Review

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Probiotics and Recurrent Respiratory Infections in Children

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Recurrent respiratory infections (RRIs) represent a significant health concern among children, affecting 6% within their first six years and 25% before reaching one year old. Despite often presenting mild symptoms, these infections persist to varying degrees, typically decreasing in frequency until complete resolution by the age of twelve. However, the transient nature of RRIs disguises the considerable medical and social burdens they impose, notably diminishing the quality of life for affected children and their families. This comprehensive review aims to distil and synthesize findings from extensive research conducted over the past seventeen years, with a particular focus on understanding the role of probiotics in both preventing and treating RRIs. By compiling key insights from these studies, the review sheds light on the complex dynamics of RRIs and explores the potential of probiotics as a promising avenue for reducing the frequency and severity of these infections. Probiotics, defined as live microorganisms conferring health benefits, have garnered attention due to their immunomodulatory properties. Recent studies have investigated the efficacy of probiotics in preventing and treating RRIs, emphasizing their ability to modulate immune responses, enhance mucosal immunity, and maintain a balanced microbial environment within the respiratory tract. Through critical examination of accumulated evidence, this review aims to provide a nuanced understanding of the intricate interplay between RRIs, the evolving immune systems of children, and the potential therapeutic contributions of probiotics. By synthesizing findings from recent research, it seeks to contribute meaningfully to ongoing discussions on effective strategies for alleviating the burden of RRIs in pediatric populations. The insights gleaned from this review are poised to inform future interventions, guiding healthcare practitioners in devising targeted and effective approaches to managing and mitigating the impact of RRIs in children.

Keywords: RRIs; probiotics; children; prevention

Introduction

During childhood, recurrent respiratory infections (RRIs) are a prevalent health concern that leads to numerous doctor visits and frequent hospitalizations. This has a significant impact on the families of affected children, pediatricians, and the pharmaceutical industry [1].

Several risk factors contribute to the recurrence of RRIs, including early age due to the relative immaturity of the immune system, early enrollment in nursery school, environmental pollution, exposure to passive smoking, low socioeconomic status, and allergic conditions [2].

As the most common cause of respiratory infections in children, viral infections are noteworthy for playing a critical role [3]. Although antibiotics and anti-inflammatory medications are frequently and ineffectively provided empirically in clinical practice, the guidelines stress that they should be used appropriately [4,5]. Notably, indiscriminate and excessive antibiotic prescriptions select multi-resistant microorganisms, so antibiotic overuse and abuse are usually linked to resistance to a wide range of bacteria. Preventing RRIs could, in this aspect, lessen antibiotic improper use and abuse and have significant socioeconomic effects. Alternative therapies have recently been proposed to limit the incidence of drug resistance, avoid inappropriate therapy, and prevent RRIs [6]. The study of the nasal microbiome has brought attention to an intriguing approach that uses "health-friendly bacteria". These bacteria interact with the local epithelium and immune cells, triggering systemic immune responses and eliminating invasive species [7,8]. Given these positive traits, authors successfully turned to the beneficial microorganisms, more often known as probiotics, to support microbiome homeostasis as a further and more powerful defence against the development of RRIs [9,10] (Table 1).

This review aims to consolidate the recent studies' significant findings, providing an understanding of the in-

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

Table 1. Possible therapies to prevent RRIs.

Therapy	Description
Antibiotics	Antibiotics are commonly used to treat bacterial infections, which can either be a cause or a complication of RRIs in certain cases.
Antiviral medication	Antiviral medications may be prescribed for specific viral infections that contribute to RRIs, such as influenza.
Probiotics	Some evidence suggests probiotics may help prevent or reduce the severity of RRIs in children.
Immunomodulators	Medications that modify the immune response may be considered in cases of recurrent or severe respiratory infections.
Allergen avoidance	If allergies exacerbate RRIs, identifying and avoiding allergens can be part of the treatment strategy.
Immunizations	Routine vaccinations can help prevent certain infections known to cause RRIs, such as influenza.
Symptomatic relief	Over-the-counter medications may be used to alleviate symptoms like fever, cough, and congestion.
Lifestyle modifications	Encouraging healthy habits like handwashing, adequate sleep, and good nutrition can support immune health.

