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The Effect of Probiotics on Prevention of Respiratory Tract Infections in Children and Adolescents: A Systematic Review

Patricia Langenegger[1], Samuel Ristovski List[1], Abril S. Perez Rivas[1], Artur Tenorio[1], Camila Roberta Caseli[1], Daniela Estrada[1], Deborah Pires[1], Edgar Acon[1], Faruk Hernandez[1], Geronimo Pacheco[1], Guilherme Gradim Fabbron[1], Heberti Silva[1], Hellen Rose Salazar[1], Ivan Morales[1], Lucas Gremaschi[1], Maíra Fabiana Rodrigues Neves[1], Maria Baron[1], Muhannad Abu Abthan[1], Orlando Loyola[1], Paula Figueroa[1], Phu Pham[1], Ruben Riera[1], Saskia J.M. Kamphuis[1], Tassia Bastos[1], Timo Schenker[1], Wilson Catapani[1], Rafael Pinto-Colmenarez[1], Luiza Sandes[1*]

[1]Principles and Practice of Clinical Research (PPCR), Harvard T.H. Chan School of Public Health.

Abstract

Background: *Respiratory tract infections (RTIs) are a common cause of illness and healthcare visits in children. Probiotics have shown promising results in reducing the incidence and duration of RTIs. However, significant gaps remain to be cleared, such as the variability in study results due to differences in probiotic strains, doses, and populations studied. The present systematic review collected evidence on the effect of various probiotic strains and administration schedules on RTIs in children and adolescents.*

Methods: *A comprehensive search strategy for randomized controlled trials (RCTs) was employed using both Medical Subject Headings (MeSH) and non-MeSH terms across Medline, EMBASE, and Web of Science databases. Screened RCTs assessed the effect of any probiotic strain, form of administration, and dosing schedule on the incidence of RTIs in healthy pediatric and adolescent populations aged 28 days to 17 years across different settings.*

Results: *According to predefined eligibility criteria, we identified 32 RCTs, with a total of 8415 subjects. Of these, 25 (78.1%) studies reported a positive effect of probiotics in reducing the incidence of RTIs. However, the results were notably heterogeneous, with 22 different probiotic strains and a variety of administration schedules and study designs. The most frequent strain genus was Lactobacillus, used in 46.8% of trials, and the doses ranged from thousands (105) to over tens of billions (1010) of colony-forming units (CFU).*

Conclusion: *The findings of the present review confirm the potential of probiotics to reduce the occurrence of RTIs in children, especially LGG strains in daycare centers. However, the wide range of probiotic strains and administration schedules emphasizes the need for further research to find the most effective strains and establish standardized guidelines for using them to prevent RTIs in children.*

Introduction

Respiratory tract infections (RTIs) are any infection on upper or lower tracts that are major causes of morbidity in children, resulting in numerous medical visits, hospitalizations, and, in severe cases, mortality. Worldwide, about 85–88% of acute RTI episodes are upper respiratory tract infections (URTIs), while the remaining are lower respiratory tract infections (LRTIs) (Jain et al., 2001; Krishnan et al., 2015). With the increase in antibiotic resistance and, consequently, the search for effective preventive strategies, probiotic supplementation has emerged as a promising alternative (Laursen & Hojsak, 2018). Probiotics are "live microorganisms that, when administered in adequate amounts, provide health benefits to the host,

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mainly through modulating the immune system and improving intestinal health" (Hill et al., 2014). However, the exact mechanisms by which probiotics exert their preventive effects on RTIs are not yet completely understood (Lei et al., 2020; Santamaria et al., 2019).

Recent research indicates that administering probiotics to children can reduce the incidence and severity of RTIs. For instance, a study by Lazou Ahrén et al. (2020) evaluated the effectiveness of *L. plantarum* HEAL9 and *L. paracasei 8700:2*, demonstrating a significant reduction in the duration and severity of RTIs among children attending daycare centers. Similarly, Andaloro et al. (2019) reported that using *S. salivarius* 24SMB and *S. oralis 89a* reduced the recurrence of streptococcal pharyngotonsillitis in children. Additionally, a recent systematic review by Zhao et al. (2022) found that probiotics were more effective than placebo or no treatment in preventing acute URTIs. However, the latter included subjects of all ages and excluded studies that did not specify acute RTIs as "upper".

Despite these promising findings, significant gaps remain in the existing literature. One major issue is considerable variability in study results due to differences in the probiotic strains used, doses administered, and populations studied, which seem to have been chosen mostly empirically in previous trials (Araujo et al., 2015; Laursen & Hojsak, 2018). Consequently, the evidence of previous individual trials is not sufficient to support consistent guidelines or recommendations. Therefore, the aim of this systematic review is to investigate the effects of probiotic supplementation on preventing RTIs in healthy pediatric and adolescent populations aged 28 days to 17 years, based solely on randomized controlled trials (RCTs). The goal is to establish clear, evidence-based guidelines and recommendations for preventive strategies in the school-going population.

Materials and Methods

Information Sources and Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021) were followed for the design and reporting. We searched the following electronic databases: MEDLINE (through PubMed), Web of Science, and EMBASE, including all articles published up to June 2024. Specific searches per database are available in the supplementary data (Appendices A, B, and C).

