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Preventive treatment of chronic bronchitis: a cost-effectiveness analysis for an immunoactive bacterial extract in Switzerland

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Summary

This study was carried out in order to assess whether the preventive treatment of patients with Broncho-Vaxom® (OM-85 BV; Laboratoires OM SA, Switzerland) is cost-effective.

To perform this evaluation a clinical scenario and an event tree were developed following a clinical expert meeting. All relevant cost data for Switzerland were then retrieved, and the direct cost of treatment of an acute exacerbation, the incremental cost per patient treated preventively and the incremental cost per prevented acute exacerbation were calculated for out-patient care only and for in- and out-patient care together. Sensitivity analyses were carried out for each parameter.

The average direct costs of treatment of an acute exacerbation of chronic bronchitis are CHF 224.45 (range CHF 218.84 – CHF 234.03) for out-patient care only and CHF 1493.12 (range CHF 1184.50 – CHF 1699.43) for out- and in-patient care together. The study showed that the preventive treatment of chronic bronchitis is also cost-effective under very conservative assumptions, eg. CHF 53.83 (range CHF 52.24 – CHF 54.54) and CHF 688.16 (range CHF 660.92 – CHF 720.25) could be saved per preventively treated patient for out-patient care and for out-patient care and in-patient care together, respectively.

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Introduction

Chronic bronchitis (CB) is a condition associated with excessive tracheobronchial mucus production sufficient to cause cough with expectoration for at least three months of the year for more than two consecutive years [1]. Apart from smoking, acute exacerbations are the greatest contributory factors to the progression of CB. Therefore, intelligent management of CB is required to prevent acute exacerbations and to convince patients to cease smoking.

CB is a common disease in industrialised countries, with a prevalence estimated at 1.5 – 2.5% in Switzerland [2], approximately 4.7% in the USA [3] and 3 – 6% in Germany [4]. In absolute figures, for Switzerland this would represent between 100,000 and 150,000 people (based on a total population of 6.5 million). Over 60% of the people affected by CB are male and around 50% are over 65 years of age [2]. The potential number of life years lost due to CB was 1380 for men and 340 for women in 1989 in Switzerland [5].

The socio-economic impact of CB is important. The quality of life of the patients may be significantly impaired in advanced stages of the disease. CB may lead to permanent incapacity, respiratory failure and death. Both the direct cost (therapy, hospitalisation, etc) and the indirect cost (absence from work, invalidity) amount to around CHF 300 million for CB patients in Switzerland (5.2 million active population, 1987 [2,5]).

Rationale for an immunotherapeutic approach in CB

Basically, the management of CB relies on the maintenance of adequate bronchial drainage and the assurance of correct pulmonary function [6,7]. In the case of an acute exacerbation of bacterial origin, antibiotics are generally efficient. The specific prevention of acute airway infections remains limited to a few vaccines (influenza, pneumococcus, haemophilus) and these are usually only recommended in selected patient populations such as immunocompromised persons [6,7]. The preventive usefulness of antibiotics in CB appears to be limited and may occasionally be accompanied by severe side effects and resistance induction [7,8].

Advances in our basic understanding of humoral and cell-mediated immune mechanisms have opened the way for different therapeutic options aimed at modulating various components of the immune response. The concept of the non-specific stimulation of the mucosal defence mechanisms is based on the principle of a common mucosal immune system (MALT = mucosa-associated lymphoid tissue) [9,10]. The oral administration of immunoactive compounds (levamisole, BCG vaccine, certain bacterial cell wall components, etc) leads to the stimulation of immunocompetent cells in the Peyer's patches in the gastrointestinal tract which, while migrating along the mesenteric lymphatic system, undergo maturation. After reaching the bloodstream via the thoracic duct, these activated cells colonise different lymphoid tissues such as the

bronchus-associated lymphoid tissue (BALT) or return to the gut-associated lymphoid tissue (GALT), which is referred to as "homing".

