Eur J Pediatr (2007) 166:365–376
DOI 10.1007/s00431-006-0248-3

ORIGINAL PAPER

Oral purified bacterial extracts in acute respiratory tract infections in childhood: a systematic quantitative review

Claudia Steurer-Stey · Leonie Lagler · Daniel A. Straub · Johann Steurer · Lucas M. Bachmann

Received: 28 December 2005 / Revised: 1 July 2006 / Accepted: 5 July 2006 / Published online: 18 November 2006

Abstract
Background Recurrent acute respiratory tract infections (ARTI) are a common problem in childhood. Some evidence suggests a benefit regarding the prevention of ARTI in children treated with the immunomodulator OM-85 BV (Bronchovaxom).
Methods We summarised the evidence on the effectiveness of the immunomodulator OM-85 BV in the prevention of ARTI in children. We searched randomised comparisons of oral purified bacterial extracts against inactive controls in children with respiratory tract diseases in nine electronic databases and reference lists of included studies. We extracted salient features of each study, calculated relative risks (RR) or weighted mean differences (WMD) and performed meta-analyses using random-effects models.
Results Thirteen studies (2,721 patients) of low to moderate quality tested OM-85 BV. Patients and outcomes differed substantially, which impeded pooling results of more than two trials. Two studies (240 patients) reporting on the number of patients with less than three infections over 6 month of follow-up in children not in day care showed a trend for benefit RR 0.82 (95% CI, 0.65–1.02). One out of two studies examining the number of children not in day care without infections over 4–6 month reported a significant RR of 0.42 (95% CI, 0.21–0.82) whereas the smaller, second study did not [RR 0.92 (95% CI, 0.58–1.46)]. Two studies reporting the number of antibiotic courses indicated a benefit for the intervention arm [WMD 2.0 (95% CI, 1.7–2.3)]. Two out of the three studies showed a reduction of length of episodes of 4–6 days whereas a third study showed no difference between the two groups.
Conclusion Evidence in favour of OM-85 BV in the prevention of ARTI in children is weak. There is a trend for fewer and shorter infections and a reduction of antibiotic use.

Keywords Bronchovaxom · Immunotherapy · Acute airway tract infections · Prevention

CS initiated the project and is the study guarantor. CS and LL searched and extracted the data. DS cross-checked extracted data. LMB and JS cross-checked and analysed extracted data. All authors participated in discussing the results and writing the paper.

C. Steurer-Stey (✉)
Medical Policlinic, Department of Internal Medicine,
University Hospital,
Raemistrasse 100,
CH-8091 Zurich, Switzerland
e-mail: claudia.stey@usz.ch

L. Lagler · J. Steurer · L. M. Bachmann
Horten Centre for Patient Oriented Research,
University of Zurich,
Zurich, Switzerland

L. Lagler
e-mail: leonie_lagler@ggaweb.ch

J. Steurer
e-mail: johann.steurer@usz.ch

D. A. Straub
Children University Hospital,
Zurich, Switzerland
email: daniel.straub@kispi.unizh.ch

L. M. Bachmann
Division of Epidemiology and Biostatistics,
Institute for Social and Preventative Medicine, University of Bern,
Bern, Switzerland
email: lucas.bachmann@usz.ch

Background

Recurrent acute respiratory tract infections (ARTI) are a common problem in childhood [2]. The majority of acute

airway tract infections are caused by viruses. However, several bacterial complications can appear, such as acute otitis media, sinusitis and bronchitis. Therefore, physicians are prone to prescribe antibiotics to treat ARTI although only a small proportion of children will benefit from this treatment. Due to this over-prescription, many bacteria have become resistant against commonly prescribed antibiotics. To overcome this treatment dilemma, several authors proposed changing the treatment strategy of ARTI from acute intervention to prophylaxis of recurrence using vaccines and immunomodulating agents [10]. Defects in the immunological system, such as selective immunoglobulin A (IgA) deficiency, are known to be linked with frequent respiratory infections by bacteria and viruses. From an epidemiologic point of view, it has been shown that over 50% of children with three or more episodes a year during at least 2 years were deficient in one of the IgG subclasses and that 17% were IgA deficient [4].

OM-85 BV (Bronchovaxom, OM Pharma, Geneva Switzerland), an orally administered immunostimulator (capsules of 3.5 mg) containing lyophilised bacterial fractions of *Haemophilus influenzae*, *Diplococcus pneumoniae*, *Klebsiella pneumoniae* and *K. ozaenae*, *Staphylococcus aureus*, *Streptococcus pyogenes* and *S. viridans* and *Moraxella catarrhalis*, provokes a local immune response via activation of the mucosa-associated lymphoid tissue and stimulates the production of salivary and bronchoalveolar serum IgA as well as serum IgA and IgG. It has been widely used in several European countries in children and adults assuming it will prevent recurrences of respiratory tract infections (RTIs). In adult patients with chronic bronchitis and chronic obstructive pulmonary disease (COPD), a systematic review could not find a preventive effect on exacerbations [22]. Recent clinical studies in children reported on significantly reduced rates of RTIs with good safety and tolerance [9, 18]. Up to now, however, the literature has not been assembled and appraised but is scattered and not easy to access. Furthermore, results from these studies are imprecise. We therefore performed a systematic review to investigate the efficacy and harm of these immunostimulating drugs in the prophylaxis of ARTI in children.

Methods

Our review was based on a prospective protocol using widely recommended methodology [1, 7].

Data sources

We searched in Medline, Premedline, EMBASE, Lilacs, Biosis, CINAHL, HealthStar, Inspec and the Cochrane Controlled Trials Register without language restriction using combinations of the terms OM-85 BV, Bronchovaxom, Luivac bacterial and lysate immunotherapy, respiratory tract disease. Searches were limited to "human". The last electronic search was in April 2005. Searches were complemented by screening reference lists of included reports and of relevant review articles, contacting authors of included reports and contacting two manufacturers of bacterial lysates: OM Pharma, Switzerland, and Sankyo Pharma, Switzerland, for additional trials and unpublished data.

