Compilation and meta-analysis of randomized placebo-controlled clinical trials on the prevention of respiratory tract infections in children using immunostimulants

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Authors' objectives
To compile and to perform a meta-analysis of the findings of randomised, placebo-controlled trials on the prevention of acute respiratory tract infections (ARTIs) in children, using immunostimulants.

Searching
The authors state that they searched for all the references of immunostimulants in the Mexican market (listed in the 'Specific Interventions' field), as they included the most popular and best-selling products worldwide and as they are also registered in Europe and South America.

MEDLINE and EMBASE were searched from 1960 to July 2000 for references containing the trade names, or the codes, of immunostimulants in any search field. In addition, references containing the terms 'bacterial lysates' or 'Klebsiella glycoprotein' and 'infection' were also checked. Additional references on immunostimulants were obtained from the special register of the Cochrane Acute Respiratory Infections Group. Papers in English, Spanish, French, Italian and German were included.

Study selection
Study designs of evaluations included in the review
Randomised placebo-controlled trials (RCTs) were eligible for inclusion in the review. Unpublished trials were excluded.

Specific interventions included in the review
Studies of the administration of immunostimulants to prevent ARTIs in children, compared with placebo, were eligible for inclusion in the review. The eligible immunostimulants included:

- bacterial extracts of respiratory tract pathogen bacteria, such as Immunobalt, LW 50020 (Luivac) and Paspat, Munostin, OM-85 BV (BronchoVaxom), Pulmonar-OM, and Ribomunyl (Ribovac or Immucytal);
- lipopolysaccharides and glycoproteins of Klebsiella pneumoniae, i.e. RU 41740 (Biostim);
- calf thymus extracts, i.e. thymomodulin (Leucotrofina);
- plant extracts, i.e. Pelargonium sidoides extract (Umckaloabo); and
- synthetic chemicals, i.e. AM3 (glycophosphophtopectical, Imunoferon AM3) and pidotimod (Adimod).

All of these were administered orally, with the exception of Paspat, which was administered by a dermal injection, and one presentation of Ribomunyl, which was administered as a nasal and pharyngeal spray. The included interventions were: LW 50020 (3 mg once daily) versus placebo; OM-85 BV (typical regimen: 3.5 mg once daily for 10 days/month for 3 months) versus placebo; pidotimod (typical regimen: 400 mg/day for 60 days, follow-up of 90 days) versus placebo; RU41740 (1 or 2 mg once daily; various regimens) versus placebo; Ribomunyl (various regimens) versus placebo; thymomodulin (various regimens) versus placebo. Some of the interventions also consisted of regimens that included initial treatment with a conventional antibiotic at entry, e.g. amoxicillin-clavulanate. Further details of the different dosages and regimens employed in the different studies are provided in the review.

Participants included in the review
Children were eligible for inclusion in the review if they were aged from 0.5 to 19 years and were either highly susceptible to ARTIs, had a history of ARTIs, or were suffering from chronic rhinosinusitis during a symptomatic
episode of the disease, chronic obstructive disease of the respiratory tract, or subacute sinusitis or, in one study, were children attending day care centres.

Outcomes assessed in the review
The outcomes assessed were the number of ARTIs during the study period, the total number of ARTIs during the follow-up period, or the monthly ARTI data.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The quality of the papers was assessed according to the instrument of Jadad et al. (see Other Publications of Related Interest). The authors do not state who performed the quality assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

Data were abstracted on the number of ARTIs during the study period; if these were unavailable, then data were abstracted on the total number of ARTIs during the follow-up period, or on the monthly ARTIs. The authors state that they preferred databases with the number of ARTIs from trials they had participated in or reconstructed databases from published data. If this was not possible, data were extracted on the mean ARTI (plus or minus the standard deviation, SD); failing this, the percentage of patients suffering certain frequencies of ARTIs (e.g. the number of patients without infection), the raw total number of infections per group, and the clinical scores or other measures (e.g. days suffering from a purulent rhinorrhea) were used. Data were also extracted on the participants' ages and dose schedules.

Methods of synthesis
How were the studies combined?
The data were combined in a meta-analysis. The weighted mean difference between the intervention and placebo groups was calculated and expressed as a percentage, using a fixed-effect model. These weighted mean differences were combined to obtain the global effect of immunostimulants.

Publication bias was assessed with a Funnel plot.
For trials with negative results, the power of the test (Student's t-test or the adjusted chi-squared test) was estimated with respect to the presence of a true difference between the immunostimulant and placebo groups in each individual trial.

Bayes factor and the corresponding reduction of null hypothesis were estimated for those trials with a Jadad score of greater than 3.

How were differences between studies investigated?
The chi-squared test was used to evaluate the homogeneity of the results.

Results of the review
A total of 27 RCTs were included in the review. There were 2 studies (n=396) of LW 50020, 9 studies (n=1,184) of OM-85 BV, 6 studies (n=1,597) of pidotimod, 4 studies (n=235) of RU41740, 2 studies (n=184) of Ribomunyl, and 4 studies (n=168) of thymomodulin. Only 16 studies (n=1,908) reporting the mean (plus or minus SD) and/or dispersion were analysed.

Four of the 5 RCTs with a Jadad score of greater than 3 showed a significant reduction of ARTIs in immunostimulant
groups. When only those trials reporting the mean plus or minus SDs and/or dispersion were included (n=16), the global weighted percentage effect of immunostimulants showed a change of -42.64% (95% confidence interval: -45.19, -40.08); the intervention group presented approximately 60% of the mean number of ARTIs in the placebo group.

Authors’ conclusions
Immunostimulants are an effective treatment for the prevention of ARTIs.

CRD commentary
The review question was clear. The study selection criteria were stated clearly, although later in the data extraction and presentation of results sections, it was unclear which studies were actually included in the analysis. The literature search was reasonably comprehensive, with the reviewers checking the Cochrane Acute Respiratory Infection Group for references, although the restriction of electronic searches to MEDLINE and EMBASE may have resulted in some studies being missed. Similarly, the authors state that only medications registered in Mexico were included in the search, which may have meant that those not registered in Mexico were missed. However, language restrictions were not applied, and the dates for the searches were unrestricted. The authors provided no information on the methodology of the review, validation and the data extraction processes.

The statistical tests employed seem to have been appropriate for the analysis carried out. There was ample graphical presentation of these tests and the results were provided. However, as noted already, preference was clearly given to some studies in the analysis, despite the original stated inclusion criteria; this resulted in only 16 of the original 27 included studies, or the 5 RCTs with Jadad scores of greater than 3, being included for global analysis.

The authors’ conclusions seem appropriate in the light of the findings of their meta-analysis, but since 11 studies originally to be included in the analysis were later excluded from the final global calculations owing to insufficient data, it is not possible to know how these would have altered the overall findings. Also, the methodological limitations noted by the review's authors (only 5 of the 27 trials scored more than 3 on the Jadad scale) would indicate that their conclusions should probably be more cautious. There is a possible conflict of interest in that one of the study’s authors was the medical manager for OM-85 BV in Mexico between 1995 and 2000, and the study was sponsored by Quimica Knoll de Mexico, BASF Pharma who market OM-85 BV in Mexico.

Implications of the review for practice and research
Practice: The authors state that the use of immunostimulants for the prevention of ARTIs should be limited to children with proven high susceptibility, or to overexposed children attending day care centres, in orphanages, or entering kindergarten or elementary school.

Research: The authors state that further high-quality RCTs are required to confirm the effect and the size of effect of each individual immunostimulant.

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Other publications of related interest

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.