

Cost-effectiveness model for a specific mixture of prebiotics in The Netherlands

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Received: 24 July 2010 / Accepted: 22 November 2010
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Abstract The objective of this study was to assess the cost-effectiveness of the use of prebiotics for the primary prevention of atopic dermatitis in The Netherlands. A model was constructed using decision analytical techniques. The model was developed to estimate the health economic impact of prebiotic preventive disease management of atopic dermatitis. Data sources used include published literature, clinical trials and official price/tariff lists and national population statistics. The comparator was no supplementation with prebiotics. The primary perspective for conducting the economic evaluation was based on the situation in The Netherlands in 2009. The results show that the use of prebiotics infant formula (IMMUNOFORTIS®) leads to an additional cost of € 51 and an increase in Quality Adjusted Life Years (QALY) of 0.108, when

compared with no prebiotics. Consequently, the use of infant formula with a specific mixture of prebiotics results in an incremental cost-effectiveness ratio (ICER) of € 472. The sensitivity analyses show that the ICER remains in all analyses far below the threshold of € 20,000/QALY.

Conclusion This study shows that the favourable health benefit of the use of a specific mixture of prebiotics results in positive short- and long-term health economic benefits. In addition, this study demonstrates that the use of infant formula with a specific mixture of prebiotics is a highly cost-effective way of preventing atopic dermatitis in The Netherlands.

Keywords Prebiotics cost-effectiveness model · Primary prevention atopic dermatitis · Nutrition economics

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JEL Classification I-18

Background

Epidemiology

Atopic dermatitis (AD) is a chronic relapsing, inflammatory skin disease, characterized by a range of clinical features of which pruritus and typically distributed eczematous lesions are the most essential [1–3]. As the result of a two to threefold increase in prevalence during the last 3 decades, AD has become one of the most common childhood disorders [3–5].

A recent survey of Australian 13- to 14-year-olds, as part of the International Study of Asthma and Allergies in Childhood (ISAAC) study, found that the current prevalence of AD in that group was 10–12% [6]. Comparison of a birth cohort from 1965 to 1969, with one from 1975 to

1979 in Denmark, showed a doubling of the incidence of AD [7]. The incidence of AD in Great Britain increased from 5% in 1946 to 12.2% in 1970 [8].

Treatment of atopic dermatitis

Different treatments for AD have been investigated with varying results. Topical corticosteroids have been effective agents and the mainstay of treatment for many years. In the treatment of AD, a step-up approach is often used: from intermittent use of mild topical corticosteroid courses up to maintenance treatment with higher classes (more potent) topical corticosteroids [9]. When corticosteroids are not effective enough or are contraindicated, topical calcineurin inhibitors can be used as initial anti-inflammatory medication followed by a maintenance treatment [9].

Quality of life

Atopic dermatitis patients are affected not only by the disease itself but also by the stigma associated with its visibility [10, 11]. Chronic skin diseases have always had a major negative impact on a patient's quality of life (QoL), and since 1987, this impact can be measured in a repeatable standardized way [12]. Several questionnaires were developed to measure QoL in dermatology, e.g. the Dermatology Life Quality Index, the Children's Dermatology Life Quality Index and the Skindex-29 [13–15]. Since then, the impairment of QoL and the psychological well-being of children with AD, as well as their parents, have been well documented [16–25]. A Dutch study by Brennkmeijer et al. studied the impairment of quality of life and the psychological well-being of children with AD [26]. Patients with severe AD in childhood showed a significant delayed social development in their course of life. Very recently, several articles were published dealing with the development and use of a child-friendly version of EQ 5D [27]. However, there are no utility data available for children with AD collected by means of this child-friendly version of the EQ 5D.

Long-term co-morbidity

In later childhood, the prevalence of AD, food allergies and food allergen sensitization decreases, and the prevalence of asthma, allergic rhinitis and sensitization to inhalant allergens rises [28, 29]. The term atopic march is commonly used to describe this typical progression from AD in young children to asthma at school age, not only in population studies but also in individual patients [30, 31]. There is substantial ecological correlation between AD and asthma in the ISAAC Phase I [6]. An association between AD and asthma in childhood has been well documented [6, 32–34], and a similar association has been demonstrated in

later life [35]. An association has also been demonstrated between AD and allergic rhinitis in childhood [36, 37]. The onset of these conditions was frequently ordered with AD being the first in a triad of events that included asthma and allergic rhinitis. Underlying atopy is considered to be the thread that linked these disorders, and the term “atopic march” was developed to describe this sequential manifestation of atopy [30, 38].

