Use of Broncho-Vaxom® in Private Practice: Phase IV Trial in 587 Children

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ABSTRACT

We conducted a Phase IV, open-label clinical trial to test the efficacy and safety of the immunomodulating agent Broncho-Vaxom® in private practice. The trial comprised 587 children younger than 12 years of age who had an acute respiratory tract infection at entry and a history of recurrent respiratory tract infections. The patients were given one capsule daily, 10 days per month, for 3 consecutive months. During the acute phase of the disease the patients also received antibiotic therapy. Comparing the infection present at entry with previous infections, the time to improvement (mean ± SD) decreased from 6.77 ± 4.42 days to 3.76 ± 2.18 days, while the time to cure decreased from 11.86 ± 8.41 days to 7.36 ± 4.93 days. During the 3 months of therapy, the number of infections decreased from 1.79 ± 0.96 1 month before treatment to 0.24 ± 0.46 in the third month of treatment; absenteeism decreased from 3.17 ± 3.07 days to 0.16 ± 0.63 days; and the number of antibiotic treatments decreased from 1.71 ± 1.06 to 0.16 ± 0.51. In the patients who experienced a recurrent respiratory tract infection during the study, the time to improvement decreased from 5.46 ± 3.28 days before treatment to 2.79 ± 1.36 days after treatment, and the time to cure decreased from 8.71 ± 3.96 days to 4.54 ± 2.26 days. Adverse events included asthenia and adynamia in 3 patients, diarrhea in 3, rash in 2, fever in 2, exacerbation of symptoms in 2, adenitis in 1, and flulike syndrome in 1. We conclude that Broncho-Vaxom is effective and safe for the treatment of acute episodes of respiratory tract infections and for preventing recurrences.

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INTRODUCTION

Broncho-Vaxom®* is prepared from lyophilized extracts of the following bacteria: *Haemophilus influenzae*, *Diplococcus pneumoniae*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus viridans*, and *Neisseria catarrhalis*. This immunomodulating agent, which exerts its effects through mucosa-associated lymphoid tissue, activates and regulates various components of the immune system.[1–9] Broncho-Vaxom is used as an adjuvant in the treatment of patients with acute respiratory tract infection and in the prevention of recurrences.

The therapeutic efficacy of the drug in children and adults with chronic sinusitis and in adults with chronic bronchitis has been demonstrated in double-masked, placebo-controlled, prospective studies.[10–14] Patients given Broncho-Vaxom experienced a reduction in the severity of symptoms, the mean duration of acute episodes, and the number of recurrences, as well as an associated reduction in the use of concomitant medications.

In a French, multicenter, double-masked, placebo-controlled clinical trial,[15] Broncho-Vaxom was shown to have a prophylactic effect on children susceptible to respiratory tract infections. The study comprised 116 children who had experienced 3 or more infections during the previous fall and winter. Sixty-one children received Broncho-Vaxom and 55 received placebo. They received one capsule daily for 10 days of each of 3 consecutive months, with an additional 90-day follow-up period. By the end of the 180-day study, 39.5% of the patients treated with Broncho-Vaxom had experienced no respiratory tract infections versus 16.5% in the placebo group ($P < 0.01$). Forty-four percent of the patients who received Broncho-Vaxom required no antibiotic treatment compared with 23.5% of those receiving placebo ($P < 0.05$). These differences were more noticeable in the group aged younger than 6 years. In this group, there were no infections in 34% of the children treated with Broncho-Vaxom versus 3.5% of the patients who received placebo ($P < 0.01$); furthermore, antibiotics were not used in 37% of the patients treated with Broncho-Vaxom compared with 10% of those who received placebo ($P < 0.05$). No serious adverse events were detected during the study. One patient in the group treated with Broncho-Vaxom had diarrhea and two in the placebo group had gastrointestinal disorders.

The primary prevention of respiratory tract infections by Broncho-Vaxom was tested in a randomized, double-masked, placebo-controlled study[16] of 423 healthy children enrolled in French day care centers. Two hundred ten children were given one capsule of Broncho-Vaxom daily for 10 days of each of 3 consecutive months, and 213 children were given placebo. The occurrence of three or more respiratory tract infections during the 3 treatment months was 9.5% in the group treated with Broncho-Vaxom compared with 18.3% in the placebo group, representing a 48% reduction in the rate of respiratory tract infections with Broncho-Vaxom. Broncho-Vaxom prophylaxis was found to be more effective in the older children (older than 18 months of age), a finding that supports the concept of an immune system that matures with age. However, no protective effect was noticed in the Broncho-Vaxom–treated patients during the follow-up period of 7.5 months. The safety pro-

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file of the two groups was similar, as patients in the Broncho-Vaxom–treated group experienced 17 adverse events versus 19 in the placebo group.

