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Probiotics for preventing acute upper respiratory tract infections (Review)

Hao Q, Dong BR, 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 trials have shown that probiotic strains can prevent respiratory infections. Even though the previous version of our review showed benefits of probiotics for acute upper respiratory tract infections (URTIs), several new studies have been published.

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.

Search methods

We searched CENTRAL (2014, Issue 6), MEDLINE (1950 to July week 3, 2014), EMBASE (1974 to July 2014), Web of Science (1900 to July 2014), the Chinese Biomedical Literature Database, which includes the China Biological Medicine Database (from 1978 to July 2014), the Chinese Medicine Popular Science Literature Database (from 2000 to July 2014) and the Masters Degree Dissertation of Beijing Union Medical College Database (from 1981 to July 2014). We also searched the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov for completed and ongoing trials on 31 July 2014.

Selection criteria

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

Data collection and analysis

Two review authors independently assessed the eligibility and quality of trials, and extracted data using the standard methodological procedures expected by The Cochrane Collaboration.

Main results

We included 13 RCTs, although we could only extract data to meta-analyse 12 trials, which involved 3720 participants including children, adults (aged around 40 years) and older people. 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) 0.53; 95% confidence interval (CI) 0.37 to 0.76, P value < 0.001, low quality evidence; at least three episodes: OR 0.53; 95% CI 0.36 to 0.80, P value = 0.002, low quality evidence); the mean duration of an episode of acute URTI (mean difference (MD) -1.89; 95% CI -2.03 to -1.75, P value < 0.001, low quality evidence); reduced antibiotic prescription rates for acute URTIs (OR 0.65; 95% CI 0.45 to 0.94, moderate quality evidence) and cold-related school absence (OR 0.10; 95% CI 0.02 to 0.47, very low quality evidence). Probiotics and placebo were similar when measuring the rate ratio of episodes of acute URTI (rate ratio 0.83; 95% CI 0.66 to 1.05, P value = 0.12, very low quality evidence) and adverse events (OR 0.88; 95% CI 0.65 to 1.19, P value

= 0.40, low quality evidence). 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 we conducted pooled analyses and the evidence level was low or very low quality.

Authors' conclusions

Probiotics were better than placebo in reducing the number of participants experiencing episodes of acute URTI, the mean duration of an episode of acute URTI, antibiotic use and cold-related school absence. This indicates that probiotics may be more beneficial than placebo for preventing acute URTIs. However, the quality of the evidence was low or very low.

PLAIN LANGUAGE SUMMARY

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

Review question

With the increasing consumption of probiotics (live micro-organisms), we carried out a review on the effects of probiotics in helping people (without immunodeficiencies) to avoid acute upper respiratory tract infections (URTIs), for example, the common cold, compared to placebo.

Background

URTIs include the common cold and 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 incidence of these infections, specific vaccines are often recommended, especially for children and old people.

Some probiotics (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. However, their effects in preventing URTIs are still poorly understood.

Study characteristics and search date

After searching for all relevant trials in scientific databases, we identified 13 randomised controlled trials (RCTs) published up to July 2014. We could extract and pool data from 12 RCTs, which involved 3720 participants (both genders), including children, adults (aged around 40 years) and older people from Finland, Spain, Sweden, the United States, Croatia, Chile, Thailand and Japan.

Key results

Probiotics were found to be better than placebo in reducing the number of participants experiencing episodes of acute URTI by about 47% and the duration of an episode of acute URTI by about 1.89 days. Probiotics may slightly reduce antibiotic use and cold-related school absence. Side effects of probiotics were minor and gastrointestinal symptoms were the most common.

Quality of the evidence

The quality of the evidence is low or very low mainly due to poorly conducted trials, for example with unclear randomisation method and blinding. Some trials were supported by manufacturers of the tested probiotics and some trials had a very small sample size.

Conclusion

Overall, we found probiotics to be better than placebo in preventing acute URTIs. However, more trials are needed to confirm this conclusion.

Summary of findings for the main comparison. Probiotics for preventing acute upper respiratory tract infections: primary outcomes

Probiotics for preventing acute upper respiratory tract infections: primary outcomes

Patient or population: adults, children and the elderly
Settings: community or care facilities or school or hospital
Intervention: probiotics

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	ITT analysis: probiotics versus placebo - primary outcome measures				
The number of participants who experienced URTI episodes: at least 1 event	**Study population**		**OR 0.53** (0.37 to 0.76)	1927 (7 trials)	⊕⊕⊖⊖ **low**[1,2]	2 of 7 trials were at risk of high bias due to funding by related companies (Berggren 2010; Sanz 2006)
	306 per 1000	**189 per 1000** (140 to 251)				
	Moderate					
	421 per 1000	**278 per 1000** (212 to 356)				
The number of participants who experienced URTI episodes: at least 3 events	**Study population**		**OR 0.53** (0.36 to 0.8)	650 (3 trials)	⊕⊕⊖⊖ **low**[1,2]	All 3 trials were unclear for sequence generation and allocation concealment (Berggren 2010; Rautava 2009; Sanz 2006) and 2 of them were at high risk of bias due to funding by related companies (Berggren 2010; Sanz 2006)
	293 per 1000	**180 per 1000** (130 to 249)				
	Moderate					
	233 per 1000	**139 per 1000** (99 to 196)				
The risk ratio of episodes of acute URTI	**Study population**		**Rate ratio 0.83** (0.66 to 1.05)	1608 (5 trials)	⊕⊖⊖⊖ **very low**[1,2,3]	2 trials had serious limitations: Berggren 2010 was unclear for sequence generation and allocation concealment; Rio 2002 had a high proportion of incomplete data. 2 of 5 trials were at high risk of bias due to funding by related compa-
	See comment	See comment				
	Moderate					

	0 per 1000	**0 per 1000** (0 to 0)			nies (Berggren 2010; Caceres 2010). Serious inconsistency: I^2 statistic was 76%
The mean duration of an episode of URTIs		The mean duration of an episode of URTI in the intervention groups was **1.89 lower** (2.03 to 1.75 lower)	831 (3 trials)	⊕⊕⊖⊖ **Low**[1,3]	1 of the 3 trials was unclear for sequence generation and allocation concealment (Vrese 2005)

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio;**URTI:** upper respiratory tract infection

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]One or more items for the bias assessment in included trials were unclear. Downgraded by 1.
[2]Serious study limitations: some trials were at high risk of bias due to funding by manufacturers of the tested probiotics. Downgraded by 1.
[3]Serious inconsistency: small sample size or have a higher I^2, or both. Downgraded by 1.

Summary of findings 2. Probiotics for preventing acute upper respiratory tract infections: time off from childcare centre, school or work

Probiotics for preventing acute upper respiratory tract infections: school absence due to URTIs

Patient or population: children
Settings: school
Intervention: probiotics

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Control	**Probiotics**				
Time off from childcare centre, school or work	**Study population**		**OR 0.10** (0.02 to 0.47)	80 (1 study)	⊕⊖⊖⊖ **very low**[1,2]	The study was unclear for randomised sequence generation and allocation concealment and only 80 participants were included (Rerksuppaphol 2012)
	350 per 1000	**51 per 1000** (11 to 202)				

	Moderate	
	350 per 1000	**51 per 1000** (11 to 202)

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio; **URTI:** upper respiratory tract infection

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Some items for the bias assessment were unclear. Downgraded by 1.
[2]Very small events and wide 95% CI range in this analysis. Downgraded by 2.

Summary of findings 3. Probiotics for preventing acute upper respiratory tract infections: prescribed antibiotics for acute URTIs

Probiotics for preventing acute upper respiratory tract infections: antibiotics usage

Patient or population: children
Settings: school or care facilities or hospital
Intervention: probiotics

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	**Corresponding risk**				
	Control	**Probiotics**				
Prescribed antibiotics for acute URTIs	**Study population**		**RR 0.65** (0.45 to 0.94)	1184 (4 trials)	⊕⊕⊕⊖ **moderate**[1]	Unclear randomised sequence generation and allocation concealment in all 4 trials (Hojsak 2010a; Hojsak 2010b; Rautava 2009; Rerksuppaphol 2012)
	98 per 1000	**64 per 1000** (44 to 92)				
	Moderate					
	179 per 1000	**116 per 1000** (81 to 168)				

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio; **URTI:** upper respiratory tract infection

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Some items for the bias assessment were unclear. Downgraded by 1.

Summary of findings 4. Probiotics for preventing acute upper respiratory tract infections: side effects or adverse events

Probiotics for preventing acute upper respiratory tract infections: adverse events

Patient or population: adults or children
Settings: community or school
Intervention: probiotics

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Probiotics				
Side effects or adverse events	Study population		OR 0.88 (0.65 to 1.19)	1234 (4 trials)	⊕⊕⊖⊖ **low**[1,2]	3 of 4 trials were unclear for randomised sequence generation and allocation concealment (Berggren 2010; Rerksuppaphol 2012; Smith 2013)
	89 per 1000	79 per 1000 (51 to 120)				
	Moderate					
	114 per 1000	102 per 1000 (66 to 153)				

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

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[1]Some items for the bias assessment were unclear. Downgraded by 1.
[2]The sample size was small and the 95% CI crossed 1. Downgraded by 1.

BACKGROUND

Description of the condition

Acute upper respiratory tract infections (URTIs), which include the common cold, acute sinusitis, acute pharyngitis, acute laryngotracheobronchitis (croup), acute epiglottitis (supraglottitis), acute rhinosinusitis 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', were 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 (Bernaola Aponte 2013), 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-Amster 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 trials 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 trials amongst children in daycare centres who were given milk containing *Lactobacillus rhamnosus* (*L. rhamnosus*) GG (ATCC 53103) during winter (Hatakka 2001). However, one study showed that the probiotics did not have any effect on upper respiratory infections after the intervention (Hatakka 2007). 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) of probiotics to prevent acute URTIs. We excluded all cross-over trials 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.

Cases of acute URTIs should be confirmed by doctors, or have specific symptoms, such as nasal symptoms (for example, runny nose, blocked nose, nose blowing, yellow secretions, bloody secretions, sneezing), pharyngeal symptoms (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).

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 participants who experienced episodes of acute URTI.
2. The rate ratio of episodes of acute URTI.
3. The mean duration of an episode of acute URTI.

Secondary outcomes

1. Time off from childcare centre, school or work (a proxy of severity of disease).
2. Prescribed antibiotics for acute URTIs (a proxy of severity of disease).
3. Side effects or adverse events.

Search methods for identification of studies

Electronic searches

For this 2014 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL 2014, Issue 6) (accessed 25 July 2014), which includes the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (March 2011 to July week 3, 2014), EMBASE (May 2011 to July 2014) and Web of Science (May 2011 to July 2014). See Appendix 1 for details of previous search dates.

We used the search strategy described in Appendix 1 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 2011). We adapted the search strategy to search EMBASE (Appendix 2), Web of Science (Appendix 3) and the Chinese Biomedical Literature Database (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)

Searching other resources

We also searched the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp) and ClinicalTrials.gov (http://clinicaltrials.gov/) for completed and ongoing trials on 31 July 2014. We searched the reference sections of the review articles to identify trials missed by electronic searching. 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. We did not impose any language or publication restrictions in the searches.

Data collection and analysis

Selection of studies

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

Data extraction and management

Two review authors (QH, BD) independently extracted data from the included trials 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.).

We resolved disagreements by discussion and, when necessary, by consulting a third review author (TW). 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, BD) independently assessed 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 that 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 of participants and personnel

- Low risk of bias: we considered masking of both the participants and study personnel who implemented the study a low risk of performance bias (for example, identical placebo tablets or similar and the study personnel did not know the groups).
- High risk of bias: open-label study.
- Unclear risk of bias: insufficient information provided to judge the level of bias.

Blinding of outcome assessment

- Low risk of bias: we considered masking of the results assessor a low risk of detection bias.
- High risk of bias: not used or non-blinding of detection of outcomes (for example, not performed or tablets versus fluids or similar).
- Unclear risk of bias: insufficient information provided to judge the level of bias.

Incomplete outcome data: assessment for potential bias of exclusion 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 the 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 or attrition, or both, is higher than 10%, whatever ITT analysis is used.

Selective reporting

- If the protocol for an included study was available, we compared the outcomes in the protocol and published report.

Other bias

- Any other potential biases.

Measures of treatment effect

We analysed data using Review Manager software (RevMan 2014). 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 odds ratios (ORs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes, both with 95% confidence intervals (CIs). We calculated the rate ratio of episode rates (events per person/year) of acute URTIs between two groups and the standard error (SE) of the rate ratio according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We used the generic inverse variance weighting when pooling trials for this outcome. In this review, when the 95% confidence interval (CI) did not span 1.0 or P value < 0.05, we considered this to be statistically significant.

Unit of analysis issues

We did not anticipate cross-over trials in this review. We combined similar groups to create a single pair-wise comparison for multiple arms from one study according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We also took care to avoid double-counting of participants where multiple interventions were used in the same trial. For the cluster-randomised trials, we calculated the effective sample size (i.e. original sample size divided by design effect) according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We sought missing data from the trial authors. We analysed the outcome measures both in an ITT population (i.e. we considered participants who dropped out of a study along with those who continued) and a per-protocol population (i.e. we excluded participants who dropped out of a study during the follow-up period).

