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Prevention of recurrent respiratory tract infections: a literature review of the activity of the bacterial lysate Lantigen B

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Abstract. – OBJECTIVE: Lantigen B, a bacterial lysate, was developed in the 1960s and showed a prophylactic effect in patients with recurrent respiratory tract infections. The objective of this article is to review the literature to update the efficacy and safety profile of Lantigen B in preventing recurrent respiratory tract infections (RRTI).

MATERIALS AND METHODS: Articles available from international data banks and producing company archives were used. Only clinical studies providing a control group were considered. The effects of Lantigen B on the number of infectious episodes or comparable parameters were analyzed.

RESULTS: 22 randomized clinical trials on 4,571 patients published between 1963 and 2014, with different methodologic accuracy, consistently demonstrated that Lantigen B reduced RRTI vs. placebo (RR -0.47; 95% CI = -0.38 to -0.56). The RR always favored Lantigen B in all the other subsets analyzed in adults with RRTI (RR = -0.48; 95% CI = - 0.33 to -0.62) and children (RR = -0.490; 95% CI = - 0.36 to -0.61). Unfortunately, some studies performed in the past evaluated a small number of patients, and clinical procedures were not always performed according to the more recent good clinical practices. Despite these evident limitations of considered studies, the response frequency has remained almost unchanged since the first articles in the 1960s.

CONCLUSIONS: These data confirm the efficacy of Lantigen B alone in the prophylaxis of acute respiratory infections in adults and children but also suggest that Lantigen B, used with novel therapeutic strategies, can further improve clinical outcomes.

Key Words:
Lantigen B, Bacterial lysate, Recurrent respiratory tract infection, Prophylaxis.

Introduction

Lantigen B is a lysate of the most common bacterial strains causing respiratory tract infections (RTIs; *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Hemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus,* and *Streptococcus pyogenes*) obtained by chemical inactivation with chlorhexidine and then by long-term inactivation in an alkaline buffer for 45 days. Lantigen B was jointly developed in the 1960s by Edinburgh Laboratories (Australia) and Ashe Laboratories Ltd (UK) and has been made clinically available as a therapeutic option by Bruschettini Srl (Genoa, Italy) since 1992. The approved indication is for the prophylaxis of recurrent RTIs. Over the past decades, evidence has been collected on the mechanism of action of bacterial lysates. Lantigen B can induce the maturation of dendritic cells necessary for the immune response[1-3]. In addition, it was demonstrated that specific IgAs are secreted in response to the administration of Lantigen B[4-7]. Lantigen B, containing a particulate fraction in combination with a soluble fraction, can be administered by the sublingual route, allowing the contact between the antigens and the immune-competent cells of the mouth mucosa and sub-mucosa to exalt this latter effect.

The efficacy of Lantigen B in the prevention of recurrent RTI has been shown by several clinical studies published in the 1960s. This article revises and reappraises available evidence on the efficacy of Lantigen B in RTIs, to discuss its role in the present therapeutic approach.

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Materials and Methods

This review could not adhere to the PRISMA guidelines because of certain characteristics of available studies (including lack of data in some articles). For this reason, a dedicated study protocol was prepared.

Eligibility of Studies

Eligible studies were controlled, randomized clinical trials evaluating the prevention of RTIs by Lantigen B in adults with recurrent RTIs, chronic bronchitis, and chronic obstructive pulmonary disease (COPD), and in children with acute/recurrent RTIs, and otherwise adult healthy subjects, comparing Lantigen B with placebo, another conventional bacterial lysate, or no treatment (control). On the contrary, studies focused on the mechanism of action and evaluating relevant immunologic parameters were not considered, although their results were used to support the discussion of clinical studies when needed. Follow-up was ≥12 months because an immunological effect cannot be correctly evaluated in a short period of time (such as 1 month) or too long (years).

Sources

PubMed/MEDLINE, Google Scholar, and China National Knowledge Infrastructure were searched with appropriate keywords (respiratory tract infection, recurrence, Lantigen B). Articles cited in other retrieved ones were considered, although not indexed. Finally, the manufacturer of Lantigen B (Bruschettini Srl, Genova, Italy) provided unpublished data and studies published in non-indexed national journals.

Articles Analysis

Articles published in peer-reviewed international journals in English or with English abstracts and articles from local journals in the local language (mainly the case of studies from the first decades of drug evaluation) were considered.

