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Cost-effectiveness analysis, prevention of atopic dermatitis by oral application of bacterial lysate in newborns/small children

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Abstract

Objectives The aim of this analysis was to determine the cost-effectiveness compared to placebo of prophylactic treatment with sterile bacterial lysate (*Escherichia coli* and *Enterococcus faecalis*) (verum) of newborns/small children with heredity for atopy [atopic dermatitis (AD)]. Infants were followed from the age of 5 weeks until 3 years of age. During this time, the number of children with AD who were treated with verum or placebo was observed at eight visits. Cost-effectiveness analyses were performed at different time points.

Methods A randomized, double-blind placebo-controlled clinical trial performed in Germany included 606 newborns. After randomization, $n = 303$ patients were classified in the placebo group and $n = 303$ in the verum group. A total of 119 participants left the study, so data from $n = 250$ patients of the placebo group and $n = 237$ patients of the verum group were available for analysis. At the beginning of the study, newborns were treated prophylactically with bacterial lysate or placebo for 26 weeks. After this, children were observed until the age of 3 years. A systematic literature research was done to evaluate treatment costs of atopic eczema in newborn/small children. Finally, 17 publications were included and checked for searched treatment costs of AD. A study was then initiated to evaluate the direct costs to statutory health insurance. Based on the described clinical trial, a decision tree model was developed. Using the evaluated direct costs and prevalence according to the clinical trial, the developed model can be used in cost-effectiveness analyses.

Results The focus of the analyses was on the subgroup “single heredity for atopy” in clinical trials. Cost-effectiveness analysis showed an advantage for bacterial lysate after 3 years. To further support this result a model extension was executed; the model was expanded from 3 to 6 years. Cost-effectiveness of bacterial lysate was also proven after 6 years.

Conclusion Prophylactic treatment with bacterial lysate of infants with single heredity for atopy for 26 weeks in the 1st year of life is cost-effective at the age of 3 and 6 years, i.e. prophylactic use of bacterial lysate generated lower costs by leading to lower prevalence compared to placebo.

Keywords Cost-effectiveness · Atopic dermatitis · Newborns · Small children · Prophylactic treatment · *Escherichia coli* · *Enterococcus faecalis* · Sterile bacterial lysate · Model · Decision tree

JEL Classification I10

Introduction

Atopic dermatitis (AD) is an inflammatory, chronically relapsing, non-contagious and pruritic skin disorder [1]. In Germany, AD is the most common skin disease in children, with a prevalence of 10–20 % [2–4]. Approximately 3.2 million people are adversely affected by AD in Germany [5]. Recent years have seen a prominent and significant increase in the incidence of AD [6–8]. Genetic factors, psychosocial influences, increasing allergen exposure in the domestic environment, reduced stimulation of the immune system and greater environmental pollution are all discussed as causes for the rising prevalence of AD. However, no definitive explanation for increasing number

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of cases of AD is available [9]. According to epidemiological studies, 10–32 % of children with AD continue to be affected beyond adolescence [10, 11]. Permanent itching, obvious skin lesions and the necessity for long-term therapy lead to emotional stress, fatigue and social isolation. The quality of life of AD-patient's is significantly restricted [12]. Moreover, treatment of AD incurs costs for both patients and the state. In Germany, the estimated total healthcare cost of AD is €1.5–3.5 billion [5, 13, 14].

Given this background, the avoidance of AD is becoming an increasingly important issue. A randomized, double-blind placebo-controlled trial has shown that the prophylactic use of bacterial lysate in newborns is able to reduce AD in infants and small children depending on their heredity for atopy [15]. In the present trial, 606 newborns with at least single heredity for atopy were enrolled. Infants were treated with bacterial lysate or placebo from week 5 until the end of month 7. Children were followed until 3 years of age. The primary outcome was prevalence of atopic eczema under either bacterial lysate treatment or placebo at the end of the prophylactic period at 7 months of age.

To analyse the cost-effectiveness of the prophylactic use of bacterial lysate compared to placebo, a cost-effectiveness analysis based on a decision tree model was performed. The above-mentioned clinical trial and its results formed the basis of the model and the analysis. First, cost-effectiveness was calculated for the end of the prophylactic period (at the end of month 7) and for the end of the study (after 3 years). In a second step, the time horizon of the model was extended to 6 years and cost-effectiveness was computed again.