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 trials. 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 trials (i.e. fewer than 10) in a meta-analysis. We did not assess the presence of publication bias in this review, but if more trials are included in future updates, we will use a funnel plot to assess the presence of publication bias.

Data synthesis

Regardless of heterogeneity between the pooled trials, 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 for some of the review outcomes.

Sensitivity analysis

We performed sensitivity analysis according to the quality of included trials in the pooled meta-analysis.

Overall quality of evidence

In our review, we only included RCTs and we downgraded the evidence from 'high quality' by one level for serious (or by two for very serious) study limitations (risk of bias), indirectness

of evidence, inconsistency, imprecision of effect estimates or potential publication bias, according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Furthermore, we used GRADE profiler to help us create 'Summary of findings' tables (GRADEpro 2008), and reported primary and secondary outcomes based on an ITT population in these tables. The tables included data from participants (all ages) from the community, care facilities, schools or hospitals.

RESULTS

Description of studies

Results of the search

We retrieved records from CENTRAL (204 records), MEDLINE (219 records), EMBASE (335 records), Web of Science (296 records) and the Chinese Biomedical Literature Database (seven records) in our electronic literature searches. We removed duplicates and were left with 737 records. Finally, we included 13 trials in this review (Figure 2). We also retrieved 104 registered trials from WHO ICTRP (http://www.who.int/ictrp) and ClinicalTrials.gov and found two ongoing trials for this review after assessment (Characteristics of ongoing studies).

Figure 2. Study flow diagram.

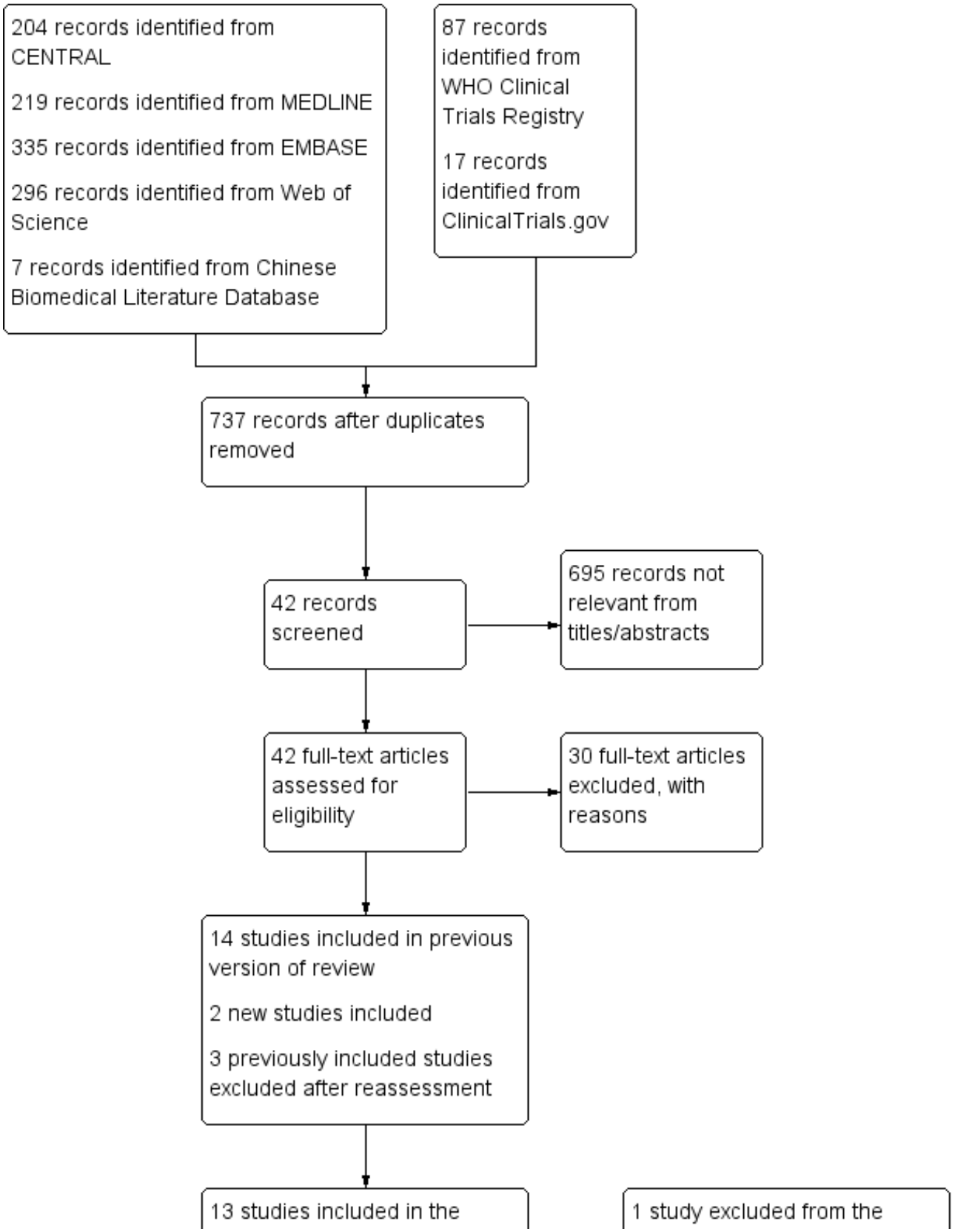
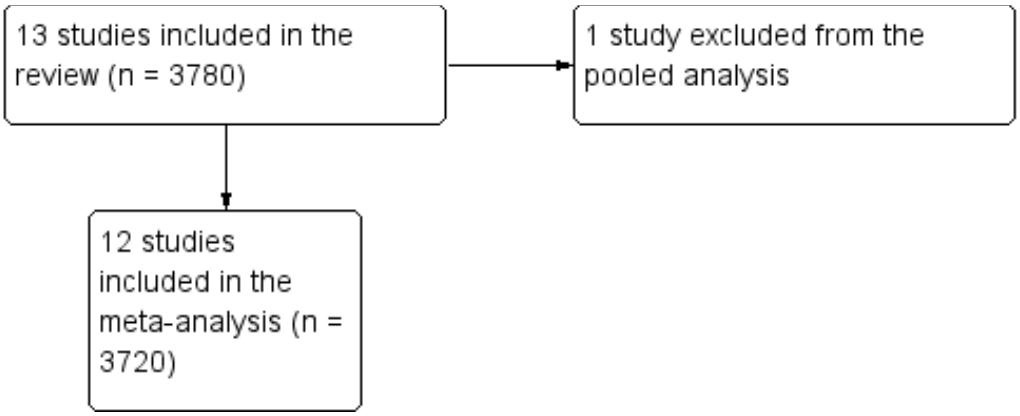


Figure 2. (Continued)



Included studies

We identified 42 full texts of clinical trials and included 13 randomised controlled trials (RCTs) in this review. We also reassessed the previously included trials and excluded four of them according to the review inclusion criteria (Gleeson 2010; Hatakka 2007; Kekkonen 2007; West 2011). We excluded three trials because the participants were competitive athletes and one study included otitis-prone children. Out of the 13 RCTs, we extracted and pooled data from 12 trials. We did not pool data from Makino 2010a because the study did not report outcomes related to our review.

Design

All included RCTs used a two-arm parallel design (Berggren 2010; Caceres 2010; Fujita 2013; Hojsak 2010a; Hojsak 2010b; Makino 2010a; Merenstein 2010; Rerksuppaphol 2012; Rio 2002; Sanz 2006; Smith 2013; Vrese 2005).

Participants

Three trials focused on adults aged from 18 to 65 years (Berggren 2010; Smith 2013; Vrese 2005), older people (Fujita 2013; Makino 2010a), and children (Hojsak 2010a; Hojsak 2010b; Merenstein 2010; Rautava 2009; Rerksuppaphol 2012; Rio 2002; Sanz 2006). Trials were performed in Finland (Rautava 2009), Spain (Sanz 2006), Sweden (Berggren 2010), the United States (Merenstein 2010; Smith 2013), Croatia (Hojsak 2010a; Hojsak 2010b), Chile (Caceres 2010), Thailand (Rerksuppaphol 2012), and Japan (Fujita 2013; Makino 2010a). It was not clear in which countries the other two trials were conducted (Rio 2002; Vrese 2005). Baseline data were stated and comparability was analysed in all trials except one (Rio 2002).

Interventions

The included trials involved different types of probiotics including *Lactobacillus plantarum*, *Lactobacillus paracasei 8700:2*,*Lactobacillus rhamnosus (GG or HN001)*, *Lactobacillus casei Shirota*, *Lactobacillus bulgaricus OLL 073R-1*,*Lactobacillus acidophilus*,*Lactobacillus gasseri*,*Streptococcus thermophilus OLS 3059*,*Bifidobacterium lactis BB-12*, *Bifidobacterium bifidum MF 20/5*,*Bifidobacterium animalis* and*Bifidobacterium longum SP 07/3*, usually compared with placebo. Most of the probiotics were given along with milk-based food (Caceres 2010; Fujita 2013; Hojsak 2010a; Hojsak 2010b; Makino 2010a; Merenstein 2010; Rio 2002; Sanz 2006). Three trials administered the probiotics in powder form (Berggren 2010; Smith 2013; Vrese 2005), and two trials administered the probiotics in capsules (Rautava 2009; Rerksuppaphol 2012). Three strains of probiotics were used in two trials (Merenstein 2010; Vrese 2005), two strains of probiotics were used in six trials (Berggren 2010; Makino 2010a; Rautava 2009; Rerksuppaphol 2012; Rio 2002; Smith 2013), and only one strain of probiotic was used in five trials (Caceres 2010; Fujita 2013; Hojsak 2010a; Hojsak 2010b; Sanz 2006). Most of the trials were conducted over three months or longer. One trial, Hojsak 2010a, used probiotics for the duration of hospitalisation and one trial, Makino 2010a, administered the probiotics for eight to 12 weeks. Most the trials used 10^9 or 10^{10} colony-forming units (CFU)/day of the probiotics, excepted one study, which used 5×10^7 CFU/day (Vrese 2005).

Outcome measures

Different outcome measures were reported in the included trials. Most trials reported the number of acute URTIs or the duration of acute URTI episodes (Berggren 2010; Fujita 2013; Hojsak 2010a; Hojsak 2010b; Rautava 2009; Rerksuppaphol 2012; Sanz 2006; Smith 2013; Vrese 2005). The rate ratio of episodes of acute URTI was calculated in five trials (Berggren 2010; Caceres 2010; Fujita 2013; Merenstein 2010; Rio 2002). The outcome measures also included symptoms of unrelated diseases and infections. Four trials reported antibiotic use (Hojsak 2010a; Hojsak 2010b; Rautava 2009; Rerksuppaphol 2012). Five trials reported side effects including vomiting, diarrhoea, flatulence and increased bowel irritability (pain, loose stools etc.) (Berggren 2010; Merenstein 2010; Rautava 2009; Rerksuppaphol 2012; Smith 2013). One trial assessed time off from school due to the common cold (Rerksuppaphol 2012). None of the trials assessed time off from childcare centres or work due to acute URTIs. One trial reported the number of days absent from daycare centres due to 'infections', but the trial did not separate URTIs from 'infections' (Hojsak 2010a).

Excluded studies

We excluded 30 trials for the reasons documented in the Characteristics of excluded studies table.

Risk of bias in included studies

The overall risk of bias is presented graphically in Figure 3 and summarised in Figure 4.