Study selection

Reports were considered if they described randomised controlled trials of an oral bacterial extract (active) compared with an inactive control (placebo or no treatment) in children with respiratory tract diseases. Relevant studies had to report on clinical endpoints of efficacy or harm. Studies on immunological parameters were not considered. There was the intention to consider data from abstracts of scientific meetings if the study methods were clearly described and data reporting was adequate.

Validity assessment

One author (CS) screened all retrieved reports. Three authors (LL, CS, LMB,) assessed the selected studies for methodological quality using components of study design that would ensure internal validity [1]. Information was sought for the adequacy of patient enrolment, sequence generation, concealment of allocation, blinding (patient, caregiver, outcome assessment, data analysis), a statement on how dropouts were handled and details to enable intention-to-treat analysis (maximum score 6 points). We sought information on these aspects because random allocation of subjects (with concealment of allocation sequence) prevents selection bias and ensures that comparison groups are balanced on average for known, unknown and unmeasured confounding variables [19, 20]. Blinding statisticians to group allocation was used, as it prevents bias in analysis. An intention-to-treat analysis is important in preventing attrition bias by considering data for all patients, including those who dropped out. Discrepancies were resolved by discussion.

Data extraction

Information about bacterial lysate regimens (drug, dose, route of administration, duration of treatment), number of patients enrolled and analysed, length of follow-up, and outcome measures were entered in standard collection sheets. Particular attention was given to specifying whether

children attended day schools since previous studies identified an increased risk for upper respiratory infections in those children. This was done by one investigator (LL) and cross-checked by two others (LMB, CS). The primary outcome measure was prevention of ARTI. An upper ARTI was defined as the presence of at least one of the following signs: rhinorrhea, sore throat or cough. Lower ARTI was defined as the presence of at least one of the following signs: rales or crepitations, wheezing, pathologic respiratory rate or stridor. If not defined in detail in the original study, information about infections was taken as reported in the original trials. Secondary outcome measures were symptom duration and improvement as assessed by the observers and the patients, rate of hospitalisation due to infections, reduction of antibiotic requirements, school absences and adverse effects.

Analysis

From each study, outcome data and data on harm were abstracted into 2×2 tables. Heterogeneity (i.e. differences between studies) of risk ratios was assessed graphically using forest plots and statistically using the chi-squared test to aid in decisions on how to proceed with quantitative synthesis. This formal statistical analysis examined whether the observed variation in study results was compatible with the variation expected by chance alone. Exploration of the causes of heterogeneity was planned using variation in features of the population (inclusion and exclusion criteria) intervention (drug regimens) and study outcome and quality. If appropriate, we planned to perform meta-analysis where relative risks from individual studies would be pooled using a fixed effects model if no heterogeneity was detected. In case of heterogeneity, we decided to pool using a random effects model [5]. Results are presented as weighted mean differences (WMD), relative risks (RR) and corresponding 95% confidence intervals. Statistical analy-

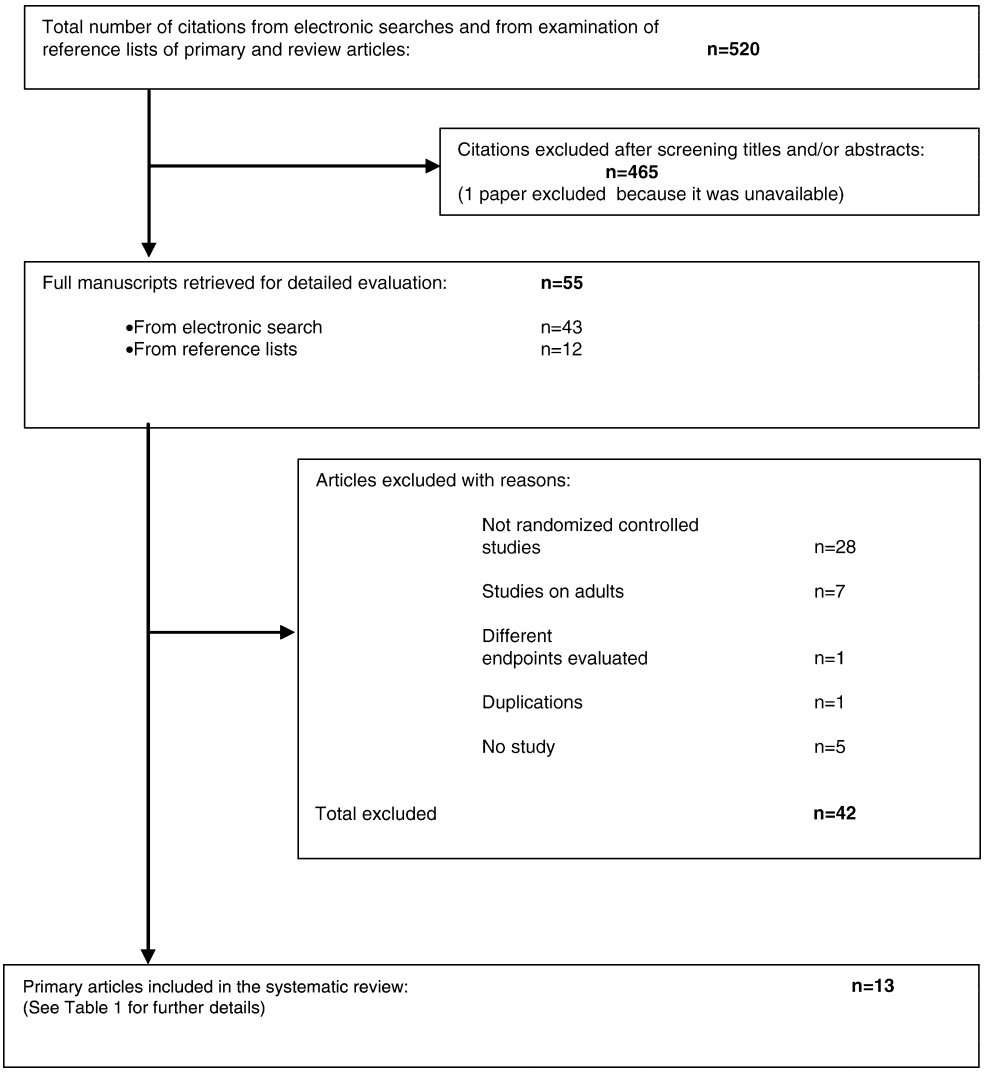


Fig. 1 Study selection process

ses were carried out using the STATA software package (Stata Corp. 2005, Stata Statistical Software: Release 8.2 College Station, TX, USA).