Standard questionnaires have been used in several studies[17–19] to determine the incidence of respiratory tract infections as well as the impact of various risk factors. While these retrospective studies have the disadvantage of depending on the recall of signs and symptoms experienced in the past, they allow researchers to study large populations at minimal costs and to produce results in relatively short time periods. The retrospective data in the current study were obtained in a similar fashion.

Before drugs are marketed they are tested in preclinical and clinical trials to assess their efficacy and safety. In the early clinical phases of drug testing, the focus is on the safety of the treated inpatients; in contrast, studies in the postmarketing phases (late III and IV) involve outpatients in private practice. In the premarketing clinical trials the selection criteria and dosing schedules are stringent, while the postmarketing trials reflect the use of the drugs in private practice, meaning that the inclusion criteria and dosing schedules are less strict.[20,21] The postmarketing trials are used to detect less-frequent adverse events and to assess the efficacy of the proposed dosing schedule in populations that would not normally be included in clinical trials.[22–24] Sometimes, the results of a drug study in outpatients in private practice differ from those reported in inpatients in controlled clinical trials: adverse events occur, the dosage must be adjusted, or the drug is found to be not as effective as expected.[25,26]

Therefore, it is necessary to establish the efficacy and safety of drugs used in private practice. We therefore organized this study in which pediatricians and general practitioners treated patients with recurrent respiratory tract infections with Broncho-Vaxom.

PATIENTS AND METHODS

In this trial, children of both sexes younger than 12 years of age were included at the time of a recurrent respiratory tract infection. The physicians were familiar with the medical histories of the patients. Patients were given one capsule of Broncho-Vaxom daily for 10 days per month for 3 consecutive months. If necessary, they also received an antibiotic selected by their physician during the acute infectious episode.

The following data were recorded on each patient's case report form at study entry: sex, age, type of acute infection, history of respiratory tract infections in the 3 months before entering the study, time to clinical improvement (the number of days before signs and symptoms diminished), time to clinical cure (the number of days before signs and symptoms resolved completely) in similar previous infections and in the current infection, and the antibiotic prescribed. Additionally, during the 3 months of the trial, the following data were recorded: the number of respiratory tract infections (including relapses and recurrences), absenteeism from school or day care center (number of days lost), the number of antibiotic treatments, and the number of days to achieve clinical improvement and cure.

The case report form did not contain an explicit question on adverse events; instead, a line was provided to register medical observations, including any significant medical concerns arising during treatment.

The study began in March 1995 and ended in November 1995. The trial was 3

months in duration and patients could enter and complete the trial at any time between March 1995 and November 1995. All the case report forms that were completed properly and all forms, completed properly and improperly, listing adverse events were included in the assessment of results. Data recorded before the entry to the trial were considered retrospectively.

RESULTS

A total of 587 patients—358 boys, 225 girls, and 4 whose sex was not specified—were included. The mean age of the patients was 5.24 ± 2.81 years. The most common diagnoses at the beginning of the treatment were pharyngitis (13%), tonsillitis (7.7%), pharyngotonsillitis (34.6%), and bronchitis (13.6%).

The antibiotics used most frequently during infectious episodes at study entry were various forms of penicillin (6%), ampicillin (4.4%), amoxicillin (16.9%), amoxicillin-clavulanate (9.4%), classic macrolides and related compounds (4.9%), new macrolides and related compounds (9.2%), and cephalosporins (27.9%). Approximately 1.9% of the patients were not given antibiotic treatment.

The time elapsed to improvement and cure was reduced significantly ($P < 0.001$) by 44.4% and 37.9%, respectively, with the Broncho-Vaxom treatment compared with similar infections during the 3 months before entering the study (Table I, Figure 1).

During the 3 months of the trial, treatment with Broncho-Vaxom was found to be beneficial. The number of infections, absenteeism, and the number of antibiotic treatments were reduced by 86% to 95% (Table II). In the children who became ill, the time to improvement and cure decreased by 49% and 48%, respectively (Table II, Figure 2). Using analysis of variance for repeated measures, these changes were determined to be statistically significant ($P < 0.001$).