Figure 3. 'Risk of bias' graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

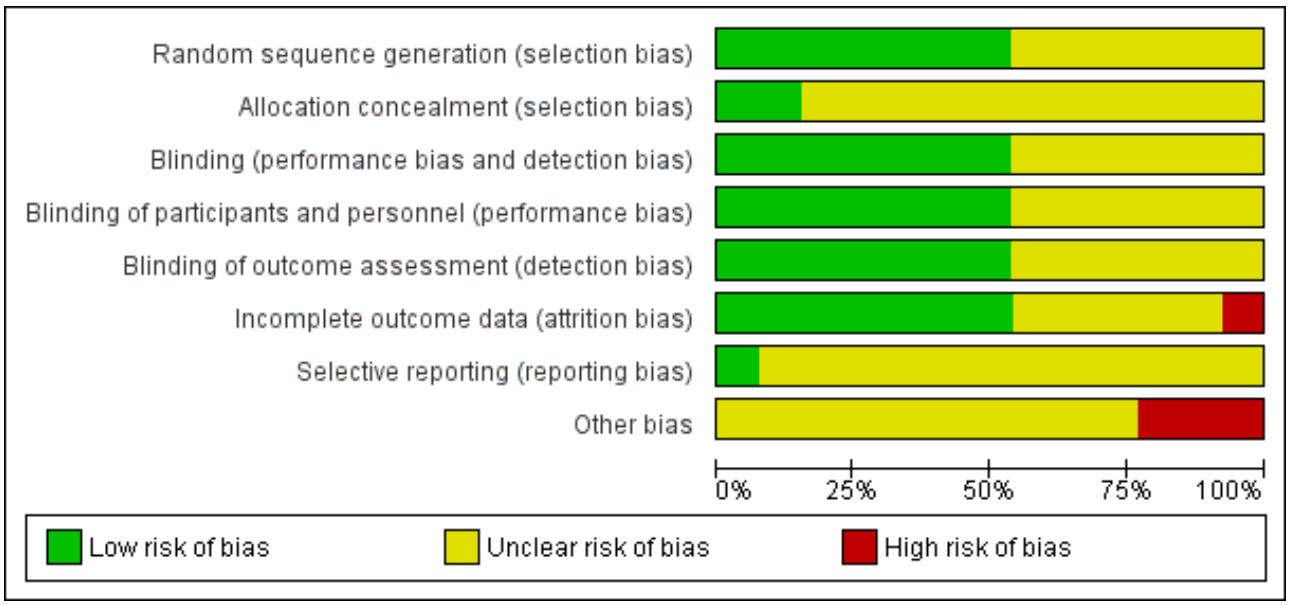


Figure 4. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

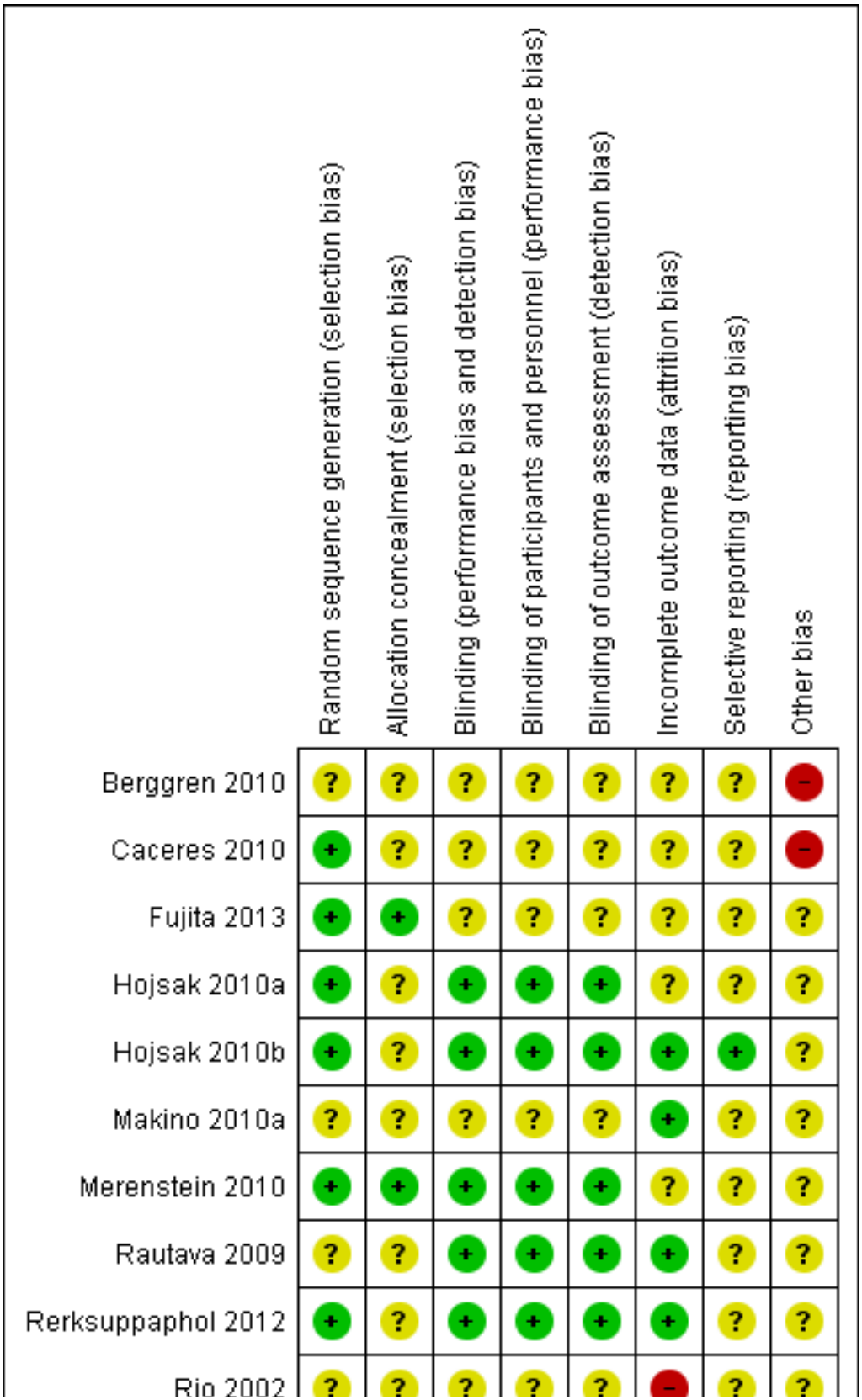
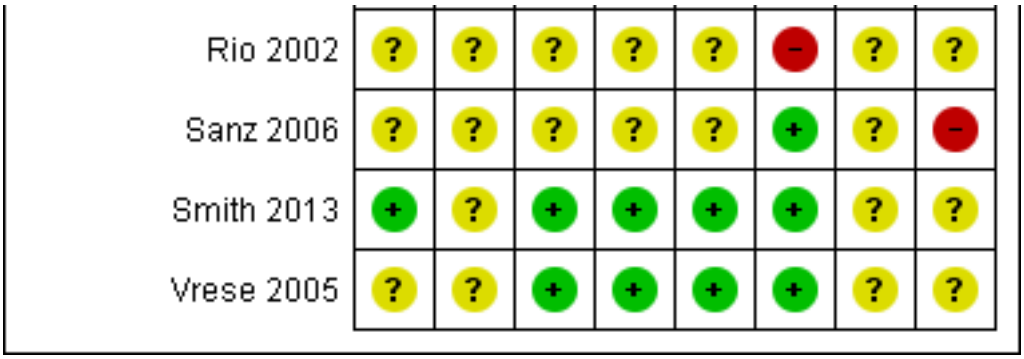


Figure 4. (Continued)



Allocation

Seven trials clearly described adequate sequence generation methods (Caceres 2010; Fujita 2013; Hojsak 2010a; Hojsak 2010b; Merenstein 2010; Rerksuppaphol 2012; Smith 2013). The remaining six trials did not describe the sequence generation method. Two trials described adequate allocation concealment (Fujita 2013; Merenstein 2010). Although we approached the remaining trial authors for further clarification, we did not receive any replies.

Blinding

Eleven trials reported double-blinding (Berggren 2010; Caceres 2010; Fujita 2013; Hojsak 2010a; Hojsak 2010b; Merenstein 2010; Rautava 2009; Rerksuppaphol 2012; Sanz 2006; Smith 2013; Vrese 2005), and seven trials described the blinding methods in detail (Hojsak 2010a; Hojsak 2010b; Merenstein 2010; Rautava 2009; Rerksuppaphol 2012; Smith 2013; Vrese 2005). Two trials did not report the type of blinding (Makino 2010a; Rio 2002).

Incomplete outcome data

All included trials provided sufficient information for the incomplete outcome data to be calculated or they described the withdrawal rate. Withdrawal rates varied from 3.7% in Rautava 2009 to 42% in Rio 2002. Seven trials had a low risk of incomplete outcome data bias (Hojsak 2010b; Makino 2010a; Rautava 2009; Rerksuppaphol 2012; Sanz 2006; Smith 2013; Vrese 2005); one study had a high risk of incomplete outcome data bias (Rio 2002), and the other five trials had a moderate risk of this bias (Berggren 2010; Caceres 2010; Fujita 2013; Hojsak 2010a; Merenstein 2010).

Selective reporting

We only had access to one protocol for the included trials and this had a low risk of selective reporting bias (Hojsak 2010b). We could not obtain the protocols for the remaining trials, so there was not enough information to assess their selective reporting bias.

Other potential sources of bias

Three trials had a high risk of conflict of interest due to the study funding source and the job positions of the study authors (Berggren 2010; Caceres 2010; Sanz 2006). Six included trials had small sample sizes (Fujita 2013; Hojsak 2010a; Makino 2010a; Rerksuppaphol 2012; Rio 2002; Vrese 2005). Therefore, all of these factors might have led to other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Probiotics for preventing acute upper respiratory tract infections: primary outcomes; **Summary of findings 2** Probiotics for preventing acute upper respiratory tract infections: time off from childcare centre, school or work; **Summary of findings 3** Probiotics for preventing acute upper respiratory tract infections: prescribed antibiotics for acute URTIs; **Summary of findings 4** Probiotics for preventing acute upper respiratory tract infections: side effects or adverse events

We meta-analysed 12 trials with a total of 3720 participants. We analysed all outcome measures based on both an intention-to-treat (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) and a per-protocol population (i.e. participants who dropped out of a study during the follow-up period were excluded).

Intention-to-treat (ITT) analysis

Primary outcomes

1. The number of participants who experienced episodes of acute URTI

Seven trials reported participants who experienced episodes of acute URTI (Berggren 2010; Fujita 2013; Hojsak 2010a; Hojsak 2010b; Rautava 2009; Rerksuppaphol 2012; Sanz 2006). There were 986 participants in the probiotics group and 941 participants in the placebo group. All of the trials reported participants who experienced at least one episode of acute URTI and three trials reported participants who experienced at least three episodes of acute URTI (Berggren 2010; Rautava 2009; Sanz 2006).

Pooling of these seven trials showed a benefit of the use of probiotics in preventing the occurrence of at least one episode of URTI (odds ratio (OR) 0.53; 95% confidence interval (CI) 0.37 to 0.76). One study, Berggren 2010, was conducted in adults and one study, Fujita 2013, was conducted in the elderly. The results show that there was no statistically significant difference in these age groups between the probiotics group and the placebo group in terms of the number participants who experienced at least one episode of acute URTI (Analysis 1.1). However, the remaining five trials conducted in children show that the probiotics intervention was better (OR 0.43; 95% CI 0.29 to 0.63; P value < 0.001) (Analysis 1.1). Looking at the outcome of at least three episodes of URTI there was a beneficial effect of probiotics: OR 0.53; 95% CI 0.36 to 0.80; P value = 0.002)

(Analysis 1.2). For the outcome 'at least one episode' the level of heterogeneity was moderate and therefore we downgraded it from high to low quality for possible bias.

2. The rate ratio of episodes of acute URTI

Five trials reported the total number of episodes of acute URTI or the rate of acute URTIs (Berggren 2010; Caceres 2010; Fujita 2013; Merenstein 2010; Rio 2002). In order to perform group comparisons, we calculated the rate ratio of episode rates (events per person/year) of acute URTIs between the probiotic and control groups and the standard error (SE) of the rate ratio according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). There were 802 participants in the probiotics group and 806 participants in the placebo group. This result changed after we included one study in this update (Fujita 2013). Pooled analyses showed that across these trials, the episode rates of acute URTIs were not statistically significant and the 95% CI crossed 1.0 (rate ratio 0.83; 95% CI 0.66 to 1.05, P value = 0.12) (Analysis 1.3). The level of heterogeneity between these trials was high (Chi^2 test 16.86; df = 4, P value = 0.002; I^2 statistic = 76%). We downgraded this outcome from high to very low quality for possible bias and high heterogeneity.

3. The mean duration of an episode of acute URTI

Three trials reported the mean duration of an episode of acute URTI (Fujita 2013; Smith 2013; Vrese 2005). There were 415 participants in the probiotics group and 416 participants in the placebo group. In two trials conducted among an adult population, the results show that the probiotics intervention was better (Smith 2013; Vrese 2005) (mean difference (MD) -1.90; 95% CI -2.04 to -1.76; P value < 0.001) (Analysis 1.4). One study, Fujita 2013, included old people (the mean age was 83 years old) and the results also showed that probiotics were better than placebo (MD -1.69; 95% CI -2.75 to -0.63; P value = 0.002) (Analysis 1.4). Pooled analyses showed that the mean duration of an episode of acute URTI after treatment was statistically significant (MD -1.89; 95% CI -.2.03 to -1.75; P value < 0.001). No significance was found on testing for heterogeneity in terms of the mean duration of an episode of acute URTI (Chi^2 test 0.44; df = 2, P value = 0.80; I^2 statistic = 0%). Although this outcome indicates that the difference in the mean duration of an episode of acute URTI was statistically significant between the probiotic and placebo groups, the data were only from the adult and elderly population and there was a small sample size. We downgraded this outcome from high to low quality for possible bias and small sample size.

See Summary of findings for the main comparison for overall assessment of the primary outcomes.

Secondary outcomes

1. Time off from childcare centre, school or work

One trial reported the number of participants who experienced cold-related school absence during the follow-up period (Rerksuppaphol 2012). Therefore, this outcome is from only this one study, which involved 40 participants in the probiotics group and 40 participants in the placebo group. There were 14 participants in the placebo group who experienced cold-related absence, whereas there were only two in the probiotics group. The difference was statistically significant (OR 0.10; 95% CI 0.02 to 0.47; Analysis 2.1). None of the included trials reported time off from childcare centres or work for acute URTIs. No data were available for this outcome. However, if data become available, we will include these data when the review is updated again. We downgraded this outcome from high to very low quality for possible bias and small sample size.