Results

Our searches identified 520 references out of which 465 were subsequently excluded after screening of titles and abstracts (where available). Full texts of the remaining 55 articles were obtained and evaluated for inclusion in the review. Ultimately, 13 studies including 2,721 patients fulfilled our inclusion criteria. (For details, see Fig. 1)

Nine studies [3, 6, 9, 11, 13, 15, 18, 21, 23] were published in English, two [16, 17] in German, one [14] in French and one [8] in Spanish. There was a large variety in reported endpoints. Four trials [9, 11, 18, 21] reported on absences from school, nine [3, 6, 8, 9, 11, 16, 17, 21, 23] on the number of ARTIs during the study and seven [8, 9, 11, 16, 17, 21, 23] on infection duration. Seven (53.9%) [8, 9, 11, 15–17, 23] reported the number of antibiotic courses. Only two trials [8, 23] reported about the improvement of symptoms, and no study reported hospitalisation rate due to infections.

Methodological quality

All trials were placebo controlled; there were no head-to-head comparisons. In general, methodological quality was poor to moderate (Table 1). The median score was 2.69; no trial scored 6 and only three trials scored 5 [6, 9, 18] (Table 2). Five studies [6, 9, 11, 16, 18] reported on consecutive patient enrolment, and four [3, 6, 9, 18] reported on details of generation of random sequence and concealment of treatment allocation. All studies but one [21] included a statement on how they dealt with dropouts and were using an intention-to-treat analysis. Only four studies [6, 9, 11, 18], however, provided details about

Table 1 Results of quality assessment

Study/year	Consecutive patient enrolment	Description of generation of random sequence	Description of concealment of randomisation	Blinding	Statement on how dropouts were handled	Intention-to-treat analysis	Score
Gutierrez 2001 [9]	Yes	Yes	Not reported	Yes	Yes	Yes	5
Schaad 2002 [18]	Yes	Yes	Not reported	Yes	Yes	Yes	5
Del-Rio-Navarro 2003 [6]	Yes	Yes	Not reported	Yes	Yes	Yes	5
Jara-Perez 2000 [11]	Yes	Not reported	Not reported	Yes	Yes	Yes	4
Collet 1993 [3]	Not reported	Yes	Not reported	Not reported	Yes	Yes	3
Martin du Pan 1982 [14]	Not reported	Not reported	Not reported	Not reported	Yes	Yes	2
Maestroni 1984 [13]	Not reported	Not reported	Not reported	Not reported	Yes	Yes	2
Schaad 1986 [17]	Not reported	Not reported	Not reported	Not reported	Yes	Yes	2
Zagar 1988 [23]	Not reported	Not reported	Not reported	Not reported	Yes	Yes	2
Paupe 1991 [15]	Not reported	Not reported	Not reported	Not reported	Yes	Yes	2
Riedl-Seifert 1993 [16]	Yes	Not reported	Not reported	Not reported	Yes	Yes	2
Gomez 1998 [8]	Not reported	Not reported	Not reported	Yes	Not reported		1
Sramek 1986 [21]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	0

Table 2 Description of included trials

Reference	Year	Comparisons	Regimen	Study duration	Patient characteristics							Beneficial effect†	Sponsor
		In () are number of analysed patients		Months	Risk factors	Selection criteria	Endpoints	Age (years)* Mean ± SD median (range)	gender	Previous infections	Previous medication Co-interventions		
Del Rio Navarro [6]	2003	OM-85 BV (22) Placebo (21)	1 caps 3.5mg/d 10d/mo for 36 mo		Not reported	-At least 3 ARTIs in the previous 6 months (based on the number of medication prescriptions) -No anatomic alterations of the respiratory tract by physical examination -No chronic respiratory diseases (tuberculosis, cystic fibrosis) -No autoimmune diseases -No liver or kidney failure -No cancer -No treatment with corticosteroids, immunostimmulants, immunosuppressants, gammaglobulins or anticonvulsive drugs in the last six months	-Median IgG subclass levels before and after the trial -No of ARTIs,	A 4.0 ± 0.9 C 4.1 ± 0.9	Males: A 12, C 11 Females: A 10, C 10		None	+	Quimica Knoll de Mexico SA de CV BASF Pharma, Dr. A.Berber was the medical manager for OM-85 BV in Mexico from 1995-2000.
Schaad [18]	2002	OM-85 BV (99) 2. Placebo (100)	1 caps 3.5mg/d 10d/mo for 36 mo		Not reported	-Age between 36 to 96 months -History of recurrent URTIs (= three or more ARTIs during the last 12 months) -Presenting with URTI at hospital admission; current episode presenting with at least 2 of the following: rhinitis, pharyngitis, cough, hoarseness, temperature> 38,5°C, prescription of an antibiotic for a URTI, occurring after an asymptomatic period of at least 1 week without antibiotics -no occurrence of otitis media and/or sinusitis and/or infection of the lower respiratory tract (ie, bronchitis, pneumonia), and/or proven group A streptococcal angina at the enrolment visit -no allergic asthma, mucoviscidosis, significant systemic disease (eg, hepatic and/or renal disease, malignancy) -no immune system disorders, suspected malabsorption, known allergy to the bacterial extract -no major surgical procedure within 3 months of commencement of the study -no recent immunosuppressive or immunostimulant therapy, or corticosteroids	-Reduction of URTIs during treatment and over entire observations period -Rating of rthinitis, pharingitis, cough, hoarseness (coded as none, mild, or severe), fever (coded as 0=absent, 1= 38.5 to 39,4°C, 2 = 39.5°C or more) -number of days absence from school -incidence of otitis, sinusitis or other related infections	A 9.8 ± 1.9 C 9.6 ± 1.9	Males: A 69, C 61 Females: A 51, C 38	Three or more URTIs during the last 12 months	None	+	OM PHARMA, Switzerland. 1 author is project leader of this clinical trial at OM PHARMA

