RESEARCH PAPER

Bacterial lysates (OM-85 BV): a cost-effective proposal in order to contrast antibiotic resistance

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Keywords

Antibiotic resistance • General practice • Bacterial lysates • Adults

Summary

Background. *Chronic Obstructive Pulmonary Disease (COPD) is one of the most frequent pathologies in which antibiotics are used because 50% of the exacerbations are attributable to a bacterial infection. The aims of our study were: i) to perform a meta-analysis on the efficacy of the bacterial lysate OM-85 BV in preventing acute exacerbations in patients with COPD; ii) to evaluate whether this preventive treatment can lead to significant savings for the National Health Service (NHS).*
Methods. *A systematic research was conducted in the electronic database MEDLINE (PubMed) in June 2017-July 2020, collecting evidences without time restrictions. Only randomized controlled trials (RCTs) were included. The keywords used were "OM 85 BV AND chronic bronchitis" and "OM 85 BV AND COPD". A cost-effectiveness analysis (CEA) was performed considering the costs for a treatment with OM-8BV, the costs for the treatment of an acute exacerbation and the number of prevented exacerbations.*
Results. *59 publications were found, but the meta-analysis was conducted on 13 studies that met the inclusion criteria. OM-85 BV is responsible of a statistically significant reduction in the mean number of COPD exacerbations ($p < 0.01$; WMD = -0.86; CI 95%: -1.38, -0.34) and in the days of antibiotic therapy ($p < 0.01$; WMD = -9.49; CI 95%: -11.93, -7.05). The cost-effectiveness ratio with a negative value is in favor to treatment.*
Conclusions. *OM-85 BV is effective in reducing exacerbations, and could lead to significant savings for the NHS. Moreover, reducing the number of exacerbations it could avoid an over-use of antibiotics and the consequent antibiotic resistance.*

Introduction

The development and use of antibiotics, since the second half of the twentieth century, has revolutionized the approach to the treatment and prevention of infectious diseases and of infections considered incurable in the past. However, although resources and energy have been invested in order to increase the knowledge about the mechanisms of resistance and in the search for increasingly effective molecules, the antibiotic resistance is currently faster than the development of new molecules [1]. Antibiotic resistance is spread anywhere in the world, compromising the treatment of infectious diseases and undermining many other advances in health and medicine [2-5].
One of the most frequent conditions of antibiotic use is the Chronic Obstructive Pulmonary Disease (COPD). It is in fact known that the development of an infection in the bronchial tree is one of the most frequent causes of COPD exacerbations. Furthermore, more than half of the exacerbations are attributable to a bacterial infection [6].
The evidence shows that the use of antibiotics and corticosteroids strongly reduce the hospitalization rate during exacerbations [7] and today the tendency is to prefer broad-spectrum antibiotics, given the increasing antibiotic resistance shown by *Streptococcus pneumoniae* and *Haemophilus influenzae* [6]. However, multi-drug resistant bacteria (MDR) are increasingly common, especially in cases of exacerbation of the disease requiring intubation and mechanical ventilation. In fact t is well known that an overuse and misuse of antibiotics is responsible for most of the recent increases in antibiotic resistance [8]. The preventive use of bacterial lysates (such as OM-85 BV) in reducing exacerbations in patients with COPD is well documented in several randomized controlled trials [9]. OM-85 BV is the product of alkaline proteolysis of the following bacteria: *Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella pneumoniae, Klebsiella ozaenae, Staphylococcus aureus, Streptococcus pyogenes, Streptococcus viridans* and *Moraxella catarrhalis* [10]. The effects of OM-85 BV in patients with COPD and the cost effectiveness of this preventive treatment has been already investigated by other authors [9, 11]. So, the aims of the present study were to update what has been already published in literature and, therefore, i) to perform a meta-analysis on the efficacy of OM-85 BV in preventing acute exacerbations in patients with COPD and ii), to evaluate whether this preventive treatment can lead to significant savings for the National Health Service (NHS) thanks to an absolute reduction in the number of disease exacerbations.

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Methods

Search strategy

A systematic research of peer-reviewed literature was conducted in the electronic database MEDLINE (PubMed) in the period June 2017-July 2020, collecting all the evidences without time restrictions.
The keywords used were "OM 85 BV AND chronic bronchitis" and "OM 85 BV AND COPD".

