Safety and Efficacy of Two Courses of OM-85 BV in the Prevention of Respiratory Tract Infections in Children During 12 Months*

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Background: **Acute respiratory tract infections (ARTIs) are among the main causes of morbidity and mortality in children. The bacterial extract OM-85 BV (bronchovaxom) has shown protective effect for ARTIs on children. We report a double-blind, placebo-controlled, parallel, prospective clinical trial to assess the safety and efficacy of two courses of OM-85 BV in the prevention of ARTIs in susceptible children during 12 months.**

Methods: **Fifty-four susceptible children from 1 to 12 years of age living in the metropolitan area of Chihuahua City were selected. They were randomized to receive either OM-85 BV or placebo (one capsule a day for 10 days a month for 3 consecutive months) at the beginning of the trial and 6 months later with the same schedule. Patients were followed up for 12 months, including the administration period. The trial began in July 1997 and ended in April 1999.**

Results: **The number (mean ± SD) of ARTIs was 5.04 ± 1.99 (median, 5.0) in the OM-85 BV group vs 8.0 ± 2.55 (median, 8.0) in the placebo group, with a mean difference of − 2.96 (95% confidence interval [CI], − 4.22 to − 1.7). The number of antibiotic courses was 2.46 ± 2.08 (median, 1.5) in the treatment group vs 4.46 ± 2.08 (median, 4.0) in the control group, a difference of − 2.0 (95% CI, − 3.14 to − 0.86). The total duration of ARTIs was 35.23 ± 17.64 days (median, 30.5 days) in the OM-85 BV group vs 60.75 ± 25.44 days (median, 55.0 days) in the placebo group, *ie*, a difference of − 25.52 days (95% CI, − 37.56 to − 13.47 days), $p < 0.001$ by Student's *t* test and Mann-Whitney *U* test for all the items. Four patients in the OM-85 BV group had five adverse events. Only one episode of skin rash was related to the medication intake. Six patients in the control group had six adverse events.**

Conclusions: **OM-85 BV had a preventive effect on ARTI in the susceptible children for 12 months with an important reduction on the antibiotic requirements and the number of days of suffering ARTIs.**

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Key words: acute respiratory tract infection; immunostimulant; OM-85 BV; prevention

Abbreviations: ANOVA = analysis of variance; ARTI = acute respiratory tract infection; CI = confidence interval; IL = interleukin; RTI = respiratory tract infection

Respiratory tract infections (RTIs) are considered by the World Health Organization as the forgotten pandemic[1]; they are the worldwide main cause of death in children < 5 years old and produce 8.2% of the total disease burden.[1] In the developed countries, RTIs are the leading cause of morbidity, accounting for 20% of medical consultations, 30% of labor absenteeism. and 75% of all antibiotic prescriptions[1–3]. Acute RTIs (ARTIs) in children are associated with acute otitis media, which is an important cost for health-care services and can be related to hearing loss[2] and learning problems,[4,5] even in those treated properly.[6]

The main measure to avoid deaths and disabilities related to RTI is to prevent these infections and provide early antibiotic treatment when indicated.[1,7,8] Several interventions to induce nonspecific protection against ARTIs have been recently studied, such as zinc supplementation,[9] administration of *Echinacea purpurea* extract,[10] as well as intranasally administered immunoglobulins for the prevention of rhinitis,[11] and the use of xylitol sugar syrup and chewing gum for protection against otitis media.[12]

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On this line, OM-85 BV (bronchovaxom; OM PHARMA; Geneva, Switzerland; marketed in Mexico by Química Knoll de México) is an immunostimulant for the prevention of ARTIs. OM-85 BV is the product of alkaline proteolysis from lysates of the following bacteria: *Haemophilus influenzae*; *Streptococcus pneumoniae*; *Klebsiella pneumoniae*; *Klebsiella ozaenae*; *Staphylococcus aureus*; *Staphylococcus pyogenes*; *Streptococcus viridans*; *Moraxella catarrhalis*.[13] Each strain contributes the same relative proportion to the total protein. OM-85 BV is mainly made of d-amino acids polypeptides (data on file).