RRIs, recurrent respiratory infections.

tricate dynamics of RRIs and investigating the potential of probiotics as a promising approach to reducing the frequency and severity of these infections.

Definition of Recurrent Respiratory Infections

In 2020, an Italian inter-company consensus document was developed to provide an updated definition of RRIs through the analysis of international scientific literature using the GRADE method [11]. A panel of experts representing various disciplines such as paediatrics, otorhinolaryngology, pneumology, allergology, immunology, oncohematology, pediatric infectious diseases, pharmacology, microbiology, pediatric radiology, territorial public health, nursing sciences, research methodology, and epidemiology was selected by the scientific societies of relevant fields to establish this consensus.

To devise a new definition, the initial assessment involved examining the diversity of studies found in the literature related to pediatric RRIs, encompassing observational studies, randomized controlled trials, original studies, reviews, meta-analyses, and epidemiological studies. The Delphi approach was employed to share and approve the newly proposed definition after considering all definitions identified in the literature search [11]. According to the Consensus, the criteria for defining a child with RRIs in the pediatric age group include:

■ Children aged 1–3 years:

-Experience 6 or more respiratory tract infections within a year, with one potentially being pneumonia, including severe pneumonia; or

-Encounter 2 mild cases of pneumonia confirmed by clinical criteria and/or x-ray within a year.

■ Children aged 3–6 years:

-Have 5 or more respiratory tract infections within a year, with one potentially being pneumonia, including severe pneumonia; or

-Experience 2 mild cases of pneumonia confirmed by clinical criteria and/or x-ray within a year.

■ Children aged 6–12 years:

-Encounter 3 or more respiratory tract infections within a year, with one potentially being pneumonia, including severe pneumonia; or

-Experience 2 mild cases of pneumonia confirmed by clinical criteria and/or x-ray within a year.

Children meeting the following conditions were excluded from this definition:

-Recurrent infections in one specific area only (e.g., recurrent rhinosinusitis, recurrent otitis media, recurrent wheezing, or recurrent pharyngotonsillitis).

-Known primary or secondary immunodeficiencies (including IgA deficiency).

-Cystic fibrosis.

-Primary ciliary dyskinesia.

-Non-cystic fibrosis-related bronchiectasis.

-Genetic disorders.

-Known cardio-respiratory malformations.

-Neuromuscular disorders.

-Other preexisting chronic lung diseases.

Probiotics

According to the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) in 2001, probiotics are live microorganisms which, when ingested in sufficient quantities, provide a positive health effect on the host [12]. The inhibition of the growth of pathogens, the consolidation of epithelial barrier function, and most importantly, immuno-modulating activity demonstrate how some probiotic strains of live microorganisms, when consumed in sufficient amounts, have beneficial effects on the health of the host organism [12]. Recently, specific topical probiotic strains (bacteriotherapy) have been embraced to enhance the composition of the pertinent microbiota (in the rhinopharynx and middle ear), aiming to prevent recurrent upper respiratory tract diseases. These strains include *Lactobacillus salivarius PS7*, *Streptococcus salivarius K12*, and *Streptococcus salivarius 24SMB*. The intricate relationship between the immune system and diverse microbial communities presents in body compartments, such as the intestines, oro-pharynx, nasal cavities, lungs, skin, and

