Review Article

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Use of probiotics in the prevention of respiratory infections in childhood

Uso de probióticos na prevenção de infecções respiratórias na infância

Uso de probióticos en la prevención de infecciones respiratorias en la infancia

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ABSTRACT

Introduction: Acute respiratory infections are diseases that affect any segment of the respiratory tract within a period of up to 7 days. In childhood, their relevance is due to their high frequency and, at times, unfavorable outcomes, such as hospitalization and death. Recent studies have investigated the use of probiotics in preventing these infections, evaluating the benefits of immunomodulation by these live microorganisms in the host. **Objective:** To evaluate the effectiveness of probiotics in preventing respiratory infections in children. **Methods:** A systematic review was conducted, gathering randomized clinical trials. Using platforms such as Scopus, PubMed, Scielo, Clinical Trials, and Embase, in May 2024, filters were applied and data that answered the question "Is the use of probiotics or similar products associated with a reduced risk of respiratory tract infections in children?". A total of 1,157 articles were narrowed down to 33 articles included in the study. Trials emphasizing treatment, symptom reduction, and/or other effects contrary to the focus were excluded. **Results:** In the 33 articles reviewed, we observed whether there was a decrease in respiratory infection episodes. The results varied depending on the type of probiotic used, the microorganism, the dose, the route of administration, and the duration of use. Some studies demonstrated successful prevention, while others did not. **Conclusion:** Considering numerous influencing factors (age group, atopy variables, and recurrent infections), conflicting results were obtained. The use of probiotics in the prevention of respiratory infections remains controversial, requiring studies with methodological rigor.

Keywords: Probiotic; Prebiotic; Symbiotic; Respiratory tract infection; Children; Prevention.

RESUMO

Introdução: Infecções respiratórias agudas são doenças que acometem qualquer segmento do trato respiratório no período de até 7 dias. Na infância, sua relevância deve-se à alta frequência e, por vezes, desfechos desfavoráveis, como internação e óbito. Recentemente, estudos têm avaliado o uso de probióticos na prevenção dessas infecções, verificando os benefícios da imunomodulação desses microrganismos vivos no hospedeiro. **Objetivo:** Avaliar a eficácia dos probióticos na prevenção de infecções respiratórias em crianças. **Métodos:** Realizou-se estudo de revisão sistemática, reunindo ensaios clínicos randomizados. Por meio de plataformas como Scopus, PubMed, Scielo, Clinical Trial e Embase, em maio de 2024, foram aplicados filtros e selecionados dados que respondessem à pergunta: "O uso de probióticos ou similares está associado a uma redução do risco de infecções de vias aéreas em crianças?". Houve 1.157 artigos, reduzidos até 33 artigos incluídos no estudo. Foram excluídos ensaios com ênfase em tratamento, redução de sintomas e/ou outros efeitos contrários ao foco. **Resultados:** Nos 33 artigos revisados, avaliou-se a ocorrência de diminuição dos episódios de infecções respiratórias. Os resultados obtidos foram variáveis, dependendo do tipo de probiótico usado, de microrganismo, dose, via de administração e tempo de uso. Alguns estudos demonstraram sucesso na prevenção, enquanto outros, não. **Conclusão:** Considerando inúmeros fatores de influência (faixa etária, variáveis de atopia e infecções de repetição), foram observados resultados divergentes na literatura. O uso de probióticos na prevenção de infecções respiratórias permanece controverso, necessitando de estudos com rigor metodológico.

Palavras-Chave: Probiótico; Prebiótico; Simbiótico; Infecção do trato respiratório; Crianças; Prevenção.

RESUMEN

Introducción: Las infecciones respiratorias agudas son enfermedades que afectan cualquier segmento del tracto respiratorio en un período de hasta 7 días. En la infancia, su relevancia se debe a su alta frecuencia y, en ocasiones, a sus consecuencias desfavorables, como la hospitalización y la muerte. Recientemente, estudios han evaluado el uso de probióticos en la prevención de estas infecciones, verificando los beneficios de la inmunomodulación de estos microorganismos vivos en el huésped. **Objetivo**: Evaluar la eficacia de los probióticos en la prevención de infecciones respiratorias en niños. **Métodos**: Se realizó una revisión sistemática que recopiló ensayos clínicos aleatorizados. Utilizando plataformas como Scopus, PubMed, Scielo, Clinical Trials y Embase, en mayo de 2024, se aplicaron filtros y se seleccionaron los datos que respondían a la pregunta: "¿El uso de probióticos o productos similares se asocia con una reducción del riesgo de infecciones de las vías respiratorias en niños?". Se incluyeron 1157 artículos, que se redujeron a 33 en el estudio. Se excluyeron los ensayos que enfatizaban el tratamiento, la reducción de síntomas u otros efectos contrarios al enfoque. **Resultados**: En los 33 artículos revisados, se evaluó la disminución de los episodios de infecciones respiratorias. Los resultados obtenidos variaron según el tipo de probiótico utilizado, el microorganismo, la dosis, la vía de administración y la duración del uso. Algunos estudios demostraron éxito en la prevención, mientras que otros no. **Conclusión**: Considerando numerosos factores influyentes (rango de edad, variables de atopia e infecciones recurrentes), se observaron resultados divergentes en la literatura. El uso de probióticos en la prevención de infecciones respiratorias sigue siendo controvertido, por lo que se requieren estudios con rigor metodológico.

