Asia Pacific allergy

pISSN 2233-8276 · eISSN 2233-8268

Original Article

http://dx.doi.org/10.5415/apallergy.2015.5.2.84
Asia Pac Allergy 2015;5:84-97

Economic value of atopic dermatitis prevention via infant formula use in high-risk Malaysian infants

Abhijeet J Bhanegaonkar[1], Erica G Horodniceanu[1], Amir Hamzah Abdul Latiff[2], Sanjay Woodhull[3], Phaik Choo Khoo[3], Patrick Detzel[4], Xiang Ji[1], and Marc F Botteman[1,*]

[1]Pharmerit International, Bethesda, MD 20814, USA
[2]Department of Pediatrics, Pantai Hospital Kuala Lumpur, 59100 Kuala Lumpur, Malaysia
[3]Department of Pediatrics, Ramsay Sime Darby, Subang Jaya Medical Centre, 47500 Subang Jaya, Malaysia
[4]Nestlé Research Center, 1000 Lausanne 26, Switzerland

Background: Breastfeeding is best for infants and the World Health Organization recommends exclusive breastfeeding for at least the first 6 months of life. For those who are unable to be breastfed, previous studies demonstrate that feeding high-risk infants with hydrolyzed formulas instead of cow's milk formula (CMF) may decrease the risk of atopic dermatitis (AD).

Objective: To estimate the economic impact of feeding high-risk, not exclusively breastfed, urban Malaysian infants with partially-hydrolyzed whey-based formula (PHF-W) instead of CMF for the first 17 weeks of life as an AD risk reduction strategy.

Methods: A cohort Markov model simulated the AD incidence and burden from birth to age 6 years in the target population fed with PHF-W vs. CMF. The model integrated published clinical and epidemiologic data, local cost data, and expert opinion. Modeled outcomes included AD-risk reduction, time spent post AD diagnosis, days without AD flare, quality-adjusted life years (QALYs), and costs (direct and indirect). Outcomes were discounted at 3% per year. Costs are expressed in Malaysian Ringgit (MYR; MYR 1,000 = United States dollar [US $]316.50).

Results: Feeding a high-risk infant PHF-W vs. CMF resulted in a 14% point reduction in AD risk (95% confidence interval [CI], 3%–23%), a 0.69-year (95% CI, 0.25–1.10) reduction in time spent post-AD diagnosis, additional 38 (95% CI, 2–94) days without AD flare, and an undiscounted gain of 0.041 (95% CI, 0.007–0.103) QALYs. The discounted AD-related 6-year cost estimates when feeding a high-risk infant with PHF-W were MYR 1,758 (US $556) (95% CI, MYR 917–3,033) and with CMF MYR 2,871 (US $909) (95% CI, MYR 1,697–4,278), resulting in a per-child net saving of MYR 1,113 (US $352) (95% CI, MYR 317–1,884) favoring PHF-W.

Conclusion: Using PHF-W instead of CMF in this population is expected to result in AD-related costs savings.

Key words: Cost-benefit analysis; Dermatitis atopic; Infant formula

Correspondence: Marc Botteman
Pharmerit International, 4350 East West Highway, Suite 430, Bethesda, MD 20814, USA
Tel: +1-240-821-1289
Fax: +1-240-821-1296
E-mail: mbotteman@pharmerit.com

Received: June 20, 2014
Accepted: March 5, 2015

INTRODUCTION

Atopic dermatitis (AD) is one of the most prevalent inflammatory skin disorders affecting infants and young children [1, 2]. As a chronic disorder with increasing prevalence worldwide, AD imposes substantial economic and quality of life (QoL) burden on patients, families, and societies [3-7]. Studies in the Asia-Pacific region show that the annual direct AD cost alone (expressed in 2013 United States dollars [US $]) ranges from US $199 in Thailand [8], to US $1,253 in South Korea [9], and to US $4,842 in Australia [6].

A combination of genetic, immunologic, and environmental factors affect AD incidence risk. In particular, exposure within the first 6 months of life to dietary allergens such as proteins found in standard cow's milk formula (CMF) can increase this risk. Such exposure can be particularly problematic among high-risk infants with atopic heredity (e.g., those having 1 or more parent or sibling with a history of allergic disease/first degree atopic heredity [10-12]). As a result, the standing World Health Organization (WHO) recommendation of exclusive breastfeeding through the first 6 months of life [13-15] may apply particularly in this high risk population. However, in some cases following these recommendations is impossible and infant formulas are used as nutritional supplement to or replacement for breast milk. In such instances, partially hydrolyzed formulas (PHF) or extensively hydrolyzed formulas (EHF) containing whey (W) and/or casein (C) as a protein source [16, 17] may be used as an alternative to CMF as hydrolyzed infant formulas may reduce the risk of AD and other allergies [10, 18, 19]. In particular, results from the German Infant Nutritional Intervention (GINI) study, the largest trial comparing the impact of a 17-week early nutritional intervention with PHF-W vs. CMF among nonexclusively breastfed infants with atopic heredity, showed a lower 6-year cumulative AD incidence with PHF-W relative to CMF (adjusted relative risk [RR], 0.64; 95% confidence interval [CI], 0.48–0.86) [10]. In addition, results from a randomized trial of genetically predisposed Singaporean infants found that the cumulative AD incidence at 24 months of age was 22.6% with PHF-W and 43.9% with CMF [20]. These results, confirmed via meta-analyses [19, 21], have led national and international allergy organizations to suggest the use of hydrolyzed formulas as an allergy risk-reduction strategy for formula-fed high-risk infants who are not exclusively breastfed [12, 22-24].

AD risk reduction with PHF-W in high-risk infants may result in clinical, economic, and QoL benefits. These benefits however, must be weighed against the potentially higher costs of PHF-W relative to CMF during the 17-week interventional period. Several economic studies conducted in developed countries suggest that PHF-W is cost-effective, if not cost saving, versus CMF in high-risk infants not exclusively breastfed [25-31]. However, a search of the literature indicates that comparable evidence is extremely limited for developing nations. A study has recently reported that PHF-W is cost effective vs. CMF in the Philippines [31], saving US $237 per infant.

Relying upon health economic modeling techniques to aggregate data from multiple sources, including the GINI study [10] and expert opinion, this study was conducted to estimate the long-term (i.e., birth to 6 years of life) clinical and economic impact of feeding with PHF-W versus CMF for the first 17 weeks of life on AD risk reduction among high-risk infants in urban Malaysia.

MATERIALS AND METHODS

Model overview and key assumptions

Markov cohort modeling techniques [32, 33] were used to compare costs and outcomes in the first 6 years of life associated with AD risk reduction using PHF-W (here assumed to be NAN HA, Nestlé (M) Sdn Bhd, Petaling Jaya, Selangor, Malaysia) vs. CMF (here assumed to be Enfalac A+, Mead Johnson Nutrition (M) Sdn Bhd, Petaling Jaya, Selangor, Malaysia) in the first 17 weeks of life among healthy (i.e., without a previous AD diagnosis), nonexclusively breastfed, high-risk (with first degree atopic heredity) infants in urban areas of Malaysia. The target population, risk reduction, formula feeding and duration, and AD incidence were based on the GINI study [10, 18].

