Review

Probiotics for the prevention of respiratory tract infections: a systematic review

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ABSTRACT

We evaluated the clinical evidence regarding probiotic use for the prevention of respiratory tract infections (RTIs). Randomised controlled trials (RCTs) studying the effects of probiotics for the prevention of upper or lower RTIs were systematically identified. Fourteen RCTs (twelve involving healthy subjects and two involving patients with RTIs) were included. Various *Lactobacillus* strains were used in seven RCTs, combinations of *Lactobacillus* and *Bifidobacterium* strains were used in five RCTs, and a *Bifidobacterium* strain and a non-pathogenic *Enterococcus faecalis* strain were used in one RCT, respectively. In ten RCTs no difference was found regarding the incidence of RTIs in the probiotic arm compared with the control arm, whereas the remaining four RCTs favoured the use of probiotics. Reduction in the severity of symptoms related to RTIs was noted in five of six RCTs that provided relevant data. In three of nine RCTs that provided relevant data, the clinical course of RTIs was shorter in the probiotic arm, whereas no difference was found in the remaining six RCTs. In conclusion, probiotics may have a beneficial effect on the severity and duration of symptoms of RTIs but do not appear to reduce the incidence of RTIs.

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1. Introduction

Respiratory tract infections (RTIs) affect a large proportion of the population and are associated with substantial morbidity and mortality. Antibiotics are often used inappropriately for the treatment of these infections, leading to increasing bacterial drug resistance rates [1–3]. Therefore, use of new methods for the prevention or treatment of RTIs is an appealing approach currently under investigation.

Probiotics are by definition live organisms that, when administered in adequate quantities, confer health benefits to the host [4]. Recent scientific data demonstrate potential benefits of the administration of probiotics for urogenital, gastrointestinal and surgical infections [5–13]. The clinical utility of probiotics may extend to fields such as allergic disease and cancer [14–22]. The effects of probiotics on human RTIs have not been adequately substantiated. However, experimental studies on animal models support the hypothesis for a potentially beneficial effect of probiotics on human RTIs. This could be mediated by the stimulation of cellular and humoral immunological functions [23–29].

In this regard, we aimed to review systematically the available evidence regarding the potential utility of the administration of probiotics for the prevention or amelioration of RTIs.

2. Data sources

The PubMed, Cochrane Central Register of Controlled Trials (CENTRAL) and Scopus databases were searched up to 5 February 2008 to identify clinical trials eligible for inclusion in this review. The literature search strategy used in PubMed was 'respiratory tract infections AND (probiotics OR prebiotics OR synbiotics OR *Lactobacillus* OR *Bifidobacterium*)'. The search term applied to both CENTRAL and Scopus was '(respiratory tract infections) AND (probiotics)'.

3. Study selection criteria

Randomised controlled trials (RCTs) referring to the clinical utility or safety of the administration of probiotics for the prevention of upper or lower RTIs were considered eligible for inclusion in this review. Studies with a cross-over design, animal studies, studies reported in abstracts presented in scientific conferences, and studies published in languages other than English, German, French, Italian and Spanish were excluded from the review. Two reviewers (GCM and EKV) independently performed the literature search, evaluation of the eligibility of the retrieved studies and data extraction.

4. Data extraction

Data extracted from each of the included RCTs referred to the study design, the characteristics of the included populations, the

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type of RTIs, the type and form of the administered probiotic, the duration and dosing schedule of probiotic treatment, any concomitantly administered therapy, the outcomes regarding RTIs and any treatment-related adverse events observed.

5. Definitions

5.1. Respiratory tract infections

RTIs were infections of the upper respiratory tract, including common cold, acute otitis media, tonsillitis/tonsillopharyngitis, sinusitis and recurrent sinusitis, as well as infections of the lower respiratory tract, including bronchitis and pneumonia.

5.2. Probiotics

Probiotics are dietary supplements containing potentially beneficial bacteria or yeasts. Commonly used probiotics include lactic acid bacteria (such as *Lactobacillus acidophilus*, *L. casei*, *L. lactis*, *L. plantarum*, *L. reuteri*, *L. rhamnosus*, *L. salivarius* and *L. johnsonii*) as well as various bifidobacteria (such as *Bifidobacterium animalis*, *B. infantis*, *B. lactis*, *B. longum* and *B. breve*),

non-pathogenic strains of *Escherichia coli* or *Enterococcus* spp., and *Saccharomyces* spp.