Palabras Clave: Probiótico; Prebiótico; Simbiótico; Infección del tracto respiratorio; Niños; Prevención

INTRODUCTION

Acute respiratory infections (ARIs) are diseases that affect any segment of the respiratory tract and last up to seven days.[1] They can be classified according to their anatomical location as: upper respiratory tract infections (URTIs) and lower respiratory tract infections (LRTIs).[2] Their relevance can be highlighted due to the significant morbidity and mortality, and the fact that they are very frequent, with most children experiencing 4 to 6 episodes per year.[1]

ARIs are generally viral and self-limiting diseases, although those affecting the lower airways are important causes of morbidity and mortality. In 2015, lower respiratory tract infections were responsible for almost 800,000 deaths among children and adolescents ≤ 19 years.[3] Thus, early diagnosis, appropriate treatment, vaccination, and hygiene measures are fundamental elements in the better prognosis of acute respiratory infections.[4]

Another measure that has recently emerged is the use of probiotics in the prevention of ARIs in childhood. Probiotics are defined as live microorganisms that, when ingested in adequate amounts, can exert benefits to hosts, since a healthy gut microbiota can have a modulating effect on immune and anti-inflammatory activity. On the other hand, prebiotics, which are non-digestible carbohydrates, stimulate the growth and/or activity of beneficial bacteria in the colon. The combination of probiotic and prebiotic use is called a synbiotic.[5,6]

The antiviral effect of probiotics may be caused by their ability to produce antimicrobial peptides, dehydrogenases, and nitric oxide. Probiotics can modulate the functions of epithelial and dendritic cells, CD4+ and CD8+ T lymphocytes, and Natural Killer (NK) cells. Furthermore, they activate B lymphocytes, leading to the production of immunoglobulins, which contribute to neutralizing the virus.[7]

Thus, this study aims to analyze the effectiveness of the prophylactic use of probiotics in the prevention of respiratory infections in childhood.

METODOLOGY

This is a systematic review study, considered secondary in scope, since the results for discussion are derived from the available literature – in this case, on the use of probiotics as prophylaxis for respiratory tract infections.

The systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[8] The structured question was: Is the use of probiotics or similar products associated with a reduced risk of respiratory tract infections in children?

P: Children and pre-teens (0-12 years)

I: probiotics

C: placebo

O: number of episodes of respiratory tract infections

The data were collected from randomized clinical trials, without restriction as to language or year of publication, including some observational studies. Articles emphasizing treatment, symptom reduction, and/or any other effects contrary to the focus were excluded. Furthermore, field research articles that did not report a control group were also excluded.

The search was conducted on the Medline (via PubMed), Scielo, Scopus, ClinicalTrials, and Embase platforms in May 2024.

The search strategy was:

1. PubMed: Respiratory Tract Infections [MeSH] AND probiotic [MeSH] AND children [MeSH];
2. Scielo: (probiotic) AND (Infection);
3. Clinical Trials: (Probiotics) AND (Respiratory Tract Infections);
4. Embase: 'respiratory tract infection' AND 'probiotic agent' AND child;
5. Scopus: respiratory tract infection AND probiotic AND child.

We identified 1,157 articles. After applying the inclusion and exclusion criteria, 33 articles were included (Figure 1). The risk of bias was assessed using the Cochrane risk-of-bias tool randomized trials (Rob2),[9] as shown in Table 1.

In all stages, there was independent evaluation by double reviewers.