Selection of the Studies and Data Extraction

The selection of the studies was done first by screening the title and abstract, followed by full-text screening. Each phase was performed by two independent reviewers, and discrepancies were resolved by a third reviewer. All authors participated in the screening and data extraction processes. To automate this process, we utilized the Covidence systematic review online tool (Veritas Health Innovation, Melbourne, Australia), available at www.covidence.org.

Eligibility Criteria

The criteria for studies' inclusion were as follows: studies conducted with children and adolescents aged 28 days to 17 years, including only phase I, I/II, and III clinical trials that used probiotics as an intervention. The studies needed to report URTI and/or LRTI confirmed by patients, their parents or legal representatives, or physicians. URTIs included cases of pharyngitis, acute rhinitis, acute rhinosinusitis, common cold, and laryngitis, while LRTIs included cases of pneumonia, tracheitis, bronchiolitis, and acute bronchitis (Hothan et al., 2022). Only RCTs were considered for analysis, and articles were required to be written in English, Spanish, Portuguese, German, or French.

The analysis excluded several study types, including narrative reviews, correspondence letters, case reports, editorials, preclinical studies, observational clinical studies, abstracts, posters, systematic reviews, meta-analyses, expert opinions, and guidelines. Trials involving pregnant women, adults, and elderly populations were also excluded, along with the studies that used interventions other than probiotics. Additionally, studies were excluded if they lacked information on population, intervention, comparator, and/or outcome. Populations with chronic respiratory illnesses, such as cystic fibrosis, asthma, chronic bronchitis, pneumonia, allergic rhinitis, sinusitis, otitis, and chronic obstructive pulmonary disease were excluded. The review also excluded populations with severe chronic comorbidities, including inflammatory bowel disease, allergies, obesity, genetic diseases, congenital heart defects, diabetes, anemia, malnutrition, neurological or neuropsychomotor development disorders, diseases related to premature-born children, cancers, kidney diseases, and rheumatological conditions, as well as studies involving hospitalized children and adolescents.

PICOS Framework

The study selection was guided by the Population, Intervention, Comparison, Outcome, and Study Design (PICOS) framework, focusing on children and adolescents aged 28 days to 17 years with confirmed

upper or lower respiratory tract infections (URTIs or LRTIs). The intervention involved probiotic administration, with no restrictions on strain, dose, duration, or administration route, and was compared to populations who either did not receive probiotics or were given a placebo. Outcomes of interest included the incidence and frequency of respiratory tract infections and other relevant intervention measures. Only randomized controlled trials (RCTs) were included.

Data Synthesis

The following variables were extracted from each of the included studies: title, first author, year of publication, location, study design, sample size, age of participants, control group, probiotic strain, dose, administration route, type of RTI (URTI vs. LRTI), setting, follow-up and outcomes (rates and incidence).

Risk of Bias Assessment

The quality of each study was independently assessed by two reviewers using the Cochrane Collaboration's Risk of Bias Assessment Tool (ROB1) in Covidence (Higgins et al., 2011). The following domains were assessed: sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other biases. Each domain was evaluated as low, high, or unclear risk of bias.

Results

Description of the Studies

The search strategy yielded 936 publications. Duplicates were removed, and 674 articles were screened. As a result, 601 publications were excluded during the title and abstract screening, resulting in 73 studies sought for retrieval. Only one study could not be retrieved as it was unavailable through established channels, and 72 studies underwent the full-text screening, of which 41 were manually excluded (Figure 1). Ultimately, 32 studies were included in the review, with a total of 8,415 subjects. Among the included studies, 20 (62.5%) were carried out in European countries, with Italy being the country with the greatest number of studies. 8 (25%) were performed in Asia, 2 in South America, and 2 in North America. The children were followed in different settings, including daycare facilities, outpatient clinics, and home environments.

Study Designs

All studies were randomized parallel designs, including 30 RCTs and 2 cluster RCTs. 26 studies (81.2%) used placebo as a comparator. Three studies compared probiotics with no intervention (Di Pierro et al., 2016; Di Pierro et al., 2020; Lin et al., 2009). Two studies used a three-arm design with two groups of probiotics and one placebo control group (Dekker et al., 2022; Leyer et al., 2009). Blinding was not performed in 3 studies (Di Pierro et al., 2016; Di Pierro et al., 2020; Guo et al., 2022). One study was single-blinded (Andaloro et al., 2019) and 28 were double-blinded.

Population

The population included individuals aged from 1 month to 15 years old. The mean age varied largely because different studies used different age ranges for the intervention. Most studies included children between 1 and 6 years old. Eight studies (25%) included children under 1 year (Dekker et al., 2022; Laursen et al., 2017; Taipale et al., 2011; Di Pierro et al., 2020; Taipale et al., 2016; Gutierrez-Castrellon et al., 2014; Maldonado et al., 2012; Scalabrin et al., 2017) and only two studies (6.25%) involved adolescents (Rerksuppaphol & Rerksuppaphol, 2012; Campanella et al., 2018).

