**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 it 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, 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.
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:

\[
CM = CBV - (CTAE \times PAE)
\]

\[
CER = \frac{|CBV - (CTAE \times PAE)|}{PAE}
\]

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.

**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).

---

### Table I: Main characteristics of the studies included in the systematic review

| Study | Treatment | Observation Period | Cases | Placebo | Age in T | Age in P | WMD | CI 95% | Number of exacerbations | Number of exacerbations | Hospitalization days | Days of antibiotic therapy | Severity Score |
|-------|-----------|--------------------|-------|---------|----------|----------|------|--------|------------------------|------------------------|-----------------|---------------------------|-----------------|

---

**Tab. 1.** 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).
Fig. 2. Meta-analysis of the average number of exacerbations.

| Study or Subgroup | Experimental | Control | Mean Difference | Mean Difference |
|-------------------|--------------|---------|----------------|----------------|
|                   | Mean | SD | Total | Mean | SD | Total | IV, Fixed, 95% CI | Year | IV, Fixed, 95% CI |
| Hulak, 1993*      | 2.8  | 3.1 | 60   | 2.5  | 1.3 | 54   | 0.30 [-0.56, 1.16] |      |                  |
| Magyar, 1995*     | 2.3  | 1.5 | 39   | 3.3  | 1.4 | 21   | 3.8% -1.00 [-1.78, -0.24] | 1995 |                  |
| Cvorsuc, 1989     | 6.2  | 2.3 | 52   | 8.1  | 2.3 | 52   | 2.8% -2.10 [-2.98, -1.22] | 1989 |                  |
| Ocel, 1994        | 0.8  | 1   | 147  | 1.2  | 1.1 | 143  | 37.8% -0.40 [-0.64, -0.16] | 1994 |                  |
| Li, 2004          | 2.1  | 0.8 | 49   | 3.8  | 1.3 | 41   | 10.6% -1.70 [-2.16, -1.24] | 2004 |                  |
| Soler, 2007       | 0.62 | 0.83| 142  | 1.04 | 1.08| 131  | 41.0% -0.42 [-0.65, -0.19] | 2005 |                  |
| Total (95% CI)    | 489 | 442 | 100.0% | -0.60 [-0.75, -0.45] |      |                  |

Heterogeneity: Chi² = 43.61, df = 5 (P < 0.00001), I² = 89%
Test for overall effect: Z = 7.65 (P < 0.00001)

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

| Study or Subgroup | Experimental | Control | Risk Ratio | Risk Ratio |
|-------------------|--------------|---------|------------|------------|
|                   | Events | Total | Events | Total | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Dibbik, 1980      | 113    | 156   | 113    | 156   | 0.72 [0.63, 0.83] | 1980 |
| Xingoguos, 1993   | 13     | 198   | 13     | 198   | 0.57 [0.25, 0.81] | 1993 |
| Collet, 1997      | 95     | 191   | 95     | 191   | 1.02 [0.91, 1.28] | 1997 |
| Soler, 2007       | 96     | 142   | 96     | 142   | 0.73 [0.65, 0.83] | 2007 |
| Tang, 2011*       | 45     | 192   | 45     | 192   | 0.70 [0.51, 0.97] | 2011 |
| Tang, 2015        | 84     | 103   | 84     | 103   | 0.89 [0.72, 1.11] | 2015 |
| Total (95% CI)    | 939    | 911   | 100.0% | 0.80 [0.73, 0.87] |      |

Total events: 436 528
Heterogeneity: Chi² = 9.91, df = 5 (P = 0.08), I² = 50%
Test for overall effect: Z = 5.34 (P < 0.00001)
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.**

| Study or Subgroup | Experimental | Control | Mean Difference | Year |
|-------------------|-------------|---------|-----------------|------|
| Xinogalos, 1993  | 1.33 1.27   | 1.58 1.26 | 0.25 (0.68, 0.38) | 1993 |
| Li, 2004         | 1.6 0.6     | 2.7 0.8  | -1.10 (1.40, -0.80) | 2004 |

Total (95% CI) - 82

Heterogeneity: $X^2 = 5.71, df = 1, P = 0.02, I^2 = 82$

Test for overall effect: $Z = 6.90 (P < 0.00001)$

**Fig. 7. Cost-effectiveness analysis.**

(A) Savings, in Euros, on an exacerbation with Hospitalization, (B) CER.

### A.

| Effect Level | OM-85 BV 1 pack | OM-85 BV 2 packs |
|--------------|-----------------|-----------------|
| Minimum      | 613,4652        | 638,4652        |
| Medium       | 1513,4708       | 1538,4708       |
| Maximum      | 2413,4764       | 2438,4764       |

### B.

| Pack Type       | 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       |
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 by lyse 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 lyse 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 lyse 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

Funding sources: this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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.