Approximately 80% of the patients showed improvement in one or more of the measured variables ($P < 0.001$, Wilcoxon matched-pairs test). Thus 74.5% of the patients experienced fewer infections in the third month of treatment than 1 month before treatment; 77.4% had fewer absentee days; and 77.9% required fewer anti-

Table I. Effect of Broncho-Vaxom®* on the time to improvement and cure in the acute respiratory tract infection present at entry compared with infections occurring during the previous 3 months.

	Previous Infections (mean over 3 previous months)	Infection Treated with Broncho-Vaxom at Entry	Reduction
Time to improvement (mean ± SD)	6.77 ± 4.42 days (n = 552)	3.76 ± 2.18† days (n = 517)	44.4%
Time to cure (mean ± SD)	11.86 ± 8.41 days (n = 539)	7.36 ± 4.93† days (n = 498)	37.9%

*Trademark: Laboratoires OM, Geneva, Switzerland.
†$P < 0.001$, paired Student's t test.

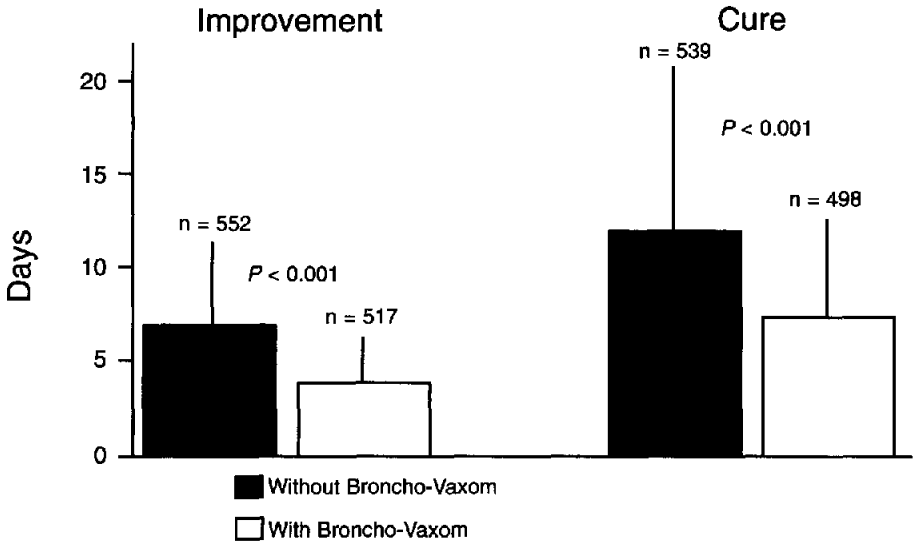

Figure 1. Elapsed days (mean ± SD) to improvement and cure in patients with an acute respiratory tract infection who received Broncho-Vaxom®* compared with similar infections in these patients during the 3 months before the study (without Broncho-Vaxom). ($P < 0.001$, by Student's t test.) *Trademark: Laboratoires OM, Geneva, Switzerland.

biotic treatments. In the patients with recurrent infections during the study, decreases in the time to show improvement and the time to cure were 79.6% and 82.6%, respectively.

The percentage of patients without infections 1 month before treatment was 3.5% (n = 569); this figure increased to 76.8% (n = 531) in the third month of treatment. As for absenteeism, 1 month before treatment 19.7% (n = 386) of the patients had not been absent due to infections, while during month 3 of treatment this figure increased to 91.1% (n = 403). The proportion of patients not requiring antibiotic treatment increased from 7% (n = 556) to 86.2% (n = 528) during the same period. Figures 3 to 5 show the monthly changes in the number of infections, the number of absentee days, and the number of antibiotic treatments as percentages of patients.

Fourteen (2.4%) of the 587 patients reported adverse events: asthenia and adynamia in 3 patients, diarrhea in 3, rash in 2, fever in 2, exacerbation of symptoms in 2, adenitis in 1, and flulike syndrome in 1. The adverse events were mild to moderate in severity and disappeared spontaneously; all affected patients completed the treatment. It is worth noting that weight gain and increased appetite were reported in 16 (2.7%) patients.

