Probiotics for preventing acute upper respiratory tract infections (Review)

Hao Q, Lu Z, Dong BR, Huang CQ, Wu T

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[Intervention Review]

Probiotics for preventing acute upper respiratory tract infections

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ABSTRACT

Background

Probiotics may improve a person's health by regulating their immune function. Some studies show that probiotic strains can prevent respiratory infections. However, no evidence of the benefits of probiotics for acute upper respiratory tract infections (URTIs) and related potential adverse effects has been published.

Objectives

To assess the effectiveness and safety of probiotics for preventing acute URTIs.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 2), which includes the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (Ovid) (1950 to May week 1, 2011), EMBASE (1974 to May 2011), Web of Science which includes Science Citation Index (from 1900 to May 2011) and Conference Proceedings Citation Index (from 1991 to May 2011), the Chinese Biomedical Literature Database, which includes the China Biological Medicine Database (from 1978 to May 2011), the Chinese Medicine Popular Science Literature Database (from 2000 to May 2011) and the Masters Degree Dissertation of Beijing Union Medical College Database (from 1981 to May 2011).

Selection criteria

Randomised controlled trials (RCTs) comparing probiotics with placebo to prevent acute URTIs.

Data collection and analysis

Two review authors independently assessed eligibility, quality of trials and extracted data.

Main results

We included 14 RCTs, although we could only extract available data to meta-analyse in 10 trials which involved 3451 participants. We found that probiotics were better than placebo when measuring the number of participants experiencing episodes of acute URTI: at least one episode: odds ratio (OR) 0.58; 95% confidence interval (CI) 0.36 to 0.92; at least three episodes: OR 0.53; 95% CI 0.36

to 0.80; rate ratio of episodes of acute URTI: rate ratio 0.88; 95% CI 0.81 to 0.96; and reduced antibiotic prescription rates for acute URTIs: OR 0.67; 95% CI 0.45 to 0.98. Probiotics and placebo were similar when measuring the mean duration (MD) of an episode of acute URTI: MD -0.29; 95% CI -3.71 to 3.13 and adverse events: OR 0.92; 95% CI 0.37 to 2.28. Side effects of probiotics were minor and gastrointestinal symptoms were the most common. We found that some subgroups had a high level of heterogeneity when conducting pooled analyses.

Authors' conclusions

Probiotics were better than placebo in reducing the number of participants experiencing episodes of acute URTIs, the rate ratio of episodes of acute URTI and reducing antibiotic use. This indicates that probiotics may be more beneficial than placebo for preventing acute URTIs. However, the results have some limitations and there were no data for older people.

PLAIN LANGUAGE SUMMARY

Probiotics (live micro-organisms) to prevent upper respiratory tract infections (for example, the common cold)

Acute upper respiratory tract infections (URTIs) include the common cold, inflammation of the trachea and larynx with symptoms including fever, cough, pain and headaches. Most acute URTIs are caused by viral infections and usually resolve after three to seven days. To reduce the course of the infection and make the person feel more comfortable, paracetamol, ibuprofen or aspirin and maintaining fluid intake are often recommended to reduce fever and ease pain and headaches. Antibiotics are prescribed if the illness becomes chronic and complications develop. Some live micro-organisms can confer a health benefit to the patient when administered in adequate amounts. Lactic acid bacteria and bifidobacteria are the most common types of probiotics. They are commonly consumed in fermented foods, such as yogurt and soy yogurt, or as dietary supplements.

We searched electronic databases and identified 14 randomised controlled trials, although we could only extract available data to pool from 10 trials which involved 3451 participants, including infants, children and adults aged around 40 years. The live micro-organisms intervention was found to be better than placebo in reducing the number of participants experiencing episodes of acute URTI and the rate ratio (calculated to compare the rate of events occurring at any given point in time) of episodes of acute URTI but the results in our review showed some limitations (for example, a high level of heterogeneity, few studies in some subgroups and no data for older people). Limited information from only three of the trials showed that live micro-organisms can reduce the prescription of antibiotics. Side effects of probiotics were minor and gastrointestinal symptoms were the most common.

The evidence is weak but our review shows a benefit in using probiotics to prevent acute URTIs.

BACKGROUND

Description of the condition

Acute upper respiratory tract infections (URTIs), which include the common cold, acute sinusitis, acute pharyngitis, acute laryngo-tracheobronchitis (croup), acute epiglottitis (supraglottitis), acute rhino sinusitis and acute otitis media (AOM), are a major cause of morbidity, especially in children and the elderly (Duijvestijn 2009; Kassel 2010; Liberati 2009). They are caused by a large variety of viruses and bacteria. Acute URTIs are the most common reason for people to seek medical care in the United States (Cherry 2003) and at least one billion colds occur there per year, with a frequency of two to six colds per person (Gwaltney 2002).

Acute URTIs are usually mild, viral infections with symptoms subsiding after a few days. They account for up to 75% of all antibiotic use in high-income countries (Fendrick 2001). Antibiotics are often misused in acute URTIs with viral aetiologies (Steinman 2003), despite the fact that the development of antibiotic-resistant bacteria is inevitable. Although the causes of antibiotic resistance are multifactorial (Tenover 1996), antibiotic overuse is a major contributor (Seppala 1997).

Description of the intervention

Probiotics, a Greek word meaning "for life", was first described by Kollath more than 50 years ago (Kollath 1953). Probiotics are

now defined as "live micro-organisms administered in adequate amounts which confer a beneficial physiological effect on the host" (Reid 2003). Although the underlying mechanisms are still unclear, the application of probiotics shows some promising results and trends with respect to immune modulations. Limited evidence from systematic reviews shows that probiotics are beneficial for treating infectious diarrhoea (Allen 2010), preventing antibiotic-associated diarrhoea (D'souza 2002) and treating vaginal infections in pregnancy (Othman 2010).

How the intervention might work

There are a number of possible means by which probiotics may improve health, one of which is the immunomodulation of local immunity (by maintaining gut wall integrity) and systemic immunity (by enhancing non-specific and specific arms of the immune system). For example:

1. Probiotics and the innate immune function.
   - Enhances phagocytic capacity of peripheral blood leucocytes (polymorphonuclear and monocytes).
   - Improves phagocytic activity.
   - Granulocytes show higher increases in phagocytic cell function compared with monocytes (Donnet 1999; Schiffrin 1995; Sheih 2001).

There are significant increases in the expression of receptors (CR1, CR3, FccRI and FcaR) (Pelto 1998) involved in phagocytosis (the cellular process of engulfing and ingesting solid particles, such as bacteria by the cell membrane), the phagocytic index, oxidative burst (also known as respiratory burst, is the rapid release of reactive oxygen species from some cells) (Donnet 1999), and microbicidal capacity in neutrophils (Arunachalam 2000). Natural killer (NK) cell (a type of cytotoxic cell that constitutes an important part of the innate immune system) activity is also markedly improved, and there are increases in the percentage of NK cells in the peripheral blood (Drakes 2004).

2. Probiotics and acquired immunity.
   - Significantly higher specific IgG, IgA and IgM immunoglobulins (Link 1994; Majamaa 1995).

3. Probiotics and local immunity.
   - Enhances gut barrier function and improves the local immune response (Perdigon 1995).
   - Increases the production of cytokines (for example, IL-1, IL-2, IL-6, IL-10, IL-12, IL-18, TNF-α, interferon-α) (Gill 1998; Meydani 2000).

Why it is important to do this review

More than a century ago, Nobel Prize winner Elie Metchnikoff conducted a series of studies showing that ingesting microbes that produce lactic acid by fermentation improves ailments such as digestive and respiratory tract disorders. The first evidence that probiotic strains could prevent respiratory tract infections was shown when mice were successfully protected against influenza through the administration of *Bifidobacterium breve* (*B. breve*) YIT4064 augmented anti-influenza IgG (Yasui 1999). Soon after, Finnish researchers conducted studies amongst children in daycare centres who were given milk containing *Lactobacillus rhamnosus (L. rhamnosus)* GG (ATCC 53103) during winter (Hatakka 2001). However, one study (Hatakka 2007) showed that the probiotics did not have any effect on upper respiratory infections after the intervention. With the increasing consumption of probiotics, we feel there is a need to fully understand the effect of probiotics on acute URTIs and their potential adverse effects in humans.

OBJECTIVES

To assess the effectiveness and safety of probiotics (any specified strain or dose), compared with placebo, in the prevention of acute URTIs in people of all ages, at risk of acute URTIs.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) to prevent acute URTIs. We excluded all cross-over studies due to potential residual treatment effects.

Types of participants

Children and adults of all ages. We excluded those who had been vaccinated against influenza or other acute URTIs within the last 12 months, had taken immune-stimulating medications, undertaken abnormal physical exercise, or had known congenital or acquired immune defects or allergies.

Types of interventions

Any probiotic (single or mixture of strains, any dosage regimen and any route of administration) for more than seven days, compared to placebo or no treatment.

Types of outcome measures

Primary outcomes

1. The number of acute episodes of URTIs, and the mean duration of an episode (or the time without an acute URTI). Cases of acute URTIs should be confirmed by doctors, or have specific symptoms, such as nasal (for example, runny nose, blocked nose, nose blowing, yellow secretions, bloody secretions, sneezing), pharyngeal (for example, scratchy throat, sore throat, hoarseness), tonsillitis or pharyngitis (for example, pain on swallowing, sore throat), laryngitis (for example, hoarseness), and bronchial symptoms (for example, cough, secretions), as well as headache, myalgia, red eyes (conjunctivitis) and fever (oral temperature > 37.7 °C or rectal temperature > 38 °C).

Secondary outcomes

1. Time off from childcare centre, school or work.
2. Prescriptions (including antibiotics and herbal medications) for acute URTIs.
3. Complicated episodes of acute lower respiratory tract infections (LRTIs) (for example, bronchiolitis and pneumonia).
4. Side effects or adverse events.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2011, Issue 2, part of *The Cochrane Library,* www.thecochranelibrary.com (accessed 18 May 2011), which includes the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (Ovid) (1950 to May week 1, 2011), EMBASE (1974 to May 2011), Web of Science which includes Science Citation Index (from 1900 to May 2011) and Conference Proceedings Citation Index (from 1991 to May 2011), the Chinese Biomedical Literature Database, which includes the China Biological Medicine Database (from 1978 to May 2011), the Chinese Medicine Popular Science Literature Database (from 2000 to May 2011) and the Masters Degree Dissertation of Beijing Union Medical College Database (from 1981 to May 2011).

We used the following search strategy to search MEDLINE and CENTRAL. We combined the MEDLINE search strategy with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2009). We adapted the search strategy to search EMBASE (see Appendix 1); Web of Science (see Appendix 2) and the Chinese Biomedical Literature Database (see Figure 1).

