Pulmonary Pharmacology & Therapeutics 25 (2012) 62–68

Contents lists available at SciVerse ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

Polyvalent mechanical bacterial lysate for the prevention of recurrent respiratory infections: A meta-analysis

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ARTICLE INFO

Article history:
Received 29 October 2011
Received in revised form
14 November 2011
Accepted 19 November 2011

Keywords:
Recurrent respiratory infections
Prevention
Bacterial lysates
Meta-analysis

ABSTRACT

Background: Respiratory tract infections are common and remain a major source of morbidity, mortality and economic cost worldwide, despite advances in modern medicine. One treatment approach is to non-specifically increase the immune response or augment innate defense mechanisms through the use of bacterial lysates. Polyvalent Mechanical Bacterial Lysate (PMBL) is a bacterial lysate made from a wide range of pathogenic bacteria, including all of the most commonly occurring pathogens of the upper and lower respiratory tract obtained by mechanical lysis.
Aim: To test the available evidence that PMBL is able to prevent respiratory tract infections.
Methods: A number of studies investigating randomized comparisons of PMBL (active) with placebo or no treatment (control) were selected for analysis. The primary outcome measure was the prevention of exacerbations or acute respiratory tract infection. The results were expressed as relative risk (RR) and the number of patients needed to treat for one to benefit (NNTB).
Results: Data from 2557 patients from 15 randomized clinical trials (RCTs) was investigated. PMBL induced a significant reduction of infections *vs* placebo (RR −0.513; 95% CI; −0.722 − −0.303; $p = 0.00$). The NNTB was 1.15. The RR was always in favor of PMBL (in recurrent respiratory infections other than COPD, chronic bronchitis and tuberculosis, RR −0.502; 95% CI −0.824 − −0.181; in children RR −2.204; 95% CI −3.260 − −1.147; in COPD or chronic bronchitis, RR −0.404; 95% CI −0.864–0.057; in tuberculosis, RR −0.502; 95% CI −0.890 − −0.114).
Conclusions: The results of the present meta-analysis suggest that PBML is effective in both in children and in adults in preventing respiratory tract infections. Our current meta-analysis shows that there is a trend with PBML toward clinically significant results in patients with COPD but it did not quite achieve statistical significance due to the small number of COPD studies.

1. Introduction

Respiratory tract infections are common and remain a major source of morbidity, mortality, and economic cost worldwide, despite advances in modern medicine. They account for some 300-400 general practice consultations annually per 1000 registered patients [1] and represent one of the most frequent indications for antibiotic drug prescription [2]. There are two main types of clinically relevant respiratory tract infections: acute exacerbations of chronic bronchitis or chronic obstructive pulmonary disease (COPD) and recurrent respiratory tract infections [3].

Recurrent respiratory infections are frequent both in pediatric and in adult patients. They can involve both the upper and lower respiratory tract and are caused by a wide range of microorganisms. In particular, whilst viral infections, caused by influenza viruses, parainfluenza viruses, respiratory syncitial virus, adenovirus, rhinoviruses, are the original cause of the disease,recurrences can be also caused by different types of bacteria, including Acinetobacter spp., *Chlamydia pneumoniae*, Enterobacteriacee, *Haemophilus influenzae*, *Legionella pneumophila*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Nocardia asteroids*, *Pasturella multocida*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Stenotrophomonas maltophilia*, *Streptococcus pneumoniae* and *Streptococcus pyogenes* (group A) [3].

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doi:10.1016/j.pupt.2011.11.002

Infectious agents, including bacteria, viruses, and atypical pathogens, are currently implicated in up to 80% of acute exacerbations of chronic bronchitis or COPD [4]. The patient with COPD has airways that are prone to infections, with impaired local defenses and frequent bacterial colonization [5]. Sputum and bronchoscopy data have shown that *M. catarrhalis*, *H. influenzae*, and *S. pneumoniae* are the most common organisms associated with exacerbations of COPD [4,5], although other bacteria (e.g., Pseudomonas and Staphylococcus) have also been implicated [4,5]. Many of these bacteria may chronically colonize the airways that progress to infection after a simple viral upper respiratory infection or an environmental stress. On the other hand, a significant number of COPD infections may come from bacterial strains that are new to the patient [6].