Figure 1 – Flowchart of the selection of articles

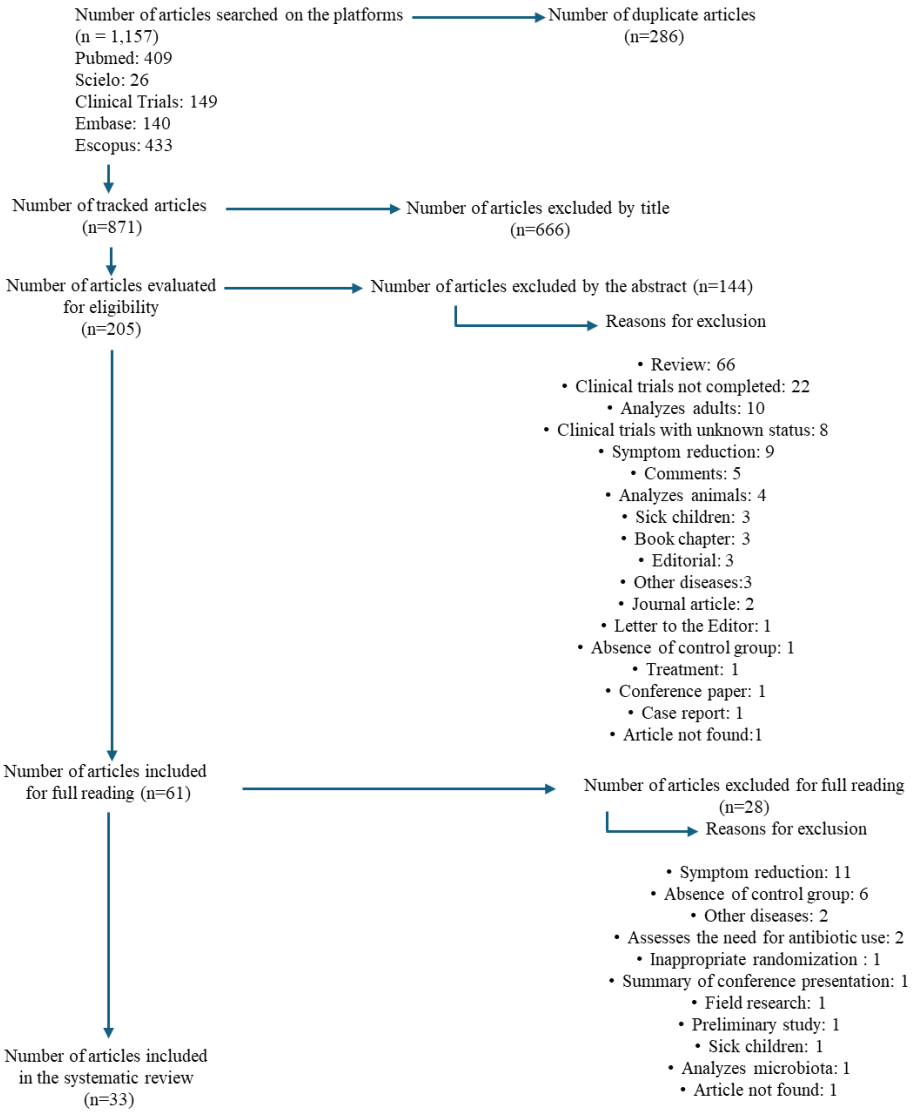

Table 1 – Risk of bias

Author, country, year	1	2	3	4	5	Global judgement
Bruzzese (2009)						
Andaloro (2019)						
Taipale (2015)						
Taipale (2010)						
Hojsak, (2015)						
Lau (2018)						
Puccio (2007)						
Dekker (2022)						
Nocerino (2015)						
Lin, (2009)						
Sertac (2008)						
Sertac (2008)						
Weizman (2002)						
Di Pierro (2016)						
Sanz (2006)						
Hatakka (2001)						
Cáceres, (2010)						
Cazzola (2010)						
Mai (2020)						
Prodeus (2016)						
Maldonado (2012)						
Picaud (2010)						
Damholt (2021)						
Hojsak (2010)						
Guo (2021)						
Sazawal (2010)						
Corsello (2014)						
Agustina (2012)						
Gerasimov (2015)						
Rautava (2008)						
Shahramia (2018)						
Di Pierro (2020)						
Conrad (2023)						

Caption: green - low risk of bias, yellow - medium risk of bias (some concerns), red - high risk of bias.

Domain 1: risk of bias in the randomization process, Domain 2: risk of bias due to deviations in the intended intervention, Domain 3: risk of bias due to missing outcome data, Domain 4: risk of bias in outcome measurement, Domain 5: risk of bias in outcome assessment.[7]

RESULTS

Based on the reading of the 33 selected articles,[8-40] the data related to the main characteristics of the sample and probiotics used were summarized in Chart 1. The effects of probiotics on the occurrence of respiratory tract infections, upper respiratory tract infections (URTIs), and lower respiratory tract infections (LRTIs) are found in Table 2.

