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John Su, Susan Prescott, John Sinn, Mimi Tang, Peter Smith, Ralf G. Heine, Jörg Spieldenner & Michael Iskedjian

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Original article

Cost-effectiveness of partially-hydrolyzed formula for prevention of atopic dermatitis in Australia

John Su
Department of Dermatology, Royal Children's Hospital, Melbourne, Australia; University of Melbourne, Melbourne, Australia; Monash University, Melbourne, Australia

Susan Prescott
School of Paediatrics and Child Health Research, University of Western Australia, Perth, Australia; Princess Margaret Hospital for Children, Subiaco, Australia

John Sinn
Department of Neonatology, Royal North Shore Hospital, St Leonard, Australia; University of Sydney, Sydney, Australia

Mimi Tang
Department of Allergy and Immunology, Royal Children's Hospital, Melbourne, Australia; Allergy and Immune Disorders, Murdoch Childrens Research Institute, Melbourne, Australia; Department of Paediatrics, University of Melbourne, Australia

Peter Smith
Queensland Allergy Services, Southport, Australia

Ralf G. Heine
Department of Gastroenterology & Clinical Nutrition, Department of Allergy & Immunology, University of Melbourne, Melbourne, Australia; Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, Australia

Jörg Spieldenner
Nestlé Nutrition Institute, Vevey, Switzerland

Michael Iskedjian
PharmIdeas Research and Consulting Inc., Oakville, ON, Canada; PharmIdeas Europe SAS, Lyon, France; Université de Montréal, Montréal, QC, Canada

Abstract

Objective:
To perform an economic evaluation of a specific brand of partially hydrolyzed infant formula (PHF-W) in the prevention of atopic dermatitis (AD) among Australian infants.

Methods:
A cost-effectiveness analysis was undertaken from the perspectives of the Department of Health and Aging (DHA), of the family of the affected subject and of society as a whole in Australia, based on a decision-analytic model following a hypothetical representative cohort of Australian newborns who are not exclusively breastfed and who have a familial history of allergic disease (i.e., are deemed 'at risk'). Costs, consequences, and incremental cost-effectiveness ratios (ICER) were calculated for PHF-W vs standard cow's milk based infant formula (SF), and, in a secondary analysis, vs extensively hydrolyzed infant formula (EHF-Whey), when the latter was used for the prevention of AD.

Results:
From a representative starting cohort of 87,724 'at risk' newborns in Australia in 2009, the expected ICERs for PHF-W vs SF were AU$496 from the perspective of the DHA and savings of AUD1739 and AU$1243 from the family and societal perspectives, respectively. When compared to EHF-Whey, PHF-W was associated with savings for the cohort of AU$5,183,474 and AU$6,736,513 from the DHA and societal perspectives.

Limitations:
The generalizability and transferability of results to other settings, populations, or brands of infant formula should be made with caution. Whenever possible, a conservative approach directing bias against PHF-W rather than its comparators was applied in the base case analysis. Assumptions were verified in one-way and probabilistic sensitivity analyses, which confirmed the robustness of the model.

Conclusions:
PHF-W appears to be cost-effective when compared to SF from the DHA perspective, dominant over SF from the other perspectives, and dominant over EHF-Whey from all perspectives, in the prevention of AD in 'at risk' infants not exclusively breastfed, in Australia.

Address for correspondence:
Michael Iskedjian, 1175 North Service Road West, Suite 211, Oakville, ON L6M 2W1 Canada.
Tel.: +1 905 465 3090 x223;
Fax: +1 905 465 3091;
miskedjian@pharmideas.com

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Introduction

Atopic dermatitis (AD), also known as eczema or IgE-associated eczema, is an inflammatory, non-contagious, and pruritic skin disorder which has its onset during the first 6 months of life[1]. The International Study of Asthma and Allergies in Childhood (covering 66 centers in 37 countries) reported national prevalence rates of 'ever having had AD' ranging between 1.2–38.6% for children aged 6–7 years, with a rate of 32.3% for Australia in 2002, a rate which had increased by 43% over 10 years[2]. The development of atopic disease depends on an interaction between genetic factors, environmental factors (including early life microbial exposures), dietary factors, and others[3].

The World Health Organization and Australian Society of Clinical Immunology and Allergy (ASCIA) recommend exclusive breastfeeding for the first six or four to six months of life, respectively[4–6]. The ASCIA and other scientific bodies recommend that feeding be introduced when infants are four to six months of age[4,7–9]. When the infant cannot be breastfed, ASCIA and various international guidelines for prevention of allergic disease recommend that 'at risk' infants be assigned hydrolyzed infant formula rather than standard cow's milk based infant formulas (SF)[4,7,10–13].

In Australia, whey-based extensively hydrolyzed infant formulas (EHF) are only available for treatment of established cow's milk and/or soy allergy and are not recommended for disease prevention. In contrast, partially hydrolyzed formula can be recommended for the purposes of prevention of allergic disease. Partially hydrolyzed formula is thought to have similar hypoallergenic properties to EHF but is associated with lower rates of discontinuation due to a host of factors such as better taste, better texture and less bitterness[14–16]. So far, only one specific brand of 100% whey-based partially hydrolyzed formula, NAN HA 1 Gold®, manufactured by Nestlé S.A, Switzerland (PHF-W), has been shown in randomized trials and meta-analyses to be effective in the prevention of AD when compared to SF[15–19]. Indeed, the relative risk (RR) of developing AD at 12 months of age or less, after having consumed PHF-W rather than SF, was reported as 0.68 (95% confidence interval of 0.48–0.98) in a meta-analysis by Szajewska and Horvath[18] and as 0.45 (0.30–0.70) in a meta-analysis of 'methodologically superior' studies published by Alexander and Cabana[19]. A third type of infant formula, amino acid-based formulas (AAF), are available for allergy treatment but at a much higher cost.

Treatment of AD accounts for a significant amount of health services financial resources and clinical time as well as placing a quality-of-life burden on the child, family, and society[20]. Two studies reported on the economic evidence pertaining to the treatment of AD in Australia[21,22]. Kemp[21] estimated that the societal costs per child per year for treatment ranged from AU$1142 for a child with mild AD to AU$6099 for a child with severe AD; overall yearly costs for treatment was conservatively estimated at AU$ 317 M. According to Su *et al.*[22], the total costs per case were estimated to the family at AU$480, 1712, and 2545 for mild, moderate, and severe AD, respectively. Furthermore, the authors postulated that families of children with moderate or severe AD had a significantly higher impact than families of diabetic children[22].

