

OM-85 BV, an immunostimulant in pediatric recurrent respiratory tract infections: a systematic review

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Background: This study was conducted to assess the efficacy of OM-85 BV (Broncho-Vaxom) in the prevention of pediatric recurrent respiratory tract infections (RTIs). Available evidence suggests that defining recurrent RTIs as ≥ 3 infections per fall-winter semester is both medically and epidemiologically justified. Therefore, this criterion was chosen as a primary endpoint.

Methods: Trials were identified through consultation of bibliographic databases and other channels. Eleven non-blinded studies plus one dealing with primary prevention were excluded and eight randomized controlled trials were included in the meta-analysis. The data were compared at 6 months, which represented the end of most studies. The complete database was examined according to the guidelines of the Cochrane collaboration.

Results: The mean age of children and the number of RTIs in the preceding year were comparable at admission. Of the patients in the OM-85 BV treated population ($n=435$), 32% had recurrent RTIs (that is, ≥ 3 RTIs/6 months) vs. 58.2% in the placebo treated population ($n=416$; $P<0.001$). Sensitivity analysis showed that this was not driven by any particular trial. The results of this review were also positive for the active treatment regarding the secondary variables, which were represented by the number of patients with at least one RTI and the mean number of RTIs.

Conclusions: This meta-analysis shows, as observed in several individual trials, that the population treated with OM-85 BV had significantly and consistently fewer cases of recurrent RTIs. The data suggest that the effect is greater in patients at increased risk of recurrent RTIs.

World J Pediatr 2010;6(1):5-12

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doi:10.1007/s12519-010-0001-x

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Key words: children;
immunostimulant;
OM-85 Broncho-Vaxom;
recurrent respiratory tract infections

Introduction

OM-85 BV (Broncho-Vaxom) is an immunostimulant medication used to prevent recurrent respiratory tract infections (RTIs). The mechanism of its action has recently been reviewed by Rozy et al.^[1] OM-85 BV has been shown to induce the terminal maturation of human dendritic cells, with an enhanced T cell-stimulatory capacity *in vitro*.^[2] The broncho-alveolar lavage of adults treated with OM-85 BV^[3,4] showed an increase in the helper/suppressor T lymphocyte ratio, a stimulation of the impaired alveolar macrophage activity, and increased concentrations of interferon- γ .

The clinical aspects of recurrent pediatric RTIs have been dealt with in detail in a recent systematic review,^[5] including pathogenesis, prevention and "key" trials with OM-85 BV. Therefore, the paper presented herein shall concentrate on a meta-analytic approach, attempting to quantify the effectiveness of OM-85 in the secondary prevention of recurrent RTIs in children.

It is widely accepted that recurrent RTIs in childhood represent a problem per se in addition to increasing predisposition to future respiratory problems. Repeated lower RTIs in the first 3 years of life show a positive association with wheezing up to the age of 7 years.^[6] However, the concept of recurrence in relation with RTIs presents some problems since there is no generally agreed definition. Preschool children may contract between four and six RTIs over the course of a year without this representing a true deviation from "normality".^[7] In a German study it was shown^[8] that the number of febrile episodes in the first year of life was superior to three in about 28% of the infants and that about 9% had two or more courses of antibiotics. Several episodes seem "normal" since several peaks of exposure to different agents occur during each season.^[9] Some authors^[10]

have attempted to define recurrence of infection by clinical presentation, e.g., three episodes of otitis over 6 months or two episodes of sinusitis and/or recurrent bronchopneumonia in 6 months or four episodes of rhinopharyngitis in 6 months. Such a classification, particularly in younger children, however seems somewhat artificial. Therefore, epidemiological and clinical observations favor the concept that the term "recurrent" should be reserved for cases of several RTIs per fall-winter season, e.g., three or more.^[5,11]

Several factors such as day care in local nursery and short duration of breastfeeding predispose to recurrent RTIs, particularly otitis media, as well as to wheezy bronchitis,^[12] and should therefore be considered as covariates in clinical studies.