References

[1] Epicentro. Resistenze agli antibiotici. 2012 3/7/2017. Available from: http://www.epicentro.iss.it/focus/resistenza_antibiotici/resistenza.asp (accessed: 25/08/2020).

[2] WHO. Antibiotic resistance: multi-country public awareness survey. Geneva: 2015.

[3] Righi L, Picat RA-G, Benmansour H, Flicoteaux R, Jacquier G, Laganà P. Hand washing in operating room: a procedural survey. Geneva: 2015.

[4] Tiroiano G, Mercurio I, Nante N, Lancia M, Bacci M. Can dida autovaccination: a new strategy to prevent antifungal resistance? J Infect Prev 2018;9:201-2 doi:https://doi.org/10.1177/1757177418759744

[5] Stilo A, Tiroiano H, Melcarne L, Goffrè ME, Nante N, Messina G, Laganà P. Hand washing in operating room: a procedural comparison. Epidemiol Biostat Public Health 2016;13:e11734-1.7. doi:https://doi.org/10.2427/11734

[6] Rossi A. Antibiotici nel trattamento della broncopneumopatia cronica ostruttiva riacutizzata. 2005. Available from: https://www.progettoasco.it/riviste/rivista_simg/2005/02_2005/3.pdf (accessed on: 25/08/2020).

[7] Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987;106:196-204. doi:https://doi.org/10.7326/0003-4819-106-2-196

[8] English BK, Gaur AH. The use and abuse of antibiotics and the development of antibiotic resistance. Adv Exp Med Biol 2010;659:73-82. doi:https://doi.org/10.1007/978-1-4419-0981-7_6
Bergemann R, Brandt A, Zoellner U, Donner CF. Preventive treatment of chronic bronchitis: a meta-analysis of clinical trials with a bacterial extract (OM-85 BV) and a cost-effectiveness analysis. Monaldi Arch Chest Dis 1994;49:302-7.

Villa E, Garelli V, Braido F, Melioli G, Canonica GW. May we strengthen the human natural defenses with bacterial lysates? World Allergy Organ J 2010;3(Suppl 8):S17-23. https://doi.org/10.1097/01.wao.0000381810.eef1d1

Pan L, Jiang X-G, Guo J, Tian Y, Liu C-T. Effects of OM-85 BV in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. J Clin Pharmacol 2015;55:1086-92. https://doi.org/10.1002/jcph.518

Ricci C, Casadei R, Taffurelli G, Toscano F, Cecioni G, Bogoni S, D’Ambra M, Pagano N, Di Marco MC, Minnì F. Laparoscopic versus open distal pancreatectomy for ductal adenocarcinoma: a systematic review and meta-analysis. J Gastrointest Surg 2015;19:770-81. https://doi.org/10.1007/s11605-014-2721-z

Omachi TA, Yelin EH, Katz PP, Blanc PD, Eiser MD. The COPD severity score: a dynamic prediction tool for health-care utilization. COPD 2008;5:339-46. https://doi.org/10.1080/15412550802522700

Lucioni C, De Benedetto F. I costi della broncopneumopatia cronica ostruttiva: la fase prospektiva dello Studio IICE (COPID). Global Costs for Exacerbations in COPID. Pharmacoconomics-Italian Research Articles 2005:7:119-34. https://doi.org/10.1007/BF03320542

Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuhara Y, Jenkins C, Rodriquez-Roisin R, Van Weel C, Zielinski J. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2007;176:532-55. https://doi.org/10.1164/rccm.200703-4560O

Ravasio R. Cost-effectiveness analysis of long-acting bronchodilators for the treatment of COPD (moderate to very severe). Global & Regional Health Technology Assessment 2015;2:143-51. https://doi.org/10.5301/GRHTA.5000204

Xingogos S, Duratos D, Varonos D. Clinical effectiveness of Broncho-Vaxom (BV) in patients with chronic obstructive pulmonary disease. Int J Immunotherapy 1993;9:135-42. https://doi.org/10.1025-9625/93/0200135 + 8 502.0010

Li J, Zheng JP, Yuan JP, Zeng GQ, Zhong NS, Lin CY. Protective effect of a bacterial extract against acute exacerbation in patients with chronic bronchitis accompanied by chronic obstructive pulmonary disease. Chin Med J (Engl) 2004;117:828-34. https://doi.org/10.1097/00001599-200412180-00013

Cvorsicec B, Ustar M, Pardon R, Palecek I, Stipic-Markovic M. Effect of a bacterial extract (OM-85 BV) and a cost-effectiveness analysis. Monaldi Arch Chest Dis 1994;49:302-7.https://doi.org/10.1159/000093933

Mutterlein SMR, Cozma G. Double-blind study of OM-85 in patients with chronic bronchitis or mild chronic obstructive pulmonary disease. Respiration 2007;74:26-32. https://doi.org/10.1159/000093933

Tang H, Fang Z, Saborio GP, Xu Q. Efficacy and safety of OM-85 in Patients with chronic bronchitis and/or chronic obstructive pulmonary disease. Lung 2015;193:513-9. https://doi.org/10.1007/s00408-015-9737-3

Tang H, Fang Z, Saborio GP, Xu Q. Efficacy and safety of bacterial lysates in patients with chronic obstructive pulmonary diseases and exacerbations. Eur Respir J 2011;38(Suppl 55):3358. https://doi.org/10.1183/00340030.0080-1973-3

Magyar P, Nagy IA, Tarjan E, Zsiray M, Lantos A. The therapeutic and preventive effects of Broncho-Vaxom, a lyophilized bacterial lysate, in chronic bronchitis: a double-blind placebo-controlled study. Proceedings 4th congress of the European Society of Pneumology (SEP). Milano/Stresa: 1985.