Economic impact of atopic dermatitis

A systematic review carried out by Mancini et al. [39] of the socioeconomic effect of AD in the USA summarized four studies that contained good data on direct costs. They found a wide variation in estimated overall direct costs of AD in the USA, from \$364 million to \$3.8 billion per year. This large variation in estimates probably reflects the very different methods used in the various studies, and only one study measured indirect costs.

Preventive approaches of atopic dermatitis

Different intervention strategies have been tried to prevent AD in infants at risk, such as avoidance of trigger factors (e.g. heat, perspiration, house mite), treating skin infections (staphylococcus aureus and herpes simplex) and dietary measures including probiotics [40–42].

Studies by Moro and Arslanoglu explored the efficacy of a specific mixture of prebiotics in a clinical trial setting [43, 44]. In a prospective, randomized, double-blind, placebo-controlled design, healthy term infants with a parental history of atopy were fed either a prebiotic-supplemented formula (8 g/L scGOS/lcFOS—IMMUNOFORTIS®) based on a mixture of neutral short-chain galactooligosaccharides (scGOS) and long-chain fructooligosaccharides (lcFOS) or placebo-supplemented (8 g/L maltodextrin) formula based on hydrolysed protein, during the first 6 months of life. Following this intervention period, blind follow-up continued until 2 years of life. Primary endpoints were cumulative incidence of allergic manifestations. Secondary endpoints were number of infectious episodes and growth. The mixture scGOS/lcFOS has been shown to reduce the incidence of AD and infectious episodes during the first 6 months of life. The results show a beneficial effect of prebiotics on the development of AD over a 6-month period in high-risk infants. The 6-months results were reported by Moro et al. and showed that 9.8% in the intervention group and 23.1% in the control group developed AD. [43] Arslanoglu et al. evaluated whether these preventive effects were lasting beyond the intervention period [44]. Cumulative incidences for AD, recurrent wheezing and allergic urticaria were higher in the placebo group, (27.9, 20.6 and 10.3%, respectively) than in the intervention group (13.6, 7.6 and 1.5%; $P < 0.05$).

Objective

In the event that the favourable clinical benefits of a specific mixture of prebiotics may have an impact on cost-effectiveness, the objective of this study is to assess the cost-effectiveness of the use of prebiotics for the primary prevention of AD in The Netherlands.

Methods

A model was constructed using decision analytical techniques [45]. The model was developed to estimate the health economic impact of prebiotic preventive disease management of AD. Data sources used include published literature, clinical trials and official price/tariff lists and national population statistics. This study was based on methodological guidance for cost-effectiveness studies in nutrition economics [46].

Model design

Decision analytical techniques are used to estimate the cost-effectiveness of the use of prebiotics for the primary prevention of AD, which is a well-accepted methodology and has been used in a number of published studies calculating the costs of medical strategies [47]. From treatment algorithms, a model can be constructed that considers the actions and their consequences over time. In effect, a model shows the consequences and complications of different therapeutic interventions, and it should correspond as much as possible, to daily practice. Models may take the form of simple decision analytic trees or they may be complex Markov models. Whereas decision tree models are appropriate for acute episodes, Markov models are the first choice for cost-effectiveness analyses of short- and

long-term consequences of transitions between multiple health states. The cost-effectiveness was calculated using a Markov model built in TreeAge Pro 2005/2006 reflecting treatment patterns and outcomes in management of AD. The Markov model was used to estimate the cost-effectiveness of the use of prebiotics for the primary prevention of AD, taking into account both the short- and long-term consequences of AD. Figure 1 shows the structure of the model. For this analysis, we defined four mutually exclusive health states:

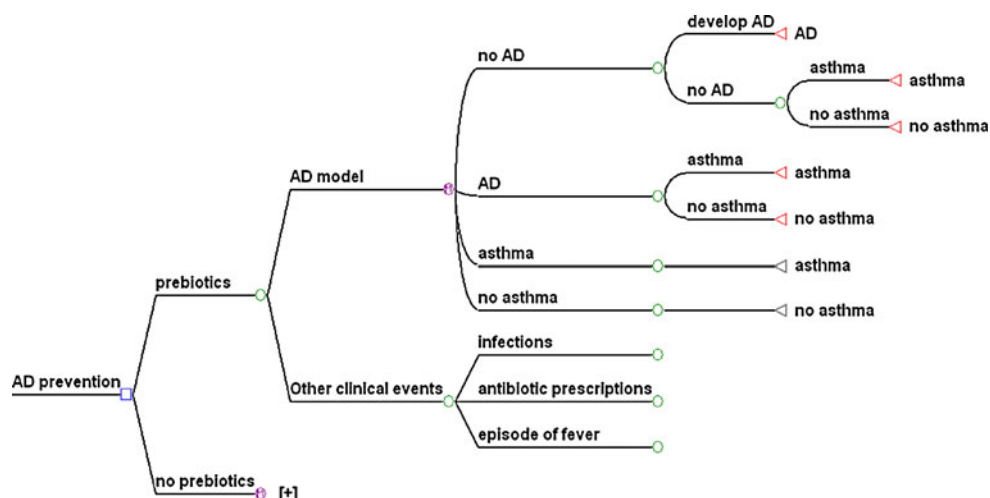
- no atopic dermatitis
- atopic dermatitis
- no asthma
- asthma

Patient progression through these states was divided into cycles of 1 year. Infants may or may not develop AD. Among the children who develop AD, a significant proportion may develop long-term respiratory sequelae (e.g. asthma) after AD. The children without AD will have much lower probability of developing asthma based on population risk. The model also includes branches for a scenario analysis, which comprises the reduction in infections, reduced antibiotic prescriptions and reduced episodes of fever.

Study population

The model considers a cohort of children at risk for AD, in line with the populations as studied in the clinical trial assessing the efficacy of prebiotics for the primary prevention of AD over a period of 2 years. Healthy term infants with a parental history of AD, allergic rhinitis, or asthma in either mother or father were eligible for the clinical trial [43, 44]. In all cases, the parental diagnosis was based on a documented physician's certification.

Fig. 1 Structure of the model used in the analysis (the base case model only includes the branches “atopic dermatitis” and “no atopic dermatitis”; the other branches are used in scenario analyses)



Inclusion criteria were gestational age between 37 and 42 weeks, birth weight appropriate for gestational age and start of formula feeding within the first two weeks of life. Breast feeding was recommended to all mothers; the parents were informed about the study at discharge from the maternity unit and were asked to contact the hospital if they started formula feeding.

Comparison

The cost-effectiveness of prebiotic preventive disease management of AD is based on a comparison with no preventive intervention according to the Dutch guidelines for pharmacoeconomic research [48].

Time horizon

Dutch guidelines for pharmacoeconomic research recommend analysis of long-term clinical effectiveness in order to evaluate healthcare technologies. [48] A reduction in the rate of AD was limited to 6-months prebiotics supplementation in the clinical trial, in which children were followed for 2 years from the point of randomization. Following the 6-month intervention period, blind follow-up continued until 2 years of life.

The model assumes that the childhood asthma developing in AD infants will not persist beyond 16 years of age, which can be considered a conservative approach towards prebiotic preventive disease management of AD.

Thus, the base case analysis assumes a 16-year follow-up period starting at the beginning of the intervention in order to capture the impact of the use of prebiotics for the primary prevention of AD on long-term morbidity and mortality resulting from AD.

Setting and perspective

A primary care/outpatient setting is chosen for the evaluation, since most patients with AD and its sequelae are treated by general practitioners (GPs). The analysis is conducted from the perspective of the health insurance in The Netherlands in 2009, as not all relevant non-medical costs could be incorporated. As a consequence, the analysis can be considered conservative.

Clinical outcomes

The model extrapolated the efficacy data from the clinical trials (reduction in the rate of AD) to calculate the likely number of Quality Adjusted Life Years (QALYs) from the use of prebiotics. AD is associated with clinical and economic consequences beyond the clinical trial period. A

proportion of the children may develop long-term sequelae (e.g. asthma) leading to a reduction in QALYs and additional medical costs. The analyses were based on 16-year time horizon in order to capture long-term costs and morbidity beyond the AD episode, which include the medical costs for management of asthma.