The cost-effectiveness of PHF-W in the prevention of AD for 'at risk' children has been established in France[23], Denmark[24], and other countries[25], but no such economic evaluation has been published for an Australian setting. The present pharmacoeconomic analysis determines the costs, consequences, and cost-effectiveness of PHF-W vs SF in the prevention of AD in 'at risk' children in Australia.

Methods

Product, disease, population, and time horizon

The product of interest was PHF-W and the main comparator in the base case analysis was SF; the use of EHF for prevention was explored in sensitivity analyses (SAs). The disease of interest was AD, which is commonly the first allergic disease manifestation observed in infants and also the most prevalent allergic condition in the first years of life. The population of interest were healthy 'at risk' subjects who were not exclusively breastfed, ranging from newborns to 3-year olds, as current international guidelines would recommend the use of hydrolyzed formulas for prevention of allergic disease in 'at risk' infants and toddlers. 'At risk' children were defined as having at least one parent or sibling with a reported history of allergies. The period of breast milk or infant formula consumption was assumed to cover the first 6 months of life. The base case analysis was undertaken for a time horizon of 12 months, covering the period by which most cases of AD would have occurred while extending beyond the period of milk consumption.

Perspective

The present study was undertaken by adopting three perspectives: the perspective of the Australian public healthcare system represented by the Department of Health and Aging (DHA), the perspective of the family of the subject, and the perspective of society as a whole which took into account both the DHA and family perspectives.

Type of economic evaluation

A cost-effectiveness approach was chosen as it offered the best means to measuring the costs and outcomes that are most relevant to both the children and their parents as well as the DHA. A cost-utility approach was not adopted as no direct measure of utility associated to AD was reported in the available literature, while the age of the population of interest signified that elicitation of utility would be impractical without the input of their parents or other proxies.

Clinical outcomes

The incidence rate of AD with SF and the RR of developing AD symptoms with PHF-W vs SF were reported in a meta-analysis by Szajewska and Horvath[18] (the only meta-analysis solely focusing on the formula of interest in the present study) and adapted for the present model into outcomes at 6, 12, 18, 24, 30, and 36 months by applying an approach described by Iskedjian *et al.*[26].

This analysis explored the prevention of AD rather than its occurrence. As such, the final clinical outcome of the base case analysis was the attributable risk for PHF-W vs SF, that is, the number of AD cases expected to be avoided (prevented) when consuming PHF-W rather than SF.

Economic outcomes and incremental ratios

The intermediate economic outcomes were the aggregated costs associated with PHF-W and SF from each perspective (i.e., DHA, family, and societal perspectives), while the final economic outcome was the incremental cost-effectiveness ratio (ICER) expressed in terms of an expected incremental cost per avoided case of AD. The simplified mathematical formulation of the ICER is presented below:

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

The application of a negative coefficient is required as this is an analysis of preventive outcomes.

Expert panel

An expert panel consisting of six expert pediatric clinicians (one neonatologist, one expert in dermatology, three experts in immunology and allergy, and one expert in gastroenterology and allergy) was convened in order to define the current medical practices and resources used in the management of AD in Australia. The input obtained from the expert clinicians was synthesized into the model, after resolving any point of contention.

Summary of model structure

As presented in Figure 1, a spreadsheet-based (MS Excel® 2003) decision-analytic economic model, based on a series of 6-month cycles, was developed in order to depict the medical practices associated with the treatment of AD in Australia.

The initial cohort entering the model represented the target population of this study and was defined by the following mathematical formulation:

$$\begin{aligned}&\big[(\text{Birth cohort in Australia})\\&\quad\times(1-\text{Average Exclusive Breastfeeding rate})\\&\quad\times(\text{Rate of }''\text{at risk}''\text{ infants})\big]\end{aligned}$$

The number of infants born in Australia in 2009 was obtained from the Australian Bureau of Statistics (ABS)[27]. The Australian Institute of Family Studies[28] reported the rate of exclusive breastfeeding for the first 12 months of age. The mean rate of exclusive breastfeeding at 2, 4, and 6 months was applied in determining the initial cohort

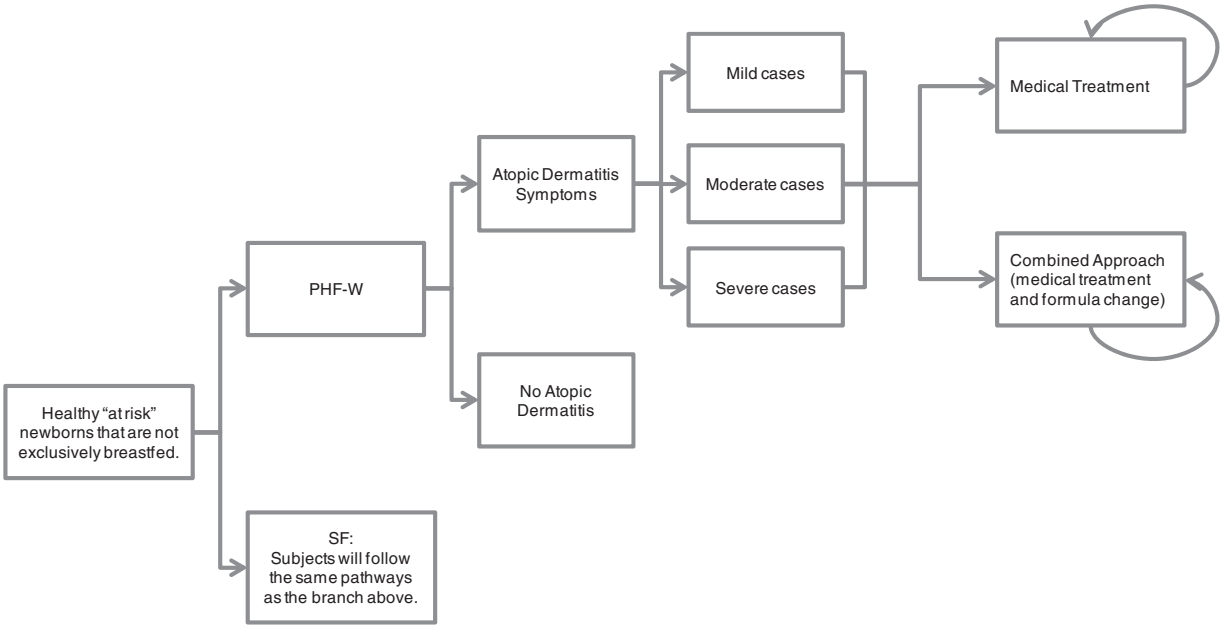

Figure 1. Illustration of decision tree model depicting the treatment patterns of atopic dermatitis in Australia in a population ranging from newborns to 3-year olds. PHF-W, Nestlé brand of 100% whey-based partially hydrolyzed formula; SF, Standard cow's milk formula.

entering the present model. Although an approximation of the rate of newborns who were 'at risk' of developing AD could be made for Europe (33%)[14,29,30], a higher rate of 50% was used in the base case analysis at the behest of the expert panel.