In addition to being the most frequent causative agents of respiratory disease, viral infections can predispose to bacterial superinfection. The proportion of children with mixed viral and bacterial RTIs found in studies using serology or antigen detection in serum or urine has been reported to be as high as 40%. However, these methods may be inadequate for assessing the clinical importance of bacterial infection or the need for antimicrobial treatment.^[13]

In order to provide a more accurate quantitative estimate of the overall treatment effects of a frequently employed immunostimulant, we performed a meta-analysis of studies in children with a history of recurrent RTIs. As in adults,^[14] limiting the assessment to the proportion of children without any RTI after treatment with an immunostimulant may provide a biased picture, so the cut-off was therefore set at 3 or more RTIs over 6 months.

Methods

Objective

The primary objective of this meta-analysis was to provide a more accurate estimate of the overall treatment effects of OM-85 BV from a clinical point of view, choosing clinically relevant end points as described in the study by Schaad et al.^[11] The cut-off for the outcomes was set at 6 months; the following criteria were defined a priori (RTI as defined in each study protocol):

- 1) Primary endpoint: proportion of patients with recurrent RTIs (that is ≥ 3 RTIs per 6 months);
- 2) Secondary endpoints: proportion of patients with at least one RTI and mean number of RTIs during 6 months.

No distinction was made between the different clinical diagnoses of RTIs. Since the frequency of RTIs decreases with the age of children and since the number of RTIs in the current season correlates with the number of events in the preceding year,^[11,15] examination of

these two variables as a control of comparability of the patient populations at admission to the trial was decided upon. The guidelines provided by the Cochrane Collaboration Handbook for Reviews^[16] have been applied in the analysis of the clinical data.

Search strategy

The data sources for the identification of trials included bibliographic databases (TOXLINE, MEDLINE, HealthSTAR, AIDSLINE and CANCERLIT, Embase, AMED, Cochrane Library, PubMed ([/www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov)), TOXMAP, TOXLINE Special, DART Special, HSDB, IRIS, ITER, GENETOX, CHEMIDplus, Haz-Map), hand-searching reference lists from pertinent review articles and books, and personal contacts with experts active in the area and manufacturers up to April 2009. Full disclosure of the product documentation including requested statistical and official reports by the manufacturer in Switzerland warranted a minimal publication bias. All papers were screened, and any dealing with prospective clinical trials were retained for classification according to the selection criteria described below. In case of double publications, the authors retained those which were most recent and/or had been published in a peer-reviewed journal.

All trials eligible were summarized in a tabulated format. The standard table included a full reference, a quality rating, the type of pathology, demographic data and treatments, end-points and adverse events. The trials dealing with pediatric respiratory tract infections were retained.

Material scrutinized

The electronic databases identified recurrent infections, OM-85, Broncho-Vaxom, Imocur, placebo, double-blind and infants (age, 1-23 months) / children (age, 2-12 years) in 22 publications. Two additional publications of clinical studies were identified through other channels as mentioned above, and duly scrutinized.

Five studies were descriptive, open-labelled pediatric studies and one was a cost-effectiveness model analysis; these had to be discarded. Ten comparative studies were excluded as they did not comply with one or more criteria (Table 1).^[17-26] Eight studies were retained as relevant trials dealing with secondary prevention, and were retained for closer examination (Table 2).^[11,27-33] Four of these trials were conducted in Western Europe and the remaining four in Mexico: they were all totally or partially industry-sponsored.

Selection criteria

Initially, all articles, published and unpublished trials, were considered for review. They were subsequently

classified by study design, screened and weighted, based on their methodological quality (methods, participants, interventions, outcome measures and results). Quality assessment was based on a rating of the trials by the criteria published by Jadad et al.^[34]

Eleven studies were excluded as they were non-blinded or incomplete. Nine studies were retained as relevant trials and, finally, eight dealing with secondary prevention were included in the meta-analysis (Table 2).^[11,27-33] All trials only admitted children with a documented history of recurrent RTIs.

