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Original article

Economic evaluation of a 100% whey-based partially hydrolyzed infant formula in the prevention of atopic dermatitis among Danish children

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Abstract

Objective:
A pharmacoeconomic analysis was undertaken to determine costs, consequences, and cost-effectiveness of a brand of partially hydrolyzed 100%-whey formula manufactured by Nestlé (PHF-W), in the prevention of atopic dermatitis (AD) in 'at risk' Danish children compared to extensively hydrolyzed formula (EHF-Whey or Casein).

Methods:
Given the non-significant differences between PHF-W and EHF, the base case analytic approach amounted to a cost-minimization analysis (CMA) reporting the difference in formula acquisition costs over the period of formula consumption for the population of interest. However, sensitivity analyses (SAs) were undertaken to explore applying the nominal efficacy of PHF-W and EHF, thus leading to a cost-effectiveness analysis (CEA). Hence, an economic model based on a 12-month time horizon was developed synthesizing treatment pathways, resource utilization, and costs associated with the treatment of AD in the population of interest. The final economic outcome of the SAs was the incremental cost per avoided case (ICER) defined as the expected cost per avoided case of AD for PHF-W vs EHF, determined from three perspectives: the Ministry of Health (MOH), the family of the subject, and society (SOC).

Results:
In the base case CMA, savings of DKK 9 M, DKK 20 M, and DKK 29 M were generated for PHF-W vs EHF from the MOH, family, and SOC perspectives. In the sensitivity CEA, PHF-W was dominant over EHF-Whey from all perspectives, while EHF-Casein displayed against PHF-W unattractive ICERs of DKK 315,930, DKK 408,407, and DKK 724,337 from the MOH, family, and SOC perspectives. Probabilistic SAs indicated that PHF-W was 86% likely to be dominant over EHF-Whey, whereas EHF-Casein had no likelihood of dominating PHF-W.

Conclusion:
Under a range of assumptions, this analysis demonstrated the attractiveness of PHF-W vs both types of EHF in the prevention of AD among 'at risk' Danish infants who are not or cannot be exclusively breastfed.

Introduction

Atopic dermatitis (AD) is one of the most common skin disorders seen in infants and children with an onset during the first 6 months of life[1,2]. The development of AD and other atopic diseases depends on an interaction between genetic factors; environmental exposure to food and inhalant allergens; and non-specific

adjuvant factors (e.g., tobacco smoke, air pollution, and infections)[3]. Hence, allergen avoidance is key in the primary prevention of allergy, as experimental and clinical data indicate that early exposure to dietary allergens may be crucial for the development of allergies such as food allergies and AD[4]. Furthermore, infants are deemed to be at high risk of developing AD if they have a parent or sibling with a history of allergy[3,5,6].

The World Health Organization as well as numerous regional and national guidelines recommend exclusive breastfeeding for the first 6 months of life[7–12]. When the infant cannot be breastfed or breastfeeding duration is shorter than recommended, extensively hydrolyzed infant formulas based on whey (EHF-Whey) or casein proteins (EHF-Casein) are indicated both for treatment and prevention of cow's milk and food allergy in 'at risk' infants in Denmark. Amino acid-based formulas (AAF) are also available for allergy treatment, but at a much higher cost.

One specific brand of 100% whey-based partially hydrolyzed formula, NAN-HA®, manufactured by Nestlé S.A, Switzerland (PHF-W) and branded under NAN-HA 1® in Denmark, has been shown in randomized trials to be as effective as EHF in the prevention of AD, a fact confirmed by two meta-analyses[13,14]. In addition, partially hydrolyzed formula is associated with lower rates of discontinuation due to a host of factors such as better taste, better texture, and less bitterness[4,6,15].

Treatment for AD engenders an important amount of health service resources (be they financial or logistical) and places a significant burden on the child, family, and society[16]. A review of the literature did not yield any studies reporting the cost of AD for Denmark. However, a 2006 study of 33 Italian children with AD reported a mean cost of €1254 per year for the family[17]; a 1999 study based in Germany estimated the annual cost of AD from the societal perspective to be DM 4827 (€2468)[18]; and a second German study, based on 91 children and published in 2003, reported annual direct healthcare costs ranging from US$164 in mild cases to US$911 in severe cases[19].

The cost-effectiveness of PHF-W in the prevention of AD for 'at risk' children has been established in France[20], but no such economic evaluation has been published for a Danish setting. This has prompted the present pharmacoeconomic analysis in order to determine the costs and consequences of PHF-W vs EHF in the prevention of AD in 'at risk' children in Denmark.

Methods

Product, disease, and population of interest

The product of interest was PHF-W and the comparators were EHF-Whey and EHF-Casein. All three were assessed for their effectiveness in preventing the disease of interest, AD, the most quantifiable of all allergic manifestations which can be associated with milk consumption. The population of interest was defined as healthy yet 'at risk' subjects who were not exclusively breastfed. The term 'at risk'