Subjects were assigned to one of two arms receiving either PHF-W or SF and were then divided into two groups: those subjects with AD and those subjects without AD. For those subjects who were affected by AD, a disease severity was assigned as per the expert panel.

As per expert opinion, discontinuation due to taste and/or texture was only taken into account for PHF-W and EHF-Whey, 3 days after the initial allocation of infant formula. In the case of discontinuation, it was assumed that subjects consumed a different brand of the same type of infant formula of equal cost to the brand that had initially been used.

Subjects with AD were presented with an age-specific plan to manage their AD, consisting of a medical treatment approach or an approach combining the medical treatment approach with one or more changes of infant formula. After the first 6 months, subjects with AD symptoms could only be treated with the medical treatment approach. Each approach was divided into up to four lines of treatment, characterized by a specific combination of therapies and/or formula as well as specific types of medical visits. The expert panel provided expected average response rates (defined as an improvement of AD symptoms) for each line of treatment.

Although AD does not affect mortality rates, the reality of a cohort of newborns aging to 3 years of age was modeled by taken into account the baseline mortality rates for infants born in Australia published by the ABS from 2007–2009[31].

Please refer to Tables 1 and 2 for a detailed breakdown of the epidemiological and clinical parameters applied in the present model.

Resource utilization and costs

Currently in Australia, the DHA does not cover the costs of SF or infant formulas used in prevention. In the present model, it was assumed that both SF and infant formulas used in prevention would be covered by the DHA at the same rate. Furthermore, should there be coverage for the cost of PHF-W, it would be ~75% covered by the DHA and 25% by the family, when taking into account coverage under concession and co-pays in various segments of the target population.

The price of each infant formula was obtained from a survey of pharmacies and large-scale retail outlets in Australia. The daily intake of infant formula was determined based on the instructions for the preparation of PHF-W (these instructions were similar for the other infant formulas) and by factoring in the rate of ever-breastfed Infants (i.e., infants receiving full or complimentary breast milk) derived from a report by the Australian Institute of Family Studies[28] and calculated in a manner described in a previous publication[25].

According to the expert panel, all first-line medical visits were standard consultations with a general practitioner. Subsequently, depending on the severity of the

Table 1. Epidemiological and clinical parameters applied in the model.

	Quantity applied	References
Initial cohort		
Newborns in Australia in 2009	295,700	[27]
Exclusively breastfed infants in Australia	41%	Calculation[28]
Percentage of 'at risk' newborns	50%	EO
Infants forming starting cohort	87,724	Calculation
Relative risk of developing AD (PHF-W vs SF)		
Time points		
0–6 months	0.30	Calculation[18,26]
6–12 months	0.81	Calculation[18,26]
12–18 months	0.82	Calculation[18,26]
18–24 months	0.83	Calculation[18,26]
24–30 months	0.84	Calculation[18,26]
30–36 months	1.05	Calculation[18,26]
*Incidence rates of AD**		
With SF		
0–6 months	7.73%	Calculation[18,26]
6–12 months	9.45%	Calculation[18,26]
12–18 months	2.34%	Calculation[18,26]
18–24 months	2.34%	Calculation[18,26]
24–30 months	3.51%	Calculation[18,26]
30–36 months	3.51%	Calculation[18,26]
With PHF-W		
0–6 months	2.32%	Calculation[18,26]
6–12 months	7.65%	Calculation[18,26]
12–18 months	1.92%	Calculation[18,26]
18–24 months	1.94%	Calculation[18,26]
24–30 months	2.95%	Calculation[18,26]
30–36 months	3.69%	Calculation[18,26]
Distribution of cases of AD		
Mild		
Face	15.0%	EO
Body	20.1%	EO
Face and body	24.9%	EO
Moderate		
Face	3.4%	EO
Body	11.3%	EO
Face and body	20.3%	EO
Severe		
Face	0.7%	EO
Body	1.3%	EO
Face and body	3.0%	EO
Treatment approach of infants less that 6 months old		
Medical treatment approach		
Mild	92%	EO
Moderate	52%	EO
Severe	20%	EO
Combined treatment approach		
Mild	8%	EO
Moderate	48%	EO
Severe	80%	EO
Estimated response rates to first-line treatment		
Mild		
Face	89%	EO
Body	88%	EO
Face and body	83%	EO
Moderate		
Face	66%	EO
Body	68%	EO
Face and body	64%	EO
Severe		
Face	51%	EO
Body	51%	EO
Face and body	50%	EO
Estimated response rates to second-line treatment		
Mild	100%	EO
Moderate	85%	EO
Severe	65%	EO
Estimated response rates to third-line treatment		
Mild	100%	EO
Moderate	100%	EO
Severe	98%	EO
Estimated response rates to fourth-line treatment	100%	EO
Discontinuation		
PHF-W	10%	EO
EHF-Whey	20%	EO
Mortality rate in the general Australian population		
At the end of the first year of life	0.44%	[31]

AD, Atopic dermatitis; EHF, Extensively hydrolyzed formula; EO, Expert opinion; PHF-W, Nestlé brand of 100% whey-based partially hydrolyzed formula; SF, Standard cow's milk formula.

disease and the response to the lines of treatment, subjects were to visit a pediatrician or a dermatologist. The exact breakdown of these visits is presented in Table 2, along with the costs of medical consultations, as obtained from the Medicare Benefits Schedule Book published by the Australian Government, Department of Health and Aging (AGDHA)[32]. Bulk billing for physician consultation fees was not taken into account.

According to the expert panel, subjects could be hospitalized for up to 4.5 days, depending on the severity of their disease. The cost of hospitalization was derived for subjects with mild, moderate, and severe AD, from a survey of a local hospital in Melbourne, Australia (based on personal communications with Dr Su, Royal Children's Hospital, Melbourne, Australia). These costs and utilization of these resources are presented in Table 2.