5.3. Synbiotics

Synbiotics consist of a combination of a probiotic with a prebiotic. Prebiotics are non-digestible dietary supplements that selectively favour the proliferation of probiotics. The most commonly used products are fructo-oligosaccharides, inulin, and transgalactosylated and soybean oligosaccharides.

5.4. Adverse events

Adverse events included any adverse event reported during the study period potentially attributed to study treatments.

6. Methodological quality of the included randomised controlled trials

The methodological quality of the included RCTs was assessed using the Jadad criteria. According to these criteria, reporting of data regarding the process of randomisation, blinding and study
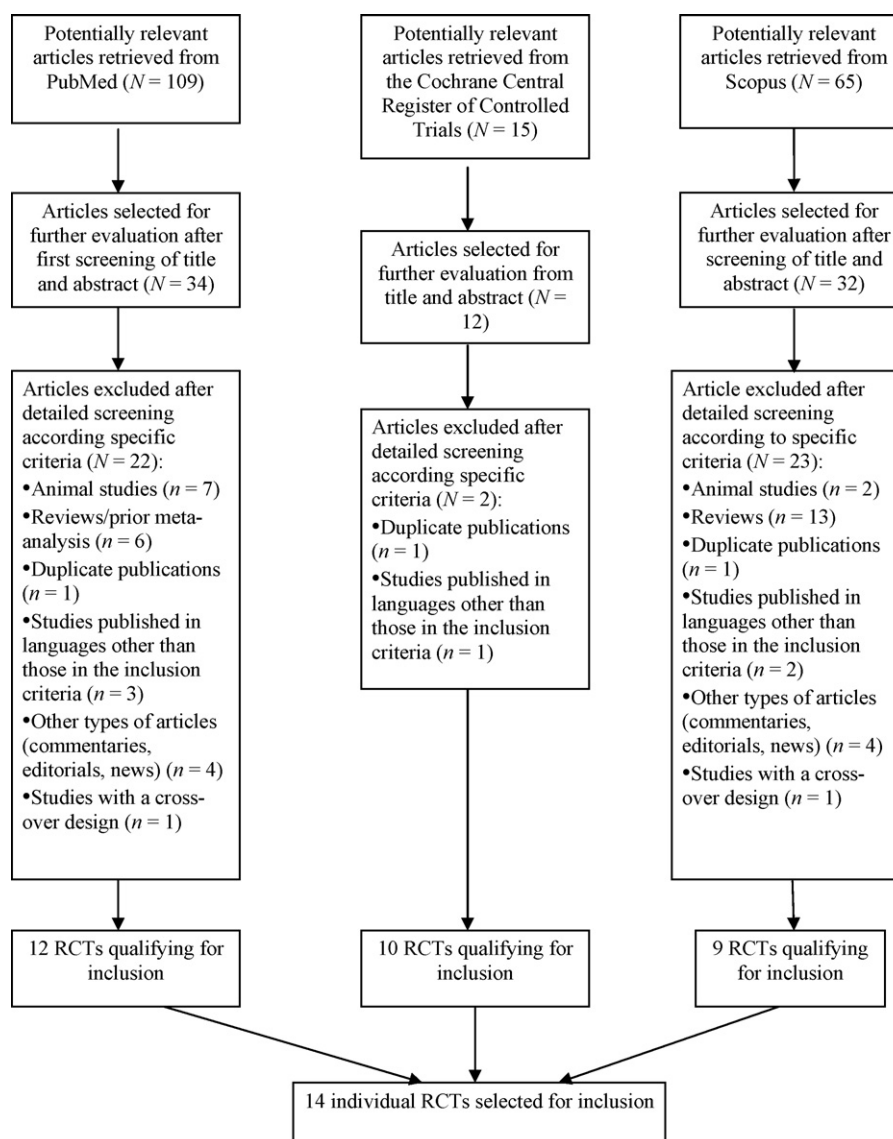

Fig. 1. Flow diagram of the detailed process of selection of trials for inclusion in the systematic review.

withdrawals is assigned one point for each one of the above study characteristics. In addition, one point is assigned or subtracted depending on whether the quality of each one of the randomisation and blinding procedures is deemed adequate. Five points is the maximum score that can be attributed to a trial. A score higher than 2 points was used to denote adequate methodological quality of a trial [30].