OM-85 BV is free of lipopolysaccharides; therefore, it does not act on lipopolysaccharides receptor CD 14.[14] In macrophage and monocytic cells, OM-85 BV increases intracellular calcium levels and induces the production of glucose regulated protein 78[15] and c-*fos*/serum response element protein.[16,17] These second messengers induce the expression of proinflammatory cytokines interleukin (IL)-1α, IL-6, IL-8, and tumor necrosis factor-α.[16–19] Additionally, OM-85 BV induces phagocytic cells to produce nitric oxide and oxygen,[19] and to express adhesion molecules.[14,20]

Patients receiving OM-85 BV have shown enhancement of cellular immune responses,[21,22] increase in secretory IgA[23–25] and serum IgA,[26,27] serum IgG and IgM,[23,27] and activation of phagocytic cells.[24,25] OM-85 BV has shown safety and efficacy in the prevention of ARTIs in exposed children attending day-care centers[28] and orphanages[29] and in highly susceptible children.[30,31] OM-85 BV has been shown to have some effect on children suffering from immune system defects such as IgG or IgA deficiency and common variable immunodeficiency.[32,33]

The longest OM-85 BV trials have comprised periods of 6 months, with only one course of administration. We proposed that two courses of OM-85 BV would provide protection for 12 months. The aims of the present trial were to evaluate the safety and efficacy of two courses of OM-85 BV in the prevention of ARTIs in susceptible children for 12 months.

Materials and Methods

A placebo-controlled, parallel, prospective trial was conducted. The patients were children from 1 to 12 years of age living in the metropolitan area of Chihuahua City, Chihuahua State, Mexico. The families were cared for under the state (Pensiones Civiles de Chihuahua, free medical services for workers of state government).

An upper ARTI was defined as the presence of at least one of the following signs: rhinorrhea; sore throat or cough, without signs of lower ARTI, for $\geq$ 48 h. Lower ARTI was defined as the presence of at least one of the following signs: rales or crepitations, wheezing, stridor, respiratory rate > 50/min, cyanosis, or chest indrawing for > 48 h. Otitis was defined as acute onset of earache with erythema and limited mobility of the tympanic membrane determined by pneumatic otoscopy. Similar upper and lower ARTI definitions have been used in epidemiologic studies[34] in developing countries.

In a previous clinical trial[35] in Mexico, the placebo group presented 2.99 $\pm$ 0.81 ARTIs in 6 months; therefore, we projected about 6 $\pm$ 1.6 ARTIs in a 12-month period, and a 50% reduction in the incidence of ARTI according to previous trials[31,34] in Mexico. Considering a difference of 3.0 $\pm$ 3.0 ARTIs between the groups during 12 months, the calculated sample size by group was 23, as calculated by software (Primer on Statistics 3.0; Mc-Graw-Hill; New York, NY).

The selection criteria were as follows: at least three ARTIs registered on clinical files of the social security system during the previous 6 months; negative familial history of allergy; no seasonal or food-related wheezing and nasal itchiness; absence of nasal folds, with no anatomic alterations of the respiratory tract by physical examination; chronic respiratory diseases (tuberculosis, cystic fibrosis); autoimmune diseases; liver failure; kidney failure, malnutrition, or cancer; and no treatment with corticosteroids, immunosuppressants, immunostimulants, γ-globulins, or anticonvulsive drugs in the last 6 months.

Informed consent for each participant was obtained from the parents at entry. Children $\geq$ 3 years old gave their oral consent. The protocol and case report form were approved by the local committee of investigation and ethics and were performed according to the Mexican regulation and the Helsinki Declaration of 1975, as revised in 1983.

After selection criteria were completed, consecutive numbers were assigned to patients. The numbers had been previously randomized to the treatment groups in balanced blocks of 10. The treatment for each patient number was prepared in advance. The boxes, blisters, and capsules had the same appearance and the taste of the powders was similar.

The patients received one capsule po, OM-85 BV (3.5 mg) or placebo, per day in a month for 10 consecutive days per month for 3 consecutive months at the beginning. Children < 5 years old received powder from open capsules, and children > 5 years old received capsules. The capsules or powder were administered by the parents, and the empty blisters were kept to control compliance. The administration schedule was repeated 6 months after the beginning.

Patients were assessed monthly and every time they presented respiratory symptoms, and all the ARTIs were followed up to the complete disappearance of all the symptoms. All the physical examinations and drug prescriptions were made by one of the authors (M.D.G.T.). Antibiotics were prescribed when purulent secretions were present, or in the case of otitis or lower ARTI. The medication codes were enclosed in opaque sealed envelopes and kept available for the researcher in the study center to be opened in case of a serious adverse event. The trial began in July 1997 and was completed by April 1999. Patients were recruited from July 1997 to April 1998.