Materials and methods

Prophylaxis of atopic and allergic manifestations and activation or modulation of the immune system by bacterial lysate treatment in newborns/small children from pre-disposed atopic parents: PAPS-study

Results of the PAPS-study (prophylaxis of atopic and allergic manifestations and activation or modulation of the immune system by bacterial lysate treatment in newborns/small children from pre-disposed atopic parents) represent the basis for modelling. A randomised, double-blind placebo-controlled clinical trial was performed in Germany. A minimum sample size of $n = 632$ newborns was planned. The study time allowed was 3 years. During this time eight visits (visit 1 = screening visit) should be provided. After the screening phase (age 0–4 weeks), enrolled infants were randomised at visit 2 (age 4–5 weeks). For 26 weeks (age 5–37 weeks), newborns were treated prophylactically by bacterial lysate or placebo (intervention phase). At the beginning, infants had to take 3×0.35 ml a day increasing

to 3×0.7 ml daily in 2 weeks. Children were observed until 3 years of age (follow-up phase). Inclusion criteria were: healthy newborn (male and female) at the age of 4 weeks, minimum birth weight 2,500 g, duration of the pregnancy more than 37 weeks, single or double heredity for atopy (AD, allergic rhinitis and/or bronchial asthma) and informed consent. Exclusion criteria were: antibiotic treatment or other medication after birth, lympho- or thrombocytopenia, intensive care after birth, lack of German language knowledge and no informed consent.

In total, 606 newborns were included in the trial. After randomisation $n = 303$ patients were classified in the placebo group and $n = 303$ in the verum group. A total of 119 participants aborted the study (verum: 66 patients, placebo: 53 patients). Mentioned causes were: adverse events (verum: $n = 16$, placebo $n = 8$), failed to appear to visits (verum: $n = 13$, placebo $n = 21$), taking back of informed consent by parents (verum: $n = 34$, placebo $n = 22$) and other non-medical events (verum: $n = 3$, placebo $n = 2$). At the end of the study, data from 250 participants in the placebo group and 237 in the verum group were available for analysis.

The primary outcome was the prevalence of atopic eczema under bacterial lysate or placebo at the end of the prophylactic period at 7 months of age. The secondary objectives were: prevalence of AD after intervention phase until 3 years of age, duration of an initial manifestation of AD, severity code of AD after manifestation, frequency, duration and severity code of an allergic/atopic manifestation of gastrointestinal- and respiratory tract, frequency of aliment allergisation and adverse events.

Cost-effectiveness analyses focused on single heredity for atopy. For this subgroup, the following results were found: 27 newborns (18.6 %) of the placebo group and 15 newborns (9.7 %) of the verum group become diseased by week 31 (visit 5). At the end of the observation (after 3 years) 27.6 % of children in the placebo group and 19.5 % of the verum group suffered from AD (see Table 1).

Literature search

In order to evaluate the treatment costs of atopic eczema in newborns/small children, a systematic literature search was performed by the by German Institute for Medical Documentation and Information (DIMDI). The following keywords were used: eczema, Ekzem, Kosten?, cost?, german?, Krankheitskosten, cost-of-illness, costofillness, Neurodermitis, neurodermatitis, baby, babies, child?, Kind?, Kosten-Effektivitäts-Analyse, cost-effectiveness analys?, dermatitis, skinallergy, Hautallergie, newborn, neugebor?, py > 2004. The search resulted in 75 articles; excluding duplicates led to 39 relevant articles. Thirty publications were excluded after reviewing title and

Table 1 Results of PAPS-study (primary outcome), single heredity for atopy

Visit	2	3	4	5	6	7	8
Age	5 weeks	13 weeks	21 weeks	31 weeks	12 months	24 months	36 months
Verum							
Atopic eczema	0	7	13	15	21	28	30
Healthy	154	147	141	139	133	126	124
Total	154	154	154	154	154	154	154
Prevalence (%)	0.0	4.5	8.4	9.7	13.6	18.2	19.5
Placebo							
Atopic eczema	0	4	13	27	31	37	40
Healthy	145	141	132	118	114	108	105
Total	145	145	145	145	145	145	145
Prevalence (%)	0.0	2.8	9.0	18.6	21.4	25.5	27.6

Prophylaxis of atopic and allergic manifestations and activation or modulation of the immune system by bacterial lysate treatment in newborns/ small children from pre-disposed atopic parents

abstracts. Exclusion criteria were: no relevant costs, indication other than AD or the observation was not carried out in Germany. A further eight publications were identified by an internet search using Google and Google Scholar. Finally, 17 publications were included and checked for treatment costs of AD.