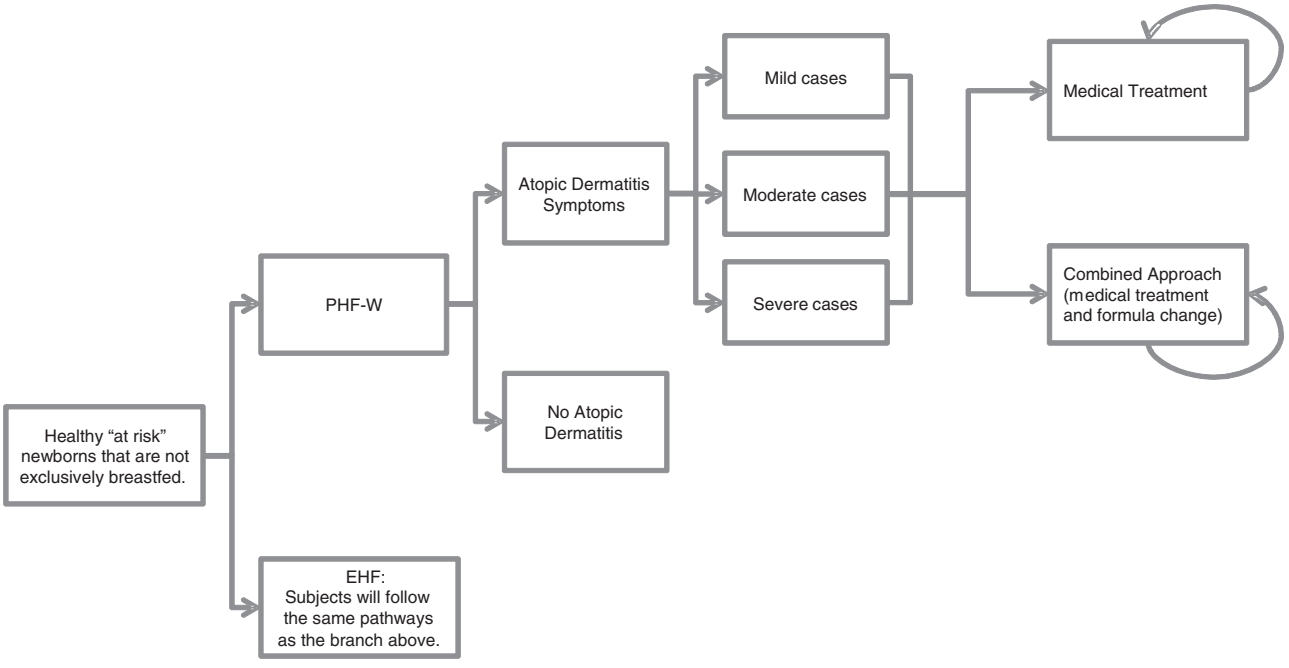

Figure 1. Decision tree model depicting the treatment patterns of atopic dermatitis in Denmark in a population ranging from newborns to 3-year olds.

refers to children with at least one parent or sibling with a diagnosed history of allergies.

Perspective

The present economic evaluation was undertaken from the perspective of the Danish Public Health System or 'Ministry of Health' (MOH), of the family of the child as well as of society as a whole. Specific resources, their utilization and costs were identified for each perspective, with the societal perspective combining the costs of both the MOH and family perspectives.

Type of economic evaluation

In a meta-analysis based on six studies comparing the efficacy of PHF-W vs EHF-Whey and/or EHF-Casein in the prevention of AD in 'at risk' children[4,15,21–25], Szajewska and Horvath[13] reported no significant difference in the relative risk (RR) of developing AD symptoms between PHF-W and either EHF preparation. Given that PHF-W and its comparators have a similar efficacy, the economic evaluation which was deemed most appropriate for the base case analysis was a cost-minimization analysis (CMA). In this type of analysis, all costs attributable to PHF-W and its comparators (i.e., the cost of treatment, medical visits, laboratory testing, hospitalization, and all indirect costs) would be equal except for the acquisition cost of the formulas themselves. Hence, the CMA would amount to an analysis of the difference in the acquisition costs of PHF-W vs EHF (Whey and Casein) when these formulas are used in prevention. This approach did not take into consideration the cost of EHF preparations for the treatment of AD, rather its prevention, although these costs were taken into account in the sensitivity analyses (SAs) described below.

Although there was no significant difference in the efficacy of PHF-W and its EHF comparators, there still existed a nominal difference in their efficacy in preventing AD symptoms. The nominal RRs for PHF-W vs both EHF preparations were reported in an extension of the Szajewska and Horvath[13] meta-analysis which was published by Iskedjian *et al.*[14]. In this latter scenario, if the statistical non-significance would not be taken into account, the outcomes and the costs associated with each infant formula would not be considered equal and would warrant the adoption of a cost-effectiveness analysis (CEA) approach, rather than a CMA.

Hence, a series of CEAs were undertaken as SAs to the base case CMA in order to explore the possible cost-effectiveness of PHF-W vs both EHFs when the nominal differences in their efficacy in prevention of AD symptoms were considered. Each formula was then assigned its nominal efficacy and, in turn, was associated with a specific set of outcomes and costs.

Parameters of the base case CMA

The starting cohort and the acquisition costs for each infant formula were the two key components of the base case CMA. These parameters also applied to the CEAs which were undertaken as SA.

Starting cohort

The starting cohort for the decision-analytic model was based on the population of interest for the present study and was calculated as follows:

(Birth cohort in Denmark) × (1 – Average Exclusive Breastfeeding rate) × (Rate of 'at risk' infants)

The number of live births in Denmark in 2010 was obtained from *Statistics Denmark*[26]. The average of the exclusive breastfeeding rates at 1 and 4 months of age was reported for Denmark by Benn *et al.*[27]. Three studies provided an approximation of the rate of newborns who were born 'at risk' of developing AD (33%)[3,5,6]. The key components of the starting cohort are presented in Table 1.

Cost of infant formula

One specific brand of EHF-Whey (Profylac®, Hørsholm, ALK, Denmark) and one specific brand of EHF-Casein (Nutramigen®, Illinois, Mead Johnson, USA) were selected as the comparators to PHF-W in the present study given that these brands had also been used as comparators in the Szajewska and Horvath[13] meta-analysis. The cost of the AAF was derived from Nutramigen AA© (Mead Johnson). The price of the infant formula was obtained from a survey of pharmacies and large-scale retail outlets in Denmark. Infant formulas used by 'at risk' infants are reimbursed by the MOH at a rate of 60% in Denmark, for up to 4 months if these formulas are used for prevention and up to 6 months if they are used for treatment (i.e., used after the occurrence of AD symptoms)[28]. The proportion of formula costs which was not covered by the MOH was assigned to the family of the subject. The impact of modifying the reimbursement rate for infant formulas and the length of such coverage was explored in a set of secondary SAs. The parameters pertaining to the cost of infant formula are presented in Table 2.

When determining the quantity of infant formula consumed, one important distinction was brought forth: not all subjects who consumed infant formula did so exclusively. Indeed, subjects who were not exclusively breastfed could be either exclusively formula-fed or fed a

Table 1. Epidemiological and clinical parameters applied in the base case analysis and in the primary sensitivity analysis.

	Quantity applied	Reference
Initial cohort		
Newborns in Denmark in 2009	63,411	[26]
Exclusively breastfed infants in Denmark	78.5%	[27]
Percentage of 'at risk' newborns	33%	[3,5,6]
Infants forming starting cohort	4544	Calculation
Of formula-fed infants in Denmark, average percentage who are exclusively formula-fed	2.5%	Calculation[29]
Of formula-fed infants in Denmark, average percentage who are both formula-fed and breastfed	97.5%	Calculation[29]
Incidence rates of AD with PHF-W		
Time points		
0–3 months	0.97%	[13,14]
3–6 months	1.35%	[13,14]
6–12 months	3.83%	[13,14]
12–18 months	0.96%	[13,14]
18–24 months	0.97%	[13,14]
24–30 months	1.48%	[13,14]
30–36 months	1.86%	[13,14]
Nominal relative risk of developing AD		
PHF-W vs EHF-Whey		
0–3 months	1.0	[14]
3–6 months	1.0	[14]
6–12 months	1.8	[14]
12–18 months	1.3	[14]
18–24 months	1.3	[14]
24–30 months	1.1	[14]
30–36 months	1.1	[14]
PHF-W vs EHF-Casein		
0–3 months	0.9	[14]
3–6 months	0.9	[14]
6–12 months	0.9	[14]
12–18 months	0.7	[14]
18–24 months	0.7	[14]
24–30 months	0.9	[14]
30–36 months	0.9	[14]
Distribution of cases of AD		
Face		
Mild	9.9%	EP
Moderate	1.8%	EP
Severe	2%	EP
Body		
Mild	28.4%	EP
Moderate	6.6%	EP
Severe	6.3%	EP
Face and Body		
Mild	28.4%	EP
Moderate	8.3%	EP
Severe	8.3%	EP
Management approach for infants less that 6 months old		
Therapeutic management	80%	EP
Combined management	20%	EP
Estimated response rates to the therapeutic management approach		
First-line treatment		
Mild	89.5%	EP
Moderate	86%	EP
Severe	82.5% on the face and 70% for the rest	EP
Second-line treatment		
Mild	95%	EP
Moderate	91%	EP
Severe	90%	EP

(continued)

Table 1. Continued.