Inclusion criteria

Only Randomized Controlled Trials (RCTs) conducted on an adult population affected by COPD were considered suitable for the meta-analysis. Articles were included only if they contained clear and statistically assessable data on: i) average or absolute number of acute exacerbations; ii) total days of antibiotic therapy; iii) days of hospitalization. Other data useful to demonstrate or not the efficacy of OM-85 BV have been registered.
Studies that provided ambiguous or insufficient data were excluded.
Only studies written in English and French have been analyzed.

Study selection and data extraction

Studies were selected in a 2-stage process. First, titles and abstracts from electronic searches were scrutinised and then full manuscripts were analysed to select the eligible manuscripts according to the inclusion criteria. A further manual research analyzing the references of the articles was then carried out to avoid losing publications of a certain importance.

Statistics

Statistical analysis was performed using Review Manager Version 5.2 (The Cochrane Collaboration, Software Update, Oxford, London).
Continuous variables have been described as averages and standard deviations (SD). The analysis of continuous variables was performed using the weighted mean difference (WMD), which indicates the difference between groups based on sample size. The significance level was set at $P < 0.05$.
To evaluate heterogeneity, the Higgins heterogeneity test or I^2 test was used. The value of I^2 describes the percentage of variability due to heterogeneity rather than a simple sampling error. In fact, I^2 does not depend on the small number of the sample. "Low" heterogeneity is considered when the I^2 value is less than 30%, moderate if between 30 and 50%, high if higher than 50%. When heterogeneity is described by an I^2 above 30% it was decided to report the models with both "fixed" and "random" effects in order to emphasize the role of heterogeneity between studies. The difference between the two models consists in excluding or including the heterogeneity in the calculation of the overall estimate: the one with fixed effects excludes any heterogeneity, while the random effects model includes it; therefore, the overall estimate thus obtained will have wider confidence intervals.
In the case of low heterogeneity, both models give very similar results and for this reason it was decided to present the results only with random effects that are more conservative [12].
Specifically, variables analyzed through meta-analysis were: average and mean number of acute exacerbations, days of antibiotic therapy and of hospitalization, Severity score (the COPD severity score is based on responses to survey items that comprise five domains of COPD severity; the possible COPD severity score range is 0 to 35, with higher scores reflecting more severe disease) [13].

Cost-effective analysis (CEA)

The cost-effective analysis was performed following the same methodology used by Bergemann et al. [9]. The estimation of cost for the management of severe or non-severe exacerbation was based on the results of an observational study evaluating the costs of chronic obstructive pulmonary disease in Italy (ICE Study - Italian Costs for Exacerbations in COPD) [14].
Dividing the average annual direct health cost of a patient with exacerbations (€ 2,423) by the average number of exacerbations [15, 16] the average cost of an exacerbation was calculated as equal to € 1,730. The average cost of a non-severe exacerbation was estimated by applying the same calculation methodology, but excluding the amount associated with hospital admission; it was thus obtained an amount of € 400.
For the cost-effectiveness analysis (CEA) the following formulas have been applied:

$$CM = CBV - (CTAE * PAE)$$

$$CER = [CBV - (CTAE * PAE)]/PAE$$

Where CM indicates the marginal costs, CER indicates the cost-effectiveness ratio (ie costs for each single prevented exacerbation), CBV indicates the costs for a treatment with OM-85 BV, CTAE indicates the costs for the treatment of an acute exacerbation and PAE indicates the number of prevented exacerbations.

Results

Bibliographic research yielded 59 publications. After the analysis of the titles and abstracts, 36 studies were excluded: 9 because they were duplicates, 6 because they were review, 16 because they focused on outcomes not in line with the present study, 9 because in other languages (2 in Russian, 3 in Polish, 1 in Romanian, and 3 in German). Of the 19 remaining articles, the full text was analyzed: 1 article was excluded because review, 1 excluded because editorial, 9 excluded because they focused on a population or outcome not in line with the study. After the analysis of the bibliographies it was decided to add, for completeness, 4 congress abstracts containing original data and 1 full text. The overall analysis was therefore conducted on 13 studies (Fig. 1). [17-29].

The main characteristics of the studies included in the review with authors, year of publication, description of the treatment protocol, observation period, cases and controls and outcomes is shown in Table I.

The studies have been conducted between 1981 and 2015 and involved a total of 1,366 patients undergoing treatment (range 33-192) and 1,282 undergoing placebo (range 20-192). The treated were aged 48.1-82 years, controls 48.4-82 years.

In 10 of the studies taken into consideration, the observation period was 6 months, in one 10 weeks, in one 22 weeks and in the last study 1 year.