The model incorporated direct and indirect costs associated with AD treatment and formula feeding from the perspective of urban populations. The analytical horizon (i.e., from birth to 6 years), consistent with the GINI study, was used to capture longer term effects [10]. The primary outcomes for each treatment arm included cost (overall and differences), AD incidence, number of days without AD flare, time spent post-AD diagnosis, and QALYs.

A simplified diagram of the model structure is presented in Fig. 1. Infant cohorts entered the model at birth and were followed in bi-weekly cycles until 6 years of age. Infants continued to be fed with the initially assigned formula (PHF-W or CMF) until week 17, unless AD developed. As in the GINI study, AD incidence varied by age and initial formula used (PHF-W or CMF). Similar to previously-published models [25-27, 29-31], up to 3 treatment

 http://dx.doi.org/10.5415/apallergy.2015.5.2.84

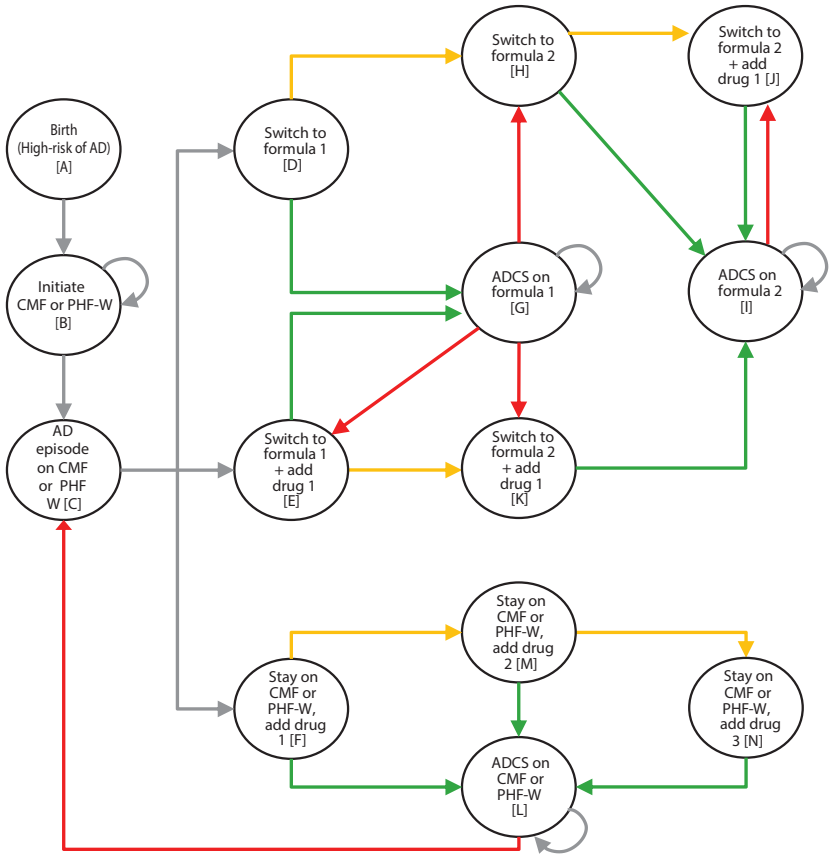

Fig. 1. Simplified presentation of the model structure. Arrow key: Red is flare; Green is response; Yellow is no response. AD, atopic dermatitis; ADCS, atopic dermatitis controlled state; CMF, standard cow's milk formula; PHF-W, partially hydrolyzed whey formula. Infant cohorts enter the model at birth [A] and initiate a 17-week course of PHF-W or CMF [B]. If and when AD develops [C], 3 treatment approaches were possible: (1) Formula change only [D]: The child enters ADCS on first-line treatment formula in case of response within 2 weeks [G], or, in case of nonresponse, she/he is switched to a second treatment formula [H]. Patients from the ADCS [G], who were previously treated with first-line treatment formula [D], upon experiencing a flare, are treated in 1 of 3 ways: adding first-line pharmacotherapy [E], switching to second-line treatment formula [H], or switching to second-line treatment formula + drug 1 [K]. In case of response to second-line of treatment formula [H], patients entered ADCS [I]. In case of nonresponse to second-line treatment formula [H] or a flare in ADCS [I], a first-line pharmacotherapy (drug 1) would be added [J]. For simplicity, the model assumes response is achieved at this point and the patient enters ADCS on AD treatment second-line treatment formula [I]. (2) Formula change combined with first-line pharmacotherapy (switch to first-line treatment formula + drug 1) [E]: Pharmacotherapy would end in case of response and the child would enter ADCS on first-line treatment formula [G]. Otherwise, they would switch to second-line treatment formula while remaining on the same pharmacotherapy [K]. At this point, response would occur and they enter ADCS on second-line treatment formula [I]. (3) First-line pharmacotherapy only (drug 1 along with the initial formula) [F]: The child experiences a response and enters ADCS on the original formula [L]. Otherwise they remain on the initial formula and switch to a second- and third-line pharmacotherapy (drug 2 [M] and drug 3 [N]) until response occurs, at which point the patient enters ADCS on the original formula [L]. Patients from the ADCS [L], who were previously treated within the addition of first-line pharmacotherapy only [F], upon experiencing flare, were assumed to be treated by either a change in formula, pharmacotherapy, or both.

approaches were considered upon AD development: formula switch only, pharmacotherapy only, and combination formula switch and pharmacotherapy. These approaches were endorsed by Malaysian pediatricians with experience treating pediatric AD patients (authors AHAL, SW, PCK). If a child responded to a formula switch, they were assumed to continue on that formula until up to 12 months of age, the next AD episode, or death, which, for simplicity, was not depicted as a separate state in Fig. 1 but was included in the model. In case a child did not respond to a formula switch, she/he was assumed to be switched to another formula. The first switch formula was assumed to be soy, followed by PHF-W for those who were initially on CMF and EHF for those

http://dx.doi.org/10.5415/apallergy.2015.5.2.84

who were initially on PHF-W. A child who responded to pharmacotherapy was assumed to complete the treatment course and remain on their formula until up to 12 months of age. Infant formula use was assumed to end at 12 months of age; hence, the pharmacotherapy only treatment approach was always used from year 1 to year 6.

Treatment success (i.e., response to treatment approach) was defined as complete AD symptom resolution and was assessed every 2 weeks. Assumptions regarding response rates determined the speed at which children experienced AD symptom resolution and transitioned to an AD-controlled state (ADCS). Response rates varied according to AD severity, treatment approach, and line of treatment. Following remission into ADCS, a child could experience a flare, the rate of which was dependent upon age group (0–1 years; >1–6 years) and AD severity (mild, moderate, and severe).

A lack of uniformity exists in methods to determine AD disease severity internationally [34]. The various available scales are rarely used in clinical practice [34]. While there is no gold standard, scoring atopic dermatitis (SCORAD) is among the most commonly used validated scales, which incorporates both objective and subjective assessments [34]. Therefore, in this analysis, AD severity (mild, moderate, severe) was assumed to be based on the SCORAD index (Eczema grading: mild < 25, moderate 25–50, severe > 50) [35], especially in discussions among the Malaysian pediatricians who provided inputs for the analysis.