Regarding similarities and differences in the trials selected, the study of Schaad et al.^[11] required the patients to actually have an episode of RTI at admission, while all the other studies only admitted children with a documented history of recurrent RTIs. The patients studied by Gomez-Barreto et al.^[28] had sinusitis, and those reported by Zagar and Löfler-Badzek^[33] had chronic rhinosinusitis. The trial of Jara-Perez and Berber^[30] included only girls living in an orphanage, and the trial of Del-Rio-Navarro et al.^[27] included children with subnormal serum IgG. Jara-Perez and Berber^[30] and Schaad et al.^[32] provided clinical descriptions of the RTIs which are not discussed herein.

The dosing schedules used in the trials included in this meta-analysis are shown in Table 3.

Statistical analysis

Data were extracted from the pertinent publications and/or study reports in order to obtain for each of the selected trials the key variables defined as end-points and the demographic data deemed of interest as set forth in the trial by Schaad et al.^[11] (age of the patient and number of RTIs over the preceding 12 months, number of patients completing trial). These data were checked for consistency and adequacy of tests employed. Missing data were reconstructed through iterative procedures. The completed database was entered in Review Manager 2.4.7 software of the Cochrane collaboration; binary data were examined by the Peto-Mantel-Haenszel test.^[35] Whenever the authors specified two sets of data, the intent to treat analysis was chosen. The denominator 'N' indicated the number of patients reported by the authors; if not specified, 'N' was the number of patients who were admitted to the trial. Sensitivity analysis was made by sequential elimination of trials and by elimination of outlier trials, with an outlier being defined as "an extreme value that

Table 1. Summary of comparative trials screened and excluded (alphabetically)

Author (year)	Recurrent RTIs?	Double blind?	Placebo?	Age 1-12 y?	Reasons for exclusion
Ahrens (1984)	Yes	Yes?	Yes	No	Not adequate blinding, age not as defined
Chen (2007)	Wheezing	No	budesonide	Yes	Indication, not adequate blinding, no placebo
Collet (1993)	Primary prevention	Yes	Yes	Yes	Indication
Field (1998)	Primary prevention	No	vs. previous year	Yes	Indication, no blinding, no placebo
Gutiérrez-Tarango (1997)	Yes	No	Conventional treatment	Yes	No blinding, no placebo
Kapellerova (1989)	Yes	No	"Bacterial vaccine"	Yes	No blinding, no placebo
Maestroni (1984)	Predisposition	Yes?	Yes	No	Indication, not adequate blinding, age not as defined
Martin du Pan (1982)	No	No	Yes	Yes	Indication, not adequate blinding
Quezada (1999)	Yes + hypogammaglobulinemia	No	Yes	Yes	Indication, not adequate blinding
Ziuzio (1994)	Allergy	No	Polyvaccium; IRS-19	Yes	Indication, no blinding, no placebo

Table 2. Summary of trials screened and selected rating by Jadad criteria

Jadad criteria	Prevention								
	Secondary								Primary
	Del-Rio (2003)	Schaad (2002)	Gutierrez-T. (2001)*	Jara-Perez (2000)	G.-Barreto (1998)†	Paupé (1990)	Zagar (1988)	Schaad (1986)	Collet (1993)
Is the study randomized?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Is the study double-blinded?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Is there a description of withdrawals?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Is the randomization adequately described?	P	Y	P	P	P	P	No	P	Y
Is the blindness adequately described?	P	Y	P	P	P	Y	No	P	Y
Score	4	5	4	4	4	4.5	3	4	5

Y (yes): 1 point; P (partial): 0.5 points; No: 0 point. *: 12 months trial; the values at 6 months were considered for the current analysis. †: after sinusitis.

might have a low probability of occurrence but cannot be statistically shown to originate from a different distribution than the rest of the data".^[36] Additional and exploratory analyses were made employing the WinSTAT™ for Excel Version 2001.1.

Results

Key demographic data, comparability at baseline

As described in the Methods section, since the age of the children and the number of RTIs in the preceding year are correlated with the number of RTIs to be expected during the trial, these two variables were regarded as a control of comparability of the patient populations at admission to the trial.

The mean number of RTIs in the previous year was similar in the two populations (mean of studies with the information: 6.12±3.74 RTIs in the OM-85 BV populations vs. 6.23±3.52 RTIs in the placebo), but no such information was available in the study by Gomez-Barreto^[28] while the study by Paupe^[31] provided some other relevant information about the similarity between therapeutic groups. With these caveats, the patient population can be accepted as homogeneous.