The study from Ehlken et al. [5] formed the basis of the decision tree model relating to treatment costs. In a multicentre, retrospective and prospective cost-of-illness study, direct and indirect costs of medical treatment for statutory health insurance and for patients were determined. According to this study, the direct costs of statutory health insurance amount to €766.00 per patient and year in the age-group “1–6 years”. Here, direct costs include drug expenses, costs for out-patient treatment and diagnostics, hospitalisation, rehabilitation and nutritional advice. The direct costs evaluated by Ehlken et al. [5] were used for modelling (Fig. 1).

Decision tree model

Based on the described PAPS study, a decision tree model was developed. The model can be used to calculate cost-effectiveness of bacterial lysate compared to placebo. Enrolled infants were randomised into one of two groups: “placebo” or “verum”. In addition to this differentiation (placebo vs verum), two states of health—“healthy” and “atopic eczema”—were classified (Fig. 2).

Direct costs

The underlying PAPS study, and therefore the decision tree model, distinguishes between placebo and verum. Thus the direct costs of the model were divided into direct costs of the placebo group and direct costs of the verum group.

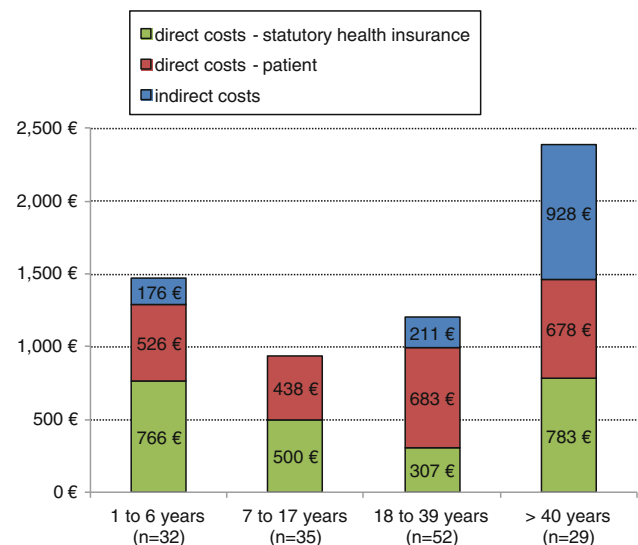


Fig. 1 Total costs per patient and year in Euro according to Ehlken et al. [5]—by age group

Furthermore, costs were classified in children without AD (“healthy”) and children with AD (“atopic eczema”). It is important to note that treatment costs accumulate only for children who fall ill. Healthy children received only the study medication and no medical treatment because of AD. So in this case drug expenses are the sole component in costs. Children with AD receive prophylaxis and additional out-patient treatment. Here, costs for both study medication and for statutory health insurance were considered for modelling.

Study medication was applied for 26 weeks (age 5–37 weeks). During this time, drug expenses of €92.40 accumulated per patient in the verum group. Based on the assumptions made, the costs of study medication were

Fig. 2 Decision tree model

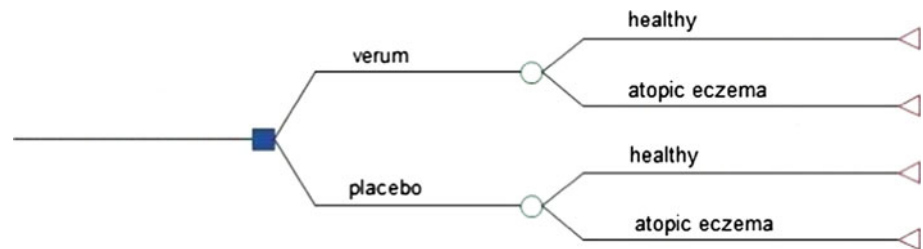


Table 2 Verum group: costs of prophylaxis (study medication), healthy children

Period	Visit 2; 5 weeks	Visit 3; 13 weeks	Visit 4; 21 weeks	Visit 5; 31 weeks	Visit 6; 12 months	Visit 7; 24 months	Visit 8; 36 months
Costs of prophylaxis (study medication) (€)	3.55	28.43	56.86	92.40	92.40	92.40	92.40