Orlandi O, Donner CF, Fumagalli G, Rimoldi R, Grassi C. Immunological treatment using lysate in the prevention of recurrent bronchitis: a multicentre Italian study. Proceedings 4th congress of the European Society of Pneumology (SEP). Milano/Stresa: 1985.

Hutas IB-NG, Kraszko P. Statistical analysis of a double blind randomized clinical study of Broncho-Vaxom vs placebo in patients suffering from bronchitis. Statistical Report, Biometrix SA, Stand 1993:412-22.

Prontuario farmaceutico 2017. Available from: http://www.paginesanitarie.com/euromedia/farmacis/989e12175897e914ec1256920053d19f5ec55724ab01379de1257632005b1c8b08Op enDocument (accessed on: 25/08/2020).

Wilkinson TM, Donaldson GC, Hurst JR, Seemungal TA, Wedzicha JA. Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004;169:1298-303. https://doi.org/10.1164/rccm.200310-1443OC

Sethi S. Infectious etiology of acute exacerbations of chronic bronchitis. Chest 2000;117(Suppl 2):380S-5S. https://doi.org/10.1378/chest.117.5_suppl.2.380s

Agabiti N. Epidemiologia delle Malattie Respiratorie Croniche in Italia. 2013.

Rajagopalan P, Douron E, Vildé JL, Poisidaliow JJ. Direct activation of human monocyte-derived macrophages by a bacterial glycoprotein extract inhibits the intracellular multiplication of virulent Legionella pneumophila serogroup 1. Infect Immun 1987;55:2234-9. https://doi.org/10.1128/IAI.55.9.2234-2239.1987

Mauel J, Van Pham T, Kreis B, Bauer J. Stimulation by a bacterial extract (Broncho-Vaxom) of the metabolic and functional activities of murine macrophages. Int J Immunopharmacol 1989;11:637-45. https://doi.org/10.1016/0192-0561(89)90149-5

Emmerich B, Esmalander HP, Pachmann K, Hallek M, Milatovic D, Busch K. Local immunity in patients with chronic bronchitis and the effects of a bacterial extract, Broncho-Vaxom, on T lymphocytes, macrophages, gamma-interferon and secretory immunoglobulin A in bronchoalveolar lavage fluid and other variables. Respiration 1990;57:90-9. https://doi.org/10.1159/0000195723

Mestecy J, Mc Gee JC, Arnold RR, Michalek SM, Prince SJ, Babb JL. Selective induction of an immune response in human external secretions by ingestion of bacterial antigen. J Clin Invest 1978;61:731-7. https://doi.org/10.1172/JCI108986

Cazzola M, Roglani P, Curradi GB. Bacterial extracts for the prevention of acute exacerbations in chronic obstructive pulmonary disease: a point of view. Respir Med 2008;102:321-7. https://doi.org/10.1016/j.rmed.2007.11.002

Emmerich B, Pachmann K, Milatovic D, Esmalander HP. Influence of OM-85 BV on different humoral and cellular immune defense mechanisms of the respiratory tract. Respiration 1992;59(Suppl 3):19-23. https://doi.org/10.1159/000196126
[40] Cimen P, Unlu M, Kirakli C, Katgi N, Ucsular FD, Ayranci A, Guclu SZ. Should patients with COPD be vaccinated? Respir Care 2015;60:239-43. https://doi.org/10.4187/respcare.03350

[41] Beaton DE, Bombardier C, Katz JN, Wright JG, Wells G, Bors M, Strand V, Shea B. Looking for important change/differences in studies of responsiveness. OMERACT MCID Working Group. Outcome measures in rheumatology. minimal clinically important difference. J Rheumatol 2001;28:400-5.

[42] Troiano G, Nardi A. Vaccine hesitancy in the era of COVID-19. Public Health 2021;194:245-51. https://doi.org/10.1016/j.puhe.2021.02.025

[43] Bekkat-Berkani R, Wilkinson T, Buchy P, Dos Santos G, Stefanidis D, Devaster JM, Meyer N. Seasonal influenza vaccination in patients with COPD: a systematic literature review. BMC Pulm Med 2017;17:79. https://doi.org/10.1186/s12890-017-0420-8