The sample size varied from 40 (Campanella et al., 2018) to 1062 children (Lin et al., 2009). The largest intervention and placebo groups were composed, respectively, of 309 and 308 individuals (Damholt et al., 2022), while the smallest placebo and intervention samples were from 10 and 9 children, respectively (Kloster Smerud et al., 2008). The number of withdrawals varied from 2 to 221 individuals and were due to not completing the study protocol, while others did not provide reasons for the dropouts. Reasons for dropout included refusal of the child to take the probiotics or moving outside of the investigated geographical region. Two studies did not clearly report withdrawal numbers (Campanella et al., 2018; Di Pierro et al., 2020), and four studies did not clearly report reasons for withdrawal (Scalabrin et al., 2017; Río et al., 2002; Leyer et al., 2009; Corsello et al., 2017).

Population Setting

All subjects included in the study were recruited from outpatient settings, with the majority (63.6%) being enrolled from daycare centers or schools (Lazou Ahrén et al., 2020; Cáceres et al., 2010; Corsello et al., 2017; Damholt et al., 2022; Laursen et

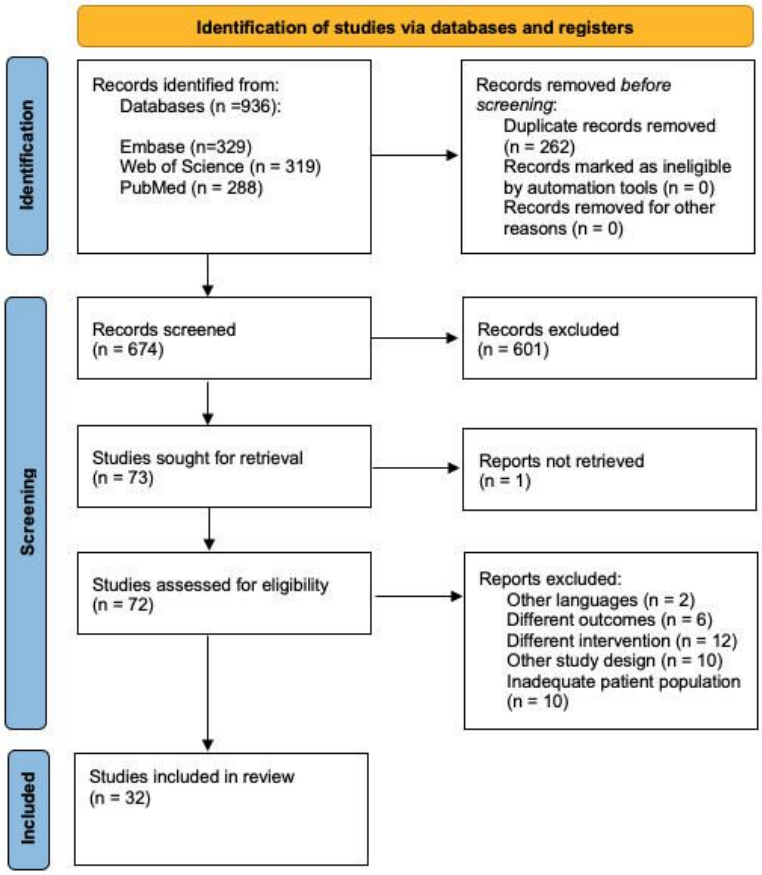

Figure 1: *PRISMA Flow diagram for the systematic review.*

al., 2017; Gutierrez-Castrellon et al., 2014; Hatakka et al., 2001; Hishiki et al., 2020; Hojsak et al., 2010; Hojsak et al., 2016; Kloster Smerud et al., 2008; Kumpu et al., 2012; Leyer et al., 2009; Lin et al., 2009; Nocerino et al., 2017; Prodeus et al., 2016; Santamaria et al., 2019; Rautava et al., 2009; Rerksuppaphol & Rerksuppaphol, 2012; Scalabrin et al., 2017; Sudarmo et al., 2019). 18.2% of subjects were enrolled in healthcare centers, such as pediatric or otolaryngology clinics (Campanella et al., 2018; Dekker et al., 2022; Di Pierro et al., 2020; Andaloro et al., 2019; Taipale et al., 2011; Taipale et al., 2016). The remaining studies did not report the recruitment setting.

Intervention Characteristics

Intervention Duration and Followup Period

The follow-up period after the intervention ranged from a minimum of 8 weeks, as reported by Guo et al. (2022) and Santamaria et al. (2019), to a maximum of 5 years (240 weeks), as reported by Scalabrin et al. (2017). The median follow-up period for all included studies was 24 weeks, with an Interquartile Range (IQR) of 20 weeks.

Administration Routes

Almost all studies (96.87%) administered probiotics orally. One study used a spray formulation for topical administration to the oral mucosa (Andaloro et al., 2019). The most common forms of probiotic administration were powder (31.25%) and fermented milk (21.87%). Other formulations included milk formula (12.5%) (Damholt et al., 2022; Rerksuppaphol & Rerksuppaphol, 2012; Sudarmo et al., 2019; Maldonado et al., 2012) and tablets (12.5%) (Di Pierro et al., 2016; Campanella et al., 2018; Taipale et al., 2016; Taipale et al., 2011). Additionally, one study used an oil formulation (Gutierrez-Castrellon et al., 2014).