The characteristics of ARTIs were registered on the case report form as they occurred: type (upper, lower, or otitis) and number of infections (main end point), and when a child had school absenteeism secondary to an ARTI (as days out of school due to ARTIs), number of antibiotic or other drug courses (any drug course including antibiotics), duration of the treatment (days taking any medication), and time of convalescence (days elapsed to clinical cure assessed) (secondary end points).

The end point differences between the groups were analyzed by analysis of variance (ANOVA) for repeated measures, Student's t test, and Mann-Whitney U test using statistical software (SPSS; Chicago, IL). Additionally, the relative risks for more than six, more than seven, and more than eight ARTIs and more than one otitis were calculated, as well as the comparison of rate of patients having less than six ARTIs throughout the 12-month period by Kaplan-Meier statistics.

Two infections were counted as such only when the patient was without symptoms for at least 72 h between the end and the beginning of the episodes. A treatment course was considered as such, when at least one drug dosage for 1 day of treatment was completed.

Clinical cure was defined as the complete resolution of all the symptoms assessed. The visual analog scale for ARTI severity was a line of 114 mm with a mark on the left end with the legend "very mild" (minimal complaint; there were no limitations for normal activities), one in the middle with the legend "moderate" (complaints did not allow to perform some normal activities), and one on the right end with the legend "very severe" (major complaints did not permit any normal activity); the scale was marked only by one of the authors.

Adverse events were registered in clinical files and in the adverse report form as they occurred and were reported monthly in the case report form. The trial medications and case report forms were provided by Química Knoll de México SA de CV BASF Pharma.

Results

Fifty-four of 100 children were selected to enter the trial. The nonincluded children suffered seasonal or food-related wheezing or nasal itchiness. Patients were reminded of follow-up visits. Only one boy in the OM-85 BV group was unavailable for follow-up in the last assessment, and the rest of the trial participants completed the scheduled clinical assessments.

All the envelopes containing the double-blind code for the treatment numbers were collected after the end of the study. Based on the empty blisters, compliance was > 90% in all the patients. In the OM-85 BV group, 18 children received powder and 8 children received capsules; in the placebo group, 16 children received powder and 12 children received capsules.

Table 1—*Demographic Characteristics of the Groups***

Characteristics	OM-85 BV (n = 26)	Placebo (n = 28)
Age, yr	3.86 ± 2.49	4.52 ± 2.75†
median (percentiles 25, 75)	3.21 (2.08, 5.52)	4.33 (2.37, 6.1)
Sex, No. (%)‡		
Male	13 (50)	18 (64.3)
Female	13 (50)	10 (35.7)
Weight, kg	15.65 ± 4.95	17.49 ± 6.55†
Height, cm	100.57 ± 22.13	104.25 ± 20.94†
ARTIs in the last year	12.33 ± 4.7	12.26 ± 3.99†
Antibiotic courses in the last year	9.87 ± 3.26	8.85 ± 3.05†

*Data are presented as mean ± SD unless otherwise indicated.
†$p > 0.05$ by Student's *t* test and Mann-Whitney *U* test.
‡$p > 0.05$ by χ^2.

Table 2—*Risks Factors for the Groups***

Factors	OM-85 BV	Placebo
Birth		
Gestational age, mo	8.85 ± 0.37	8.86 ± 0.33†
Birth weight, kg	3.2 ± 0.57	3.3 ± 0.55†
Breast feeding time, mo	5.69 ± 4.79	5.89 ± 3.0†
Birth ranking‡		
First	14	12
Second	11	13
Third	1	2
Fourth	—	1
Children living at home‡		
None	5	2
One	18	18
Two or more	3	8
Persons living at home	3.15 ± 0.78	3.39 ± 0.87†
Siblings in day-care center‡		
None	21	23
One	5	5
Siblings in school		
None	16	10
One	10	12
Two or more	—	6
Time of attendance at day-care center or school‡		
No attendance	10	10
1–11 mo	3	4
12–23 mo	4	5
≥ 24 mo	9	9
Persons smoking at home‡		
None	21	17
One	4	11
Two	1	—
Socioeconomic level‡		
Low	2	5
Middle	23	20
High	1	3

*Data are presented as No. or mean ± SD.
†$p > 0.05$ by Student's *t* test and Mann-Whitney *U* test.
‡$p > 0.05$ by χ^2.