The number of drop-outs is comparatively small in both therapeutic groups; in the majority of the cases, patients dropped out because of administrative reasons.

In Table 4 the mean ages at admission (pooled mean & SD) and the number of patients are depicted, whereas Table 5 shows the mean number of RTIs in the previous year.

Proportion of patients with RTIs

Although the data were heterogeneous, 32% of the patients within the OM-85 BV treated population had recurrent RTIs (≥ 3 RTIs per 6 months), vs. 58.2% of the placebo treated population, indicating that the active treatment led to 26.2% fewer patients with recurrent RTIs (Fig. 1). The large proportion of placebo patients without recurrent RTIs is probably best explained by the natural trend of children to suffer from fewer RTIs as they grow older.

Sensitivity analysis by sequential elimination of trials yielded odds ratios between 0.42 and 0.6, and significance level unchanged at $P < 0.001$. After elimination of the outlier trials by Jara-Perez,^[30] which showed the largest difference between treatments, and by Schaad,^[32] which tilted towards placebo, the database became homogeneous, showing that there

Table 3. Dosing schedules employed in examined trials

Author (year)	mon 1	mon 2	mon 3	mon 4	mon 5	mon 6	mon 7	mon 8	mon 9	mon 10	mon 11	mon 12
Del-Rio (2003)	■											
Schaad (2002)	■	■			■	■						
Gutierrez-Tarango (2001)							■	■	■			
Jara-Perez (2000)	■											
Gomez-Barreto (1998)	■											
Paupe (1990)	■	■										
Zagar (1988)	■	■			■	■						
Schaad (1986)	■	■										
Cut-off							→	←				
Collet (1993)	■	■	■									

Gray areas: one capsule OM-85 BV in the morning. One capsule OM-85 BV for children contains 3.5 mg of lyophilized bacterial lysates of *Haemophilus influenzae*, *Diplococcus pneumoniae*, *Klebsiella pneumoniae* and *ozaenae*, *Staphylococcus aureus*, *Streptococcus pyogenes* and *viridans*, *Neisseria catarrhalis*.

Table 4. Mean ages at admission (pooled mean & SD) and number of patients

Author (year)	Age (y) OM-85-BV		Age (y) placebo		N patients OM-85-BV		N patients placebo	
	Mean	SD	Mean	SD	Intent to treat	Completed	Intent to treat	Completed
Schaad (2002)	5.19	1.42	5.27	1.37	120	98	100	85
Gutierrez-Tarango (2001)	3.86	2.44	4.52	2.70	26	26	28	27
Del Rio (2003)	4.00	0.90	4.10	0.90	25	22	24	21
Jara-Perez (2000)	9.76	1.89	9.62	1.88	100	99	100	100
Gomez-Barreto (1998)	4.69	1.72	4.06	1.81	26	26	30	30
Paupe (1991)	6.60	5.30	7.60	5.30	64	61	63	55
Zagar (1988)	6.53	5.08	6.81	4.50	29	29	22	22
Schaad (1986)	4.33	2.79	4.09	2.49	45	45	49	49
Pooled mean & SD	6.27	3.60	6.41	3.57	435	406	416	389
Completed (%)						93.3%		93.5%

were 20.2% fewer patients with recurrent RTIs within the remaining OM-85 BV treated population than in the placebo treated population.

By the observations of individual trials, one may conclude that the population treated with OM-85 BV had significantly and consistently fewer patients with recurrent RTIs (≥ 3 RTIs per 6 months) by between 26.2% and 20.2% (the latter as a conservative estimate after obtaining a homogeneous database by eliminating the outlying trials). Likewise and as expected, there is also a significant reduction in the relative risk (RR (fixed) & 95% CI: 0.56 [0.48, 0.66]) and in the odds ratio (OR (fixed) & 95% CI: 0.33 [0.25, 0.45]).