Table 3 Verum group: direct costs, children with atopic dermatitis (AD)

Period	Visit 2; 5 weeks	Visit 3; 13 weeks	Visit 4; 21 weeks	Visit 5; 31 weeks	Visit 6; 12 months	Visit 7; 24 months	Visit 8; 36 months
Direct costs (including prophylaxis) (€)	77.20	219.92	366.19	549.03	858.40	1,624.40	2,390.40

equal to the costs of prophylactic treatment of healthy children (Table 2).

Further costs were generated for treatment of children with AD. In cases of illness, additional direct costs of statutory health insurance amounting to €766.00 per patient and year had to be considered [5] (Table 3).

Direct costs of the placebo group consist of costs of statutory health insurance. Healthy children did not generate any costs in this group. Only in the event of illness were direct costs calculated. Here, treatment costs also amounted to €766.00 per patient and year. Drug expenses, especially the costs of the study medication, were not taken into account (Table 4).

Direct costs and effectiveness of treatment in terms of prevalence were the input parameters of the model. As mentioned above these parameters were inserted in the decision tree and a cost-effectiveness analysis was performed.

The focus of the following cost-effectiveness analysis was the subgroup “single heredity for atopy” of the PAPS study.

Results

Cost-effectiveness analyses at visit 5 (age 31 weeks)

A total of 9.7 % of participants (15 newborns) in the verum group and 18.6 % of the placebo group (27 newborns) suffering AD by visit 5. According to these results, a probability of state of health can be determined. Thus, 90.3 % of patients in the verum group were in state “healthy” and 9.7 % in state “atopic eczema”. For the placebo group, the figures were 81.4 % of newborns in “healthy” and 18.6 % in “atopic eczema”. This procedure delivers the first input parameter of model, i.e. effectiveness. The second input parameter—the direct treatment cost—was considered in the analysis according to Tables 2–4. Thus all model parameters were determined and the cost-effectiveness ratio can be calculated (Table 5).

Total costs per newborn (healthy or falling ill) amounted to €136.69 in the verum group and €84.93 in the placebo group. Therefore, lower costs were calculated for the placebo group. Despite the improved probability of success in

Table 4 Placebo group: direct costs, children with AD

Period	Visit 2; 5 weeks	Visit 3; 13 weeks	Visit 4; 21 weeks	Visit 5; 31 weeks	Visit 6; 12 months	Visit 7; 24 months	Visit 8; 36 months
Direct costs (€)	73.65	191.49	309.33	456.63	766.00	1,532.00	2,298.00

Table 5 Cost-effectiveness analysis, visit 5

	Verum	Placebo	Difference
Direct costs after 31 weeks (€), total	136.69	84.93	51.76
Probability of success (%)	90.30	81.40	8.90
Effectiveness adjusted costs (€)	151.38	104.34	47.04

the verum group, cost-effectiveness for this group compared to placebo is unverifiable under the given assumptions. The reasons for this are, on the one hand, the short observation time, and on the other the considered costs. Costs were generated only in the event of illness, so healthy patients in the placebo group did not incur any costs. In contrast, patients in the verum group produced costs in both states of health. In cases of children without AD (“healthy”), newborns received prophylactic treatment with verum for 26 weeks. Thus costs were incurred and had to be accounted for in the analysis. This means that the costs of the verum group will always be higher than those of the placebo group at visit 5. In order to demonstrate the cost-effectiveness of verum, the prevalence of this group has to be lower than the prevalence of the placebo group. The model analysis showed only a marginally higher probability of success for the verum group. The difference in prevalence was not high enough to indicate cost-effectiveness in this case. The time horizon of calculation was 31 weeks, which seems to be too short to conclude anything more concrete. Additionally, the prevalence of AD is still increasing after week 31 (Table 1). Moreover, consulting the literature reveals that the prevalence of AD rises up to about the age limit of 3 years. So the time period of 31 weeks has to be expanded in order to reach a final statement of cost-effectiveness.

