

Efficacy and safety of ribosome-component immune modulator for preventing recurrent respiratory infections in socialized children

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ABSTRACT

Attending day care is associated with recurrent respiratory infections (RRIs) and asthma. Ribosomal immunotherapy may confer protection against RRIs in children. This study was designed to assess the efficacy of a ribosome-component immune modulator (RCIM) as preventive treatment of respiratory infections in socialized children aged ≤ 5 years, with or without a history of frequent RRI. In a multicenter, Italian, randomized, double-blind, placebo-controlled, parallel-group study, 164 socialized day care center children (mean age, 3.8 ± 1.1 years) were treated with RCIM or placebo for 6 months and followed-up for additional 6 months. Outcomes are presented for the intent-to-treat population. In socialized children with five or less RRIs ($n = 95$; 49 RCIM and 46 placebo, group A) the duration of the infectious episodes was significantly shorter with RCIM than with placebo (6 months, 3.7 ± 2.1 versus 4.5 ± 1.9 days, $p = 0.040$; 12 months, 3.6 ± 2.0 versus 4.7 ± 2.5 days, $p = 0.015$). The proportion of patients reporting no respiratory infectious episodes with RCIM at 6 and 12 months was also significantly larger in group A (20.4% versus 4.4% placebo; $p = 0.028$). No such differences were found in children with more than five RRIs in the preceding year ($n = 63$; 32 RCIM and 31 placebo, group B). In all children, general well-being improved significantly more under RCIM than under placebo ($11.6 \pm 1.8\%$ versus $10.2 \pm 1.8\%$; $p = 0.002$). No statistically significant between-treatment differences were observed for other end points. Both treatments were similarly well tolerated. Six-month treatment with RCIM effectively prevented the 12-month risk of RRIs in children < 5 years old and with five or less RRIs in the preceding year.

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Recurrent infections of the upper and lower respiratory tract commonly occur at all ages but particularly in children. In developed countries, $>25\%$ of infants in their first year of life and $\sim 20\%$ of children between 1 and 4 years of age suffer from recurrent respiratory infections (RRIs).^{1,2} An increased risk of respiratory infection is known to occur in children who attend day care centers³ and is usually seen in a seasonal pattern related not only to the times at which these children enter into these settings but also to the social interactions that occur there. These RRIs impact significantly on the quality of life⁴ and not only cause significant morbidity, but are also responsible for increased use of

medical resources, costs of care and medication, lost school days, and parental absence from work.^{5,6}

To address these issues, a form of bacterial immunomodulation has been developed aimed at inducing specific immunity against the bacteria most frequently involved in respiratory infections and at enhancing nonspecific immune responses against infections of different viral and bacterial origin.⁷ The overall efficacy of a ribosome-component immune modulator (RCIM) in the prevention of RRIs in high-risk subjects, such as elderly people, adults with chronic obstructive pulmonary disease, and children has been proven by several small-size clinical studies.^{8–10} However, evidence on efficacy of RCIM is scanty and dated in very young children and from large, well-conducted, double-blind, randomized, placebo-controlled trials.^{11,12} In addition, no information is available on the preventive efficacy of RCIM in relatively low-risk children such as those undergoing “social interactions,” experiencing fewer respiratory infections during the year. For these reasons the present study was performed to evaluate the efficacy and safety of RCIM compared with placebo in a large sample of such children < 5 years old with or without a history of previous RRIs.

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METHODS

Study Objective

The specific primary study end point was the comparison of the overall duration of the respiratory infectious episodes between RCIM and placebo at 6 months, separately for children with five or less recurrent respiratory infectious episodes in the preceding year (group A) and for those with more than five episodes (group B). Because there is no consensus on the number of critical episodes for the definition of recurrences in children, with most studies indicating a criterion of three to five episodes, a five-episode threshold was “*a priori*” selected for identification of the two study groups.¹⁰