2. Prescribed antibiotics for acute URTIs

Four trials reported the prescription of antibiotics for acute URTIs (Hojsak 2010a; Hojsak 2010b; Rautava 2009; Rerksuppaphol 2012). One was a two-stage study reporting the number of participants using antibiotics (Rautava 2009). There were 593 participants in the probiotics group and 591 participants in the placebo group. Pooled analyses showed that the number of participants using antibiotics was statistically significant and the 95% CI did not span 1.0 (OR 0.65; 95% CI 0.45 to 0.94) (Analysis 3.1). No significance was found on testing for heterogeneity in this subgroup (Chi^2 test 1.26; df = 3, P value = 0.74; 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. We downgraded this outcome from high to moderate quality for possible bias.

3. Side effects or adverse events

Most of the included trials reported that side effects or adverse events from 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. Four trials reported side effects including diarrhoea, vomiting, bowel pain, loose stools, flatulence, nausea, etc. (Berggren 2010; Merenstein 2010; Rerksuppaphol 2012; Smith 2013). There were 614 participants in the probiotics group and 620 participants in the placebo group. Pooled analyses showed that the side effects following treatment were not statistically significantly different between the probiotics group and the placebo group (OR 0.88; 95% CI 0.65 to 1.19) (Analysis 4.1). We downgraded this outcome from high to very low quality for possible bias and small sample size.

See Summary of findings 2, Summary of findings 3 and Summary of findings 4 for overall assessment of the secondary outcomes.

Per-protocol analysis

We also conducted a per-protocol analyses and sensitivity analyses by excluding trials at high risk of bias. We found that this did not change the inference of the original analyses, see Analysis 5.1, Analysis 5.4, Analysis 5.3, Analysis 6.1, Analysis 7.1 and Analysis 8.1.

DISCUSSION

Summary of main results

In this review, we found that probiotics are better than placebo in reducing the number of participants who experience episodes of acute upper respiratory tract infection (URTI), the mean duration of an episode of acute URTI, antibiotic use and cold-related school absence. Adverse events were minor. However, these results must be interpreted with caution because the included outcomes were unsatisfactory and susceptible to bias due to the fact that some of them were extracted from only one or two trials, and in some subgroups the level of heterogeneity between pooled trials was

substantial. In addition, some trials had small sample sizes and the quality of the methods used in these trials was not very good. Furthermore, some trials did not assess the most important outcomes defined in this review as the main outcomes in their original trials.

Overall completeness and applicability of evidence

Probiotics for acute URTIs in children

In this review, most of the included trials were conducted in children (Caceres 2010; Hojsak 2010a; Hojsak 2010b; Merenstein 2010; Rautava 2009; Rerksuppaphol 2012; Rio 2002; Sanz 2006). We analysed subgroups according to the different ages of participants and found that probiotics showed a benefit in reducing the number of children who experienced URTI episodes. However, we did not find any trial reporting the duration of an episode of URTI in children. The probiotics were given in milk-based food, such as yogurt, for three months or more in most of the trials.

A double-blind, placebo-controlled randomised controlled trial (RCT), conducted in 18 municipal daycare centres, in similar socioeconomic areas in north, west and north-east Helsinki found that *Lactobacillus rhamnosus* GG milk may reduce the rate and severity of respiratory infections and antibiotic treatment among children in daycare centres (Hatakka 2001). Another study included 309 otitis-prone children (at least four episodes of acute otitis media). We included this study in the previous version of our review (Hatakka 2007). In this update, after reassessing it, we excluded it because otitis-prone children may have an immunodeficiency (Yamanaka 1997). In this study, the author also found that probiotics did not prevent the occurrence of acute otitis media or the nasopharyngeal carriage of otitis pathogens in otitis-prone children.

Probiotics for acute URTIs in the elderly and adults

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. Until now, only four trials have been found that compare probiotics to placebo in older people (Fujita 2013; Guillemard 2010; Makino 2010a; Turchet 2003). One study was a unicentric, randomised, stratified, open, pilot study, where 360 community residents over 60 years of age were randomised to receive (a) one 100 ml bottle of Actimel (a milk fermented with yogurt cultures and *Lactobacillus casei* (*L. casei*) DN-114 001, containing 10^8 colony-forming units (CFU)/ml *L. casei* DN-114 001) twice daily for three weeks, or (b) they were in the control group (Turchet 2003). 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 was also a multicentric, double-blind controlled trial, involving 1072 volunteers (median age 76 years) randomised to consumption of either probiotic strain *L. casei* DN-114 001 or control for three months (Guillemard 2010). The probiotic group was associated with a decreased duration of common infectious diseases in comparison to the control group, especially URTIs.

In our 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 had been vaccinated against influenza three months before the study (Turchet 2003). In addition, the study did not separate acute URTIs from other winter infections. Another study included participants vaccinated against the influenza virus prior to receiving the intervention (Guillemard 2010). We therefore decided to exclude these two trials.

One included study contains reports from two trials: the Funagata study and the Arita study (Makino 2010a). The Arita study was not a RCT, so we excluded it (Makino 2010b). However, the Funagata study had no available data that could be extracted 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.

For this update, we included a study considering the effect of probiotics among elderly people (mean age 83 years) (Fujita 2013). There were 76 participants in the probiotics group and 78 participants in the placebo group. The results showed that probiotics did not reduce the episode rates of acute URTIs, but did reduce the duration of acute URTIs.

Only three trials were conducted in adults and only one or two trials have adequate data in the subgroup analysis (Berggren 2010; Smith 2013; Vrese 2005). Two or three strains of probiotics were given through powder-like food in these trials. Therefore, more trials are needed in adult and elderly populations.

Probiotics for acute URTIs in athletes

We found four trials conducted in athletes (Gleeson 2010; Gleeson 2012; Kekkonen 2007; West 2011). Participants in two trials trained regularly (predominantly endurance-based activities such as running, cycling, swimming, triathlon, team games and racquet sports) (Gleeson 2010; Gleeson 2012). They ranged from the recreationally active to Olympic triathletes. In another trial were competitive cyclists (West 2011). One study reported that the URTI symptom incidence was significantly lower in the probiotic group than in the placebo group (Gleeson 2010). However, one study, Gleeson 2012, did not show that probiotics were beneficial in reducing the frequency of URTIs and one study was conducted among marathon runners (Kekkonen 2007). The results from the three-month training period stage of the study show that placebo was better than probiotics in reducing the mean duration of an episode of URTI (Kekkonen 2007). Another study reported that the effects of probiotic supplementation on URTI load were unclear (West 2011). In the Criteria for considering studies for this review, we only included participants who did normal physical exercise because it is indicated that high-intensity exercise training may affect the effectiveness of the probiotics or immune system (Witard 2012).

Clinical interpretation of the data

The analyses showed that probiotics were better than placebo in terms of the number of participants who experienced episodes of URTI, the mean duration of an episode of acute URTI, antibiotics used and the number of participants absent from school due to acute URTIs. This was also true for the URTI episode rate, 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 or two trials in each subgroup. We only found one study that reported school absence due to the common cold; more trials are needed to measure this outcome (Rerksuppaphol 2012). In addition to this,

different kinds of probiotics and follow-up periods were used in the trials, so that heterogeneity in some outcomes could not be avoided. We also need to remember that there were not enough data for adults and older people in our review. According to the included trials probiotics are safe and adverse effects are minor. The major side effects of probiotics were gastrointestinal symptoms such as diarrhoea, vomiting, flatulence and increased irritability. The limited results showed that probiotic therapy may provide more benefit than placebo in terms of episodes of infection, the duration of an episode of acute URTI, antibiotics used and cold-related school absence.

Quality of the evidence

Limitations of the trials included in this review

Allocation concealment was only described in two included trials (Fujita 2013; Merenstein 2010). Double-blinding was reported in 11 trials and details of the blinding methods were reported in seven trials. However, two trials did not document the type of blinding and four trials did not give details of the double-blinding. All of this could potentially have biased the results in favour of treatment (Figure 3).

After assessment of the overall quality of the evidence, we downgraded our primary outcomes from high to low or very low quality, usually for unclear sequence generation or allocation concealment and high risk of bias due to funding by related companies. In addition, we also found in some subgroup analyses that there were very small sample sizes and higher levels of statistical heterogeneity, which caused serious inconsistency between the included trials.

Potential biases in the review process

In our review, 13 studies met our inclusion criteria. However, we were able to extract data for meta-analysis in 12 of the studies, which may introduce potential bias. On the other hand, we tried our best to identify all the relevant studies and performed analyses base on both ITT population and per-protocol population. These would be helpful in reducing potential bias in the review process.

Agreements and disagreements with other studies or reviews

Another systematic review has also focused on *Lactobacillus rhamnosus* GG supplementation for preventing respiratory infections among children (Liu 2013). Although they only included four RCTs, they found that probiotics have the potential to reduce the incidence of acute otitis media and respiratory infections compared with placebo. Two trials did not separate acute URTIs from the whole respiratory tract. However, the result was similar to this review.

We identified two excluded trials that did not show any benefit of probiotics compared with placebo in the duration or incidence of URTIs (Gleeson 2012; Kekkonen 2007). Both trials were performed in endurance athletes; the excessive training may have influenced the effect of the probiotics. We also found one study conducted amongst older people that found that probiotics only can reduce the duration of acute URTIs rather than the number of participants who experienced URTI episodes (Fujita 2013). Currently, we have not found any other systematic reviews that conflict with this review. However, there are systematic reviews that focus on the critically ill or ventilator-associated pneumonia patients which, according to the current evidence, have shown less beneficial effect (Barraud 2013; Gu 2012).

AUTHORS' CONCLUSIONS

Implications for practice

Currently available low quality 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 mean duration of an episode of acute URTI, antibiotic use and cold-related school absence. There was no statistically significant difference in terms of the rate ratio for episodes of acute URTI. Although this review indicates that probiotics may be more beneficial than placebo for preventing acute URTIs, the quality of the current evidence is low.

Implications for research

Future randomised controlled trials should consider:

1. a study design that incorporates adequate blinding and concealment of the allocation sequence;
2. 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. focusing on older people or performing a subgroup analysis of older people;
4. side effect outcomes: time off from childcare centre, school or work; cost-effectiveness and quality of life; and
5. studies should not be influenced by funds from manufacturers of the tested probiotics.

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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 the probiotic bacteria group; 23 in the placebo group
Participants	Country: Sweden Setting: Lund and Uppsala No. of participants: 318; 159 in the probiotic bacteria group, 159 in the placebo group

Berggren 2010 *(Continued)*

	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 (1×10^9 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	The authors are employees at Probi AB and the study was funded by Probi AB

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
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
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
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	High risk	This study was partly supported by Probi AB and the authors are employees of this company

Caceres 2010

Methods	Study design: prospective, multicentre, 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: 3 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^{10} CFU/day of the probiotic strain (*L. rhamnosus* HN001) for 3 months 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. Number of days with respiratory illnesses 2. Number of days with antibiotic treatments 3. Number of days of absence from the daycare centre due to respiratory illness
Notes	This study was supported by Danisco, Copenhagen, Denmark

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

Caceres 2010 *(Continued)*

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
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
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	High risk	This study was supported by Danisco, Copenhagen, Denmark

Fujita 2013

Methods	Study design: a multicentre, double-blind, placebo-controlled, randomised clinical study with 2 parallel arms Method of randomisation: central enrolment system (block size 4). Allocation was performed independently from researchers by the data centre allocation co-ordinator, who also retained the allocation list until observations were complete Blinding: double-blind but no description of the details. The participants and study personal may have been blinded Duration: 7 months: 1 December 2009 to 30 June 2010 Exclusions post-randomisation: 14 Losses to follow-up: 20
Participants	Country: Japan Setting: 4 daycare facilities for elderly people located around Tokyo No. of participants: 154; 76 in the LcS group; 78 in the placebo group Age: aged 83.2 ± 9.1 years Inclusion criteria: older volunteers in daycare facilities Exclusion criteria: people with a history of allergy to dairy products or people consuming lactic acid bacteria-containing food or drink on a regular basis (at least 4 days per week)
Interventions	Treatment group: *Lactobacillus casei strain Shirota* (4.0×10^{10} CFU/day) with high-fructose corn syrup, sugar and skimmed milk powder for 5 months Control group: placebo: an identical-looking and tasting control product with the same energy (62 kcal) as the intervention group
Outcomes	1. Occurrence of an URTI event 2. Duration of infection

Fujita 2013 *(Continued)*

	3. Symptom score (burden)
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central enrolment system
Allocation concealment (selection bias)	Low risk	Allocation was performed independently from the researchers by the data centre allocation co-ordinator
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind but no description of the details; the participants and study personnel may have been blinded
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of the details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of the details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	About 13% of participants were lost to follow-up and the analysis of the study was based on the intention-to-treat population
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Unclear risk	Small sample size may be a source of other bias

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 (Zagreb area) Setting: daycare centres No. of participants: 281; 139 in the probiotic bacteria group, 142 in the placebo group Age: 13 to 86 months

Hojsak 2010a *(Continued)*

	Inclusion criteria: those attending a 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 CFU/day Control group: the same post-pasteurised fermented milk product (100 ml) without LGG Length of follow-up: 3-month period
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	All authors stated that they have no conflict of interest

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
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
Incomplete outcome data (attrition bias)	Unclear risk	27 participants lost to follow-up and the analysis of the study was based on the intention-to-treat population

Hojsak 2010a *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Unclear risk	Small sample size may be a source of other bias

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 the probiotic bacteria group; 12 in the placebo group
Participants	Country: Zagreb, 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 CFU/day 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

Hojsak 2010b *(Continued)*

Notes	Probiotic strain was supplied by Valio Ltd.