Table 2 (continued)

Gutierrez [9]	2001	OM-85 BV (26) Placebo (28)	1 caps 3.5mg/d 10d/mo for 312 mo, same schedule after 6 mo	-Birth: gestational age, birth weight, birth ranking; -Breast feeding time; -Children living at home -Persons living at home -Siblings in day-care centre -Siblings in school; -Time of attendance at day-care centre/school -Persons smoking at home -Socio-economic level	-at least three ARTIs in the previous 6 mo -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 -no chronic respiratory diseases (tuberculosis, cystic fibrosis) -no autoimmune diseases -no liver and/or kidney failure, malnutrition or cancer -no treatment with corticosteroids, immunsuppressants, immunostimulants, y-globulins or anticonvulsive drugs in the last 6 months	-Nr. Of ARTIs -Total duration of illness -No of antibiotic courses -No of drug courses (including antibiotics) -Duration of treatment (days taking any drug) -Absenteeism (days out of school/day-care centre)	A 3.86 ±2.49 C 4.52 ± 2.75	Males: A 13; C 18 Females: A 13; C 10	At least 3 ARTIs during the previous 6 months	None	+	Quimica Knoll de México SA de CV BASF Pharma
Jara-Perez [11]	2000	OM-85 BV (99) Placebo (100)	1 caps 3.5mg/d 10d/mo for 36 mo	-Overcrowding in orphanage -Exposure to low temperatures during the daily morning shower due to lack of hot water	-Three or more ARTIs during the previous 6 months (according to the medical records in the orphanage) -negative familial history of allergy -no seasonal or food-related wheezing or nose itching and no nasal fold -no anatomic alterations of the respiratory tract -no chronic respiratory diseases (tuberculosis, cystic fibrosis) -no autoimmune diseases -no liver or kidney failure -no malnutrition or cancer -no treatment with corticosteroids, immunosuppressants, immunostimulants, gamma globulins or anticonvulsive drugs in the past 6 months	-Total-no of ARTIs (Upper ARTIs: more than 1 of the following: rhinorhea, sore throat or cough without signs of a lower ARTI for >48h,; Lower ARTIs: more than 1 of the following rales or crepitations, wheezing, stridor, respiratory rate>50per minute, cyanosis or chest indrawing for >48h; Otitis episodes=earache with erythema and limited mobility of the tympanic membrane determined by pneumatic otoscopy) -Duration of illness -No. of antibiotic courses -No. of drug courses -Duration of concomitant treatment -No. of days out of school	A 9.8 ± 1.9 C 9.6 ±1.9	Only girls: A 99, C 100	At least 3 ARTIs during the previous 6 months	None	+	Quimica Knoll de Mexico SA de CV BASF Pharma
Gomez [8]	1998	OM-85 BV (26) Placebo (30)	1 caps/d during 10d/mo for 6 3mo	Not reported	-subacute sinusitis, defined as: nasal discharge, nasal congestion, painful faical palpation, rash of nasal mucosa, retroorbital cephalgia, symptom persistence >30days, <90days -no asthma - no anatomic alterations of the respiratory tract by physical examination -no tuberculosis, cystic fibrosis -no autoimmune disease -no renal of liver failure -no malnutrion -no antibiotic therapy during the last 72h	-Safety and efficacy in the management of subacute sinusitis and prevention of respiratory infections -Improvement of the symptoms -No of infections -Use of antibiotics	A 56,3 ± 20.6mo C 48,7±21,7mo	Male A:13/C 20 Females A:13/C 10	Not reported	Cointervention with Amoxicillin and Clavulanacid in both groups	+	A.Berber works for Arzneimittelforschung BASF Pharma, Mexico, Distrito Federal, Mexico

Table 2 (continued)