Study Population

Children of both genders, aged 2–5 years, with no congenital and/or clinically relevant diseases, already attending or expected to attend within the following 3 months a day care setting, were eligible for study participation. Main exclusion criteria were (a) RRIs in the week preceding enrollment in the study, (b) other contemporary acute infections requiring hospitalization or intensive care, (c) gastroesophageal reflux, (d) cystic fibrosis, $\alpha 1$ antitrypsin deficit, (e) ciliary dyskinesia, (f) severe systemic diseases, (g) low weight (body mass index for age below the third percentile), (h) congenital immunodeficiencies, (i) treatment with immunostimulant or immunosuppressive agents in the past 2 weeks, and/or (j) known hypersensitivity to the drug under study. The study was registered at the Italian Agency for Drug of the Italian Ministry of Health (code PIERFAB_IV_2008_001) and at the European Medicine Agency (EudraCT no. 2008-000487-17), and was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki, and the protocol was approved by the Ethics Committees of the centers involved. Written informed consent was obtained from the parents or guardians of the children before their inclusion into the study. Children’s recruitment started in August 2008. The last patient completed the study in December 2009.

Study Design

This was a multicenter (four centers), Italian, randomized, double-blind, placebo-controlled, parallel-group study conducted at the outpatient clinic of four Italian pediatric and ear, throat, and nose institutions. Eligible patients were recruited from hospitals in Milan (one center), Genoa (one center), and Varese (two centers). Children were randomly assigned to active treatment with RCIM or to indistinguishable placebo according to a recommended administration protocol consisting of 1-month attack therapy with 1 dose in the morning for 4 days/week for 3 consecutive weeks,

followed by 5-month maintenance therapy with 1 dose in the morning for 4 consecutive days every month. At the end of the 6 months of double-blind treatment, patients were followed-up for 6 months. Thus, the overall study duration was 12 months. The active principle (RCIM) used in the present study is manufactured by Pierre Fabre Medicament, France, and it has different brand name designations in different parts of the world, *viz.*, Ribomunyl in most countries, Ribovac in South America, and Immucytal and Biomunil in Italy, where it is marketed by Pierre Fabre Pharma S.r.l. (Milan, Italy) and by Lusofarmaco S.p.A. (Milan, Italy), respectively. Each active dose contained 0.525 mg of ribosomal extracts from four bacterial strains (*Klebsiella pneumoniae*, 35%; *Streptococcus pneumoniae*, 30%; *Streptococcus pyogenes*, group A, 30%; *Haemophilus influenzae*, 5%) and 1.125 mg of *K. pneumoniae* membrane proteoglycans.¹³ Active drug or placebo was administered once daily before breakfast. The content of the sack had to be dissolved in water before ingestion. Children were regularly visited at the outpatient clinic in the course of the study. A clinical examination was performed and concomitant therapies were recorded at enrollment (day 0, randomization), and after 12, 24, 36, and 52 weeks. Between visits parents were required to fill in a weekly diary by entering any of the following complaints: runny nose, cough, cold, number of physician-diagnosed infections, days of absence from school, days of parental absence from work, antibiotic and bronchodilator use, and use of health care resources. The diary was revised by the physician on each scheduled visit. Child general well-being was evaluated by the physician through a visual analog scale (VAS) ranging between 0 and 10; the assessment was done at baseline and at weeks 24 and 52. In addition to scheduled medical visits, telephone contacts were performed at 3 and 8 days and 18, 30, and 44 weeks after randomization.

Statistical Analysis

Sample size was calculated assuming an 80% power and a reduction in the duration of respiratory infections of 4 days with a common SD of the difference of 8 days. Sample size estimation was based on a two-tailed test with a 5% significance level, taking into account a possible 10% dropout rate. All of the efficacy analyses were performed on patients valid for intent-to-treat, *i.e.*, all randomized patients receiving at least 1 dose of active treatment drug or placebo and having at least one evaluation of the primary efficacy end point. The per-protocol population (all randomized patients completing the 24-week study period without major protocol violation) was used for confirmatory analysis. Safety analysis was applied to all randomized patients treated with at least 1 dose of active study drug or