Probiotic Doses and Frequencies of Administration

The probiotic doses varied widely, ranging from hundreds of thousands (105) colony-forming units (CFU) (Hatakka et al., 2001) to over tens of billions (1010) CFU (Hishiki et al., 2020). Since the exact dose of CFU usually cannot be precisely determined or guaranteed at the time of administration, most manufacturers instead guarantee a minimum amount, such as

> 1010 CFU per 100 grams, as described by Prodeus et al. (2016). One study, however, did not specify the CFU dose of the probiotic intervention (Campanella et al., 2018).

Daily probiotic treatment was provided across all 32 studies, but with a wide range of dosing frequencies. Twelve (37.5%) studies administered a probiotic dose once a day (Lazou Ahrén et al., 2020; Andaloro et al., 2019; Cáceres et al., 2010; Damholt et al., 2022; Di Pierro et al., 2016; Guo et al., 2022; Gutierrez-Castrellon et al., 2014; Hishiki et al., 2020; Hojsak et al., 2016; Laursen et al., 2017; Rautava et al., 2009; Santamaria et al., 2019). Six studies (18.75%) administered the dose twice a day (Leyer et al., 2009; Madempudi et al., 2022; Prodeus et al., 2016; Rerksuppaphol & Rerksuppaphol, 2012; Taipale et al., 2011; Taipale et al., 2016). Six studies (18.75%) used a different frequency pattern, with irregular doses or three or more than three times-a-day administration (Campanella et al., 2018; Dekker et al., 2022; Hatakka et al., 2001; Kumpu et al., 2012; Lin et al., 2009; Sudarmo et al., 2019). Eight studies (25%) did not specify the frequency of probiotics administration (Corsello et al., 2017; Di Pierro et al., 2020; Hojsak et al., 2010; Kloster Smerud et al., 2008; Maldonado et al., 2012; Nocerino et al., 2017; Río et al., 2002; Scalabrin et al., 2017).

Probiotic Strains

The most common bacterial genus in the investigated probiotics was *Lactobacillus*, used in fifteen (46.87%) studies (Cáceres et al., 2010; Campanella et al., 2018; Corsello et al., 2017; Decker et al., 2022; Di Pierro et al., 2020; Gutierrez-Castrellon et al., 2014; Hatakka et al., 2001; Hojsak et al., 2010; Kumpu et al., 2012; Leyer et al., 2009; Lin et al., 2009; Maldonado et al., 2012; Nocerino et al., 2017; Scalabrin et al., 2017; Taipale et al., 2011), followed by *Bifidobacterium* (15.62%). Eight studies (25%) used a multi-strain probiotic intervention (Andaloro et al., 2019; Campanella et al., 2018; Decker et al., 2022; Di Pierro et al., 2020; Prodeus et al., 2016; Rerksuppaphol & Rerksuppaphol, 2012; Río et al., 2002; Santamaria et al., 2019). Three studies used a two- or three-arm study design with different probiotics in each group, comparing, for example, *Lactobacillus* vs. *Bifidobacterium* (Lin et al., 2009; Leyer et al., 2009; Dekker et al., 2022). The studied strains are listed in Table 1.

Outcomes

In eleven studies (34.4%), the measured outcome was URTIs (Lazou Ahrén et al., 2020; Cáceres et al., 2010; Campanella et al., 2018; Corsello et al., 2017; Damholt et al., 2022; Di Pierro et al., 2020; Guo et al., 2022; Madempudi et al., 2022; Maldonado et al., 2012; Nocerino et al., 2017; Rerksuppaphol & Rerksuppaphol, 2012), while twelve studies (37.5%) examined both URTIs and LRTIs (Dekker et al., 2022; Hatakka et al., 2001; Hishiki et al., 2020; Hojsak et al., 2010; Hojsak et al., 2016; Laursen et al., 2017; Lin et al., 2009; Rautava et al., 2009; Río et al., 2002; Santamaria et al., 2019; Scalabrin et al., 2017; Taipale et al., 2011). Two studies specifically assessed pharyngotonsillitis (Andaloro et al., 2019; Di Pierro et al., 2020). The majority of studies (81.25%) reported the occurrence of acute RTI, while six studies (18.75%) observed recurrent infections (Andaloro et al., 2019; Guo et al., 2022; Maldonado et al., 2012; Nocerino et al., 2017; Rautava et al., 2009; Río et al., 2002). The categorization of outcomes by infection type and frequency (acute vs. recurrent) served as the main framework to facilitate clearer comparisons across the studies.

The studies included various outcome measurements, with the incidence or frequency of RTIs being the most common, used in 20 studies (62.5%) (Lazou Ahrén et al., 2020; Andaloro et al., 2019; Cáceres et al., 2010; Campanella et al., 2018; Damholt et al., 2022; Dekker et al., 2022; Di Pierro et al., 2020; Guo et al., 2022; Leyer et al., 2009; Lin et al., 2009; Madempudi et al., 2022; Maldonado et al., 2012; Nocerino et al., 2017; Prodeus et al., 2016; Rautava et al., 2009; Rerksuppaphol & Rerksuppaphol, 2012; Río et al., 2002; Sudarmo et al., 2019; Taipale et al., 2011; Taipale et al., 2016). One study (3.13%) aimed to assess the rate of RTIs in children (Kumpu et al., 2012), while three studies (9.8%) measured the number of days with symptoms (Kloster Smerud et al., 2008; Laursen et al., 2017; Santamaria et al., 2019) and another three (9.8%) evaluated the number of children with RTIs as their primary endpoint (Hatakka et al., 2001; Hojsak et al., 2010; Hojsak et al., 2016). The remaining studies (15.63%) had primary outcomes unrelated to RTIs, making the evaluation of the incidence of RTIs a secondary objective (Corsello et al., 2017; Di Pierro et al., 2016; Gutierrez-Castrellon et al., 2014; Hishiki et al., 2020; Scalabrin et al., 2017).