Exacerbation frequency is an important outcome in patients with COPD. In fact, frequent exacerbations are associated with increased morbidity and mortality, a faster decline in lung function, and poorer health status [7]. Using data from the large observational Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort, it has been found that exacerbations become more frequent and more severe as the severity of underlying COPD increases and shows that the most important determinant of frequent exacerbations is a history of exacerbations [8]. This finding supports the hypothesis that patients who are more subject to frequent exacerbations, some of whom have milder disease, have a distinct susceptibility phenotype that is relatively stable over time and can be identified on the basis of the patient's recall of previously treated events. Because of the significant increase in morbidity and mortality from COPD exacerbations, the prevention of exacerbations is a major goal of COPD management and a global priority.

One approach to the treatment of respiratory infections is to non-specifically increase the immune response or augment innate defense mechanisms. To increase the immune response toward pathogens, particularly bacteria, different therapeutic strategies can be chosen, from antibiotic prophylaxis, or vaccinations with bacterial lysates. Immunomodulators prepared from lyophilised bacterial extracts for oral administration have been in clinical use for a number of years with the aim of improving symptoms and preventing respiratory tract infections [9]. An earlier meta-analysis suggested that such treatments may have an effect on exacerbations, but the quality of the trials included in the analysis was generally poor [10]. However, a later quantitative pooled analysis of OM-85 BV (Broncho-vaxom®) that examined 13 randomized placebo controlled clinical trials investigating 2066 patients, did not find bacteria lysates to be beneficial in the prevention of COPD exacerbations [11]. Varied results in the outcomes of hospitalitations, symptom scores and antibiotic or steroid use were found across studies [11].

OM-85 BV is the product of alkaline proteolysis from lysates of the following bacteria: *H. influenzae*, *S. pneumoniae*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *S. aureus*, *Staphylococcus pyogenes*, *Streptococcus viridans* and *M. catarrhalis*. Unfortunately, alkaline lysis may cause protein denaturation, with a consequent lower immunogenicity of the bacterial antigens leading to reduced augmentation of the immune response [12].

Polyvalent Mechanical Bacterial Lysate (PMBL) is a bacterial lysate made from a wide range pathogenic bacteria, including all the most commonly occurring pathogens of the upper and lower respiratory tract *(S. aureus*, *S. viridans*, *S. pyogenes*, *K. pneumoniae*, *K. ozaenae*, *H. influenzae* serotype B, *M. catarrhalis* and *S. pneumoniae*) obtained by mechanical lysis [13]. The mechanical method is particularly efficient in that it achieves lysis of 80–100% of the bacteria. It is even more interesting that, compared with other methods of lysis, mechanical lysis does not alter the structure of the antigens: this ensures a preparation having excellent antigenic properties [13]. The lysate thus induces a specific immunostimulation against all of the seven bacterial strains found in the PBML, selected as those that most often responsible for respiratory infections [13].

The aim of the present systematic review is to test the available evidence that PMBL treatment may be effective in preventing respiratory tract infections.

2. Methods

This systematic review was performed in accordance with the Quality of Reporting of meta-analyses (QUORUM) guidelines [14].

2.1. Study selection

A systematic searchfor relevant clinical trials with no language restrictions was made from databases like Rection, Pub Med, Inist, Toxline, Google Scholar and Scirus with search terms "PMBL", "Polyvalent lysate", "COPD", "Mechanical lysate" and "Sublingual vaccine". We also contacted the manufacturer of PMBL (Lallemand Pharma, Lugano, Switzerland), and asked for information on additional trials including obtaining access to unpublished data.

Reports were considered for review if they described randomized comparisons of PMBL treatment (active) with placebo, another conventional bacterial lysate or no treatment (control) in adults with chronic bronchitis and COPD or tuberculosis, and in children with acute/recurrent respiratory tract infections. Studies on the prevention of infections in otherwise healthy subjects or on immunologic parameters were not considered. There was an intention to consider data from the abstracts of scientific meetings if the study methods were clearly described and data reporting was adequate.

2.2. Data extraction and validity assessment

For each of the selected trials, the following information was retrieved: first author, publication year, details of study design, studied treatments (type of drug, schedule, duration), type of patients (COPD + bronchitis, tuberculosis, adult or children), study endpoints, occurrence and type of adverse events.

The quality of the selected trials was assessed according to a five-point validated scale [15] measuring a range of factors that impact the quality of a trial: randomization methods, blinding and description of withdrawals and dropouts.