The mechanism of action of Broncho-Vaxom* (Laboratoires OM SA, Meyrin/Geneva, Switzerland) relies on this process [1]. The product contains as the active agent a lyophilised bacterial extract from eight different species (*Haemophilus influenzae, Diplococcus pneumoniae, Streptococcus viridans* and *Streptococcus pyogenes, Klebsiella pneumoniae* and *Klebsiella ozaenae, Staphylococcus aureus* and *Neisseria (Branhamella) catarrhalis)*. In animal immunopharmacological models, Broncho-Vaxom was shown to stimulate B-lymphocytes and to increase the secretion of secretory immunoglobulin A (sIgA) on the respiratory mucosa; it increased *in vitro* the metabolic (oxidative metabolism) and functional (intra- and extracellular killing) activities of murine macrophages [11]. In human immunopharmacological studies, the product increased the level of sIgA in the saliva *(in vivo)* [12], enhanced the functional and metabolic activities of alveolar macrophages [11] and induced an up-regulation of certain adhesion molecules in human peripheral blood mononuclear cells *(ex vivo)* [13].

The efficacy of Broncho-Vaxom has been established in numerous double blind, controlled and open clinical trials including over 8000 patients in several European countries: it reduces the number of acute exacerbations in patients with CB and the incidence, duration and intensity of recurrent respiratory infections in adults and children [14 - 32]. Thus, its approved indications are for the prevention of acute, infectious exacerbations of CB in adult patients and the prevention of recurrent infections of the airways in adults and children. The standard regimen is one capsule daily for 10 consecutive days per month for three months, usually starting at the beginning of the cold season.

The tolerance of Broncho-Vaxom can basically be judged as good with an overall incidence of adverse drug experiences in clinical trials of between 3% and 4%. Mainly transient, minor skin reactions or gastrointestinal effects are reported [33]. Thus, Broncho-Vaxom offers an additional, genuinely alternative preventive option in the management of CB patients.

Health economic data related to the treatment of pulmonary disease are available [34], but until now data related to the preventive treatment of CB have been lacking. Therefore, a cost-effectiveness analysis (CEA) was carried out, taking the specific situation of Switzerland into account, and based on the following hypothesis: the preventive use of Broncho-Vaxom for the reduction of infections in CB patients is more cost-effective than the sum of all costs for the diagnosis and therapy of each single infectious episode.