In both treatment groups, the majority of children had at least one RTI during the study period (Table 6). Although the data were somewhat heterogeneous, over 16.2% of patients had no RTI in the period under consideration within the OM-85 BV treated population (27.3% with OM-85 BV vs. 11.1% with placebo). Likewise, there was also a significant reduction in the odds ratio (OR OM-85 BV: placebo was 0.33 [95% CI: 0.23, 0.49]). Sensitivity analysis by sequential elimination of trials yielded odds ratios between 0.38 and 0.52, significance level unchanged at $P < 0.001$.

Table 5. Mean N RTIs in the previous year

N RTIs previous year	OM-85 BV		Placebo	
	Mean	SD	Mean	SD
Schaad et al (2002)	5.76	2.38	6.06	2.13
Gutierrez-Tarango (2001)	12.62	4.82	12.32	3.85
Del Rio (2003)	9.40	3.70	10.10	2.80
Jara-Perez (2000)	4.94	0.76	5.09	0.70
Gomez-Barreto (1998)	No data		No data	
Paupe (1991)	N RTIs >4: 54%		N RTIs >4: 58%	
Zagar (1988)	6.72	6.40	5.59	6.46
Schaad (1986)	3.76	1.86	3.82	1.82

The trials therefore indicated that the population treated with OM-85 BV had significantly and consistently fewer patients with one or more RTIs in a 6-month period (Table 6). Moreover, after elimination of the largest favorable "outlier", i.e., the trial of Del-Rio-Navarro^[27] in children with IgG deficiencies, and the worst trial outcome for this variable,^[11] this figure was 17.0%, which was even more significant.

Mean number of RTIs in 6 months

The analysis of the mean number of RTIs over 6 months had to be regarded with some caution since the data were actually ordinal (that is, natural whole numbers) and not all trials were suitable for such an analysis because of differences in variances. Nevertheless, the mean number of RTIs was significantly lower in the OM-85 BV treated population, by an average of -1.15 (95% CI: -1.55, -0.75) RTIs/6 months (Table 7). After eliminating the outlier studies for this variable (i.e.,

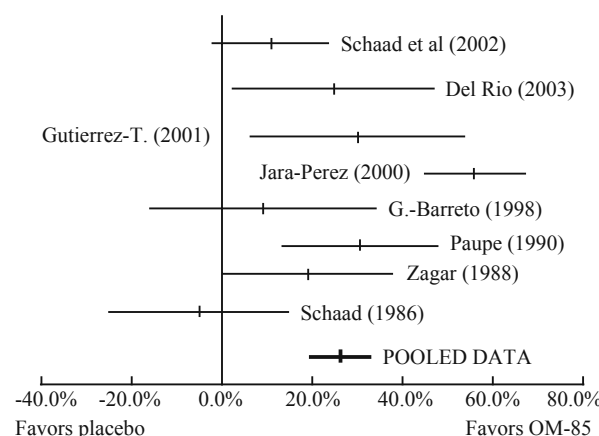


Fig. 1. Percent difference (and 95% confidence interval) between treatments for patients with recurrent RTIs (≥ 3 RTIs/6 months).

Table 6. Number of patients with RTIs (≥ 1 or ≥ 3 RTIs/6 months), per trial & treatment

Author (year)	1 or more RTIs		3 or more RTIs	
	OM-85-BV	Placebo	OM-85-BV	Placebo
Schaad et al (2002)	103 (85.8%)	87 (87%)	39 (32.5%)	44 (44%)
Gutierrez-Tarango (2001)	23 (85.2%)	28 (100%)	14 (51.9%)	23 (82.1%)
Jara-Perez (2000)	86 (86%)	100 (100%)	14 (14%)	70 (70%)
Del Rio (2003)	2 (10%)	20 (100%)	14 (70%)	19 (95%)
Paupe (1990)	37 (60.7%)	46 (83.6%)	19 (31.1%)	34 (61.8%)
Zagar (1988)	8 (27.6%)	9 (40.9%)	1 (3.4%)	5 (22.7%)
Schaad (1986)	39 (86.7%)	48 (98%)	28 (62.2%)	28 (57.1%)
Gomez-Barreto (1998)	13 (50%)	21 (70%)	8 (30.8%)	12 (40%)
Pooled (significance: $P < 0.001$)*	311 (72.7%)	359 (88.9%)	137 (32%)	235 (58.2%)
Number needed to treat	6.2		3.8	
Odds ratios OM-85-BV: placebo	0.33 (95% CI 0.23, 0.49)		0.33 (95% CI 0.25, 0.45)	
"Robust analysis" after deleting Jara-Perez (2000) as positive 'outlier' & Schaad (1986) as negative 'outlier':				
Pooled (significance: $P < 0.001$)	186 (65.7%)*	211 (82.7%)	95 (33.6%)†	137 (53.7%)