7. Selected randomised controlled trials

The searches performed in PubMed, CENTRAL and Scopus generated a total of 109, 15 and 65 search results, respectively. Among these, 14 individual RCTs were regarded as qualifying for inclusion in this review [31–44]. The detailed process of the selection of eligible trials is depicted graphically in Fig. 1.

7.1. Characteristics of the included randomised controlled trials

The main characteristics of the 14 studies included in the review (Jadad score, study design, characteristics of study population, type/form of administered probiotics, duration/dose of probiotic treatment, concomitant treatments, type of infections studied) are summarised in Table 1. Outcomes regarding the prevention, severity and duration of RTIs as well as the adverse events attributed to study treatments are also presented in Table 1. Among the 14 included RCTs, 11 had a double-blind design [31–39,42,44], 2 were open-label RCTs [40,41], whereas the remaining RCT did not provide data regarding blinding [43]. The probiotic preparations were compared with matching placebo or with no treatment. Nine of the fourteen included RCTs were assigned a Jadad score >2 [31–33,35–39,44], whereas three RCTs [34,40,42] and two RCTs [41,43] were assigned a Jadad score of 2 and 1, respectively.

7.2. Characteristics of the studied populations

Among the 14 included RCTs, 6 involved healthy children or infants [31,33,35,38,43,44], 6 involved healthy adults [32,34,36,37,39,41], an additional one involved children with a RTI [40] and the remaining RCT involved adults with a RTI [42]. Notably, 3 of the 14 included RCTs studied specific populations, which were healthy male cadets taking part in intense military training [34], free-living elderly subjects (>60 years of age) [41] and healthy marathon runners [32].

7.3. Probiotic treatment

Regarding the probiotics evaluated, strains of *Lactobacillus* spp. were used in 7 RCTs [32,34,35,37,41,43,44], a strain of *Bifidobacterium longum* was used in one RCT [33], different combinations of *Lactobacillus* and *Bifidobacterium* strains were used in 5 RCTs [31,36,38–40] and a non-pathogenic strain of *Enterococcus faecalis* was used in the remaining RCT [42]. The duration of probiotic treatment among the included studies varied between a few days and 7 months. The dosing schedule as well as the form of administration of probiotics varied considerably between RCTs. Concomitant treatments included appropriate antibiotic medications [40,42], prebiotics [33] as well as feeding supplements such as minerals and vitamins [36,39]. The compliance of study participants with the assigned treatments was difficult to evaluate since, in the majority of included trials, study treatments were administered at home and the participating individuals themselves or their parents recorded the amount of probiotic taken. Data regarding the appearance or severity of RTI-related symptoms were also mainly recorded by study participants [31–34,36–40,44].

7.4. Outcomes regarding respiratory tract infections

7.4.1. Incidence of respiratory tract infections

Ten of the fourteen included RCTs found no difference regarding the incidence of RTIs between the probiotic and placebo arms [31–34,36,38–41,44]. In one of these RCTs, although no difference was reported regarding the primary outcome of the occurrence of acute otitis media, a reduction was noted in the secondary outcome of the occurrence of recurrent upper RTIs (four or more episodes during the 6-month study period) in the probiotic-treated group compared with placebo [31]. Conversely, in another RCT in which the incidence of RTIs was found to be comparable between the probiotic-treated and placebo groups, the incidence of new rhinopharyngitis cases was higher in the probiotic group [34].

In the remaining 4 of the 14 included RCTs, the incidence of RTIs was significantly lower in the probiotic-treated patients [35,37,42,43]. Two of the latter four RCTs evaluated the incidence of lower RTIs (pneumonia, bronchitis and recurrent obstructive bronchitis) [35,43] and an additional one referred to acute relapses of chronic recurrent hypertrophic sinusitis [42]. The remaining RCT evaluated employees for sick-leave both due to respiratory and gastrointestinal infections and found a beneficial effect for probiotics. Yet, no separate data regarding RTIs in particular were reported [37].