Both groups had similar demographics at the beginning of the trial ($p > 0.05$; Table 1). The reported ARTIs incidence the year before was > 12 in both groups. Most of these ARTIs were from mild-to-moderate severity. The risks factors for ARTIs were similar ($p > 0.05$), except the number of siblings in the school that was higher in the placebo group (Table 2). Twenty children in the OM-85 BV group and 17 in the control group had antecedents of otitis with moderate severity; they suffered 2.45 ± 1.1 and 2.53 ± 2.03 otitis episodes in the last year, respectively.

During the trial, 131 ARTIs were recorded in the OM-85 BV group and 224 in the placebo group (Table 3). The patients in the OM-85 BV group had a lower relative risk of one or more otitis episodes of 0.323 (95% confidence intervals [CI], 0.100 to 1.046; a trend for a lower risk), as well as lower relative risks

Table 3—*No. and Kind of ARTIs During the Trial*

Variables	OM 85 BV (n = 26)	Placebo (n = 28)
Upper ARTIs	125	204
Lower ARTIs	3	6
Otitis	3	14

for six or more, seven or more, or eight or more ARTIs of 0.374 (95% CI, 0.205 to 0.684), 0.323 (95% CI, 0.154 to 0.677), and 0.287 (95% CI, 0.109 to 0.754), respectively.

Figure 1 represents the mean incidence of ARTIs from data organized in calendar months. There were significant lower incidences of ARTIs in the months of May, June, July, and August in the OM-85 BV group ($p < 0.05$ by Mann-Whitney U test), and a trend from January to March and from September to December. Figure 2 represents the percentage of patients having less than six ARTIs throughout the consecutive 12-month period. The OM-85 BV group had fewer ARTIs than the placebo group.

We explored the possible effect of time of inclusion in the ARTIs incidence. We performed a multiple ANOVA for repeated measures for the monthly consecutive incidence of ARTIs considering drug treatment and month of inclusion as factors; there was no effect of the time of inclusion, nor interaction between the time of inclusion and the treatment group in the global incidence of ARTIs ($p > 0.05$). In the same way, when incidence data were ordered in calendar months and tested by multivariate ANOVA, there was no effect of the time of inclusion, nor interaction between the time of inclusion and the treatment group in the global incidence of ARTIs ($p > 0.05$).

The numbers of patients included per month from July 1997 to February 1998 were 5, 1, 8, 12, 11, 5, 7, and 5, respectively. Table 4 contains the mean and SDs and difference for the trial end points; the number of ARTIs; illness duration; number of antibiotic courses; number of drug courses (treatment courses including antibiotics); duration of concomitant treatment (number of days receiving any drug treatment); and days out of school.

Except for the absenteeism, the cumulative figures of the end points showed a significant difference between the groups from the second month of the trial to the end of the trial ($p < 0.05$ by Student's t test, and Mann-Whitney U test). The ANOVA for repeated measures for the monthly evolution of such variables (except absenteeism) showed a significant difference between the groups and within the groups as well as significant interaction of the effect of the groups and the different measures throughout the trial ($p < 0.01$).

Regarding the monthly severity score in visual analog scale for consecutive months, there were significant differences ($p < 0.05$ by Student's t test) in month 2 (OM-85 BV 21.81 ± 6.81 vs placebo 30.64 ± 13.02) and month 12 (20.61 ± 5.61 vs 30.47 ± 12.05, respectively).

If we only considered the children with ages < 6 years, the OM-85 BV group (n = 23) had 4.87 ± 1.94 ARTIs and the placebo group (n = 21) had 8.28 ± 2.85 ($p < 0.01$ by Student's t test and Mann-Whitney U test), *ie*, a difference of − 3.42 (95% CI, − 4.92 to − 1.91), 41.18% fewer infections.

Four patients in the OM-85 BV group had five adverse events. One patient experienced one episode of papular rash and 9 months later bronchospasm,