Figure 1. Chinese Biomedical Literature Database search strategy.

(全部字段:上呼吸道感染 or 感冒 or 急性咽炎 or 急性扁桃体炎 or 急性中耳炎) and (全部字段:益生菌 or 益生元)

MEDLINE (Ovid)

1 Common Cold/
2 common cold*.tw.
3 exp Sinusitis/
4 sinusit*.tw.
5 Pharyngitis/
6 pharyngit*.tw.
7 exp Laryngitis/
8 laryngit*.tw.
9 laryngotracheobronchit*.tw.
10 Rhinitis/
11 rhinit*.tw.
12 Tonsillitis/
13 tonsillit*.tw.
14 peritonsillar abscess*.tw.
15 Croup/
16 croup*.tw.
17 Epiglottitis/
18 epiglottit*.tw.
19 supraglottit*.tw.
20 rhinosinusit*.tw.
21 exp Otitis Media/
22 (otitis media or aom or ome).tw.
23 (inner ear* adj2 (inflamm* or infection*)).tw.
24 Respiratory Tract Infections/
25 respiratory tract infection*.tw.
26 upper respiratory infection*.tw.
27 urti.tw.
28 (acute infection* adj5 respirat*).tw.
29 or/1-28
30 Probiotics/
31 probiotic*.tw.
32 exp Lactobacillus/
33 lactobacill*.tw.

34 Bifidobacterium/
35 (bifido* or bifidu*).tw.
36 exp Lactococcus/
37 lactococc*.tw.
38 exp Saccharomyces/
39 saccharomyc*.tw.
40 Streptococcus thermophilus/
41 streptococcus thermophilus.tw.
42 Bacillus subtilis/
43 bacillus subtilis.tw.
44 exp Enterococcus/
45 enterococcus faec*.tw.
46 bulgarian bacillus.tw.
47 or/30-46
48 29 and 47

Searching other resources

We searched the reference sections of the review articles to identify studies missed by electronic searching. We also searched grey literature. We contacted the first author of the included trials and the manufacturers of probiotic agents and authors of conference literature for additional published or unpublished data. There were no language or publication restrictions in the searches.

Data collection and analysis

Selection of studies

Two review authors (QH, ZL) independently screened all studies by title and abstract. Studies using probiotic preparations containing other substances, such as vitamins and minerals, if also contained in the placebo, were included. We resolved disagreements by discussion and, when necessary, by consulting a third review author (BD). We discussed titles or abstracts not available in English with translators.

Data extraction and management

Two review authors (QH, ZL) independently extracted data from the included studies using the Acute Respiratory Infection (ARI) Group's data extraction form. We extracted the following data:

- author;
- year of publication;
- language;
- their institutions;
- participants (age range, gender, inclusion and exclusion criteria);
- methodological design (methods of randomisation, allocation concealment, blinding, loss to follow up and intention-to-treat analysis (ITT));
- details of intervention (single or mixture of strains, dosage regimen, route of administration, duration, comparison treatment;
- results (that is, incidence of acute URTIs, reasons for withdrawal, measures of compliance and adverse effects, etc.).

Disagreements were resolved by discussion and, when necessary, by consulting a third review author (BD). We contacted trial authors and pharmaceutical companies to clarify unclear data and to request additional information on methodological quality.

Assessment of risk of bias in included studies

Two review authors (QH, ZL) independently assessed the methodological quality as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and as described in Wu 2007.

- Random sequence generation

Low risk of bias: adequate generation of allocation sequence (for example, computer-generated random numbers, table of random numbers, or similar).
High risk of bias: inadequate generation of allocation sequence (case record number, date of birth, day, month, or year of admission (Higgins 2011) or allocation by judgement of the clinician, the participant, laboratory test or a series of tests, availability of the intervention).
Unclear risk of bias: the generation of the allocation sequence was unclear.

- Allocation concealment

Low risk of bias: adequate concealment of allocation (for example, central independent unit, non-translucent sealed envelopes, or similar).
High risk of bias: inadequate concealment of allocation (any procedure which is transparent before allocation (for example, alternation, the use of case record numbers, dates of birth, or open table of random numbers or similar).
Unclear risk of bias: unclear concealment of allocation (for example, only specifying that non-translucent sealed envelopes were used or not reporting any concealment approach) or inadequate.

- Blinding: blinding of participants and personnel and blinding of outcome assessment

Low risk of bias: masking of both the participants and results assessor was considered a low risk of performance and/or detection bias (for example, identical placebo tablets or similar). Blinding was not considered necessary for mortality or other outcomes which were not influenced by blinding.
High risk of bias: not used or non-blinding for detection of outcomes includes quality of life (QOL) (for example, not performed or tablets versus fluids or similar).
Unclear risk of bias: insufficient information provided to judge 'yes' or 'no'; single blinding of the results assessor and blinding

performed on the participants but not the results assessor was considered unclear.

- Incomplete outcome data: assessment for potential bias of exclusions and attrition

Low risk of bias: trials had no missing outcome data or few exclusions, attrition is noted and an ITT analysis is possible.
High risk of bias: there are wide differences in exclusions between intervention group and control group or the rate of exclusion and/or attrition is higher than 15%, whatever ITT analysis is used.
Unclear risk of bias: the rate of exclusions and/or attrition is higher than 10%, whatever ITT analysis is used.
Low risk of bias - all quality criteria met.
Unclear risk of bias - one or more of the quality criteria only partly met.
High risk of bias - one or more criteria not met.

Measures of treatment effect

We analysed data using Review Manager (RevMan 2011). We were only able to perform limited pooled analyses. We used a random-effects model for pooled analysis of both heterogeneous data and homogeneous data. We expressed results as risk ratios (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes, both with 95% confidence intervals (CI). We calculated the rate ratio of episode rates (events per person/year) of acute URTIs between two groups and the standard error (SE) of rate ratio according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We used the generic inverse variance data to pool these studies.

Unit of analysis issues

Cross-over trials were not anticipated in this review. We took care to avoid double-counting of participants where multiple interventions were used in the same trial. We analysed the outcome of different stages in a study as different studies for the intervention.

Dealing with missing data

We sought missing data from the trial authors. We analysed the outcome measures on an ITT population (i.e. we considered participants who dropped out of a study along with those who continued).

Assessment of heterogeneity

We carried out tests for heterogeneity using the Chi^2 test with significance being set at P value < 0.1. We used the I^2 statistic to estimate the total variation across studies. An I^2 statistic < 25% is considered to be a low level of heterogeneity, 25% to 50% a moderate level and > 50% a high level (Higgins 2003).

Assessment of reporting biases

It is acknowledged that funnel plots are difficult to detect with small numbers of studies (i.e. less than 10) in systematic reviews. We did not assess the presence of publication bias in this review, but if more studies are included in future updates, a funnel plot will be used to assess the presence of publication bias.

Data synthesis

Regardless of heterogeneity between the pooled studies, we used a random-effects model to synthesise all data.

Subgroup analysis and investigation of heterogeneity

We analysed subgroups according to the different ages of participants in some outcomes of the review.

Sensitivity analysis

We did not perform a sensitivity analysis since only a few studies were included in each subgroup.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search

We retrieved 711 records from MEDLINE (174 records), Embase.com (224 records), CENTRAL (120 records), Web of Science (193 records), Chinese Biomedical Literature Database (four records) in our electronic literature searches. We removed duplicates and were left with 559 records.

Included studies

We identified 27 full texts of clinical trials and included 14 of these trials in this review. Out of the 14 included RCTs, we extracted data to synthesise from 10 trials which we then pooled.

Design

All included RCTs used a parallel design. Two of them were two-stage studies (Kekkonen 2007; Rautava 2009) and the remainder were single-stage studies (Berggren 2010; Caceres 2010; Gleeson 2010; Hatakka 2007; Hojsak 2010a; Hojsak 2010b; Makino 2010a; Merenstein 2010; Rio 2002; Sanz 2006; Vrese 2005; West 2011).

Participants

These trials focused on adults aged about 40 years (Berggren 2010; Kekkonen 2007; Vrese 2005), old people (Makino 2010a), infants (Hatakka 2007; Rautava 2009; Rio 2002) and children (Hojsak 2010a; Hojsak 2010b; Merenstein 2010; Sanz 2006). The trials were performed in Finland (Hatakka 2007; Kekkonen 2007; Rautava 2009), Spain (Sanz 2006), Sweden (Berggren 2010), United States (Merenstein 2010), Croatia (Hojsak 2010a; Hojsak 2010b), Chile (Caceres 2010), Japan (Makino 2010a) and Australia (West 2011). It was not clear in which countries the other two studies were conducted (Gleeson 2010; Rio 2002; Vrese 2005). Baseline data were stated and the comparability was analysed in all trials except one (Rio 2002).

Interventions

The studies involved different types of probiotics including *Lactobacillus plantarum (L. plantarum)*, *Lactobacillus rhamnosus (L. rhamnosus) GG or HN001*, *Bifidobacterium subsp. latis (B. latis)* breve 99, Lactoferrin, *Lactobacillus casei (L. casei)*, *Lactobacillus gasseri PA* (*L. gasseri PA)* 16/8, *Lactobacillus plantarum* HEAL 9 and *Lactobacillus paracasei* 8700:2, *Bifidobacterium longum* (*B. longum*) SP 07/3, *Bifidobacterium bifidum* (*B. bifidum*) MF 20/5, *Propionibacterium freudenreichii* (*P. freudenreichii)* ssp shermain JS, *OLL1073R-1* and *S. thermophilus OLS3059, Lactobacillus fermentum VRI-003*, usually compared with placebo without these probiotics.

Outcome measures

Different outcome measures were reported in these studies. Most trials reported the number of acute URTIs and duration of acute URTI episodes. The main outcome measures also included symptoms for unrelated diseases and infections. Four trials reported antibiotic use (Hatakka 2007; Hojsak 2010a; Hojsak 2010b; Rautava 2009). Three studies (Berggren 2010; Merenstein 2010; Rautava 2009) reported side effects including vomiting, flatulence and increased bowel irritability (pain, loose stools etc.) None of the trials assessed time off from childcare centres, school or work due to acute URTIs, or complications leading to episodes of acute LRTIs. One study (Hojsak 2010a) reported the number of days absent from daycare centres due to infections but the study did not separate URTIs from infections.
See the Characteristics of included studies table for more details.

Excluded studies

We excluded 13 trials for the reasons documented in the Characteristics of excluded studies table.

