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

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**Record Status**
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

**CRD summary**
The study investigated the cost-effectiveness of a prebiotic infant formulation (IMMUNOFORTIS®) versus a placebo formulation with no prebiotics for healthy infants at risk of atopic dermatitis in The Netherlands. The authors’ concluded that a prebiotic infant formulation was a highly cost-effective strategy in the prevention of atopic dermatitis. The methods, analyses and results were adequate, but the validity of the clinical estimates for effectiveness was unclear, so it is difficult to assess whether the authors’ conclusions are reasonable.

**Type of economic evaluation**
Cost-utility analysis

**Study objective**
The study examined the cost-effectiveness of prebiotic use for the primary prevention of atopic dermatitis in a hypothetical cohort of healthy-term infants of parents with a history of atopy, allergic rhinitis, or asthma in The Netherlands.

**Interventions**
A prebiotic-supplemented infant formulation was compared with a placebo formulation (which included no prebiotics). The prebiotic-supplemented formulation was based on a mixture of 8g/L neutral short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides (IMMUNOFORTIS®). The placebo formula was an 8g/L maltodextrin mixture based on hydrolysed protein. These formulations were administered for the first six months of life.

**Location/setting**
The Netherlands/primary care.

**Methods**

**Analytical approach:**
A Markov model was used to synthesise evidence from published studies, clinical trials and national population statistics, but was predominately based on one key trial (Moro G, et al. 2006 and Arslanoglu S, et al. 2008, see ‘Other Publications of Related Interest’ below for bibliographic details). The time horizon was 16 years. The authors’ stated the study was from a health insurance perspective.

**Effectiveness data:**
The key clinical outcomes were incidence of allergic manifestations (such as atopic dermatitis, wheezing, allergic urticarial), number of infectious episodes, and growth. The key trial was a randomised, double-blind, placebo controlled design with a six-month intervention period and up to a two-year blinded follow-up period (see Moro G, et al. 2006 and Arslanoglu S, et al. 2008). Probabilities for asthma and atopic dermatitis were also extracted from relevant published studies. The model used the reduction in cumulative incidence rates of atopic dermatitis from the trial to calculate the long-term quality-adjusted life-years (QALYs).

**Monetary benefit and utility valuations:**
Utility estimates came from adults with atopic dermatitis using the European Quality of life questionnaire (EQ-5D) in a published study (Poole D, et al. 2004, see ‘Other Publications of Related Interest’ below for bibliographic details). Decrement for mild, moderate and severe atopic dermatitis were applied. Utilities for asthma were from a study that involved children with respiratory infections using the Health Utility Index (HUI) (Greenough A, et al. 2004, see ‘Other
Measure of benefit:
QALYs were the summary measure of benefit and were discounted annually at 1.5%.

Cost data:
Direct medical costs included prebiotic and placebo formulations (based on consumption in the key trial), medical consultations (general practitioners and specialists), treatment costs of atopic dermatitis, asthma and other long-term sequelae and morbidity. Formulation costs were based on average consumer prices in The Netherlands, Italy and Germany. Treatment costs of atopic dermatitis were extracted from a relevant publication (Su JC, et al. 1997, see ‘Other Publications of Related Interest’ below for bibliographic details). Asthma health care use was taken from a published study. All costs were presented in 2009 Euros (EUR), inflated where necessary, and discounted annually at 4%.

Analysis of uncertainty:
One-way sensitivity analyses were performed on key parameters (such as discount rate, reduction in atopic dermatitis, specialist costs, prebiotic duration, utilities, and the inclusion of other clinical events). Justification for the values used were reported with the results and a table.

Results
The mean cost for the prebiotic formulation was EUR 622 compared with EUR 571 for the placebo formulation, an additional cost of EUR 51 per infant for prebiotics. The mean QALYs were 14.108 for the prebiotic formulation compared with 14.000 for the placebo formulation, an incremental gain of 0.108 QALYs for prebiotics. The incremental cost per QALY gained was EUR 472.

The sensitivity analyses showed that the base case findings were most sensitive to changes in the odds ratio for atopic dermatitis incidence (incremental cost-effectiveness ratio of EUR 325) and applying no utility loss for atopic dermatitis (utility=1.0, incremental cost-effectiveness ratio = EUR 615). Changes to other variables produced incremental cost-effectiveness ratios within this range. Including the costs of treatment for other clinical events produced cost savings with the same increase in QALYs (0.108) as the base case.

Authors’ conclusions
The study showed that infant formulation with a prebiotic mixture was a highly cost-effective strategy in the prevention of atopic dermatitis.

CRD commentary
Interventions:
The health issue, rationale and prebiotic mixture were well-described. Approval for prebiotic infant formulation use in different settings would need to be assessed, along with relative prices.

Effectiveness/benefits:
The clinical effectiveness of the agents was based on one pivotal study that was not discussed in detail in the report. It was unclear if there were any adverse events in infants who used prebiotic formulation. Sufficient justification was provided to support the values used in the model, but it was unclear whether the efficacy of the prebiotic formulation continued to be applied beyond the trial period and, if so, whether this was reasonable. Study validity and adverse event profiles would require reference to the original studies. The utility values were measured using a validated multi-attribute utility instrument on adults for atopic dermatitis in the absence of available measures for children.

Costs:
The resource use types and unit costs were clearly presented. The measurement of these resources appeared reasonable, although some of the costing included information from other countries (such as the cost of prebiotics) which might introduce some uncertainty. Costs for treatments and physician visits were appropriately based on published sources. The price year, currency, adjustments for inflation and discount rates used were reported.

Analysis and results:
The authors did not discuss whether their model underwent any validation processes. Sensitivity analyses were limited; the use of a probabilistic sensitivity analysis would have been a better way to evaluate overall model uncertainty. The authors acknowledged limitations in their study including the necessary use of a combination of data sources and the use of clinical trial data that may not reflect real-life clinical practice. The authors discussed the likely indirect costs to families as a result of caring for a child with atopic dermatitis including sleep deprivation, lost employment opportunities, working days lost, transportation, and out-of-pocket costs for dressings, special diets and medications.

Concluding remarks:
The methods, analyses and results were adequate, but the validity of the clinical data estimates for effectiveness was unclear. Therefore, it is difficult to assess whether the authors’ conclusions are reasonable.

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