The medications and therapies used by affected subjects consisted of a combination of emollients, wet dressings, naturopathic treatments, and prescription medications (including infant formulas used as treatment, not in prevention). The breakdown and price of these resources is presented in Table 2. The cost of emollients was obtained from an online directory[33], whereas the cost of wet dressings and naturopathic treatment were derived, with the input of the expert panel, from a costing analysis published by Su *et al.*[22] in 1997. These costs (i.e., costs of emollients, wet dressing, and naturopathic treatment) were entirely assigned to the family, as is currently the case in Australia. The cost of prescription medications was obtained from the AGDHA's Pharmaceutical Benefits Scheme[34]. In Australia, the reimbursement of prescription medication costs is specific to two patient demographics: the general public or concession patients.

Table 2. Economic parameters applied in the base case analysis.

	Quantity applied	Reference	Cost per unit	Reference
Formula				
PHF-W (Nestlé – NAN HA 1 Gold®)	Varied with the age of the subject and with the rate of partial breastfeeding[b]	Calculation	AU$27.65/1000 g	c
SF (various brands)[a]			AU$24.56/1000 g	c
EHF-Whey (Cow & Gate – Pepti Junior®)				
When used for prevention			AU$31.09/1000 g	c
When used for treatment			AU$109.86/3600 g	34
Amino Acid Based Formula (Nutricia – Neocate®)			AU$361.14/3200 g	34
Medical visits				
Family physician–general consultation	Varied with the severity of AD and the line of treatment[d]	E0	AU$21.00/visit	32
Dermatologist				
Initial visit			AU$3.95/visit	32
Review			AU$42.20/visit	32
Pediatrician or Allergist				
Initial visit			AU$148.10/visit	32
Review			AU$74.10/visit	32
Long consultation			AU$259.00/visit	32
Review consultation			AU$129.65/visit	32
Hospitalization				
Mild	0%	E0	AU$884.52/hospitalization	E0
Moderate	0%	E0	AU$1943.28/hospitalization	E0
Severe	5%	E0	AU$3365.30/hospitalization	E0
Treatment				
Emollient cream – Dermeze Ointment®	1500 g per 6-month period	E0	AU$12.25/500 g tube	33
Topical corticosteroids	Varied with the severity of AD and the line of treatment[d]	E0		
Hydrocortisone acetate (Cortic-DS Cream® 1%)			AU$14.02/30 g tube	34
Betamethasone dipropionate (Diprosone Cream® 0.05%)			AU$20.72/15 g tube	34
Betamethasone valerate (Celestone-M Ointment® 0.02%)			AU$31.81/100 g tube	34
Methylprednisolone aceponate (Advantan Ointment® 0.1%)			AU$19.11/15 g tube	34
Cephalexin (Ibilex Capsule®)			AU$13.85/20 capsules	34
Immunosuppressants				
Pimecrolimus (Elidel® 1%)			AU$35.40/15 g tube	34
Naturopathy				
Mild	Once in 28% of cases	E0[22]	AU$50.00/6 months	E0[22]
Moderate	Once in 20% of cases	E0[22]	AU$50.00/6 months	E0[22]
Severe	Once in 40% of cases	E0[22]	AU$150.00/6 months	E0[22]
Dressings				
Mild	Once in 10% of cases	E0[22]	AU$50.00/6 months	E0[22]
Moderate	Once in 100% of cases	E0[22]	AU$100.00/6 months	E0[22]
Severe	Once in 100% of cases	E0[22]	AU$150.00/6 months	E0[22]
Laboratory tests				
Prick Test	Once in 70% of moderate or severe cases of AD	E0	AU$38.20/test	32
Nasal swabs	Once in 5% of moderate or severe cases of AD	E0	AU$22.15/test	32
Skin swabs	Once in 5% of moderate or severe cases of AD	E0	AU$34.00/test	32
Specific IgE Test	Once in 20% of severe cases of AD	E0	AU$27.00/test	32
Skin Patch Test	Once in 5% of severe cases of AD	E0	AU$61.30/test	32
DHA reimbursement rates				
Infant formulas for prevention	75%	See text		
Infant formulas for treatment	Varies according to the formula and concession	34		
Prescribed medication	Varies according to the medication and concession	34		
Emollients	0%	E0		
Medical visits with a family physician	100%	32		
Medical visits with a specialist	85%	32		
Laboratory testing	85%	32		
Naturopathy	0%	E0		
Dressings	0%	E0		

(*continued*)

Table 2. Continued.

	Quantity applied	Reference	Cost per unit	Reference
Participation in the workforce in Australia	65.6%	[38]		
Time loss				
Physician visits and laboratory testing	4 hours for each visit	Assumption	AU$26.21/hour	[39,40]
Child care for 2 days after the initial medical visit	8 hours per day	Assumption	AU$26.21/hour	[39,40]
Application of emollient cream	20 minutes daily over the application period	Assumption	AU$26.21/hour	[39,40]
Application of topical medications (corticosteroids and immunosuppressants)	10 minutes daily over the application period	Assumption	AU$26.21/hour	[39,40]
Hospitalization	1 day, 3.5 days and 4.5 days for mild, moderate and severe AD, respectively, at 6.9 hours per day	EO[39]	AU$26.21/hour	[39,40]
Travel	Travel to and from physician visits or laboratory testing (10 km each way)	Assumption	AU$25.55/two-way trip	[41–44]

[a]The cost of SF was determined based on the average cost of the four main brands of SF in Australia: Nan 1 Pro 1 Gold (Nestlé, Switzerland), Heinz Nurture Gold Infant Formula (H. J. Heinz Company, Australia), Karicare Gold Plus 1 Starter (Nutricia, The Netherlands), andS-26 Gold Infant Formula (Pfizer, USA).
[b]An average quantity of infant formula was calculated based on product packaging, for 6 months of infant formula consumption, with infants being either fully or partially formula-fed. The full breakdown of the daily quantity of formula consumed over 6 months is available upon request.
[c]Based on a survey of costs in large-scale retailers and pharmacies.
[d]Exact breakdown of medical visits and medication use, per disease severity and line of treatment, is available upon request.
AD, Atopic dermatitis; EHF, Extensively hydrolyzed formula; EO, Expert opinion; PHF-W, Nestlé brand of 100% whey-based partially hydrolyzed formula; SF, Standard cow's milk formula.