Risk of bias in included studies

See the 'Risk of bias' table for more details. The overall risk of bias is presented graphically in Figure 2 and summarised in Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

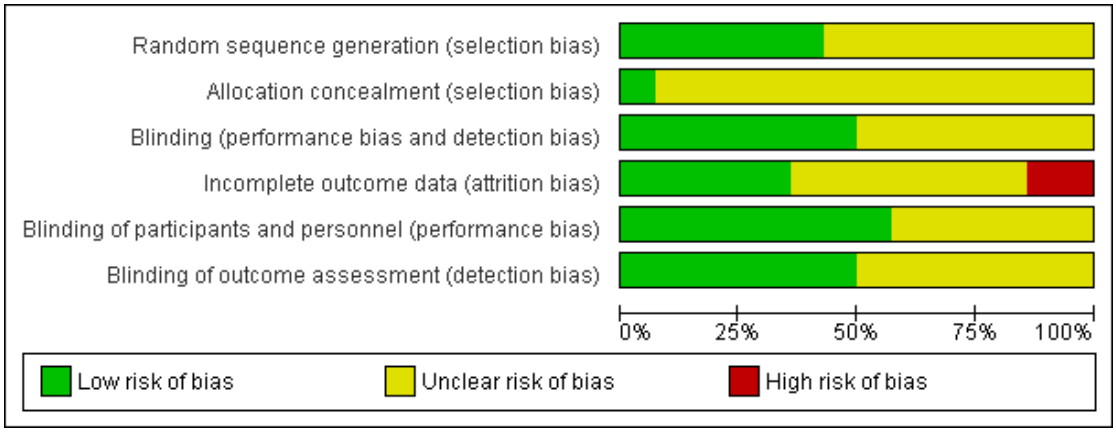
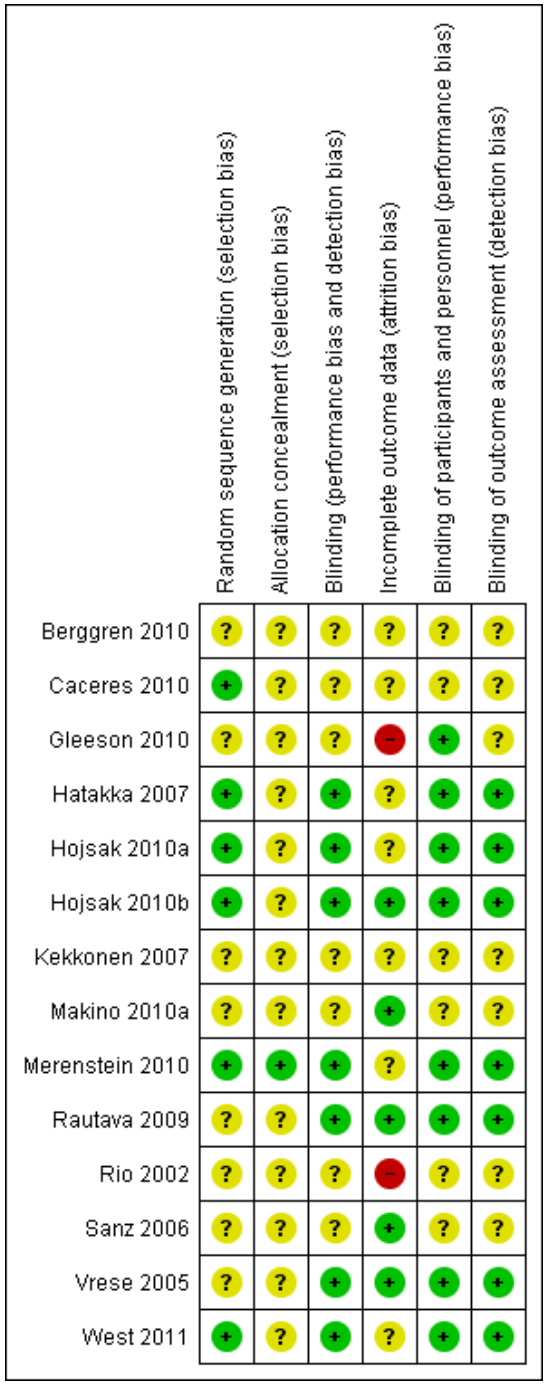


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Six trials clearly described adequate sequence generation methods (Caceres 2010; Hatakka 2007; Hojsak 2010a; Hojsak 2010b; Merenstein 2010; West 2011). The remaining eight trials did not describe the methods of randomised sequence generation. One trial (Merenstein 2010) described adequate allocation concealment. Although we approached the trial authors for further clarification, we did not receive any replies.

Blinding

Twelve trials reported double-blinding (Berggren 2010; Caceres 2010; Gleeson 2010; Hatakka 2007; Hojsak 2010a; Hojsak 2010b; Kekkonen 2007; Merenstein 2010; Rautava 2009; Sanz 2006; Vrese 2005; West 2011) and seven trials described the detail of the blinding methods (Hatakka 2007; Hojsak 2010a; Hojsak 2010b; Merenstein 2010; Rautava 2009; Vrese 2005; West 2011). One trial did not document the type of blinding (Rio 2002).

Incomplete outcome data

All included trials provided sufficient information for the incomplete outcome data to be calculated or else described the withdrawal rate. Withdrawal rates varied from 3.7% (Hojsak 2010b; Rautava 2009) to 42% (Rio 2002). Five trials had a low risk of addressing incomplete outcome data bias (Hojsak 2010b; Makino 2010a; Rautava 2009; Sanz 2006; Vrese 2005); one study had a high risk of addressing incomplete outcome data bias (Rio 2002) and the other eight studies had a moderate risk of this bias (Berggren 2010; Caceres 2010; Gleeson 2010; Hatakka 2007; Hojsak 2010a; Kekkonen 2007; Merenstein 2010; West 2011).

Selective reporting

We do not have access to the protocols of the included studies, so there was not enough information to assess selective reporting bias.

Other potential sources of bias

Some included studies had small sample sizes and this might have lead to other potential sources of bias.

Effects of interventions

Fourteen trials with a total of 3451 participants were included in the review. We analysed all outcome measures based on an ITT population (that is, all of the participants who dropped out of the study were analysed according to their original group, regardless of whether or not they completed or received that treatment).

Intention-to-treat (ITT) analysis

Primary outcome measures

Number of participants who experienced episodes of acute upper respiratory tract infections (URTIs)

Six studies (Berggren 2010; Hojsak 2010a; Hojsak 2010b; Kekkonen 2007; Rautava 2009; Sanz 2006) reported participants who experienced episodes of acute URTIs. There were 940 participants in the probiotics group and 896 participants in the placebo group. All of them reported participants who experienced at least one episode of acute URTI and three trials (Berggren 2010; Rautava 2009; Sanz 2006) reported participants who experienced at least three episodes of acute URTI. Pooled analyses showed that the number of participants who experienced acute URTI episodes was statistically significant and the 95% confidence interval (CI) did not cross 1.0 (at least one episode: OR 0.58; 95% CI 0.36 to 0.92; at least three episodes: odds ratio (OR) 0.53; 95% CI 0.36 to 0.80) (Analysis 1.1). No significance was found on testing for heterogeneity in at least three episode subgroups (Chi^2 test 0.52; df = 2, P = 0.77; I^2 statistic = 0%). However, in at least one episode subgroup, the level of heterogeneity between these studies was substantial (Chi^2 test 16.15; df = 5, P = 0.006; I^2 statistic = 69%). Although this outcome indicates that the number of participants who experienced episodes of URTIs was statistically significantly lower in the probiotics group than the placebo group, the substantial heterogeneity must be considered when we use this outcome in the future.

The rate ratio of episodes of acute URTI

Four trials (Berggren 2010; Caceres 2010; Merenstein 2010; Rio 2002) reported the total number of episodes of acute URTI or the rate of acute URTIs. In order to perform group comparisons, we calculated the rate ratio of episode rates (events per person/year) of acute URTIs between probiotics and control groups and the standard error (SE) of rate ratio according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). There were 523 participants in the probiotics group and 533 participants in the placebo group. Pooled analyses showed that across these studies, the episode rates of acute URTIs were statistically significant and the 95% CI did not cross 1.0 (rate ratio (RR) 0.88; 95% CI 0.81 to 0.96) (Analysis 1.3). The level of heterogeneity between these studies was moderate (Chi^2 test 5.37; df = 3, P = 0.15; I^2 statistic = 44%). Although this outcome indicates that probiotics may significantly decrease the episode rate of acute URTIs, the

level of heterogeneity must be considered when we use this outcome in the future.

The mean duration of an episode of acute URTI

Two trials reported the mean duration of an episode of acute URTI (Kekkonen 2007; Vrese 2005). One study consisted of two stages (Kekkonen 2007). In the review we only use the three-month training period stage and in the study conducted among marathon runners; the results show that the placebo was better than probiotics in the mean duration of an episode of URTI (mean difference (MD) 1.60; 95% CI -0.34 to 3.54) (Analysis 1.2.1). However, in the other study conducted among a general healthy population (Vrese 2005), the results show that the probiotics intervention was better (MD -1.90; 95% CI -2.04 to -1.76) (Analysis 1.2.2). Pooled analyses showed that the mean duration of an episode of acute URTI after treatment was not statistically significant (MD -0.29; 95% CI -3.71 to 3.13). The level of heterogeneity between these studies was high (Chi^2 test 12.43; df = 1, P < 0.0001; I^2 statistic = 92%).

There were two other trials (Gleeson 2010; West 2011) conducted among athletes. Participants in one study (Gleeson 2010) were trained regularly (predominantly endurance-based activities such as running, cycling, swimming, triathlon, team games and racquet sports). They ranged from recreationally-active to Olympic triathletes. In the other trial (West 2011) were competitive cyclists. However, in the two studies, there were no available data to extract in order to conducted a meta-analysis. One study (Gleeson 2010) reported that the URTI-symptom incidence was significantly lower in the probiotic group than in the placebo group. The other study (West 2011) reported that the effects of probiotic supplementation on upper respiratory tract illness load were unclear. Although this outcome indicates that the mean duration of an episode of acute URTI was not statistically significant between the probiotic and placebo groups, substantial heterogeneity and high-intensity exercise training may affect the effectiveness of the probiotics and must be considered when we use this outcome in the future.

Secondary outcome measures

Prescribed antibiotics for acute URTIs

Three studies reported the prescription of antibiotics for acute URTIs (Hojsak 2010a; Hojsak 2010b; Rautava 2009). One study (Rautava 2009) was a two-stage study reporting the number of participants using antibiotics. Pooled analyses showed that the number of participants using antibiotics were statistically significant and the 95% CI did not span 1.0 (OR 0.67; 95% CI 0.45 to 0.98) (Analysis 2.1). No significance was found on testing for heterogeneity in this subgroup (Chi^2 test 0.87; df = 2, P = 0.65; I^2 statistic = 0%). This indicates that the number of participants using antibiotics and the infections requiring antibiotic prescriptions were statistically significantly lower in the probiotics treatment group than in the placebo group.