7.4.2. Severity of symptoms related to respiratory tract infections

A significant reduction regarding the severity of symptoms of RTIs associated with probiotic treatment was found in five [35,36,38,39,41] of six RCTs that provided relevant data, whilst in the remaining RCT [34] no difference was noted. It should be mentioned that in one of the above RCTs [38] clinical benefits were related to the administration of one of the probiotic products evaluated. Specifically, the product containing *L. reuteri* was associated with a more favourable clinical course both compared with the *Bifidobacterium* product and placebo.

7.4.3. Duration of respiratory tract infections

Nine of the fourteen included trials provided data regarding the duration of the clinical manifestations of RTIs. Among these, three RCTs [35,36,41] reported a significant difference in favour of the probiotic group, whereas in the remaining six [31,32,34,37–39] no difference was found between the compared treatment groups.

7.4.4. Outcomes regarding the safety of probiotic treatment

Data regarding adverse events were reported in all except 4 [31,34,39,43] of the 14 included RCTs. In six RCTs [32,35–38,44] no adverse events were noted that could be attributed to study treatments. Adverse events of minor clinical severity, mainly nausea, vomiting, bloating and diarrhoea, were reported in three RCTs [33,40,42]. In one additional RCT [41] the appearance of dyspepsia (including bloating, meteorism and nausea) in 19 men (31.7%) and 26 women (21.7%) receiving probiotic treatment warranted a reduction in the intake of the probiotic product from two to one bottle per day. Serious adverse events were not reported in any of the included RCTs.

8. Discussion

The main finding of this review is that probiotics, when taken prophylactically by healthy individuals or by patients with a RTI, do not reduce the incidence of RTIs, as shown in the majority of included RCTs. However, a beneficial effect of the use of probiotics on the severity and duration of subsequent RTIs was documented in the majority of relevant RCTs. Furthermore, the administration of probiotics appeared to have a good safety profile, since the majority of the included RCTs did not report adverse events related to

Table 1

Baseline characteristics and outcomes of the analysed clinical trials regarding the use of probiotics for the prevention of respiratory tract infections (RTIs).

Reference	Jadad score	Design of RCT	Study population	Type/form of probiotic	Duration/dose of probiotic treatment	Concomitant treatment	Outcomes	Outcomes (probiotic vs. control)	Adverse events
Hatakka et al. (2007) [31]	4	Double-blind, placebo-controlled	309 otitis-prone children (10 months to 6 years old)[a]	*Lactobacillus rhamnosus* GG and LC705, *Bifidobacterium breve* 99 and *Propionibacterium freudenreichii* JS/gelatin capsule with a mixture of probiotics ($8–9 \times 10^9$ CFU/capsule of each strain) + milk or milk product	6 months/1 capsule daily	NR	Occurrence or duration of AOM, no. of recurrent upper RTIs	AOM (≥ 1 episode): 72% vs. 65% (aOR = 1.48, 95% CI 0.87–2.52; P = NS) Recurrent AOM (≥ 3 episodes): 18% vs. 17% (aOR = 1.04, 95% CI 0.55–1.96; P = NS) Decrease in AOM episodes (intervention period vs. 6 months before): 82% vs. 72% (P = NS) Median duration of AOM (days): 5.6 vs. 6.0 (P = NS) Mean time without AOM (days): 85 (95% CI 74–96) vs. 99 (95% CI 87–111) (P = NS) No. of upper RTIs: 4.3 vs. 4.6 (P = NS) Mean time without upper RTIs (days): 13 (95% CI 10–17) vs. 11 (95% CI 9–13) (P = NS) Recurrent (≥ 4 episodes) upper RTIs: OR = 0.56, 95% CI 0.31–0.99; P = 0.046	NR
Kekkonen et al. (2007) [32]	3	Double-blind, placebo-controlled	141 (healthy) marathon runners	*L. rhamnosus* GG (ATCC 53103)/milk-based fruit drink 3.0×10^8 CFU/mL, or capsules 5×10^9 CFU/capsule	During a 3-month athletic training period/two 65 mL bottles of milk daily (total of 4×10^{10} bacteria/day) or two capsules daily (total of 1×10^{10} bacteria/day)	NR	Number of upper RTIs	3-month training period: Subjects with upper RTIs, 46% vs. 37% (P = 0.52) No. of RTIs (mean), 0.7 (0.9) vs. 0.5 (0.7) (P = 0.32)[b] Days with upper RTIs (mean), 7.9 (7.1) vs. 6.3 (4.3) (P = 0.69). 2-week follow-up period: Subjects with upper RTIs, 10% vs. 7% (P = 0.61) No. of RTIs (mean): 0.1 (0.3) vs. 0.1 (0.3) (P = 0.61)[b] Duration (days) of upper RTIs (mean): 5.1 (2.9) vs. 4.2 (2.2) (P = 0.55)	None
Puccio et al. (2007) [33]	3	Double-blind, reference-controlled	138 healthy infants (not breast-fed after 14th day of birth)	*Bifidobacterium longum* BL999/powdered starter formula for infants (<6 months) 2×10^7 CFU	7 months (received formula until they were 112 days old)/powdered starter formula with probiotic[c]	4 g/L of prebiotic mixture (90% GOS and 10% FOS)	Incidence of RTIs	≥ 1 RTI: 28% vs. 42% (P = 0.14)	NS