For the general public, the cost of prescription medication includes the cost of the medication itself, mark-up, and dispensing fees as well as, in some instances, Pharmaceutical Benefit Scheme Safety Net recording fees and allowable extra fees[34,35]. The family of the patient is responsible for all prescription medication costs under AU$35.40, with the DHA covering any costs over that threshold[34]. This is also true of families with concession cards, except that the maximum amount payable by the family per prescription is AU$5.80[34]. Barozzi *et al.*[36] reported that 24% of the Australian population were included in the concession scheme. However, given that an important proportion of this population is elderly[37], it was assumed, in the present analysis, that the proportion of patients on concession, rather than in the general public, was 20%.

According to the expert panel, subjects with mild AD were not administered any diagnostic tests, while those with moderate or severe AD would be administered the specific IgE test, the prick test, the patch test, and/or skin or nasal swabs. The costs and reimbursement rates for these laboratory tests were obtained from AGDHA's Medicare Benefits Schedule Book[32].

From the family and societal perspectives, indirect costs due to leisure time loss and/or productivity loss were included in the model. These indirect costs were determined by taking into account the population rate of participation in the workforce in Australia in 2011[38], as well as the average gross hourly wage and daily hours of work for each economic activity in Australia[39,40]. As per expert opinion, it was also assumed that 4 hours were required for physician visits and for laboratory testing (including travel to and from the medical office), that 2 full days were needed for childcare after the initial medical visit, and 10 minutes were required for each application of emollients or topical prescription medications.

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), taxi, and operating a personal car (using the per-kilometer rate for the taxis excluding the flag fall as well as the booking and time fees) in Melbourne and Sydney[41–44].

Discounting

All costs beyond 1 year were discounted at 5%, but outcomes were defined with or without such discounting as per the national guidelines defined by the AGDHA[45].

Comparisons to EHF-whey

Although not indicated for prevention, some physicians choose to recommend EHF-Whey in the prevention of AD symptoms. This scenario was explored in a secondary analysis where, based on the reported non-significant difference between the RR of PHF-W vs EHF-Whey[18], the same efficacy was applied to both formula preparations, amounting to a cost-minimization exercise based on the difference in the acquisition cost of the formulas. In this secondary analysis, the same pattern was applied for

Table 3. Parameter estimates and distributions for variables tested in the Monte Carlo sensitivity analysis.

Parameter	Distribution type	Selected range or [alpha, beta]
DHA milk program coverage for prevention	Uniform	23.21–100%
Daily quantity consumed by partially formula-fed infants	Uniform	Increased and decrease BC by 25%
Alternative to PHF-W in case of discontinuation	Uniform	PHF-W 50–100%, SF and EHF 0–25%
Relative risk	Log Normal	95%CI
Incidence rates consideration	Triangular	Most likely = BC,minimum and maximum = 95%CI
Rounding down or up the number of cans used	Discrete Uniform	Round down or up
Number of physician visits per year	Discrete Uniform	1–3 visits for mild cases, 2–5 visits for moderate cases, and 7–10 visits for severe cases
Laboratory tests from the diagnostic approach	Beta	[0.65, 3.06]
Transportation costs	Gamma	[1, 25.54]
Cost of time lost	Gamma	[1, 26.21]
Days lost due to child at home	Discrete Uniform	1 or 2 days
Percentage of hospitalization	Beta	[0.7, 3.97]
Cost of dressings		
Mild	Gamma	[1, 50]
Moderate	Gamma	[1, 100]
Severe	Gamma	[1, 150]
Cost of naturopathy		
Mild	Gamma	[1, 50]
Moderate	Gamma	[1, 50]
Severe	Gamma	[1, 150]
Concession rate	Beta	[12.6, 50.4]
Time horizon	Discrete Uniform	6 months, 1 year, 3 years
Discounting of outcomes beyond 1 year	Discrete Uniform	Include or exclude

*A uniform distribution was applied when only two data points were available with an assumed equal likelihood for all points in between, while a discrete uniform distribution was applied when only two or three specific data points were considered likely. A triangular distribution was used when determining whether to use the base case incidence rates or the upper or lower bound of the 95% confidence interval. As these data points were not distributed normally, a triangular distribution, which appeared to best fit the data set, was applied. As argued by Briggs *et al.*[47], a log normal distribution was applied to the relative risk of developing AD as well as a gamma distribution for costs and a beta distribution for probabilities.

BC, Base case; CI, Confidence interval; DHA, Department of Health and Aging; EHF, Extensively hydrolyzed formula; PHF-W, Nestlé brand of 100% whey-based partially hydrolyzed formula; SF, Standard cow's milk formula.

the combined management of AD with PHF-W, while subjects consuming EHF-Whey were immediately assigned AAF.

Variability and uncertainty

One-way SAs were carried out to test the robustness of the model by varying numerous parameters such as time horizon, reimbursement rates, resource utilization, as well as direct and indirect costs. Furthermore, using a set of 10,000 Monte Carlo simulations, probabilistic SAs were performed by simultaneously varying multiple parameter values according to pre-defined ranges and types of distribution (presented in Table 3).

Results

Base-case analysis

For a birth cohort of 295,700 newborns in Australia in 2009, the starting cohort entering the model had 87,724 'at risk' newborns, assumed to be taking either PHF-W or SF.

Table 4 presents the results of the base case analysis from the three perspectives (DHA, family, and society) when comparing subjects who consumed PHF-W to those who consumed SF. From the DHA, the highest cost was attributable to formula, while the cost of time lost was the main cost driver from the perspective of the subject's family. The expected incremental costs per avoided case of AD (i.e., the expected ICERs) were AU$496 from the perspective of the DHA and savings of AU$1739 and AU$1243 from the family and societal perspectives, respectively.

PHF-W vs EHF analysis

PHF-W was dominant over EHF-Whey in the scenario where the latter was used in the prevention of AD symptoms given the assumption that both formulae are equally effective in the prevention of AD. The savings for the cohort with the use of PHF-W over EHF-Whey would amount to AU$6,736,513 from the societal perspective, including savings of AU$5,183,474 from the perspective of the DHA.

One-way sensitivity analyses

Table 5 presents the results of the one-way SAs which were undertaken to evaluate the effect of key parameters on the outcomes of the economic model. The greatest variation

Table 4. Base case results presented from the perspective of the Department of Health and Aging, of the family of the subject, and of society as a whole.