placebo. Secondary study end points were between-treatment comparison, for groups A and B, of (a) overall duration of the infectious episode at 12 months; (b) frequency of infectious episodes over 6 and 12 months; (c) children's well-being according to VAS; (d) treatment efficacy according to physician's global evaluation; (e) time interval (days) between start of treatment and occurrence of the first infectious episode; and (f) number of days lost for medical consultation (visits or phone calls), school days lost by children, work days lost by parents, and number of days of care by a babysitter or relatives. The analysis of the number of infectious episodes was also performed according to the type of respiratory infection. Categorical variables were compared between groups by a chi-square test, and continuous variables were compared by a Student's *t*-test. The risk and predictors of infectious episodes were also evaluated by a logistic regression analysis, including as independent variables, treatment, age, gender, body mass index, number of episodes in the last year, baseline VAS, change in VAS from baseline to 6 months, presence or absence of smokers in the household, number of children in the same community, and presence of younger children (<12 years old) in the family. The odds ratio and corresponding 95% confidence interval was computed. Data are always shown as absolute and relative frequency (percentages) for categorical variables and as averages and SD or 95% confidence interval for continuous variables. The minimum level of statistical significance was set at $p < 0.05$.

RESULTS

Baseline Demographic and Clinical Characteristics

A total of 164 children were screened and randomized, 84 to RCIM and 80 to placebo. Of these children, 156 completed the study, and 8 discontinued the study because of lack of compliance to study procedures (1 RCIM and 2 placebo), consent withdrawal (1 RCIM), or other reasons unrelated to treatment (2 RCIM and 2 placebo). Overall, 158 patients were valid for the intent-to-treat analysis, of which 81 were in the RCIM group (49 group A and 32 group B) and 77 were in the placebo group (46 group A and 31 group B). The per-protocol population included 155 children (80 for the RCIM and 75 for the placebo group); for all of the evaluated outcomes no results for the per-protocol analysis are reported throughout this article, because these results were in line with those of the intent-to-treat analysis. Table 1 shows the baseline demographic and clinical characteristics of the children of the intent-to-treat population. The two randomization groups were homogeneous for all the variables explored, with no statistically significant between-treatment differences. The overall sample age was 3.8 ± 1.1 years. Most

of the children were of male gender (58.2%), lived together with other children <12 years of age (69.6%), had no smokers in the household (62.7%), and attended a day care community (97.5%). The most common type of RRI in the preceding year was rhinitis, followed by pharyngitis or tonsillitis. The VAS score averaged to 68.9 ± 17.0 .

Duration of the Infectious Episode

In group A the duration of the infectious episode was significantly shorter with RCIM, either over 6 months (3.7 ± 2.1 days versus 4.5 ± 1.9 days with placebo, $p = 0.040$) or 12 months (3.6 ± 2.0 days versus 4.7 ± 2.5 days, $p = 0.015$) of treatment (Fig. 1). This was not the case for group B (0–6 months, 5.4 ± 3.4 days RCIM versus 4.9 ± 3.3 days placebo, $p = \text{NS}$, and 0–12 months, 5.6 ± 3.4 days versus 5.3 ± 3.2 days, $p = \text{NS}$).

Characteristics and Determinants of the of Infectious Episodes

The multivariate logistic regression analysis revealed that the most predictive and significant factor for the development of RRIs during the 6 months of treatment in the whole group of children was the absence or presence of RCIM treatment (odds ratio, 3.7 [95% confidence interval, 1.1, 12.7]; $p = 0.039$; Fig. 2). Both at 6 and 12 months, the most frequently recurring respiratory infectious disease was rhinitis (Fig. 3). According to the multivariate logistic regression analysis the risk of developing rhinitis after 6 months was significantly higher with placebo (odds ratio, 2.3 [95% confidence interval, 1.1, 5.0]; $p = 0.036$; Fig. 2). The time to the first respiratory episode was not significantly different between the two treatments (RCIM, 135.2 ± 8.3 days versus placebo, 129.8 ± 8.4 days; $p = \text{NS}$). The proportion of patients reporting no respiratory infectious episodes was significantly larger in group A under RCIM either at 6 months (20.4% versus 4.4% with placebo; odds ratio, 5.6 [1.2, 27.3]; $p = 0.028$) or 12 months (20.4% versus 4.4%; odds ratio 5.6 [1.2, 27.3]; $p = 0.028$; Fig. 4). No statistically significant between-treatment differences were observed for this measure in group B (6 months: 6.3% RCIM versus 12.9% placebo, $p = \text{NS}$; 12 months, 6.3% RCIM versus 9.7% placebo, $p = \text{NS}$).