Cost-effectiveness analyses at visit 8 (age 3 years)

At the age of 3 years, 19.5 % of patients in the verum group and 27.6 % in the placebo group were suffering from AD. The input parameters (prevalence and direct costs) were inserted in the decision tree model and cost-effectiveness analyses were performed (Table 6).

After 3 years, direct costs of €540.51 accumulated per patient in the verum group and €634.25 per patient in the placebo group. The difference amounts to a €93.74 advantage to the verum group. This means that the direct

Table 6 Cost-effectiveness analysis, visit 8

	Verum	Placebo	Difference
Direct costs after 3 years (€), total	540.51	634.25	−93.74
Probability of success (%)	80.50	72.40	8.10
Effectiveness adjusted costs (€)	671.44	876.03	−204.59

costs per child (healthy or falling ill) are lower in the verum group than in the placebo group for the observed time horizon of 3 years. Moreover, the probability of success is higher for patients with prophylactic treatment (verum group). Finally, there was a higher probability of success at lower direct costs, leading to cost-effectiveness of the verum group compared to placebo (verum: €671.44, placebo: €876.03). Therefore prophylactic treatment of infants for 26 weeks in the 1st year of life is cost-effective at the age of 3 years.

Verum compared to placebo achieved cost-effectiveness because the direct costs per child of the placebo group were significantly higher. The higher costs of the placebo group are due to the higher number of children with AD in this group. This fact is also shown by the difference in prevalence between both groups. The probability of success is better for patients in the verum group (80.50 %) than for patients in the placebo group (72.40 %). This means that fewer children who received prophylactic treatment suffer from AD than children in the comparison group. All in all, patients in the verum group generate lower costs by lower numbers falling ill. So, under the assumptions made here, the cost-effectiveness of the verum group is verifiable for a time period of 3 years.

Cost-effectiveness analyses at age 6 years

At visit 5, the cost-effectiveness of the verum group could not be proven. Cost-effectiveness analysis after 3 years showed an advantage for verum. To further investigate the positive trend of the cost-effectiveness of the prophylactic treatment requires a model extension. The time horizon of the model is still 3 years. In accordance with the literature, and the fact that children suffering from AD are generally between the ages of 3 and 6 years, the model was expanded to 6 years. Thus, the input parameters of the model were upgraded from 3 to 6 years. Treatment costs and prevalence of AD are explanatory variables. Direct costs were determined to be €766.00 per patient per year [5]. The annual average costs for each additional year of model extension must be added. It is important to note that the costs of prophylactic treatment in the form of the verum administered are not part of the extension. These costs were generated only in the first 26 weeks of study. After this no further costs of prophylaxis should be considered. This annual treatment cost of €766.00 is a unique cost-component that had to be added (Fig. 3).

As a second input parameter, prevalence was extracted from the PAPS study (see Table 1). The results for 3 years are available. The observed prevalence showed a linear increasing during the study period. Hence, prevalence could be expanded by linear extrapolation to obtain the probability of state of health for 6 years. Linear