Manuscripts were analyzed based on accepted criteria of meta-analysis, in particular: peer-reviewed or non-peer-reviewed articles, international or national articles, placebo-controlled or non-controlled studies, primary endpoints, number of patients and relevant study size, treatment of healthy volunteers or patients with recurrent RTIs, description of the dates and place of the study, inclusion and exclusion criteria, number of patients lost during the follow-up, description of the treatment and the placebo, the procedure of randomization, statistical analysis, evaluation of the outcomes, toxic effects or adverse reactions, and evaluation of the results in patient subgroups. Endpoints, such as using antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, mucolytics, etc., or modification of laboratory parameters, were not considered in the study outcomes evaluation.

The risk of biases was also considered during the evaluation of the studies. Indeed, unpublished studies, as well as other manuscripts published in non-peer-reviewed or very old and non-English-written journals, were at risk of uncontrollable biases. For this reason, the manuscripts whose results were not completely convincing (for example, for an unexplained excess of efficacy) or obtained by questionable methods were excluded from the evaluation before the beginning of the procedures.

Data Extraction and Validity Assessment

The following information was retrieved from each included study: first author, publication year, details of study design, study treatments (type of drug, schedule, duration), type of patients (recurrent RTIs, COPD, bronchitis), age intervals (as adult or children), study endpoints, incidence and type of adverse events. The quality of the selected trials was assessed according to a 5-point validated scale measuring a range of factors that impact the quality of a trial[8].

Analyzed Variables

Primary outcomes included: the number of exacerbations during the study period, days of illness for recurrent RTIs, number of days with fever, and number of days of absence from work or school.

Statistical Analysis

The results were analyzed according to Neyeloff et al[9]. Bibliographic data were pooled, calculating the random effect summary model, with standardized mean differences (SMDs) and 95% CIs because of the variability observed. Statistical heterogeneity was defined as an I^2 statistic[10], and the Cochrane Q statistics were calculated[11]. According to Higgins et al[10], for the I^2, a naive categorization of these values would not be appropriate for all circumstances. However, we would tentatively assign low, moderate, and high adjectives to I^2 values of 25%, 50%, and 75%.

In the same article, Higgins et al[10] showed that about a quarter of meta-analyses have I^2 values over 50%.

Forest Plots were prepared using Microsoft Excel as described[9], starting from data obtained in studies with a certain heterogeneity, as stated before, for mere descriptive reasons.

Results

Study Selection

A total of 37 studies were collected following the abovementioned criteria. The full text of nine articles[12-20] was unavailable because they were published before 1970, and the journals were no longer available in Scientific Libraries. Seven selected articles[21-26] by Chinese authors were present only in the China Knowledge Resource Integrated Database. They could not be downloaded outside China. Seven studies[1-7] were excluded because they were focused on laboratory data.

Thus, 22 articles published between 1963 and 2014 were used in this review (Table I). A total of 4,571 patients were evaluated in these studies, of which 2,421 were treated with Lantigen B, and 2,150 were controls.

The most common treatment schedule for adults was sublingual administration of 15 drops twice daily with a second cycle after 2 weeks without treatment. Half doses were administered for children under 10 years with the same schedule.

The endpoints were: clinical improvement as judged by the patient, two studies (Phelan 1966 – Report on a clinical trial with Lantigen B conducted at Messrs. Tickopres LTD, data on file; Cerreta 1983 – Controlled clinical trial of the new vaccine, data on file); the number of days

Table I. Summary of included studies evaluating the efficacy of Lantigen B.

Source	Setting	No. of patients	Age, years (range or mean)	Inclusion criteria	Concomitant treatments	Follow-up, months
Braido et al 2014[46]	Adults	160	42	RRTI	ATB, NSAID, AAD	6
Carta et al 1994[41]	Adults	30	45-72	RRTI	ATB, NSAID	2
Castello et al 1996[43]	Ped	30	2-12	RRTI	ATB, NSAID	3
Cerreta 1983 – Controlled clinical trial of the new vaccine, Data on file	Adults	20	NS	RRTI	NS	1
De Bernardi et al 1992[40]	Adults	60	63	RRTI	ATB	4
Galli et al 1987[36]	Ped	33	2-14	RRTI	NS	6
Leigh 1963[17]	Adults	125	20-60	ARP	NS	6
Magnolfi et al 1987[39]	Ped	20	3-7	RRTI	ATB, NSAIDs	6
Meichen 1981[38]	Adults	2888	> 15	ARP	NS	7
Moratti et al 1999[44]	Ped	53	3-12	RRTI	ATB	6
Nespoli 1987[28]	Ped	18	4.6	RRTI	Yes, NS	6
Newbold and Savage 1971[32]	Adults	52	17-30	ARP	NS	7
Peona et al 1984[27]	Adults	25	NS	RRTI	NS	
Phelan K (1966). Report on a clinical trial with Lantigen B conducted at Messrs, Tickopress, Harwich during winter 1965/1966. Data on file	Adults	157	30-50	ARP	NS	
Pozzi 2004[45]	Adults Ped	118	72 94	RRTI 6	NS	6
Price and Henley 1974[33]	Ped	225	10-17	ARP	NS	6
Price and Henley 1976[34]	Ped	110	8-13	ARP	NS	6
Rollet 1965[31]	Adult	24	NS	ARP	NS	7.5
Rossi et al 1994[47]	Ped	40	1-5	RRTI	NS	3
Rossi et al 1994[29]	Ped	30	2-8	RRTI	ATB, NSAID	1
Sorge et al 1994[30]	Ped	40	1-13	RRTI	ATB, NSAID	4
Tyrrell et al 1972[37]	Adults	112	18-68	ARP	NS	3-6