Materials and methods

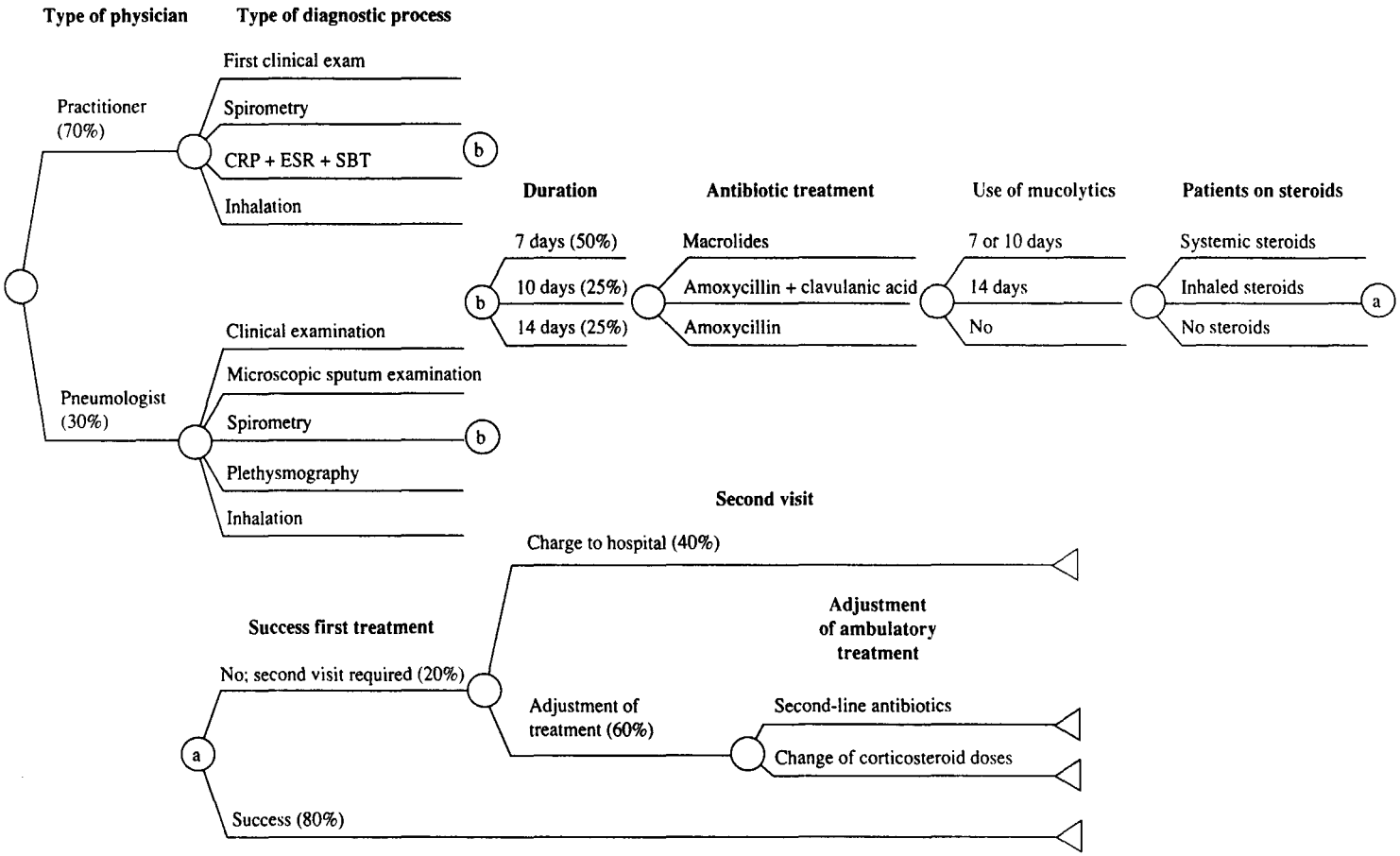
Data collection

Expert meeting

The outcome of the expert meeting formed the basis for the development of the clinical scenario and the event tree (Figure 1). The authors collected additional information from the medical literature [2,5].

* *Registered trade mark*

FIGURE 1. *Logical structure for the diagnosis and treatment of acute exacerbations in CB patients consulting a physician in Switzerland (see Table 1 for details of the different probabilities). (CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, SBT = small blood test: leucocyte and erythrocyte count, haematocrit, haemoglobin.)*



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Medical and economical data sources

The tariff items were identified as follows:

- for the effectiveness of Broncho-Vaxom, the authors referred to the effectiveness calculated in the meta-analysis for Broncho-Vaxom carried out by the Institute for Medical Informatics and Biostatistics in 1994 [35]. The sources of the data for the meta-analysis were placebo-controlled, randomised, double blind trials conducted in private practice settings in different European countries
- for the medical doctor tariffs, "UVG Ärztetarif 1995" [36] and "Eidgenössische Analysenliste" [37] were used.

The authors used these tariffs to calculate the cost of the different diagnostic and therapeutic (except medication) procedures. For laboratory work and analyses, the authors applied the UVG Ärztetarif wherever possible; if this was not available they used the Eidgenössische Analysenliste. All calculations are based on a price of CHF 4.95 per UVG Ärztetarif-tax point, CHF 1.15 per UVG Ärztetarif-tax point for laboratory work and CHF 1.00 per Eidgenössische Analysenliste-tax point.

Other costs were calculated as follows:

- for prices of medication, information on suitable package sizes and the total time-dependent treatment cost, Ref. 38 was used
- for the most frequently prescribed medications for CB in Switzerland, data from the International Medical Statistics (IMS) list [39] were used
- for the mean length of hospital stay, the VESKA statistic was referred to [40] (the VESKA statistic is an annual survey of about 45% of all Switzerland's hospitals, containing the ICD-9 related total numbers of diagnoses from hospitalised patients, the mean ICD-9 related hospital stay and other statistical data)
- for the number of practitioners and pneumologists, Ref. 41 was used.

In order to calculate the medication prices, the authors screened the IMS [39] list for all medication groups being prescribed for CB and related diseases. They then identified all antibiotics and the most frequently prescribed mucolytics and corticosteroids from each group in Ref. 38 and for each medication calculated the treatment cost based on the treatment duration (seven, 10 or 14 days). The arithmetic means were then calculated for all groups. The CEA includes only the medication groups mentioned by the expert committee: amoxycillin, amoxycillin and clavulanic acid, macrolides, mucolytics, and inhaled and systemic corticosteroids.

CEA

The cost-effectiveness study was carried out from the third party payer perspective, and thus only direct costs were taken into account. The authors chose the incremental approach to compare non-treated and Broncho-Vaxom-treated patients.