Two independent reviewers assessed the quality of the trials to be included. Differences in the evaluation were resolved by consensus, referring back to the original article/report.

2.3. Statistical analysis

The primary outcome measure was the prevention of exacerbations or acute respiratory tract infection. Definitions of exacerbation or acute respiratory tract infection were taken as reported in the original trials.

Trials were grouped into double blind placebo controlled randomized clinical trials and then sub grouped as COPD + Bronchitis, Pediatric trials or Tuberculosis. Data are classified into treated and placebo.

The summary measure for the end of treatment used mean values in both treatment and placebo groups.

Global estimates of effect size treatment versus placebo and the corresponding 95% confidence intervals (95% CIs) were calculated using difference of means method for continuous variables [16].

For the pooling of the estimates both fixed and random effect models were considered, depending on the presence of statistical heterogeneity, Statistical heterogeneity was defined as an I^2 statistic gt; 50% [17]. In order to assess the heterogeneity of the included trails, the Cochrane Q statistics was calculated [18]. For *P*-values <0.10, the homogeneity was deemed not valid.

All statistical analysis were made using Excel as well as CMA version 2.2.

The results are presented as relative risks (RRs) and the number needed to treat for one to benefit (NNTB), with corresponding 95% CIs.

3. Results

3.1. Study selection

Nineteen potentially relevant studies were retrieved [19–37] (Fig. 1). Three of these were excluded because they had insufficient data on the total number of patients treated and/or the total number of infections/exacerbations [34–36]. Another one was excluded because of inadequate study design [37]. Therefore, 15 RCTs [19–33] enrolling a total of 2557 subjects were included in the final analysis and are summarized in Table 1.

3.2. Outcomes

The efficacy of PMBL was determined with respect to the number of recurrences of respiratory tract infections. Combining the studies, PMBL induced a significant reduction of infections *vs* placebo (RR −0.513; 95% CI; −0.722 − −0.303; $p = 0.00$) (Fig. 2). We also calculated the NNTB for 1 year to avoid one infection. The infection rate in patients treated with PMBL was 1.27, whilst that in patients treated with placebo was 2.01, the absolute risk reduction being 0.87 and an NNTB of 1.15.

Data for a sub analysis was available for 7 RCTs in adults suffering from recurrent respiratory infections other than COPD, chronic bronchitis and tuberculosis (475 patients treated with PMBL and 457 patients treated with placebo) documented that PMBL had a significantly positive impact on the reduction in the total number of infections (RR −0.502; 95% CI −0.824 − −0.181; $p = 0.002$) (Fig. 3).

Data from three RCTs investigating the effect of PMBL in children (192 treated and 153 placebo participants) showed a significant beneficial effect with PMBL treatment (RR −2.204; 95% CI−3.260 − −1.147; $p = 0.00$) (Fig. 4).

Three RCTs (305 treated and 335 placebo participants) reported on the prevention of exacerbations in patients with COPD or bronchitis. (RR −0.404; 95% CI −0.864–0.057), but the difference between the use of PMBL and placebo was not statistically significant ($p = 0.086$) (Fig. 5).

Data from two RCTs investigating the effect of PMBL in patients with tuberculosis (330 treated and 330 placebo participants) were significantly in favor of the use of PMBL (RR −0.502; 95% CI −0.890 − −0.114; $p = 0.011$) (Fig. 6).

Statistical analysis did not suggest any potential bias either for study quality or publication.

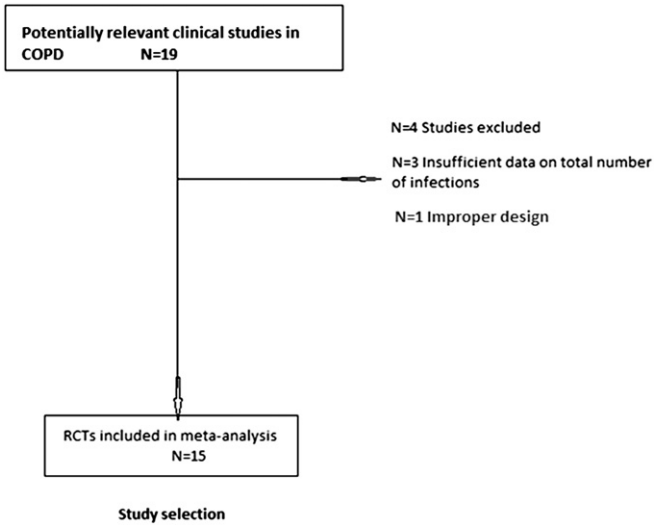

Fig. 1. Flowchart for identification of studies.