AAD: anti allergic drugs; ARP: at-risk patients; ATB: antibiotic; NS: not specified; NSAID: non-steroidal anti-inflammatory drug; Ped: pediatric patients; RRTI: recurrent respiratory tract infections.

with fever, four studies[27-30]; absence from work or school, seven studies[17,31-36]; episodes of a common cold, one study[37]; and number of days with RTIs, nine studies[38-46].

Seven studies[20,28,29,36,39,43,44] were performed in children; one study[45] was performed in both children and adults; all other studies were performed in adults [Phelan K (1966). Report on a clinical trial with Lantigen B conducted at Messrs, Tickopress, Harwich during winter 1965/1966. Data on file][17,27,30-32,34,37,38,40,41,45-47].

Significant heterogeneity of the study methods and the accuracy of the reports was observed (Table II). Additionally, according to the (CONsolidated Standards of Reporting Trials) (CONSORT) rules[48], the location and the dates of the study were indicated in 13 studies [Phelan K (1966). Report on a clinical trial with Lantigen B conducted at Messrs, Tickopress, Harwich during winter 1965/1966. Data on file;][17,30-35,37,38,41,43,46]; healthy volunteers were investigated in 8 studies [Phelan K (1966). Report on a clinical trial with Lantigen B conducted at Messrs, Tickopress, Harwich during winter 1965/1966. Data on file][31-34,37,38,41], while, in 13 studies, patients with recurrent RTIs were included (Cerreta 1983 – Controlled clinical trial of the new vaccine, Data on file)[17,27-30,36,39,40,43,44,46,47]; inclusion and exclusion criteria were clearly described in all studies; the number of patients lost in the study was

Table II. Quality measures of the included studies.

Trials	Concealment of randomization	Number of withdrawn patients	Patients blinded	Healthcare providers	Blinded data collectors	Blinded outcome assessors blinded	Tolerability
Braido et al 2014[46]	Yes	No	Yes	Yes	Yes	Yes	SARs: 2 P; 1 L
Carta et al 1994[41]	Yes	2	Yes	NS	NS	NS	ARs: 1 P; 1 L
Castello et al 1996[43]	Yes	NS	Yes	NS	NS	NS	NS
Cerreta 1983 – Controlled clinical trial of the new vaccine, Data on file	Yes, nbs	NS	Yes	NS	NS	NS	NS
De Bernardi et al 1992[40]	Yes	NS	Yes	Yes	NS	NS	Well-tolerated
Galli et al 1987[36]	Not needed	NS	NS	NS	NS	NS	NS
Leigh 1963[17]	Yes	11	Yes	Yes	NS	NS	NS
Magnolfi et al 1987[39]	Yes	NS	Yes	Yes	NS	NS	Well-tolerated
Meichen and Howell 1981[38]	Yes, nbs	187 P, 184 L	Yes	NS	NS	NS	NS
Moratti et al 1999[44]	Yes, nbs	0	Yes	NS	NS	NS	Well-tolerated
Nespoli et al 1987[28]	Yes, nbs	NS	Yes	NS	NS	NS	ARs: 2 L
Newbold and Savage 1971[32]	Yes	2	Yes	Yes	NS	NS	Well-tolerated
Peona et al 1984[27]	NS	NS	NS	NS	NS	NS	NS
Phelan K (1966). Report on a clinical trial with Lantigen B conducted at Messrs, Tickopress, Harwich during winter 1965/1966. Data on file	Yes	26	Yes	NS	NS	NS	NS
Pozzi 2004[45]	Yes	23	Yes	Yes	NS	NS	ARs: 13 P;1 3 L
Price and Henley 1974[33]	Yes, nbs	45	Yes	NS	NS	NS	NS
Price and Henley 1976[34]	Yes, nbs	NS	Yes	NS	NS	NS	NS
Rollet 1965[31]	Yes	NS	Yes	NS	NS	NS	Well-tolerated
Rossi et al 1994[47]	Yes, nbs	1	Yes	NS	NS	NS	AR: 1 L
Rossi et al 1994[29]	Yes, nbs	3L, 3P	Yes	NS	NS	NS	Well-tolerated
Sorge et al 1994[30]	Yes	0	Yes	NS	NS	NS	Well-tolerated
Tyrrell et al 1972[37]	Yes	NS	Yes	NS	NS	NS	NS