	PHF-W	SF
Outcomes		
Number of cases	8750	15,073
Incremental cases	−6323	
Costs		
DHA perspective		
Cost of formula	AU$38,309,440	AU$34,362,838
Physician cost	AU$907,972	AU$1,580,582
Medication cost	AU$20,938	AU$36,068
Cost of lab test	AU$99,028	AU$170,589
Hospitalization cost	AU$73,614	AU$126,810
Total cost	AU$39,410,993	AU$36,276,887
Incremental cCost		AU$3,134,105
ICER		AU$496
Family perspective		
Cost of formula	AU$12,739,054	AU$11,351,747
Physician cost	AU$141,584	AU$246,806
Medication cost	AU$224,378	AU$386,519
Emollients costs	AU$321,556	AU$553,922
Cost of lab test	AU$17,476	AU$30,104
Dressing cost	AU$398,117	AU$685,808
Naturopathy cost	AU$159,971	AU$324,185
Cost of time lost	AU$14,812,744	AU$25,727,595
Travel cost	AU$625,003	AU$1,127,978
Total cost	AU$29,439,883	AU$40,434,664
Incremental cost		−AU$10,994,781
ICER*		−AU$1,739
Societal perspective		
Total cost	AU$68,850,876	AU$76,711,552
Incremental cost		−AU$7,860,676
ICER*		−AU$1,243

*Negative ICERs are indicative of cost savings due to the prevention of AD cases with PHF-W vs SF, hence, dominance of PHF-W over SF.
DHA, Department of Health and Aging; ICER, Incremental cost-effectiveness ratio; PHF-W, Nestlé brand of 100% whey-based partially hydrolyzed formula; SF, Standard cow's milk formula.

from the base case ICERs of the DHA and societal perspectives was observed when applying the upper bound of the 95% CI of the RR of developing AD. In that SA, the advantage of PHF-W over SF in prevention was greatly diminished, hence presenting a 'worst case' scenario for PHF-W. From the perspective of the family of the subject, the greatest variation from the base case ICER was noted in the SA wherein the DHA did not cover the cost of infant formulae, thus shifting this cost driver over to the family.

In the one-way SA where PHF-W was introduced into a new program where there was no formula previously covered for prevention of AD under the DHA (i.e., SF was not covered), the ICER associated with the societal perspective remained unchanged (savings of AU$1243) as cost of formula was shifted from the DHA to the family perspective. Furthermore, from the DHA perspective, the ICERs were higher than the base case when the DHA paid 100%, 75%, or 25% of PHF-W costs AU$7803, AU$5797, and AU$1784, respectively), but similar to the base case when the DHA covered the difference of PHF-W and SF costs (AU$674) and when the DHA paid 10% of PHF-W costs (AU$580). A cost-neutral ICER was observed when the DHA paid for 2.77% of PHF-W costs.

Probabilistic sensitivity analyses

Presented in Figure 2 are the results of the probabilistic SAs from all three analytical perspectives. The expected average Monte Carlo ICERs were AU$330 and savings of AU$1715 and AU$1385 from the DHA, family, and societal perspectives, respectively, with a 91.7%, 27.3%, and 37.8% probability for Monte Carlo results to fall below a line linking the base case ICERs to the origin.

Discussion

This is the first published study pertaining to the cost-effectiveness of PHF-W in the prevention of AD in 'at risk' children in Australia. Based on a series of inputs and assumptions provided and/or verified by a panel of experts in Australia, PHF-W appears to be dominant when compared to SF in the prevention of AD among 'at risk' infants who are not exclusively breastfed from the perspectives of the family or society as a whole and dominant from the DHA perspective. This was confirmed in an SA based on another meta-analysis pertaining to infant formula and AD prophylaxis[12], indicating that the two most recently-published meta-analyses yielded congruent results. Similar findings have been observed in previously-published analyses undertaken in other settings[23–25].

The main cost drivers were the cost of infant formula from the DHA perspective and the cost of productivity or leisure time lost due to child care from the perspective of the family of the affected child. The present study adopted a conservative approach by limiting the disease of interest to AD, rather than broader allergic manifestations, and by not taking into account other significant outcomes of AD such as pain and suffering, given that they would be difficult to evaluate and monetize in the population of interest.

A secondary analysis exploring a scenario wherein EHF-Whey would be used in prevention yielded important cost savings with PHF-W, hence suggesting that this use of EHF-Whey would be incongruous, especially in view of the greater rates of non-compliance due to taste or texture associated with EHF-Whey.

Limitations

This analysis, based on a predictive model, is based on a certain number of assumptions and may involve a certain

Table 5. Results of the one-way sensitivity analyses presented from the perspective of the Ministry of Health, of the family of the subject, and of society as a whole.

	Outcomes		Costs in AU4								
	Cases		Ministry of Health			Subject's family			Society		
	PHF-W	SF	PHF-W	SF	ICER	PHF-W	SF	ICER	PHF-W	SF	ICER
Base case	8750	15,073	39,410,993	36,276,887	496	29,439,883	40,434,664	−1739	68,850,876	76,711,552	−1243
Sensitivity analyses											
DHA covered 100% of infant formula program for prevention	8750	15,073	52,096,173	47,449,057	735	16,754,702	29,262,495	−1978	68,850,876	76,711,552	−1243
DHA covered 85% of infant formula program for prevention	8750	15,073	44,485,065	40,745,755	591	24,365,811	35,965,796	−1835	68,850,876	76,711,552	−1243
DHA covered 65% of infant formula program for prevention	8750	15,073	34,336,921	31,808,020	400	34,513,955	44,903,532	−1643	68,850,876	76,711,552	−1243
DHA covered 50% of infant formula program for prevention	8750	15,073	26,725,812	25,104,718	256	42,125,063	51,606,834	−1500	68,850,876	76,711,552	−1243
Threshold analysis: Cost neutral for DHA when covering 23% of infant formula program for prevention	8750	15,073	13,134,452	13,134,452	0	55,716,424	63,577,100	−1243	68,850,876	76,711,552	−1243
Quantity consumed by partially formula fed infants is increased by absolute 25% in the first 3 months	8750	15,073	39,603,678	36,308,869	521	29,504,111	40,445,325	−1730	69,107,790	76,754,194	−1209
Quantity consumed by partially formula fed infants is decreased by absolute 25% in the first 3 months	8750	15,073	37,784,824	34,693,047	489	28,897,826	39,906,717	−1741	66,682,650	74,599,764	−1252
Increased the cost of SF by 10%	8750	15,073	39,410,993	39,628,538	−34	29,439,883	41,551,881	−1916	68,850,876	81,180,419	−1950
Decreased the cost of SF by 10%	8750	15,073	39,410,993	32,925,237	1026	29,439,883	39,317,447	−1562	68,850,876	72,242,684	−536
Discontinuation of PHF-W—change to SF	9382	15,073	38,951,079	36,276,887	470	30,490,526	40,434,664	−1747	69,441,606	76,711,552	−1278
Discontinuation of PHF-W—change to EHF	8700	15,073	39,857,284	36,276,887	562	29,496,366	40,434,664	−1717	69,353,651	76,711,552	−1155
Hypothetical patients 'at risk' was 33%	5833	10,048	26,273,995	24,184,592	496	19,626,588	26,956,443	1739	45,900,584	51,141,034	−1243
Hypothetical patients 'at risk' was 20%	3500	6029	15,764,397	14,510,755	496	11,775,953	16,173,866	−1739	27,540,350	30,684,621	−1243
The lower bound CI of the relative risk was used	4824	15,073	38,855,302	36,276,887	252	21,925,576	40,434,664	−1806	60,780,877	76,711,552	−1554
The upper bound CI of the relative risk was used	15,675	15,073	40,423,194	36,276,887	−6886	42,745,774	40,434,664	−3838	83,168,969	76,711,552	−10,724
The lower bound CI of incident rates was used	6199	10,679	39,056,835	35,593,489	773	24,569,937	31,945,756	−1646	63,626,772	67,539,244	−873
The upper bound CI of incident rates was used	11,922	20,538	39,851,534	37,126,975	316	35,497,665	50,994,117	−1799	75,349,199	88,121,092	−1482
The rounded down number of cans was taken	8750	15,073	37,592,138	34,661,065	464	28,833,598	39,896,057	−1750	66,425,736	74,557,122	−1286