Other Secondary End Points

At 6 months, children's well-being improved in both treatment arms but significantly ($p = 0.002$) more under RCIM ($11.6 \pm 1.8\%$) than under placebo ($10.2 \pm 1.8\%$). This was the case also at 12 months (data not shown). The physician's evaluation of treatment efficacy was slightly, but not significantly, better for RCIM. At 6 months, physicians determined that the clinical status improved in 52.3% of patients treated with RCIM and in 48.7% of patients treated with pla-

Table 1 Baseline demographic and clinic characteristics of the children of the intent-to-treat population

	Five or Less Respiratory Infections in the Last Year (group A)		More Than Five Respiratory Infections in the Last Year (group B)		All	
	RCIM (n = 49)	Placebo (n = 46)	RCIM (n = 32)	Placebo (n = 31)	RCIM (n = 81)	Placebo (n = 77)
Age (yr, means ± SD)	3.6 ± 1.0	3.6 ± 1.2	3.8 ± 0.9	3.9 ± 1.2	3.7 ± 1.0	3.8 ± 1.2
Male subjects (n, %)	28 (57.1)	22 (47.8)	21 (65.6)	21 (67.7)	49 (60.5)	43 (55.8)
White subjects (n, %)	49 (100.0)	45 (97.8)	31 (96.9)	31 (100.0)	80 (98.8)	76 (98.7)
Weight (kg, means ± SD)	16.6 ± 3.8	17.1 ± 5.5	16.8 ± 4.5	18.4 ± 4.5	16.7 ± 4.0	17.6 ± 5.1
Height (cm, means ± SD)	100.0 ± 8.8	100.0 ± 8.9	102.0 ± 10.3	103.4 ± 9.9	100.5 ± 9.4	101.3 ± 9.8
Presence of smokers in the family (n, %)	16 (32.7)	14 (30.4)	15 (46.9)	14 (45.2)	31 (38.3)	28 (36.4)
Presence of other children aged <12 yr in the family (n, %)	31 (63.3)	29 (63.0)	23 (71.9)	27 (87.1)	54 (66.7)	56 (72.7)
No. of children in the household (means ± SD)	22.5 ± 10.9	21.2 ± 4.2	22.1 ± 19.9	23.4 ± 21.6	22.3 ± 15.0	22.1 ± 14.0
Community attendance (n, %)	49 (100.0)	46 (100.0)	31 (96.9)	28 (90.3)	80 (98.8)	74 (96.1)
Day care	49 (100.0)	46 (100.0)	31 (96.9)	28 (90.3)	80 (98.8)	74 (96.1)
Kindergarten	10 (20.4)	16 (34.8)	2 (6.5)	4 (12.9)	12 (14.8)	20 (26.0)
Concomitant diseases (n, %)	39 (79.6)	30 (65.2)	29 (93.5)	24 (77.4)	68 (84.0)	54 (70.1)
Total no. of episodes of recurrent respiratory infection in the last year (n, %)	181 (50.1)	180 (49.9)	383 (64.2)	324 (45.8)	564 (52.8)	504 (47.2)
No. of episodes of recurrent respiratory infection in the last year (means ± SD)	3.69 ± 1.67	3.91 ± 1.39	11.97 ± 5.75	10.45 ± 4.76	21 (25.9)	15 (19.5)
Rhinitis	1.59 ± 1.51	1.74 ± 1.44	5.41 ± 3.96	4.87 ± 2.90	9 (11.1)	5 (6.5)
Pharyngitis–tonsillitis	1.06 ± 1.52	1.00 ± 1.43	4.19 ± 4.21	2.90 ± 2.98	5 (6.2)	1 (1.3)
Otitis media	0.67 ± 1.03	0.54 ± 0.98	1.31 ± 1.51	1.52 ± 1.71	21 (25.9)	15 (19.5)
Tracheitis–bronchitis	0.08 ± 0.34	0.35 ± 0.88	0.88 ± 1.66	0.84 ± 1.85	9 (11.1)	5 (6.5)
Bronchitis–pneumonia	0.27 ± 0.73	0.26 ± 0.58	0.19 ± 0.41	0.23 ± 0.43	5 (6.2)	1 (1.3)
Sinusitis	0.02 ± 0.14	0.02 ± 0.14	—	0.10 ± 0.40	21 (25.9)	15 (19.5)
No. of subjects with >10 episodes of recurrent respiratory infection in the last year (n, %)	—	—	21 (65.6)	15 (48.4)	21 (25.9)	15 (19.5)
No. of subjects with >10 episodes of rhinitis in the last year (n, %)	—	—	9 (28.1)	5 (16.1)	9 (11.1)	5 (6.5)
No. of subjects with >10 episodes of pharyngitis–tonsillitis in the last year (n, %)	—	—	5 (15.6)	1 (3.2)	5 (6.2)	1 (1.3)
Level of child well-being (VAS score, means ± SD)	72.5 ± 13.4	70.5 ± 17.7	62.4 ± 19.1	67.6 ± 17.4	68.5 ± 16.5	69.3 ± 17.5