Sixteen studies (50%) had the outcome assessment conducted through medical evaluation (Cáceres et al., 2010; Corsello et al., 2017; Dekker et al., 2022; Di Pierro et al., 2016; Di Pierro et al., 2020; Guo et al., 2022; Gutierrez-Castrellon et al., 2014; Hishiki et al., 2020; Leyer et al., 2009; Lin et al., 2009; Maldonado et al., 2012; Nocerino et al., 2017; Prodeus et al., 2016; Rautava et al., 2009; Río et al., 2002; Sudarmo et al., 2019). Five studies (15.63%) used questionnaires completed by proxies (Lazou Ahrén et al., 2020; Hatakka et al., 2001; Kloster Smerud et al., 2008; Rerksuppa-

Probiotic Strain	Article
Bacillus clausii UBBC-07	Madempudi et al, 2022
Bifidobacterium animalis subsp. lactis	Decker et al., 2022, Laursen et al., 2017, Taipale et al., 2016, Taipale et al., 2011, Di Pierro et al., 2020
Bifidobacterium bifidum	Rerksuppaphol et al., 2012, Sudarmo et al., 2019
Bifidobacterium breve M-16V	Santamaria et al., 2019
Bifidobacterium infantis M-63	Santamaria et al., 2010
Bifidobacterium longum BB536	Santamaria et al., 2019
Lactobacillus acidophilus	Rerksuppaphol et al., 2012, Leyer et al., 2009, Río et al., 2002
Lactobacillus casei	Campanella et al., 2018, Rio et al., 2002, Prodeus et al., 2016
Lactobacillus fermentum	Maldonado et al., 2012
Lactobacillus paracasei	Campanella et al., 2018
Lactobacillus paracasei CBA L74	Corsello et al., 2017, Nocerino et al., 2017
Lactobacillus reuteri	Campanella et al., 2018, Gutierrez-Castrellon et al., 2014
Lactobacillus rhamnosus	Decker et al., 2011, Hojsak et al., 2016, Kumpu et al., 2012, Hojsak et al., 2010, Lin et al., 2009, Rautava et al., 2009, Scalabrin et al., 2017, Cáceres et al., 2010, Kloster Smerud et al., 2008
Lacticaseibacillus rhamnosus GG DSM 33156	Damholt et al., 2022, Hatakka et al., 2001
Pediococcus acidilactici K15	Hishiki et al., 2020
Streptococcus salivarius 24SMB	Andaloro et al., 2019
Streptococcus salivarius M18	Campanella et al., 2018
Streptococcus oralis 89a	Andaloro et al., 2019
Streptococcus salivarius ENT K12	Guo et al., 2022, Di Pierro et al., 2016
Streptococcus thermophilus	Prodeus et al., 2016
Lactobacillus plantarum HEAL9 (DSM 15312)	Ahrén et al., 2020
Lactobacillus paracasei 8700:2 (DSM 13434)	Ahrén et al., 2020

Table 1: *Probiotics strains in included articles.*

phol & Rerksuppaphol, 2012; Santamaria et al., 2019), three studies (9.38%) relied solely on proxy reports (Campanella et al., 2018; Taipale et al., 2011; Taipale et al., 2016), and eight studies (25%) employed a combination of these methods (Andaloro et al., 2019; Damholt et al., 2022; Hojsak et al., 2010; Hojsak et al., 2016; Kumpu et al., 2012; Laursen et al., 2017; Madempudi et al., 2022; Scalabrin et al., 2017).

Four studies (12.5%) did not include safety reporting, and therefore, no adverse events (AEs) related to the treatment were reported (Cáceres et al., 2010; Lin et al., 2009; Río et al., 2002; Sudarmo et al., 2019). The remaining 28 studies (87.5%) assessed the safety of probiotics consumption by AE reporting (Lazou Ahrén et al., 2020; Andaloro et al., 2019; Campanella et al., 2018; Corsello et al., 2017; Di Pierro et al., 2016; Di Pierro et al., 2020; Hatakka et al., 2001; Damholt et al., 2022; Dekker et al., 2022; Guo et al., 2022; Gutierrez-Castrellon et al., 2014; Hishiki et al., 2020; Hojsak et al., 2010; Hojsak et al., 2016; Kloster Smerud et al., 2008; Kumpu et al., 2012; Laursen et al., 2017; Leyer et al., 2009; Madempudi et al., 2022; Maldonado et al., 2012; Nocerino et al., 2017; Prodeus et al., 2016; Rautava et al., 2009; Rerksuppaphol & Rerksuppaphol, 2012; Santamaria et al., 2019; Scalabrin et al., 2017; Taipale et al., 2011; Taipale et al., 2016). In these studies, the reported AEs were deemed non-serious. Details on safety reporting for each study are provided in Table 2.