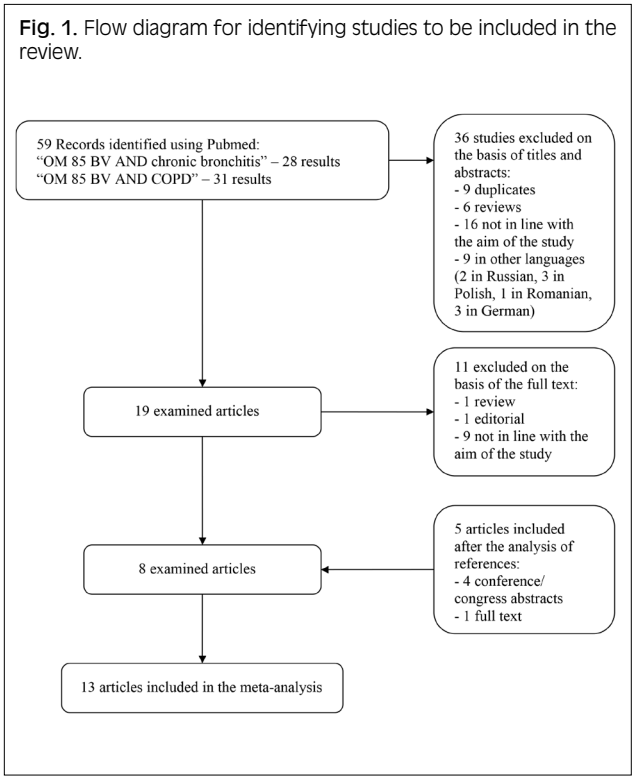


Fig. 1. Flow diagram for identifying studies to be included in the review.

Average number of exacerbations (Fig. 2)

The meta-analysis conducted on the 6 studies that reported these data demonstrates, using the random effects model, that OM-85 BV treatment is responsible for a statistically significant reduction in the average number of COPD exacerbations in the observation period ($p < 0.01$; WMD = -0.86; 95% CI: -1.38, -0.34).

Absolute number of exacerbations (Fig. 3)

The meta-analysis conducted on the 6 studies reporting these data shows, using the random effects model, that OM-85 BV treatment is a protective factor against the absolute number of COPD exacerbations in the observation period ($p < 0.01$; RR = 0.79; CI 95%: 0.70, 0.90).

Days of antibiotic therapy (Fig. 4)

The meta-analysis conducted on the 4 studies reporting these data shows, using the random effects model, that OM-85 BV treatment is responsible for a statistically significant reduction in antibiotic therapy days in the observation period ($p < 0.01$; WMD = -9.49; CI 95%: -11.93, -7.05).

Hospitalization days (Fig. 5)

The meta-analysis conducted on the 3 studies reporting these data shows, using the random effects model, that OM-85 BV treatment is responsible for a non-statistically significant reduction in hospitalization days in the observation period ($p = 0.12$; WMD = -7.28; CI 95%: -16.39, 1.83).

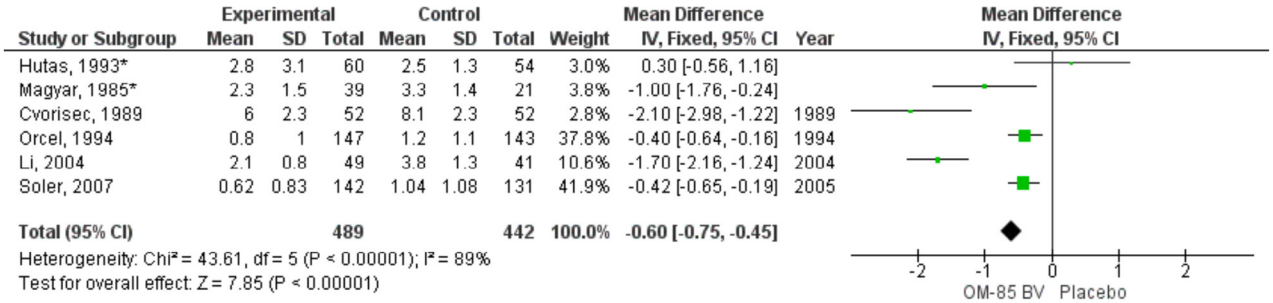
Severity Score (Fig. 6)

The meta-analysis conducted on the 2 studies that reported these data shows, using the random effects model, that the treatment with OM-85 BV is responsible for a non-statistically significant reduction of the Severity Score ($p = 0.09$; WMD = -0.72; CI 95%: -1.55, 0.11).