Cost assessment

The cost assessment is based on:

- The costs for the use of infant formula with a specific mixture of prebiotics for the primary prevention of AD.
- The cost associated with treatment of sequelae and long-term morbidity (asthma).

The costs due to lost productivity are not included, as the model assumes that the childhood asthma associated with AD will not persist beyond 16 years.

Discounting and inflation

Future outcomes and costs are discounted at equal rates, when the time horizon of the model extends beyond a period of 1 year. Discounting is not applied within the base case analysis as the time horizon was less than 1 year. However, costs and benefits are discounted at a rate of, respectively, 4.0 and 1.5% per annum in sensitivity analyses using time horizons greater than 12 months. Finally, costs are updated to 2009 by applying an inflation correction.

Data sources

Probabilities

The probabilities are mainly based on efficacy measures from the clinical trial reports by Moro and Arslanoglu. The cumulative incidences for AD are 27.9 and 13.6% for, respectively, the placebo and the intervention group (Table 1).

Asthma

The probability of the development of asthma was derived from the overview by Van der Hulst [34]. The pooled odds ratio for the risk of asthma after AD, compared with children without AD, in birth cohort studies was 2.14 (95% CI, 1.67–2.75). As the health economic model is based on probabilities, we used directly a probability of 0.20 (111/560) and 0.13 (335/2,543) for the development of asthma in, respectively, children with and without AD. However,

Table 1 Probabilities from clinical trials

Moro [43] and Arslanoglu [44]	Probability (%) (cumulative over 2 years)		<i>P</i> value
	Intervention	Placebo	
Atopic dermatitis	13.6	27.9	<0.05
Recurrent wheezing	7.6	20.6	<0.05
Allergic urticaria	1.5	10.3	<0.05
Infections (episodes)	1.8	2.7	<0.05

Table 2 Risk of asthma

	Probability (%)		<i>P</i> value	OR
	AD	No AD		
Van der Hulst [34]	20	13	<0.05	2.14
Van der Hulst [34]/RIVM [49]	20	5.5 (4–7)	NA	4.3
MACS [50]	Asthma			3.52
	Asthma + allergic rhinitis			6.30
MACS/RIVM	0.17	0.055		

in the RIVM report describing the ISAAC-II study and PIAMA study, it is reported that 4–7% of the children (0–12 years) has asthma in The Netherlands [49]. Therefore, the probability of the development of asthma in children either with or without AD may be based on an average of 5.5%. The OR is 4.3 based on probabilities of 0.20 and 0.055.

Data for a scenario analysis were drawn from the Melbourne Atopic Cohort Study (MACS) [50]; the investigators found that infants with atopic eczema (eczema plus sensitization) were at greater risk at ages 6 and 7 years of having childhood asthma (OR 3.52; 95% CI 1.88–6.59), allergic rhinitis (2.91; 1.48–5.71) and both childhood asthma and allergic rhinitis (6.30; 2.35–16.88) than infants with non-atopic eczema, even after excluding infants with early wheeze. The OR of 3.52 is for asthma only, which is lower than 4.3 based on the Dutch data. On the other hand, the OR is 6.30 for asthma and allergic rhinitis. However, allergic rhinitis will have a lower impact on costs and QALYs than asthma. Alternatively, the OR of 3.52 may be applied to the Dutch prevalence of 0.055 in the normal population in order to calculate the probability of asthma after AD (0.17).

The base case analysis is based on data from the review by Van der Hulst: 0.20 (AD) and 0.13 (no AD) risk of development of asthma. As indicated above, a scenario analysis is based on the OR (3.52) from the Melbourne Atopic Cohort Study, which was applied to average of 5.5% prevalence of asthma according to RIVM data: 0.17 (AD) and 0.055 (no AD) risk of development of asthma. The children will only develop asthma from 6 years of onset, which was based on the finding from the Melbourne Atopic Cohort Study (Table 2).