The marginal or incremental costs were defined as follows:

$$CM = CBV - (CTAE \times PAE) \qquad (1)$$

where CM is the marginal cost (incremental cost), CBV is the cost for Broncho-Vaxom treatment, CTAE is the cost for the treatment

of one acute exacerbation and PAE is the number of prevented acute exacerbations in Broncho-Vaxom-treated patients per six months (clinical efficacy of Broncho-Vaxom).

The cost-effectiveness was defined as the ratio between the incremental cost and the clinical effectiveness of Broncho-Vaxom, as follows:

$$CER = (CBV - (CTAE \times PAE))/PAE \quad (2)$$

where CER is the cost-effectiveness ratio (incremental cost per prevented acute exacerbation).

The direct costs for the treatment of one acute exacerbation of CB and the incremental cost per prevented acute exacerbation of CB were calculated using Decision Programming Language (DPL) software [42]. In order to estimate the influence of changing the price and effectiveness parameters, a sensitivity analysis was performed [42]. The cost and incremental cost ranges indicated were calculated with the DPL built-in Monte-Carlo simulation technique.

The study was performed in two parts. In part one the ambulatory treatment costs were taken into account, in the second part the total costs for the treatment of an acute exacerbation were calculated, and hence the hospitalisation cost was included.

Results

Expert meeting

Following the expert meeting, the authors developed a clinical scenario and constructed an event tree for CB (Figure 1).

After structuring this process, the probabilities for all events mentioned by the expert team were put into the model. Ranges (eg. 0.50 – 0.70) were converted to arithmetic means for modelling purposes (Table 1), although the ranges were taken into account in the sensitivity analysis.

Cost data

Table 2 gives a summary of the cost of the treatment of an uncomplicated acute exacerbation of CB in Switzerland, including all relevant diagnostic and therapeutic procedures, and laboratory tests.

The relevant medication cost data for the treatment of CB in Switzerland are listed in Table 3 and illustrated in Figure 2.

Table 4 indicates the major ICD-9 491.0-9 (CB) diagnoses for hospitalised patients stratified by age group and the cost of the mean hospital stay for the treatment of CB. The mean costs of the hospital stay are calculated on the basis of CHF 800 per hospital day.

Cost analyses

Direct cost

Direct cost for the treatment of an acute exacerbation of CB (out-patient care only)

The direct costs for the diagnosis and treatment of one acute exacerbation in a CB patient were calculated as an average of CHF 224.45 (range CHF 218.84 – CHF 234.03) for treatment without hospitalisation. Figure 3 shows the distribution of the out-patient costs.

TABLE 1. *Probabilities of all the events expressed during the expert meeting.*

Probability of seven days of antibiotics	0.5
Probability of 10 days of antibiotics	0.25
Probability of 14 days of antibiotics	0.25
Probability of the use of macrolides	0.6
Probability of the use of amoxycillin	$(1 - p_{macrolides})/2$
Probability of the use of amoxycillin and clavulanic acid	$(1 - p_{macrolides})/2$
Probability of the use of mucolytics	0.6
Probability of the use of mucolytics for seven or 10 days	0.4
Probability of the use of mucolytics for 14 days	0.2
Probability of the use of systemic corticosteroids	0.15
Probability of the use of inhaled corticosteroids	0.15
Probability of the use of no corticosteroids	0.6
Probability of dyspnoea	0.5
Probability of obstruction	0.3
Probability of plethysmography at pneumologist	0.015
Probability of success of first antibiotic treatment	0.8
Probability of second visit	0.2
Probability of charge to hospital at second visit	0.4
Probability of adjustment of medical treatment	0.6
Probability of treatment by a pneumologist	0.3
Probability of treatment by a practitioner	0.7
Broncho-Vaxom effectiveness	0.5

Direct cost for the treatment of an acute exacerbation of CB (including in-patient care)

For the treatment of CB including the hospitalisation cost, the direct costs for the diagnosis and treatment of one acute exacerbation in a CB patient were calculated as an average of CHF 1493.12 (range CHF 1184.50 – CHF 1699.43).