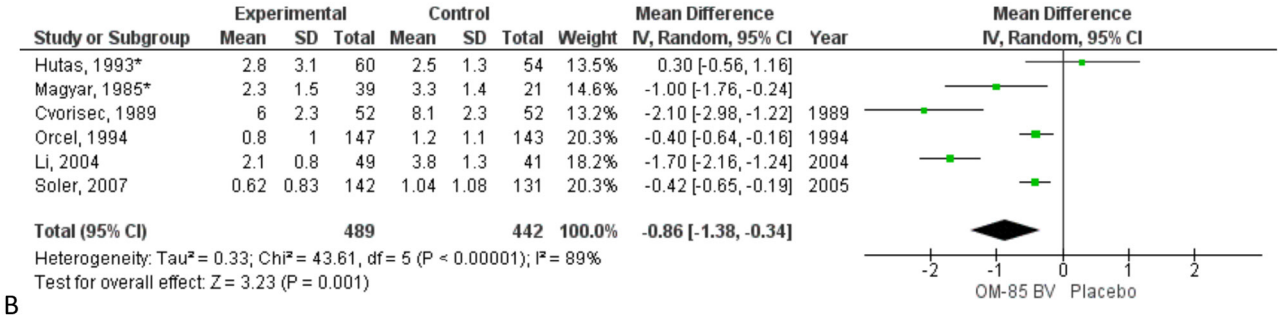
Tab. I. Main characteristics of the studies included in the systematic review (T = treatment, P = placebo; n.r. = not reported; *= conference abstract; SD = standard deviation; RCT = randomized controlled trial; A = 1 capsule per day for 30 days, 1 month without treatment, and then 1 capsule/day for 10 days/month for 3 consecutive months; B = 1 capsule for 10 days/month for 3 consecutive months).

Author, year of publication	Study design	Treatment protocol	Observation period	Treated patients (T)	Placebo patients (P)	Selected sample	Age (T)	Age (P)	Mean number of acute exacerbations (T)	Mean number of acute exacerbations (P)	Absolute number of acute exacerbations (T)	Absolute number of acute exacerbations (P)	Total days of antibiotic treatment (T)	Total days of antibiotic treatment (P)	Days of hospitalization (T)	Days of hospitalization (P)	Severity score (T)	Severity Score (P)
Tang, 2015	RCT	B	22 weeks	183	171	Age 40-75 years	63.2 (SD 8.9)	63.0 (SD 9.4)	n.r.	n.r.	84	88	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Soler, 2007	RCT	A	6 months	142	131	Age 40-75 years	57.3 (SD 1.6)	57.9 (SD 1.7)	0.62 (SD 0.83)	1.04 (SD 1.08)	96	121	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Orcel, 1994	RCT	B	6 months	147	143	> 65 years	82 (SD 7)	82 (SD 8)	0.8 (SD 1.0)	1.2 (SD 1.1)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Li, 2004	RCT	B	1 year	49	41	Age 55-82 years	67 (SD 4)	65 (SD 5)	2.1 (SD 0.8)	3.8 (SD 1.3)	n.r.	n.r.	16.7 (SD 7.0)	28.6 (SD 6.5)	21.3 (SD 6.1)	39.6 (SD 8.7)	1.6 (SD 0.6)	2.7 (SD 0.8)
Debbas, 1990	RCT	B	6 months	198	198	Mean age 82 years	81.8 (SD 8.0)	81.89 (SD 8.2)	n.r.	n.r.	113	156	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Cvorisec, 1989	RCT	A	6 months	52	52	Age 20-69 years	48.1 (SD 3.5)	48.4 (SD 3.1)	6 (SD 2.3)	8.1 (SD 2.3)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Collet, 1997	RCT	B	6 months	191	190	Adult patients	65.3 (SD 7.7)	66.9 (SD 7.7)	0.57	0.57	85	83	n.r.	n.r.	6.5 (SD 7.9)	10.2 (SD 14.4)	n.r.	n.r.
Magyar, 1985*	RCT	A	6 months	39	21	Adults	51.7 (SD 12.4)	52.8 (SD 8.8)	2.3 (SD 1.5)	3.3 (SD 1.4)	n.r.	n.r.	32.3 (SD 29.1)	52.4 (SD 28.0)	n.r.	n.r.	n.r.	n.r.
Orlandi, 1985*	RCT	A	6 months	45	40	Adults	61.4 (SD 8.8)	59.6 (SD 14.5)	n.r.	n.r.	n.r.	n.r.	4.8 (SD 5.6)	11.3 (SD 9.4)	n.r.	n.r.	n.r.	n.r.
Hutas, 1993*	RCT	A	6 months	60	54	Adults	52.8 (SD 11.9)	51.1 (SD 13.0)	2.8 (SD 3.1)	2.5 (SD 1.3)	n.r.	n.r.	9.6 (SD 1.3)	18.6 (SD 2.4)	n.r.	n.r.	n.r.	n.r.
Messerli, 1981	RCT	B	6 months	35	20	Adults	54.6	55.5	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	1.11	1.25
Tang, 2011*	RCT	B	10 weeks	192	192	Adults	n.r.	n.r.	n.r.	n.r.	45	64	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Xinogalos, 1993	RCT	A	6 months	33	29	Adults	56.03 (SD 12.67)	59.75 (SD 12.89)	n.r.	n.r.	13	16	n.r.	n.r.	2.67 (SD 1.84)	2.83 (SD 1.96)	1.33 (SD 1.27)	1.58 (SD 1.26)