Fig. 3 Model extension—direct costs

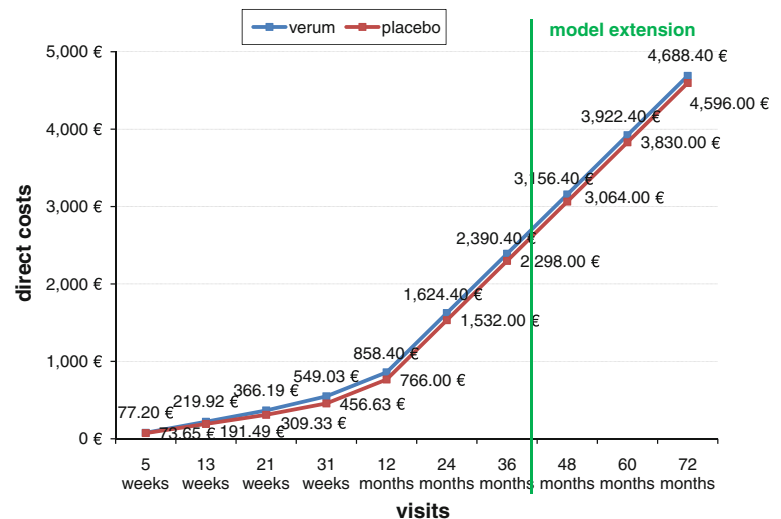
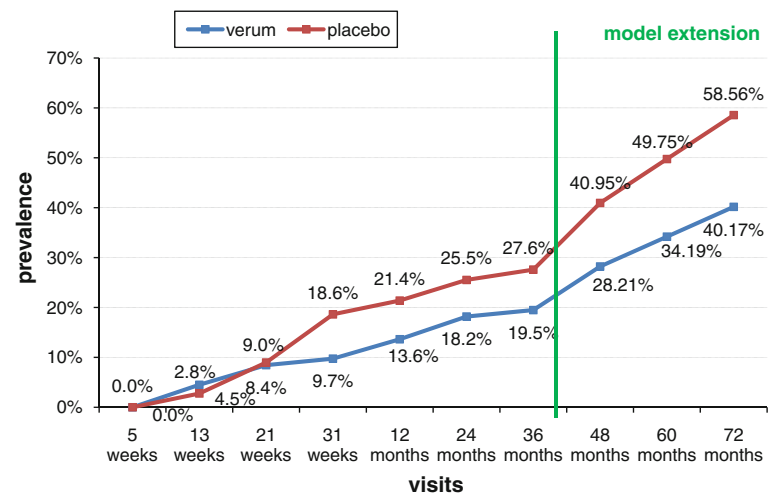


Fig. 4 Model extension—prevalence



extrapolation using the program Excel led to values of prevalence for the known results of 3 years (Fig. 4).

According to the extrapolation, 40.17 % children in the verum group and 58.56 % in the placebo group would suffer from AD after 6 years. Using these data, the probabilities of the decision tree model can be calculated and included in the model. Thus, the analysis regarding cost-effectiveness can be reassessed together with extended costs (Table 7).

Direct costs per child (healthy or falling ill) of €1,938.62 accumulated in the verum group and €2,691.20 in the placebo group, i.e. an advantage of €752.58 to verum. Prophylactic treatment with verum generated lower costs during an observation time of 6 years. Moreover, patients of the verum group have shown a better probability of success. Here, the benefit of verum reaches 18.39 %. The lower costs and higher probability of success induces cost-effectiveness of prophylactic treatment with verum after

6 years. Thus, the observed cost-effectiveness after 3 years can be consolidated by model extension.

Sensitivity analysis

Prevalence as an input parameter of the model was further investigated by a sensitivity analysis. The influence of an expanded prevalence-value on the cost-effectiveness result was examined. All other model parameters were unchanged. The prevalence of the verum group after 6 years was varied in a fixed interval between 40.0 % and 60.0 % in steps of 0.2 %. Prophylactic treatment with study medication was cost-effective with a prevalence value of 57.6 % for patients in the verum group and 58.6 % in the placebo group at the age of 6 years. The difference in effectiveness-adjusted costs gives a €43.90 advantage to verum. Until a prevalence-rate of 57.8 %, the superiority of the verum group is preserved, but this changes at prevalence rates

Table 7 Cost-effectiveness analysis after 6 years

	Verum	Placebo	Difference
Direct costs after 6 years (€), total	1,938.62	2,691.20	−752.58
Probability of success (%)	59.83	41.44	18.39
Effectiveness adjusted costs (€)	3,240.23	6,493.49	−3,253.26

higher than 57.8 %. Here, effectiveness adjusted costs for placebo are €8.50 lower than for prophylactic treatment with the study medication.

Thus, sensitivity analysis confirmed the cost-effectiveness of verum up to a prevalence of verum of 57.6 %. The prevalence rate of verum can rise up to nearly 20 %. Therefore, the model is considered robust under assumptions made.