Main Results

Twenty-five studies (78.1%) showed a beneficial effect of probiotics in reducing RTI compared to a placebo or no treatment. In 7 studies (21.8%), no significant difference in the RTI incidence rate has been found. One study (Prodeus et al., 2016) reported statistically significant outcomes only in the reduction of rhinopharyngitis. A summary can be found in Table 3.

The rate of infections varied significantly due to differences in the length of follow-up. Most studies lasting 12 weeks or less used different strains of Lactobacillus (e.g., LGG, L. reuteri, L. paracasei CBA L74, L. casei), while one study used Bifidobacterium animalis subsp. lactis BB-12. All but one (Damholt et al., 2012) demonstrated a reduction in the incidence of URTIs. In contrast, the study by Scalabrin et al. (2017), which had a much longer follow-up period of 240 weeks, did not show positive results regarding RTI incidence rates.

In the intervention groups, a total of 1257 infections were recorded across 26 studies, averaging 48 RTIs per study. In the placebo or no intervention groups, a total of 1653 RTIs were diagnosed, averaging 64 infections per study. Probiotics prevented the occurrence of RTIs in 70% of studies and decreased the incidence rate of acute URTIs in 81.8% of studies. The mean prevalence was 42% for the intervention groups and 59% for the placebo or no intervention groups.

Assessment of Risk of Bias in Individual Studies

Only 6 studies (Damholt et al., 2022; Gutierrez-Castrellon et al., 2014; Hojsak et al., 2010; Nocerino

Author	Safety Assessment	Type	Severe AE reported?
Dekker, 2022	Yes	Unrelated and related to treatment AEs	No
Guo, 2022	Yes	Treatment associated AEs	No
Maldonado, 2012	Yes	Treatment associated AEs	No
Madempudi, 2022	Yes	Treatment and prevalence of AEs and the need to require concomitant therapies	No
KlosterSmerud, 2008	Yes	Unrelated and related to treatment AEs	No
Taipale, 2016	Yes	Treatment associated AEs	No
Nocerino, 2017	Yes	Unrelated and related to treatment AEs	No
Hojsak, 2016	Yes	Unrelated and related to treatment AEs	No
Rautava, 2009	Yes	Treatment associated AEs	No
Ahrén, 2020	Yes	Unrelated and related to treatment AEs	No
Santamaria, 2019	Yes	Unrelated and related to treatment AEs	No
Kumpu, 2012	Yes	Treatment associated AEs	No
Scalabrin, 2017	Yes	Unrelated and related to treatment AEs	No
Hojsak, 2010	Yes	Treatment associated AEs	No
Andaloro, 2019	Yes	Treatment associated AEs	No
Damholt, 2022	Yes	Treatment associated AEs	No
Rerksuppaphol, 2012	Yes	Unrelated and related to treatment AEs	No
Hishiki, 2020	Yes	Treatment associated AEs	No
Leyer, 2009	Yes	Treatment associated AEs	No
Campanella, 2018	Yes	Treatment associated AEs	No
Laursen, 2017	Yes	Treatment associated AEs	No
Prodeus, 2016	Yes	Unrelated and related to treatment AEs	No
Taipale, 2011	Yes	Unrelated and related to treatment AEs	No
Gutierrez-Castrellon, 2014	Yes	Unrelated and related to treatment AEs	No
Corsello, 2017	Yes	Unrelated and related to treatment AEs	No
Cáceres, 2010	No	Unrelated to treatment AEs	No
DiPierro, 2016	Yes	Unrelated and related to treatment AEs	No
DiPierro, 2020	Yes	Unrelated and related to treatment AEs	No
Hatakka, 2001	No	Unrelated and related to treatment AEs	No
Lin, 2009	No	Unrelated to treatment AEs	No
Rio, 2002	No	Unrelated to treatment AEs	No
Sudarmo, 2019	No	Unrelated to treatment AEs	No

Table 2: *Safety assessment.*

Study Identifier	Country	Sample Size	Age range	Follow up period (weeks)	Comparison	Reduction of RTI after intervention
Madempudi 2022	India	90	4-7 y	24	Placebo	YES
Dekker 2022	China	192	6-12 m	12	Placebo	YES
Guo 2022	China	97	3-10 y	8	NI	YES
Damholt 2022	United Kingdom	619	2-6 y	16	Placebo	NO
Hishiki 2020	Japan	179	3-6 y	16	Placebo	NO
Santamaria 2019	Italy	55	3-6 y	8	Placebo	YES
Andaloro 2019	Italy	84	6-11 y	24	Placebo	YES
Campanella 2018	Italy	40	12-15 y	12	Placebo	YES
Laursen 2017	Denmark	290	8-14 m	24	Placebo	YES
Corsello 2017	Italy	146	12-48 m	12	Placebo	YES
Di Pierro 2020	Italy	203	33-45 m	90	NI	YES
Nocerino 2017	Italy	377	12-48 m	12	Placebo	YES
Taipale 2016	Finland	109	1-24 m	96	Placebo	YES
Hojsak 2016	Croatia	210	1-7 y	12	Placebo	NO
Gutierrez-Castrellon 2014	Mexico	336	6-36 m	24	Placebo	YES
Kumpu 2012	Finland	523	2-6 y	28	Placebo	NO
Rerksuppaphol 2012	Thailand	80	8-13 y	12	Placebo	YES
Maldonado 2012	Spain	215	6-12 m	48	Placebo	YES
Taipale 2011	Finland	109	1-2 m	32	Placebo	YES
Hojsak 2010	Croatia	281	13-86 m	12	Placebo	YES
Leyer 2009	China	326	3-5 y	24	Placebo	YES
Lin 2009	Taiwan	1062	4-5y	32	NI	YES
Rautava 2009	Finland	81	0-2 m	48	Placebo	YES
Río 2002	Argentina	100	6-24 m	12	Placebo	YES
Hatakka 2001	Finland	571	1-6 y	32	Placebo	YES
Ahrén 2020	Sweden	131	1-6 y	12	Placebo	YES
Sudarmo 2019	Indonesia	267	1-5 y	26	Placebo	YES
Prodeus 2016	Russia	599	3-6 y	16	Placebo	YES
Di Pierro 2016	Italy	222	6-36 m	12	NI	YES
Scalabrin 2017	United States	183	4-60 m	240	Placebo	NO
Cáceres 2010	Chile	398	1-5 y	12	Placebo	NO
Kloster Smerud 2008	Norway	240	1-3 y	28	Placebo	NO