AR: adverse reaction; L: Lantigen B; nbs: not better specified; NS: not specified; P: placebo; SAR: severe adverse reaction.

described in five studies[17,33,41,45,46]; the randomization procedure was accurately described in five studies[38,40,41,45,46], was not described in seven (Cerreta 1983 – Controlled clinical trial of the new vaccine, data on file)[17,27,28,36,39,44] and was only partially described in the remaining studies; the sample size was accurately calculated in seven studies[17,33,34,37,38,45,46], and described but not justified by a statistical analysis in the others; an accurate statistical analysis of the results was reported in eight studies[17,33,34,37,38,45,46]; the analysis of subgroups was carried out only in one study[46]; adverse events as well as toxic effects were described in four studies[27,30,39,46].

Concerning the classification of studies according to Jadad and co-workers[8], two studies[33,34] were mega-trials with a control group (Level 1a); one study[46] was a randomized placebo-controlled multicenter study (Level 1b); 9 were randomized studies with no other specific characteristics (Level 1d) [Phelan K (1966). Report on a clinical trial with Lantigen B conducted at Messrs, Tickopress, Harwich during winter 1965/1966. Data on file; Cerreta 1983 – Controlled clinical trial of the new vaccine, data on file;][32,37,38,40,41,44,45]; six studies[17,28-30,36,47] were case-control studies (Level 3); and two studies[27,31] reported case series (Level 4).

Analysis of Data

Forrest plots were produced to analyze results summarized in Table III, although data were not included in a meta-analysis.

Table III. Analysis of the random-effects summary models and the confidence intervals for the different conditions analyzed.

	Average	95% CI
All studies	-0.47	-0.38 to-0.56
Healthy subjects	-0.31	-0.18 to -0.44
All adults	-0.46	-0.34 to -0.57
Adult patients with RRTI	-0.48	-0.34 to -0.64
All children	-0.50	-0.38 to-0.62
Children with RRTI	-0.49	-0.36 to -0.62

RRTI: recurrent respiratory tract infections.

Figure 1 shows the efficacy results of all 22 studies included in this review. Overall, a reduction of -47% of the main objectives of studies was observed. The measures of heterogeneity were high (Q = 447.0, I^2 = 95.1). The objective was the reduction in infections, measured as the number of infectious episodes, number of days with fever, or number of days of absence from work/school. Patients were adults or pediatric subjects, healthy patients at risk, or patients with recurrent RTI.

Figure 2 shows the effectiveness of Lantigen B in healthy subjects (both adults and children) at risk of respiratory infection due to environmental factors such as industrial assets or school attendance. Overall, a -31% reduction in the study's main objective was observed. The objective was reducing infections, measured as the number of days with RTIs, number of days of absence

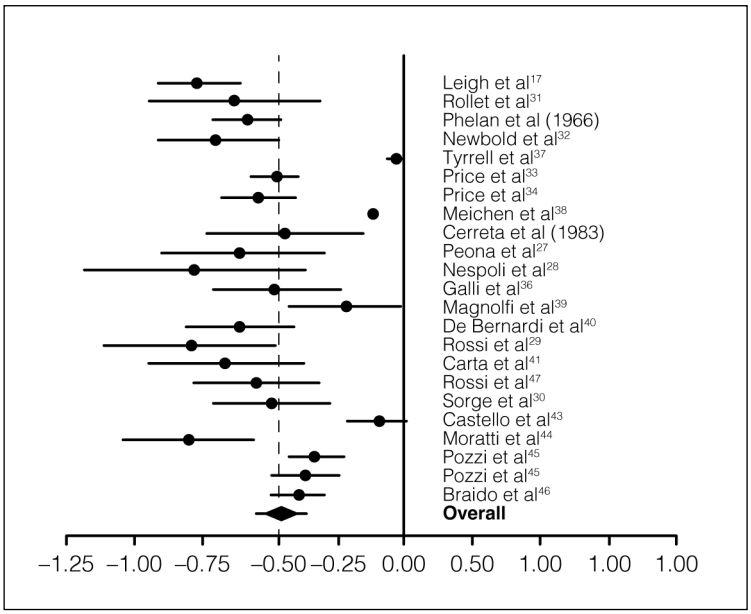

Figure 1. Effect of Lantigen B: all studies. The objective was the reduction in infections measured as the number of infectious episodes, number of days with fever, or number of days of absence from work/school.