urogenital region, is characterized by a dynamic communication network. This interaction is facilitated through the exchange of metabolites and cytokines, fostering a complex crosstalk. The immune system acts as a sentinel, responding to signals from these microbial communities to maintain homeostasis and defend against potential threats. Conversely, the microbiota influences immune responses, contributing to the overall health of the host. This symbiotic communication underscores the crucial role of a balanced and harmonious interaction between the immune system and microbial communities in various anatomical niches, highlighting the intricate dance of signals that occurs to preserve the delicate equilibrium within the human body [13]. In a narrative review, Lehtoranta *et al*. [14] analyze crucial pre-clinical and clinical evidence to evaluate the current understanding of probiotics' immunomodulatory effects concerning viral RRIs. Probiotics exhibit strain-specific immunomodulatory actions on immune cells and the host by activating toll-like receptors (TLRs), thereby initiating interferon (IFN) pathways, as demonstrated *in vitro*. Research suggests that probiotics play a beneficial role in inhibiting the proliferation of various respiratory viruses, including influenza viruses and respiratory syncytial virus (RSV), indicating that heightened IFN response enhances cellular resistance to viral infections. Studing in mice corroborate these findings, showing reduced virus levels in lung tissues and altered expression of pro-inflammatory and antiviral genes both pre- and post-infection [15].

Probiotics have emerged as a valuable strategy for both preventing and treating respiratory infections in the pediatric population. Research has explored their efficacy in warding off upper respiratory tract infections in infants and children who attend daycare centers. Additionally, probiotics have shown promise in preventing exacerbations in children with chronic lung diseases, such as cystic fibrosis. Their effectiveness stems from their dual action: a competitive influence on the bacterial flora within mucous membranes and an immunomodulatory effect. By competing with harmful bacteria for resources, probiotics help maintain a balanced microbial environment, while their immunomodulatory properties contribute to a strengthened immune response [16,17]. This multifaceted approach positions probiotics as a versatile tool in the arsenal against respiratory infections in pediatric settings, offering potential benefits in both prevention and management scenarios.

Studies on the Efficacy of Probiotics in the Treatment of RRIs

Probiotics in Treatment of Respiratory Tract Infections

In this review, we have collected the results of the last seventeen years of studies regarding RRIs and the role of probiotics in their prevention and treatment. We searched on PubMed and Google Scholar, using the keywords RRI, otitis, probiotics, and children and we exclusively selected pediatric studies.

In the study by Manti *et al*. [18], *Streptococcus salivarius 24SMBc* and *Streptococcus oralis 89a* were given to 100 caucasian children with RRIs as 2 puffs for each nostril twice a day for seven days after a nasal saline lavage program. Children were assessed at the start of the trial, at one and three months (treatment period). The parents were contacted by phone following 1 and 3 months, monitoring the clinical progressions and assessment of the treatment responses. Children treated with *Streptococcus salivarius 24SMBc* and *Streptococcus oralis 89a* have shown a significant reduction in symptoms such as fever, cough, bronchospasm, rhinorrhea, and otalgia since the first month of treatment. In the third month of the medication, there was no further improvement. On the other hand, up to the third month of treatment, a progressive and significant reduction in cough has been seen. Despite the brief observation period, the study found that administering *Streptococcus salivarius 24SMBc* and *Streptococcus oralis 89a* significantly reduced the incidence of bouts of fever, cough, bronchospasm, rhinorrhea, and otalgia in a pediatric population suffering from RRIs. In fact, all symptoms improved clinically following probiotic therapy. Furthermore, the benefits of the treatment were not only evident at the commencement but persisted consistently throughout the entire treatment duration. *Streptococcus salivarius 24SMBc* and *Streptococcus oralis 89a* treatment also showed efficacy in high-risk groups including atopic individuals and kids exposed to environmental smoke. In the study by Tarantino *et al*. [19] using an oral spray comprising *Streptococcus salivarius 24SMB* and *Streptococcus oralis 89* (Orogermina, DMG, Rome, Italy), 51 children, with a history of RRIs in the previous year, were treated. 2 puffs once each day for 30 days for three consecutive months were administered. The number of RRIs and the number of days missed at school in the past year (T0) and the present year (T1) were analyzed. Bacteriotherapy considerably reduced the average number of RRI events from 5 in the previous year to 2 in the current year (T1). Additionally, the therapy decreased by around 35% the number of missed school days from 3 at T0 to 1 at T1. However, this study has significant drawbacks including the lack of a control or placebo group, the focus solely on clinical results without taking into account cultural factors, and the retrospective collection of data from parents for the previous year. Guo *et al*. [20] conducted a single-center, open, randomized controlled trial at Wuhan's China Resources (CR) & WISCO General Hospital from January to March 2021. The study aimed to assess the clinical effectiveness and safety of oropharyngeal probiotic *Streptococcus salivarius K12* (ENT-K12) as either a dietary intervention or supplemental medication alongside routine medical treatment for children with RRIs during the cold season. In the probiotic group, 47 children (22 males,