Riedl-Seifert[16]	1993	Luivac (115) Placebo (118)	1 caps/d during 28d, then break of 28d, then 1 caps/d during 28d	14 weeks= 3.5 months	Not reported	-4-6 year old children: at least 10 RTI during the last 12 months -7-9 year old children: at least 8 RTIs during the last 12 months, or at least 4 severe infections lasting longer than 2 weeks during the last 12 months -No autoimmune diseases -No severe disease of internal organs -No treatment with immunosuppressants or immunomodulants during the last 2 months -No chronic infections -Patients with less than 2 infection free weeks during the last 8 weeks were excluded	-Severity score of Infection (coded as: 0=none, 1=little, 2=mild, 3= severe. Score x days of infection over all symptoms) -Adverse effects -No of infections -Median no of infection-days -No of antibiotic courses	A 5.9 ±1.52 C 5.8 ±1.56	Male A: 52.5% (=52) C: 58.3% (=63) Females A: 47.5% (=47) C: 41.7% (=45)	Not reported	None	+	Not reported
Collet[13]	1993	OM-85 BV (210) Placebo 213)	1 caps/d during 10d/mo for 3 consecutive mo	7.5	-Breast fed >1 month -Child's case history: Wheezy bronichiolitis, Rhinitis with fever, Otitis media, Gastroentritis, -Previous hospitalisations -Family history (in %, mother, father) of: Otitis media, Asthma, Hay fever -No of siblings -1 parent who smokes -Living in a house (vs. apartment) -Central heating -Followed by a paediatrician	-Children older than 6 months -likely to complete follow-up -no severe concomitant illness -no immunosuppressants, immunostimulants, gamma-globulins in the 6 months preceding the study -no long term use (>2 weeks) of corticosteroids in the 6 months preceding the study	-4 or more upper respiratory infections -2 or more otitis media, -2 or more gastroenteritis	A <12mo: 28%, 12-18mo:33%, >18mo:39 C < 12mo:37%, 12-18mo: 34%, >18mo:29%	Male A: 105/ C: 120 Female A: 105/ C: 93	Not reported	None	+	Laboratoires Fournier (Dijon, France), City of Lyon, Laboratoire National de la Santé
Paupe[15]	1991	OM-85 BV (64) Placebo (63)	1 caps 3.5mg/d 10d/mo for 36 mo		-No of patients with recurrent respiratory or ear, nose or throat infections (= ENT infections) -No of infections during pre-trial period (rhinopharyngitis, bronchitis, otitis, sinusitis, tonsillitis)	-3 or more respiratory or ENT infections in the previous autumn and winter or in the 6 months immediately preceding the trial -No known allergy to products of bacterial origin -No therapy with corticosteroids -No severe immune deficiency or systemic disease -No patients were included who were known to be unlikely to comply with the trial protocol or to be unsuitable on ethical grounds for the administration of placebo	-No. of patients without respiratory and ENT infections -No. of the patients who did not require concomitant treatments, in particular antibiotics -White blood cell counts -Erythrocyte sedimentation rate	A 6.6 ±5.3 C 7.6 ± 5.3	Males A: 37/ C: 24 Females A: 24/ C: 31	-Three or more respiratory or ENT infections in the previous autumn or winter or in the 6 months immediately preceding the trial	None	+	Laboratoires Fournier (Dijon, France)

Table 2 (continued)

Zagar [23]	1988	1. OM-85 BV (29) 2. Placebo (22)	Mo1: 1 caps 3.5mg/d for 30d, mo2: no therapy, mo3-5:1 caps 3.5mg/d 10d, mo6 no therapie (follow-up)	6	-Duration of disease (years) -No of recurrence rate of disease	-Children presenting with an acute episode of chronic rhinosinusitis	-Reduction of incidence of cough (1=none, 2= moderately frequent (weekly), 3= frequent (daily) -Improvement of presence of nasal discharge (same code as cough) -Frequency and intensity of nasal discharge (sever congestion: 1=none, 2.5= moderately frequent (weekly), 3=frequent (daily); mild congestion: 1=none, 1.5=moderately, 3=frequent) -Acute episodes, duration (days) and number of acute exacerbations -Laboratory parameters (leukocyte counts, ESR) -No. of courses and duration of concomitant treatment -Sinus X-ray findings	A 6.53 ± 0.96 C 6.81 ± 0.8	Males A: 15/ C: 13 Females A: 14/ C: 9	-Acute episode of chronic rhinosinusitis	None	+	OM Laboratories, Geneva (Switzerland), Lek Ljubljana (Yugoslavia)
Schaad [17]	1986	OM-85 BV (45) Placebo (49)	1 caps 3.5mg/d 10d/mo in mo 1,3,4,5	6	Not reported	-Children with recurrent respiratory tract or ENT infections -No treatment with immunostiumulats in preceding year	-No. of infections -Intensity of infections -Duration of infections -Duration of antibiotic courses	A 4.3 ±2.79 C 4.09 ± 2.49	Males A: 58% (=28)/ C: 51% (=26) Females A: 42% (=21) C: 49% (=24)	-Recurrent infections of respiratory tract or ENT	None	-	Not reported
Sramek [21]	1986	I.R.S. 19 (416) Placebo (409) Control group (327)	Intranasal spray, 2x daily in each nostril, totally 20 spraying days	6	Not reported	-Children under dispensary care for allergy and children whose parents' consent was not obtained were not included in the study	-Absence from school due to ARD (=acute respiratory disease) -Mean duration of one ARD case -Incidence of ARD	No data reported	Not reported	Not reported	none	-	Hefa Fernon, Arzneimittel, Werne Germany
Maestroni [13]	1983	OM-85 BV (11) Placebo (9)	1 caps 3.5mg/d 10d/mo for 36 mo		Not reported	-Children with predisposition to upper respiratory tract infections	-Mixed lymphocyte culture-response -Relative distribution of surface markers of mononuclear cells (surface immunoglobulins, surface thymic antigens, esterase reactions) -Enzymatic activity of mononuclear cells -Frequency of infectious episodes (before and after treatment, considered infections: bronchitis, tonsillitis, pharyngitis, sinusitis, rhinitis, otitis)	8.3	Not reported	-Children with predisposition to upper respiratory tract infections	None	+	Not reported
Martin du Pan [20]	1982	OM-85 BV (36) Placebo (34)	1 caps 3.5mg/d 10d/mo for 34 mo		-Attending a day-care centre	-Children attending day-care centre were all included if the parents gave their agreement -Children living at home were included because of infections of upper respiratory tract	-Frequency of clear or purulent nasal discharge	2.5	Not reported	Not reported	None	+	Laboratoires OM SA, Meyrin