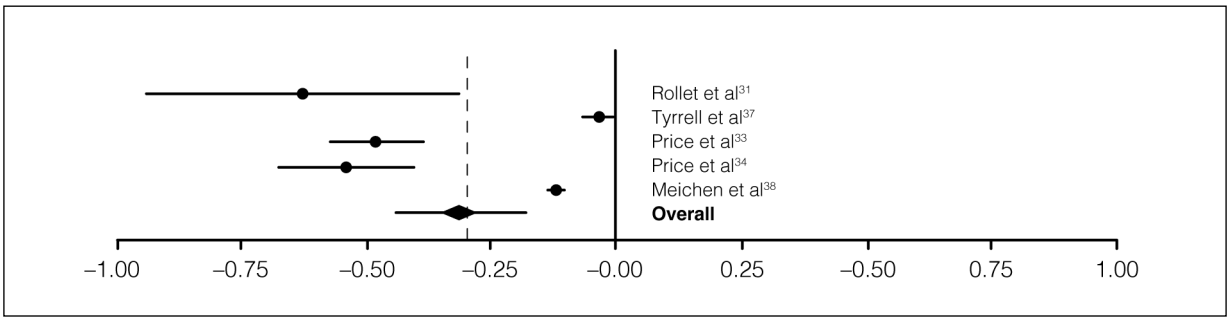

Figure 2. Effect of Lantigen B: Healthy subjects. The objective was the reduction in infections measured as number of days with RTIs, number of days of absence from work/school, number of episodes of a common cold.

from work/school, and number of common cold episodes. Studies[33,34,37] evaluating common cold prophylaxis could not demonstrate the efficacy of Lantigen B. In addition, in this group of studies, a large heterogeneity of the results was observed (Q = 125.8 and I^2 = 93.6).

Figure 3 shows studies on adults with or without RTI with a reduction in infections of -46% in subjects receiving Lantigen B. These studies had a high heterogeneity (Q = 267.2 and I^2 = 95.9). The objective was the number of days of absence from work/school, the clinical improvement as judged by the patient, the number of episodes of a common cold, the number of days with RTIs, and the number of days with fever.

Figure 4 shows the efficacy of Lantigen B in studies on adult patients with recurrent RTI (including repeated infections of the upper respiratory airways but also, in a few cases, older patients with COPD). The objective was the number of days with RTIs, the number of days of absence from work/school, the clinical improvement as judged by the patient, and the number of days with fever. Lantigen B efficacy was slightly higher than in the whole group of studies (-48% of infections compared with controls). The heterogeneity of studies is high but lower than in the whole sample and in studies with healthy subjects (Q = 77.7 and I^2 = 90.1)

Figure 5 shows the analysis of studies performed in children with or without RRTI. The objective of studies in children was the number of days of absence from school, the number of days with fever, and the number of days with RTIs. The use of Lantigen B reduced the number of infections by -50%; the data heterogeneity was also large (Q = 51.2 and I^2 = 82.4) in this cohort of patients. Figure 6 shows the selection of studies performed on pediatric patients with documented RRTIs (objectives were the number of days with

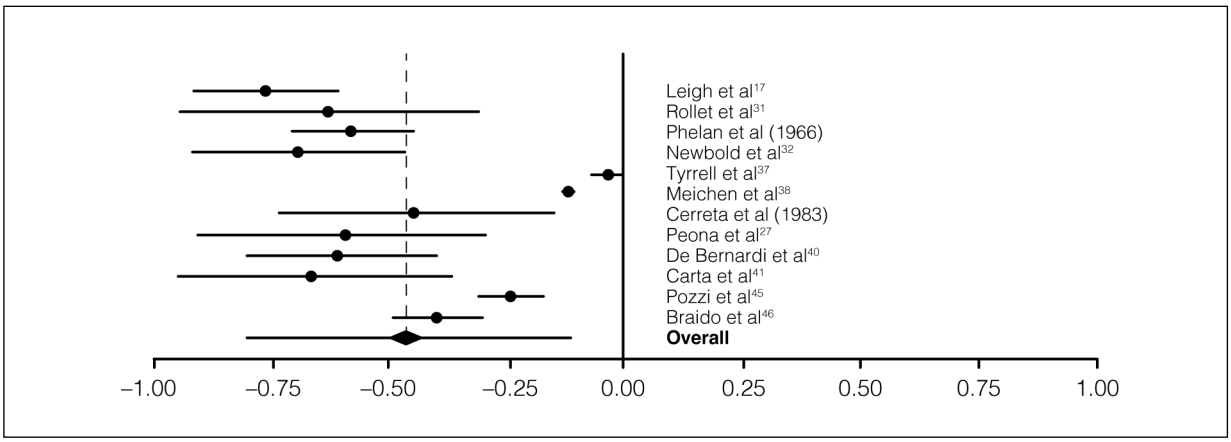

Figure 3. Effect of Lantigen B: Adults. The objective was the reduction in infections measured as number of days of absence from work/school, clinical improvement as judged by the patient, number of episodes of a common cold, number of days with RTIs, number of days with fever.