(*continued*)

Table 5. Continued.

	Outcomes		Costs in AU4								
	Cases		Ministry of Health			Subject's family			Society		
	PHF-W	SF	PHF-W	SF	ICER	PHF-W	SF	ICER	PHF-W	SF	ICER
Used the relative risks reported in another meta-analysis[19]	7672	15,073	39,321,935	36,276,887	411	27,480,686	40,434,664	−1750	66,802,621	76,711,552	−1339
First referral was made to a pediatricians only	8750	15,073	39,446,193	36,337,524	492	29,447,626	40,448,002	−1740	68,893,818	76,785,526	−1248
Severe patients will make two subsequent visits to a dermatologist	8750	15,073	39,392,161	36,244,448	498	29,368,113	40,311,032	−1731	68,760,275	76,555,480	−1233
Concession rate is 25%	8750	15,073	39,418,932	36,294,920	494	29,428,211	40,410,201	−1737	68,847,143	76,705,121	−1243
Concession rate is 15%	8750	15,073	39,403,054	36,258,855	497	29,451,555	40,459,127	−1741	68,854,609	76,717,982	−1244
Concession rate is 0%	8750	15,073	39,379,237	36,204,758	502	29,486,571	40,532,516	−1747	68,865,808	76,737,274	−1245
Concession rate is 100%	8750	15,073	39,538,017	36,565,405	470	29,253,130	40,043,256	−1707	68,791,147	76,608,661	−1236
Excluded hospitalization	8750	15,073	39,337,378	36,150,077	504	29,419,569	40,399,671	−1737	68,756,947	76,549,748	−1232
Changed hospitalization to 5% of mild, 15% of moderate, and 30% of severe referred cases*	8750	15,073	42,091,055	40,893,639	189	30,333,174	41,973,474	−1841	72,424,230	82,867,113	−1652
Excluded cost of dressing	8750	15,073	39,410,993	36,276,887	496	27,459,368	37,022,973	−1513	66,870,361	73,299,861	−1017
Excluded cost of naturopathy	8750	15,073	39,410,993	36,276,887	496	28,558,138	38,647,789	−1596	67,969,131	74,924,677	−1100
Excluded cost of laboratory testing	8750	15,073	39,311,965	36,106,298	507	29,102,992	39,854,326	−1700	68,414,956	75,960,624	−1193
Excluded transportation costs	8750	15,073	39,410,993	36,276,887	496	28,814,880	39,306,686	−1659	68,225,873	75,583,573	−1164
Excluded the cost of time lost for the application of emollients	8750	15,073	39,410,993	36,276,887	496	22,459,560	28,410,163	−941	61,870,553	64,687,050	−445
Excluded the cost of time lost for the application of corticosteroids	8750	15,073	39,410,993	36,276,887	496	28,927,799	39,552,534	−1680	68,338,791	75,829,421	−1185
Medical visits and laboratory tests were aligned	8750	15,073	39,410,993	36,276,887	496	29,120,467	39,884,430	−1702	68,531,460	76,161,317	−1207
Cost of leisure time lost was not taken into account	8750	15,073	39,410,993	36,276,887	496	24,344,299	31,584,371	−1145	63,755,291	67,861,259	−649
No day lost due to child care at home	8750	15,073	39,410,993	36,276,887	496	26,275,394	34,983,426	−1377	65,686,387	71,260,314	−882
Time Horizon—6 months	2035	6782	38,563,222	35,208,779	707	16,577,497	24,146,558	−1594	55,140,719	59,355,337	−888
Time Horizon—3 years, discounted at 5%	17,224	24,531	40,535,599	37,537,979	410	46,588,898	59,694,221	−1793	87,124,497	97,232,200	−1383
Time Horizon—3 years, only costs discounted at 5%	17,924	25,296	40,535,599	37,537,979	407	46,588,898	59,694,221	−1778	87,124,497	97,232,200	−1371

*These referral rates were suggested for sensitivity analysis by the expert panel.

CI, Confidence interval; DHA, Department of Health and Aging; EHF, Extensively hydrolyzed formula; ICER, Incremental cost-effectiveness ratio; PHF-W, Nestlé brand of 100% whey-based partially hydrolyzed formula; SF, Standard cow's milk formula.