Clinical and epidemiologic inputs

Epidemiologic inputs are listed in Table 1. The probability of AD for PHF-W and CMF was obtained using linear interpolation of the 1-, 3-, and 6-year cumulative incidence data from the GINI study [10]. The distribution of AD cases and probability of flares by severity and age group were derived from the aforementioned expert opinion. Clinical management and treatment effectiveness inputs which include rates of AD management modality and response rates were stratified by AD severity, treatment line, and age group (Table 2).

Resource use inputs

Daily formula intake was derived using a previously reported method [26] and accounted for partial breast feeding and age-related nutrition requirements.

Table 3 details the other resources used to manage AD. Information on the type and amount of resources used with each treatment modality based on AD severity was provided by the experts. Specifically, the frequency of outpatient visits (general pediatrician or specialist, i.e., allergist, dermatologist) and inpatient visits were dependent on AD severity and treatment response. Based on the experts' opinions, hospitalizations were assumed to occur in 2 out of 1,000 subjects with severe AD less than 1 year old upon initial AD development. Whereas hospitalizations were assumed to occur in approximately 4 out of 100 severe AD patients 1–6 years of age upon initial development of AD.

Diagnostic tests were assumed to be performed in some but not all AD patients. Skin prick tests, specific IgE and oral challenge tests were assumed to be performed upon initial AD development depending on AD severity. Inpatient and outpatient visits and diagnostic tests costs were based on average fees charged in Malaysia in selected private or government hospitals or laboratories in the Kuala Lumpur Metropolitan Area where information was available.

Nearly all AD patients were assumed to be prescribed emollient and/or moisturizer creams upon initial AD development and again during reassessment consultation visits in case of non-response and/or flare.

Cost inputs

Table 4 provides data on cost. Formula acquisition costs were based on the market share in Malaysia (Source: Packaged Food: Euromonitor from trade sources/national statistics, February 2013) and reflected the formula cost paid "out-of-pocket" by families because infant formula is not covered by private or public insurance companies in Malaysia. Only the additional costs incurred as a result of feeding an alternative infant formula for AD prevention or treatment (such as PHF-W, soy-based formula, and EHF) as opposed to CMF were included in the analysis. Medicine acquisition costs were obtained from an online drug information tool (http://www.mims.com/Malaysia) commonly used in Malaysia. Reduced productivity (i.e., indirect costs) included lost work days to care for a child with AD following the initial physician visit (irrespective of AD severity).

Utility inputs

A utility of 1.000 was assumed for children who did not develop AD; a utility of 0.980 was assumed for children in ADCS to recognize that mild, subclinical episodes can reduce QoL. A utility of 0.863 was associated with ongoing mild, 0.690 with moderate,

 http://dx.doi.org/10.5415/apallergy.2015.5.2.84

Table 1. Epidemiologic inputs

Epidemiologic input	Base case	Value in uSA*		PSA distribution
		Low	High	
AD probability: CMF†				
0 to 1 year	16.80%	6.96%	29.85%	Beta
>1 to 3 years	20.07%	9.00%	34.19%	Beta
>3 to 6 years	8.42%	0.18%	29.66%	Beta
AD, cumulative RR; PHF-W vs. CMF†				
0 to 1 year	0.54	0.33	0.89	Lognormal
>1 to 3 year	0.57	0.36	0.90	Lognormal
>3 to 6 year	0.82	0.40	1.70	Lognormal
Initial AD case severity distribution, 0–1 yr‡		Based on Dirichlet distributions used in PSA§		Dirichlet
Mild	43.30%			
Moderate	36.70%			
Severe	20.00%			
Initial AD case severity distribution, >1 yr‡		Based on Dirichlet distributions used in PSA§		Dirichlet
Mild	50.00%			
Moderate	28.30%			
Severe	21.70%			
12-Week AD flare probability, 0–1 yr‡				
Initial AD presentation: mild	40.00%	35.37%	44.72%	Beta
Initial AD presentation: moderate	50.00%	45.36%	54.64%	Beta
Initial AD presentation: severe	58.00%	52.19%	63.70%	Beta
12-Week AD flare probability, >1 yr‡				
Initial AD presentation: mild	40.00%	35.37%	44.72%	Beta
Initial AD presentation: moderate	53.00%	48.49%	57.48%	Beta
Initial AD presentation: severe	60.00%	54.32%	65.55%	Beta
Mortality‖	0.0085%			

uSA, univariate sensitivity analyses; PSA, probabilistic sensitivity analysis; AD, atopic dermatitis; CMF, standard cow's milk formula; RR, relative risk; PHF-W, partially-hydrolyzed whey-based formula.

*Due limited data sources, some value inputs were based on arbitrary variation in the univariate sensitivity analysis. †Source: von Berg et al. 2008 for PHF-W vs. CMF [10]. ‡Source: Expert panel. §The distribution of cases was varied simultaneously as scenario analysis of all severities in order to add up to 100%. Individual values are not relevant for univariate range thus not presented. ‖Source: Mortality data for children <5, specific to Malaysia (Source: World Bank data).

and 0.450 with severe AD episodes based on previously published data [36, 37]. Death was associated with a utility of 0.000.

Statistical analysis

Using the model structure and inputs detailed herein, several incremental cost effectiveness ratios (ICERs) were computed to estimate the economic value of PHF-W compared to CMF. These outcomes included the incremental costs per AD case avoided, per days without AD flare gained, and QALYs gained. In addition, AD costs per AD patient overall and per year and AD visits per AD patient per year were derived from the model to allow validation of these values with other published estimates.

Sensitivity analyses were conducted to evaluate the robustness of the results. First, deterministic univariate sensitivity analyses (uSA) varied individual model parameters while keeping other base-case values unchanged (see Tables 1–3 for ranges). Scenario