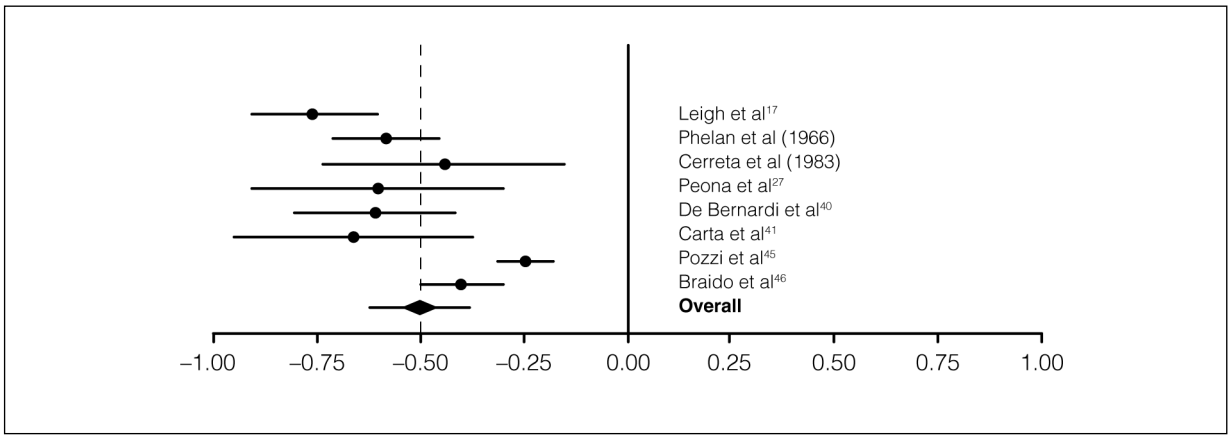

Figure 4. Effect of Lantigen B: Adults patients with recurrent respiratory tract infections. The objective was the reduction in infections measured as number of days with RTIs, number of days of absence from work/school, clinical improvement as judged by the patient, number of days with fever.

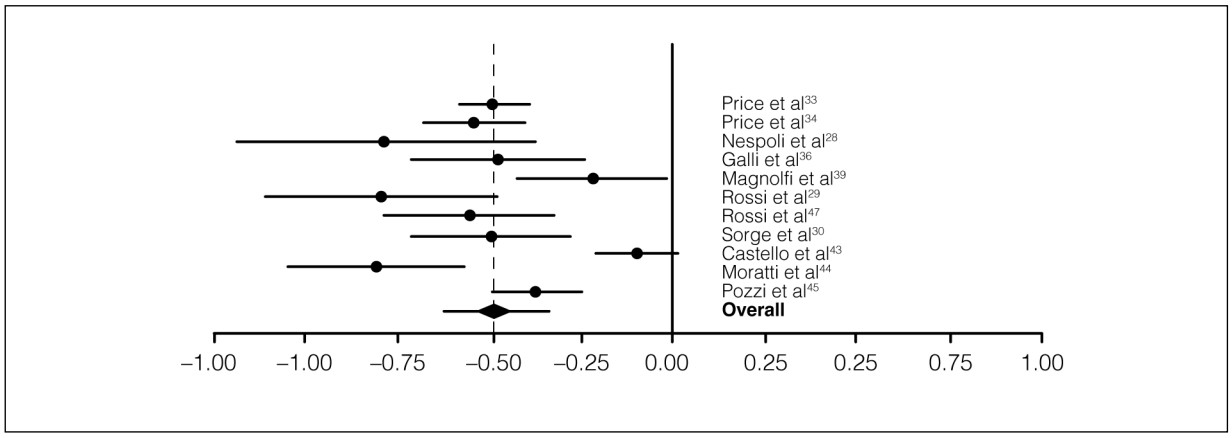

Figure 5. Effect of Lantigen B: Pediatric patients. The objective was the reduction in infections measured as number of days of absence from school, number of days with fever, number of days with RTIs.