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
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
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
Selective reporting (reporting bias)	Low risk	The study reported all the outcomes
Other bias	Unclear risk	Probiotic strain was supplied by Valio Ltd.

Makino 2010a

Methods	Study design: randomised, placebo-controlled, parallel-group intervention study Method of randomisation: not clearly stated Blinding: not clearly stated Duration: 8 weeks: 13 March 2006 to 5 February 2007 Exclusions post-randomisation: 0 Losses to follow-up: 3: 1 in the probiotic group; 2 in the placebo group
Participants	Country: Japan Setting: Yamagata Prefecture No. of participants: 60; 30 in the probiotic bacteria group, 30 in the 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 1.8 to 3.2 × 10^{10} CFU/day and 5.7 to 7.9 × 10^{10} CFU/day, 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
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
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Unclear risk	Small sample size may be a source of other bias

Merenstein 2010

Methods	Study design: double-blind, placebo-controlled, randomised, patient-oriented trial 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: 90 consecutive days

Merenstein 2010 *(Continued)*

	Exclusions post-randomisation: 0 Losses to follow-up: 74: 22 in the probiotic bacteria group; 52 in the placebo group
Participants	Country: Washington, DC USA Setting: attending daycare centre/school 5 days a week No. of participants: 638; 314 in the probiotics group; 324 in the placebo group Age (years): between the age of 3 and 6 years Gender: 309 female, 329 male: probiotics group (157 female, 157 male); placebo group (152 female, 172 male) 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 2×10^{10} CFU/day of *L. casei* DN-114001; symbiotic cultures, *S. thermophilus* and *L. bulgaricus* were also present in the final product at levels 10^9 CFU/day 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. Change of behaviour because of illness as assessed by parents 2.Rate of CIDs Secondary endpoints: 1. Absences from daycare or school because of illness 2. Missed parental work 3. Adverse events
Notes	This was an investigator-initiated industry-funded study by The Dannon Company, Inc. However, the non-industry authors performed the study

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
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)	Low risk	Double-blind: patient, provider and assessor were blinded

Merenstein 2010 *(Continued)*

All outcomes		
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
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
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Unclear risk	This was an investigator-initiated industry-funded study by The Dannon Company, Inc. However, the non-industry authors performed the study

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 probiotic bacteria group; 1 in the placebo group
Participants	Country: Finland Setting: Turku No. of participants: 81; 38 in the probiotic bacteria group; 43 in the placebo group Age: 0 to 2 month-old infants Gender: male 35: 16 in the probiotic bacteria group; 19 in the 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} CFU/day 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

Rautava 2009 *(Continued)*

Notes	The probiotics were acquired without cost from the company

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	Double-blind: patient, provider and assessor were blinded
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
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 3 participants lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Unclear risk	The probiotics were acquired without cost from the company

Rerksuppaphol 2012

Methods	Study design: a double-blind, placebo-controlled, randomised clinical study with 2 parallel arms Method of randomisation: a computerised program using blocks of 2 by a person not involved in the study Blinding: double-blind: the investigators, teachers, children and parents were blinded Duration: November 2011 to January 2011 Exclusions post-randomisation and losses to follow-up: 4: 2 in the probiotic group; 2 in the control group
Participants	Country: Thailand Setting: a public school in a rural area No. of participants: 80; 40 in the probiotic group; 40 in the placebo group Age: aged 8 to 13 years Inclusion criteria: healthy children

Rerksuppaphol 2012 *(Continued)*

	Exclusion criteria: history of chronic illnesses, such as chronic cough or chronic respiratory disease, asthma, chronic gastrointestinal conditions, behavioural or psychiatric problems or other neurological conditions, immune deficiency, diabetes mellitus, malignancy, chronic renal diseases, congenital heart diseases or chronic liver disease were excluded. Children who were taking vitamin or mineral supplements or had a history of any drug allergy were also excluded
Interventions	Treatment group:*Lactobacillus acidophilus* (minimum of 10^9/capsule) and *Bifidobacterium bifidum* (minimum of 10^9/capsule) twice a day for 3 months Control group: placebo: an identical-looking control
Outcomes	1. Symptoms of common cold 2. Number of symptoms of common cold 3. Duration of symptoms, school absence and antibiotic usage
Notes	The manufacturer had no role in the planning, execution or analysis of the study and no financial or material support was received from them

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computerised program was used
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: the investigators, teachers, children and parents were blinded
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The investigators, teachers, children and parents were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigators, teachers, children and parents were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	5% of participants lost to follow-up and the analysis of the study was based on the intention-to-treat population
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Unclear risk	Small sample size may be a source of other bias

Rio 2002

Methods	Study design: randomised, placebo-controlled trial Method of randomisation: not clearly stated

Rio 2002 *(Continued)*

	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 probiotic 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 the probiotic bacteria group; 50 in the 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, 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 (10^9/10^{10} CFU/day) Control group: an equivalent amount of fluid milk Length of follow-up: at least 90 days
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
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

Rio 2002 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	42% of participants lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Unclear risk	Small sample size may be a source of other bias

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 the probiotic bacteria group; 6 in the placebo group
Participants	Country: Spain Setting: infant schools in Barcelona No. of participants: 251; 142 in the probiotic bacteria group; 109 in the placebo group Age: 3 to 12 years Gender: 133 female, 118 male: probiotic bacteria group (88 female, 54 male); placebo group (45 female, 64 male) Inclusion criteria: sample included all children aged 3 to 12 years studying in selected schools Exclusion criteria: none
Interventions	Treatment group: 2 units daily of Actimel (a milk fermented with *Lactobacillus casei* (DN-114 001) for 20 weeks Control group: during the same period, 2 units of 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	The study was funded by Danone

Sanz 2006 *(Continued)*

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
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of the details; the participants may have been blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of the details
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
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	High risk	The study was funded by Danone

Smith 2013

Methods	Study design: a double-blind, placebo-controlled, randomised clinical study with 2 parallel arms Method of randomisation: using an Internet-based random number generator (GraphPad Random Number Generator, 2005) Blinding: double-blind: the investigators and participants were blinded Duration: February 2011 to May 2011 Exclusions post-randomisation: 23: 13 in the probiotic group; 20 in the control group Losses to follow-up: 18: 6 in the probiotic group; 12 in the control group
Participants	Country: USA Setting: Framingham State University No. of participants: 198: 97 in the probiotic group; 101 in the placebo group Age: aged 18 to 24 years Inclusion criteria: all students living on campus in residence halls Exclusion criteria: under 18 years of age or over 25 years of age; experienced chronic perennial allergies; pregnant; with medical conditions affecting immune function; acute pancreatitis, undergoing

Smith 2013 *(Continued)*

	treatment for cancer or taking immunosuppressive drugs for an autoimmune disease or post-transplant
Interventions	Treatment group: 10^9 CFU *Lactobacillus rhamnosus LGG* and *Bifidobacterium animalis ssp. lactis BB-12* in powder form (Chr. Hansen A/S)/stick/day for 12 weeks Control group: placebo: an identical-looking and tasting control
Outcomes	1. Health-related quality of life 2. Missed school and work days
Notes	The present study was funded by Chr Hansen, which was only in the role of study design and final report

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Internet-based random number generator (GraphPad Random Number Generator, 2005)
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: the investigators and participants were blinded
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The investigators and participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigators and participants were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	9% of participants lost to follow-up and the analysis of the study was based on the intention-to-treat population
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Unclear risk	The present study was funded by Chr Hansen, which was only in the role of study design and final report

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

Vrese 2005 *(Continued)*

	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 the probiotic bacteria group; 12 in the placebo group
Participants	Country and setting: not clearly stated No. of participants: 479; 238 in the probiotic bacteria group, 241 in the placebo group Age: (average age, 38 ± 13): probiotic bacteria group (average age, 37 ± 12); placebo group (average age, 38 ± 14) Gender: male: 185: 86 in the probiotic bacteria group; 99 in the placebo group Inclusion criteria: 479 healthy women and men were included after physical examination Exclusion criteria: those with 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 were 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
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded

Vrese 2005 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	The assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	5.2% of participants lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Unclear risk	Small sample size may be a source of other bias

AOM: acute otitis media
ARI: acute respiratory infection
CFU: colony-forming units
CIDs: common infectious diseases
FOS: fructo-oligosaccharides
GI: gastrointestinal
GOS: galacto-oligosaccharides
IcFOS: long-chain fructo-oligosaccharides
LcS: *Lactobacillus casei strain Shirota*
LGG: *Lactobacillus rhamnosus* GG
scGOS: short-chain galacto-oligosaccharides
URI: upper respiratory infection
URTI: upper respiratory tract infection

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

Study	Reason for exclusion
Agustina 2012	The study did not separate URTIs from other respiratory infections
Arslanoglu 2008	The study used prebiotics (GOS and FOS)
Di Pierro 2014	The study is a non-randomised trial
Gil-Campos 2012	The study did not separate URTIs from other respiratory infections
Gleeson 2010	The study focuses on endurance training athletes
Gleeson 2012	The study focuses on endurance training athletes
Guillemard 2010	The study included participants vaccinated against the influenza virus
Gutierrez-Castrellon 2014	The study did not separate URTIs from other respiratory infections
Hatakka 2001	The study did not separate URTIs from other respiratory infections
Hatakka 2007	The participants in this study were otitis-prone children, which may be associated with immunodeficency
Haywood 2014	This is a cross-over study
Kekkonen 2007	The study focuses on marathon running athletes

Study	Reason for exclusion
Kukkonen 2008	The study did not separate URTIs from other respiratory infections and did not separate AOM from middle ear infections
Kumpu 2012	The study did not separate URTIs from other respiratory infections
Kumpu 2013	The study did not separate URTIs from other respiratory infections
Lehtoranta 2012	The study only analysed the bocavirus in the nasopharynx and included children who had at least 3 episodes during the preceding 12 months
Leyer 2009	The study only reported cold or influenza-like symptoms but did not diagnose URTIs
Lin 2009	The study compared 2 different probiotics
Luoto 2013	The study only reported symptoms of respiratory tract infection, but did not diagnose URTIs
Makino 2010b	The Arita was study reported in this trial but was not a RCT
Maldonado 2012	The study included about 70% of participants vaccinated against rotavirus
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 not adequate data to extract from 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 against influenza 3 months before the study and the study did not separate URTIs from other respiratory infections
West 2011	The study focuses on cyclists and triathletes
West 2014	The participants in this study included competitive athletes at a regional level

AOM: acute otitis media
FOS: fructo-oligosaccharides
GOS: galacto-oligosaccharides
RCT: randomised controlled 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	Not known
Interventions	Not known

Kaplan 1968 *(Continued)*

Outcomes	Not known
Notes	Not known

Marushko 2000

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

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

NCT01935986

Trial name or title	The effect of a probiotic on protection against upper respiratory tract infections in children
Methods	A double-blind, placebo-controlled, randomised clinical study with parallel arms
Participants	Aged 1 to 6 years; included both genders
Interventions	Probiotic and placebo
Outcomes	No information provided
Starting date	August 2013
Contact information	anna.broman@foodfiles.se
Notes	—

NCT02013934

Trial name or title	Probiotics in prevention of common cold
Methods	A double-blind, placebo-controlled, randomised clinical study with parallel arms
Participants	Aged 18 to 70 years; included both genders
Interventions	Probiotic and placebo
Outcomes	Primary outcome measures: severity of cold symptoms Secondary outcome measures: incidence of common cold episodes
Starting date	October 2013