http://dx.doi.org/10.5415/apallergy.2015.5.2.84

Table 2. Clinical management and effectiveness inputs*

Variable	Base case (%)	Value in uSA†		PSA distribution
		Low (%)	High (%)	
Mild AD management, 0–1 yr‡		Based on Dirichlet distributions used in PSA		Dirichlet
Switch formula alone	3.33			
Combined switch formula and pharmacotherapy	26.67			
Pharmacotherapy alone	70.00			
Moderate AD management, 0–1 yr‡		Based on Dirichlet distributions used in PSA		Dirichlet
Switch formula alone	3.33			
Combined switch formula and pharmacotherapy	35.00			
Pharmacotherapy alone	61.67			
Severe AD management, 0–1 yr‡		Based on Dirichlet distributions used in PSA		Dirichlet
Switch formula alone	1.67			
Combined switch formula and pharmacotherapy	45.00			
Pharmacotherapy alone	53.33			
Any AD severity management, >1 yr				
Pharmacotherapy alone	100	100	100	NA
AD management, 0–1 yr, all severity levels				
Formula change response rate; PHF-W cohort	7.00	0.06	27.60	Beta
Formula change response rate; CMF cohort	7.00	0.06	27.60	Beta
First-line combination treatment response rate, 0–1 yr				
Initial AD presentation: mild	77.00	71.19	82.34	Beta
Initial AD presentation: moderate	77.00	71.50	82.08	Beta
Initial AD presentation: severe	77.00	70.38	83.01	Beta
Second-line combination treatment response rate, 0–1 yr				
Initial AD presentation: mild	77.00	64.40	87.52	Beta
Initial AD presentation: moderate	77.00	65.10	87.04	Beta
Initial AD presentation: severe	77.00	62.59	88.73	Beta
Third-line combination treatment response rate, 0–1 yr				
Initial AD presentation: mild	77.00	48.77	95.70	Beta
Initial AD presentation: moderate	77.00	50.41	95.07	Beta
Initial AD presentation: severe	77.00	44.49	97.09	Beta
First-line pharmacotherapy response rate, 0–1 yr				
Initial AD presentation: mild	85.00	82.11	87.68	Beta
Initial AD presentation: moderate	67.00	62.14	71.69	Beta
Initial AD presentation: severe	53.00	44.66	61.25	Beta
First-line pharmacotherapy response rate, >1 yr				
Initial AD presentation: mild	83.00	80.63	85.25	Beta
Initial AD presentation: moderate	67.00	62.66	71.20	Beta
Initial AD presentation: severe	52.00	46.10	57.87	Beta
Second-line pharmacotherapy response rate, any year				
Initial AD presentation: mild	68.00	85.00	85.00	Beta
Initial AD presentation: moderate	68.00	60.47	75.09	Beta
Initial AD presentation: severe	68.00	60.88	74.73	Beta
Third-line pharmacotherapy response rate, any year				
Initial AD presentation: mild	83.00	68.01	93.90	Beta
Initial AD presentation: moderate	83.00	72.59	91.32	Beta
Initial AD presentation: severe	83.00	74.50	90.07	Beta

uSA, univariate sensitivity analyses; PSA, probabilistic sensitivity analysis; AD, atopic dermatitis; PHF-W, partially-hydrolyzed whey-based formula; CMF, standard cow's milk formula.
*Source: Expert panel. †Due limited data sources, some value inputs were based on arbitrary variation in the univariate sensitivity analysis. ‡Instead of varying single proportion of case distribution, all 3 categories were varied simultaneously (formula switch, combined, and pharmacotherapy) using Dirichlet distributions. Individual values are not relevant for univariate range thus not presented.

 http://dx.doi.org/10.5415/apallergy.2015.5.2.84

Table 3. Quantity of resources used per patient to treat AD by severity at presentation*

Variable	Upon initial development of AD			During follow-up treatment of AD (in cases of nonresponse and/or flares)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Physician visits						
Generalist/pediatrician	1.00	1.00	1.33	1.50	1.93	2.58
Specialists	0.22	0.21	1.01	0.46	0.55	1.32
Diagnostic tests						
Specific IgE test	0.23	0.38	0.50	-	-	-
Skin prick test	0.32	0.25	0.18	-	-	-
Oral challenge test	0.25	-	-	-	-	-
Pharmacotherapies (for patients treated with pharmacotherapy)						
Emollient cream 500 g/unit	1.00	0.98	1.99	0.50	0.98	1.99
Hydrocortisone 15 g/unit	0.30	0.55	1.83	0.30	0.55	1.33
Mometasone 15 g/unit	-	-	1.50	-	-	0.80
Tacrolimus 10 g/unit	-	0.52	0.53	-	0.42	1.00
Atopiclair 100 g/unit	0.45	0.47	0.70	0.48	0.45	0.93
Oral antibiotics (Augmentin)	-	-	0.20	-	-	0.20
Surgibath 100 mL	-	0.65	1.50	-	-	-
Ceradan cream 30 g/unit	0.70	1.60	1.90	0.70	1.60	1.50
Fucidin H 15 g/unit	-	0.55	1.05	-	0.65	1.13
Bactroban 15 g/unit	-	-	0.90	-	-	0.90
Cloxacillin 125–250 mg/unit	-	-	0.90	-	-	-
Other costs						
Hours loss to attend AD	4.00	4.00	4.00	-	-	-
Hours loss per physician visit	2.00	2.00	2.00	2.00	2.00	2.00
Trip per physician visit	1.00	1.00	1.00	1.00	1.00	1.00

AD, atopic dermatitis.
Source: Expert panel.
*All parameters were varied by ±25% in univariate and multivariate sensitivity analyses (via uniform distributions).

analyses were conducted to test the impact of changing key model assumptions either alone or in combination. These included omitting any flares from the analysis and restricting the analysis to 1 year (as opposed to the 6-year time frame). Multivariate, probabilistic sensitivity analysis (PSA) was conducted whereby the model was run 5,000 times via Monte Carlo simulation to estimate bootstrapped 95% Bayesian CIs.

In accordance with common health economics research guidelines, clinical and economic outcomes occurring after the first year were discounted at 3% per annum to estimate the net present value of the different strategies, reflecting society's preference for the present. Costs reported in this study represent 2013 values, expressed in Malaysian Ringgit and US dollars (MYR; MYR 1,000 = US $316.50; 25-Oct-2013).

Finally, this study was exempted from the Malaysian Medical Research Ethics Committee review and approval as per its guidelines 4a.

RESULTS

Children who developed AD within the first 6 years of life were predicted to incur an undiscounted total (direct and indirect) AD cost of MYR 7,990 (US $2,529; 95% CI, MYR 6,211–9,826) on aver-

http://dx.doi.org/10.5415/apallergy.2015.5.2.84

Table 4. Summary of economic inputs (2013 MYR)*

Variable	Cost per unit (MYR)	Value in uSA (MYR)	
		Low	High
Formula†			
PHF-W (NAN HA) (per 400 g)	44.60	33.49	55.81
CMF (Enfalac A+) (per 650 g)	71.60	53.70	89.50
Soy (Isomil, Abbott Laboratories Sdn Bhd) (per 400 g)	35.80		
EHF (Mamex Gold Pepti, Danone Dumex (M) Sdn Bhd) (per 400 g)	70.00		
First-line treatment formula (per 400 g)	35.80	26.85	44.75
Second-line treatment formula (per 400 g)	57.33	42.99	71.66
Pharmacotherapy‡			
Emollient cream	20.00	15.00	25.00
Hydrocortisone	5.00	3.75	6.25
Mometasone	33.90	25.43	42.38
Tacrolimus	128.50	96.38	160.63
Atopiclair	95.00	71.25	118.75
Oral antibiotics (Augmentin)	24.75	18.56	30.94
Surgibath	20.00	15.00	25.00
Ceradan cream	38.00	28.50	47.50
Fucidin H	29.00	21.75	36.25
Bactroban	12.50	9.38	15.63
Cloxacillin	2.80	2.10	3.50
Medical Visits§			
General pediatrician	52.50	39.38	65.63
Allergist/dermatologist	155.00	116.25	193.75
Hospitalizations§			
Initial AD presentation: mild	1,050.00	787.50	1,312.50
Initial AD presentation: moderate	3,400.00	2,550.00	4,250.00
Initial AD presentation: severe	3,750.00	2,812.50	4,687.50
Laboratory tests§			
Initial AD presentation: mild	74.33	55.75	92.92
Initial AD presentation: moderate	72.13	54.09	90.16
Initial AD presentation: severe	142.67	107.00	178.33
Other costs			
Travel (10 km at MYR 1.50 per km)	15.00	11.25	18.75
Cost per hour of time lost ‖	33.04	24.78	41.30

MYR, Malaysian Ringgit; uSA, univariate sensitivity analyses; PHF-W, partially-hydrolyzed whey-based formula; CMF, standard cow's milk formula; EHF, extensively hydrolyzed formula; AD, atopic dermatitis.