Side effects or adverse events associated with the intervention

Most included studies reported that side effects or adverse events of the intervention were minor. One study described the main adverse effects as gastrointestinal symptoms such as vomiting, flatulence and increased irritability (Rautava 2009). The probiotics used in the study were *Lactobacillus rhamnosus* (*L. rhamnosus)* and *Bifidobacterium lactis* (*B. lactis*) Bb-12. Two studies (Berggren 2010; Merenstein 2010) reported side effects including bowel pain, loose stools, flatulence, nausea etc. Pooled analyses showed that the side effects following treatment were not statistically significantly different between the probiotics group and the placebo group (OR 0.92; 95% CI 0.37 to 2.28) (Analysis 3.1).

Time off from childcare centre, school or work

None of the included trials reported time off from childcare centres, school or work for acute URTIs. No data were available for this outcome. However, if data are available in future, these will be included when the review is updated.

Lower respiratory tract infection (LRTI) complications from acute URTIs

None of the included trials reported on acute LRTI complications from acute URTIs. If data are available in future, this outcome will be included when the review is updated.

Per-protocol (PP) analysis

We also conducted a per-protocol (PP) analysis and found that it did not change the inference of the ITT analysis, see Analysis 4.1, Analysis 4.2, Analysis 4.3, Analysis 5.1 and Analysis 6.1.

DISCUSSION

Summary of main results

The results for the included outcomes were unsatisfactory and susceptible to bias due to the fact that some of them were extracted from only one or two studies, and in some subgroups the level of heterogeneity between pooled studies was substantial. In addition, there were no synthesised data for older people in the review. Some studies had small sample sizes and the quality of the methods of these studies was not very good. Furthermore, some studies did

not assess the most important outcomes defined in this review as the main outcome in their original studies.

Overall completeness and applicability of evidence

Probiotics for acute upper respiratory tract infections (URTIs) in older people

Infections often occur in older people as the immune system weakens with age (Valente 2009). As such, it is very important to compare the treatment effect between older people. However, all the studies included in this review consisted of infants, children and adults (aged about 40 years). Until now, only three studies (Guillemard 2010; Makino 2010a; Turchet 2003) have been found comparing probiotics to placebo in older adults.

One study (Turchet 2003) is a unicentric, randomised, stratified, open pilot study, where 360 community residents over 60 years of age were randomised to receive either (a) one 100 ml bottle of Actimel (a milk fermented with yogurt cultures and *Lactobacillus casei* (*L. casei*) DN-114 001, containing 10^8 CFU/ml *L. casei* DN-114 001) twice daily for three weeks, or (b) they were in the control group. The study found no difference in the incidence of winter infections between groups. However, they found that the duration of all pathologies and maximal temperature was significantly lower in the treatment group than in the control group. The other study (Guillemard 2010) was also a multicentric, double-blind controlled trial, involving 1072 volunteers (median age 76 years) randomised for consumption of either probiotic strain *L. casei* DN-114 001 or control for three months. The probiotic group was associated with a decreased duration of common infectious diseases in comparison to the control group, especially for URTIs. In the Criteria for considering studies for this review, we only included participants who were not vaccinated against influenza or other acute URTIs within the last 12 months; 82% of participants in one study (Turchet 2003) had been vaccinated against influenza three months before the study. In addition, the study did not separate acute URTIs from other winter infections. The other study (Guillemard 2010) included participants vaccinated against the influenza virus at at least 14 days. Therefore we decided to exclude these two studies.

One included trial contains reports from two studies: the Funagata study and the Arita study (Makino 2010a). The Arita study was not a randomised controlled trial (RCT), so we excluded it (Makino 2010b). However, the Funagata study had no available data to extract to conduct a meta-analysis. The study reported that the risk of catching the common cold or influenza virus infection was about 3.4 times lower in the probiotic group than in the placebo group.

Clinical interpretation of the data

The outcomes of the analysis show that probiotics were better than placebo in terms of the number of participants who experienced episodes of URTIs, the rate ratio of episodes of acute URTIs and antibiotics used. This was also true for the mean duration of an episode of acute URTI, where there was no statistically significant difference observed between the treatment and control groups. The primary outcome of mean duration of an episode of acute URTI was based only on one study in each subgroup. In addition to this, there were different kinds of probiotics and follow-up periods used in the studies so that heterogeneity cannot be avoided in some outcomes. We need to remember that there were no data for older people in our review findings. Probiotics were safe and adverse effects were minor according to the included studies. The major side effect of probiotics was gastrointestinal symptoms such as vomiting, flatulence and increased irritability. The limited results showed that probiotic therapy may provide more benefit than placebo in terms of infections, the episode rate of acute URTIs and antibiotics used. However, the results did not show any benefit in terms of duration of episodes of acute URTI.

Quality of the evidence

Limitations of the studies included in this review

Allocation concealment was only described in one included study (Merenstein 2010). Double-blinding was reported in nine studies and the details of the blinding methods were reported in six of them. However, one trial did not document the type of blinding and two studies did not report the detail of the blinding. All of this could potentially have biased the results in favour of treatment (Figure 2).

Potential biases in the review process

Sample sizes

Some outcome measures in this review only come from two or three trials. Any real effects of probiotics may have remained undetected because of small sample sizes in some subgroups.

Heterogeneity

When pooled analyses were performed in some subgroups, high levels of heterogeneity were found in terms of the number of participants who experienced episodes of acute URTIs: at least one episode, rate ratio of episodes of acute URTIs and mean duration

of an episode of acute URTI. We analysed differences in the type of probiotics, patient selection, baseline values, bias, design and methods that could possibly explain the heterogeneity.

Heterogeneity did not appear to result from differences in methods used for the mean duration of an episode of acute URTI. These may be a consequence of the different types of probiotics and different participants included in pooled studies. In the subgroup of the mean number of episodes of acute URTIs, one study (Kekkonen 2007) included marathon runners and the other (Vrese 2005) included ordinary healthy adults. The types of probiotics were different among these studies (see the Characteristics of included studies table for more details).

Agreements and disagreements with other studies or reviews

A double-blind, placebo-controlled RCT, conducted in 18 municipal daycare centres, in similar socioeconomic areas in north, west and north-east Helsinki found that *Lactobacillus* GG milk may reduce the rate and severity of respiratory infections and antibiotic treatment among children in daycare centres (Hatakka 2001). The study did not separate acute URTIs from the whole respiratory tract and so we excluded this study. However, the result was similar to this review. Currently, we have not found any other studies which conflict with this review.

AUTHORS' CONCLUSIONS

Implications for practice

Current available evidence shows that probiotics are better than placebo in reducing the number of participants who experience episodes of acute upper respiratory tract infection (URTI), the rate ratio of episodes of acute URTI and reducing antibiotic use, although there were no data concerning older people in the review. However, the review indicates that probiotics may be more beneficial than placebo for preventing acute URTIs.

Implications for research

Future randomised controlled trials should consider:

1. a study design which incorporates adequate blinding and concealment of allocation sequence;

2. the assessment of common outcomes (for example, the number of episodes of acute URTI and the mean duration of an episode of acute URTI, should be primary outcome measures);

3. focus on older people or perform a subgroup analysis of older people; and

4. consider side effect outcomes: time off from childcare centre, school or work; acute lower respiratory tract infection complications; cost-effectiveness and quality of life.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Berggren 2010

Methods	Study design: a double-blind, placebo-controlled, randomised clinical study with 2 parallel arms Method of randomisation: not clearly stated Blinding: double-blind. Not clearly stated. The children may have been blinded Duration: between January 2007 and May 2007 Exclusions post-randomisation: 0 Losses to follow up: 43; 20 in probiotic bacteria group; 23 in placebo group
Participants	Country: Sweden Setting: Lund and Uppsala No. of participants: 318; 159 in probiotic bacteria group, 159 in placebo group Age: aged 18 to 65 Inclusion criteria: healthy volunteers Exclusion criteria: known intolerance or allergy to any ingredient included in the formulations, medically-treated allergy, current treatment for severe gastrointestinal disorders, pregnancy or lactation, vaccination against influenza within the last 12 months or smoking
Interventions	Treatment group: *Lactobacillus plantarum* HEAL 9 and *Lactobacillus paracasei* 8700:2 (1 × 9 10~9 CFU/day) for 12 weeks Control group: placebo: an identical-looking and tasting control product
Outcomes	1. Faecal recovery of probiotic bacteria 2. Adverse events 3. Incidence of common cold 4. Symptom scores 5. Cellular immune response following the ingestion of the study product
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind but no description of the details

Berggren 2010 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	40 participants lost to follow up and the analysis of the study was not based on the intention-to-treat population
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided

Caceres 2010

Methods	Study design: prospective, multi-centre, randomised, controlled, double-blind trial Method of randomisation: using a computer-generated random numbers table Blinding: double-blinding not clearly stated. The children may have been blinded Duration: 4 months of the cold season: June to September 2006 Exclusions post-randomisation: 0 Losses to follow up: 49 (33 in the probiotic bacteria group; 16 in the placebo group)
Participants	Country: Chile Setting: Santiago: 4 daycare centres No. of participants: 398 (203 in the probiotic bacteria group, 195 in the placebo group) Age: 1 to 5 Inclusion criteria: asymptomatic children of both sexes and attending day centres regularly Exclusion criteria: antibiotic treatment at the time of enrolment; unwillingness on the part of the parents to interrupt the intake of other probiotic-containing products, signs of current respiratory insuffiencey, immune deficiency, congenital malformations including heart disease, inborn errors of metabolism, cystic fibrosis, chronic enteropathies or malabsorption, diabetes mellitus, treatment with prokinetic drugs or with systemic or inhaled corticosteroids, children whose parents would not comply with the requirements of the study protocol or who had been participating in another clinical trial during the 4 weeks prior the beginning of this study
Interventions	Treatment group: milk-based product containing approximately 10-8 colony-forming units/ml of the probiotic strain (*L. rhamnosus* HN001) Control group: placebo (an identical-looking control product did not contain the probiotic)
Outcomes	Primary outcome: the number of episodes of ARI per child Secondary endpoints: 1. the number of days with respiratory illnesses 2. the number of days with antibiotic treatments 3. the number of days absence from the daycare centre due to respiratory illness
Notes	

Caceres 2010 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was carried out using a computer-generated random numbers table
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind but no description of the details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	49 participants lost to follow up and the analysis of the study was based on the intention-to-treat population
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided

Gleeson 2010

Methods	Study design: a prospective, randomised, controlled, double-blind trial Method of randomisation: not clearly stated Blinding: double-blinded. Not clearly stated whether participants were blinded Duration: 16 weeks of winter training Exclusions post-randomisation: 0 Losses to follow up: 26 (10 in the probiotic bacteria group; 16 in the placebo group)
Participants	Country: not clearly stated Setting: not clearly stated No. of participants: 84; 42 in the probiotic bacteria group, 42 in the placebo group Age: 18 to 55 Inclusion criteria: currently healthy, had been involved in endurance training for at least 2 years, engaged in at least 3 sessions and at least 3 hours of moderate to high-intensity training time per week Exclusion criteria: smoking or use of any medication, currently taking probiotic supplements, suffered from or had a history of cardiac, hepatic, renal, pulmonary, neurological, GI, haematological or psychiatric illness, objected to the prescription of diet