Utilities

Atopic dermatitis

A study by Poole et al. provided utilities for the model [51]. This study showed that patients with AD of all severities presented considerable decrements in health-related utility. Although this utility study was performed in adults, the utilities were included in the model. There is no evidence that utilities for children may be different from those for adults. Although the psychological impact of visible eczema may not be relevant for small children, the physiological impact in this population may be worse than in adults. A sensitivity analysis was performed on the utilities to capture any uncertainty in our assumptions.

In the study by Poole et al., utilities are reported for mild, moderate and severe AD. The health economic model is based on the utilities of the EQ-5D questionnaire, which is the most accepted utility scale. The utilities are mild—0.848, moderate—0.796 and severe—0.760.

This study shows that patients with AD will experience a utility of 0.027 improvement following treatment. In our model, we therefore used the following utility values: mild—0.875 (0.848 + 0.027), moderate—0.823 (0.796 + 0.027) and severe—0.787 (0.760 + 0.027). The distribution in the study by Poole was 28.7% mild, 36.0% moderate and 35.3% severe. A weighted average utility (0.825) was used in our model based on the distribution of mild, moderate and severe.

Asthma A study by Greenough et al. reported utilities in children with a history of RSV infection using the Health Utility Index (HUI), a multi-attribute score that includes measures for sensation, mobility, emotion, cognition,

self-care, pain, vision, hearing, speech, ambulation and dexterity [52]. Investigations of the long-term prognosis of patients with severe RSV disease in infancy have shown measurable respiratory abnormalities, such as asthma and recurrent wheezing, which may persist for several years following infection [53, 54]. These long-term respiratory abnormalities are comparable for children developing AD. Therefore, we used the utilities from the study of Greenough et al. [52]. In the analysis, it was assumed that high-risk children who did not experience asthma following AD would have a utility corresponding with a median HUI 2 for non-RSV-infected children ($u = 0.95$); high-risk children who experienced asthma following AD would have a utility corresponding with a median HUI 2 for RSV-infected children ($u = 0.88$); all children above 16 years of age and all children without AD would have perfect health ($u = 1$; Table 3).

Use of prebiotics

The cost of a 6-month period consumption of infant formula with a specific mixture of prebiotics is € 325, which is based on average consumer price in The Netherlands, Italy and Germany and total dosage of 19,500 g. The model is based on the 6-month period in the trial by Moro and Arslanoglu, and therefore, cost of a 6-month period prebiotics consumption was used. The 6-month cost of no preventive approach was € 250.

Other medical costs

Medication: In the treatment of AD, a step up approach is used often: patients receive mild topical corticosteroid courses of variable duration and no subsequent maintenance therapy to speak of [9]. The costs of corticosteroids are minimal and are therefore excluded from the model, as prescribing patterns are not available in the literature. This is a conservative assumption for the model, especially because more expensive medication may also be considered (e.g. topical calcineurin).

Table 3 Utilities of asthma

AD (Poole) [51]	Utility	
	No treatment	Treatment
Mild	0.848	0.875
Moderate	0.796	0.823
Severe	0.760	0.787
No AD	1.00	1.00
Asthma (Greenough) [51]	<16 years	
Asthma after AD	0.88	
No asthma after AD	0.95	

Consultations: There are no Dutch data available on the cost of treatment of AD. The study by Su provides annual consultations for treatment of AD [55]. Although costing information is country-specific, we used these data as starting point for a validation by Dutch clinical experts (Table 4). The base case analysis is based on GP consultations only, which was considered a conservative approach by the Dutch clinical experts.

The costs were incorporated in the model for a period of 2 years. We assume that this is the average duration of AD. The cost of a GP is € 20.20 and of a specialist is € 50.00 for non-academic and € 100.00 for academic hospital, which are used in the current health economic model after inflation correction for 2009. A sensitivity analysis is based on the inclusion of a specialist visit varying from lower to upper limit.

Costs of long-term morbidity

A recent report presents information on healthcare use and costs related to asthma and chronic obstructive pulmonary disease (COPD) in The Netherlands [56]. Total costs for treating asthma in 2000 were estimated to be €141 million. Annual costs per patient in the 0–14 age group came to approximately € 233, which is used in the current health economic model after inflation correction to 2009.