DISCUSSION AND CONCLUSIONS

In contrast to other types of infectious diseases, upper respiratory tract infections are difficult to control; they are highly

Table II. Effects of Broncho-Vaxom®* treatment during the 3 months of follow-up compared with 1 month before trial entry (mean ± SD).

	1 Month Before Entry	Month 1 of Treatment	Month 2 of Treatment	Month 3 of Treatment	Reduction (month 3 of treatment vs 1 month before entry)
No. of infections†	1.79 ± 0.96 (n = 569)	0.92 ± 0.75 (n = 581)	0.47 ± 0.59 (n = 575)	0.24 ± 0.46 (n = 531)	87%
p‡		<0.001	<0.001	<0.001	
Absenteeism (days)§	3.17 ± 3.07 (n = 386)	1.15 ± 1.98 (n = 421)	0.36 ± 0.98 (n = 432)	0.16 ± 0.63 (n = 403)	95%
p‡		<0.001	<0.001	<0.001	
No. of antibiotic treatments†	1.71 ± 1.06 (n = 556)	0.76 ± 0.79 (n = 576)	0.3 ± 0.53 (n = 574)	0.16 ± 0.51 (n = 528)	86%
p‡		<0.001	<0.001	<0.001	
Time to improvement (days)‖	5.46 ± 3.28 (n = 540)	3.71 ± 2.47 (n = 404)	3.0 ± 1.59 (n = 231)	2.79 ± 1.36 (n = 106)	49%
p‡		<0.001	<0.001	<0.001	
Time to cure (days)‖	8.71 ± 3.96 (n = 522)	5.98 ± 3.49 (n = 397)	4.86 ± 2.35 (n = 230)	4.54 ± 2.26 (n = 108)	48%
p‡		<0.001	<0.001	<0.001	

*Trademark: Laboratoires OM, Geneva, Switzerland.
†Based on total number of observed patients.
‡Probability assessed by using Wilcoxon matched-pairs test.
§Includes only patients attending day care centers or schools.
‖Includes only patients experiencing a recurrent respiratory tract infection during the study.

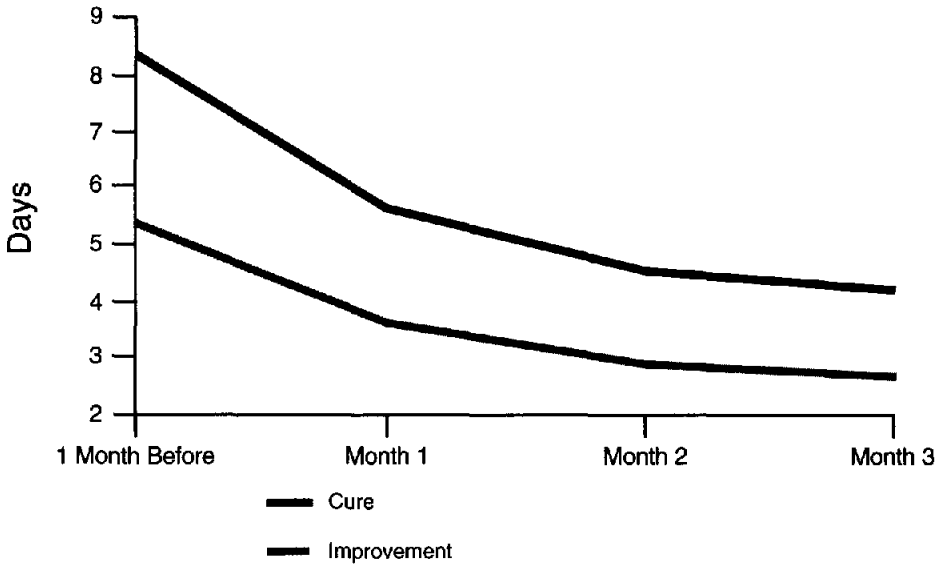

Figure 2. Mean elapsed days to improvement and cure in children with an acute respiratory tract infection before entering the study and after receiving 1, 2, and 3 months of treatment with Broncho-Vaxom®*. *Trademark: Laboratoires OM, Geneva, Switzerland.