[a] A=active; C=control

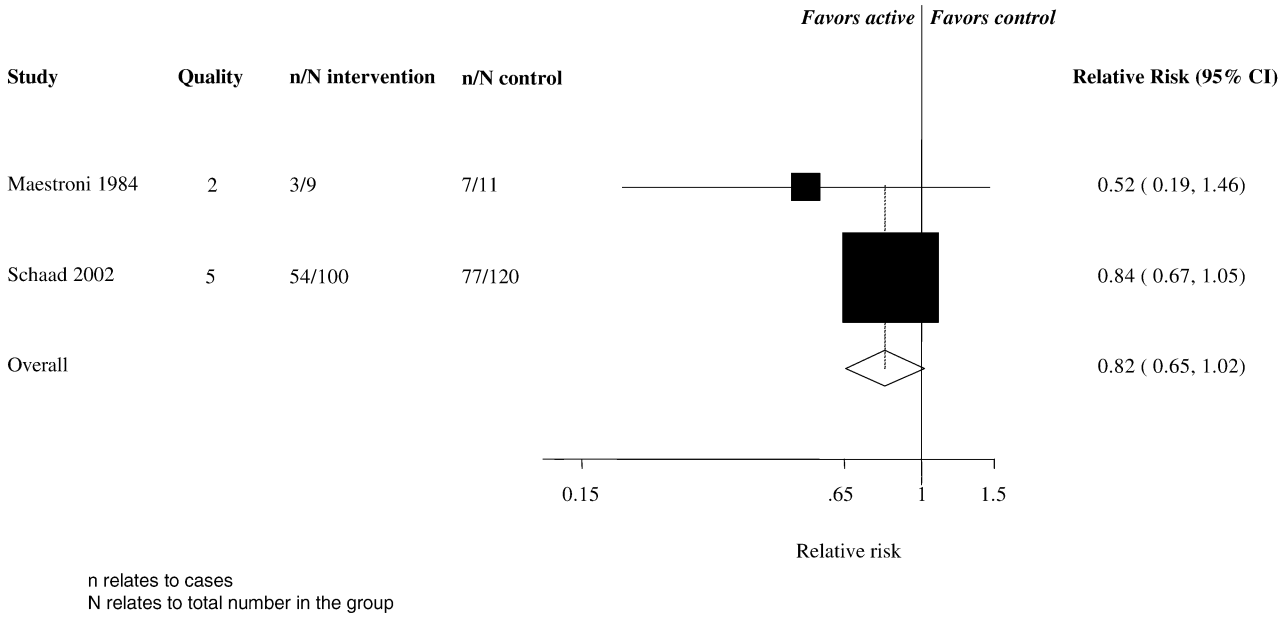
[b] as reported in the trial + yes, - no

blinding of patients and caregivers. Ten trials (76.92%) [3, 6, 8, 9, 11, 14, 15, 18, 21, 23] acknowledged sponsorship by a manufacturer; in one study [8], one author was collaborator of a manufacturer.

Patients

Nine trials reported on demographic data [3, 6, 8, 9, 11, 15–18, 23]; there were more females than males (767 females vs. 700 males). Inclusion criteria were three or more infections in the previous 6 months in six trials [6, 9, 11,

a



b

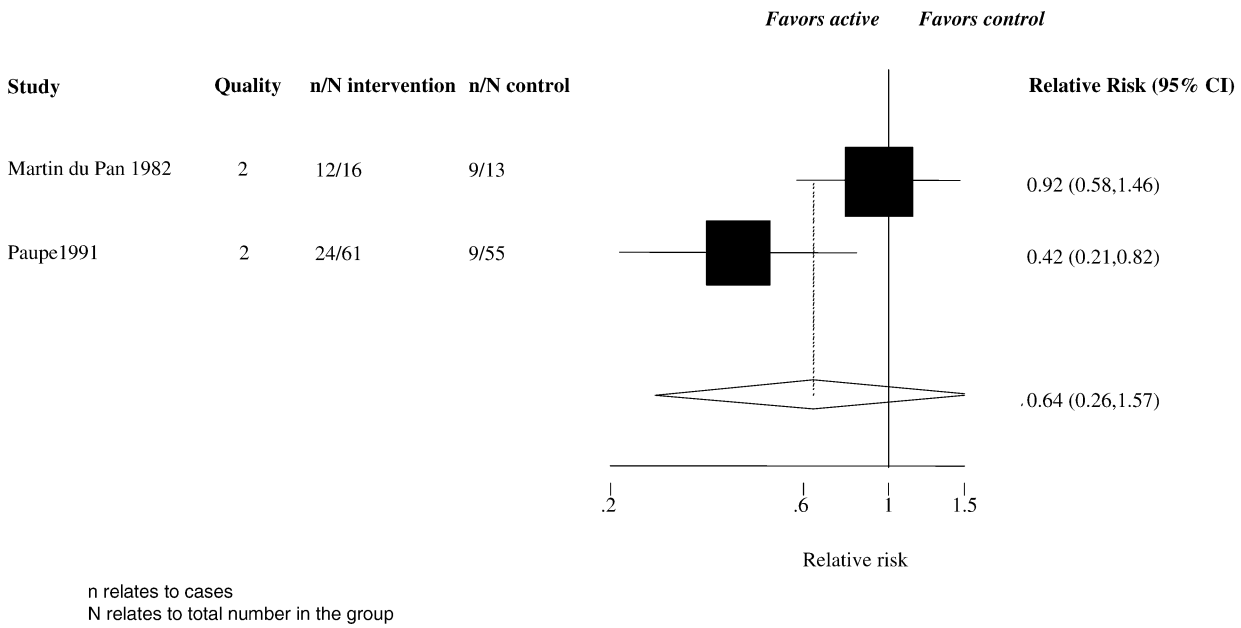


Fig. 2 **a** Children not in day care. Number of patients with less than three infections over 6 months of follow-up: In Maestroni (1984), more patients in the OM-85 BV group had less than three infections than patients treated in the placebo group. In Schaad (2002), pooled results (random effects) show a favourable effect in the active group. **b** Patients not in day care. Number of patients without infections over 4–6 month: In one study, Paupe (1991), the relative risk to have infections over 4–6 months was significantly reduced. The second smaller study, Martin du Pan (1982), showed no beneficial effect. Pooling these two studies using a random-effects model resulted in a non-significant effect of OM-85 BV

15, 16, 18]; no anatomic alterations of the respiratory tract in four [6, 8, 9, 11]; no treatment with corticosteroids, immunostimulants or immunosuppressants in eight [3, 6, 9, 11, 15–18] and no chronic respiratory disease, autoimmune diseases or liver or kidney failure in five [6, 8, 9, 11, 18] (Table 2).