Fig. 2. Meta-analysis of the average number of exacerbations.



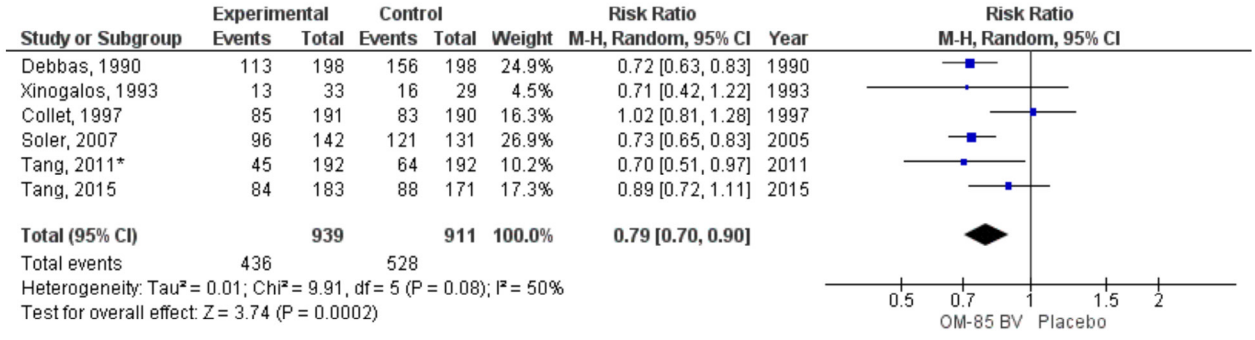
A



B

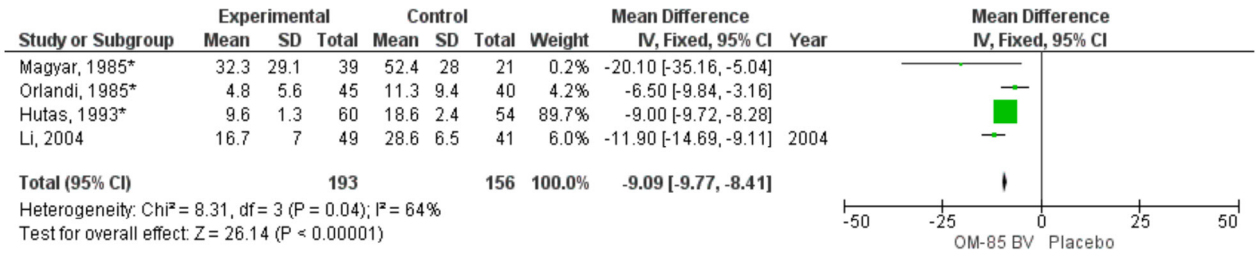
Fig. 3. Meta-analysis of the absolute number of exacerbations.

A



B

Fig. 4. Meta-analysis of the days of antibiotic therapy.