CEA

Incremental cost of Broncho-Vaxom per preventively treated patient (out-patient care only)

The incremental (marginal) costs of the preventive treatment with Broncho-Vaxom are dependent on the cost per prevented acute exacerbation and on the clinical effectiveness of Broncho-Vaxom. Considering the mean figures of 0.5 prevented acute exacerbations per six months per patient, and treatment cost of CHF 224.45 for one acute exacerbation, the CEA gave a CHF -53.83 additional cost (range CHF -52.24 – CHF -54.54) per preventively treated patient (the minus sign indicates that CHF 53.83 could be saved per preventively treated patient). As outlined in the materials and methods section, this result is obtained from the following calculation:

marginal cost = cost for Broncho-Vaxom treatment – (cost for the treatment of one acute exacerbation x number of prevented acute exacerbations by Broncho-Vaxom)

ie. CHF 58.40 – (224.45 x 0.5) = -CHF 53.83.

TABLE 2. *Cost of diagnostic and therapeutic procedures for CB in Switzerland.*

	Medical doctor tariffs in CB according to UVG (variant 1) **Value of 1 tax point at 1 January 1995 = CHF 4.95**	
	Tax points	**Value (CHF)**
Clinical examination	8	39.6
Second clinical examination	5.5	27.23
Spirometry	4	19.8
Plethysmography	30	148.5
First chest radiography (two projections)	24	118.8
Second chest radiography (two projections)	8	39.6
Arterial blood sample	6	29.7
Venous blood sample	2	9.9
Blood gases in the praxis	24	118.8
Vital capacity	2	9.9
Vital capacity with aleudrin or equivalent	3	14.85
Tiffeneau test	2	9.9
Tiffeneau test with aleudrin or equivalent	3	14.85
Spirographical pulmonary function testing	15	74.25
Inhalation 4	19.8	
Sputum sample and macroscopic evaluation	0	0
	Laboratory tariffs in Switzerland (variant 1) **Value of 1 tax point at 1 January 1995 = CHF 1.15**[b]	
	Tax points	**Value (CHF)**
Small blood test[a, b]	10	10
Full blood test[b]	40	40
C-reactive protein[b]	10	10
Erythrocyte sedimentation rate	3	3.45
Native microscopic sputum sediment	8	9.20
Microscopic sputum evaluation including colouring 10	11.5	
Sputum culture[b]	25	25
Resistance testing – six antibiotics[b]	15	15

[a] *Leucocyte and erythrocyte count, haemoglobin, haematocrit.*

[b] *Value of 1 tax point according to eidgenössische Analysenliste at 1 January 1994 = CHF 1.*

TABLE 3. *Average medication group cost included in the CEA.*

	Average cost (CHF) per medication group		
	7 days	10 days	14 days
Amoxycillin and clavulanic acid	95.00	95.00	142.50
Amoxycillin	54.50	60.80	89.76
Macrolide	57.36	88.25	100.15
Corticosteroids, systemic	46.05	46.05	46.05
Corticosteroids, inhaled	57.56	57.56	57.56
Mucolytics	25.33	25.33	33.33

Price of Broncho-Vaxom = CHF 58.40 (30 capsules).

FIGURE 2. *Relative distribution of prescribed drugs for the treatment of acute exacerbations in CB patients (based on the expert meeting) (■, treatment for seven days; □, treatment for 10 days; ■, treatment for 14 days).*