	Quantity applied	Reference
Third-line treatment		
Mild	100%	EP
Moderate	97%	EP
Severe	95%	EP
Fourth-line treatment		
Mild	Not required	EP
Moderate	100%	EP
Severe	99%	EP
Estimated response rates to the combined management approach		
First-line treatment		
Mild	98.75% on the face and 98.25% for the rest	EP
Moderate	89.25%	EP
Severe	61%	EP
Second-line treatment		
Mild	100%	EP
Moderate	96.25%	EP
Severe	88.5%	EP
Third-line treatment		
Mild	Not required	EP
Moderate	99%	EP
Severe	93.5%	EP
Fourth-line teatment		
Mild	Not required	EP
Moderate	100%	EP
Severe	99%	EP
Rates of AD flare-ups		
Mild	25%	EP
Moderate	30%	EP
Severe	50%	EP
Mortality rate in the general Danish population		
At the end of the first year of life	0.39%	[30]
At the end of the second year of life	0.03%	[30]

AD, Atopic dermatitis; EHF, Extensively hydrolyzed formula; EP, Expert panel; PHF-W, Nestlé brand of 100% whey-based partially hydrolyzed formula.

combination of mother's milk and infant formula. In order to determine the percentage of infants who are exclusively formula-fed within those who receive formula, the following equation was applied:

[100% – (% ever-breastfed)]/[100% – (% exclusively breastfed)].

The rate of infants who were ever-breastfed in Denmark (including those exclusively breastfed) was derived from the Organization of Economic Cooperation and Development[29]. In turn, the percentage of infants consuming both formula and breast milk among those infants who were not exclusively breastfed amounted to:

100% – % of exclusively formula-fed infants.

The daily intake of infant formula was determined for each of the first 6 months of life, based on the manufacturer's instructions for the preparation of PHF-W (4.7 g of formula/30 ml of water with various volumes of water, depending on the age of the infant). These instructions were comparable to those for both EHF brands and for AAF. Exclusively formula-fed infants followed this feeding regimen for the entire 6 months of formula consumption. It was assumed that infants who consumed both formula and breast milk were fed formula 20% of the time in the first month, 50% in the second month, 75% in the third month, and fully formula-fed for the remainder of the first 6 months of life.

Expert panel

Five Danish expert clinicians (SH and AH, two pediatricians with an expertise in nutrition and allergy, BFV, a pediatrician, as well as PS and ML, two family physicians) were presented with questionnaires developed in a similar fashion to those used in a previous publication by Iskedjian *et al.*[20]. The answers to these questionnaires were synthesized to determine an average approach to treatment pathways and evaluate the resources utilized in the management of AD symptoms in a Danish setting.

In order to undertake the sensitivity CEAs mentioned in the 'Type of Economic Evaluation' section above, a

Table 2. Economic parameters applied in the base case analysis and in the primary sensitivity analysis.

	Quantity applied	Reference	Cost per unit	Reference
Formula				
PHF-W (Nestlé – NAN-HA 1®)	Varied with the age of the subject and with the rate of partial breastfeeding[a]	Calculation	DKK 80.95/600 g	*b*
EHF-Whey (ALK – Profylac®)		Calculation	DKK 198.50/400 g	*b*
EHF-Casein (Mead Johnson – Nutramigen®)		Calculation	DKK 198.00/400 g	*b*
Amino Acid Based Formula (Mead Johnson – Nutramigen AA®)		Calculation	DKK 198.00/400 g	*b*
Medical visits				
General Practitioner	All 1st-line Tx, 2nd-line Tx of all mild cases and 50% of moderate cases	EP	DKK 129.40/visit	32
Specialist (Dermatologist or Allergist)	2nd-line Tx of 50% of moderate cases and all severe cases, 3rd-line Tx and beyond of mild, moderate, and severe cases	EP	DKK 650.00/first two visits, then DKK 462.00/visit	33
Re-assessment visit in case of non-response to Tx	2 weeks after Tx failure	EP	As above	32,33
Hospitalization	1% of severe cases	EP	DKK 3528	Survey of a local hospital
Treatment				
Emollient Creams Archiv®	2 L per 2-month period	EP	DKK 67/200 ml	*b*
Topical Corticosteroids				
Class I – Hydrocortisone 10 mg/g (Mildison Lipid®)	Varied with severity and location of AD and subject's age[c]	EP	DKK 34.50/15 g	35
Class II – Clobetasone 0.05% (Emovat®)		EP	DKK 52.15/25 g	35
Class III – Betamethasone 1 mg/g (Betnovate®)		EP	DKK 51.15/30 g	35
Class IV – Clobetasol 0.5 mg/g (Dermovat®)		EP	DKK 42.25/25 g	35
Immunosuppressants				
Pimecrolimus (Elidel®)	Varied with severity and location of AD and subject's age[c]	EP	DKK 240.60 €/15 g	35
Tacrolimus 0.03% (Protopic®)		EP	DKK 131.25 €/10 g	35
Tacrolimus 0.1% (Protopic®)		EP	DKK 147.40 €/10 g	35
Laboratory tests				
Prick Test	Used once in 50% of moderate cases and all severe cases	EP	DKK 220.00/test	Survey of a local clinic
Oral Provocation Test	Used once in 50% of moderate cases and all severe cases	EP	DKK 289.00/test	See above
Food Eviction Test	Used once in 10% of severe cases	EP	DKK 707.00/test	See above
Specific IgE Test	Used once in 10% of moderate or severe cases	EP	Included in the medical visit	See above
MOH reimbursement rates				
Infant formulas used for prevention	60% for up to 4 months	28		
Infant formulas used for treatment	60% for up to 6 months	28		
Prescribed medication	60% for up to DKK 1410; 75% between DKK 1410–3045; 85% if over DKK 3045	36		
Emollients	0%	EP		
Medical visits, laboratory testing, and hospitalization	100%	EP		
Participation in the workforce in Denmark	76.7%	37		

(continued)

Table 2. Continued.