Nota: **NI:** No intervention ; **RTI:** Respiratory tract infection; **y**: years ; **m**: months

Table 3: *Characteristics of the included studies.*

Figure 2: *The risk of bias domains.*

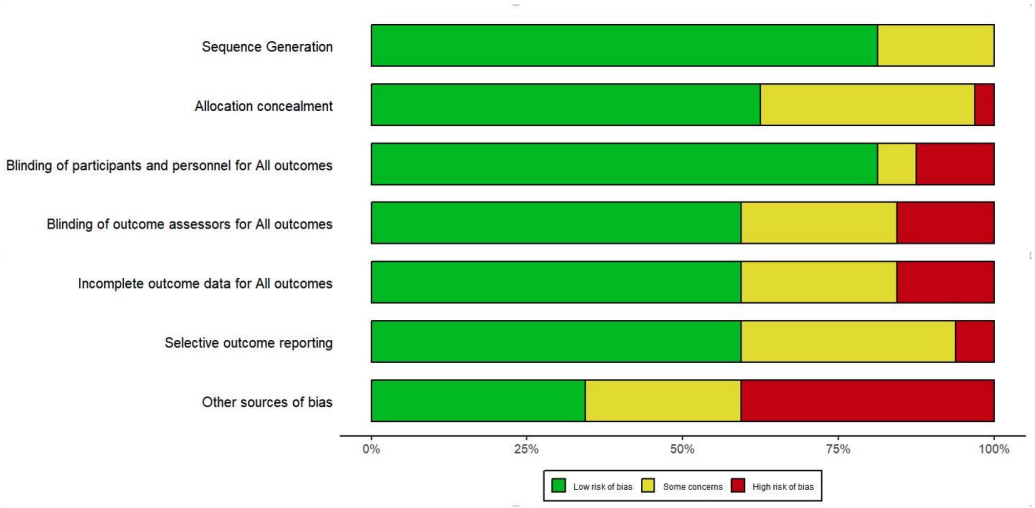

Figure 3: *The risk of bias assessment results.*

et al., 2017; Prodeus et al., 2016; Taipale et al., 2016) had a low risk of bias across all seven domains in the RoB2 analysis. The risk of bias assessment results are summarized in Figures 2 and 3.

Discussion

This systematic review aimed to evaluate the effect of probiotics on pediatric and adolescent populations to prevent RTIs. Studies from different continents were included; however, most studies were conducted in Europe, with fewer studies from Asia and the Americas. Most articles demonstrated that probiotic treatment was associated with a reduction in RTIs.

Our findings align with previous systematic reviews and meta-analyses assessing the same topic. For instance, Hojsak & Kolacek (2013) reviewed six studies involving 2880 preschool children aged 3 months to 7 years attending daycare centers. Specific probiotic strains (e.g., *LGG, B. lactis + S. thermofilus, B. lactis Bb-12 or L. reuteri, L. casei rhamnosus, L. rhamnosus T cell-1, L. casei + S. thermofilus, and L. bulgaricus)* and doses between 107-1010 CFU, had a positive effect in reducing URTIs. Furthermore, in a Cochrane review of 13 studies excluding influenza-vaccinated subjects, probiotics reduced acute URTI, antibiotic use, and school absences (Hao et al., 2015). Similarly, a review by Weizman (2015), which included 12 studies on children aged 3 to 86 months, found probiotics safe and beneficial for preventing RTIs. However, the latter review also included prebiotics. In a review, De Araujo et al. (2015) analyzed eleven studies on probiotics' impact on URTIs and LRTIs in healthy children from birth to 10 years of age with mixed results: six studies showed a decrease in infections, three showed no significant difference, and two studies did not report outcomes. Laursen & Hojsak (2018) further analyzed 15 studies on 5121 children aged 3 months to 7 years old, focusing on the effects of probiotic strain, dosage, and administration regimen, and found that probiotics reduced the risk of RTIs by 22% compared to a placebo. They also found that LGG slightly reduced the duration of infections. More recently, Zhao et al. (2022) conducted a Cochrane review of 23 single RCTs and one cluster RCT, confirming the efficacy of probiotics in reducing the incidence of URTIs in different settings, such as communities, care facilities, schools, and hospitals. The latter included 4798 subjects encompassing the whole population (children, adults, and elderly).