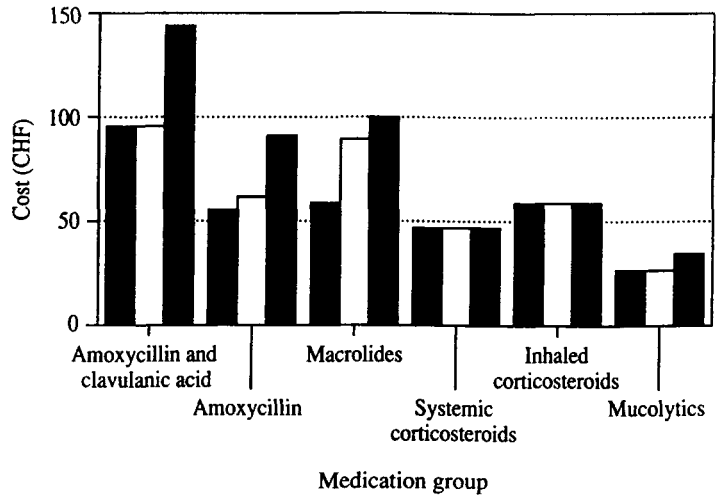
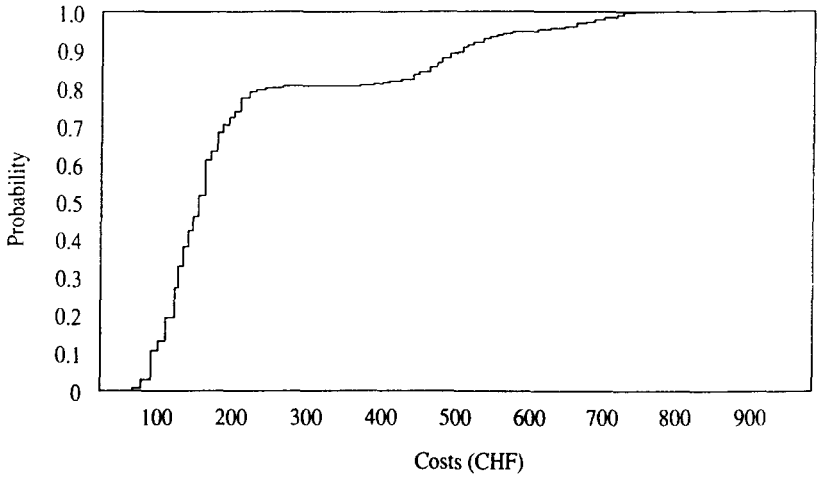


TABLE 4. *ICD 491.X VESKA statistic for CB (1993).*

Age (years)	Major diagnosis (cases)			Mean hospital stay (days)			Mean hospital cost (CHF)		
	Total	Male	Female	Total	Male	Female	Total	Male	Female
Total	3883	2695	1188	19.9	19.6	20.5	15,920	15,680	16,400
< 16	60	39	21	6.7	6.8	6.4	5360	5440	5120
16 – 65	1158	810	348	19.2	19.2	19.2	15,360	15,360	15,360
> 65	2665	1846	819	20.5	20.0	21.4	16,400	16,000	17,120

FIGURE 3. *Distribution of out-patient treatment costs. (The figure shows the distribution of treatment costs for acute exacerbations of CB. As the figure shows, the price is most likely to be situated between CHF 100 and CHF 250. It is very unlikely that an acute exacerbation costs more than CHF 400.)*



Incremental cost per prevented acute exacerbation (out-patient care)
Savings per prevented acute exacerbation without hospital treatment amounted to CHF 107.65.

Figure 4 shows the results for the range 0.3 – 0.9 prevented acute exacerbations, as well as the isolines for cost neutrality and an additional cost or saving of CHF 50. The graph clearly shows that with increasing treatment costs per acute exacerbation, cost neutrality could be reached with a much lower effectiveness than shown in the meta-analysis and the randomised double blind trials.

Incremental cost of Broncho-Vaxom per preventively treated patient (in-patient care and out-patient care)
If, in addition, the cost of an eventual hospitalisation is taken into account, CHF -688.16 additional costs (range CHF -660.92 – CHF -720.25) per preventively treated patient are calculated, where the minus indicates that CHF 688.16 could be saved per preventively treated patient.

Incremental cost per prevented acute exacerbation (including in-patient care)
Including the cost of in-patient care, mean savings of CHF 1376.30 per prevented acute exacerbation could be obtained (range CHF 1287 – CHF 1415).

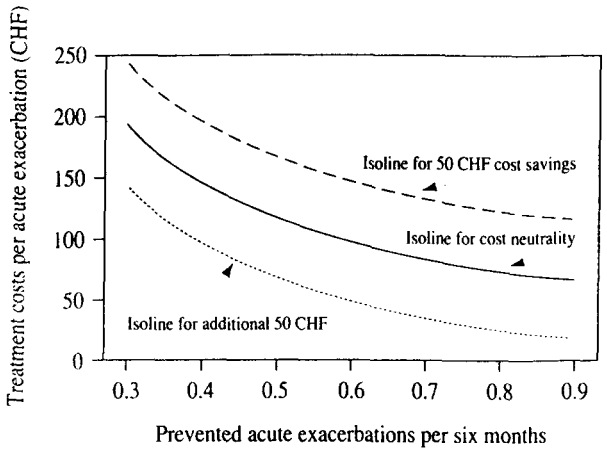
Sensitivity analyses

Sensitivity analyses for every outcome were carried out. The results are presented here for out- and in-patient care (incremental cost).