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

25 females) with an average age of 5.71 years (Standard Deviation (SD) = 1.99) completed the trial, while the control group consisted of 50 children (32 males, 18 females) with an average age of 6.12 years (SD = 1.98). Over the 30-day intervention period, children in the probiotic group experienced a total of 7 upper respiratory tract infections, whereas those in the control group had 17 episodes. The incidence of upper respiratory tract infections in the probiotic group (14.89%) was significantly lower than in the control group (34.00%). Furthermore, the probiotic group had significantly fewer days of antibiotic and antiviral drug administration compared to the control group. Additionally, the onset of respiratory symptoms was shorter and less severe in the probiotic group. Additionally, the probiotic group exhibited significantly fewer days of school absenteeism for children and fewer days of work absenteeism for parents compared to the control group [20]. In the review by Esposito *et al*. [21], selecting studies up to April 2020, probiotics, especially *Lactobacillus* and *Bifidobacterium species*, have been advocated for use in the treatment and prevention of RRIs. Regrettably, the majority of the included studies in pediatrics on RRIs prevention were conducted on otherwise healthy kids, not children who were prone to RRIs. Moreover, the total number of children enrolled was almost always relatively small, and the majority of the research used highly dubious procedures and yielded ambiguous findings. In addition, the degree of study variability in terms of probiotic type, dosage, and duration was very high. Taking into account all these variables, the conclusion is drawn that it is presently impractical to determine whether probiotics can effectively prevent recurrent respiratory tract infections, and if they do, which specific probiotics, at what dosages, and under what conditions [22]. A Cochrane meta-analysis of 10 clinical trials with 3451 infants, children, and adults revealed that probiotics were superior to placebo in terms of preventing infections. They also decreased the frequency of antibiotic use and the rate of acute upper respiratory tract infections (URTIs), but they did not shorten the course of each trial. Probiotic treatment of upper respiratory tract infections (URTIs) and its potential to lessen symptom severity have not been documented, nor have data been gathered in pediatric patients with long-term underlying illnesses. The scant research that has been released thus far fails to identify the specific microbe or dosage schedule that may be effective in preventing Respiratory Tract Infections (RTIs) in both healthy and URTI-prone youngsters [16]. Khan Laghari *et al*. [23] evaluated the effect of a straightforward probiotic approach on reducing the intensity and frequency of RRIs. Probiotics containing a combination of *Bifidobacterium* and *Lactobacillus Acidophilus*, given to children with RRIs for two weeks resulted in a significant reduction in RRIs during the following six months. During this period, all RRIs episodes decreased, the most significant decrease was found in recurrent infectious rhinitis, recurrent otitis media and recurrent bronchiolitis. They observed that *Lactobacillus* and *Bifidobacterium* probiotic combination used in this trial was efficient enough to reduce the frequency and severity of several RRIs.

The study by Li *et al*. [24] aimed to investigate the clinical effects of *Bifidobacterium* tetravaccine tablets on Recurrent Respiratory Tract Infections (RRTI), aiming to provide an effective method for prevention and treatment. Additionally, a healthy group of 30 children was included, while 120 children with RRTI were randomly assigned to different groups: active, remission, intervention, and control. Over two months, the intervention group received oral *Bifidobacterium* tetravaccine tablets, while the control group received standard medical care. Stool samples were collected to examine bacterial strains. During a one-year follow-up, the incidence of Respiratory Tract Infections (RTI) was compared among the groups. Significant decreases in Bifidobacteria and Lactobacilli levels were observed in all RRTI groups compared to the healthy group. However, the intervention group showed significantly higher levels of Bifidobacteria and Lactobacilli compared to other RRTI groups. Furthermore, compared to the control group, the intervention group experienced significantly reduced average annual frequencies of acute RTIs and antibiotic usage. Moreover, the average duration of fever, cough, and antibiotic use per episode was significantly shorter. These findings suggest that children with RRTI often experience intestinal flora imbalances, but oral probiotics can effectively restore balance and reduce the frequency of RTIs [24].