Results

The base case analysis does only include AD, and other clinical events are not included. The use of infant formula with a specific mixture of prebiotics leads to an additional cost of € 51 and an increase in QALYs of 0.108, when compared with no prebiotic supplementation (Table 5). Consequently, the use of infant formula with prebiotics results in an ICER of € 472/QALY. The informal threshold in The Netherlands is € 20,000/QALY, and therefore, the use of infant formula with prebiotics can be considered very cost-effective with only an ICER of € 472/QALY.

Table 5 shows also the results for an analysis without discounting. The use of infant formula with prebiotics

Table 4 Medical consultations per year as reported by Su [55]

Type of consultation	Degree of eczema		
	Mild	Moderate	Severe
General practitioner	4.0	7.0	11.7
Paediatrician	0.5	2.8	1.6
Allergist	0.2	0.3	3.3
Dermatologist	2.7	3.2	6.4

Table 5 Results

	Prebiotics	No prebiotics	Diff.
Base case			
Costs	€ 622	€ 571	€ 51
QALYs	14.108	14.000	0.108
ICER-QALY	€ 472		
No discounting			
Costs	€ 760	€ 719	€ 41
QALYs	15.716	15.598	0.118
ICER-QALY	€ 348		
OR Melbourne			
Costs	€ 476	€ 438	€ 38
QALYs	14.184	14.067	0.117
ICER-QALY	€ 325		
Cost specialist (non-academic)			
Costs	€ 626	€ 579	€ 47
QALYs	14.108	14.000	0.108
ICER-QALY	€ 439		
Cost specialist (academic)			
Costs	€ 632	€ 590	€ 42
QALYs	14.108	14.000	0.108
ICER-QALY	€ 393		
Full year prebiotics			
Costs	€ 797	€ 754	€ 43
QALYs	14.108	14.000	0.108
ICER-QALY	€ 398		
Utility AD = 1 (base case 0.825)			
Costs	€ 622	€ 571	€ 51
QALYs	14.132	14.049	0.083
ICER-QALY	€ 615		
Including other clinical events			
Costs	€ 897	€ 1,364	– € 467
QALYs	14.108	14.000	0.108
ICER-QALY	Dom.		

results in an ICER of € 348/QALY, which is lower than the ICER in the base case analysis (€ 472/QALY).

Table 5 shows also the results for an analysis based on the OR from the Melbourne Atopic Cohort Study, which was applied to average of 5.5% prevalence of asthma according to RIVM data. The use of prebiotics results in an ICER of € 325/QALY, which is slightly lower than the ICER in the base case analysis (€ 472/QALY).

A sensitivity analysis was based on the cost of consultation. The assumption in the base case is that all consultations for treatment of AD are by a GP. A sensitivity analysis is based on cost of specialist (non-academic hospital and academic hospital tariffs as indicated above). The ICER changes from € 472 to € 439 and € 393 (Table 5).

A sensitivity analysis was based on the assumption that infant formula with a specific mixture of prebiotics is used

for a full year: the ICER decreases from € 472 to € 398 (Table 5).

A sensitivity analysis was based on the assumption that AD has no impact on utility of a child. Therefore, utility value for AD was 1 in this sensitivity analysis: the ICER increases from € 472 to € 615 (Table 5).

Finally, a scenario analysis was performed, which includes the costs of treatment of the other clinical events: recurrent wheezing, allergic urticaria, infection and fever. The assumption is that each side effect leads to one extra GP visit. This analysis shows a cost saving of € 467 per patient (Table 5). The use of prebiotics is considered dominant over “no prebiotics”: cost savings and a higher effectiveness.

Overall, the sensitivity analyses show that ICER remains in all analyses far below the threshold of € 20,000/QALY.

Discussion

This economic evaluation demonstrates that the supplementation of infant formula with a specific mixture of prebiotics is a highly cost-effective approach for prevention of AD, costing € 472/QALY gained relative to “no prebiotics”. This ICER is well below the “threshold” range of € 20,000 per QALY. Extensive sensitivity analyses indicate that the conclusions are extremely robust, remaining unaltered despite significant changes in key model parameters.