4. Discussion

The present meta-analysis provides evidence that the population treated with PMBL has significantly and consistently fewer cases of respiratory tract infections. We believe that our meta-analysis is really unbiased because we have used only data coming from RCTs and have included unpublished studies and papers written in languages other than English.

The conclusions from a meta analysis (whether positive or negative) can provide useful information and the popularity of meta-analysis may at least partly come from the fact that it makes life simpler and easier for reviewers as well as readers [38]. However, summarizing all of the information contained in a set of trials into a single relative risk may greatly oversimplify an extremely complex issue [38]. Nonetheless, in medicine, meta-analyses of randomized controlled trials are regarded as the highest level of evidence for evaluating interventions [39]. Standard approaches to meta-analysis consider the individual studies to be free from selection biases (and from internal and external quality/validity biases) [40].

The results of this meta-analysis deserve some comments. First of all, it seems very important that the number of patients who would have to receive PMBL for 1 year for one of them to benefit is 1.15. Expressed in another way, for every 100 patients treated with PMBL for 1 year, 87 recurrences of respiratory tract infections would be prevented. Although we must admit that pooled NNTBs derived from meta-analyses have been highlighted as being potentially misleading because of the often marked variation in baseline risk between trials [41], nevertheless we consider this information extremely useful from a clinical perspective and certainly from a pharmacoeconomic point of view. A cost-effectiveness analysis to assess the economic impact of using PMBL to prevent recurrences of respiratory tract infections has not yet been carried out. However, in an Italian study conducted on 57 patients aged over 75 years suffering from chronic obstructive bronchitis and affected by at least one exacerbation over the past 12 months, treatment with PMBL significantly reduced the absolute number of exacerbations, their length and seriousness, as well as the need to use antibiotic treatments, and the overall cost of the treatment of these patients during the period of treatment compared to the same period for the previous year, during which time no antibacterial prophylaxis had been administered [29]. The mean cost of the antibiotic therapy during the period from September to February of the year before the use of PMBL was €3459.60, while during the period from September to February of the year of the trial it was only €1499.40 (−57%) [29]. Adding the latter amount to the cost of the prophylactic therapy with PMBL, equal to €1295.04, the total cost of €2794.44 was in any case significantly lower (−20%) than the cost for the same period of the previous year [29]. This surely represents an extremely important saving for the health system.

Table 1
Summary of various study characteristics and outcomes of the fifteen studies included in the systematic review.