Probiotics in the Treatment of Otitis in Children

Scott *et al*.'s [25] meta-analysis aimed to assess the effectiveness of probiotics in reducing the severity and occurrence of acute otitis media (AOM) in children. The analysis included 17 randomized controlled trials (RCTs) involving 3488 children. The probiotic strains evaluated varied among the trials; eleven RCTs examined probiotics containing *Lactobacillus*, while six RCTs examined probiotics containing *Streptococcus*. The meta-analysis revealed that children who consumed probiotics had a decreased likelihood of experiencing one or more episodes of AOM during treatment (relative risk [RR] 0.77, 95% confidence interval (CI) 0.63 to 0.93; 16 trials; 2961 participants; number needed to treat to benefit [NNTB] = 10; moderate-certainty evidence). Moreover, probiotics were associated with a reduced need for antibiotics in children for any infection (RR 0.66, 95% CI 0.51 to 0.86; 8 trials; 1768 participants; NNTB = 8; moderate-certainty evidence). Subgroup analysis did not demonstrate significant variations in antibiotic usage specifically for AOM or for infections other than AOM. Additionally, there was no notable difference in the average number of school days missed between the probiotic and control groups (mean difference (MD) –0.95, 95% CI –2.47 to 0.57; 5 trials; 1280 participants; moderate-certainty evidence), nor in the level of compli-

ance with the intervention (RR 1.02, 95% CI 0.99 to 1.05; 5 trials; 990 participants). Probiotics were also found to lower the proportion of children experiencing other infections (RR 0.75, 95% CI 0.65 to 0.87; 11 trials; 3610 participants; NNTB = 12; moderate-certainty evidence) [25]. The primary aim of the double-blind, placebo-controlled, randomized trial conducted by Katja Hatakka *et al*. [26] was to explore whether probiotics could mitigate the frequency or duration of AOM and the presence of associated microorganisms in children predisposed to this condition. Overing a 24-week intervention period, 309 children aged between 10 months and 6 years, who were prone to otitis media, were administered either a daily probiotic capsule containing *Lactobacillus rhamnosus GG (GG)* and *LC705*, *Bifidobacterium breve 99*, and *Propionibacterium freudenreichii JS* (n = 155), or a placebo (n = 154). Throughout the study, nasopharyngeal samples were collected thrice, along with clinical evaluations, while parents recorded symptoms of upper respiratory infections (URIs) in provided diaries. The results revealed no significant reduction in either the incidence or recurrence of AOM among children receiving probiotics. Notably, the median duration of AOM episodes was similar between the probiotic and placebo groups, averaging 5.6 days and 6.0 days, respectively [26].