Data are shown for the two groups of children with five or less (group A) or more than five (group B) respiratory infections in the previous year and for the whole group of children, separately for the two groups of randomization, i.e., RCIM and placebo. RCIM = ribosome-component immune modulator; VAS = visual analog scale.

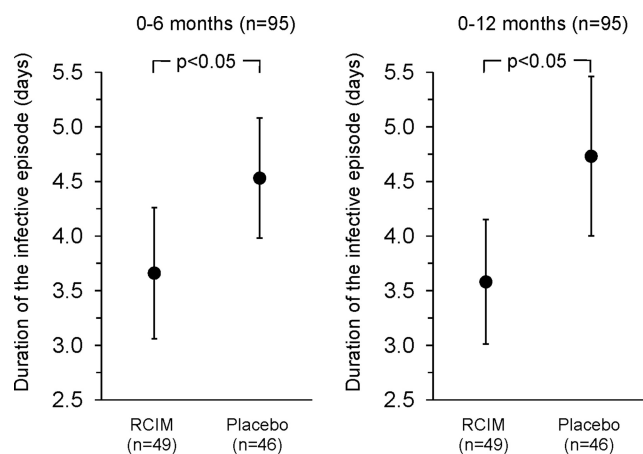


Figure 1. Average duration (95% confidence interval) of respiratory infectious episodes in children with five or less respiratory infectious episodes in the preceding year, during 6 and 12 months of treatment with ribosome-component immune modulator (RCIM; $n = 49$) and placebo ($n = 46$). The value of p indicates the statistical significance of the difference between the two treatment groups.

cebo ($p = \text{NS}$). The corresponding figure at 12 months was 64.2% RCIM versus 61.2% placebo ($p = \text{NS}$). No between-treatment differences were observed for the mean number of days lost for medical visits, the mean number of days of absence from school or nursery, or the mean number of leave days necessary for parents for the care of their sick children (data not shown).

Safety

Safety analysis was performed in 163 children, *i.e.*, in all randomized patients except one who never took any study drug dose. For these 163 children, most of the doctors judged tolerability of RCIM as excellent (62.5%) or good (35.0%) with no statistically significant ($p = 0.850$) difference when compared with placebo (excellent, 61.8%; good, 36.8%). Overall, 88 children (54%) reported an adverse event, of which 47 were under RCIM (56.6%) and 41 were under placebo (51.3%), with no statistically significant ($p = 0.491$) between-group differences. The total number of adverse events occurred in the study population was 136, of which 75 (55%) were in the RCIM and 61 (45%) were in the placebo group; only one event (fever) of a mild severity determined as possibly correlated to treatment was reported in 1 patient treated with RCIM. Most of the events (60%) had a mild severity and only two were classified as serious adverse events (one for each treatment group). Only two patients were withdrawn from the study because of the occurrence of nondrug-related adverse events, one for each treatment group. Table 2 details the types of adverse events by treatment group. Gastroenteritis and influenza were the most commonly reported adverse events.