Efficacy endpoints

Although several studies reported on the same outcome category, variation in outcome parameter (e.g. less than six infections vs. less than three infections) impeded combining results of more than two trials. Two studies (240 patients) reported on the number of patients with less than three infections over 6 months of follow-up in children not in day care [13, 18]. The two studies showed a trend for benefit (RR 0.82; 95% CI 0.65–1.02) (Fig. 2a). Two studies reported on the number of patients without infections over 4–6 months in children not in day care. In one study, the number of infections over 4–6 months was significantly reduced (RR 0.42; 95% CI 0.21–0.82) [15]. The other smaller study did not show a beneficial effect (RR 0.92; 95% CI 0.58–1.46) [14] (pooled RR using a random-effects model 0.64 (95%CI 0.26–1.57) (Fig. 2b).

Three studies [8, 17, 23] reported on duration of episodes. Two out of the three showed a reduction of 4–6 days whereas one study showed no difference between the two groups (Fig. 3). Finally, two studies [9, 11] reporting on the number of antibiotic courses indicated a benefit for the intervention arm [WMD 2.0 (95% CI, 1.7–2.3)]. (For the complete list of assessed endpoints, see Table 1.)

Adverse events

Nine studies reported on gastrointestinal, urinary tract, skin and allergic adverse effects [3, 6, 9, 11, 15–18, 23]. Paupe [15] reported diarrhoea in one patient in the active group and two patients in the control group. In the study of Schaad [18], adverse reactions in the OM-85 group were diarrhoea (two patients), abdominal pain (two patients), fatigue, urinary frequency (twice in the same patient) and exanthema. In the placebo group, there was one allergic reaction. In Schaad [17], there was one case of urticaria in the control group; no adverse event was reported in the Bronchovaxom group. Collet [3] recorded 17 medical events for the treated group and 19 for the placebo group. The adverse effects were very infrequent and appeared unlikely to be related with the study medication. Del Rio Navarro [6] recorded eight patients in the active group with ten adverse events; only three were related to drug administration: gastroenteritis, gastroenteritis with melena and diarrhoea. Nine patients taking placebos had ten adverse effects; four were related to the administration of the placebo: gastritis, diarrhoea (trial withdrawal), vomit and asthma. Riedl-Seifert [16] recorded eight patients in the active group with gastrointestinal symptoms: three with skin problems and one with other side effects. In the placebo group were five patients with gastrointestinal manifestations and one patient with skin problems. Jara Perez [11] and Zagar [23] reported that there were no adverse effects.

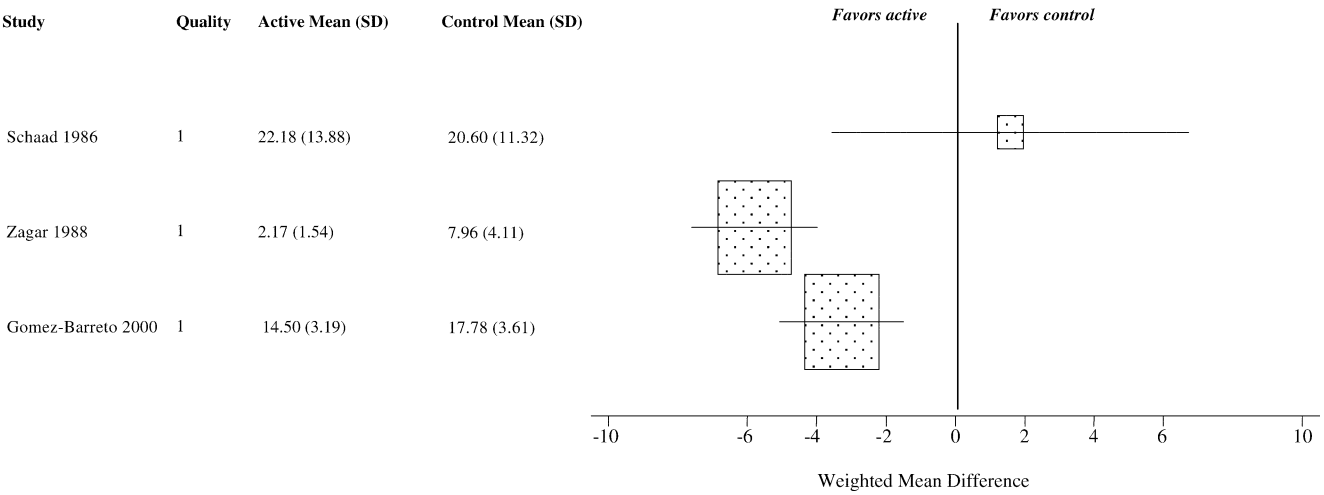


Fig. 3 Duration of episodes (days): Zagar (1988) and Gomez-Barreto (1998) showed that in the group treated with OM-85 BV, the duration of episodes was shorter than in the control group (Zagar: 6 days shorter; Gomez: 4 days shorter). In Schaad's study (1986), the duration of episodes was shorter in the control group (2 days). (We refrained from pooling the results of these strongly heterogeneous studies.)

Discussion

Our systematic review provides weak evidence that oral immunostimulation with bacterial extracts prevents ARTIs in children. There was a trend for fewer infections over 6 months of follow-up in children not in day care and a small reduction in number of antibiotic courses. Safety and tolerance of Bronchovaxom were good.

What are the limitations of this review? We think that searches and selection procedures were adequate. However, some important limitations of our review are related to the limited validity of the original trials. The overall quality of the trials was moderate to poor. While, for example, the included trials reported on clinically homogenous settings, treatment regimens and similar follow-up periods, important methodological items such as patient enrolment, generation of random sequence, concealment of treatment allocation and details about statistical analyses were seldom reported. Furthermore, most trials were of limited size. The problem with small trials is that they may generate treatment effects by random chance. Pharmaceutical companies sponsored ten of the trials; in one study, a co-author was working for the manufacturer. An association between competing interests and authors' conclusions has been shown [12]. In our meta-analysis, however, authors' conclusions per se were not considered. We do not know how potential competing interests may influence the way a clinical trial is designed and conducted or the way data are analysed and reported. The trials reported on a large variety of different endpoints. It was impossible to compare outcome data from more than three trials. Although the main endpoint, reduction of the number of infections, was reported in nine trials, differences in outcome definition (e.g. less than six vs. less than three infections) allowed combining the results of two trials only. Finally, data were too sparse to allow formal sensitivity analyses, addressing, for instance, the impact of treatment duration.