*: Test for heterogeneity: $P = 0.001$ for 1 or more RTIs, $P < 0.00001$ for 3 or more RTIs; †: Test for heterogeneity: $P > 0.1$.

Gutierrez-Tarango^[29] & Schaad^[32]) the mean number of RTIs continued to be significantly lower in the OM-85 BV treated population, by an average of -1.10 (95% CI: -1.64, -0.56) RTIs/6 months.

The weighted mean difference (WMD; also defined as "effect size") between mean numbers of RTIs over 6 months was -1.21 [95% CI: -1.39, -1.03] in favor of the active treatment ($P < 0.00001$), although the test for heterogeneity was also highly significant. This heterogeneity was probably due to the differences in age of patients and in the number of RTIs in the preceding year.

Several co-variables were likely to influence the outcomes and might explain the heterogeneity found in some variables. They were briefly illustrated, although they had not been submitted to a formal analysis. The mean number of RTIs was consistent with the number of RTIs in the preceding year and with the age of the patients (Fig. 2). Namely, the number of RTIs in the preceding year appeared to have a major bearing on the results, the benefit of OM-85 BV was markedly greater in children with a history of very frequent RTIs (confirmed by multiple stepwise regression analysis in a subset of trials with raw data available, data not shown).

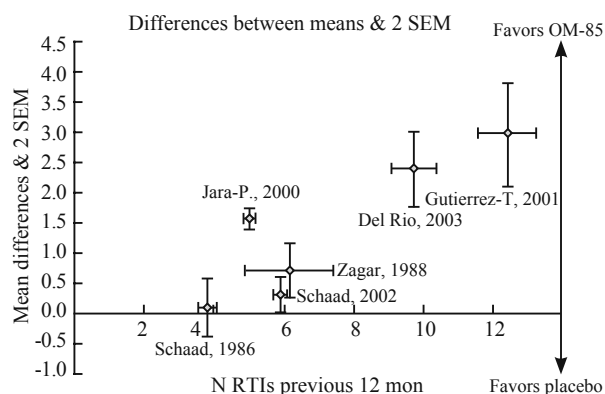


Fig. 2. Differences (and 95% confidence interval) between treatments, mean number of RTIs by N RTIs in the year before admission.

The quality assessment of the studies, i.e., the Jadad rating system, had no evident influence on the outcomes. The funnel plots, which should be regarded as a generic instrument for examining small study effects rather than a tool to diagnose specific types of bias, did not suggest the existence of publication or any other major bias in this meta-analysis.

Safety

The incidence of minor adverse events in the clinical trials was 17.7% for the OM-85 BV treated and 18.2% for the placebo treated patients; the majority of adverse events were gastrointestinal or cutaneous findings. Serious adverse events were reported in 1% vs. 0.5%, withdrawals due to adverse event in 1.3% vs. 0.7%, respectively. No causal relationship has been established for any of these adverse events. No laboratory abnormalities in relation with OM-85 BV have been reported in the literature. There were neither deaths nor serious adverse events attributed or possibly attributable to the study medication.

Discussion

Steurer-Stey et al^[37] used a partially meta-analytical approach of published data with OM-85 BV; their findings, however, remained fragmentary due to failure to request additional information from the manufacturer or other sources. Moreover, their report also analyzed other bacterial immunostimulants. They concluded that their "systematic review provides weak evidence that oral immunostimulation with bacterial extracts prevents acute RTIs in children." There was a trend for fewer infections over 6 months of follow-up in children not in day care as well as a small reduction in number of antibiotic courses.