Tiollier et al. (2007) [34]	2	Double-blind, placebo-controlled	47 healthy male cadets (21 ± 0.4 years old)	*Lactobacillus casei*/fermented milk by yogurt cultures and with probiotic	1 month/300 mL of probiotic product or placebo daily	NR	Incidence of RTIs (rhinopharyngitis,[d] tonsillitis, sinusitis, otitis, bronchitis, pneumonia), duration and severity of symptoms (mild, moderate or severe)	Incidence of RTIs: 0.8 ± 0.2 vs. 0.6 ± 0.1 episodes ($P = 0.98$) Mean no. of days with symptoms: 5.5 ± 1.6 vs. 6.1 ± 1.7 ($P = 0.67$) Mean no. of symptoms: 0.7 ± 0.2 vs. 1.3 ± 0.3 ($P = 0.23$) Greater proportion of rhinopharyngitis in probiotic group ($P < 0.05$)	NR
Cobo Sanz et al. (2006) [35]	3	Double-blind, placebo-controlled	251 healthy children (3–12 years old)	Actimel/special by-product of probiotics	20 weeks/2 daily units of Actimel or placebo	NR	Upper (otitis, pharyngoamigdalitis, catarrhal with or without fever) and lower (bronchitis or pneumonia) RTIs	Incidence of lower RTIs: 31.7% vs. 48.6% ($P < 0.05$) Incidence of fatigue: 2.8% vs. 12.8% ($P < 0.05$) Duration of lower RTIs (days): 1.32 ± 3.93 (0–33) vs. 1.80 ± 3.03 (0–14) ($P < 0.05$)[e]	None
De Vrese et al. (2005) [36]	5	Double-blind, placebo-controlled	479 healthy volunteers (18–67 years old)	*Lactobacillus gasseri* PA 16/8, *B. longum* SP 07/3, *Bifidobacterium bifidum* MF 20/5/tablets with spray-dried probiotic bacteria, 5×10^7 CFU per tablet	3–5.5 months (winter–spring)/1 tablet per day	Minerals and vitamins in both groups	Prevention of common cold	Total no. of common colds: 158 vs. 153 (NS) Days of symptom duration: 7.0 ± 0.5 vs. 8.9 ± 1.0 ($P = 0.045$) Days of fever: 0.24 ± 0.1 vs. 1.0 ± 0.3 ($P = 0.017$) Total symptom score: 79.3 ± 7.4 vs. 102.5 ± 12.2 ($P = 0.056$)[f]	None
Tubelius at al. (2005) [37]	4	Double-blind	262 healthy employees (18–65 years old)	*Lactobacillus reuteri* Protectis (ATCC55730)/drinking straw together with at least 100 mL of liquid	80 days/daily dose of 10^8 CFU of the probiotic	NR	Symptoms related to the respiratory tract resulting in sick-leave, duration of sick-leave	No. of subjects reporting sick days: 10/94 (11%) vs. 23/87 (26%), $P < 0.01$ No. of sick days (median): 3 vs. 3 Frequency of sick days: 0.4% vs. 0.9% ($P < 0.01$)[g]	None
Weizman et al. (2005) [38]	4	Multicentre, double-blind, placebo-controlled	201 healthy infants (4–10 months old)	*Bifidobacterium lactis* (BB-12), *L. reuteri*/humanised cow's milk formula, 1×10^7 CFU/g of formula powder	12 weeks/NR	NR	RTIs (upper, lower or mixed respiratory signs)	Days with fever: 0.86 (0.33–1.39) vs. 0.17 (0.04–0.30) vs. 0.83 (0.50–1.16) ($P < 0.001$) (*L. reuteri* vs. BB-12 and controls)[h] Episodes of fever: 0.27 (0.17–0.37) vs. 0.11 (0.04–0.18) vs. 0.41 (0.28–0.54) ($P < 0.001$) (BB-12 and *L reuteri* vs. controls)[h] Days with RTIs: 0.68 (0.17–1.19) vs. 0.38 (0.10–0.66) vs. 0.60 (0.31–0.89) ($P = 0.169$)[h] RTIs episodes: 0.25 (0.15–0.35) vs. 0.17 (0.08–0.26) vs. 0.24 (0.13–0.35) ($P = 0.457$)[h]	None