Gleeson 2010 (*Continued*)

Interventions	Treatment group: the probiotic drink contained a minimum of 6.5 × 10-9 live cells of *L. casei* Shirota in each pot, twice a day for 16 weeks Control group: placebo: identical in taste and colour to the probiotic but contained no *L. casei* Shirota, twice per day for 16 weeks
Outcomes	1. Training loads 2. Infection-symptom incidence 3. Severity and mean duration of URTI symptoms 4. Incidence of GI-discomfort symptoms 5. Plasma and saliva immunoglobulins 6. Blood leukocyte counts and lymphocyte subsets 7. Stimulated whole-blood-culture cytokine production
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind. Not clearly stated
Incomplete outcome data (attrition bias) All outcomes	High risk	31% of participants lost to follow up
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided

Hatakka 2007

Methods	Study design: a double-blind, placebo-controlled, randomised clinical study Method of randomisation: the study co-ordinator randomly allocated each child according to a computer-generated blocked randomisation list drawn up by the statistician. A block size of 4 was used, stratified according to gender, age and form of daycare Blinding: double-blind. The investigators, parents and children were all unaware of which child was in the treatment group until the statistical analysis was performed Duration: between September 2001 and April 2002 Exclusions post-randomisation: 0 Losses to follow up: 40: 20 in probiotic bacteria group; 20 in placebo group
Participants	Country: Finland Setting: primary healthcare centres and daycare centres and other areas No. of participants: 309; 155 in probiotic bacteria group, 154 in placebo group Age: otitis-prone children aged 10 months to 6 years. Probiotic bacteria group (2.4 (0.8 to 6.0); placebo group (2.4 (0.9 to 5.6)) Gender: not clearly stated Inclusion criteria: otitis-prone children (at least 4 episodes of AOM during the preceding 12 months, or at least 3 episodes during the preceding 6 months) aged 10 months to 6 years Exclusion criteria: children on regular medication, with chronic illnesses, Down's syndrome, lip or palatal cleft, otitis media with effusion, or who were scheduled for tympanostomy or adenoidectomy during the study were excluded. Those who had undergone tympanostomy or adenoidectomy during the preceding 6 months were also excluded, unless they had suffered at least 3 episodes of AOM since the operations
Interventions	Treatment group: gelatin capsule containing a combination of probiotic bacteria (*L. rhamnosus* GG, ATCC 53103; *L. rhamnosus* LC 705; *Bifidobacterium breve* 99; *propionibacterium freudenreichii* ssp shermanii JS, Valio Ltd, Helsinki, Finland) 8 to 9×10^9 CFU/capsule of each strain Control group: placebo: an identical-looking placebo capsule containing cellulose microcrystalline Length of follow up: 6 months
Outcomes	Primary outcome: the occurrence and duration of AOM episodes Secondary endpoints: 1. the frequency of pathogen carriage 2. the occurrence of recurrent URI 3. the number of antimicrobial treatments
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A computer-generated blocked randomisation list drawn up by the statistician
Allocation concealment (selection bias)	Unclear risk	No information provided

Hatakka 2007 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	The investigators, parents and children were all unaware of which child was in the treatment group until the statistical analysis was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	40 participants lost to follow up and the analysis of the study was based on the intention-to-treat population
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants were all unaware of which child was in the treatment group until the statistical analysis was performed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigators were all unaware of which child was in the treatment group until the statistical analysis was performed

Hojsak 2010a

Methods	Study design: a double-blind, placebo-controlled, randomised clinical study Method of randomisation: randomisation procedure performed with computer-generated numbers Blinding: double-blind. Patient, provider and assessor were blinded Duration: during the 4-month intervention period (from 19 November 2007 to 20 February 2008) Exclusions post-randomisation: 0 Losses to follow up: 27: 12 in the probiotic bacteria group; 15 in the placebo group
Participants	Country: Croatia (Zegreb area) Setting: daycare centres No. of participants: 281; 139 in probiotic bacteria group, 142 in placebo group Age: 13 to 86 months Inclusion criteria: those attending daycare centre and whose parents or legal guardians provided written informed consent Exclusion criteria: children with cow's milk allergy (probiotics were given in a fermented cow's milk product); those who were receiving probiotic and/or prebiotic products prior to or at the time of enrolment; those who had a neoplasm, other chronic severe illness, or immunodeficency; and children who disliked fermented milk products
Interventions	Treatment group: *Lactobacillus rhamnosus* strain GG (LGG strain from Valio), was administered in 100 ml of a fermented milk product at a dose of 10-9 colony-forming units (CFU) Control group: the same post-pasteurised fermented milk product (100 ml) without LGG Length of follow up: 3-month period

Hojsak 2010a (*Continued*)

Outcomes	Primary outcome: 1. number of children with gastrointestinal infections 2. number of children with respiratory tract infections Secondary endpoints: 1. number of children with vomiting episodes and diarrhoeal episodes 2. number of gastrointestinal infections lasting longer than 2 days 3. number of children with upper and lower respiratory tract infection 4. number of respiratory tract infections lasting longer than 3 days 5. total number of days with respiratory and gastrointestinal symptoms 6. number of days absent from daycare centre due to infections
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation procedure performed with computer-generated numbers
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: patient, provider and assessor were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	27 participants lost to follow up and the analysis of the study was based on the intention-to-treat population
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The assessors were blinded

Hojsak 2010b

Methods	Study design: a double-blind, placebo-controlled, randomised clinical study Method of randomisation: randomisation procedure performed with computer-generated numbers Blinding: double-blind. Patient, provider and assessor were blinded Duration: from November 2007 to May 2008 Exclusions post-randomisation: 0 Losses to follow up: 28: 16 in probiotic bacteria group; 12 in placebo group
Participants	Country: Zegreb, Croatia Setting: hospitalised at the paediatric department No. of participants: 742; 376 in the probiotic bacteria group, 366 in the placebo group Age: older than 12 months Inclusion criteria: all patients who were older than 12 months and hospitalised at the paediatric department Exclusion criteria: children with gastrointestinal and/or respiratory tract infections on admission, children with immunodeficency, cow milk allergy, neoplasm, chronic severe illnesses, or an anticipated hospital stay of 3 days; children who had received probiotic and/or prebiotic products before enrolment (7 days before hospitalisation); and children who disliked fermented milk products
Interventions	Treatment group: *Lactobacillus rhamnosus* strain GG (LGG strain (Valio Ltd, Helsinki, Finland)),was administered in 100 ml of a fermented milk product at a dose of 10~9 colony-forming units Control group: the same post-pasteurised fermented milk product (100 ml) without LGG Length of follow up: duration of the hospitalisation
Outcomes	Primary outcome: 1. gastrointestinal infections 2. respiratory tract infections Secondary endpoints: 1. number of vomiting episodes and diarrhoeal episodes 2. number of gastrointestinal infections lasting longer than 2 days 3. number of children with upper and lower respiratory tract infection 4. number of respiratory tract infections lasting longer than 3 days 5. duration of hospitalisation
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation procedure performed with computer-generated numbers
Allocation concealment (selection bias)	Unclear risk	No information provided

Hojsak 2010b (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: patient, provider and assessor were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	28 participants lost to follow up and the analysis of the study was based on the intention-to-treat population
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The assessor was blinded

Kekkonen 2007

Methods	Study design: randomised, double-blind, placebo-controlled, parallel-group intervention study Method of randomisation: not clearly stated Blinding: double-blind but no description of the details Duration: 3 months training period and 2 weeks after the marathon Exclusions post-randomisation: 0 Losses to follow up: 22: 9 in LGG group; 13 in placebo group
Participants	Country: Finland Setting: not clearly stated No. of participants: 141; 70 in LGG group; 71 in placebo group Age (years): LGG group (40 (22 to 58)); placebo group (40 (23 to 69)) Gender: 16 women, 125 men: LGG group (8 women, 62 men); placebo group (8 women, 63 men) Inclusion criteria: those who participated in the Helsinki city marathon. If they were healthy and not participating in any other study and their personal-best marathon time was less than 3 hours 45 minutes for women and less than 3 hours 30 minutes for men Exclusion criteria: those using antibiotics for 2 months or less before the study, acute gastrointestinal disorders 2 months before the study, gastrointestinal disease and related medication, pregnancy and lactation
Interventions	Treatment group: LGG was given in the form of a milk-based fruit drink containing LGG (ATTCC 53103) bacteria 3.0×10^8 colony-forming units (CFU)/ml (Valio research centre, Helsinki, Finland). The participants were asked to drink two 65 ml bottles of LGG or placebo drink per day for 3 months. The two LGG bottles provided a total of 4×10^{10} bacteria. The participants were allowed to take the study products as capsules if they wished. The LGG capsules contained 5.0×10^9 CFU/capsule. The participants were asked to take 2 capsules per day (total of 1×10^{10} LGG bacteria) Control group: placebo: drink was similar but without LGG bacteria and placebo capsules were otherwise similar but without LGG bacteria

Kekkonen 2007 (*Continued*)

	Length of follow up: 3 months training period and 2 weeks after the marathon
Outcomes	Mean outcome measure: 1. the number of healthy days 2. the number of URTIs and gastrointestinal-symptom episodes
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind but no description of the details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	22 participants lost to follow up and the analysis of the study was based on the intention-to-treat population
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided

Makino 2010a

Methods	Study design: randomised, placebo-controlled, parallel-group intervention study Method of randomisation: not clearly stated Blinding: not clearly stated Duration: 8-week: 13 March 2006 to 7 May 2005 Exclusions post-randomisation: 0 Losses to follow up: 3: 1 in probiotic group; 2 in placebo group
Participants	Country: Japan Setting: Yamagata Prefecture No. of participants: 60; 30 in probiotic bacteria group, 30 in placebo group Age: 69 to 80 years Inclusion criteria: residents of Funagata who were in good health with no previous history of relevant physical or psychiatric illness

Makino 2010a (*Continued*)

	Exclusion criteria: any recent history of virus infection, cancer or immunological disorders and abnormalities in haematological or biochemical serum parameters
Interventions	Treatment group: the cell counts of *L. bulgaricus* OLL1073R-1 and *S. thermophilus* OLS3059 in the yogurts were 2.0 to 3.5 × 10~8 colony-forming units/g and 6.3 to 8.8 × 10~8 colony-forming units/g, respectively Control group: milk was used as a reference food
Outcomes	1. Occurrence of common colds and influenza 2. Effects on immune parameters 3. Safety
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants lost to follow up
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided

Merenstein 2010

Methods	Study design: double-blind, placebo-controlled, randomised, patient-oriented trials Method of randomisation: randomisation scheme was generated using SAS software by data managers; study identification was generated and a number from 0 to 9 was assigned Blinding: double-blind. Patient, provider and assessor were blinded Duration: no information provided Exclusions post-randomisation: 0 Losses to follow up: 74: 22 in probiotic bacteria group; 52 in placebo group
Participants	Country: Washington, DC USA Setting: attending daycare centre/school 5 days a week No. of participants: 638; 314 in probiotics group; 324 in placebo group Age (years): between the age of 3 and 6 years Gender: 309 women, 329 men: probiotics group (157 women, 157 men); placebo group (152 women, 172 men) Inclusion criteria: healthy children between the age of 3 and 6 years attending daycare centre/school 5 days a week in Washington, DC area Exclusion criteria: taking any regular medicines at initiation of study, lactose intolerance, allergy to strawberry, inability of a parent to speak English or Spanish, active respiratory or gastrointestinal infection, or chronic disease or consuming other probiotic foods or supplements
Interventions	Treatment group: 'Actimel' contains the probiotic strain *L. casei* DN-114 001/CNCM I-1518 (also named *Lactobacillus paracasei subsp. paracasei* after the current nomenclature) combined with 2 cultures commonly used in yogurt, *Streptococcus thermophilus* and *Lactobacillus bulgaricus*. 1 bottle per day, at the end of shelf life met targets of 1 × 10-8 CFU/g of *L. casei* DN-114 001; symbiotic cultures, *S. thermophilus*, and *L. bulgaricus* were also present in the final product at levels 10 × 7 CFU/g Control group: a sweetened, flavoured non-fermented acidified dairy drink without the active components of the tested product: 1 bottle per day Length of follow up: 90 consecutive days
Outcomes	Primary outcome: 1. the change of behaviour because of illness as assessed by parents 2. the rate of CIDs Secondary endpoints: 1. absences from daycare or school because of illness 2. missed parental work 3. adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation scheme was generated using SAS software by data managers

Merenstein 2010 (*Continued*)

Allocation concealment (selection bias)	Low risk	Study identification was generated and a number from 0 to 9 was assigned
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: patient, provider and assessor were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	74 participants lost to follow up and the analysis of the study was based on the intention-to-treat population
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The assessor was blinded

Rautava 2009

Methods	Study design: randomised, double-blind, placebo-controlled trial Method of randomisation: random allocation was generated independently from the investigators by the manufacturer of the capsules Blinding: double-blind: patient, provider and assessor were blinded Duration: between September 2000 and May 2002 Exclusions post-randomisation: 13 Losses to follow up: 3: 2 in the probiotics bacteria group; 1 in the placebo group
Participants	Country: Finland Setting: Turku No. of participants: 81; 38 in probiotics bacteria group; 43 in placebo group Age: 0 to 2 months infants Gender: male 35: 16 in probiotics bacteria group; 19 in placebo group Inclusion criteria: need for infant formula before the age of 2 months Exclusion criteria: infants with chronic disease were excluded
Interventions	Treatment group: 1×10^{10} colony-forming units of both *Lactobacillus rhamnosus* and *Bifidobacterium lactis* Bb-12 Control group: placebo Length of follow up: 12 months after birth
Outcomes	1. The effect of probiotics on the incidence of early and recurrent infections 2. Adverse effects
Notes	
Risk of bias	

Rautava 2009 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: patient, provider and assessor were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 3 participants lost to follow up
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The assessor was blinded

Rio 2002

Methods	Study design: randomised, placebo-controlled trial Method of randomisation: not clearly stated Blinding: not clearly stated Duration: during autumn and winter, April to September, at least 90 days Exclusions post-randomisation: 0 Losses to follow up: 42: 28 in the probiotics bacteria group; 14 in the placebo group
Participants	Country: not clearly stated Setting: study was performed on an outpatient basis except when there were cases of pneumonia that necessitated hospitalisation No. of participants: 100; 50 in probiotics bacteria group; 50 in placebo group Age: between 6 and 24 months of age Gender: not clearly stated. Inclusion criteria: study was conducted in 100 children, between 6 and 24 months of age, selected according to the following schedule: anthropometrical children, clinically normal and healthy or malnourished Grade I or II depending on the parameter weight/height % according to the classification of Ariza Macias (18), without another medical condition diagnosed at baseline Exclusion criteria: none
Interventions	Treatment group: dietary supplement of *Lactobacillus acidophilus* and *Lactobacillus casei* 250 to 300 ml of fermented milk to a concentration of 10^7 to 10^8/ml Control group: an equivalent amount of fluid milk Length of follow up: at least 90 days

Rio 2002 (*Continued*)

Outcomes	1. Frequency and severity of respiratory diseases 2. Influence of nutritional status
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	42% of participants lost to follow up
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided

Sanz 2006

Methods	Study design: a cluster-randomised, double-blind, placebo-controlled, parallel-group intervention study Method of randomisation: not clearly stated Blinding: double-blind but no description of the details; the participants may have been blinded Duration: 20 weeks Exclusions post-randomisation: 0 Losses to follow up: 22: 16 in probiotics bacteria group; 6 in placebo group
Participants	Country: Spain Setting: infant schools in Barcelona No. of participants: 251; 142 in probiotics bacteria group; 109 in placebo group Age: 3 to 12 years Gender: 133 women, 118 men: probiotics bacteria group (88 women, 54 men); placebo group (45 women, 64 men) Inclusion criteria: sample included all children aged 3 to 12 years studying in selected schools

Sanz 2006 (*Continued*)

	Exclusion criteria: none
Interventions	Treatment group: 2 units daily Actimel (a milk fermented with *Lactobacillus casei* (DN-114 001) for 20 weeks Control group: during the same period, 2 units placebo daily Actimel Length of follow up: 20 weeks
Outcomes	1. Number of diseases 2. Duration in days of illness 3. Number of days without symptoms 4. Number of children with school absence due to illness 5. Immune response through measurement of IgA in saliva 6. Overall satisfaction with the nutritional intervention
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind but no description of the details; the participants may have been blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	8.7% of participants lost to follow up and the analysis of the study was based on the intention-to-treat population
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of the details, maybe the participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of the details.

Vrese 2005

Methods	Study design: randomised, double-blind, placebo-controlled, parallel-group intervention study Method of randomisation: not clearly stated Blinding: double-blind: patient and assessor were blinded Duration: 242 participants during a 3-month period (between January and May 2001); 237 participants during a 5.5-month period (between December 2001 and June 2002) Exclusions post-randomisation: 0 Losses to follow up: 25: 13 in probiotics bacteria group; 12 in placebo group
Participants	Country and setting: not clearly stated No. of participants: 479; 238 in probiotics bacteria group, 241 in placebo group Age: (average age, 38 ± 13): probiotics bacteria group (average age, 37 ± 12); placebo group (average age, 38 ± 14) Gender: male: 185: 86 in probiotics bacteria group; 99 in placebo group Inclusion criteria: 479 healthy women and men were included after physical examination Exclusion criteria: those laboratory parameters outside the normal range, known congenital or acquired immune defects, allergies and other chronic or acute diseases requiring treatment, alcohol or drug misuse or both, pregnancy or lactation, interfering dietary habits, or vaccination against influenza within the last 12 months were excluded
Interventions	Treatment group: 5×10^7 CFU of the spray dried probiotic bacteria with vitamins and minerals. (The probiotic strains used in this study were *L. gasseri* PA 16/8, *B. longum* SP 07/3, *B. bifidum* MF 20/5) Control group: just the vitamin mineral preparation Length of follow up: 8.5 months
Outcomes	1. All symptoms recorded daily by questionnaires 2. Duration and incidence of episodes 3. Flow cytometric analysis 4. Viral infections 5. Faecal lactobacilli and bifidobacteria
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Patient and assessor were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	5.2% of participants lost to follow up

Vrese 2005 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The assessors were blinded

West 2011

Methods	Study design: randomised, double-blind, placebo-controlled, parallel-group trial Method of randomisation: using a computer-generated list Blinding: double-blind: patients and the study team were blinded Duration: 11 weeks Exclusions post-randomisation: 0 Losses to follow up: 11 participants in the whole study
Participants	Country and setting: Canberra, Australia and its surrounding regions No. of participants: 99 participants Age: average age, 35 ± 10 years Inclusion criteria: participants not taking antibiotics or supplements/foods containing probiotics for at least 1 month prior to and during the study period. Participants were also required to have a maximal oxygen uptake (VO_2 max) of at least 45 ml/kg/min for women and 50 ml/kg/min for men Exclusion criteria: all participants on immuno-modulatory medications
Interventions	Treatment group: the probiotic capsule contained a minimum of one billion (10~9) colony-forming units of *Lactobacillus fermentum* VRI-003 PCC® (Probiomics Ltd, Sydney, Australia) Control group: the placebo supplement consisted of microcrystalline cellulose
Outcomes	1. Symptoms of illness 2. Systemic immunity 3. Mucosal immunity 4. Faecal microbiology
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Using a computer-generated list
Allocation concealment (selection bias)	Unclear risk	No information provided

Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and the study team were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	11.2% of participants lost to follow up
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and the study team were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and the study team were blinded

AOM: acute otitis media
ARI: acute respiratory infection
CFU: colony-forming units
CIDs: common infectious diseases
FOS: fructooligosaccharides
GI: gastrointestinal
GOS: galactooligosaccharides
IcFOS: long-chain fructooligosaccharides
LGG: *Lactobacillus rhamnosus* GG
scGOS: short-chain galactooligosaccharides
URI: upper respiratory infection
URTI: upper respiratory tract infection

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arslanoglu 2008	The study used prebiotics (GOS and FOS)
Guillemard 2010	The study included participants vaccination against the influenza virus at least 14 days
Hatakka 2001	The study did not separate URTIs from other respiratory infections
Kukkonen 2008	The study did not separate URTIs from other respiratory infections and did not separate AOM from middle ear infections
Leyer 2009	The study only reported cold or influenza-like symptoms but did not diagnose URTIs
Lin 2009	The study compared 2 different probiotics

(*Continued*)

Makino 2010b	The Arita was study reported in this trial but was not a RCT
Moyad 2010	The study did not use probiotics as the intervention
Pitkaranta 2003	The study was published as an abstract. We cannot find the unpublished data and there were no adequate data to extract in this study
Pregliasco 2008	The study used symbiotic formulas: probiotics plus prebiotics (FOS/GOS)
Smerud 2008	The study did not separate URTIs from other respiratory infections
Tajima 1995	Not a RCT
Tiollier 2007	The study did not separate URTIs from other respiratory infections
Turchet 2003	82% of participants had been vaccinated 3 months before the study against influenza and the study did not separate URTIs from other respiratory infections