Probiotics and SARS-CoV-2 Infection

Andrade *et al*. [27] delved into the extensive research surrounding the role of respiratory microbiota in both general viral infections and specifically Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) infection. Their review examined the scientific literature supporting the potential benefits of probiotic microorganisms with immunomodulatory properties in reducing the severity of respiratory viral infections, notably focusing on recent studies investigating probiotic bacteria's role in modulating immunity during SARS-CoV-2 infection. Strains like *L. plantarum* and *D. pigrum*, targeting the respiratory tract, showed promise in enhancing the immune response to SARS-CoV-2 infection and combating the coronavirus disease-19 (COVID-19) pandemic. This underscores probiotics as a promising avenue for developing innovative strategies to bolster the body's defences against viral infections [27]. In a prospective, multicenter, randomized, double-blind, placebo-controlled trial, Kolesnyk *et al*. [28] investigated the impact of probiotics on COVID-19, post-disease symptoms, and humoral immune responses to viral antigens. The study revealed that patients receiving probiotics exhibited fewer overall, respiratory, and constitutional symptoms compared to the control group. The assessment on the 10th day, a crucial time point for patient prognosis, showed significant differences in symptom severity. While gastrointestinal symptoms were minimal and statistically similar between groups initially, the probiotic group consistently showed a reduced percentage of patients experiencing such issues over the first 10 days, with shorter symptom durations observed. Notably, hospitalized patients with severe COVID-19 who received a daily dose of *B. longum*, *L. bulgaricus*, and *S. thermophilus* above 6×10^7 CFU for seven days experienced significantly shorter diarrheal episodes, averaging 2.41 days less than those in the control group [28]. M. Kumpu *et al*. [29] conducted a randomized, double-blind, placebo-controlled trial to investigate whether regular long-term consumption of probiotic-containing milk, specifically *Lactobacillus rhamnosus GG (GG)*, could reduce pediatric respiratory infections. The study involved 523 children aged two to six years who attended daycare centers in Finland. For 28 weeks, the participants consumed three daily meals containing either regular milk or milk mixed with *GG*. Parents recorded their children's symptoms daily. Fecal samples from 128 participants were analyzed for *GG* recovery, while primary outcome data from 501 subjects were included in the study. The *GG* group reported an average of 5.03 days with at least one respiratory symptom per month, compared to 5.17 days in the placebo group. The recurrent respiratory infections (RRIs) for both groups was 0.97. In the completed cases, the *GG* group experienced 4.71 days/month compared to 5.67 days/month in the placebo group. The results showed that *GG* consumption reduced the incidence of respiratory illnesses in children attending daycare centers in the subgroup of completed cases, but not in the overall population [29].

The studies on probiotics and recurrent respiratory infections (RRIs) in children are summarised in the table below (Table 2, Ref. [18–20,22,24,29]).

Discussion

RRIs present a substantial challenge in pediatric medicine, aggravated by associated consequences, particularly the inappropriate use of antibiotic therapy. The urgency of addressing this issue has spurred the quest for effective preventive measures [11]. Consequently, our review embarked on a thorough examination of the latest literature to evaluate the efficacy of various forms of bacteriotherapy as a means of prevention or mitigation of infectious episodes. The focus of our investigation centered on the promising potential of probiotics, to understand their role in reducing the frequency, severity, and dependence on antibiotic therapy in RRIs. Recent reviews have explored the involvement of probiotics in recurrent respiratory infections during childhood. The research by Caffarelli *et al*. in 2015 [30] summarized the available data offering suggestions for the use of probiotics in the treatment of infectious disorders in children. However, no evidence and recommendations for the use of probiotics in childhood RRIs emerged. In the systematic review by Hao *et al*. [16], probiotics were considered helpful in lowering the frequency and severity of URTIs, according to the majority of the data. This was especially crucial for high-risk populations like kids, the elderly, and people with chronic medical issues.

Table 2. Studies on probiotics and RRIs in children.