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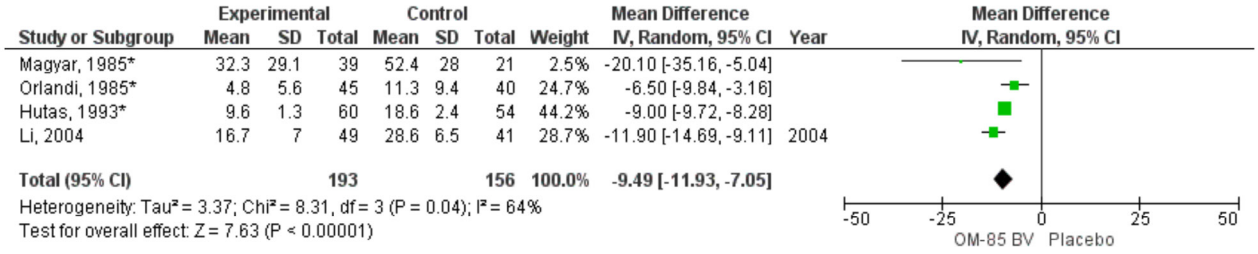
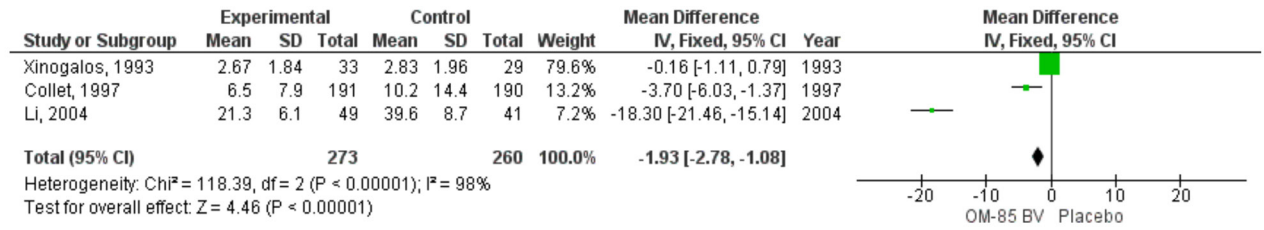
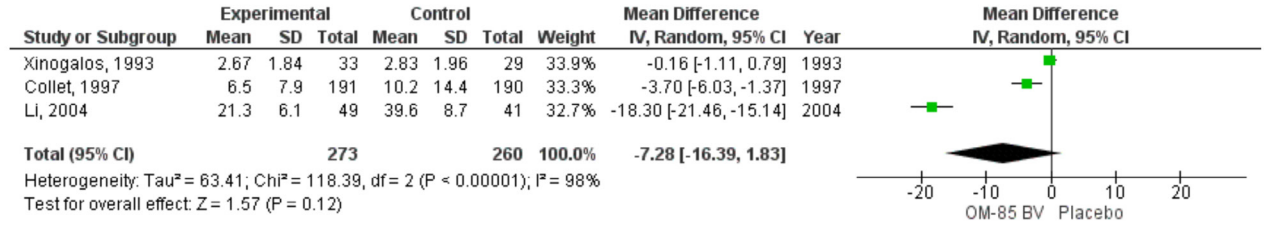


B

Fig. 5. Meta-analysis of the hospitalization days.



A

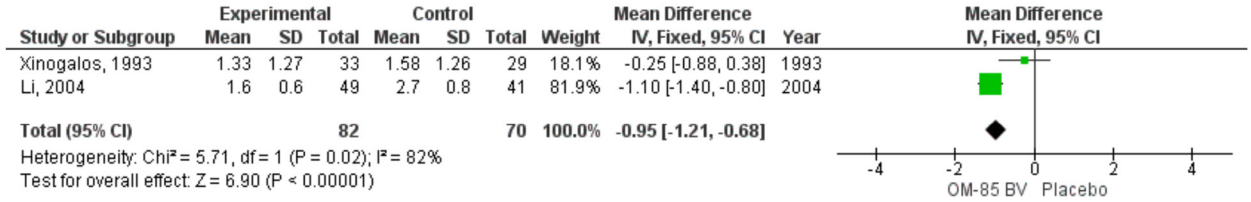


B

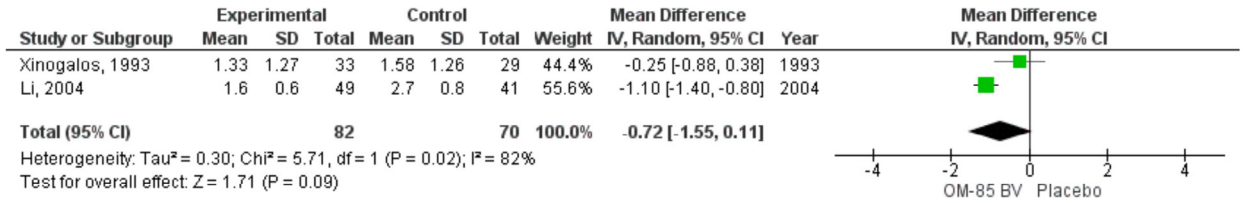
Cost-effective analysis

The OM-85 BV lysate recruitment protocols, as described in the studies included in our study, are two: i) one tablet a day of lysate for 30 days, followed by a period of 1 month suspension and then a 3 month period in which one tablet is taken a day only for the first 10 days of the month; ii) one tablet a day for the first 10 days of the month for three months. Considering that the price of OM-85 BV adults 30 tablets is equal to € 25 per pack[30], a treatment can cost from € 25 to € 50. The summary of the cost-effectiveness analysis is shown in the following figures (Figs. 7, 8).