	Quantity applied	Reference	Cost per unit	Reference
Time loss				
Physician visits and laboratory testing	4 h for each visit	Assumption	DKK 248.81/hour	38,39
Child care for 2 days after the initial medical visit	8 h per day	Assumption	DKK 248.81/hour	38,39
Application of emollient cream	20 min daily over the application period	Assumption	DKK 248.81/hour	38,39
Application of topical medications (corticosteroids and immunosuppressants)	10 min daily over the application period	Assumption	DKK 248.81/hour	38,39
Hospitalization	2 days, 7.27 h per day	EP	DKK 248.81/hour	38,39
Travel	Travel to and from physician visits or laboratory testing (10 km each way)	Assumption	DKK 232.00/two-way trip	Surveyed in Aarhus, Denmark

[a]The full breakdown of the daily quantity of formula consumed over 6 months is available upon request.
[b]Based on a survey of costs in pharmacies and in large retailers.
[c]Details of the medical treatment regimen are available upon request.
Note: At time of analysis, 1 DKK = 0.134 € = 0.194 USD.
AD, atopic dermatitis; DKK, Danish kroner; EHF, Extensively hydrolyzed formula; EP, Expert panel; PHF-W, Nestlé brand of 100% whey-based partially hydrolyzed formula; Tx, Treatment.

decision-analytic economic model (presented in Figure 1) reflecting the evidence-based medical practices associated with the treatment of AD in Denmark was constructed, in line with the input of the expert panel. The remaining sections of the Methods describe this model and the analyses performed based on that model.

Structure of the model

MS Excel® 2003 was used to construct a spreadsheet model applying a series of 3-month cycles, starting with birth. Subjects were assigned to one of two arms receiving either PHF-W or its EHF comparator allowing for a juxtaposition of costs and consequences between the two formulas. PHF-W was first compared to EHF-Whey and then to EHF-Casein.

Subjects within each arm were then divided into two groups: those subjects without AD and those subjects with AD. Three main factors, namely, the age of the subject (which was inherent to the model) as well as the severity (mild, moderate, or severe) and location on the body (face, rest of the body, or both) of the AD manifestation, were used to characterize the cases of AD occurring in the model. The two latter rates were obtained from the expert panel.

At their first medical visit, subjects with AD were presented with an age-specific plan to manage their symptoms. Subjects who were 6 months of age or younger could be treated in one of two ways: a medical treatment approach or an approach combining the medical treatment approach with one or more changes of infant formula. Beyond 6 months of age, it was assumed that infant formulas were no longer consumed. Hence, AD symptoms could only be managed using the medical treatment approach.

The medical treatment approach consisted of up to four lines of a treatment regimen of emollients, topical corticosteroids (Class I, II, III, and IV), and immunosuppressants, assigned to the subject (in accordance with the opinion of the expert panel) based on the severity of AD symptoms, their location on the body, and the age of the subject. In the combined approach to the management of AD symptoms, subjects were also assigned a new infant formula, while being prescribed medications in accordance to the medical treatment approach above. Patients who had been consuming PHF-W, EHF-Whey, or EHF-Casein were assigned EHF-Whey, EHF-Casein, and EHF-Whey, respectively. In the case of response, subjects continued consuming the new milk formula until 6 months of age. If a second change of formula was required, subjects who had started with PHF-W were then assigned EHF-Casein, while the others were assigned AAF. The response rate for each line of treatment in each management approach was supplied by the expert panel. In a series of

secondary SAs, the estimated response rates for each line of therapeutic or combined management were reduced by 50% in order to test the effect of these parameters on the results of the sensitivity CEAs.

In addition to treatment, the economic model also took into consideration the resource utilization and costs of medical visits, of laboratory testing and of hospitalization, as well as all the indirect costs associated with these resources (further explained below).

Statistics Denmark published the baseline mortality rates for infants born in Denmark in 2008–2009[30]. Although AD does not affect mortality rates, these rates were applied at the end of the first and second years of the economic model in order to make it more dynamic.

Parameters unique to the sensitivity CEAs

The epidemiological, clinical, and economic inputs for the SAs are presented in Tables 1 and 2.

Calculation of the incremental cost-effectiveness ratios

The final outcome of the sensitivity CEAs were incremental cost-effectiveness ratios (ICERs) detailing the expected cost per avoided case of AD by adopting PHF-W rather than either EHF preparation. The ICER in this study is the difference in costs between PHF-W and EHF preparations divided by the negative value of the difference in the number of cases between PHF-W and EHF preparations, as presented in the following simplified mathematical formulation:

$$\text{ICER} = \frac{\text{Cost}_{\text{PHF-W}} - \text{Cost}_{\text{EHF}}}{-(\text{Cases}_{\text{PHF-W}} - \text{Cases}_{\text{EHF}})}$$

The number of cases of AD attributable to each infant formula was determined by applying the nominal RRs for PHF-W vs EHF-Whey and PHF-W vs EHF-Casein. This approach using *avoided* cases rather than *occurring* cases was warranted as this economic evaluation explored the prevention of AD when PHF-W was consumed. A similar approach has previously been adopted in the analysis of other preventative interventions such as vaccines[31].

The intermediate economic outcomes associated with each infant formula were the aggregated costs applicable to the MOH perspective (i.e., the reimbursed costs of formula, medical visits, medications, and laboratory tests), the perspective of the family (i.e., the non-covered portion of formula costs, travel costs, as well as such indirect costs as time loss and productivity loss), and the societal perspective (all of the above-mentioned costs).

Time horizon

In the primary SA, a time horizon of 12 months was adopted as it represented the time during which most cases of AD first occur while extending beyond the period of milk consumption. Secondary SAs were carried out by applying a time horizon of 6 months (the period of milk consumption) or of 3 years, at which point most AD symptoms have either dissipated or have evolved into broader allergic manifestations such as rhinitis or asthma.

Resource utilization and costs

According to the expert panel, all first-line medical visits were with a family physician (general practitioner). Subsequently, 50% of subjects with moderate AD and all subjects with severe AD were immediately referred to a specialist (a pediatrician, a dermatologist, or an allergist). Of those subjects who had not been referred to a specialist, failure of second-line treatment prompted such a referral. For subjects who did not respond to treatment, all subsequent medical visits occurred every time a treatment was revised or a change of formula was assigned. In Denmark, medical visits are fully reimbursed, but the cost of medical visits varies according to the specialty of the consulted physician and the number of medical visits[32,33].