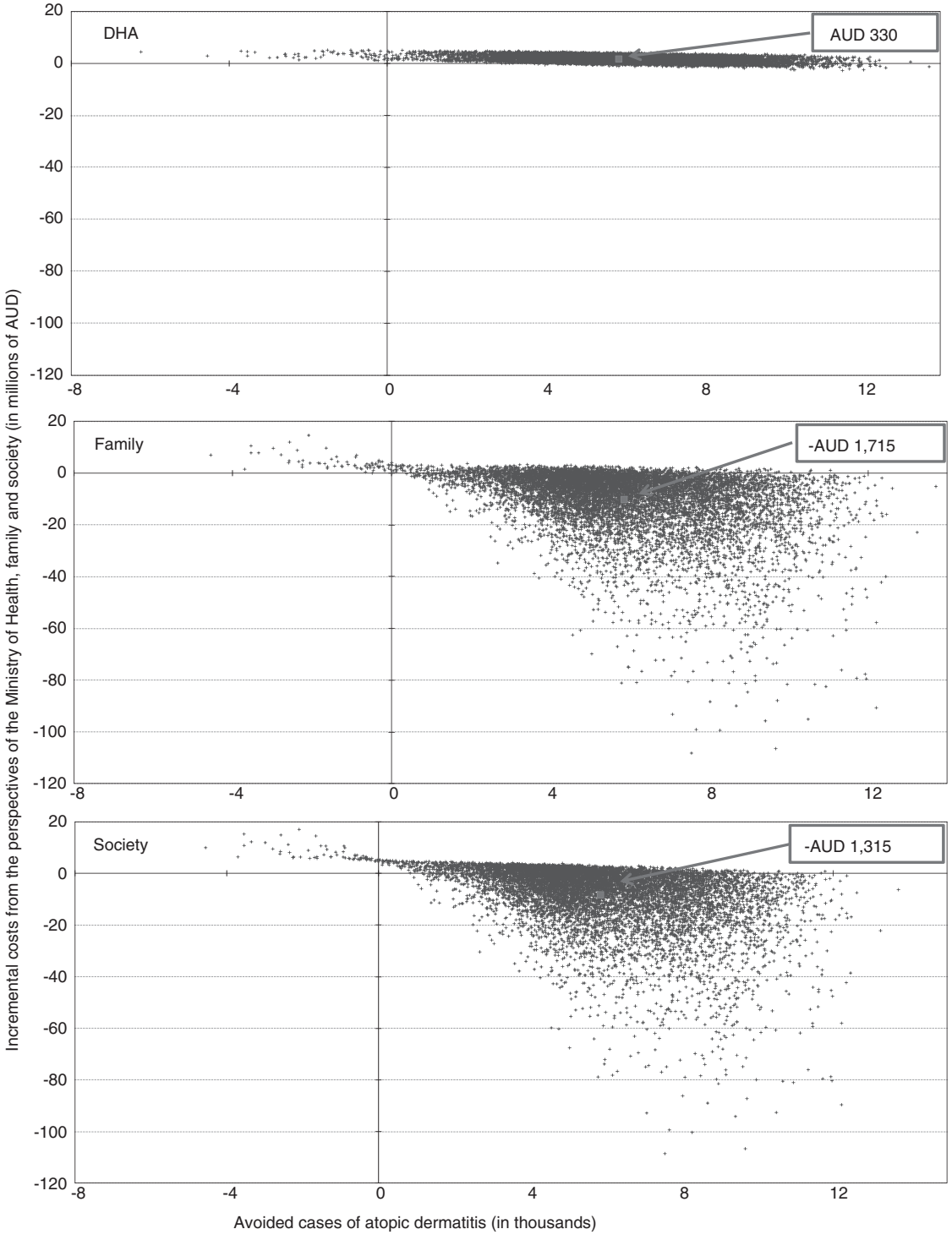

Figure 2. Results of the Monte Carlo simulations from the DHA, family and societal perspectives. The ICERs presented in boxes above were obtained by dividing the average incremental costs by the average avoided cases of AD which were generated from the 10,000 Monte Carlo simulations. The base case incremental cost-effectiveness ratios were AU$496, −AU$1739, and −AU$1243 from the DHA, family, and societal perspectives, respectively. By accounting for the incremental costs and outcomes of each simulation, median ICERS of AU$328, −AU$1146, and −AU$761 were generated from the DHA, family, and societal perspectives, respectively. Quadrant 1 is associated with potential cost-effectiveness of PHF-W as it displays positive incremental costs and avoided cases (probabilities of 92.6%, 9.6%, and 24.2% from the DHA, family, and societal perspectives). Quadrant 2 represents dominance by SF, as incremental costs for PHF-W vs SF are positive while avoided cases are negative (probabilities of 0.7% from all three perspectives). Quadrant 3 represents the unlikely scenario where incremental costs are negative but so are avoided cases (no probability from any perspective). Quadrant 4 denotes dominance by PHF-W over SF as incremental costs and avoided cases are both negative (probabilities of 6.7%, 89.7%, and 75.1% from the DHA, family, and societal perspectives). DHA, Department of Health and Aging; ICER, Incremental cost-effectiveness ratio.

amount of bias, as any predictive model would. However, the base case analysis was performed, whenever feasible, by applying a conservative approach which would direct the bias against PHF-W rather than its comparators. Furthermore, the assumptions and inputs of the present model were overseen by a panel of experts wholly familiar with the management of AD in the population of interest in Australia. All assumptions were verified in one-way and probabilistic SAs, which confirmed the robustness of the model.

In the secondary analysis comparing PHF-W to EHF-Whey, it was assumed, as per the findings of a recent meta-analysis[18], that both of those infant formulas had the same efficacy. According to the findings of another meta-analysis which reported no significant difference in the preventive efficacy of EHF-Whey vs SF[46], the approach adopted in the present secondary analysis may have overestimated the preventive efficacy of EHF-Whey and, in turn, introduced a bias against PHF-W.

The present analysis was targeted to a specific brand of partially hydrolyzed formula, to a specific population and to a specific setting. As a consequence, the generalizability and transferability of results to another setting, population, or brand of infant formula should be made with caution, especially that the clinical outcomes applied in the present analysis were based on evidence from meta-analyses directed to the specific brand of partially hydrolyzed formula of interest in the present study (PHF-W).

Conclusions

PHF-W appears to be cost-effective when compared to SF for the prevention of AD symptoms in 'at risk' infants and very young children who are not exclusively breastfed, when analysed from the perspective of the DHA in Australia, and dominant over SF from the perspectives of the family or of society as a whole. PHF-W also yielded cost savings in comparison to EHF-Whey when the latter was used for the prevention, rather than treatment, of AD.

Transparency

Declaration of funding
This study was funded by Nestlé Nutrition Institute (NNI).

Declaration of financial/other relationships
MI is the president of PharmIdeas, which performed this study under contract with NNI; JS is employed by NNI; JS, SP, MT, PS, RH, and JS have received honoraria for their participation.

The peer reviewers on this manuscript have disclosed that they have no relevant financial relationships.

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Notice of Correction

The version of this article published online ahead of print on 19 September 2012 contained an error on the second page. There was an error in the wording of the Introduction which has been corrected for this version.