Reference	Study Population	Probiotic Strain	Objective	Results
[18]	100 children with RRIs received 2 probiotic strain puffs for each nostril twice a day for seven days	-*Streptococcus salivarius 24SMBc* -*Streptococcus oralis 89a*	Effectiveness of probiotics in reducing the severity and occurrence of RRIs	Significant reduction in symptoms such as fever, cough, bronchospasm, rhinorrhea, and otalgia since the first month of treatment.
[19]	51 children with a history of RRIs in the previous year, were treated with 2 puffs once each day for 30 days for three consecutive months	-*Streptococcus salivarius 24SMB* -*Streptococcus oralis 89*	Effectiveness of probiotics in reducing the severity and occurrence of RRIs	Probiotic treatment considerably reduced the average number of RRI events from 5 in the previous year to 2 in the current year. The therapy decreased by around 35% the number of missed school days from 3 at T0 to 1 at T1.
[20]	Case group: 47 children Control group: 50 children	*ENT-K12*	Clinical efficacy and safety of the supplementation of oropharyngeal probiotic during acute respiratory infections in children with RRIs during the cold season, along with routine medical treatment	The probiotic group's incidence of upper respiratory tract infections (14.89%) and the antibiotics and antiviral drugs administered were significantly lower than that of the control group during the intervention period.
[22]	70 children with RRIs were treated for two weeks with a probiotic mixture	-*Lactobacillus Acidophilus* -*Bifidobacterium*	Probiotics used to reduce the intensity and frequency of RRIs	All RRIs episodes decreased, the most significant decrease was found in recurrent infectious rhinitis, recurrent otitis media and recurrent bronchiolitis.
[24]	30 healthy children vs 120 children with RRTI randomly assigned to different groups: active, remission, intervention, and control	The intervention group received oral *Bifidobacterium* tetravaccine tablets for one year	Effectiveness of probiotics in reducing the severity and occurrence of RRTIs	Significant decreases in Bifidobacteria and Lactobacilli levels were observed in all RRTI groups compared to the healthy group. The intervention group showed significantly higher levels of Bifidobacteria and Lactobacilli compared to other RRTI groups. The intervention group experienced significantly reduced average annual frequencies of acute RTIs and antibiotic usage, compared to the control group.
[29]	523 children	*Lactobacillus rhamnosus GG (GG)*	Investigate whether regular long-term consumption of probiotic-containing milk could reduce pediatric respiratory infections	The *GG* group had fewer average days per month with at least one respiratory symptom compared to the placebo group. However, this reduction was significant only in the subgroup of completed cases, not in the overall population.

ENT-K12, *Streptococcus salivarius K12*; RTIs, Respiratory Tract Infections; RRTI, Recurrent Respiratory Tract Infections; RRIs, recurrent respiratory infections.

While the review uncovered favourable outcomes, indicating a positive impact of probiotics, it is imperative to acknowledge the limitations inherent in each study under consideration. Challenges such as small sample sizes, insufficient standardization, and constrained study durations introduce a degree of uncertainty, preventing the definitive establishment of probiotics as a recognized and robust preventative or therapeutic intervention for RRIs. Navigating this complex landscape, it becomes apparent that further research endeavours are essential. These efforts should delve into refining our understanding of probiotics, considering factors like strain specificity, optimal dosages, and the duration of intervention. By addressing these nuances, future studies can provide a more comprehensive and nuanced insight into the potential of probiotics as a valuable tool in combating the burden of recurrent respiratory infections in pediatric populations. According to the Italian consensus, the use of oral probiotic formulations for the prevention of RRIs shouldn't be advised because of the lack of evidence of their efficacy (weak negative recommendation). In contrast, *Streptococcus salivarius 24SMB* nasal spray formulations shouldn't be used to prevent RRIs because there isn't enough data to support them (weak negative recommendation) [11].

Conclusion

In conclusion, our findings underscore the potential efficacy of probiotics in mitigating the frequency, severity, and reliance on antibiotic therapy in RRIs. The current data offer a solid foundation, but ongoing research endeavours will be essential to establish a more comprehensive and tailored approach to incorporating probiotics into the prevention and treatment strategies for recurrent respiratory infections. These future studies should consider factors such as strain specificity, optimal dosages, and duration of intervention, ensuring a more nuanced and evidence-based application of probiotics in the realm of respiratory health.

Abbreviations

RRIs, recurrent respiratory infections; FAO, Food and Agriculture Organization; WHO, World Health Organization; SD, Standard Deviation; RTIs, Respiratory Tract Infections.

Availability of Data and Materials

Not applicable.

Author Contributions

CI, EDA and CLB designed the research study and drafted the manuscript. GD, AK, AP and MMM performed the research. FD, GC and MMdG contributed to the concept and designed the research study and revised critically the manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The other authors declare no conflict of interest. Cristiana Indolfi and Giorgio Ciprandi are serving as Editorial Board members of this journal. We declare that Cristiana Indolfi and Giorgio Ciprandi had no involvement in the peer review of this article and have no access to information regarding its peer review.

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Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

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