Pharmacies in Denmark were surveyed to obtain the cost of emollients and the brand with the lowest price was selected. In accordance with the recommendations of the expert panel, all subjects used 2000 g of emollient creams for a period of 2 months at every occurrence of AD symptoms, as per the quantity per month (1000 g) reported in a study by Beattie and Lewis-Jones[34].

Depending on the age of the subject as well as the severity and location of AD symptoms, the expert panel recommended the use of one or a combination of corticosteroid creams (of very low, low, moderate, or high potency) and immunosuppressants (details of the regimen are available upon request). The *Danish Medicines Agency* provided the cost of the medications[35] and the reimbursement rate for these medications for each range of medication costs[36].

According to the expert panel, subjects with mild symptoms of AD were not administered any laboratory tests. However, 50% of subjects with moderate AD and all subjects with severe AD were given a Prick Test and an Oral Provocation Test. In addition, 10% of all moderate or severe cases were eligible for a Specific IgE Test and 10% of severe cases were also subject to the Food Eviction Test. Furthermore, according to the expert panel, 1% of all severe cases are hospitalized for a period of 2 days. The cost of the laboratory testing and hospitalization are fully reimbursed in Denmark; these costs were obtained from a survey of a local medical clinic and hospital, respectively.

When analyzing the family perspective and the societal perspective, indirect costs due to leisure time and/or productivity loss were included in the model. The calculation of time lost was based on the population rate of participation in the workforce in Denmark (published by the *Statistics Denmark* for 2010)[37] as well as the average gross hourly wage and weekly hours of work published for 2007 and 2008, respectively, by the International Labour Organization[38,39]. This calculation yielded a daily number of hours worked of 7.27. A total of 4 hours loss was granted to the family for physician visits and laboratory testing (including travel to and from the medical office). Two full days were assumed to be needed for childcare after the initial medical visit while, as per expert opinion, time lost for applying topical cream to the skin of the affected subject was taken into account at a rate of 10 min per application. It was assumed that all topical interventions (such as emollients and corticosteroids) were applied once daily.

The cost of travel to and from the physician's office, for an assumed distance of 10 km, was established by using an average of the cost of public transportation (bus and metro), the cost of using a taxi, and the cost of operating a personal car in the city of Aarhus, Denmark. The cost of operating a personal car was approximated by using the per kilometer rate for a taxi (i.e., excluding service charges and the additional fare for waiting in traffic).

Discounting

Costs beyond 1 year were discounted, but outcomes were considered with or without discounting as the discounting of outcomes is still controversial[40]. Discount rates of 0, 3, and 5% were applied as per the recommendations by Alban *et al.*[41].

Probabilistic sensitivity analyses

A set of 10,000 Monte Carlo simulations was undertaken to provide a broad evaluation of use of PHF-W vs both EHF with the context of a CEA. This probabilistic SA allowed the simultaneous variation of key parameter values in a random fashion according to ranges and types of distribution, thus covering a wide breadth of possibilities within the CEA analysis. Monte Carlo ICERs were obtained by dividing the average incremental costs by the average avoided cases which were obtained as a result of the simulations while median ICERs were identified by using the ICERs generated from each Monte Carlo simulation, thus accounting for the incremental costs and outcomes of each simulation.

Results

Cost minimization analysis—Base case analysis

For a birth cohort of 63,411 newborns in Denmark in 2009, the starting cohort entering the model had 4544 'at risk' newborns consuming infant formula. Table 3 presents the results of the base case analysis from three perspectives (MOH, family, and society) when comparing subjects who consumed PHF-W to those who consumed EHF-Whey or EHF-Casein for prevention. The formula acquisition costs for PHF-W, EHF-Whey, and EHF-Casein were DKK 10,639,893, DKK 39,583,835, and DKK 39,491,205, respectively. Hence, the base case CMA yielded savings of DKK 28,943,942 for PHF-W vs EHF-Whey and savings of DKK 28,851,312 when PHF-W was compared to EHF-Casein, including savings from the MOH perspective of DKK 9,442,695 and DKK 9,411,420, respectively. Therefore, from all three perspectives, PHF-W was dominant over both EHF preparations.

Cost effectiveness analysis—Primary and secondary sensitivity analyses

PHF-W vs EHF-Whey

In the primary SA wherein the nominal efficacy of PHF-W and EHF-Whey were taken into account (see Table 4), the expected numbers of cases attributed to PHF-W and EHF-Whey were 453 and 728, respectively, yielding a total of 274 avoided cases of AD by selecting PHF-W over EHF-Whey. The total direct and indirect costs associated with PHF-W and EHF-Whey were DKK 16,460,337 and DKK 48,856,577, respectively, yielding savings with PHF-W. From all three perspectives, the highest cost was attributable to formula. The expected incremental costs per

Table 3. Results of the base case analysis presented from the perspective of the Ministry of Health, of the family of the subject, and of society as a whole.

Perspective	Formula acquisition costs (in DKK)			Savings with PHF-W (in DKK)*	
	PHF-W	EHF-Whey	EHF-Casein	PHF-W vs EHF-Whey	PHF-W vs EHF-Casein
Danish MOH	3,526,041	12,968,735	12,937,461	(9,442,695)	(9,411,420)
Family	7,113,852	26,615,100	26,553,744	(19,501,247)	(19,439,892)
Society	10,639,893	39,583,835	39,491,205	(28,943,942)	(28,851,312)

*These savings are presented in parentheses because they are negative values.
Note: At time of analysis, 1 DKK = 0.134 € = 0.194 USD.
DKK, Danish kroner; EHF, Extensively hydrolyzed formula; MOH, Ministry of Health; PHF-W, Nestlé brand of 100% whey-based partially hydrolyzed formula.

Table 4. Results of the primary sensitivity analysis comparing PHF-W to EHF-Whey, presented from the perspective of the Ministry of Health, of the family of the subject, and of society as a whole.