Author	PMBL (n. subjects)	Control (n. subjects)	Age	Sex	Diagnosis	Mode of admin PMBL	Main outcomes	Side effects
Vecchio [19]	40	20	26–75	M&F	Recurrent respiratory infections	1 tab SL	Sig decrease in no. of acute episodes of respiratory infec. In PMBL vs Placebo	None recorded
Macchi [20]	23	23	40 ave	M&F	Recurrent upper respiratory tract infections	1 tab SL	BLML sig. reduces no. of episodes of urti cf placebo & BLCL	None recorded
Tricarico [21]	24	23	49 ave	F	Respiratory infections	1 tab SL	No. respiratory infections and duration sig. lower in PMBL gp	None recorded
Palmeiri [23]	30	30	82 ave	M &F	Respiratory infections	1 tab/day	No. infectious episodes statistically lower in PMBL gp	None reported
Boris [25]	150	150	63 ave	M & F	Winter airways infections in patients with TB	1 tab SL	PMBL gp had a reduced no of infections cf placebo	None reported
Boris [22]	298	300	21–40	M	Bacterial respiratory infections	1 tab/day 10 days/mth, 3 mths	Reduction of the average number of infections/patient, of the average number of days on ATB/patient and Reduction severity	None reported
Rossi & Tazza [24]	23	23	18–82	M & F	Prophylaxis of Acute Lower Respiratory Tract Infections	1 tab/day 10 days/mth, 3 mths	Reduction of the respiratory infection more efficient in PMBL than with chemically lysis compound/	None reported
Boris [26]	180	180	40–79	M & F	Prophylaxis of episodes of respiratory infection in a population with latent tuberculosis	1 tab/day 10 days/mth, 3 mths	1. Reduction of the number of patients developing tuberculosis: 2. Reduction of number of concomitant infections 3. Decrease of lymphocytes response to PPD (purified protein derivative M.tuberculosis). 4. Increase of lymphocyrtes response to PHA (phytohemagglutinin) 5. Increase of specific antibodies against *S. pneumoniae*, *S. pyogenes*, *S. aureus*	None reported
Cazzola [27]	229	86	92	66–67	Reduction of infectious exacerbations in moderate to very severe COPD	1 tab/day 10 days/mth, 3 mths	Reduction of average episodes of AECOPD/patient/ yearReduction of duration of AECOPD Reduction of hospitalization duration	None reported
Cazzola [28]	63	30	33	Over 50	Therapy of COPD in patients under regular treatment with salmeterol/fluticasone	1 tab/day 10 days/mth, 3 mths	Trend to reduce total number of AECOPD Trend to reduce rate of AECOPD/patient Trend to reduce use of oral corticosteroids Trend to reduce total number of hospitalizations	None reported
Cogo [29]	57	NA	57	Over 75	Prophylaxis for acute exacerbations of chronic bronchitis	1 tab/day 10 days/mth, 3 mths	Reduction of the incidence of bronchial infections Reduction of the number od days on ATB Reduction of the severity	None reported
Aksic [30]	180	90	90	5–10	Clinical efficacy	1 tab/day 10 days/mth, 3 mths	Reduction of the mean number of episodes of infection Reduction of school absenteism	None reported
Mantia [31]	120	40	40	4–9	Immunoprophylaxis of recurring bacterial infections of respiratory tracts in pediatric age	1 tab/day 10 days/mth, 3 mths	Increase of healthy children Reduction od use of complementary treatment (ATB, antipyretics, antiphlogistics	None reported
Rosaschino [32]	89	24	65	10 monts-10years	Optimizing compliance of paediatric patients for seasonal antibacterial vaccination	1 tab/day 10 days/mth, 3 mths	Reduction of the mean number of infective episodes compared to previous winter and control: 4,78 (PMBL); 7,84 (previous winter); 6,78 (Control). Decrease of White blood cells, PCR and plasma mucopr compared to previous winter: 9723 (PMBL) vs 11983 (previous winter); 6,84 (PMBL) vs 16,32 (previous winter); 3,88 (PMBL) vs 8,32 (previous winter). Increase of B lymphocytes compared to previous winter	None reported
Macchi [33]	46	23	23	18–80	Prophylaxis of upper respiratory tract infections	1 tab/day 10 days/mth, 3 mths	Reduction of the mean number of upper respiratory tract infections (URTI) after treatment Increase of number of patients without URTI after treatment Decrease of the mean duration of URTI after treatment Decrease of mean working days lost after treatment No Need of ATB treatment during the 6 Months study	None reported

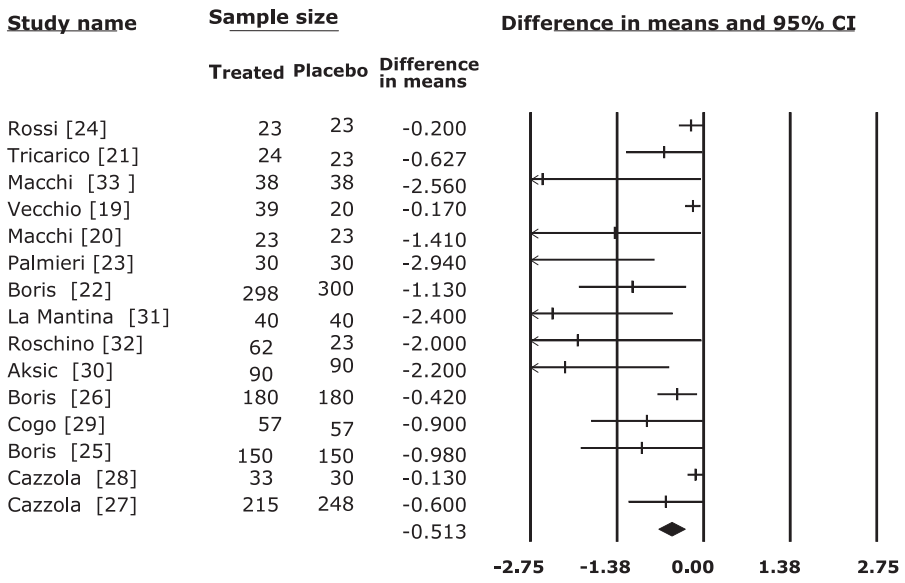

Fig. 2. Comparison of PMBL vs. placebo, another conventional bacterial lysate or no treatment in combined trials.