Table 1 (*Continued*)

Reference	Jadad score	Design of RCT	Study population	Type/form of probiotic	Duration/dose of probiotic treatment	Concomitant treatment	Outcomes	Outcomes (probiotic vs. control)	Adverse events
Winkler et al. (2005) [39]	5	Double-blind, placebo-controlled	477 healthy adults (18–70 years old)	*L. gasseri* PA 16/8, *B. longum* SP 07/3 and *B. bifidum* MF 20/5 B/tablets with the spray-dried probiotic, 5×10^8 CFU	3–5.5 months/1 tablet per day	Minerals and vitamins	Incidence and severity of symptoms of RTIs	Incidence of virally induced RTIs: 0.53 vs. 0.60 ($P=0.07$) Average duration of symptoms (days): 6.8 ± 0.4 vs. 7.5 ± 0.6 ($P=0.19$) Total symptom score: 74.6 ± 6.7 vs. 92.5 ± 8.7 ($P=0.12$) Influenza symptoms: 44.6 ± 4.9 vs. 59.2 ± 6.4 ($P=0.09$)[i] Days with fever: 0.3 ± 0.1 vs. 0.7 ± 0.2 ($P=0.03$)	NR
Schrezenmeir et al. (2004) [40]	2	Open-label	129 children (1–6 years old) who required antibiotics for acute bacterial infections (tonsillitis, pharyngitis, otitis media or bronchitis/mild pneumonia not requiring hospitalisation)	*Lactobacillus acidophilus* and *Bifidobacterium* spp./provided in powder form, 1×10^9 CFU/g, and 3.5 g/L FOS	During antibiotic therapy for acute respiratory bacterial infection/1–3 years, 360 mL/day; 4–6 years, > 480 mL/day	Appropriate antibiotic medication (amoxicillin, cefadroxil, clarithromycin)	New occurrence or relapse of acute bacterial RTIs (tonsillitis, pharyngitis, otitis media, bronchitis/mild pneumonia not requiring hospitalisation)	% Children without evidence of bacterial infection 14 days after completion of antibiotic therapy: 94.3% (G1) vs. 80.6% (G2) vs. 87.8% (G3), NS[j]	Worsening of diarrhoea and vomiting in 1 subject in the symbiotic group (G1)
Turchet et al. (2003) [41]	1	Open-label, stratified (according to sex and vaccine status), double-blind	360 free-living subjects (>60 years of age)	Actimel: *L. casei* DN-114 001/fermented milk by yogurt cultures and with probiotic, 10^8 CFU/mL	3 weeks/one 100 mL bottle of Actimel twice daily	NR	Incidence and severity (duration, intensity and maximal temperature) of winter pathologies: influenza syndromes, respiratory diseases, ENT pathologies	Incidence of influenza syndrome: 28.9% vs. 27.8% ($P=0.815$) Incidence of ENT pathology: 0% vs. 1.7% ($P=0.248$) Incidence of bacterial bronchopneumopathy: 2.2% vs. 4.4% ($P=0.240$) Duration of all pathologies (days): 7.0 ± 3.2; 7 (0–17) vs. 8.7 ± 3.7; 8 (2–20) ($P=0.024$)[k]	Dyspepsia (bloating, meteorism, nausea) in 19 men (31.7%) and 26 women (21.7%) in the probiotic group leading to reduction in intake
Habermann et al. (2002) [42]	2	Multicentre, double-blind, placebo-controlled	157 patients (18–70 years old) with chronic recurrent sinusitis	A bacterial immunostimulant comprised of cells and autolysate of human *Enterococcus faecalis* bacteria (Symbioflor 1)/NR, $1.5–4.5 \times 10^7$ bacteria/mL	6 months/30 mL daily ($11.25–33.75 \times 10^7$ bacteria/day)	Antibiotic therapy in 2 patients in the probiotic group and 6 patients in the placebo group	Occurrence of acute relapses of chronic recurrent sinusitis during the 6-month treatment period and the 8-month follow-up period	Occurrence of relapses during study period: 50 vs. 90 ($P=0.045$) Occurrence of relapses during treatment: 17 vs. 33 ($P=0.019$) Occurrence of relapses during follow-up: 33 vs. 57 ($P=0.013$) Median time to first relapse (days): 513 vs. 311 RR for a relapse during study period: 49.0% and 55.8%, respectively Median time to two relapses (days): 703 vs. 413	Nausea, emesis, meteorism and feeling of disgust in 12 vs. 13 patients. None serious