Discussion

The present model was based on a randomised, double-blind placebo-controlled clinical trial performed in Germany. The results of this study—PAPS (prophylaxis of atopic and allergic manifestations and activation or modulation of the immune system by bacterial lysate treatment in newborns/small children from pre-disposed atopic parents)—suggest prevalence as one of two input parameters of the developed model. The second input parameter of model was evaluated by a literature search. Treatment costs of atopic eczema in newborns/small children were searched for by the German Institute for Medical Documentation and Information (DIMDI). Finally, one publication was found that described the direct costs of AD for statutory health insurance and for patients. Annual average direct costs of €766.00 per patient for statutory health insurance in the age-group “1–6 years” were evaluated.

Within the PAPS study, enrolled infants were randomised in one of two groups: “placebo” or “verum”. Following this structure, the model was divided into a placebo arm and a verum arm. In addition to this differentiation two states of health, “healthy” and “atopic eczema”, were classified. The developed model can be used to calculate cost-effectiveness of bacterial lysate compared to placebo taking both input parameters into account.

At visit 5 (at the age of 31 weeks) cost-effectiveness of prophylactic treatment by bacterial lysate could not be proven. Total costs per newborn (healthy or falling ill) amounted to €136.69 in the verum group and €84.93 in the placebo group, i.e. lower costs were calculated for the placebo group. Although the probability of success is higher for patients in the verum group (verum: 90.30 %, placebo: 81.40 %) cost-effectiveness of bacterial lysate is not achieved. The reasons for this are, on the one hand, short observation time (just 26 weeks) and on the other, the

considered costs. Costs were generated only in the event of illness, meaning that healthy children in the placebo group did not incur any costs. In contrast, patients in the verum group produced costs in both states of health. For example “healthy”-arm newborns were administered prophylactic verum (study-medication) for 26 weeks. Here, costs were induced and had to be accounted for in the analysis. In comparison, costs of study-medication did not have to be accounted for in the placebo group. So the costs of the verum group will always be higher than in the placebo group at visit 5. Moreover, differences in the probability of success are not high enough to intercept higher costs at this time.

The results of the PAPS-study revealed an increasing prevalence-rate during the study period, in particular after visit 5 (at the age of 31 weeks). So a cost-effectiveness analysis was performed at the end of the study, i.e. after 3 years. At this time, an advantage for prophylactic treatment with the study medication could be proved. After 3 years, direct costs of €540.51 per patient accumulated in the verum group and €634.25 per patient in the placebo group. So patients of the verum group generated €93.74 lower costs in 3 years. Moreover, the probability of success is higher for patients with prophylactic treatment (verum: 80.50 %, placebo: 72.40 %). Finally, the higher probability of success coupled with lower direct costs lead to the cost-effectiveness of the verum group compared to placebo (verum: €671.44, placebo: €876.03).

In accordance with the literature and the fact that children continue suffering from AD between the ages of 3 and 6 years, a model extension was performed [4, 6]. Furthermore, the positive trend of cost-effectiveness beyond the study period can be investigated by model expansion. Thus, the input parameters of the model have to be upgraded from 3 to 6 years. For each additional year of the expanded model, the annual average costs have to be added. It is important to note that the costs of prophylactic treatment in the form of administration verum are not part of the extension. The latter costs were generated only in the first 26 weeks of study. After this no further costs of prophylaxis should be considered. As the second input parameter, the prevalence rate had to be expanded. During the study period, a linear increase in prevalence was observed. Hence, prevalence had to expand by a linear extrapolation to obtain the probability of state of health for 6 years. Cost-effectiveness analysis was again calculated under assumptions of expanding input parameters. As a result, the cost-effectiveness of prophylactic treatment with bacterial lysate after 6 years compared to placebo could be shown. At the age of 6 years, direct costs per child (healthy or falling ill) of €1,938.62 accumulated in the verum group compared to €2,691.20 in the placebo group. Therefore prophylactic treatment with verum generates lower costs

during the extrapolated time of 6 years. Moreover, patients in the verum group exhibited a higher probability of success. Here the benefit of the verum was 18.39 %. The lower costs and the higher probability of success lead to the cost-effectiveness of the prophylactic treatment with study medication after 6 years. Thus, the observed cost-effectiveness after 3 years can be consolidated by model extension.

In conclusion, prophylactic treatment of atopic eczema with bacterial lysate for 26 weeks in the 1st year of life is cost-effective in comparison to placebo at 3 and 6 years.

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