NCT02013934 *(Continued)*

Contact information	ila@probi.se
Notes	—

DATA AND ANALYSES

Comparison 1. ITT analysis: probiotics versus placebo - primary outcome measures

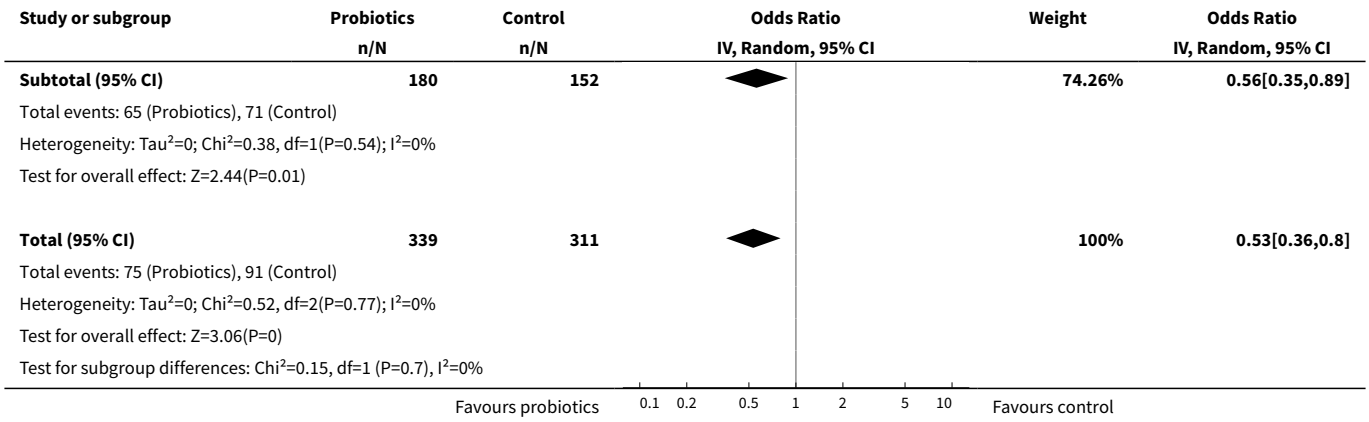
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The number of participants who experienced URTI episodes: at least 1 event	7	1927	Odds Ratio (IV, Random, 95% CI)	0.53 [0.37, 0.76]
1.1 Adults	1	318	Odds Ratio (IV, Random, 95% CI)	0.68 [0.44, 1.06]
1.2 Children	5	1457	Odds Ratio (IV, Random, 95% CI)	0.43 [0.29, 0.63]
1.3 Elderly	1	152	Odds Ratio (IV, Random, 95% CI)	0.95 [0.50, 1.81]
2 The 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]
2.1 Adults	1	318	Odds Ratio (IV, Random, 95% CI)	0.47 [0.21, 1.03]
2.2 Children	2	332	Odds Ratio (IV, Random, 95% CI)	0.56 [0.35, 0.89]
3 The rate ratio of episodes of acute URTI	5	1608	Rate Ratio (Random, 95% CI)	0.83 [0.66, 1.05]
3.1 Adults	1	318	Rate Ratio (Random, 95% CI)	0.71 [0.56, 0.90]
3.2 Children	3	1136	Rate Ratio (Random, 95% CI)	0.77 [0.57, 1.05]
3.3 Elderly	1	154	Rate Ratio (Random, 95% CI)	1.37 [0.94, 1.99]
4 The mean duration of an episode of URTI	3	831	Mean Difference (IV, Random, 95% CI)	-1.89 [-2.03, -1.75]
4.1 Adults	2	677	Mean Difference (IV, Random, 95% CI)	-1.90 [-2.04, -1.76]
4.2 Elderly	1	154	Mean Difference (IV, Random, 95% CI)	-1.69 [-2.75, -0.63]

Analysis 1.1. Comparison 1 ITT analysis: probiotics versus placebo - primary outcome measures, Outcome 1 The number of participants who experienced URTI episodes: at least 1 event.

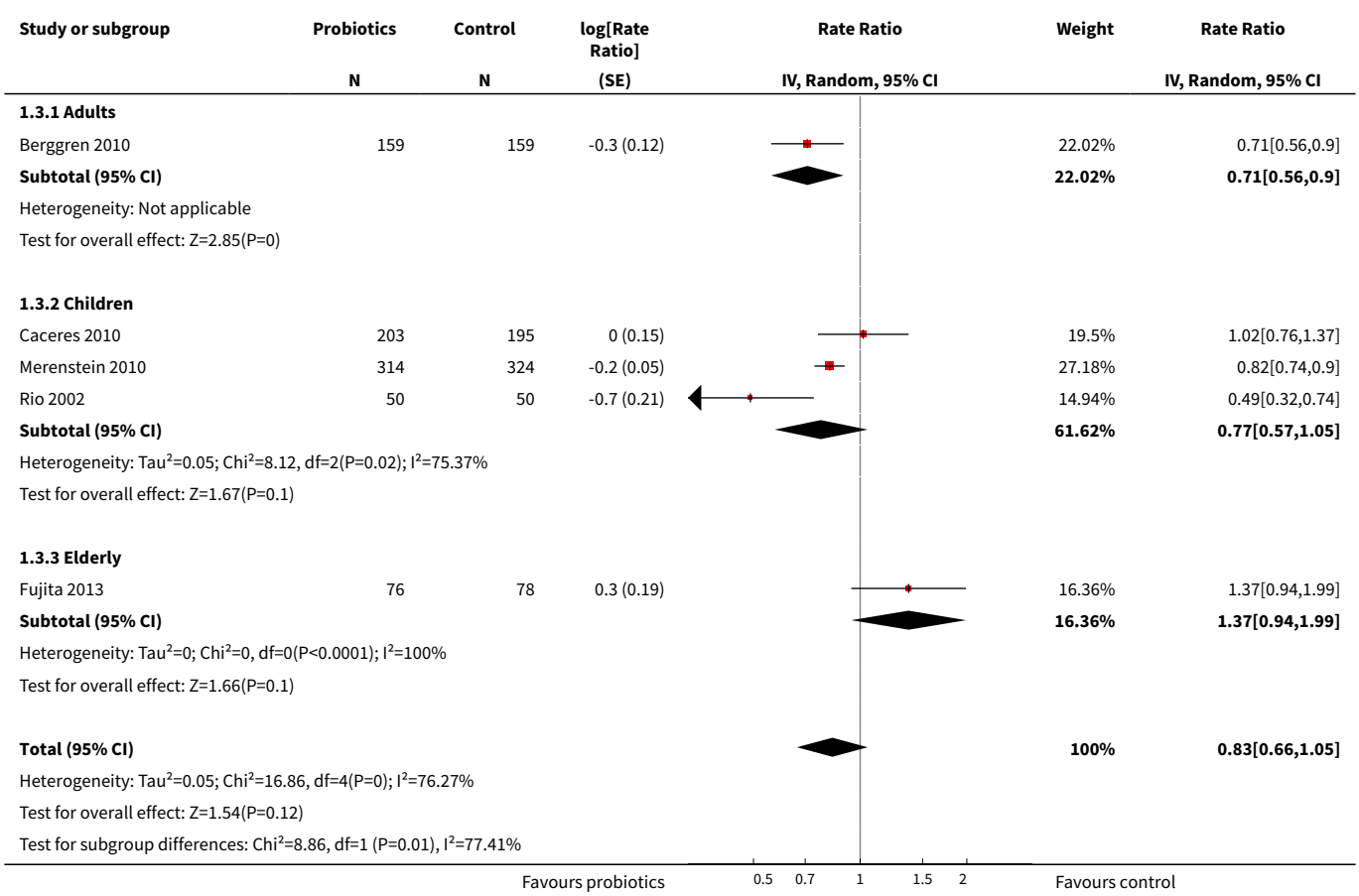
Study or subgroup	Probiotics n/N	Control n/N	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
1.1.1 Adults					
Berggren 2010	76/159	91/159		21.45%	0.68[0.44,1.06]
Subtotal (95% CI)	**159**	**159**		**21.45%**	**0.68[0.44,1.06]**
Total events: 76 (Probiotics), 91 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.68(P=0.09)					
1.1.2 Children					
Hojsak 2010a	58/139	95/142		20.06%	0.35[0.22,0.58]
Hojsak 2010b	8/376	20/366		11.58%	0.38[0.16,0.87]
Rautava 2009	7/38	20/43		8.82%	0.26[0.09,0.72]
Rerksuppaphol 2012	6/40	12/40		7.84%	0.41[0.14,1.24]
Sanz 2006	21/158	18/115		14.7%	0.83[0.42,1.63]
Subtotal (95% CI)	**751**	**706**		**62.99%**	**0.43[0.29,0.63]**
Total events: 100 (Probiotics), 165 (Control)					
Heterogeneity: Tau^2=0.04; Chi^2=5.19, df=4(P=0.27); I^2=22.86%					
Test for overall effect: Z=4.33(P<0.0001)					
1.1.3 Elderly					
Fujita 2013	31/76	32/76		15.56%	0.95[0.5,1.81]
Subtotal (95% CI)	**76**	**76**		**15.56%**	**0.95[0.5,1.81]**
Total events: 31 (Probiotics), 32 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.16(P=0.87)					
Total (95% CI)	**986**	**941**		**100%**	**0.53[0.37,0.76]**
Total events: 207 (Probiotics), 288 (Control)					
Heterogeneity: Tau^2=0.1; Chi^2=11.34, df=6(P=0.08); I^2=47.11%					
Test for overall effect: Z=3.48(P=0)					
Test for subgroup differences: Chi^2=5.2, df=1 (P=0.07), I^2=61.51%					

Analysis 1.2. Comparison 1 ITT analysis: probiotics versus placebo - primary outcome measures, Outcome 2 The number of participants who experienced URTI episodes: at least 3 events.

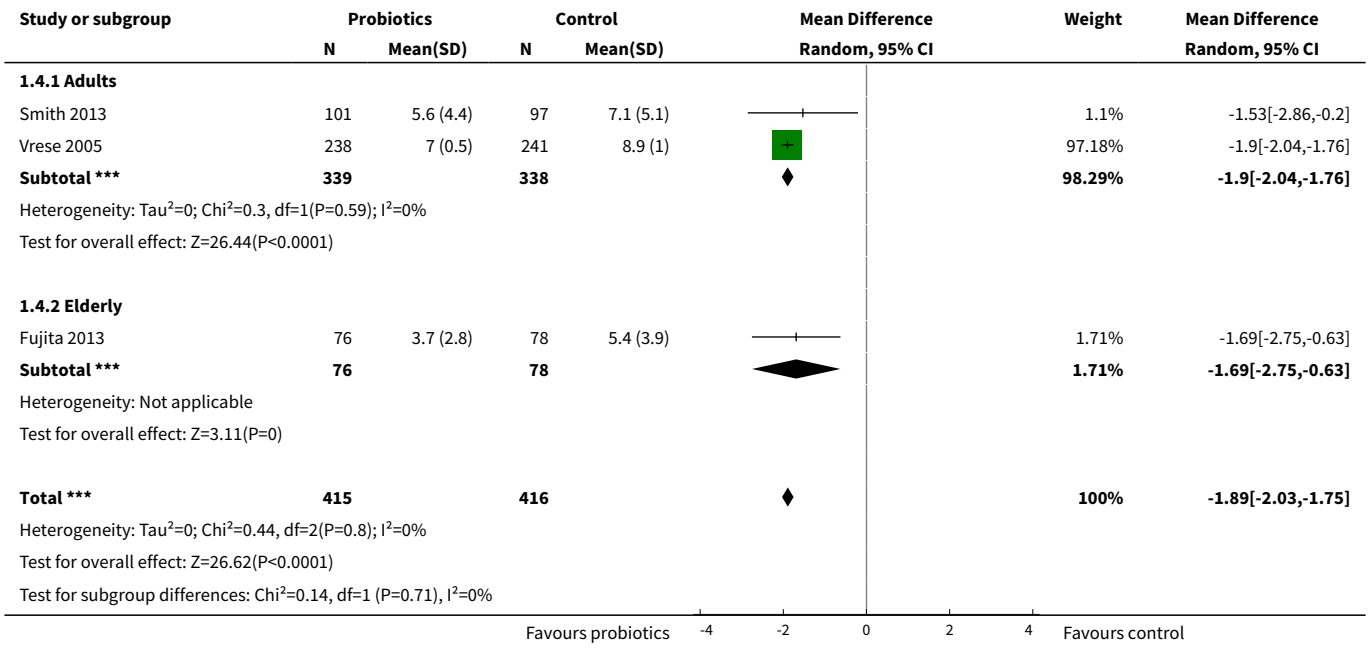
Study or subgroup	Probiotics n/N	Control n/N	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
1.2.1 Adults					
Berggren 2010	10/159	20/159		25.74%	0.47[0.21,1.03]
Subtotal (95% CI)	**159**	**159**		**25.74%**	**0.47[0.21,1.03]**
Total events: 10 (Probiotics), 20 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.88(P=0.06)					
1.2.2 Children					
Rautava 2009	4/38	10/43		10.3%	0.39[0.11,1.36]
Sanz 2006	61/142	61/109		63.96%	0.59[0.36,0.98]



Analysis 1.3. Comparison 1 ITT analysis: probiotics versus placebo - primary outcome measures, Outcome 3 The rate ratio of episodes of acute URTI.



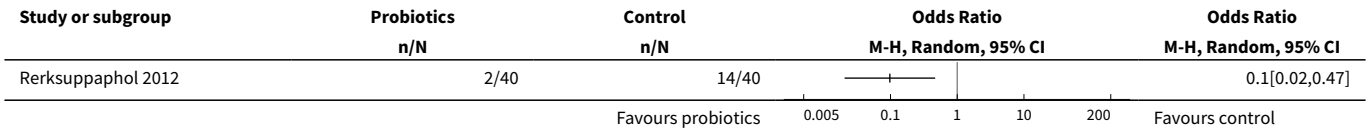
Analysis 1.4. Comparison 1 ITT analysis: probiotics versus placebo - primary outcome measures, Outcome 4 The mean duration of an episode of URTI.



Comparison 2. ITT analysis: probiotics versus placebo - time off from childcare centre, school or work

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The number of participants who were absent due to URTIs	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 ITT analysis: probiotics versus placebo - time off from childcare centre, school or work, Outcome 1 The number of participants who were absent due to URTIs.

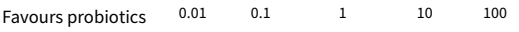


Comparison 3. ITT analysis: probiotics versus placebo - prescribed antibiotics for acute URTIs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The number of participants who used antibiotics	4	1184	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.45, 0.94]

Analysis 3.1. Comparison 3 ITT analysis: probiotics versus placebo - prescribed antibiotics for acute URTIs, Outcome 1 The number of participants who used antibiotics.