In this review, the included studies focused on children who were either at home, or attended daycare and/or school, which are common settings where children develop in their early life. Additionally, our study boasts a large total sample size, encompassing various probiotic strains and formulations, as well as examining both acute and recurrent RTIs, including different types of RTIs. Thus, the results are generalizable to healthy infants and preschool children. Since only two studies included children older than 12 years (Rerksuppaphol & Rerksuppaphol, 2012; Campanella et al., 2018), the findings may not be generalizable to adolescents.

Regarding the intervention, the probiotics studied were quite wide-ranging as well, including *Bifidobacterium animalis subsp lactis* BB-12, *S. salivarius, S. oralis, L. paracasei, L. reuteri, L. rhamnosus, Bacillus clausii, and Enterococcus faecium.* Not only were the strains heterogeneous, but the duration of the intervention also varied among the studies. Most trials lasted for 90 days, with some extending from 90 to 730 days. There were also significant variations in sample sizes, ranging from smaller studies with 55 subjects to larger trials with up to 1062 subjects.

A further advantage of the present review is that it includes more recent studies that were not previously analyzed, allowing a comprehensive analysis of probiotic efficacy across different settings and interventions. However, it also presents challenges due to the varying quality of the included studies, making it difficult to draw definitive conclusions. One limitation was the differing quality of the studies, mainly regarding the lack of formal measures of association. There were only 6 high-quality studies with a low risk of bias across all seven domains, and the remaining studies had varying risks of bias and uncertainty in different areas, affecting the reliability of the findings. Additionally, variations in study designs, strains, treatment plans, and the number of participants limited the evidence of effectiveness in this population of children.

Lastly, there is a lack of clear and consistent safety reporting, which concerns the majority of the included studies. This limitation may stem from inconsistencies in how adverse events (AEs) were documented and classified. Without standardized guidelines, it becomes challenging to accurately assess and compare the safety profiles across studies, potentially leading to underreporting or misclassification of serious adverse events (SAEs). Establishing uniform safety reporting protocols could improve data reliability and allow for better assessment of product-related risks.

With many research gaps in a relatively new research area, this review also opens the door for further research projects. Identifying optimal probiotic strains and dosage regimes could further improve the impact in reducing RTIs. Furthermore, assessing the possible long-term effects of probiotics would provide additional know-how, as most studies only covered a short follow-up period. Lastly,

more population-specific studies are required to investigate the effect of probiotics in more narrowly defined groups and identify potential populations at risk. The gaps identified are attributed to the lack of standardized strains and doses, varying oral administration methods, and unanswered questions about the time it takes for probiotic supplementation to modify microbiota and lead to health benefits. While short-term studies show a reduction in RTIs, longer studies do not, leading to concerns about the quality of trials due to potential bias. Also, while no safety reports or adverse events were documented, this absence does not imply that adverse events were nonexistent.

Conclusion

Our systematic review suggests that probiotics may reduce RTI incidence in healthy children and adolescents when compared to placebo or no intervention. The analysis included a large total sample size, covering different probiotics strains and presentations, settings, age ranges, and evaluated both upper and lower RTIs. However, high data heterogeneity is a major limitation, with 22 different strains, various administration schedules, and RTIs incidence, posing challenges when analyzing the results. *Lactobacillus* was the most common strain (46.8%), with doses ranging from hundreds of thousands (105) to over tens of billions (1010), most studies being in the upper range. These data could be used as a base for further studies. Only a few studies demonstrated a low risk of bias in all domains, which may affect the validity of their findings. Further research should aim to identify optimal strains and doses of probiotics for the prevention of RTIs, assess the long-term effects, and investigate their effect on more narrowly defined groups and potential at-risk populations.

Abbreviations

B. lactis: Bifidobacterium lactis
B. lactis Bb-12: Bifidobacterium animalis subsp. lactis BB-12
CFU: Colony Forming Units
IQR: Interquartile Range
LGG: Lactobacillus rhamnosus GG
LRTI(s): Lower Respiratory Tract Infection(s)
L. casei: Lacticaseibacillus casei
L. casei rhamnosus: Lacticaseibacillus rhamnosus
L. bulgaricus: Lactobacillus bulgaricus
L. plantarum: Lactobacillus plantarum
L. paracasei: Lactobacillus paracasei
L. reuteri: Lactobacillus reuteri
L. rhamnosus: Lacticaseibacillus rhamnosus
RCT(s): Randomized Controlled Trial(s)
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RTI(s): Respiratory Tract Infection(s)
URTI(s): Upper Respiratory Tract Infection(s)
S. oralis: Streptococcus oralis
S. salivarius: Streptococcus salivarius
S. thermophilus: Streptococcus thermophilus
T-cell-1: Thymus-derived lymphocytes

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Supplementary Materials

Appendix A. PubMed search
Appendix B. Web of Science search
Appendix C. Embase search
Appendix D. Eligibility Criteria: Inclusion
Appendix E. Eligibility Criteria: Exclusion

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Conflicts of Interest

The authors declare no conflict of interest.

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