AOM: acute otitis media
GOS: galactooligosaccharides
FOS: fructooligosaccharides
RCT: randomised clinical trial
URTIs: upper respiratory tract infections

Characteristics of studies awaiting assessment *[ordered by study ID]*

Kaplan 1968

Methods	We cannot find the details of the study
Participants	
Interventions	
Outcomes	
Notes	

Marushko 2000

Methods	We cannot find the details of the study
Participants	
Interventions	
Outcomes	
Notes	

DATA AND ANALYSES

Comparison 1. ITT analysis: Probiotics versus placebo: primary outcome measures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants who experienced URTI episodes	6		Odds Ratio (IV, Random, 95% CI)	Subtotals only
1.1 Number of participants who experienced URTI episodes: at least 1 event	6	1836	Odds Ratio (IV, Random, 95% CI)	0.58 [0.36, 0.92]
1.2 Number of participants who experienced URTI episodes: at least 3 events	3	650	Odds Ratio (IV, Random, 95% CI)	0.53 [0.36, 0.80]
2 The mean duration of an episode of URTI	2	620	Mean Difference (IV, Random, 95% CI)	-0.29 [-3.71, 3.13]
2.1 Marathon runners	1	141	Mean Difference (IV, Random, 95% CI)	1.60 [-0.34, 3.54]
2.2 General healthy population	1	479	Mean Difference (IV, Random, 95% CI)	-1.90 [-2.04, -1.76]
3 The episode rate of URTIs (events per person/year)	4	1454	Rate Ratio (Random, 95% CI)	0.88 [0.81, 0.96]

Comparison 2. ITT analysis: Probiotics versus placebo: prescribe antibiotics for acute URTIs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The number of participants who used antibiotics	3	1104	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.45, 0.98]

Comparison 3. ITT analysis: Probiotics versus placebo: adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Probiotics versus placebo: adverse events	2	956	Odds Ratio (IV, Random, 95% CI)	0.92 [0.37, 2.28]

Comparison 4. PP analysis: Probiotics versus placebo: primary outcome measures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants who experienced URTI episodes	6		Odds Ratio (IV, Random, 95% CI)	Subtotals only
1.1 Number of participants who experienced URTI episodes: at least 1 event	6	1669	Odds Ratio (IV, Random, 95% CI)	0.54 [0.32, 0.90]
1.2 Number of participants who experienced URTI episodes: at least 3 events	3	582	Odds Ratio (IV, Random, 95% CI)	0.56 [0.37, 0.84]
2 The mean duration of an episode of URTI	2	573	Mean Difference (IV, Random, 95% CI)	-0.31 [-3.73, 3.10]
2.1 Marathon runners	1	119	Mean Difference (IV, Random, 95% CI)	1.60 [-0.50, 3.70]
2.2 General healthy population	1	454	Mean Difference (IV, Random, 95% CI)	-1.90 [-2.05, -1.75]
3 The episode rate of URTI (events per person/year)	4		Rate Ratio (Random, 95% CI)	0.89 [0.83, 0.94]

Comparison 5. PP analysis: Probiotics versus placebo: prescribe antibiotics for acute URTIs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The number of participants who used antibiotics	3	1046	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.46, 0.98]

Comparison 6. PP analysis: Probiotics versus placebo: adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Probiotics versus placebo: adverse events	2	839	Odds Ratio (IV, Random, 95% CI)	0.85 [0.34, 2.11]

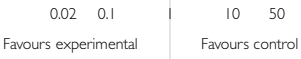
Analysis 1.1. Comparison 1 ITT analysis: Probiotics versus placebo: primary outcome measures, Outcome 1 Number of participants who experienced URTI episodes.

Review: Probiotics for preventing acute upper respiratory tract infections

Comparison: 1 ITT analysis: Probiotics versus placebo: primary outcome measures

Outcome: 1 Number of participants who experienced URTI episodes

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
1 Number of participants who experienced URTI episodes: at least 1 event					
Berggren 2010	76/159	91/159		20.7 %	0.68 [0.44, 1.06]
Hojsak 2010a	58/139	95/142		20.0 %	0.35 [0.22, 0.58]
Hojsak 2010b	8/376	20/366		14.2 %	0.38 [0.16, 0.87]
Kekkonen 2007	32/70	26/71		16.7 %	1.46 [0.74, 2.86]
Rautava 2009	7/38	20/43		11.7 %	0.26 [0.09, 0.72]
Sanz 2006	21/158	18/115		16.6 %	0.83 [0.42, 1.63]
Subtotal (95% CI)	**940**	**896**		**100.0 %**	**0.58 [0.36, 0.92]**
Total events: 202 (Experimental), 270 (Control)					
Heterogeneity: Tau^2 = 0.23; Chi^2 = 16.15, df = 5 (P = 0.01); I^2 =69%					
Test for overall effect: Z = 2.28 (P = 0.022)					
2 Number of participants who experienced URTI episodes: at least 3 events					
Berggren 2010	10/159	20/159		25.7 %	0.47 [0.21, 1.03]
Rautava 2009	4/38	10/43		10.3 %	0.39 [0.11, 1.36]
Sanz 2006	61/142	61/109		64.0 %	0.59 [0.36, 0.98]
Subtotal (95% CI)	**339**	**311**		**100.0 %**	**0.53 [0.36, 0.80]**
Total events: 75 (Experimental), 91 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.52, df = 2 (P = 0.77); I^2 =0.0%					
Test for overall effect: Z = 3.06 (P = 0.0022)					



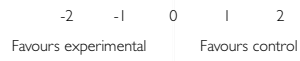
Analysis 1.2. Comparison 1 ITT analysis: Probiotics versus placebo: primary outcome measures, Outcome 2 The mean duration of an episode of URTI.

Review: Probiotics for preventing acute upper respiratory tract infections

Comparison: 1 ITT analysis: Probiotics versus placebo: primary outcome measures

Outcome: 2 The mean duration of an episode of URTI

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Marathon runners							
Kekkonen 2007	70	7.9 (7.1)	71	6.3 (4.3)		46.0 %	1.60 [-0.34, 3.54]
Subtotal (95% CI)	**70**		**71**			**46.0 %**	**1.60 [-0.34, 3.54]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.62 (P = 0.11)							
2 General healthy population							
Vrese 2005	238	7 (0.5)	241	8.9 (1)		54.0 %	-1.90 [-2.04, -1.76]
Subtotal (95% CI)	**238**		**241**			**54.0 %**	**-1.90 [-2.04, -1.76]**
Heterogeneity: not applicable							
Test for overall effect: Z = 26.35 (P < 0.00001)							
Total (95% CI)	**308**		**312**			**100.0 %**	**-0.29 [-3.71, 3.13]**
Heterogeneity: Tau^2 = 5.63; Chi^2 = 12.43, df = 1 (P = 0.00042); I^2 =92%							
Test for overall effect: Z = 0.17 (P = 0.87)							
Test for subgroup differences: Chi^2 = 12.43, df = 1 (P = 0.00), I^2 =92%							



Analysis 1.3. Comparison 1 ITT analysis: Probiotics versus placebo: primary outcome measures, Outcome 3 The episode rate of URTIs (events per person/year).

Review: Probiotics for preventing acute upper respiratory tract infections

Comparison: 1 ITT analysis: Probiotics versus placebo: primary outcome measures

Outcome: 3 The episode rate of URTIs (events per person/year)

Study or subgroup	Favours experimental N	Control N	log [Rate Ratio] (SE)	Rate Ratio IV,Random,95% CI	Weight	Rate Ratio IV,Random,95% CI
Berggren 2010	159	159	-0.14 (0.057)		29.3 %	0.87 [0.78, 0.97]
Caceres 2010	203	195	0.01 (0.15)		7.3 %	1.01 [0.75, 1.36]
Merenstein 2010	314	324	-0.086 (0.024)		50.2 %	0.92 [0.88, 0.96]
Rio 2002	50	50	-0.31 (0.105)		13.2 %	0.73 [0.60, 0.90]
Total (95% CI)					**100.0 %**	**0.88 [0.81, 0.96]**

Heterogeneity: Tau² = 0.00; Chi² = 5.37, df = 3 (P = 0.15); I² =44%

Test for overall effect: Z = 2.87 (P = 0.0041)

Analysis 2.1. Comparison 2 ITT analysis: Probiotics versus placebo: prescribe antibiotics for acute URTIs, Outcome 1 The number of participants who used antibiotics.

Review: Probiotics for preventing acute upper respiratory tract infections

Comparison: 2 ITT analysis: Probiotics versus placebo: prescribe antibiotics for acute URTIs

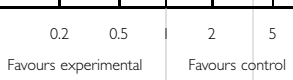
Outcome: 1 The number of participants who used antibiotics

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Hojsak 2010a	22/139	33/142		62.7 %	0.68 [0.42, 1.11]
Hojsak 2010b	1/376	4/366		3.1 %	0.24 [0.03, 2.17]
Rautava 2009	10/38	16/43		34.2 %	0.71 [0.37, 1.37]
Total (95% CI)	**553**	**551**		**100.0 %**	**0.67 [0.45, 0.98]**

Total events: 33 (Experimental), 53 (Control)

Heterogeneity: Tau² = 0.0; Chi² = 0.87, df = 2 (P = 0.65); I² =0.0%

Test for overall effect: Z = 2.05 (P = 0.040)



Analysis 3.1. Comparison 3 ITT analysis: Probiotics versus placebo: adverse events, Outcome 1 Probiotics versus placebo: adverse events.

Review: Probiotics for preventing acute upper respiratory tract infections

Comparison: 3 ITT analysis: Probiotics versus placebo: adverse events

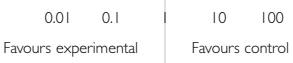
Outcome: 1 Probiotics versus placebo: adverse events

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
Berggren 2010	3/159	3/159		31.7 %	1.00 [0.20, 5.03]
Merenstein 2010	6/314	7/324		68.3 %	0.88 [0.29, 2.65]
Total (95% CI)	**473**	**483**		**100.0 %**	**0.92 [0.37, 2.28]**

Total events: 9 (Experimental), 10 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.02$, df = 1 (P = 0.90); $I^2 = 0.0\%$

Test for overall effect: Z = 0.18 (P = 0.85)



Analysis 4.1. Comparison 4 PP analysis: Probiotics versus placebo: primary outcome measures, Outcome 1 Number of participants who experienced URTI episodes.