Study or subgroup	Probiotics 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		59.21%	0.68[0.42,1.11]
Hojsak 2010b	1/376	4/366		2.93%	0.24[0.03,2.17]
Rautava 2009	10/38	16/43		32.26%	0.71[0.37,1.37]
Rerksuppaphol 2012	2/40	5/40		5.6%	0.4[0.08,1.94]
Total (95% CI)	**593**	**591**		**100%**	**0.65[0.45,0.94]**
Total events: 35 (Probiotics), 58 (Control)					
Heterogeneity: Tau²=0; Chi²=1.26, df=3(P=0.74); I²=0%					
Test for overall effect: Z=2.26(P=0.02)					

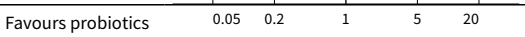


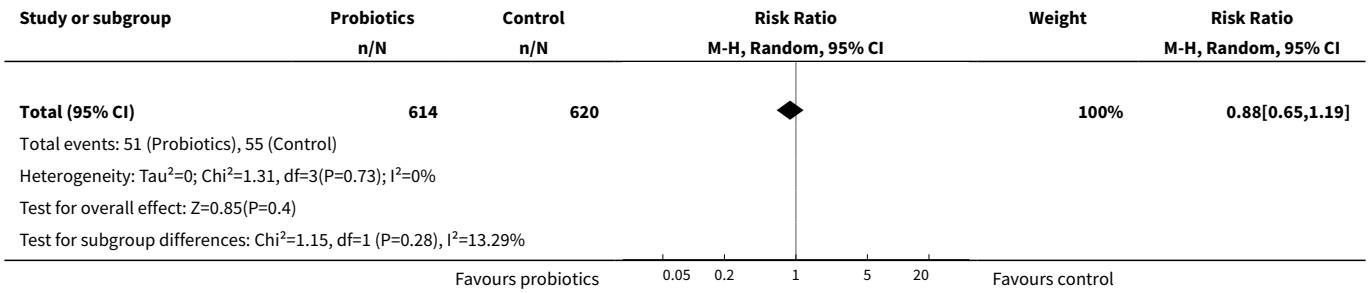
Comparison 4. ITT analysis: probiotics versus placebo - side effects or adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The number of side effects	4	1234	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.65, 1.19]
1.1 Adults	2	516	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.66, 1.81]
1.2 Children	2	718	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.53, 1.13]

Analysis 4.1. Comparison 4 ITT analysis: probiotics versus placebo - side effects or adverse events, Outcome 1 The number of side effects.

Study or subgroup	Probiotics n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 Adults					
Berggren 2010	3/159	3/159		3.65%	1[0.2,4.88]
Smith 2013	23/101	20/97		32.55%	1.1[0.65,1.88]
Subtotal (95% CI)	**260**	**256**		**36.2%**	**1.09[0.66,1.81]**
Total events: 26 (Probiotics), 23 (Control)					
Heterogeneity: Tau²=0; Chi²=0.01, df=1(P=0.91); I²=0%					
Test for overall effect: Z=0.35(P=0.73)					
4.1.2 Children					
Merenstein 2010	6/314	7/324		7.86%	0.88[0.3,2.6]
Rerksuppaphol 2012	19/40	25/40		55.94%	0.76[0.51,1.14]
Subtotal (95% CI)	**354**	**364**		**63.8%**	**0.77[0.53,1.13]**
Total events: 25 (Probiotics), 32 (Control)					
Heterogeneity: Tau²=0; Chi²=0.07, df=1(P=0.79); I²=0%					
Test for overall effect: Z=1.32(P=0.19)					



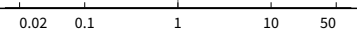


Comparison 5. Per-protocol analysis: probiotics versus placebo - primary outcome measures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants who experienced URTI episodes: at least 1 event	7	1760	Odds Ratio (IV, Random, 95% CI)	0.51 [0.34, 0.77]
1.1 Adults	1	275	Odds Ratio (IV, Random, 95% CI)	0.60 [0.37, 0.97]
1.2 Children	5	1351	Odds Ratio (IV, Random, 95% CI)	0.41 [0.25, 0.69]
1.3 Elderly	1	134	Odds Ratio (IV, Random, 95% CI)	1.00 [0.51, 1.96]
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]
2.1 Adults	1	275	Odds Ratio (IV, Random, 95% CI)	0.45 [0.20, 1.00]
2.2 Children	2	307	Odds Ratio (IV, Random, 95% CI)	0.60 [0.37, 0.98]
3 The rate ratio of episodes of acute URTI	5	1380	Rate Ratio (Random, 95% CI)	0.91 [0.71, 1.16]
3.1 Adults	1	275	Rate Ratio (Random, 95% CI)	0.70 [0.55, 0.89]
3.2 Children	3	971	Rate Ratio (Random, 95% CI)	0.89 [0.64, 1.23]
3.3 Elderly	1	134	Rate Ratio (Random, 95% CI)	1.37 [0.94, 1.99]
4 The mean duration of an episode of URTI	3	768	Mean Difference (IV, Random, 95% CI)	-1.89 [-2.04, -1.75]
4.1 Adults	2	634	Mean Difference (IV, Random, 95% CI)	-1.90 [-2.04, -1.75]
4.2 Elderly	1	134	Mean Difference (IV, Random, 95% CI)	-1.69 [-2.83, -0.55]

Analysis 5.1. Comparison 5 Per-protocol analysis: probiotics versus placebo - primary outcome measures, Outcome 1 Number of participants who experienced URTI episodes: at least 1 event.

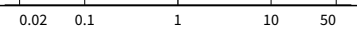
Study or subgroup	Probiotics n/N	Control n/N	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
5.1.1 Adults					
Berggren 2010	76/139	91/136		19.21%	0.6[0.37,0.97]
Subtotal (95% CI)	**139**	**136**		**19.21%**	**0.6[0.37,0.97]**
Total events: 76 (Probiotics), 91 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.07(P=0.04)					
5.1.2 Children					
Hojsak 2010a	58/127	95/127		18.32%	0.28[0.17,0.48]
Hojsak 2010b	8/360	20/354		12.72%	0.38[0.16,0.87]
Rautava 2009	7/36	20/42		10.08%	0.27[0.1,0.74]
Rerksuppaphol 2012	6/38	12/38		9.12%	0.41[0.13,1.23]
Sanz 2006	21/126	18/103		15.15%	0.94[0.47,1.89]
Subtotal (95% CI)	**687**	**664**		**65.4%**	**0.41[0.25,0.69]**
Total events: 100 (Probiotics), 165 (Control)					
Heterogeneity: Tau^2=0.17; Chi^2=8.18, df=4(P=0.09); I^2=51.1%					
Test for overall effect: Z=3.4(P=0)					
5.1.3 Elderly					
Fujita 2013	31/66	32/68		15.4%	1[0.51,1.96]
Subtotal (95% CI)	**66**	**68**		**15.4%**	**1[0.51,1.96]**
Total events: 31 (Probiotics), 32 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.01(P=0.99)					
Total (95% CI)	**892**	**868**		**100%**	**0.51[0.34,0.77]**
Total events: 207 (Probiotics), 288 (Control)					
Heterogeneity: Tau^2=0.17; Chi^2=14.1, df=6(P=0.03); I^2=57.46%					
Test for overall effect: Z=3.21(P=0)					
Test for subgroup differences: Chi^2=4.17, df=1 (P=0.12), I^2=52.04%					



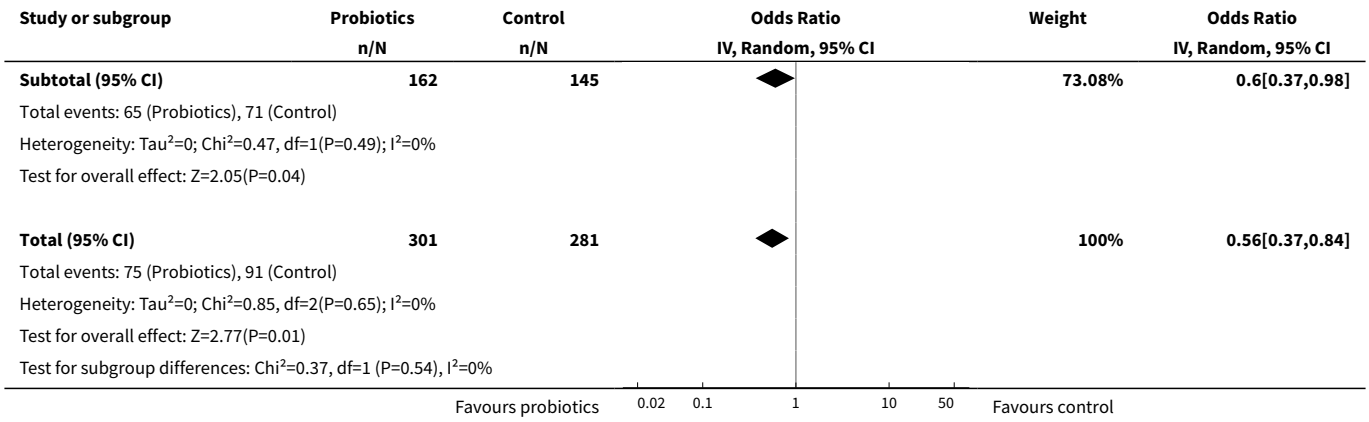
Favours probiotics — Favours control

Analysis 5.2. Comparison 5 Per-protocol analysis: probiotics versus placebo - primary outcome measures, Outcome 2 Number of participants who experienced URTI episodes: at least 3 events.

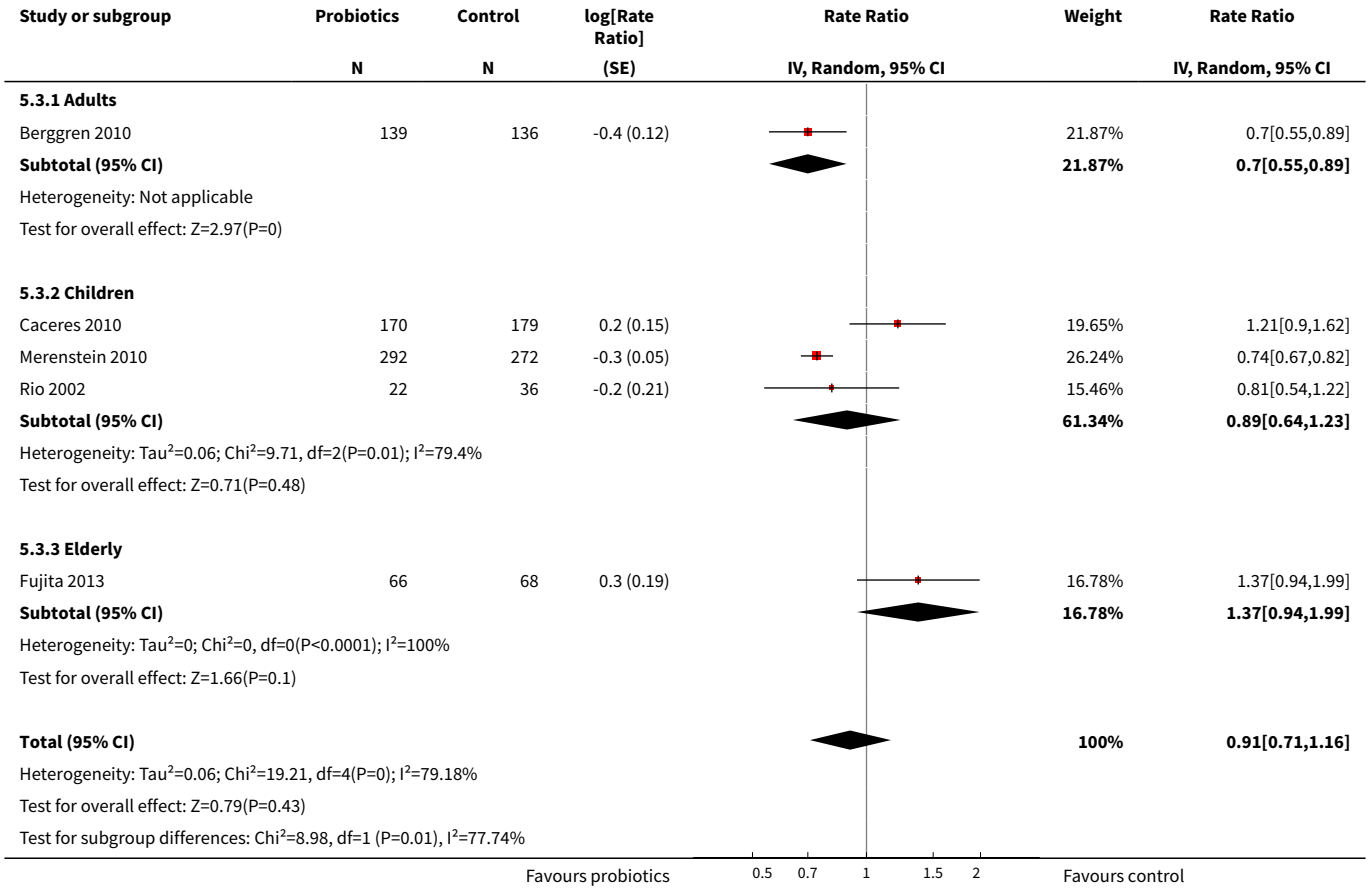
Study or subgroup	Probiotics n/N	Control n/N	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
5.2.1 Adults					
Berggren 2010	10/139	20/136		26.92%	0.45[0.2,1]
Subtotal (95% CI)	**139**	**136**		**26.92%**	**0.45[0.2,1]**
Total events: 10 (Probiotics), 20 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=1.96(P=0.05)					
5.2.2 Children					
Rautava 2009	4/36	10/42		10.86%	0.4[0.11,1.41]
Sanz 2006	61/126	61/103		62.22%	0.65[0.38,1.09]