DISCUSSION

Children attending day care are subject to social interactions that enhance the risk of respiratory infection in these settings. The symptoms of these infections, although seemingly trivial,¹⁴ can be predictive markers of more serious pathologies and often masquerade under the headings of runny nose, upper airway blockage, or “cough.”¹⁵ In the current study, a major investigative effort was directed to the reassessment of the preventive effects of RCIM and was focused on the rate of respiratory infections reported among “healthy” toddlers attending, or planning to attend, a day care center in Northern Italy. In the present study RCIM was found to be more effective than placebo at 6 and 12 months, in prevention of respiratory infections, in young children with or without a history of previous RRIs. Children with a history of five or less respiratory infections in the previous year treated with RCIM had infectious episodes of a shorter duration than children treated with placebo. In addition, the proportion of children free from any acute respiratory infection during the observation period was higher under RCIM treatment (20% versus 4% under placebo) with an odds ratio of ~ 6 , with a chance that a given treated child would benefit from treatment of 1 of 6. The superiority of RCIM over placebo returned significant even after correction for additional recurrence risk factors, such as age of smokers in the family, children in the household, *etc.* The superiority of RCIM with respect to placebo also translated in improved children’s well-being, as evaluated by their parents. Efficacy of immune modulators in reducing the number of respiratory recurrent infections in children has been proven in several randomized placebo-controlled studies. In two meta-analyses including 16 and 34 trials, respectively, treatment with immunostimulants reduced the rate of acute respiratory tract infections by $\sim 40\%$ with respect to placebo.^{16,17} In a meta-analysis of 19 randomized, double-blind placebo-controlled studies, the administration of RCIM for a 3- to 6-month period in 608 children was associated with a significant decrease in the frequency of recurrences of upper acute infectious episodes at 3 months by 47% when compared with placebo; this effect was maintained at 6 months, with a 45% risk reduction for upper and lower airway infections.⁸ A meta-analysis of 11 double-blind studies conducted in Italy on 584 children with RRIs treated for 3–6 months with RCIM showed a significantly larger rate of infectious episodes in the group receiving placebo (66.7%) compared with the RCIM group (44.7%).^{10,18} The most recent systematic review of randomized, placebo-controlled studies confirmed that RCIM provides a reduction in the number, duration, and severity of infectious episode and reduces antibacterial use and the likelihood of conse-

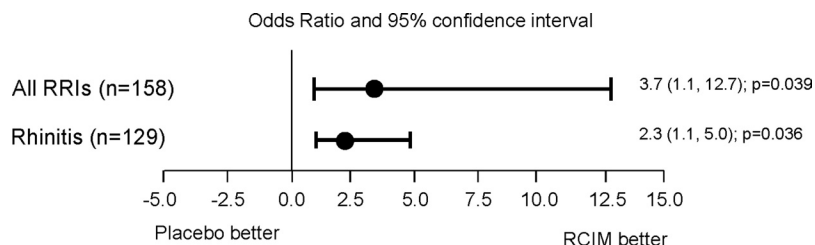


Figure 2. Odds ratio (and 95% confidence interval) for all recurrent respiratory infections (RRIs) and for rhinitis during 6 months of treatment with ribosome-component immune modulator (RCIM) and placebo in the intent-to-treat population. The value of *p* refers to the statistical significance of the odds ratio.