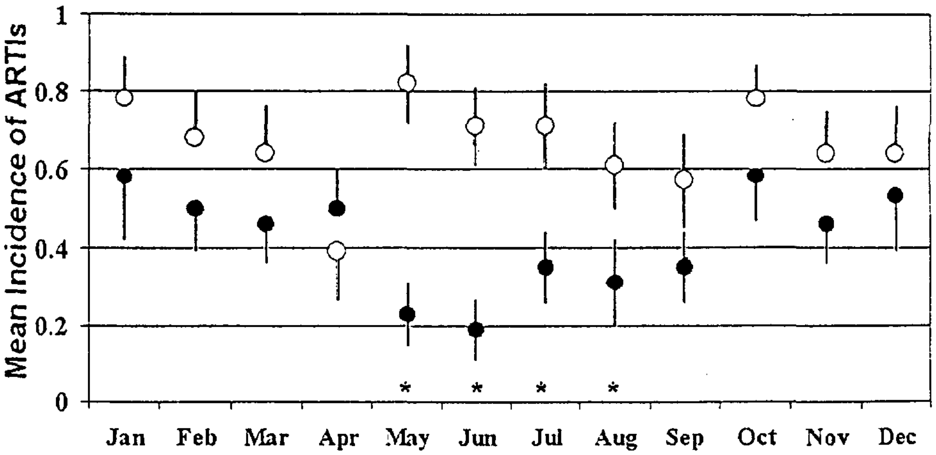

FIGURE 1. Number of ARTIs by calendar month. The graphic represents the mean ± SE ARTIs by group monthly. The bold figures and bars correspond to the OM-85 BV group and the open figures and bars to the placebo group. * = $p < 0.05$ by Mann-Whitney U test.

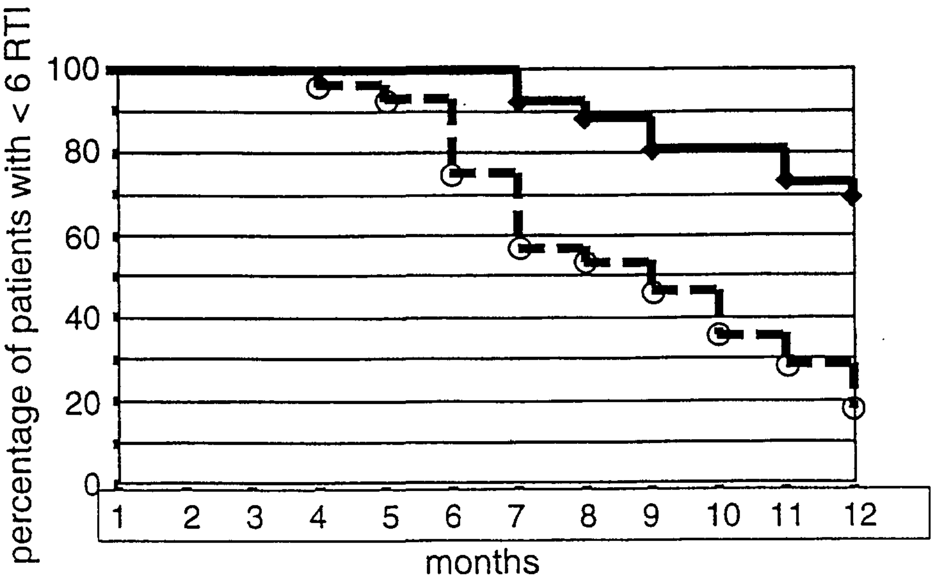

FIGURE 2. Percentage of patients having less than than six ARTIs throughout the consecutive 12-month period. This graphic represents the occurrence of the event of six ARTIs in the Kaplan-Meier survival plot fashion and statistics. The bold line corresponds to the OM-85 BV group and the broken line to the placebo group. The evolution of the groups was statistically different ($p < 0.001$ by test log rank, Breslow and Tarone-Ware).

another patient underwent kidney surgery to correct hydronephrosis, another suffered tongue and lip herpes, and another had conjunctivitis. Only the rash was considered to be related to the medication intake. Six patients in the control group had six adverse events. One patient had bronchospasm, another had otitis externa, another had salmonellosis, two patients suffered seizures due to fever provoked by ARTI, and another patient underwent a tonsillectomy.

Discussion

RTIs are important causes of morbidity, mortality, and disability in children,[1–3] and therefore are one of the main costs for the health-care system.[36,37] In order to reduce the incidence and complications of RTIs, it is necessary to explore new alternatives for the prevention of this kind of infection.