*Distributions for costs in probabilistic sensitivity analysis were uniform. †Costs for PHF-W, CMF, Soy, and EHF were employed based on the availability and market share in the Malaysia using Packaged Food: Euromonitor from trade sources/national statistics. Recommended quantities from the package inserts were used to determine daily formula consumption quantity and varied based on age and percentage of feeding from breastfeeding. Complete daily formula quantity consumption available upon request. ‡Costs obtained from MIMS (http://www.mims.com/Malaysia/home/Index). Quantity applied varied based on AD severity and treatment line. §Costs are based on average fees charged in Malaysia. ‖Costs associated with time loss estimated using average hourly wages in Kuala Lumpur (MYR 51.3, http://www.salaryexplorer.com/salary-survey.php?loc=1515&loctype=3, last accessed March 30th 2014), labor force participation (64.40%) (Source: Nestle Malaysia affiliate), and hours spent was obtained from expert panel.

 http://dx.doi.org/10.5415/apallergy.2015.5.2.84

age. The cost of AD was MYR 5,245 (US $1,660) for mild cases, MYR 7,397 (US $2,341) for moderate cases, and MYR 15,060 (US $4,767) for severe cases. The estimated average annual undiscounted total (direct and indirect) cost for an infant developing AD within the first 6 years of life was MYR 1,885 (US $584; 95% CI, MYR 1,567–2151) including MYR 1,256 (US $398) in direct costs alone. The corresponding costs if all cases were assumed to be mild were MYR 1,211 (US $383), moderate MYR 1,708 (US $541), and severe MYR 3,478 (US $1,101). Finally, the total annual number of visits per AD case was estimated at 6.88 visits across all cases and 4.38 visits for mild, 7.02 for moderate, and 12.26 for severe cases.

As Table 5 shows, compared to CMF, PHF-W was associated with lower AD incidence (-14%, 39% vs. 25%; 95% CI for the difference: 3%–23%), fewer years post-AD diagnosis (–0.69 years, 1.69 years vs. 1.01 years; 95% CI for the difference: 0.25–1.10 years), and fewer AD-flare days (–38 days, 55 days vs. 93 days; 95% CI for the difference: 2–94 days). Discounted QALYs with PHF-W were 5.517 QALY (95% CI, 5.440–5.547 QALY) versus 5.479 QALY (95% CI, 5.369–5.528 QALY) with CMF, for a net difference of 0.038 QALY (95% CI, 0.016–0.079).

The total discounted costs (direct and indirect) of AD risk reduction among the nonexclusively breastfed infants with atopic heredity were lower among those fed PHF-W (MYR 1,758 [US $556]; 95% CI, MYR 917–3,033) compared to CMF (MYR 2,871 [US $909], 95% CI, MYR 1,697–4,278). Primary drivers of total costs were those associated with pharmacological treatments followed by indirect costs and physician visits.

The resulting 6-year net savings due to AD risk reduction with

Table 5. Base-case model results for 6-year time horizon comparing PHF-W and CMF administration in children with a family atopic history

Variable	PHF-W	CMF	Difference
Discounted costs (2013 MYR)			
Initial formula (for risk reduction)*	5	-	5
Formula treatment*	3	6	–3
Physician visits	512	855	–343
Pharmacotherapy	663	1,055	–392
Diagnostic testing	21	33	–12
Hospitalization	4	5	–2
Total direct costs	1,208	1,954	–746
Indirect costs	550	916	–366
Total (95% CI)†	1,758 (917–3,033)	2,871 (1,697–4,278)	–1,113 (–1,884 to –317)
Total discounted costs in US $ (95% CI)†	556 (290–960)	909 (537–1,354)	–352 (–596 to –100)
Undiscounted clinical effects (95% CI)†			
Proportion of children developing AD	25% (13%–46%)	39% (24%–57%)	–14% (–23% to –3%)
Years of life post AD diagnosis	1.01 (0.56–1.67)	1.69 (1.03–2.44)	–0.69 (–1.10 to –0.25)
Days with AD flare	55 (32–111)	93 (58–169)	–38 (–2 to –94)
QALYs	5.938 (5.854–5.971)	5.897 (5.777–5.950)	0.041 (0.007–0.103)
Discounted QALYs (95% CI)†	5.517 (5.440–5.547)	5.479 (5.369–5.528)	0.038 (0.016–0.079)
Incremental cost effectiveness ratios			
Cost per AD-case avoided			PHF-W dominant‡
Cost per day without AD flare gained			PHF-W dominant‡
Cost per QALY gained			PHF-W dominant‡

PHF-W, partially-hydrolyzed whey-based formula; CMF, standard cow's milk formula; MYR, Malaysian Ringgit; CI, confidence interval; US $, United States dollar; AD, atopic dermatitis; QALY, quality adjusted life-year.
*Includes only excess cost over and above the cost of CMF. †Percentile distributions (2.5th and 97.5th) to represent uncertainty around mean parameter value. ‡Dominance refers to a situation where one intervention (here, PHF-W) is said to dominate another (here, CMF) when its effectiveness is found to be higher and the costs lower.

http://dx.doi.org/10.5415/apallergy.2015.5.2.84

PHF-W was MYR 1,113 (US $352) (95% CI, MYR 317–1,884), irrespective of AD development (Table 5). After 1 year, the total discounted cost for PHF-W versus CMF was MYR 173 (US $55) versus MYR 312 (US $99). In fact, PHF-W was associated with a net cost-savings almost immediately after formula initiation.

Comparison of PHF-W versus CMF using ICER values showed PHF-W to be a net cost-saving strategy which also resulted in reductions in avoided AD cases, gains in days without AD flare, and QALY gains (i.e., PHF-W is the "dominant" strategy) relative to CMF (Table 4). Additionally, results from the PSA indicated that PHF-W was dominant (more effective and less expensive) in 99.6% of the 5,000 model runs (Fig. 2).

In uSA, the RR of developing AD between CMF and PHF-W and the absolute risk of AD with CMF had the largest influence on the difference in cost between PHF-W and CMF. Other variables with potentially minor effects on net cost savings were PHF-W, CMF, and emollient costs. Finally, PHF-W remained cost dominant resulting in a net saving of MYR 407 (US $129) and discounted gains of 0.016 QALY when it was conservatively assumed that no AD patient would experience a flare.

DISCUSSION

Based on the model presented herein, early nutritional intervention with PHF-W in healthy infants with atopic heredity who are not exclusively breastfed is cost saving and improves health relative to CMF. In the base case, PHF-W was associated with a decrease in AD risk and an increase in days without AD flare and QALYs. Accordingly, PHF-W also resulted in net statistically significant discounted cost decreases of MYR 1,113 (US $352) (95% CI, MYR 317–1,884) per infant (from MYR 2,871 [US $909] to MYR 1,758 [US $556]), after including the additional cost of PHF-W over CMF. The robustness of these results was confirmed via comprehensive sensitivity analyses.