Fig. 6. Meta-analysis of the Severity Score.



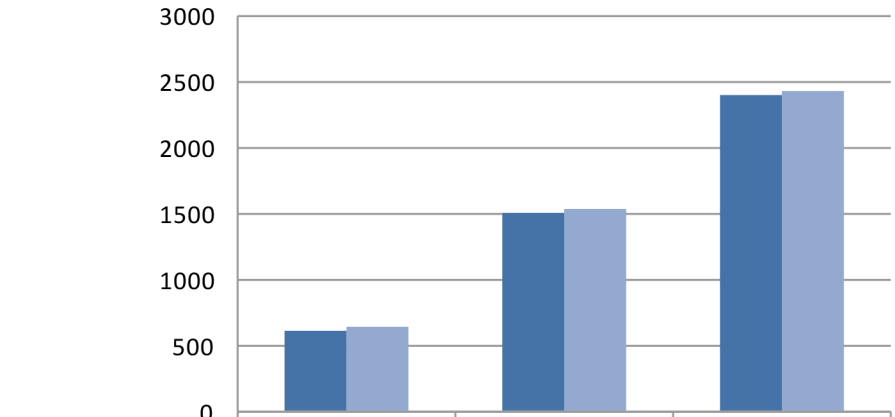
A



B

Fig. 7. Cost-effectiveness analysis: (**A**) savings, in Euros, on an exacerbation with Hospitalization, (**B**) CER.

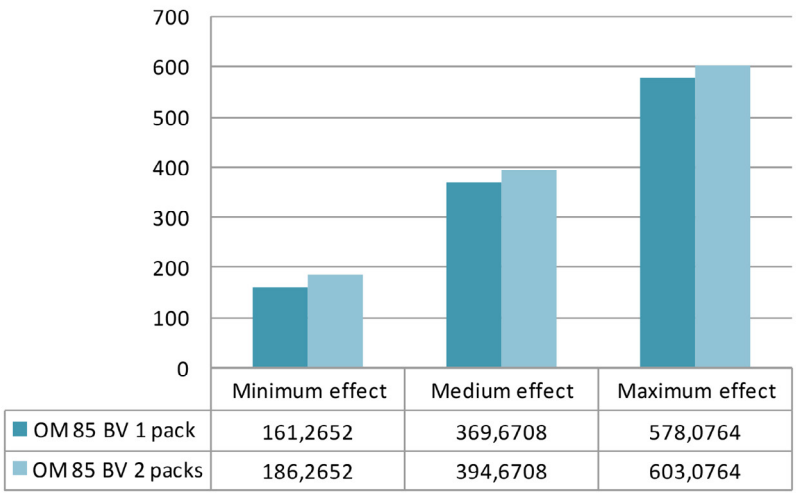
A



B

	Minimum effect	Medium effect	Maximum effect
OM-85 BV 1 pack	-1804.31	-1759.85	-1748.9
OM-85 BV 2 packs	-1877.84	-1788.92	-1767.01

Fig. 8. Cost-effectiveness analysis: (**A**) savings, in Euros, on an exacerbation without hospitalization, (**B**) CER



A

	Minimum effect	Medium effect	Maximum effect
OM-85 BV 1 pack	-474.309	-429.85	-418.896
OM-85 BV 2 packs	-547.839	-458.92	-437.012

B

Discussion

Acute exacerbations have a significant negative impact on several aspects of COPD, including the rapid decline in lung function, poor prognosis, impaired quality of life, and increased socioeconomic costs. Various studies have extensively shown that the prevention of acute recurrent exacerbations is able to slow down the progression of COPD [31]. Bacterial infections are the most common cause of exacerbation of the disease, contributing to 40% of all exacerbations [32]. This is the reason why the use of bacterial vaccines, such as those containing pneumococcal polysaccharides, is a highly recommended strategy for managing COPD [15].

The administered orally OM-85 BV (bacterial lysate obtained from eight pathogenic bacteria), is effective in preventing respiratory tract infections in adults and children.