We consider the effect of PMBL in children to be particularly interesting as recurrent acute respiratory tract infections are a common problem in childhood. A previous systematic quantitative review concluded that oral purified bacterial extracts were only modestly useful in the prevention of acute respiratory tract infections in children [42], although another analysis indicated that bacterial immunostimulants, mainly OM-85 BV, that is the product of alkaline proteolysis from bacterial lysates, is more pronounced in patients at high risk of recurrent respiratory tract infections [43]. The discrepancy of results between our meta-analysis and that performed by Steurer-Stey and colleagues [42] could be explained by differences in the studied populations, but we cannot exclude a better activity of PMBL that is obtained by mechanical lysis, a method that, as highlighted before, does not alter the structure of the antigens and, consequently, can lead to a more specific antibody response to the surface antigens on pathogenic bacteria. This opinion is supported by data from the study of La Mantia and colleagues [31] that documented a greater protective efficacy of PMBL compared to conventional bacterial lysate in children with nasopharyngitis and/or otitis media and/or recurrent pharyngotonsillitis.

The analysis of the subgroup of RCTs that studied the impact of PMBL in COPD or bronchitis suggests a positive trend in preventing COPD. It must be mentioned that a previous systematic review of 13 randomized, controlled clinical trials of bacterial lysates compared with placebo suggested that these treatments may have an effect

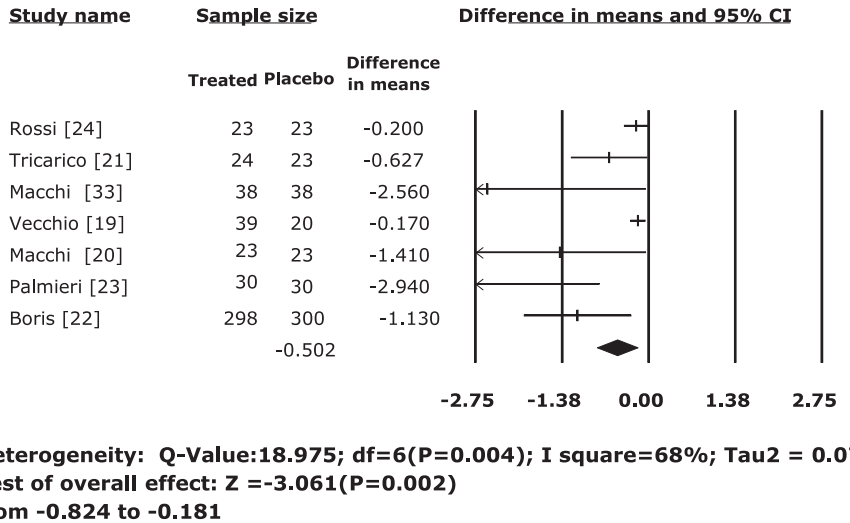

Fig. 3. Comparison of PMBL vs. placebo, another conventional bacterial lysate or no treatment in adults suffering from recurrent respiratory infections other than COPD, chronic bronchitis and tuberculosis.

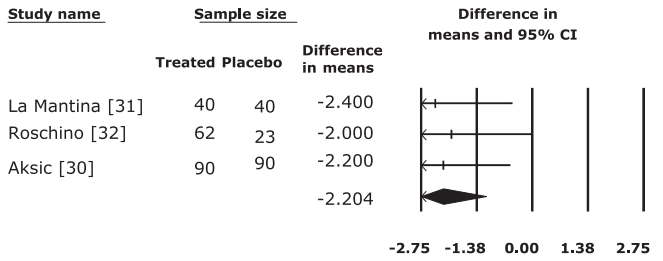

Fig. 4. Comparison of PMBL vs. placebo, another conventional bacterial lysate or no treatment in children.