	PHF-W	EHF-Whey
Outcomes		
Number of Cases	453	728
Avoided Cases	274	
Costs (in DKK)		
Ministry of Health Perspective		
Cost of Formula	3,591,340	13,034,530
Physician Costs	371,749	596,623
Treatment Costs	10,057	16,167
Hospitalization Costs	47,975	77,016
Cost of Lab Tests	63,020	101,169
Total Cost	4,084,141	13,825,505
Incr Cost		−9,741,364
Incr C/AC (ICER)		−35,502*
Family Perspective		
Cost of Formula	7,157,386	26,658,963
Treatment Costs	310,399	498,312
Cost of Time Lost	4,621,057	7,412,350
Travel Costs	287,355	461,447
Total Cost	12,376,196	35,031,072
Incr Cost		−22,654,875
Incr C/AC (ICER)		−82,565*
Societal Perspective		
Total Cost	16,460,337	48,856,577
Incr Cost		−32,396,239
Incr C/AC (ICER)		−118,067*

*EHF-Whey is dominated by PHF-W.
Note: At time of analysis, 1 DKK = 0.134 € = 0.194 USD.
DKK, Danish kroner; EHF, Extensively hydrolyzed formula; ICER, Incremental cost-effectiveness ratio; Incr, Incremental; PHF-W, Nestlé brand of 100% whey-based partially hydrolyzed formula.

avoided case of AD (i.e., the expected ICERs) were −DKK 35,502, −DKK 82,565, and −DKK 118,067 from the MOH, family, and societal perspectives, respectively. These negative ICER values and the fact that more cases were avoided by using PHF-W rather than EHF-Whey indicate dominance of PHF-W over EHF-Whey from all three perspectives. The findings of the secondary SAs which were undertaken by varying some parameters of the primary SA are presented in Table 5. PHF-W was again dominant over EHF-Whey in all scenarios except one: when applying the upper bound of the 95% CI of the RR of developing AD, a scenario with low probability.

EHF-Casein vs PHF-W

Given that the nominal efficacy of EHF-Casein is better than that of PHF-W, the CEA comparing these two formulas was geared towards evaluating the incremental cost of EHF-Casein, not PHF-W; this analysis effectively became an analysis of EHF-Casein vs PHF-W. Hence, the formula presented in the Methods was reversed to show the incremental cost of EHF-Casein, which had a higher acquisition cost, for each additional expected avoided case of AD.

The results of the primary CEA are presented in Table 6. The expected number of avoided cases by selecting EHF-Casein over PHF-W was 26. The total costs associated with EHF-Casein were DKK 44,982,191 and the highest cost driver was the cost of formula. The expected ICERs for EHF-Casein vs PHF-W were DKK 365.585, DKK 746,073, and DKK 1,111,658 from the MOH, family, and societal perspectives, respectively. These ICERs convey an unattractive cost-effectiveness for EHF-Casein vs PHF-W, an outcome which was confirmed in the secondary SAs (particularly the SA where the time horizon was limited to 6 months), presented in Table 7. The only secondary SA which yielded a negative ICER (displaying dominance for PHF-W) was the SA applying the lower bound of the 95% CI of the RR of developing AD, where the advantage of PHF-W over EHF-Casein was greatly increased.

Cost effectiveness analysis—Probabilistic sensitivity analyses

PHF-W vs EHF-Whey

The parameter distribution and variation applied in the probabilistic SAs comparing PHF-W, EHF-Whey, and EHF-Casein are displayed in Table 8, along with the results of the probabilistic SA for PHF-W vs EHF-Whey. The obtained average and median Monte Carlo ICERs confirmed the cost-effectiveness of PHF-W over EHF-Whey with an 86% probability of showing dominance.

EHF-Casein vs PHF-W

As in the primary SA, the probabilistic SA comparing EHF-Casein to PHF-W used EHF-Casein as the basis for the analysis, given its higher nominal efficacy. EHF-Casein was associated with a 76% likelihood of causing less cases of AD than PHF-W but with average Monte Carlo ICERs of DKK 315,930, DKK 408,407, and DKK 724,337, from the MOH, family, and societal perspectives, respectively. This probabilistic SA did not yield any probability of EHF-Casein being dominant over PHF-W, but the opposite, with PHF-W causing less cases of AD and costing less than EHF-Casein, was true in 24% of observed cases.

Discussion

To our knowledge, this is the first published economic evaluation of PHF-W in the prevention of AD in Danish 'at risk' children. This study differs in some aspects from a similar study published for France[20]: the French MOH does not reimburse EHF for prevention, thus prompting a CEA comparing PHF-W to the most commonly used infant formula, standard cow's milk-based formula. In the present analysis, EHF-Whey and EHF-Casein were

Table 5. Results of the secondary sensitivity analyses comparing PHF-W to EHF-Whey, presented from the perspective of the Danish Ministry of Health, of the family of the subject, and of society as a whole.

	Outcomes		Costs in DKK								
	Cases		Ministry of Health			Subject's family			Society		
	PHF-W	EHF-Whey	PHF-W	EHF-Whey	ICER	PHF-W	EHF-Whey	ICER	PHF-W	EHF-Whey	ICER
MOH covered 100% of infant formula program for treatment	453	728	4,127,674	13,869,368	− 35,503	12,332,663	34,987,209	−82,564	16,460,337	48,856,577	−118,067
MOH covered 100% of infant formula program for prevention	453	728	6,434,835	22,471,329	−58,444	10,025,503	26,385,248	−59,622	16,460,337	48,856,577	−118,067
MOH covered 100% of infant formula program for prevention up to 6 months of age	453	728	11,197,994	40,440,605	−106,574	5,262,344	8,415,972	−11,493	16,460,337	48,856,577	−118,067
MOH covered 60% of infant formula program for prevention up to 6 months of age	453	728	6,942,036	24,607,071	−64,380	9,518,301	24,249,506	−53,687	16,460,337	48,856,577	−118,067
Lower bound CI of the relative risk used	251	731	3,828,725	13,807,400	−20,804	10,033,821	35,082,065	−52,221	13,862,547	48,889,464	−73,024
Upper bound CI of the relative risk used	812	785	4,566,747	13,935,723	349,304	16,543,350	35,650,714	712,381	21,110,098	49,586,437	1,061,684
Lower bound CI of incident rates used	325	531	3,921,094	13,593,755	−47,022	10,889,416	32,779,762	−106,416	14,810,510	46,373,517	−153,438
Upper bound CI of incident rates used	585	932	4,249,493	14,063,954	−28,294	13,897,674	37,361,897	−67,644	18,147,167	51,425,851	−95,937
The rounded down number of cans was taken	453	728	3,860,886	13,281,711	−34,334	12,227,360	34,668,542	−81,786	16,088,246	47,950,252	−116,120
Cases included more severe and moderate cases	453	728	4,295,959	14,165,263	−35,968	12,661,372	35,488,266	−83,192	16,957,331	49,653,530	−119,160
Reduced the response rate to therapeutic management and combined management by 50%	453	728	4,282,771	14,145,261	−35,943	13,032,950	36,086,343	−84,017	17,315,721	50,231,604	−119,961
Excluded hospitalization	453	728	4,036,167	13,748,489	−35,396	12,315,525	34,940,487	−82,456	16,351,692	48,688,977	−117,852
Time Horizon – 6 months	105	106	3,706,122	13,150,471	−8,870,265	8,367,160	27,880,958	−18,327,633	12,073,282	41,031,428	−27,197,898
Time Horizon – 3 years, discounted at 0%	930	1280	4,586,043	14,407,617	−28,115	17,857,049	41,373,188	−67,317	22,443,092	55,780,804	−95,432
Time Horizon – 3 years, discounted at 3%	908	1254	4,562,602	14,381,176	−28,336	17,596,905	41,080,273	−67,771	22,159,507	55,461,448	−96,107
Time Horizon – 3 years, discounted at 5%	894	1239	4,547,994	14,364,683	−28,476	17,434,944	40,897,751	−68,060	21,982,938	55,262,434	−96,537
Time Horizon – 3 years, only costs discounted at 3%	930	1280	4,564,977	14,383,849	−28,107	17,599,217	41,082,879	−67,224	22,164,194	55,466,728	−95,331
Time Horizon – 3 years, only costs discounted at 5%	930	1280	4,551,848	14,369,024	−28,102	17,438,572	40,901,844	−67,165	21,990,420	55,270,868	−95,268

Note: At time of analysis, 1 DKK = 0.134 € = 0.194 USD.