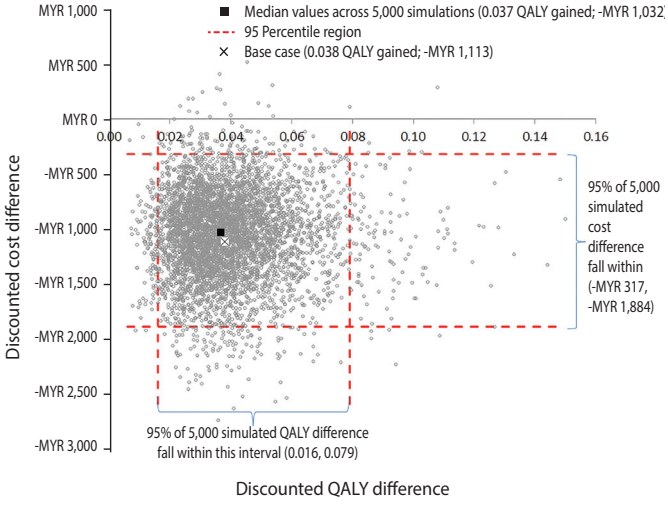

Fig. 2. Scatter plot of 5,000 simulations from multivariate probabilistic sensitivity analysis. MYR, Malaysian Ringgit; QALY, quality adjusted life-year.

The cost differential between the two arms considered herein was driven primarily by the following cost categories: pharmacotherapy, indirect costs, and physician visits. All other costs had minimal impact, including the formula costs for PHF-W and CMF, which were nearly similar. Pharmacotherapy costs were high because it was the most common treatment method utilized either alone or in combination with formula change. Physician visit costs were relatively expensive because of the number needed for AD management, averaging 6.92 visits per year reflecting in part the need for visits associated with frequent flare recurrence. To assess how the assumptions regarding flare recurrence impacted the results, a scenario analysis assumed no relapse. In this case, PHF-W-associated cost-savings were reduced from MYR 1,113 (US $352) to MYR 407 (US $129).

Outcomes presented herein are consistent with similar analyses in developed countries [25-30] whereby PHF-W was cost effective or cost saving (depending on whether a third party payer or societal perspective was adopted). These are also consistent with an analysis conducted in the Philippines which showed that PHF-W results in savings of US $247 (95% CI, 94–323) in a similar target population. These similarities can be partially attributed to shared methodology and assumptions [25-30]. In contrast, the annual total (MYR 1,845 [US $584]) and direct (MYR 1,256 [US $398]) AD costs among those who developed AD were somewhat higher than in Thailand [8] (US $199 for direct cost), but lower than in South Korea [9] (total cost, US $3,522; direct cost, US $1,253 in a sample of pediatric patients from an allergy clinic) or Australia [6] (total cost, US $6,187; direct cost, US $4,842 in a sample of pediatric patients from a dermatologic clinic). Differences reflect variations in study design and methods, target patient populations, and per-capita income. Consistent with disparities reported in other studies [6, 8], annual AD costs increased with worsening disease severity, from MYR 1,211 (US $383) for mild cases to MYR 3,478 (US $1,101) among severe cases.

The annual number of physician visits necessary to manage

AD (6.88 across all cases, 4.38 visits in mild, 7.02 visits in moderate, and 12.26 visits in severe cases) may be conservative when compared to values for Australia [6] (12.88 visits overall; 7.0 visits in mild, 13.0 visits in moderate, and 23.2 visits in severe cases) but very consistent with Thailand [8] (approximately 4.3 to 4.6 visits overall; 4.0 visits in mild, 8.0 visits in moderate, and 12 to 13 visits for severe cases).

This analysis was limited by a lack of published data specific to Malaysia regarding AD epidemiology and treatment patterns and the impact of PHF-W and CMF on AD incidence. Consequently, we relied on the GINI trial results [10] and the clinical opinion of 3 physicians in Malaysia experienced in treating pediatric AD patients. This challenge is not unique to Malaysia. In both developed and developing countries, AD is diagnosed clinically and severity is assessed subjectively. It is not routinely recorded administratively (e.g., for reimbursement). Hence, in many nonprospective studies, AD severity cannot be asserted definitely. Many AD treatments (e.g., formula replacement or over-the-counter topical agents) require out-of-pocket expenditure borne by families. These may be under-recorded and are difficult to estimate. As a result, even analyses conducted in developed countries [25-30] relied heavily on similar evidence and input generation methods reported herein.

Exclusive reliance on GINI trial data as the efficacy source for different infant formulas in this analysis was justified on the grounds that it is the largest randomized, double-blind, interventional trial with the longest follow-up period comparing PHF-W and CMF [19, 21]. In addition, the cumulative AD incidence rates observed in GINI for PHF-W and CMF are consistent with and perhaps conservative compared to those observed in a smaller study by Chan et al. [20], 2002 (n = 110) in hereditarily predisposed Singaporean infants. Specifically, cumulative AD incidence in the CMF arm was 43.9% and in the PHF-W arm 22.6% at 24 months of age in the Singaporean study (odds ratio, 0.37; $p = 0.019$) [20]. Conversely, corresponding unadjusted rates in the GINI trial were 33.5% and 39.1% in the CMF arm and 19.5% and 27.4% in the PHF-W arm after 3 (adjusted RR, 0.58; 95% CI, 0.41–0.82) and 6 years (adjusted RR, 0.64; 95% CI, 0.48–0.86) respectively [10]. These relatively high rates of AD are also in line with a 39.3% prevalence of eczema observed among Malaysian adolescents (age 11–20 years) with a family history of asthma and allergy [38].

Little evidence is available regarding AD severity in Malaysia and elsewhere. In the present analysis, AD severity was assumed to be moderate in 37% of cases in children less than 1 year of age and in 28% of cases in children aged 1 to 6 years; AD was assumed to be severe in 20% of cases in children aged less than 1 year and in 22% of cases in children aged 1 to 6 years. In the International Study of Asthma and Allergies in Childhood [39], severe AD (defined as current eczema associated with sleep disturbance 1 or more nights per week) accounted for 7% of AD cases in those aged 6 to 7 years old. Results from a survey of Southeast Asian dermatologists assessing knowledge, attitudes, and practices on AD management [40], found that 14% of patients initially presented with severe, 18% with mild, and 68% with moderate disease. Thus, the assumptions used herein may be considered reasonable given that the population considered was high-risk infants (≥1 parent or sibling with history of allergic disease/first degree atopic heredity). At the same time, it should be noted that the assumptions regarding both the severity and prevalence of AD adopted herein were meant to be applicable to an urban population. Thus, the outcomes of this analysis could have been dramatically different had we adopted a rural or government practice perspective.