Rio et al. (2002) [43]	1	RCT	58 children (21 undernourished, 37 with normal weight/height) (6–24 months old)	*L. acidophilus* and *L. casei*/fermented milk + 10^7–10^8 per mL of probiotic milk	3 months (autumn to winter)/NR	NR	RTIs, classified according to severity as: pneumonia, bronchitis, recurrent obstructive bronchitis and upper RTIs	No. of RTIs: 34 vs. 69 (1.55 vs. 1.92 episodes/child) Maximum no. of episodes/child: 3 vs. 7 (P = 0.0373)	NR
Hatakka et al. (2001) [44]	5	Multicentre, double-blind, placebo-controlled	571 healthy children (1–6 years old)	*L. rhamnosus* GG (ATCC 53103)/milk (1% fat + 5–10 × 10^5 CFU/mL of probiotics)	7 months (winter)/260 mL of milk daily	NR	Upper and lower RTIs (otitis media, sinusitis, bronchitis, and pneumonia)	% reduction of RTIs (95% CI): 8.6 (0.1–17.2) (P = 0.05) Age-adjusted OR for RTIs (95% CI): 0.75 (0.52–1.09) (P = 0.13) % reduction of antibiotic treatments for RTIs (95% CI): 9.6 (1.0–18.2) (P = 0.03) Age-adjusted OR for antibiotic treatment for RTIs (95% CI): 0.72 (0.50–1.03) (P = 0.08) Absence from day-care OR (95% CI): 4.9 (4.4–5.5) vs. 5.8 (5.3–6.4) (P = 0.003) Age-adjusted OR for absence from day-care (95% CI): 5.1 (4.6–5.6) vs. 5.7 (5.2–6) treatment and follow-up period	None

RCT, randomised controlled trial; AOM, acute otitis media; CFU, colony-forming units; NR, not reported; aOR, adjusted odds ratio; CI, confidence interval; NS, not significant; OR, odds ratio; GOS, galacto-oligosaccharides; FOS, fructo-oligosaccharides; SD, standard deviation; ENT, ear, nose and throat; RR, relative risk.

[a] At least four episodes of AOM during the preceding 12 months, or at least three episodes during the preceding 3 months.
[b] At least 2 days of upper RTI symptoms after a symptom-free period of at least 3 days.
[c] Among the infants who completed the trial (112 days), the consumed amount of formula was significantly higher in the group fed by the experimental formula (P = 0.02).
[d] Defined as inflammation of the mucous membranes of the nasal and the pharyngeal cavities.
[e] Data are mean ± S.D. (minimum–maximum).
[f] Total symptom score was calculated according to self-assessment questionnaires.
[g] Data refer to any illness symptoms related to the respiratory tract and/or the gastrointestinal tract resulting in sick-leave and, if so, the duration of sick-leave.
[h] Data are mean (95% CI) between BB-12 vs. *L. reuteri* vs. controls.
[i] Pharyngeal symptoms + bronchial symptoms + headache + myalgia + fatigue + loss of appetite + fever.
[j] G1 received a nutritional supplement with synbiotics; G2 received a standard nutritional supplement without synbiotics; G3 received a fruit-flavoured drink.
[k] Data are mean ± S.D., median (minimum–maximum) and refer to respiratory pathologies plus gastrointestinal syndrome.

probiotic treatment or reported adverse events of mild severity only.