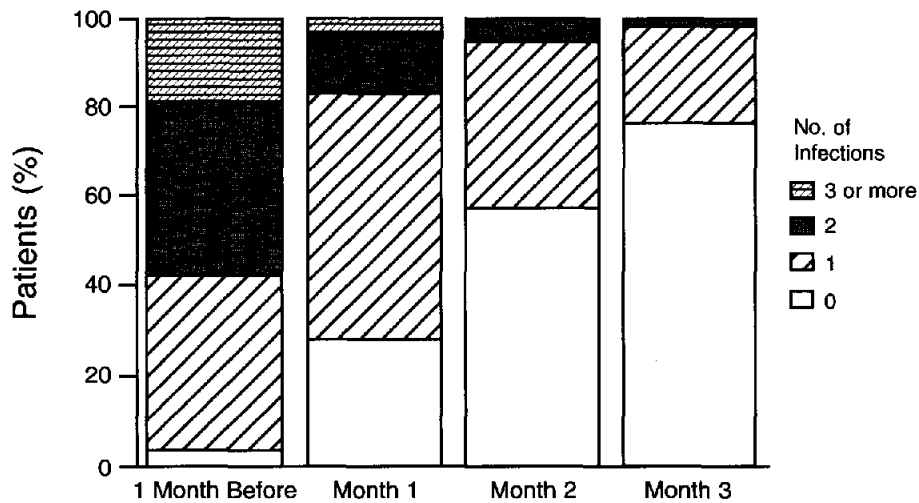

Figure 3. Distribution in percentages of patients suffering from 0, 1, 2, or 3 or more infections per month during the month before starting treatment with Broncho-Vaxom®*, and after 1, 2, and 3 months of treatment. *Trademark: Laboratoires OM, Geneva, Switzerland. $P < 0.001$, Wilcoxon matched-pairs test, month 1 versus month 3.

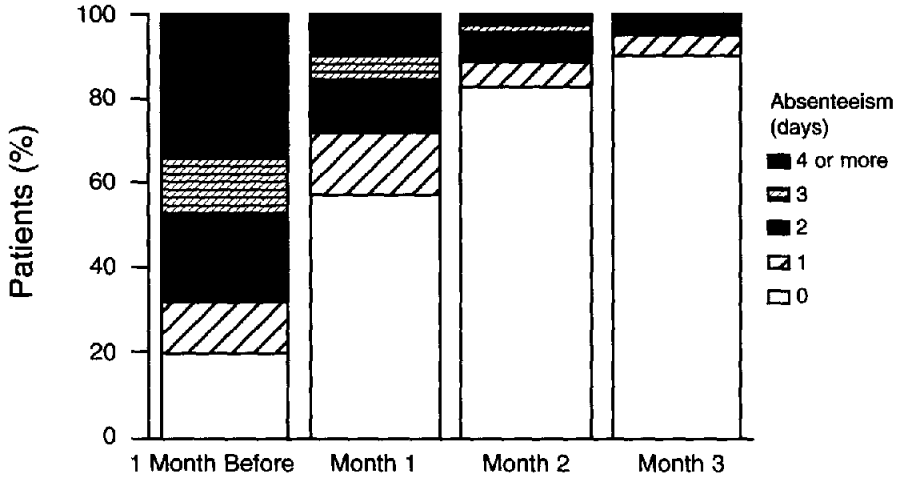

Figure 4. Distribution in percentages of patients with 0, 1, 2, 3, or 4 or more absentee days during the month before starting treatment with Broncho-Vaxom®*, and after 1, 2, and 3 months of treatment. *Trademark: Laboratoires OM, Geneva, Switzerland. $P < 0.001$, Wilcoxon matched-pairs test, month 1 versus month 3.