Treatment and resource use patterns for AD are poorly documented in Malaysia. A literature search identified one survey of 44 dermatologists regarding AD management treatment patterns in Malaysia [40]. Moisturizers were reported to be always used by 77% of respondents in the clearance phase of treatment and in 86% of patients in the maintenance phase of treatment. Participants reported prescribing topical steroids for approximately 34% of infants with mild, 57% with moderate, and 9% with severe AD. Low potency topical corticosteroids were used most frequently (93%) in infants and children. Eighty percent reported 'always' prescribing oral antihistamines to treat AD patients. In severe AD, oral steroids were used by 93% of dermatologists. Phototherapy was reportedly used by 25% of dermatologists. Finally, 5% recommended the use of alternative medicines such as traditional Chinese medicines and homeopathy. These treatment patterns—while different than assumed herein in part perhaps because the survey respondents were dermatologists whereas the present analysis adopts a primary care view point—indicate that the management of AD in Malaysia may be relatively intense. In the present analysis, it was assumed that a high proportion of patients would receive topical therapy (with moisturizers and/or topical steroids). On the other hand, the use of oral steroids and phototherapy was not considered.

Food allergens, especially cow's milk, are often implicated as major triggers for AD relapse/flare-ups in infants. Whether con-

firmed by diagnostic testing or suspected by clinical history, shifting to a non-CMF is common practice. Here, the use of soy-based formulas was selected as a method to manage AD triggered by a cow's milk allergy to reflect current practice in Malaysia, after taking into account the lower cost and superior palatability of soy formula relative to other formulas. However, soy-based formulas, as a rule, are not recommended for AD treatment unless a substitute formula is necessary for cow's milk-allergic children with moderate to severe AD who cannot afford the cost of EHF. In part, this assumption could be considered conservative because the use of the least expensive dietary modification available in Malaysia (i.e., soy formula) may underestimate AD management costs and subsequently the value of preventing and/or reducing AD. This study did not account for any wastage factor while estimating costs for formula consumption; although, varying formula acquisition costs in sensitivity analysis indicated by proxy that this consideration has a limited impact on outcomes.

This study was conservative in additional aspects. First, any effects of AD beyond the first 6 years of life were excluded. In addition, any other allergic manifestations (within and after the initial 6 years) that may be preventable via PHF-W were also ignored. The impact of AD on parents' productivity and, in particular, lost productivity while at work as a result of a poor night sleep to attend to a crying child, etc. was only partially considered, in part due to a lack of data. The impact of AD on parents' QoL was ignored entirely.

In conclusion, exclusive breastfeeding is recommended by the WHO for the first 6 months of life. The present analysis modeled the long-term cost-effectiveness of AD risk reduction via early nutritional intervention with PHF-W versus CMF in healthy Malaysian urban infants with atopic heredity (high-risk) who are not exclusively breastfed. The results suggest that PHF-W used in this population may be a dominant strategy compared to CMF as it reduces the clinical and QoL burden of AD while decreasing overall costs, even after including formula costs. The results provide valuable insights into the long-term risk reduction of AD in children that can be helpful for physicians. Furthermore, it may help private health insurance planners make decisions regarding reimbursement/coverage policies for infant formulas among infants who are predisposed to developing AD and who are not exclusively breastfed. While the analysis was conducted on the basis of limited evidence, various sensitivity and scenario analyses show that these conclusions may be robust. Nevertheless, additional research regarding the epidemiology, severity, treatment patterns, and resource use associated with the risk reduction and treatment of AD in Malaysia are warranted.

CONFLICT OF INTEREST

AJB, EGH, XJ, and MFB are and/or were employees and/or owner of Pharmerit International which received partial research funding from the Nestlé Nutrition Institute, Vevey, Switzerland to conduct this study. PD is an employee of Nestlé Research Center, Lausanne, Switzerland, which funded this study. AHAL, SW and PCK: None declared. The Nestlé Research Center, Lausanne, Switzerland, is part of Nestlé, which manufactures and commercializes a range of infant food products, including one of the products evaluated in this study. Pharmerit International retained independent control of the methodology and presentation of this study. The role of the 3 physicians in this study was to provide the clinical experience input and in this context does not directly or indirectly imply promotion of any infant formula products mentioned in this study.

ACKNOWLEDGEMENTS

This research was sponsored by Nestlé Nutrition Institute. The authors would like to thank John Carter and Beth Lesher of Pharmerit International for their contributions during editorial review of this publication.

REFERENCES

1. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. J Allergy Clin Immunol 2003;112(6 Suppl):S118-27.
2. Catherine Mack Correa M, Nebus J. Management of patients with atopic dermatitis: the role of emollient therapy. Dermatol Res Pract 2012;2012:836931.
3. Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. Int J Clin Pract 2006;60:984-92.
4. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, Williams H; ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat

multicountry cross-sectional surveys. Lancet 2006;368:733-43.