We have presented a trial to investigate the safety and efficacy of the bacterial extracts OM-85 BV covering a period of 12 months with two courses of administration. We tried to exclude the patients with the clinical suspicion of allergy from the trial (familial history of allergy, seasonal or food-related wheezing or nasal itchiness, or nasal folds); yet, presence of allergy cannot be completely ruled out. As the definitions for upper and lower ARTIs overlap with allergy symptoms, it is possible that some allergy

Table 4—*End Point Data**

Variables	OM-85 BV (n = 26)	Placebo (n = 28)	Difference, 95% CI
ARTIs, No.	5.04 ± 1.99	8.0 ± 2.55	− 2.96 (− 4.22, − 1.7)†
	5.0 (4.0, 6.25)	8.0 (6.0, 10.0)	
Total duration of illness, d	35.23 ± 17.64	60.75 ± 25.44	− 25.52 (− 37.56, − 13.47)†
	30.5 (21.5, 45.5)	55.0 (43.0, 78.5)	
Antibiotic courses, No.	2.46 ± 2.08	4.46 ± 2.08	− 2.0 (− 3.14, − 0.86)†
	1.5 (1.0, 4.25)	4.0 (3.0, 6.0)	
Drug courses (including antibiotics), No.	5.04 ± 1.99	7.96 ± 2.56	− 2.92 (− 4.18, − 1.67)†
	5.0 (4.0, 6.25)	7.5 (6.0, 10.0)	
Duration of treatment (days taking any drug), No.	35.65 ± 18.61	60.79 ± 24.01	− 25.13 (− 36.93, − 13.33)†
	31.0 (20.0, 46.25)	55.5 (46.25, 76.5)	
Absenteeism (days out of the school or day-care center), No.‡	3.64 ± 3.18	5.81 ± 9.76	− 2.17 (− 7.68, 3.35)
	3.5 (0.75, 6.0)	2.0 (0.5, 6.5)	

*Data are presented as mean ± SD or median (percentiles 25, 75) unless otherwise indicated.
†$p < 0.001$ by Student's t test and Mann-Whitney U test.
‡Due to ARTI, only children attending school or day-care center.

clinical pictures were diagnosed as ARTIs. However, the randomization would distribute the effect in both groups.

The mean number of infections showed a reduction in the OM-85 BV group with respect to the placebo group. In contrast, Mexican 6-month trials have showed a reduction in infections of 2.25 ± 0.58 vs 4.68 ± 0.94, *ie*, 52% (ages, 1 to 11 years),[31] and another reduction of 1.43 ± 0.94 vs 2.99 ± 0.81 (52%) in patients aged 6 to 13 years.[35]

When ARTI data were grouped by calendar months, the OM-85 BV effect was significant from May to August and had a trend from September to December: larger sample sizes would be required to detect these monthly differences. In a previous trial,[35] when all the patients began treatment with the trial medications in September, the preventive effect of OM-85 BV could be demonstrated from October to February.

It is important to note that the number of ARTIs as well as the number of antibiotic courses decreased in both groups regarding the period before the trial. It is possible that as the children grew older, they had a lower incidence of ARTI or that there had been a previous overreport. The reduction in the use of antibiotic may be ascribed to the decrease in the number of ARTIs and to close follow-up of the patients. It was not possible to detect a consistent effect of the medication in the severity of ARTIs, because of the small number of patients suffering from ARTIs in the OM-85 BV group.

The duration of the illness, courses of antibiotics or other drugs, and the duration of therapy are dependent on the number of ARTIs and their decrease; in fact, it could be considered that only the number of ARTIs is significantly different. Considering a low cost of treatment-day of $5 (US dollars) (for instance, the public price of a day of penicillin treatment in Mexico is $5) and duration of treatment of 7 days per episode, a reduction of three ARTIs per patient would save at least $105 in medications per year. Seventy percent of the children receiving OM-85 BV had less than six ARTIs compared to 20% in the placebo group.

There was a trend to have lower absenteeism in the OM-85 BV group, but it was not significant, in contrast to the other Mexican trials[31,35] that showed this effect. Days out of school or day-care center may depend more on the parents criteria or in the policy of each center in this study. Similarly, there was a trend toward reduced otitis media in the OM-85 BV group regarding the placebo group. The protection against otitis was found in the other trials.[31,35] The small sample size is a major shortcoming of this study. The safety of OM-85 BV was good; only one patient suffered an adverse event, a rash that was related to the capsule administration.

It would be important to conduct multicenter trials to validate the benefits of OM-85 BV treatment in younger children, those with viral RTI, and children prone to otitis, including an adequate number of patients in each month. The use of immunostimulation may be considered as an important tool to reduce the incidence of ARTI and its complications, such as otitis media, and therefore to diminish the costs associated with ARTIs. We conclude that OM-85 BV is an important option for the prevention of ARTI. Further larger multicenter investigations in the prevention of otitis and other RTI complications are suggested.

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