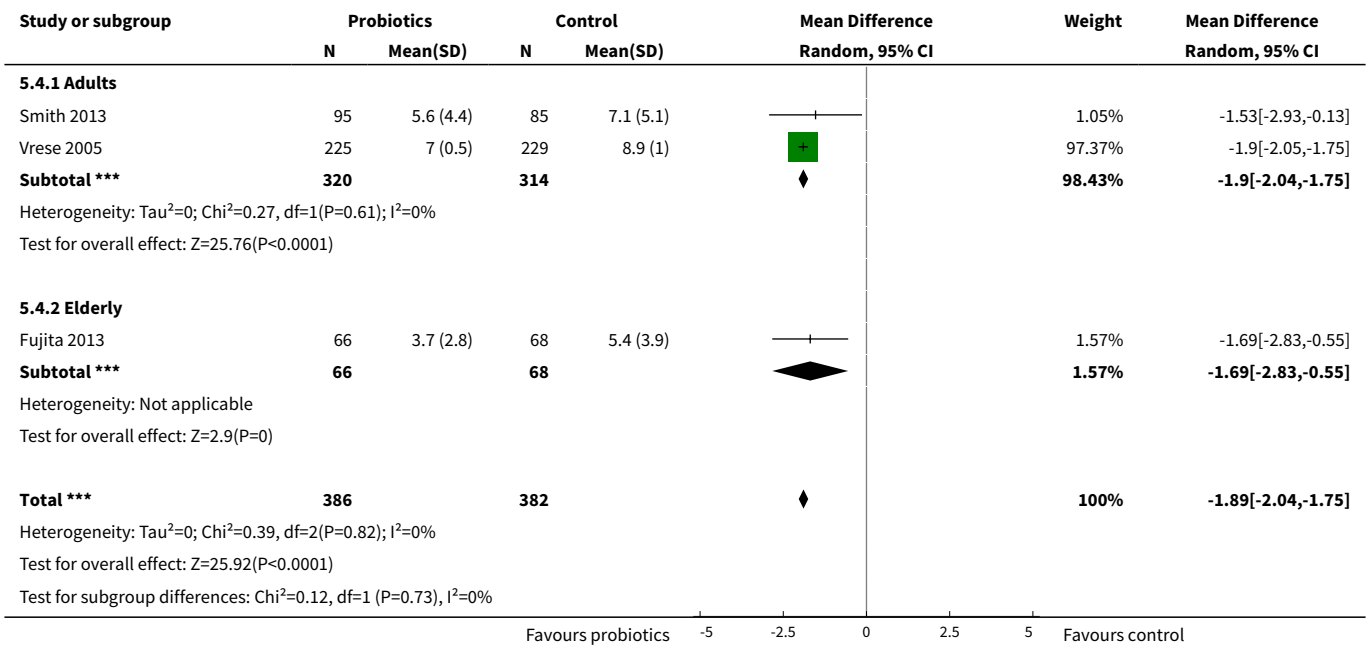
Favours probiotics — Favours control



Analysis 5.3. Comparison 5 Per-protocol analysis: probiotics versus placebo - primary outcome measures, Outcome 3 The rate ratio of episodes of acute URTI.



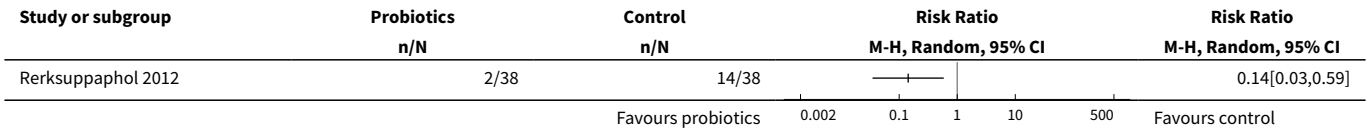
Analysis 5.4. Comparison 5 Per-protocol analysis: probiotics versus placebo - primary outcome measures, Outcome 4 The mean duration of an episode of URTI.



Comparison 6. Per-protocol analysis: probiotics versus placebo - time off from childcare centre, school or work

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The number of participants who experienced school absence due to URTIs	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 6.1. Comparison 6 Per-protocol analysis: probiotics versus placebo - time off from childcare centre, school or work, Outcome 1 The number of participants who experienced school absence due to URTIs.

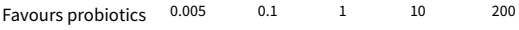


Comparison 7. Per-protocol analysis: probiotics versus placebo - prescribed antibiotics for acute URTIs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The number of participants who used antibiotics	4	1122	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.45, 0.94]

Analysis 7.1. Comparison 7 Per-protocol analysis: probiotics versus placebo - prescribed antibiotics for acute URTIs, Outcome 1 The number of participants who used antibiotics.

Study or subgroup	Probiotics 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		59.45%	0.67[0.41,1.08]
Hojsak 2010b	1/360	4/354		2.87%	0.25[0.03,2.19]
Rautava 2009	10/36	16/42		32.17%	0.73[0.38,1.4]
Rerksuppaphol 2012	2/38	5/38		5.51%	0.4[0.08,1.94]
Total (95% CI)	**561**	**561**		**100%**	**0.65[0.45,0.94]**
Total events: 35 (Probiotics), 58 (Control)					
Heterogeneity: Tau²=0; Chi²=1.28, df=3(P=0.73); I²=0%					
Test for overall effect: Z=2.29(P=0.02)					

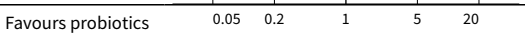


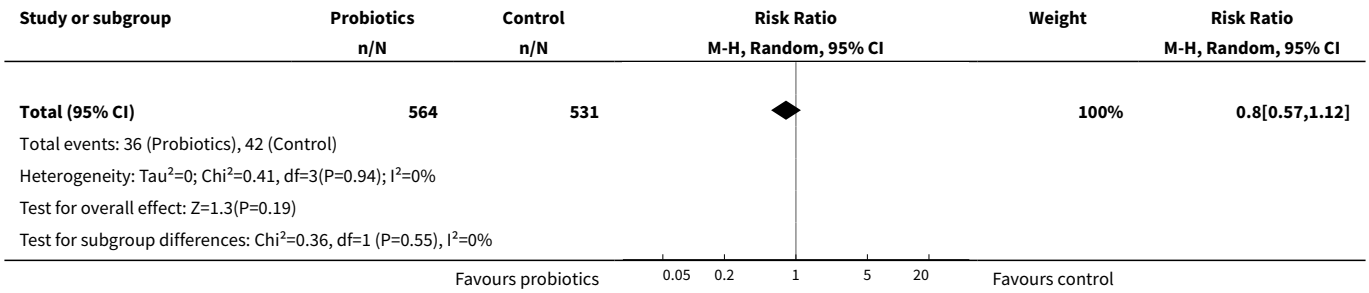
Comparison 8. Per-protocol analysis: probiotics versus placebo - side effects or adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The number of side effects	4	1095	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.57, 1.12]
1.1 Adults	2	455	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.44, 2.31]
1.2 Children	2	640	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.53, 1.10]

Analysis 8.1. Comparison 8 Per-protocol analysis: probiotics versus placebo - side effects or adverse events, Outcome 1 The number of side effects.

Study or subgroup	Probiotics n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.1.1 Adults					
Berggren 2010	3/139	3/136		4.52%	0.98[0.2,4.76]
Smith 2013	8/95	7/85		12.01%	1.02[0.39,2.7]
Subtotal (95% CI)	**234**	**221**		**16.53%**	**1.01[0.44,2.31]**
Total events: 11 (Probiotics), 10 (Control)					
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.96); I²=0%					
Test for overall effect: Z=0.02(P=0.98)					
8.1.2 Children					
Merenstein 2010	6/292	7/272		9.75%	0.8[0.27,2.35]
Rerksuppaphol 2012	19/38	25/38		73.72%	0.76[0.51,1.12]
Subtotal (95% CI)	**330**	**310**		**83.47%**	**0.76[0.53,1.1]**
Total events: 25 (Probiotics), 32 (Control)					
Heterogeneity: Tau²=0; Chi²=0.01, df=1(P=0.93); I²=0%					
Test for overall effect: Z=1.43(P=0.15)					





APPENDICES

Appendix 1. Details of previous search strategy

Previously 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 2011). We adapted the search strategy to search EMBASE; Web of Science and the Chinese Biomedical Literature Database (see Figure 1).

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

Appendix 2. Embase.com search strategy

#52 #44 AND #51
#51 #47 NOT #50
#50 #49 NOT #48
#49 [animals]/lim
#48 'human'/exp
#47 #45 OR #46
#46 random*:ab,ti OR placebo*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR allocat*:ab,ti OR ((singl* OR doubl*) NEXT/1 blind*):ab,ti OR trial:ti
#45 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
#44 #27 AND #43
#43 #28 OR #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
#42 'bulgarian bacillus':ab,ti
#41 (enterococcus NEXT/1 faec*):ab,ti
#40 'enterococcus'/exp
#39 'bacillus subtilis':ab,ti
#38 'bacillus subtilis'/de
#37 'streptococcus thermophilus':ab,ti
#36 'streptococcus thermophilus'/exp
#35 saccharomyc*:ab,ti
#34 'saccharomyces'/exp
#33 'lactococcus'/exp
#32 bifido*:ab,ti OR bifidu*:ab,ti
#31 'bifidobacterium'/exp
#30 lactobacill*:ab,ti
#29 'lactobacillus'/exp
#28 'probiotic agent'/de
#27 #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
#26 urti:ab,ti
#25 (upper NEAR/2 'respiratory infection'):ab,ti OR ('acute infection' NEAR/3 respiratory):ab,ti
#24 'upper respiratory tract infection'/de OR 'viral upper respiratory tract infection'/de
#23 'respiratory tract infection'/de
#22 ('middle ear' NEAR/2 (infect* OR inflam*)):ab,ti
#21 'otitis media':ab,ti OR aom:ab,ti OR ome:ab,ti
#20 'otitis media'/exp
#19 nasopharyngit*:ab,ti OR rhinopharyngit*:ab,ti
#18 nasosinusit*:ab,ti OR rhinosinusit*:ab,ti
#17 epiglottit*:ab,ti OR supraglottit*:ab,ti
#16 'epiglottitis'/exp
#15 croup:ab,ti
#14 'croup'/de

#13 tonsillit*:ab,ti OR 'peritonsillar abscess':ab,ti
#12 'tonsillitis'/exp
#11 rhinit*:ab,ti
#10 'rhinitis'/exp
#9 laryngotracheobronchit*:ab,ti
#8 laryngit*:ab,ti
#7 'laryngitis'/exp
#6 pharyngit*:ab,ti
#5 'pharyngitis'/exp
#4 sinusit*:ab,ti
#3 'sinusitis'/exp
#2 'common cold':ab,ti OR 'common colds':ab,ti
#1 'common cold'/de OR 'common cold symptom'/de

Appendix 3. 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.

WHAT'S NEW

Date	Event	Description
25 July 2014	New citation required but conclusions have not changed	Our conclusions remain unchanged.
25 July 2014	New search has been performed	We included three new trials in this update (Fujita 2013; Rerksuppaphol 2012; Smith 2013) and excluded 15 new trials (Agustina 2012; Di Pierro 2014; Gil-Campos 2012; Gleeson 2010; Gleeson 2012; Gutierrez-Castrellon 2014; Hatakka 2007; Haywood 2014; Lehtoranta 2012; Luoto 2013; Maldonado 2012; Kumpu 2012; Kumpu 2013; West 2011; West 2014).

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 the quality of trials, extracted data, analysed data and drafted the review.
Bi Rong Dong (BD) advised and assisted in writing the protocol and the review, searched for trials and developed the review.

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

DECLARATIONS OF INTEREST

Qiukui Hao: none known.
Bi Rong Dong: none known.
Taixiang Wu: 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). We also revised the outcomes and used GRADE to assess the overall quality of the evidence following the instructions in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We did not include all respiratory tract infections because many studies just reported the respiratory tract infection rather than specifying whether it was a lower or upper respiratory traction infection, which may increase the levels of clinical heterogeneity.

NOTES

In the next update of this review, we will include a subgroup to assess the effects of prebiotics on acute respiratory tract infections.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Probiotics [*therapeutic use]; Randomized Controlled Trials as Topic; Respiratory Tract Infections [*prevention & control]

MeSH check words

Adult; Aged; Child; Female; Humans; Male