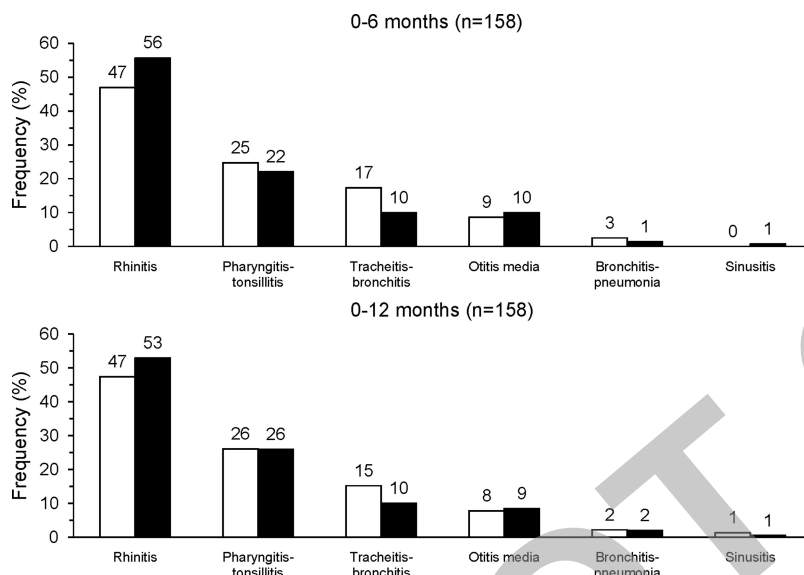


Figure 3. Frequency (%) of occurrence of the possible different types of upper and lower respiratory tract infections during 6 and 12 months of treatment with ribosome-component immune modulator (RCIM; open bars, *n* = 81) and placebo (full bars, *n* = 77).

quent development of bacterial resistance; it also decreases absence from work or school, which has important social and economic consequences.¹⁹ The most relevant feature of our study is related to the characteristics of the studied children. Indeed, RCIM efficacy was tested in children with social interactions, independently from a previous diagnosis of RRIs. The results of the present study would appear to have greater relevance to more real-life situations, where decision making to start treatment is based not only on the number of previous infectious episodes, but also on other related factors (*e.g.*, economic reasons, possible resistance to antimicrobials, concomitant disease, *etc.*).¹⁰ A number of other clinically relevant findings were observed from the present study. The studies published to date suggest that clinically significant prevention of recurrence might be observed after 3 months of treatment, with persistence or even an improvement of the efficacy after 6 months of treatment, but no follow-ups longer than 6 months were ever performed. Conversely, we studied children over a 12-month period, *viz.*, on a time interval suitable for a proper evaluation of the therapeutic coverage during the epidemic season. RCIM preventive efficacy was well maintained over such a long follow-up period. Second, this is one of the largest studies assessing the efficacy of RCIM according to a double-blind, randomized, placebo-controlled design. To our knowledge,

there are only a few studies that have evaluated a similar or even larger sample of children. One study included 320 children, of which 158 were treated with RCIM, but all patients suffered from otitis only.⁸ Another study reported on 172 children with either upper or lower respiratory tract infections, 86 randomized to RCIM.⁸ Other published studies enrolled 160 children with recurrent pharyngotonsillitis,²⁰ 155 children with otitis,⁸ 154 with upper airway respiratory infections,^{8,21,22} and 136 with ear-nose-throat infections,^{8,19,22,23} respectively. Only one of these studies was published in an English peer-review journal,²⁰ and all the others were only included in subsequent meta-analyses. Third, a unique feature of this study was that it was specifically performed in children aged ≤ 5 years; this is particularly relevant because, regardless of the social conditions and preexisting risk factors, acute respiratory infections are an important source of morbidity and mortality in this age category, both in developed and developing countries.^{1,24} To date, only two randomized controlled studies in children < 5 years have been published, but they included a relatively small sample of subjects.^{11,12} RCIM was also well tolerated in our children, with a placebo-like frequency of adverse events, confirming that risk associated with the use of RCIM is negligible, even in particularly vulnerable populations, such as children and elderly people.⁹

