (radiology procedures, laboratory tests, ambulance)	27.26	19.08	35.44

^a pMDI, pressurized metered-dose inhaler.^b Unit cost for albuterol pMDI 100 mcg, 200 doses/inhaler.^c Unit cost for beclomethasone dipropionate pMDI 250 mcg, 200 doses inhaler.^d Unit cost for beclomethasone dipropionate pMDI 50 mcg, 200 doses inhaler.^e Unit cost per tablet.

TABLE 3

Resource Use and Costs Associated with Model Health States (US\$, 2011)

		Weekly cost per patient	Weekly cost per patient
Health state	Resources costed	Daily ICS	Intermittent ICS
A. School patients			
No symptoms	GP ^a consultation, pediatrician consultation, spirometry, BDP ^b via pMDI ^c × 250 mcg	2.51	2.11
Sub-optimal control, no exacerbation	GP consultation, pediatrician consultation, spirometry, albuterol via pMDI, BDP via pMDI × 250 mcg	33.23	32.83
Asthma exacerbation	GP consultation, pediatrician consultation, spirometry, albuterol via pMDI, treatment in the ED ^d , hospitalization for asthma exacerbation, prednisolone × 5 mg, others (radiology procedures, laboratory tests, ambulance), BDP via pMDI × 250 mcg	397.40	397.40
B. Preschool patients			
No symptoms	GP consultation, pediatrician consultation, spirometry, BDP via pMDI × 50mcg	2.70	2.11
Sub-optimal control, no exacerbation	GP consultation, pediatrician consultation, spirometry, albuterol via pMDI, BDP via pMDI × 50 mcg	33.42	32.83
Asthma exacerbation	GP consultation, pediatrician consultation, spirometry, albuterol via pMDI, treatment in the ED, hospitalization for asthma exacerbation, prednisolone × 5 mg, others (radiology procedures, laboratory tests, ambulance), BDP via pMDI × 50 mcg	397.59	397.59

^aGP consultation, consultation with general practitioners.^bBDP, beclomethasone dipropionate.^cpMDI, pressurized metered-dose inhaler.^dED, emergency department.

TABLE 4

Base-Case Cost-Utility Analysis of Daily Therapy vs. Intermittent Therapy with Inhaled Corticosteroids for Pediatric Patients with Recurrent Wheezing and Mild Persistent Asthma

Category	Strategy	Cost (US\$)	Incremental cost	Utility	Incremental utility	Cost/utility
A. School patients						
Undominated	Daily ICS ^a	437.02	—	0.9629	—	453.86
Absolutely dominated	Intermittent ICS	585.03	148.01	0.9392	−0.0237	622.90
B. Preschool patients						
Undominated	Daily ICS	704.62	—	0.9238	—	762.78
Absolutely dominated	Intermittent ICS	749.81	45.19	0.9130	−0.0108	821.26

^aICS, inhaled corticosteroids.

TABLE 5

Parameter Distributions used in the Probabilistic Sensitivity Analysis

A. School patients		
Probability distribution	Distribution parameters	Distribution parameters
Beta distribution	Alpha	Beta
Probability from no symptoms to no symptoms		
Daily ICS ^a	106.106	7.607
Intermittent ICS	226.582	37.545
Probability from no symptoms to asthma exacerbation		
Daily ICS	396.254	42029.30
Intermittent ICS	395.869	38038.08
Probability from sub-optimal control, no exacerbation to no symptoms		
Daily ICS	44.313	5.645
Intermittent ICS	72.383	16.213
Probability from sub-optimal control, no exacerbation to asthma exacerbation		
Daily ICS	393.584	24205.42
Intermittent ICS	390.777	16599.53
Probability from asthma exacerbation to no symptoms		
Daily ICS	297.745	869.882
Intermittent ICS	357.895	3050.629
Probability from asthma exacerbation to asthma exacerbation		
Daily ICS	395.148	32261.70
Intermittent ICS	392.942	21933.33
Utilities		
No symptoms state	3.411	0.038
Sub-optimal control, no exacerbation state	117.295	49.081
Asthma exacerbation state	289.725	763.820
Gamma distribution	Alpha	Lambda
Cost of no symptoms state	44.444	21.063
Cost of sub-optimal control, no exacerbation state	44.444	1.353
Cost of weekly use of daily ICS	25.60	64.0
Lognormal distribution	Mean for ln(x)	SD for ln(x)
Cost of asthma exacerbation	5.477	1.006
B. Preschool patients		
Probability distribution	Distribution parameters	Distribution parameters
Beta distribution	Alpha	Beta
Probability from no symptoms to no symptoms		
Daily ICS	75.19	17.637
Intermittent ICS	87.22	24.600
Probability from no symptoms to asthma exacerbation		
Daily ICS	396.230	41755.96

A. School patients		
Probability distribution	Distribution parameters	Distribution parameters
Intermittent ICS	395.869	38038.08
Probability from sub-optimal control, no exacerbation to no symptoms		
Daily ICS	44.313	5.645
Intermittent ICS	72.383	16.213
Probability from sub-optimal control, no exacerbation to asthma exacerbation		
Daily ICS	393.584	24205.42
Intermittent ICS	390.777	16599.53
Probability from asthma exacerbation to no symptoms		
Daily ICS	297.745	869.882
Intermittent ICS	357.895	3050.629
Probability from asthma exacerbation to asthma exacerbation		
Daily ICS	391.178	17389.64
Intermittent ICS	392.301	20040.03
Utilities		
No symptoms state	3.411	0.038
Sub-optimal control, no exacerbation state	117.295	49.081
Asthma exacerbation state	289.725	763.820
Gamma distribution	Alpha	Lambda
Cost of no symptoms state	44.444	21.063
Cost of sub-optimal control, no exacerbation state	44.444	1.353
Cost of weekly use of daily ICS	37.76	64.0
Lognormal distribution	Mean for ln(x)	SD for ln(x)
Cost of asthma exacerbation	5.477	1.006

^aICS, inhaled corticosteroids.