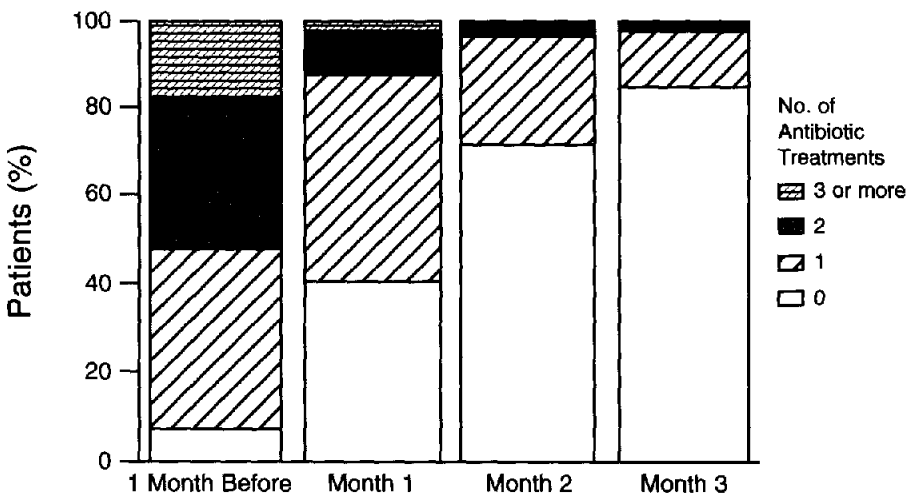

Figure 5. Distribution in percentages of patients receiving 0, 1, 2, or 3 or more antibiotic treatments per month during the month before starting treatment with Broncho-Vaxom®*, and after 1, 2, and 3 months of treatment. *Trademark: Laboratoires OM, Geneva, Switzerland. $P < 0.001$, Wilcoxon matched-pairs test, month 1 versus month 3.

contagious, yet immunizing children against each etiologic agent is impractical. Although upper respiratory tract infections generally are not serious conditions, they are the most frequent cause of absenteeism from school and day care centers and, therefore, they are a principal cause of absenteeism from work for parents.[27,28] Additionally, upper respiratory tract infections are associated with otitis and hearing impairment.[27–29] Thus preventing such infections is important. In Europe, immunomodulation therapy has been found to be a practical way to prevent upper respiratory tract infections.[7–16,30,31]

Although the exact mode of action of the immunomodulator Broncho-Vaxom is not fully understood, we know it enhances the body's main mechanisms of defense, such as the production by phagocytes of immunoglobulins in serum and secretions and the reactivity of T cells.[1,2,8,9]

In this study, Broncho-Vaxom was evaluated by physicians in private practice in several major Mexican cities. (The results of the study represent the perception of physicians about this agent.) The aim of this study was to learn how effective and safe the drug would be in this setting. Such Phase IV studies complement controlled clinical trials with restrictive patient selection criteria, because the Phase IV studies comprise the heterogeneous patient population found in private practices.[20,22,24]

In this study, 2.4% of the patients experienced adverse events while receiving Broncho-Vaxom. The incidence of adverse events is similar to that found in previous clinical trials.[30] The most frequently reported adverse events were gastrointestinal disorders, rash, headache, fever, and exacerbation of symptoms. In the worldwide postmarketing surveillance of Broncho-Vaxom, 220 patients were reported to have experienced 290 adverse reactions.[31] All the documented adverse events were of limited duration and resolved completely.

Broncho-Vaxom proved to be efficacious in the acute phase of respiratory tract infections present at study entry, markedly reducing the time to improvement and cure. Furthermore, patients treated with Broncho-Vaxom experienced fewer recurrences of infection, were absent less frequently, and required fewer antibiotic treatments. When infections did occur, the time to improvement and cure decreased. The early effect might be attributed to the modulation in the phagocytic system, while the prophylactic effect might be ascribed to the activation of the humoral and cellular immune system. The decrease in absenteeism was due to the lower incidence of infections and probably also to the decreased severity and shorter duration of the disease.

The decrease in the use of antibiotics could be attributed to the lower incidence of infections, to the decreased severity of the infections, and to the higher proportion of infections considered to be viral in origin. These results must be viewed in light of the possible role of the placebo effect.

Our findings are consistent with previous controlled studies[11–16] of patients with sinusitis, chronic bronchitis, and other respiratory tract infections. In these earlier studies, Broncho-Vaxom therapy was associated with reductions in the symptoms and the mean duration of the acute episodes and the number of recurrent infections. Consequently, less concomitant medication was used by the patients.

A meta-analysis[32] of Broncho-Vaxom trials showed the beneficial pharmacoeconomic effects in adults with exacerbations of chronic bronchitis infections. We found

the drug to be an effective complement to antibiotic treatment in the acute phase of respiratory tract infections, as it appears to reduce the susceptibility to such infections. Broncho-Vaxom appears to have an important pharmacoeconomic impact on the lives of patients by reducing absenteeism and the need for concomitant antibiotic treatment. Although pharmacoeconomic variables were not directly assessed in our trial, it appears that Broncho-Vaxom could have a positive pharmacoeconomic impact in the treatment of children as it was shown to have in adults.[32]

We conclude that Broncho-Vaxom is effective and safe for the treatment of the acute phase of respiratory tract infections and for preventing recurrences of these infections in children younger than 12 years of age.

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