The results of any modelling exercise need to be treated with some degree of caution. Decision analytic techniques, upon which our model is based, have several weaknesses. Various data sources were used for the model, which all have their pros and cons from a clinical and health economic perspective. Among the general model limitations is the fact that clinical trial data do not necessarily represent real clinical practice. Data from clinical trials do not necessarily have a high degree of external validity as the results are often contingent upon protocol adherence, a situation that may not be easily replicated outside the trial setting. Therefore, we applied a scenario analysis, which was based on a different underlying source: the Melbourne Atopic Cohort Study [50]. The analysis showed that the use of prebiotics results in an ICER of € 325/QALY, which is in line with the ICER in the base case analysis (€ 472/QALY).

A review of the literature shows that AD can be a major disorder with significant costs and morbidity. An Australian study of the impact on families of the care of a child with AD found that looking after a child with moderate or severe AD was significantly more stressful than looking after a child with insulin-dependent diabetes mellitus [55]. There are many reasons for the impact of AD on the

family. Disturbed sleep is a significant factor that may contribute to both child and parental morbidity. For children with severe eczema, the average number of hours sleep lost by parents per night averaged 1.9 h, and the parental estimate of loss of childhood sleep was 2.1 h per night. These Australian findings are comparable to the 2.6 h of parental sleep lost per night reported by a recent English study [57]. Care of a child with AD can interfere significantly with other activities. Thus, the time spent treating children per day was of the order of 1.5–3 h. Parental employment was reduced, ceased or not started for 40% of parents looking after children in the moderate or severe eczema groups, in the recent Australian study. Direct costs include cost of medications, dressings, special diet and out-of-pocket costs for professional consultations. Income loss for parental time off work was also estimated. A study by Kemp showed that the costs of care per year vary from \$A 1,142 yearly for mild eczema, to \$A 6,099 for severe allergic eczema [58].

Based on this overview, we can conclude that our model was based on a number of conservative assumptions, as all cost and morbidity of AD reported in the previous section were not included in the model. Indirect costs due to working days lost for the parents for AD and asthma were not included. Other non-medical costs, like transportation costs to the hospital, due to AD and asthma were also not included in the model. Studies indicate that episodes with asthma in children may lead to a significant number of days lost from school, interference with physical exercise and underfunctioning at school because of interrupted sleep [59]. In cases of more severe asthma, the more frequent school absences may affect the individual's education and, possibly, choice of career. In addition to the extensive individual burden of asthma, the burden on the family is substantial. Additional housework may be required to reduce the child's exposure to potential environmental triggers. Time "off work" may be required to take care of a sick child. The costs of treatment of the other clinical events: recurrent wheezing, allergic urticaria, infection and fever were not included in the base case analysis and only included in a sensitivity analysis. The model assumes that the childhood asthma developing after AD will not persist beyond 16 years of age, which can be considered as a conservative approach towards disease management of AD, as many children will also suffer from asthma as adults. Summarizing, this analysis can be considered conservative from a societal perspective, as not all relevant costs could be incorporated. The inclusion of non-medical costs would have resulted in more cost savings by prebiotics in the primary prevention of AD and therefore even a lower ICER in terms of Cost per QALY than the current analysis from a health insurance perspective.

Given that there are some limitations to the modelling technique, its advantages should also be pointed out. The ideal design to demonstrate the possible long-term health economic outcomes associated with prebiotics would be a naturalistic prospective study, which may require a follow-up period varying from 10 to 20 years. The use of a Markov model allowed us to extrapolate clinical outcomes beyond the duration of the existing clinical trials. Sensitivity analyses confirmed the robustness of the model.

Finally, there are also potential cost savings at a national level, as shown by the scenario analysis, which includes the other clinical events. The cost savings per child are € 467, which may result in a substantial positive impact on the budget. The incidence of AD in children was estimated at 5% in Spain and 20% in England. Dutch data from national statistics show total of 181,000 babies born in 2007 [60]. Thus, the number of at-risk babies varies between 9,050 and 36,200. The total annual national cost saving may be at least € 4.2 million, when saving € 467 in 9,050 babies.

Conclusion

This study shows that the favourable health benefit of the use of infant formula with a specific mixture of prebiotics results in positive short- and long-term health economic benefits. Furthermore, this study demonstrates that the use of infant formula with a specific mixture of prebiotics (IMMUNOFORTIS®) is a highly cost-effective approach for prevention of atopic dermatitis in The Netherlands. This may also lead to substantial cost savings at a national level, when all clinical events are included.

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