What are the implications for research? We think that further studies should examine which children benefit most. For example, otherwise healthy children reporting more than five ARTIs per six months before study inclusion could be studied. Furthermore, infants with chronic lung diseases or immunocompromised children should be enrolled because these populations are at very high risk for severe morbidity and have higher risk for mortality.

Conclusions

Evidence in favour of Bronchovaxom in the prevention of ARTIs in children is weak. There is a trend for fewer and shorter infections and a reduction of antibiotic use.

Acknowledgements We thank Dr. P. Estermann, information specialist from the Library Service of the Zurich University Hospital, for his help in searching electronic databases.

References

1. Undertaking Systematic Reviews of Research on Effectiveness CRD's Guidance for those Carrying Out or Commissioning Reviews. CRD Report Number 4 (2nd Edition) (2001) Ref type internet communication
2. Anonymous (1998) Acute respiratory infections: the forgotten pandemic. Bull World Health Organ 76:101–107
3. Collet JP, Ducruet T, Kramer MS, Haggerty MSC, Floret D, Chomel JJ, Durr F, Epichrèche Research Group (1993) Stimulation of nonspecific immunity to reduce the risk of recurrent infecions in children attending day-care centers. Pediatr Infect Dis J 12:648–652
4. DeBaets F, Kint J, Pauwels R, Leroy J (1992) IgG subclass deficiency in children with recurrent bronchitis. Eur J Pediatr 151:274–278
5. Deeks JJ, Altman DG, Bradburn MJ (2001) Statistical methods for examining heterogeneity and combining results from several studies in meta-analyses. Systematic Reviews in Health Care - Meta-analysis in context, Second Edition Chapter 15, page 285
6. Del-Rio-Navarro B, Luis Senre-Monge JJ, Berber A, Torres-Alcantara S, Avita-Castanon L, Gomez Barreto D (2003) Use of OM-85 Bv in children suffering from recurrent respiratory tract infections and subnormal IgG subclass levels. Allergologia et Immonopahtologia 31:7–13
7. Egger M, Smith GD, Altman DG (2001) Systematic Reviews in Health Care. BMJ Publishing Group, London, pp 3–487
8. Gomez Barreto D, De la Torre C, Alvarez A, Faure A, Berber A (1998) Safety and efficacy of OM-85-BV plus amoxicillin/clavulanate in the treatment of subacute sinusitis and the prevention of recurrent infections in children. Allergol Immunopathol (Madr) 26:17–22
9. Gutierrez-Tarango MD, Berber A (2001) Safety and efficacy of two courses of OM-85 BV in the prevention of respiratory tract infections in children during 12 months. Chest 119:1742–1748
10. Heikkinen T, Thint M, Chonmaitree T (1999) Prevalence of various respiratory viruses in the middle ear during acute otitis media. N Engl J Med 340:260–264
11. Jara-Perez JV, Berber A (2000) Primary prevention of acute respiratory tract infections in children using a bacterial immunostimulant: a double-masked, placebo-controlled clinical trial. Clin Ther 22:748–759
12. Kjaergard LL, Als-Nielsen B (2002) Association between competing interests and authors' conclusions: epidemiological study of randomised clinical trials published in the BMJ. BMJ 325:249
13. Maestroni GJ, Losa GA (1984) Clinical and immunobiological effects of an orally administered bacterial extract. Int J Immunopharmacol 6:111–117
14. Martin du Pan RE, Martin du Pan RC (1982) Etude clinique de prévention des infections des voies respiratoires supérieures de l'enfant de l'âge préscolaire. Schweizerische Rundschau für Medizin Praxis 71:1385–1389
15. Paupe J (1991) Immunotherapy with an oral bacterial extract (OM-85 BV) for upper respiratory infections. Respiration 58:150–154
16. Riedl-Seifert RJ, van Aubel A, Kämmereit A, Elsasser U (1993) Infektrezidive im Kindesalter- noch immer eine Crux medicorum? Ergebinsse einer plazebokontrollierten Doppelblindstudie mit einem

oralen Baktrienlysat bei infektanfälligen Kindern. J Pharmacol u Ther 3:108–117
17. Schaad UB, Farine JC, Fux T (1986) Prospective placebo-controlled double-blind study using a bacterial lysate in infections of the respiratory tract and ENT region in children. Helv Paediatr Acta 41:7–17
18. Schaad UB, Mütterlein R, Goffin H (2002) Immunostimulation with OM-85 BV in children with recurrent infections of the upper respiratory tract. A double-blind, placebo-controlled multicenter study. Chest 122:2042–2049
19. Schulz KF, Grimes DA (2002) Allocation concealment in randomised trials: defending against deciphering. Lancet 359:614–618
20. Schulz KF, Grimes DA (2002) Generation of allocation sequences in randomised trials: chance, not choice. Lancet 359:515–519
21. Sramek J, Josifko M, Helcl J, Holoubkova E, Janout V, Kozesnik B, Macatova I (1986) Bacterial lysate (I.R.S. 19) applied intranasally in the prevention of acute respiratory diseases in children: a randomized double-blind study. J Hyg Epidemiol Microbiol Immunol 30:377–385
22. Steurer-Stey C, Bachmann LM, Steurer J, Tramer MR (2004) Oral purified bacterial extracts in chronic bronchitis and COPD: systematic review. Chest 126:1645–1655
23. Zagar S, Lofler-Badzek D (1988) Broncho-Vaxom in children with rhinosinusitis: a double-blind clinical trial. ORL J Otorhinolaryngol Relat Spec 50:397–404