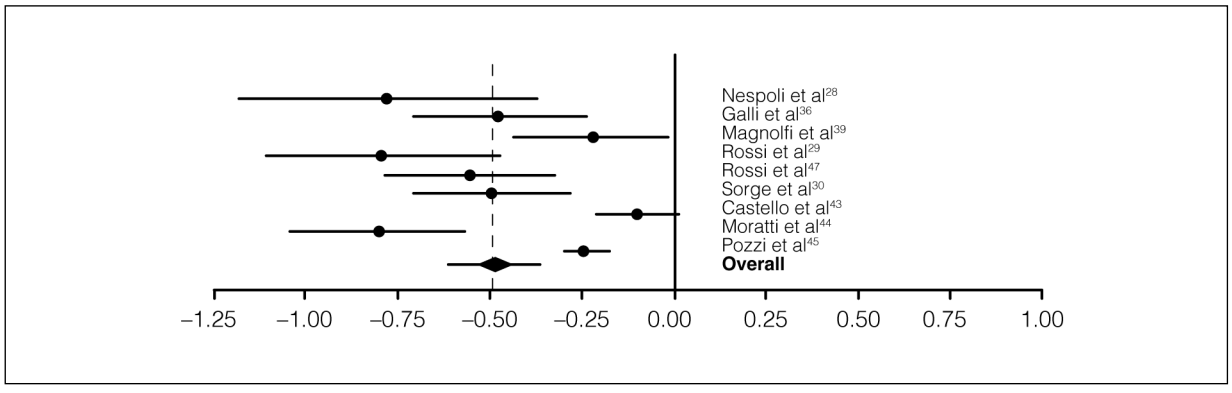

Figure 6. Effect of Lantigen B: Pediatric patients with recurrent respiratory tract infections. The objective was the reduction in infections measured as number of days with fever, number of days of absence from school, number of days with RTIs.

fever, the number of days of absence from school, and the number of days with RTIs). Administration of Lantigen B resulted in a similar reduction of risk (RR-0,49 ranging from -36 to -61; Q=47.1; I^2 87.3).

Overall, the confidence intervals shown in Table III indicate that a positive result can be expected in all conditions. Even with relevant heterogeneity among the studies, clearly indicated by the two parameters used here (the Q and the I^2), the absence of inter-trial quality heterogeneity was evident because in none of the trials, the control groups were worse off than the treated groups. The effect of no trials resulted in the right of the equivalence line or confidence intervals. Consequently, the result of the effect summary (and the relevant confidence intervals) consistently remained on the left of the equivalence line.

Discussion

This literature review was carried out to understand the role of Lantigen B in the prophylaxis of recurrent RTI. Overall, the studies included in the review showed that the risk of recurrent RTI was reduced by 47% in subjects treated with standard therapies plus Lantigen B compared with controls receiving standard therapies without Lantigen B.

The efficacy of Lantigen B in the whole population was slightly higher than in healthy subjects at risk of respiratory infection (Figures 1 and 2). Studies on common cold prophylaxis in healthy subjects confirmed this finding: the study of Tyrrell et al[37] found almost no differences in the treated and the placebo group, and the two original studies by Price and Henley[33,34] clearly showed the absence of any effects in the subgroups of healthy students with a common cold.

Accordingly, the efficacy of Lantigen B was slightly more evident in patients with recurrent RTI than in the overall population, suggesting that the prophylactic effect is more pronounced in patients with a history of recurrent respiratory tract infections.

Finally, Lantigen B efficacy was observed in both adults and children. Recurrent RTIs are extremely common in children in the pre-scholar age and the first year of primary school. Antibiotic treatment is not supported by practical guidelines in this indication and is deemed related to the risk of increased antibiotic resistance. Thus, prophylaxis with a bacterial lysate may be an acceptable strategy to reduce antibiotic usage.

Bacterial lysates were originally developed in a period ranging from the 1960s to the 1980s, during which the role of specific (adaptive) immunity in the control of infectious diseases was actively investigated. However, new antibiotics were developed and made available in human therapy. Therefore, the role of immunity potentiation in patients at risk of recurrent RTI was considered a minor line of therapy, and further development was not considered strategic. Only at the beginning of the third millennium, the discovery of the role of dendritic cells and the central role of the Toll-like receptor system in the defense against infectious diseases drew attention to the mechanism of action of bacterial lysates. In the meantime, the increasing number of antibiotic-resistant bacterial strains and the virtual absence of new antibiotics in pharma industries' pipelines prompted research on immune-potentiating drugs. In this context, some meta-analyses were planned for bacterial lysates. For example, Broncho-Vaxom activity was evaluated in two reviews[49,50], and the polyvalent mechanical bacterial lysate activity was also evaluated[51]. In both cases, the activity of bacterial lysates was documented by the statistical evaluation of the results of published papers. Lantigen B was considered in a meta-analysis on the efficacy of a heterogeneous group of drugs, including a few bacterial lysates, accounting for a reduced number of treated patients[52].