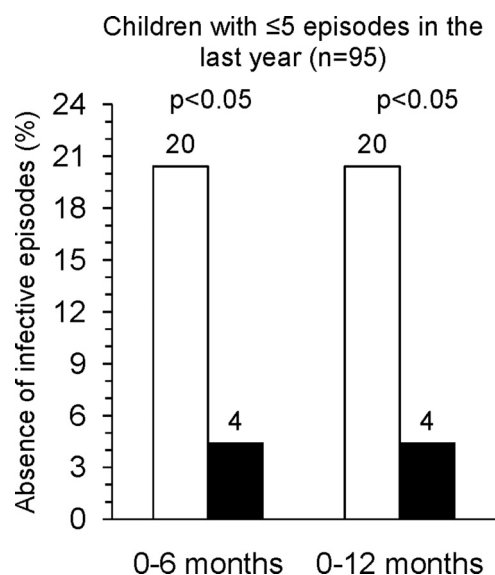


Figure 4. Frequency (%) of children with no infectious episodes during 6 and 12 months of treatment with ribosome-component immune modulator (RCIM; open bars, $n = 49$) and placebo (full bars, $n = 46$) in the group of children with five or less respiratory infectious episodes in the previous year. The value of p indicates the statistical significance of the difference between the two treatment groups.

Finally, some limitations of our study deserve to be highlighted and discussed. First, we did not consider among the efficacy criteria the number and duration of antibacterial courses and other medications or surgery, and we did not categorize the infections as viral or bacterial based on specific laboratory tests, as done by previous studies.^{8,19,21} However, we must acknowledge that our children were at relatively lower risk of respiratory infections; this also explains the lack of differences between RCIM and placebo for other secondary end points, such as absenteeism of children from school and of parents from the workplace. Furthermore, our intent was to test the preventive efficacy of RCIM and not its therapeutic effect, and it was beyond the scope of this study to specifically assess the origin of respiratory infection in the studied children. Second, we are aware that drug efficacy might have been underestimated in our study, because the average number of episodes reported in the placebo group during the 12-month observation period was unusually low (two episodes per patient) when compared with what was observed during regular epidemic season (five to six episodes per patient). Third, our study showed that RCIM does not eliminate acute infections, but provides immune protection, with a reduction in the frequency and severity of such infections. This was the case for children with five or less infectious episodes per year, but not for the group of children at higher risk. The fact that RCIM was of no particular benefit for children with more than five respiratory

Table 2 Distribution of adverse events by frequency of occurrence between the two groups of randomization, *i.e.*, RCIM and placebo, in the 163 children of the safety population

	RCIM ($n = 83$)	Placebo ($n = 80$)
Gastroenteritis	22	16
Influenza	8	9
Chickenpox	6	6
Fever*	7	4
Cough	6	2
Vomiting	4	3
Conjunctivitis	2	3
Impetigo	2	2
Scarlet fever	2	2
Whitlow	2	1
Urticaria	2	1
Adenoidectomy	1	1
Fifth disease	1	1
Abdominal pain	1	1
Diarrhea	—	1
Dental abscess	—	1
Appendicitis	1	—
Head injury	1	—
Head hematoma	1	—
Catarrh	1	—
Cystitis	1	—
Otalgia	—	1
Erythema	1	—
Laryngospasm	1	—
Lice infestation	—	1
Ocular hyperemia	—	1
Ocular itching	—	1
Pityriasis rosea	1	—
Stomatitis	—	1
Trauma	—	1
Arm fracture	1	—
Other	—	1
Total adverse events	75	61
Total patients	47 (56.6)	41 (51.3)

Data are shown as absolute (n) and relative (%) frequency.

*One adverse event in the RCIM group judged as related to treatment.

RCIM = ribosome-component immune modulator.

infectious episodes per year might be explained by the fact that approximately one-half of patients in this group had 5–10 episodes in the previous year, which classifies these children at a relatively high risk. We recognize that future randomized controlled studies should try to specifically provide more evidence on this particularly high-risk category of subjects.

In conclusion, our results show that ribosomal immunostimulant significantly reduces the number of days of disease and the frequency of recurrences of upper and lower respiratory tract infections in children <5 years of age and with a lower usual frequency of respiratory infections. The therapeutic benefit was seen after 6 months of treatment and was maintained during the subsequent 6 months of follow-up.

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