Chart 1. Description of the studies selected for review

Author, country, year	**Age**	**Previously healthy children**	**Probiotics** **Dose** **Administrative route**	**Sample (probiotics x placebo)**	**Intervention and study time**
E. Bruzzese, Italy (2009)	15-120 days	Y	Galacto/Fructo- oligosaccharides 0.4g/100ml Oral route (formula)	342 (169 x 173)	12 months
C. Andaloro, Italy (2019)	6-11 years	N (recurrent infections)	*Streptococcus salivarius* 24SMB + *Streptococcus oralis* 89a 125 x 10^9 UFC/ml Oral Route (spray)	84 (42 x 42)	I: 3 months E: 6 months
T. J. Taipale, Finland (2015)	1 month	NA	*Bifidobacterium animalis subsp. lactis BB-12* 1 x 10^10 UFC/day Oral route (tablet)	109 (55 x 54)	2 years
T. J. Taipale, Finland (2010)	1 month	NA	*Bifidobacterium animalis subsp. lactis BB-12* 1 x 10^10 UFC/day Oral Route (tablet)	109 (55 x 54)	8 months
I. Hojsak, Croatia (2015)	1-7 years	Y	*Bifidobacterium animalis subsp. lact*is BB-12 1 x 10^9 UFC/g Oral route (sachet)	210 (104 x 106)	3 months
A S-Y Lau, Malasia (2018)	2-6 years	Y	*Bifidobacterium longum* BB536 5 x 10^9 UFC/g Oral route (sachet)	520 (259 x 261)	10 months
G. Puccio, Italy (2007)	< 14 days	Y	*Bifidobacterium longum* BL999 + prebiotics mixture (90% GOS + 10% FOS) 2 x 10^7 UFC + 4g of prebiotics/ L Oral route (formula)	138 (69 x 69)	112 days
J. Dekker, China (2022)	6-12 months	Y	*Bifidobacterium animalis subsp. lactis* HN019 (G1) **OR** *Lacticaseibacillus rhamnosus HN001* (G2) 1x10^6 UFC/g Oral route (formula)	192 (64 B. animalis x 64 L. rhamnosus x 64 controle)	12 weeks
R. Nocerino, Italy	1-2 years	S	*Lactobacillus paracasei* CBA L74	432	3 months

(2015)			5,9 x 10^9 UFC/g Oral route (cow's milk or fermented rice)	(144 fermented cow milk x 144 fermented rice x 144 control)	
J.Maldonado, Spain (2012)	6-12 months	Y	*Lactobacillus fermentum* CECT5716 2 x 10^8 UFC/day Oral route (formula)	215 (117 x 98)	6 months
J. C. Picaud, France (2010)	4-6 months	Y	Fructooligosaccharides + *Bifidobacterium longum* + *Streptococcus thermophilus* 28mg/g + 10^7 UFC/g + 10^6 UFC/g Oral route (formula)	771 (422 x 349)	3 months
A Damholt, Scotland (2021)	2-6 months	Y	*Lacticaseibacilluss rhamnosus* GG DSM 33156 1x10^9 UFC/ day Oral route	619 (309 X 310)	16 weeks
I. Hojsak, Croatia (2010)	1-6 months	Y	*Lactobacillus rhamnosus strain* GG 1 x 10^9 UFC/ dose Oral route (fermented milk)	281 (139 x 142)	3 months
J. S. Lin, Taiwan (2009)	< 5 years	NA	*L. casei rhamnosus* (G1 – sachets 1 x 10^8 CFU) OR *L. rhamnosus* T cell-1 (G2 - capsules - 1 x 10^10 CFU) OR Multiple probiotics (G3 - capsules - 12 types of bacteria) Oral route	1062 (303 L. casei x 239 L. rhamnosus x 315 multiple probiotics x 205 control)	I: 3 months (short) 7 months (long) E: 3 years and 5 months
H. Guo, China (2021)	3-10 years	N (recurrent infections)	Bactoblis (*Streptococcus salivarius* ENT-K12) 2 x 10^9 UFC Oral route (tablets)	100 (50 x 50)	60 days
S. Sazawal, India (2010)	1-3 years	NA	*Bifidobacterium lactis* HN019 + Prebiotic oligosaccharides 1.9 X 10^7 UFC + 2.4g / day Oral route (fermented milk)	624 (312 x 312)	1 year
G. Corsello, Italy (2014)	1-2 years	Y	*Lactobacillus paracasei* CBA L74 5.9 x 10^11 UFC/g Oral route (fermented milk)	146 (73 X 73)	3 months
S. Arslanoglu, Italy (2008)	0-2 years	Y	Prebiotics scGOS/lcFOS 8 g/L Oral route (formula)	134 (68 x 66)	2 years
S. Arslanoglu, Italy (2008)	0-6 months	Y	Prebiotics scGOS/lcFOS 8 g/L Oral route (formula)	206 (104 x 102)	6 months
Z. Weizman, Israel (2002)	4-10 months	Y	*Bifidobacterium lactis* BB12 (G1) OU *Lactobacillus reuteri* (G2)	201	12 weeks