Our study showed that with the active treatment there were 26.2% fewer patients with recurrent RTIs

Table 7. Mean number of RTIs in 6 months (pooled mean & SD) by treatment

N RTIs/6 months	OM-85 BV		Placebo		Comments
	Mean	SD	Mean	SD	
Schaad et al (2002)	2.12	1.44	2.48	1.63	
Gutierrez-Tarango (2001)	5.04	1.95	8.00	2.51	Variances, * $P=0.06$
Del Rio (2003)	2.80	1.40	5.20	1.50	
Jara-Perez (2000)	1.43	0.94	2.99	0.81	
G.-Barreto (1998)	1.56	1.53	2.22	2.43	
Paupé (1991)	2.07	2.09	3.51	2.97	SD estimated†
Zagar (1988)	0.38	0.71	1.09	1.50	Variances, * $P=0.003$
Schaad (1986)	2.89	1.77	2.98	1.56	
Pooled mean & SD	2.09	1.79	3.24	2.40	$P < 0.001$
Pooled mean & SD after eliminating 'outlier' trials of Gutierrez-Tarango (2001) & Schaad (1986)					
Pooled mean & SD	1.78	2.51	2.88	4.21	$P < 0.001$

*: Bartlett-Test for homogeneity of variances; †: SD estimated to be equal to average ratio SD/mean of the other trials.

(i.e., ≥ 3 RTI/6 months). The fact that the population of the different trials included in the meta-analysis is homogeneous (after excluding the two 'outliers') in terms of this variable lends strength to the highly significant results in favor of OM-85 BV.

The proportion of patients with any RTI (i.e., ≥ 1 RTI/6 months) was reduced by 16.2% in our study, but this variable is of lesser clinical relevance in view of the multiple agents which can cause acute symptoms of an RTI during one single season, probably involving different defence mechanisms. Sensitivity analysis was made for all variables and no particular trial driving the efficacy outcomes was identified, thus corroborating the results. In line with similar analyses,^[38,39] the mean number of RTIs was reduced by 35.5% but the data, although a highly significant difference was found in favor of OM-85 BV, are very heterogeneous. The heterogeneity in the secondary outcomes is probably explained by clinical and methodological diversity, dependent on the age, the risk of RTIs (as N RTIs in the preceding year) and other variables. For example, the 'outlier' study of Jara-Perez^[30] had several particular characteristics as it was conducted under the very controlled conditions of an orphanage for girls.

Exploratory analysis indicates that efficacy is more pronounced in patients at high risk of recurrent RTIs; the benefit of OM-85 BV as compared to placebo was notoriously greater in children with a history of very frequent RTIs.

The influence of industry-sponsoring on the outcomes of trials has been discussed controversially; that is, no influence was found in some cases^[40] while in others the results tipped in favor of the sponsored drug.^[41] Meta-analysis sponsored by industry came to more "drug-friendly" conclusions than independent studies, even if the estimated treatment effect was similar.^[42]

The positive and negative predictive value of meta-analysis should be taken into consideration. Agreement between meta-analyses and large clinical trials of therapeutic interventions can be expected in 68% of the cases, while a statistically significant difference was found in only 12% of the cases; in no case, however, there was a divergence in which the randomized clinical trial and the meta-analysis yielded statistically significant and opposite results.^[43] It is important to note that the outcomes concerning the primary variable were homogeneous in robust analysis since heterogeneity in the outcomes of individual trials appears to be an important predictor of discrepancy between meta-analyses and large clinical trials.^[44]

We believe that this analysis may help both the practitioner in identifying the best candidates for this immunostimulant therapy and the investigators in setting up new randomized controlled trials in this complex field. Future studies should provide details

of the RTIs occurring during the observation period employing a standardized clinical classification.

Acknowledgements

The author is thankful to Dr. Reto G. Brignoli for assistance with the statistical analysis and preparation of the manuscript.

Funding: This project was partially funded by OM Pharma, Geneva, Switzerland. The sponsors had no involvement in the study design, analysis and interpretation of the data, writing of the manuscript, or in the decision to submit the manuscript for publication.

Ethical approval: Not needed.

Competing interest: None.

Contributors: Schaad UB is the single author of this paper.

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Received November 21, 2008

Accepted after revision May 25, 2009