It should be mentioned that the utility of probiotics in reducing the incidence or severity of RTIs has also been evaluated in several trials with a different methodological design than those eligible for inclusion in this review. Specifically, in a double-blind, randomised, cross-over trial, prophylactic oral administration of *Lactobacillus fermentum* VRI-003 to endurance athletes resulted in a substantial reduction in the number of days of respiratory illness as well as in the severity of relevant symptoms [45]. Additionally, in a retrospective study, a reduction in the frequency of repeated RTIs, the great majority of which involved the upper respiratory tract, was noted 10 years but not 20 years after intentional colonisation of preterm infants with a probiotic strain of *Escherichia coli* compared with controls [46].

A beneficial effect of probiotics has also been noted in a significant number of studies regarding patients with various clinical entities. The majority of relevant reports refer to diseases of the gastrointestinal tract, including enteric viral infections, *Helicobacter pylori* colonisation and diarrhoea in human immunodeficiency virus (HIV)-infected patients [20,47–52]. The clinical utility of probiotics has also been noted in patients with urinary tract and gynaecological infections and in allergic disease [5–7,53].

However, the utility of administration of probiotics with regard to various types of patients has not been corroborated in all relevant reports. Specifically, a recent review regarding adult Intensive Care Unit (ICU) patients indicated that the use of probiotics/prebiotics and synbiotics conferred no benefit in lowering the incidence of nosocomial infections and in decreasing the length of ICU stay and hospital mortality [54]. Additionally, administration of a synbiotic supplement in critically ill patients resulted in no benefit compared with placebo in terms of subsequent septic complications or mortality [55]. Furthermore, the findings regarding probiotic administration in patients with severe acute pancreatitis are controversial, since in one relevant RCT administration of a preparation containing *L. plantarum* reduced the incidence of infected pancreatic necrosis and abscess [56] whereas a subsequent RCT reported a greater number of infectious complications and deaths in patients treated with a multispecies probiotic preparation compared with placebo [57].

The concept of a beneficial role of probiotics for human disease is based on various suggested mechanisms. Probiotics have been found to produce antimicrobial substances [58–60] and to modify specific toxin receptors and thus block toxin-mediated responses [61,62]. A reduction of infectious or other complications with the administration of probiotics is also postulated to be mediated through bacterial interference. According to this concept, colonising probiotic bacteria compete with pathogenic bacteria for nutrients or adhesion sites [63–71]. Moreover, the beneficial effect of probiotics beyond the site of colonisation may be attributed to modulation of systemic immunological responses. Enhancement of humoral and cellular immunity following administration of probiotics has been noted in various animal [72,73] and human studies [74–77]. This has been particularly shown for RTIs [5–7,24,26–29,78]. Notably, two of the RCTs included in this review reported an appreciable increase in the total numbers of CD4$^+$ and CD8$^+$ T-lymphocytes in the probiotic-treated group compared with the placebo group [36,39].

Several limitations should be taken into consideration in the interpretation and extrapolation of the findings of this review. A significant heterogeneity among the included RCTs was observed regarding the type of studied populations, the probiotic bacteria administered, the duration of probiotic treatment and the evaluated outcomes for the various types of RTIs. Since the effect of different probiotic organisms for various types of human diseases may be considerably different, the heterogeneity observed

among the included RCTs precluded us from performing a meta-analysis.

In conclusion, the majority of RCTs included in this review indicate that the incidence of RTIs does not appear to be considerably influenced by prophylactic administration of probiotics, although probiotics may have a beneficial role in reducing the severity and duration of subsequent RTIs. A few adverse events were reported in association with probiotic use, all of which were of mild severity. Since different probiotic organisms may have variable effects, as has also been shown in other types of human disease, further research is recommended to explore the potential utility of certain probiotic preparations for the prevention of RTIs.

9. Summary points

- Fourteen RCTs evaluated the prophylactic administration of different probiotics for the prevention of upper or lower RTIs in adults or children.
- A beneficial role of probiotics in reducing the incidence of RTIs was found in four of these trials, whilst no effect was found in ten trials.
- Reduction in the severity of subsequent RTIs was found in five of six trials that reported relevant data.
- A reduction in the duration of RTIs was found in three of nine trials.
- Minor adverse events related to probiotic use were reported in four of ten trials.

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