Review: Probiotics for preventing acute upper respiratory tract infections

Comparison: 4 PP analysis: Probiotics versus placebo: primary outcome measures

Outcome: 1 Number of participants who experienced URTI episodes

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
1 Number of participants who experienced URTI episodes: at least 1 event					
Berggren 2010	76/139	91/136		20.0 %	0.60 [0.37, 0.97]
Hojsak 2010a	58/127	95/127		19.4 %	0.28 [0.17, 0.48]
Hojsak 2010b	8/360	20/354		14.9 %	0.38 [0.16, 0.87]
Kekkonen 2007	32/61	26/58		16.5 %	1.36 [0.66, 2.79]
Rautava 2009	7/36	20/42		12.4 %	0.27 [0.10, 0.74]
Sanz 2006	21/126	18/103		16.9 %	0.94 [0.47, 1.89]
Subtotal (95% CI)	**849**	**820**		**100.0 %**	**0.54 [0.32, 0.90]**

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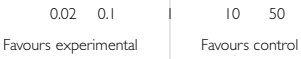
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
Total events: 202 (Experimental), 270 (Control)					
Heterogeneity: Tau² = 0.28; Chi² = 17.15, df = 5 (P = 0.004); I² =71%					
Test for overall effect: Z = 2.35 (P = 0.019)					
2 Number of participants who experienced URTI episodes: at least 3 events					
Berggren 2010	10/139	20/136		26.9 %	0.45 [0.20, 1.00]
Rautava 2009	4/36	10/42		10.9 %	0.40 [0.11, 1.41]
Sanz 2006	61/126	61/103		62.2 %	0.65 [0.38, 1.09]
Subtotal (95% CI)	**301**	**281**		**100.0 %**	**0.56 [0.37, 0.84]**
Total events: 75 (Experimental), 91 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 0.85, df = 2 (P = 0.65); I² =0.0%					
Test for overall effect: Z = 2.77 (P = 0.0056)					



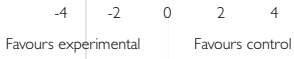
Analysis 4.2. Comparison 4 PP analysis: Probiotics versus placebo: primary outcome measures, Outcome 2 The mean duration of an episode of URTI.

Review: Probiotics for preventing acute upper respiratory tract infections

Comparison: 4 PP analysis: Probiotics versus placebo: primary outcome measures

Outcome: 2 The mean duration of an episode of URTI

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Marathon runners							
Kekkonen 2007	61	7.9 (7.1)	58	6.3 (4.3)		45.3 %	1.60 [-0.50, 3.70]
Subtotal (95% CI)	**61**		**58**			**45.3 %**	**1.60 [-0.50, 3.70]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.50 (P = 0.13)							
2 General healthy population							
Vrese 2005	225	7 (0.5)	229	8.9 (1)		54.7 %	-1.90 [-2.05, -1.75]
Subtotal (95% CI)	**225**		**229**			**54.7 %**	**-1.90 [-2.05, -1.75]**
Heterogeneity: not applicable							
Test for overall effect: Z = 25.67 (P < 0.00001)							
Total (95% CI)	**286**		**287**			**100.0 %**	**-0.31 [-3.73, 3.10]**



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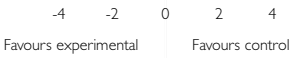
Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Heterogeneity: Tau^2 = 5.55; Chi^2 = 10.65, df = 1 (P = 0.001); I^2 =91%							
Test for overall effect: Z = 0.18 (P = 0.86)							
Test for subgroup differences: Chi^2 = 10.65, df = 1 (P = 0.00), I^2 =91%							



Analysis 4.3. Comparison 4 PP analysis: Probiotics versus placebo: primary outcome measures, Outcome 3 The episode rate of URTI (events per person/year).

Review: Probiotics for preventing acute upper respiratory tract infections

Comparison: 4 PP analysis: Probiotics versus placebo: primary outcome measures

Outcome: 3 The episode rate of URTI (events per person/year)

Study or subgroup	log [Rate Ratio] (SE)	Rate Ratio IV,Random,95% CI	Weight	Rate Ratio IV,Random,95% CI
Berggren 2010	-0.15 (0.0572)		31.2 %	0.86 [0.77, 0.96]
Caceres 2010	0.05 (0.16)		4.0 %	1.05 [0.77, 1.44]
Merenstein 2010	-0.12 (0.0429)		55.5 %	0.89 [0.82, 0.96]
Rio 2002	-0.09 (0.105)		9.3 %	0.91 [0.74, 1.12]
Total (95% CI)			**100.0 %**	**0.89 [0.83, 0.94]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.49, df = 3 (P = 0.69); I^2 =0.0%				
Test for overall effect: Z = 3.75 (P = 0.00018)				

Analysis 5.1. Comparison 5 PP analysis: Probiotics versus placebo: prescribe antibiotics for acute URTIs, Outcome 1 The number of participants who used antibiotics.

Review: Probiotics for preventing acute upper respiratory tract infections

Comparison: 5 PP analysis: Probiotics versus placebo: prescribe antibiotics for acute URTIs

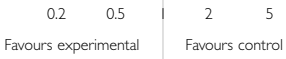
Outcome: 1 The number of participants who used antibiotics

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Hojsak 2010a	22/127	33/127		62.9 %	0.67 [0.41, 1.08]
Hojsak 2010b	1/360	4/354		3.0 %	0.25 [0.03, 2.19]
Rautava 2009	10/36	16/42		34.0 %	0.73 [0.38, 1.40]
Total (95% CI)	**523**	**523**		**100.0 %**	**0.67 [0.46, 0.98]**

Total events: 33 (Experimental), 53 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.89$, df = 2 (P = 0.64); $I^2 = 0.0\%$

Test for overall effect: Z = 2.09 (P = 0.037)



Analysis 6.1. Comparison 6 PP analysis: Probiotics versus placebo: adverse events, Outcome 1 Probiotics versus placebo: adverse events.

Review: Probiotics for preventing acute upper respiratory tract infections

Comparison: 6 PP analysis: Probiotics versus placebo: adverse events

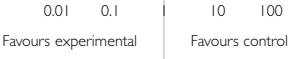
Outcome: 1 Probiotics versus placebo: adverse events

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
Berggren 2010	3/139	3/136		31.7 %	0.98 [0.19, 4.93]
Merenstein 2010	6/292	7/272		68.3 %	0.79 [0.26, 2.39]
Total (95% CI)	**431**	**408**		**100.0 %**	**0.85 [0.34, 2.11]**

Total events: 9 (Experimental), 10 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.04$, df = 1 (P = 0.84); $I^2 = 0.0\%$

Test for overall effect: Z = 0.35 (P = 0.72)



APPENDICES

Appendix 1. Embase.com search strategy

1. 'common cold'/exp
2. 'common cold':ti,ab OR 'common colds':ti,ab
3. 'sinusitis'/exp
4. sinusit*:ti,ab
5. 'pharyngitis'/exp
6. pharyngit*:ti,ab
7. 'laryngitis'/exp
8. laryngit*:ti,ab
9. laryngotracheobronchit*:ti,ab
10. 'rhinitis'/exp
11. rhinit*:ti,ab
12. 'tonsillitis'/exp
13. tonsillit*:ti,ab
14. 'peritonsillar abscess':ti,ab OR 'peritonsillar abscesses':ti,ab
15. 'croup'/exp
17. 'epiglottitis'/exp
18. epiglottit*:ti,ab
19. supraglottit*:ti,ab
20. rhinosinusit*:ti,ab
21. 'otitis media'/exp
22. 'otitis media':ti,ab OR ome:ti,ab OR oam:ti,ab
23. 'respiratory tract infection'/exp
24. 'respiratory tract infections':ti,ab OR 'respiratory tract infection':ti,ab OR 'upper respiratory infection':ti,ab OR 'upper respiratory infections':ti,ab
25. urti:ti,ab
26. 'acute infection':ti,ab AND respirat*:ti,ab
27. 'acute infections':ti,ab AND respirat*:ti,ab
28. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
29. 'probiotic agent'/exp
30. probiotic*:ti,ab
31. 'lactobacillus'/exp
32. lactobacill*:ti,ab
33. 'bifidobacterium'/exp
34. bifido*:ti,ab OR bifidu*:ti,ab
35. 'lactococcus'/exp
36. lactococc*:ti,ab
37. 'saccharomyces'/exp
38. saccharomyc*:ti,ab
39. 'streptococcus thermophilus'/exp
40. 'streptococcus thermophilus':ti,ab
41. 'bacillus subtilis'/exp
42. 'bacillus subtilis':ti,ab
43. 'enterococcus'/exp
44. 'enterococcus faecalis':ti,ab OR 'enterococcus faecium':ti,ab
45. 'bulgarian bacillus':ti,ab
46. #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR # 36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45
47. #28 AND #46

48. 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'randomized controlled trial'/exp OR 'crossover procedure'/exp
49. random*:ti,ab OR factiorial*:ti,ab OR crossover*:ti,ab OR 'cross over':ti,ab OR placebo*:ti,ab OR 'double blind':ti,ab OR 'single blind':ti,ab OR assign*:ti,ab OR allocat*:ti,ab OR volunteer*:ti,ab
50. #48 OR #49
51. #47 AND #50

Appendix 2. Web of Science search strategy

Topic=(probiotic* or lactobacill* or bifido* or bifidu* or lactococc* or saccharomyc* or streptococcus thermophilus or bacillus subtilis or enterococcus faec* or bulgarian bacillus) AND
Topic=(common cold* or sinusit* or pharyngit* or laryngit* or laryngotracheobronchit* or rhinit* or tonsillit* or peritonsillar abscess* or croup or epiglottit* or supraglottit* or rhinosinusit* or otitis media or aom or ome or respiratory tract infection* or upper respiratory infection* or acute respiratory infection*)
Refined by: Topic=(placebo* or random* or clinical trial* or double blind* or single blind* or rct)
Timespan=All Years. Databases=SCI-EXPANDED, CPCI-S.

HISTORY

Protocol first published: Issue 1, 2008

Review first published: Issue 9, 2011

Date	Event	Description
10 May 2009	Amended	Contact details updated.
17 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Qiukui Hao (QH) searched for trials, assessed quality of trials, extracted data, analysed data and drafted the review.

Zhenchan Lu (ZL) drafted the protocol, searched for trials, assessed quality of trials, extracted data.

Birong Dong (BD) advised and assisted in writing the protocol and the review, searched for trials and developed the review.

Changquan Huang (CH) suggested the title for the review and provided background material.

Taixiang Wu (TW) contributed to the development of the methods of the review and assisted with data extraction and analysis.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Chinese Cochrane Center, West China Hospital of Sichuan University, China.

External sources

- Editorial base and team of the Cochrane ARI Group, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have replaced the 'Quality assessment of included studies' in the original version with 'Assessment of risk of bias in included studies' and the methods of analysis according to the new version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

There was only one study focusing on acute otitis media (AOM). Therefore, we treated AOM as one kind of URTI and analysed the data together.