on exacerbations, but most of the studies were of low methodological quality and did not conclusively demonstrate an effect on the prevention of exacerbations [10]. Moreover, one systematic review of OM-85 BV investigating a number of outcomes has concluded that this treatment does not clearly demonstrate any clinical benefit of this treatment [11]. Our current meta-analysis results show that there is a trend with PBML toward clinically significant results in patients with COPD. It did not quite achieve statistical significance due to the small number of COPD studies. We have already mentioned the paper published by Cogo and colleagues [29] in which treatment with PMBL significantly reduced the absolute number of exacerbations, their length and seriousness, as well as the need to use antibiotic treatments, and the overall cost of the treatment of these patients during the period of treatment compared with the same period for the previous year, during which time no antibacterial prophylaxis had been administered. In another study, 178 patients were randomized into two different groups: one group was treated with PMBL and the other with placebo [27]. At the end of treatment, patients were followed for a further 9 months. Selected clinical endpoints were seen to be significantly lower in the group treated with the lysate than in the placebo group. PMBL treatment also led to a highly significant reduction in the frequency (215 versus 248 cases) and duration (10.6 days versus 15.8 days) of exacerbations, as well as a decrease in antibiotic consumption (−270 doses) and hospitalization time (275 days versus 590 days). It is likely that failure to reach statistical significance in the current meta-analysis is due to the third RCT, which presented a positive trend but statistic significance was not reached due to low number of patients [28]. This study investigated the value of adding PMBL to existing therapy of COPD patients (FEV_1<60% predicted) with salmeterol/fluticasone combination. It is well known that the combination of salmeterol/fluticasone is able to significantly decrease the annual rate of exacerbations when

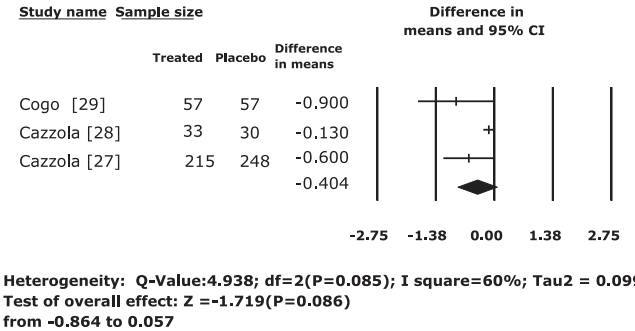

Fig. 5. Comparison of PMBL vs. placebo, another conventional bacterial lysate or no treatment in patients with COPD or bronchitis.

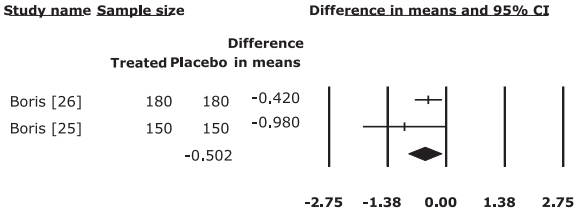

Fig. 6. Comparison of PMBL vs. placebo, another conventional bacterial lysate or no treatment in patients with tuberculosis.

compared with placebo [44]. Consequently, the fact that the addition of PMBL was able to further decrease the number of exacerbations per patient per year (0.67 in group without PMBL and 0.54 in group under PMBL), the number of exacerbations that needed treatment with oral corticosteroids and the rate of hospitalization [28], although in a non significant manner, is noteworthy, but its lack of statistical power, which has not allowed to reach the statistic significance, has affected the results of the current meta-analysis.

Little experience is available on the effect of bacterial extracts in post tubercular patients. The results of the present meta-analysis show a significant signal in favor of the use of PMBL in this patient group. Consequently, we believe that PMBL should be considered as a therapeutic option in post tubercular patients with airways dysfunction that experience recurrent respiratory infections.

In conclusion, the results of the present meta-analysis suggest that PMBL is effective in both children and in adults in preventing respiratory tract infections. Nonetheless, we completely agree with Braido and colleagues [3] that, even though the results of the analyzed studies are encouraging, it would be worthwhile to carry out further trials and that these new trials should include a higher number of patients, selected according to the disease and its severity, and be well-designed in term of blinding and randomization procedures. This would allow an even greater level of evidence to support the recommendation for a more widely use of PMBL as a prophylactic treatment of respiratory infections.

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