In this case, the sensitivity analyses revealed five parameters which have a major influence on the outcome. Three have a remarkably large influence:

- $p_{success}$ (success rate of the first antibiotic treatment)

FIGURE 4. *Incremental cost at different clinical efficacies of Broncho-Vaxom (without hospital treatment).*



- sensitivity factor (SF) for the second diagnostic process
- effectiveness of Broncho-Vaxom.

The prices of the medications have a very small influence on the outcome, as can be seen in Figure 5. The lengths of the bars show the contribution of a relative change of the variable on the outcome. The numbers at the ends of the bars (price and probability) indicate the range of variation for the sensitivity analyses and show the results from a 20% change in the variable values.

The sensitivity analyses of the three parameters which have a major influence on the treatment cost of an acute exacerbation clearly show the influence of the additional hospital cost. The variation of parameters by 20%, leading to increased cost, results in a higher treatment cost. A decrease results in a lower treatment cost for acute exacerbations. If there is a high possibility of a second diagnostic process and therefore a higher probability of a hospital charge, the potential savings from prevention of an acute exacerbation increase.

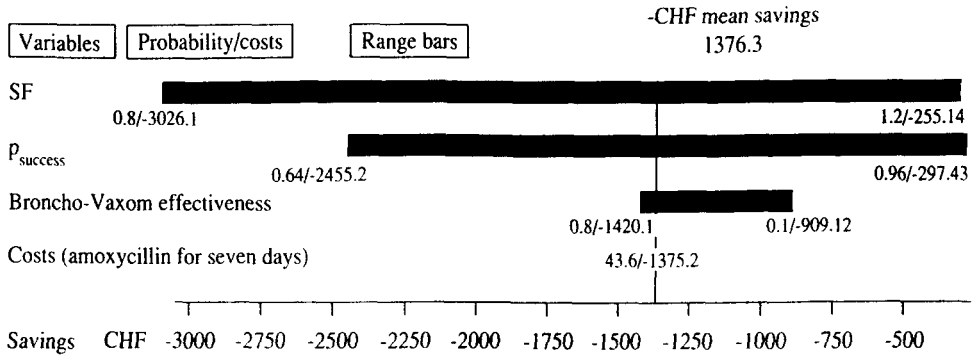
Discussion

Preventive treatment with Broncho-Vaxom leads to cost savings of CHF 53.83 per patient without a hospital stay and of CHF 107.65 per prevented acute exacerbation. When both the in- and out-patient care costs are evaluated, the cost savings increase to CHF 688.16 per patient and CHF 1376.30 per prevented acute exacerbation, based on a Broncho-Vaxom cost of CHF 58.40. This statement is valid using the mean values for clinical efficacy and treatment cost per acute exacerbation.

The current average cost of the treatment of one acute exacerbation amounts to CHF 224.45 without a hospital stay and CHF 1493.12 with a hospital stay.

A closer examination of the incremental cost and the cost-effectiveness ratios shows that cost savings are possible over a wide range of parameter combinations. The sensitivity analysis shows that a change of 20% in the probability of success from the first antibiotic treatment has a much smaller influence on the costs without a hospital stay

FIGURE 5. *Sensitivity analyses of the parameters of the incremental analysis which have an influence on the outcome (per acute exacerbation, including hospital cost).*



(CHF -171.61/CHF -43.69) than on the costs with a hospital stay (CHF -2455.2/ CHF -297.43). With a hospital stay there would also be cost savings with a Broncho-Vaxom effectiveness of only 0.1 prevented acute exacerbations per patient per six months. The analysis is based on the results of randomised, double blind clinical trials conducted in the private practice setting, so the data can therefore be considered to be easily reproducible and valid.

The robust results of the sensitivity analysis indicate that even when the variation in the experts' opinions about the treatment probabilities and/or outcomes is taken into account, the hypothesis formulated could *a priori* be confirmed.

According to the sensitivity analysis, the situation will change if the success rate of the first antibiotic treatment initiated increases. This would lead to a decline in the costs of the cost-intensive, second diagnostic and therapeutic procedure.

The overall conclusion from the CEA is that preventive treatment with Broncho-Vaxom in CB patients will lead to remarkable cost savings. Even when extremely conservative figures are used, the hypothesis that preventive treatment with Broncho-Vaxom is cost-effective can be confirmed.

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