CI, Confidence interval; EHF, Extensively hydrolyzed formula; ICER, Incremental cost-effectiveness ratio; PHF-W, Nestlé brand of 100% whey-based partially hydrolyzed formula.

Table 6. Results of the primary sensitivity analysis comparing EHF-Casein to PHF-W, presented from the perspective of the Ministry of Health, of the family of the subject, and of society as a whole.

	EHF-Casein	PHF-W
Outcomes		
Number of Cases	428	453
Avoided Cases	26	
Costs (in DKK)		
Ministry of Health perspective		
Cost of Formula	12,999,064	3,591,340
Physician Costs	350,706	371,749
Treatment Costs	9,488	10,057
Hospitalization Costs	45,259	47,975
Cost of Lab Tests	59,453	63,020
Total Cost	13,463,971	4,084,141
Incr Cost		9,379,830
Incr C/AC (ICER)		365,585
Family perspective		
Cost of Formula	26,594,813	7,157,386
Treatment Costs	292,829	310,399
Cost of Time Lost	4,359,488	4,621,057
Travel Costs	271,090	287,355
Total Cost	31,518,220	12,376,196
Incr Cost		19,142,024
Incr C/AC (ICER)		746,073
Societal perspective		
Total Cost	44,982,191	16,460,337
Incr Cost		28,521,853
Incr C/AC (ICER)		1,111,658

Note: At time of analysis, 1 DKK = 0.134 € = 0.194 USD.
DKK, Danish kroner; EHF, Extensively hydrolyzed formula; ICER, Incremental cost-effectiveness ratio; Incr, Incremental; PHF-W, Nestlé brand of 100% whey-based partially hydrolyzed formula.

selected as the main comparators to PHF-W because their use is currently reimbursed at a rate of 60% by the Danish MOH when used in the target population of the present study, namely 'at risk' infants who are not exclusively breastfed.

The present base case analysis which applied equal efficacy to PHF-W and its EHF comparators (as the difference in the nominal efficacy rate of each of these formulas did not reach the level of statistical significance)[13,14] amounted to a CMA with PHF-W displaying significant savings when compared to both EHF preparations. These savings were comparable, as the acquisition cost of each EHF preparation was almost equal. For all three formulas, the acquisition costs were higher from the family's perspective than from the Danish MOH perspective given that the 60% reimbursement rate for infant formulas in 'at risk' infants only applies for a period of 4 months. This entailed that the family covered 40% of formula acquisition costs for the first 4 months and 100% of these costs for the last 2 months of formula consumption. If the observed savings for PHF-W vs either EHF preparation are converted into savings per child in the starting cohort, savings of ~DKK 2000, DKK 4300, and DKK 6300 were observed from the MOH, family, and societal perspectives, respectively.

A series of SAs were undertaken to explore a scenario wherein the nominal efficacy of PHF-W and its comparators were applied, thus requiring a CEA approach. In the primary comparison to EHF-Whey, PHF-W displayed dominance from all perspectives. These findings were confirmed by a set of secondary SAs in which PHF-W was always dominant over EHF-Whey except for the scenario which applied the upper bound of the 95% CI of the RR of developing AD, a low-probability scenario wherein the advantage of PHF-W over EHF-Whey in prevention was greatly diminished. The probabilistic SA yielded an 86% probability of PHF-W being dominant over EHF-Whey.

For the comparison of PHF-W and EHF-Casein when nominal efficacy was taken into account, the SAs used EHF-Casein as the basis for the analyses as its nominal efficacy was, very moderately, better than that of PHF-W. The observed expected ICERs for the primary and secondary SAs did not point to EHF-Casein as being an attractive alternative to PHF-W when used in prevention. The expected ICERS of DKK 365,582 for the MOH and DKK 1,111,658 for society would indicate that the cost of preventing one case of AD would be much higher when selecting EHF-Casein over PHF-W. This can be explained by the fact that their nominal efficacies are quite similar, whereas the acquisition cost of EHF-Casein is much greater than that of PHF-W. The probabilistic SA based on the comparison of these two formulas pointed to a similar conclusion while also dispelling the possibility of EHF-Casein showing dominance over PHF-W.

Limitations

The main limitation of the CMA consists of the fact that it was based on the lack of statistical significant differences in efficacy. However, in order to address any uncertainty arising from that approach, a full CEA model was built and various analyses performed. Those analyses confirmed the dominance of PHF-W over EHF-Whey while they failed to show any attractive cost-effectiveness for WHF-Casein.

With regard to uncertainties arising from the CEA model, several SAs, including probabilistic Monte Carlo simulations, were carried out. These SAs confirmed the robustness of the CEA model and the direction of the analyses.

As for generalizability of results, while the economic model was created and populated with an 'average' approach synthesized on input from various clinical practitioners and experts in the area, although there may be differences in individual practices and between various geographic areas, the probabilistic SAs have covered a wide array of results, all leading towards superiority of PHF-W.

Table 7. Results of the secondary sensitivity analyses comparing EHF-Casein to PHF-W, presented from the perspective of the Danish Ministry of Health, of the family of the subject and of society as a whole.