Lantigen B represents a unique member of the bacterial lysate family. It is obtained by chemical lysis in an alkaline buffer; the final suspension, used for patient treatment, contains not only the soluble fraction of bacterial antigens but also a small but substantial particulate fraction derived from killed but not completely solubilized bacterial strains. This characteristic makes Lantigen B different from mechanical (such as Immubron and Ismigen) and thermal lysates (such as Buccalin), which consist only of the particulate fraction and from pure chemical lysates (such as Broncho-Vaxom), which in turn consist only of the soluble fractions of the bacterial lysates. From an experimental perspective, the particulate fraction is highly active in recruiting efficient dendritic cells[53]. In contrast, the soluble fraction contributes to activating the helper arm of the T-cell-mediated immune response[54].

Despite the heterogeneity of the evaluated studies, which is a limitation of this review, we found a strong homogeneity of observed results, which suggests that a conclusion can be drawn

from the literature review notwithstanding the issues described in the quality of included studies. The standard errors were very small in the studies performed on a large "at risk" population but still healthy subjects[33,34,37]. The standard errors within expected limits were observed in the two most recent and well-conducted studies[45,46]. In the other studies, the standard errors were wider mainly because of the small number of patients involved. In addition, the heterogeneity parameters, particularly the I^2, were extremely high and always >75% of the cut-off limit provided by Higgins to identify highly heterogeneous studies[10]. According to this parameter, the value of the present meta-analysis could be considered sub-optimal. Indeed, according to Higgins et al[10], most meta-analyses showed I^2 values around 50%.

However, it is noteworthy that no study with negative results is available. Indeed, only the study of Tyrrell et al[37], who evaluated the effect of Lantigen B on common cold episodes in a population of virtually healthy students, showed a non-significant reduction in the number of episodes in the treated group. In all the other studies, an advantage in the treated group was always observed. Meta-analyses were developed to define the true activity of treatment when both positive and negative results were observed in different studies. For this reason, a statistical value that considers all (positive and negative) studies was used. In the case of Lantigen B, no study has crossed the line of 'negativity'. This is particularly interesting because an almost constant frequency of positive results was observed in more recent and well-conducted studies[29,30,40,41,43-47] and in older studies conducted[17,27,28,31-34,36-39] in years when the controlled clinical trial concept was a characteristic of oncologists belonging to international excellence institutions. In other hospitals and medical practices, the rules of controlled randomized clinical trials were virtually unknown or only partially used. Indeed, the CONSORT statements[48] were proposed in 1996, when many works considered in this meta-analysis had already been published. In this context, despite the large standard errors observed, the fact that the frequencies of response resulted very similar, at least in studies where patients with recurrent RTI were treated, is significant. This finding is even more interesting if we consider that the therapeutic armamentarium available 30 years ago differs substantially from that available today.

Limitations

This review has some limitations. The studies included were published between 1963 and 2014, over a long period, and this results in different methodological approaches. Many studies are very old, and none were published after 2014. Some studies could not be retrieved as they were published in China. Indeed, the CONSORT rules were only partially complied, and only the most recent study followed almost all rules[46]; in particular, studies performed in the 1980s and 1990s were carried out without a formal definition of all relevant parameters to be considered. In addition, no original case report forms are available for these studies; therefore, no original 'raw' data can be evaluated. The two statistical parameters used to define the heterogeneity of the studies (the Q and the I^2) suggested that studies were heterogeneous. However, despite this methodological problem, the fact that all studies (from the first pioneering studies to the last performed according to rigorous modern rules) reported, with some variability, a positive effect is highly suggestive of the clinical efficacy of Lantigen B in the RTI prophylaxis in both adults and children.

Conclusions

In conclusion, this literature review shows that Lantigen B is active in the prophylaxis of recurrent RTI in adults and children. Notably, Lantigen B did not significantly modify its prophylactic efficacy during the 50 years of use. Indeed, the first studies indicated that a halving of RTIs could be experienced in treated patients. More recent studies (performed with the support of modern and highly effective drugs) had similar results. This finding seems another solid proof of Lantigen B's capacity to significantly reduce the number of acute episodes in patients with recurrent RTI. This analysis of available evidence is quite encouraging and prompts to design of more appropriate studies to further explore Lantigen B efficacy.

Conflict of Interest

GM was a consultant of Bruschettini Srl, and GN was employed in Bruschettini Srl when this review was carried out.

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Availability of Data and Materials
"Data on file" is a conclusive and signed study report, archived by the author or the sponsor.

Authors' Contribution
Study conception and design: GM; collection and interpretation of data: GM; statistical analysis: GM; manuscript drafting: FB, GM, GN, GWC; manuscript editing: FB, GM, GN, GWC; approval to submit: FB, GM, GN, GWC.

Ethics Approval and Informed Consent
Not applicable.

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