5. Aziah MS, Rosnah T, Mardziah A, Norzila MZ. Childhood atopic dermatitis: a measurement of quality of life and family impact. Med J Malaysia 2002;57:329-39.
6. Su JC, Kemp AS, Varigos GA, Nolan TM. Atopic eczema: its impact on the family and financial cost. Arch Dis Child 1997;76:159-62.
7. Williams H, Stewart A, von Mutius E, Cookson W, Anderson HR; International Study of Asthma and Allergies in Childhood (ISAAC) Phase One and Three Study Groups. Is eczema really on the increase worldwide? J Allergy Clin Immunol 2008;121:947-54.e15.
8. Ngamphaiboon J, Kongnakorn T, Detzel P, Sirisomboonwong K, Wasiak R. Direct medical costs associated with atopic diseases among young children in Thailand. J Med Econ 2012;15:1025-35.
9. Kang KH, Kim KW, Kim DH. Utilization pattern and cost of medical treatment and complementary alternative therapy in children with atopic dermatitis. Pediatr Allergy Respir Dis 2012;22:27-36.
10. von Berg A, Filipiak-Pittroff B, Kramer U, Link E, Bollrath C, Brockow I, Koletzko S, Grubl A, Heinrich J, Wichmann HE, Bauer CP, Reinhardt D, Berdel D; GINIplus study group. Preventive effect of hydrolyzed infant formulas persists until age 6 years: long-term results from the German Infant Nutritional Intervention Study (GINI). J Allergy Clin Immunol 2008;121:1442-7.
11. von Berg A, Filipiak-Pittroff B, Kramer U, Hoffmann B, Link E, Beckmann C, Hoffmann U, Reinhardt D, Grubl A, Heinrich J, Wichmann HE, Bauer CP, Koletzko S, Berdel D; GINIplus study group. Allergies in high-risk schoolchildren after early intervention with cow's milk protein hydrolysates: 10-year results from the German Infant Nutritional Intervention (GINI) study. J Allergy Clin Immunol 2013;131:1565-73.
12. Greer FR, Sicherer SH, Burks AW; American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. Pediatrics 2008;121:183-91.
13. Halken S, Host A, Hansen LG, Osterballe O. Effect of an allergy prevention programme on incidence of atopic symptoms in infancy. A prospective study of 159 "high-risk" infants. Allergy 1992;47:545-53.
14. Host A, Halken S, Muraro A, Dreborg S, Niggemann B, Aalberse R, Arshad SH, von Berg A, Carlsen KH, Duschen K, Eigenmann PA, Hill D, Jones C, Mellon M, Oldeus G, Oranje A, Pascual C, Prescott S, Sampson H, Svartengren M, Wahn U, Warner JA, Warner JO, Vandenplas Y, Wickman M, Zeiger RS. Dietary prevention of allergic diseases in infants and small children. Pediatr Allergy Immunol 2008;19:1-4.
15. World Health Organization. Infant and young child nutrition: global strategy on infant and young child feeding. Report by the Secretariat. In: Fifty-fifth World Health Assembly. Provisional agenda item 13.10; 2002 Apr 16. Geneva: World Health Organization; 2002.
16. Hays T, Wood RA. A systematic review of the role of hydrolyzed infant formulas in allergy prevention. Arch Pediatr Adolesc Med 2005;159:810-6.
17. Jin YY, Cao MYR, Chen J, Kaku Y, Wu J, Cheng Y, Shimizu T, Takase M, Wu SM, Chen TX. Partially hydrolyzed cow's milk formula has a therapeutic effect on the infants with mild to moderate atopic dermatitis: a randomized, double-blind study. Pediatr Allergy Immunol 2011;22:688-94.
18. von Berg A, Koletzko S, Grubl A, Filipiak-Pittroff B, Wichmann HE, Bauer CP, Reinhardt D, Berdel D; German Infant Nutritional Intervention Study Group. The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomized double-blind trial. J Allergy Clin Immunol 2003;111:533-40.
19. Alexander DD, Cabana MD. Partially hydrolyzed 100% whey protein infant formula and reduced risk of atopic dermatitis: a meta-analysis. J Pediatr Gastroenterol Nutr 2010;50:422-30.
20. Chan YH, Shek LP, Aw M, Quak SH, Lee BW. Use of hypoallergenic formula in the prevention of atopic disease among Asian children. J Paediatr Child Health 2002;38:84-8.
21. Szajewska H, Horvath A. Meta-analysis of the evidence for a partially hydrolyzed 100% whey formula for the prevention of allergic diseases. Curr Med Res Opin 2010;26:423-37.
22. Host A, Koletzko B, Dreborg S, Muraro A, Wahn U, Aggett P, Bresson JL, Hernell O, Lafeber H, Michaelsen KF, Micheli JL, Rigo J, Weaver L, Heymans H, Strobel S, Vandenplas Y. Dietary products used in infants for treatment and prevention of food allergy. Joint Statement of the European Society for Paediatric Allergology and Clinical Immunology (ESPACI) Committee on Hypoallergenic Formulas and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition. Arch Dis Child 1999;81:80-4.
23. NIAID-Sponsored Expert Panel, Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, Plaut M, Cooper SF, Fenton MJ, Arshad SH, Bahna SL, Beck LA, Byrd-Bredbenner C, Camargo CA Jr, Eichenfield L, Furuta GT, Hanifin JM, Jones C, Kraft M, Levy BD, Lieberman P, Luccioli S, McCall KM, Schneider LC, Simon RA, Simons FE, Teach SJ, Yawn BP, Schwaninger JM. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol 2010;126(6 Suppl):S1-58.
24. Fleischer DM, Spergel JM, Assa'ad AH, Pongracic JA. Primary preven-

tion of allergic disease through nutritional interventions. J Allergy Clin Immunol Pract 2013;1:29-36.
25. Iskedjian M, Belli D, Farah B, Navarro V, Detzel P. Economic evaluation of a 100% whey-based partially hydrolyzed infant formula in the prevention of atopic dermatitis among Swiss children. J Med Econ 2012;15:378-93.
26. Iskedjian M, Dupont C, Spieldenner J, Kanny G, Raynaud F, Farah B, Haschke F. Economic evaluation of a 100% whey-based, partially hydrolysed formula in the prevention of atopic dermatitis among French children. Curr Med Res Opin 2010;26:2607-26.
27. Iskedjian M, Haschke F, Farah B, van Odijk J, Berbari J, Spieldenner J. Economic evaluation of a 100% whey-based partially hydrolyzed infant formula in the prevention of atopic dermatitis among Danish children. J Med Econ 2012;15:394-408.
28. Iskedjian M, Szajewska H, Spieldenner J, Farah B, Berbari J. Meta-analysis of a partially hydrolysed 100%-whey infant formula vs. extensively hydrolysed infant formulas in the prevention of atopic dermatitis. Curr Med Res Opin 2010;26:2599-606.
29. Su J, Prescott S, Sinn J, Tang M, Smith P, Heine RG, Spieldenner J, Iskedjian M. Cost-effectiveness of partially-hydrolyzed formula for prevention of atopic dermatitis in Australia. J Med Econ 2012;15:1064-77.
30. Mertens J, Stock S, Lungen M, von Berg A, Kramer U, Filipiak-Pittroff B, Heinrich J, Koletzko S, Grubl A, Wichmann HE, Bauer CP, Reinhardt D, Berdel D, Gerber A. Is prevention of atopic eczema with hydrolyzed formulas cost-effective? A health economic evaluation from Germany. Pediatr Allergy Immunol 2012;23:597-604.
31. Bhanegaonkar AJ, Horodniceanu EG, Gonzalez RR, Canlas Dizon MV, Detzel P, Erdogan-Ciftci E, Verheggen B, Botteman MF. Cost-effectiveness of partially hydrolyzed whey protein formula in the primary prevention of atopic dermatitis in at-risk urban filipino infants. Value Health Reg Issues 2014;3:124-35.
32. Beck JR, Pauker SG. The Markov process in medical prognosis. Med Decis Making 1983;3:419-458.
33. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making 1993;13:322-38.
34. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, Berger TG, Bergman JN, Cohen DE, Cooper KD, Cordoro KM, Davis DM, Krol A, Margolis DJ, Paller AS, Schwarzenberger K, Silverman RA, Williams HC, Elmets CA, Block J, Harrod CG, Smith Begolka W, Sidbury R. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol 2014;70:338-51.
35. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology 1993;186:23-31.
36. Pitt M, Garside R, Stein K. A cost-utility analysis of pimecrolimus vs. topical corticosteroids and emollients for the treatment of mild and moderate atopic eczema. Br J Dermatol 2006;154:1137-46.
37. Stevens KJ, Brazier JE, McKenna SP, Doward LC, Cork MJ. The development of a preference-based measure of health in children with atopic dermatitis. Br J Dermatol 2005;153:372-7.
38. Leung R, Ho P. Asthma, allergy, and atopy in three south-east Asian populations. Thorax 1994;49:1205-10.
39. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI; ISAAC Phase Three Study Group. Global variations in prevalence of eczema symptoms in children from ISAAC phase three. J Allergy Clin Immunol 2009;124:1251-8.e23.
40. Chan YC, Tay YK, Sugito TL, Boediardja SA, Chau DD, Nguyen KV, Yee KC, Alias M, Hussein S, Dizon MV, Roa F, Chan YH, Wananukul S, Kullavanijaya P, Singalavanija S, Cheong WK. A study on the knowledge, attitudes and practices of Southeast Asian dermatologists in the management of atopic dermatitis. Ann Acad Med Singapore 2006;35:794-803.