	Outcomes		Costs in DKK								
	Cases		Ministry of Health			Subject's family			Society		
	PHF-W	EHF-Casein	EHF-Casein	PHF-W	ICER	EHF-Casein	PHF-W	ICER	EHF-Casein	PHF-W	ICER
MOH covered 100% of infant formula program for treatment	453	428	13,505,040	4,127,674	365,489	31,477,151	12,332,663	746,169	44,982,191	16,460,337	1,111,658
MOH covered 100% of infant formula program for prevention	453	428	22,088,945	6,434,835	610,129	22,893,246	10,025,503	501,529	44,982,191	16,460,337	1,111,658
MOH covered 100% of infant formula program for prevention up to 6 months of age	453	428	40,017,715	11,197,994	1,123,268	4,964,476	5,262,344	−11,610	44,982,191	16,460,337	1,111,658
MOH covered 60% of infant formula program for prevention up to 6 months of age	453	428	24,221,233	6,942,036	673,468	20,760,958	9,518,301	438,190	44,982,191	16,460,337	1,111,658
Lower bound CI of the relative risk used	251	339	13,352,890	3,828,725	−107,980	30,514,033	10,033,821	−232,194	43,866,923	13,862,547	−340,175
Upper bound CI of the relative risk used	812	531	13,600,874	4,566,747	32,131	32,680,785	16,543,350	57,394	46,281,659	21,110,098	89,525
Lower bound CI of incident rates used	325	307	13,315,837	3,921,094	510,781	30,138,718	10,889,416	1,046,562	43,454,555	14,810,510	1,557,343
Upper bound CI of incident rates used	585	552	13,614,525	4,249,493	282,977	32,931,459	13,897,674	575,132	46,545,985	18,147,167	858,109
Number of cans rounded down	453	428	12,921,702	3,860,886	353,151	31,156,707	12,227,360	737,784	44,078,409	16,088,246	1,090,935
Cases included more severe and moderate cases	453	428	13,663,799	4,295,959	365,118	31,787,253	12,661,372	745,444	45,451,052	16,957,331	1,110,561
Reduction of the response rate to therapeutic management and combined management by 50%	453	728	13,651,357	4,282,771	365,147	32,137,799	13,032,950	744,624	45,789,156	17,315,721	1,109,771
Exclusion of hospitalization	453	428	13,418,712	4,036,167	365,691	31,460,983	12,315,525	746,207	44,879,695	16,351,692	1,111,898
Time Horizon – 6 months	105	99	13,107,349	3,706,122	1,575,679	27,736,110	8,367,160	3,246,305	40,843,459	12,073,282	4,821,984
Time Horizon – 3 years, discounted at 0%	930	821	13,876,992	4,586,043	84,915	36,036,560	17,857,049	166,153	49,913,552	22,443,092	251,069
Time Horizon – 3 years, discounted at 3%	908	802	13,857,291	4,562,602	87,802	35,817,626	17,596,905	172,121	49,674,916	22,159,507	259,922
Time Horizon – 3 years, discounted at 5%	894	790	13,845,021	4,547,994	89,707	35,681,409	17,434,944	176,059	49,526,430	21,982,938	265,766
Time Horizon – 3 years, only costs discounted at 3%	930	821	13,859,289	4,564,977	84,946	35,819,570	17,599,217	166,526	49,678,859	22,164,194	251,473
Time Horizon – 3 years, only costs discounted at 5%	930	821	13,848,263	4,551,848	84,965	35,684,458	17,438,572	166,760	49,532,722	21,990,420	251,725

Note: At time of analysis, 1 DKK = 0.134 € = 0.194 USD.

CI, Confidence interval; EHF, Extensively hydrolyzed formula; ICER, Incremental cost-effectiveness ratio; PHF-W, Nestlé brand of 100% whey-based partially hydrolyzed formula.

Table 8. Parameter distributions and variations in the probabilistic sensitivity analyses and presentations of the results of the probabilistic sensitivity analysis for PHF-W vs EHF-Whey.

Parameter	Distribution type	Selected range	
MOH milk program coverage for prevention for a period of 4 months	Uniform	60–100%	
MOH milk program coverage for treatment	Uniform	60–100%	
Quantity of milk consumed	Uniform	85–141 grams	
Relative risk	Log Normal	95%CI	
Incidence rates consideration	Uniform	95%CI	
Number of subsequent physician visits after finalizing treatment	DUD	1–2 visits	
Rounding down or up the number of cans used	DUD	round down or up	
Laboratory tests from the diagnostic approach	DUD	include or exclude	
Transportation costs	DUD	include or exclude	
Cost of time lost for the application of emollients	DUD	include or exclude	
Cost of time lost for the application of medication	DUD	include or exclude	
Align medical visits and laboratory tests or not	DUD	same or different times	
Cost of leisure time lost	DUD	include or exclude	
Days lost due to child at home[a]	DUD	1 or 2 days	
Time horizon	DUD	6 months, 1 year, 3 years	
Discount rate	Uniform	0–5%	
Discounting of outcomes	DUD	include or exclude	
Monte Carlo results for PHF-W vs EHF-Whey	MOH	Family	Society
PHF-W			
Average Costs (in DKK)	5,213,150	10,539,607	15,752,757
Average Number of AD Cases	485	485	485
EHF-Whey			
Average Costs (in DKK)	17,861,541	28,995,136	46,856,677
Average Number of AD Cases	711	711	711
Monte Carlo ICERs (in DKK)[a]	(55,892)	(81,554)	(137,446)
Median ICERs (in DKK)[b]	(41,339)	(61,855)	(103,264)
Distribution			
Quadrant 1	0%	0%	0%
Quadrant 2	0%	0%	0%
Quadrant 3[c]	14%	14%	14%
Quadrant 4[d]	86%	86%	86%

[a]These Monte Carlo ICERs were obtained by dividing the average incremental costs by the average avoided cases of AD which were generated from the 10,000 Monte Carlo simulations. The values are in parentheses because they are negative, i.e., they represent savings.
[b]These median ICERS were generated from each Monte Carlo simulation (accounting for the incremental costs and outcomes of each simulation). The values are in parentheses because they are negative, i.e., they represent savings.
[c]Quadrant 3 represents the scenario where PHF-W yielded lower incremental costs but fewer avoided cases than EHF-Whey.
[d]Quadrant 4 denotes dominance by PHF-W over EHF-Whey as PHF-W is associated with lesser costs and more avoided cases than EHF-Whey.
Note: At time of analysis, 1 DKK = 0.134 € = 0.194 USD.
AD, Atopic dermatitis; CI, Confidence interval; DKK, Danish kroner; DUD, Discreet uniform distribution; EHF, Extensively hydrolyzed formula; ICER, Incremental cost-effectiveness ratio; MOH, Ministry of Health; PHF-W, Nestlé brand of 100% whey-based partially hydrolyzed formula.

Conclusions

Under a certain range of assumptions and using both a CMA and CEA approach, the present analysis has established the attractiveness of NAN HA 1®, a specific brand of 100% whey-based partially hydrolyzed formula, in the prevention of AD in infants and very young children in Denmark. NAN HA 1® demonstrated dominance over EHF-Whey and EHF-Casein from all perspectives in the base case CMA. In a series of SAs, a CEA approach confirmed dominance of PHF-W over EHF-Whey, while it failed to establish attractive cost-effectiveness ratios for EHF-Casein, effectively confirming PHF-W to be the alternative of choice in the prevention of AD in Denmark.

Transparency

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