In our study we conducted a meta-analysis of randomized clinical trials comparing the efficacy of OM-85 BV *vs* placebo. The most important parameters were the number of exacerbations in the months following the treatment and the days of antibiotic therapy. From the meta-analysis of the analyzed studies, OM-85 BV treatment is responsible of a statistically significant reduction in the mean number of COPD exacerbations in the observation period ($p < 0.01$; WMD = -0.86; CI 95%: -1.38, -0.34) and also a statistically significant reduction in days of antibiotic therapy ($p < 0.01$; WMD = -9.49; CI 95%: -11.93, -7.05). The cost-effectiveness analysis gathered the three elements: the cost of treatment with the lysate, the number of prevented exacerbations and the average cost of each exacerbation (for completeness divided into "with admission" and "without admission"). Considering an average of 0.86 prevented exacerbations, treatment with OM-85 BV is responsible (applying the formula for calculating marginal costs) of a saving of € 1,513 in the case of exacerbation requiring hospitalization, and € 369 in the case of exacerbation that does not require hospitalization. The meta-analysis and cost-effectiveness analysis therefore confirm not only the efficacy of OM-85 BV in reducing the exacerbations, but highlight further positive effects of the lysate: in fact it allows a considerable saving for the National Health System (considering the almost 3 million patients affected in Italy) [33] and can improve the quality of life by reducing the number of infectious episodes. Reducing the number of exacerbations also slows the further progression of the disease towards respiratory failure, and avoids over-use of antibiotics and the consequent antibiotic resistance. The cost-effectiveness ratio with a strongly negative value is remarkably favorable to treatment.

The mechanisms that explain the effectiveness of OM-85

BV are not totally understood: it is supposed that it acts on the cells of the immune system and on the mediators of inflammation [34-36].
The theoretical basis for oral immunization is that the administered bacterial fractions can be recognized by the gut-associated lymphoid tissue (GALT), then they could activate the bronchial-associated lymphoid tissue (BALT) through cooperation and cellular traffic between these two systems [37]. It should be remembered that the intestine is the largest organ producing antibodies and, in humans, more than 80% of activated B cells reside in the intestinal mucosa. Once the respiratory tract is reached, the B cells, transformed into plasma cells, release specific IgA which represent the most important form of defense against respiratory tract infections [38]. In addition, the upregulation of the expression of the adhesion molecules of the phagocytes, the increase in the number and activity of T helper with an increase in the production of interferon gamma and CD4 +, and the increase in antibodies in the respiratory tract represent further mechanism activated after lysate administration [11, 36].
Mauel et al. [35] demonstrated that lysates are able to increase the production of superoxide and nitrite anion by alveolar macrophages, enhancing microbicidal and cytolytic activity. In the same way they enhance the production of proinflammatory cytokines (tumor necrosis factor (TNF-)α, IL-8, IL-6, monocyte chemotactic protein (MCP) -1).
Finally, lysates are able to stimulate a Th1 response and increase the CD4 + / CD8 + cells ratio in the airways [39].
Our study has several limitations: as already highlighted by Pan et al. in their previous meta-analysis [11], the enrolled patients were very different from each other (by age, ethnicity and stage of the disease), and this can contribute to increasing the risk of selection bias; the index of heterogeneity was high; for the hospitalization days and the Severity Score only few studies reported analyzable data.
Moreover, one important limitation is the exiguous number of new studies on this topic that could add only a limited contribution to what has been already published in previous meta analyses [9, 11].
It is also important to say that vaccinations (such as the influenza vaccine) could prevent some exacerbations in patients with COPD [40-42]: in fact, influenza is a frequent cause of exacerbations of chronic obstructive pulmonary disease (COPD) [43].
It is therefore possible to create an overlap between the protection provided by the influenza vaccine and that provided by the OM-85 BV which may alter the estimate of its real effectiveness.

Conclusions

Exacerbations in patients with COPD are associated with a more rapid deterioration of lung function, reduction of quality of life, and a prolongation of days of hospitalization and antibiotic therapy.

The meta-analysis conducted on randomized clinical trials in which the effect of lysate was compared with placebo partially updated what has been previously published in literature and confirmed the protective capacity of OM-85 BV against bacterial exacerbations in patients with COPD. The cost-effectiveness analysis subsequently carried out highlighted the considerable savings for the National Health Service deriving from the use of the lysate and, secondly, the reduction in the use of antibiotics, which are normally used in bacterial infections, can represent an additional strategy to contain the phenomenon of antibiotic resistance.

Acknowledgements

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

GT had the idea of the study, collected data and wrote the article. GM and NN helped to conceptualize the ideas and to write the article

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