			1 x 10^7 UFC/g Via oral (fórmula)	(73 B. lactis x 68 L. reuteri x 60 control)	
F. Di Pierro, Italy (2016)	33-45 months	Y	*Streptococcus salivarius* K12 (BLIS K12) 1 x 10^9 UFC Oral route (tablets)	222 (111 x 111)	I: 6 months E: 9 months
J. M. C. Sanz, Spain (2006)	3-12 years	Y	*Lactobacillus casei* (DN-114001) 2 units of Actimel Oral route (fermented milk)	251 (142 x 109)	20 weeks
K. Hatakka, Finland (2001)	1-6 years	Y	*Lactobacillus* GG (LGG) (ATCC 53103) 5 - 10 x 10^5 UFC/mL, Oral route (fermented milk)	571 (282 x 289)	7 months
P. Cáceres, Chile (2010)	1-5 years	Y	*Lactobacillus rhamnosus* HN001 1 x 10^10 UFC/mL Oral route	398 (195 x 203)	3 months
M. Cazzola, Italy (2010)	3-7 years	Y	*Lactobacillus helveticus* R0052 + *Bifidobacterium longum subsp* infant R0033 + *Bifidobacterium bifidum* R0071 5 x 10^9 UFC/1.5g Oral route (sachet)	135 (73 x 62)	3 months
T. T. Mai, Vietnan (2020)	3-5 years	Y	*Lactobacillus casei Shirota* (LcS) 1x10^8 ufc/mL Oral route (fermented milk)	1003 (510 x 493)	12 weeks
A. Prodeus, Russia (2016)	3-6 years	Y	*Lactobacillus casei* + *Streptococcus thermophilus* e *delbrueckii subsp. Bulgaricus*, 10x^10 UFC + 10x10^9 each 100g Oral route (dairy beverage)	599 (300 x 299)	I: 3 months E: 4 months
R. Agustina, Indonesia (2012)	1-6 years	Y	*Lactobacillus casei* CRL431 - G1 (5x10^8 U/day) OR *Lactobacillus reuteri* DSM17938 – G2 (5x10^8 U/day) Oral route (dairy beverage)	497 (122 L. casei x 124 L. reuteri x 126 control)	6 months
S. V. Gerasimov, Ukraine (2015)	3-12 years	Y	*L. acidophilus* DDS-1 + B. lactis UABLA-12 5x10^9 UFC Oral route (powder)	225 (113 x 112)	2 weeks
S. Rautava, Finland (2008)	1 year	NA	*L. rhamnosus* GG + B. *lactis* BB-12 1x10^10 UFC + 1x10^10 UFC Oral route (capsule)	72 (32 x 40)	20 months
I. Shahramia, Iran (2018)	< 12 months	Y	Prebiotics scGOS/lcFOS (9:1) Oral route (formula)	120 (60 x 60)	12 months
F. Di Pierro, Italy (2020)	6-36 months	Y	*Bifidobacterium animalis subsp. lactis* BB-12 + E. faecium L3	203 (94 X 109)	4 months

			2 x 10^9 UFC + 2 x 10^9 UFC) Oral route (sachet)		
L. A. Conrad, USA (2023)	6, 12, 18 and 24 months	Y	*Lactobacillus rhamnosus* GG (LGG) 10x10^9 UFC Oral route (formula)	183 (91 x 92)	6 months

Caption: Y - yes; N - no; NA - not addressed.

Table 2. Effects of probiotics on the occurrence of RTIs, URTIs, and LRTIs

Author, country, year	**I / C**	**Respiratory tract infections**		**Upper respiratory tract infections**		**Lower respiratory tract infections**	
		M ± SD or % or n	p-Value	M ± SD or % or n	p-Value	M ± SD / % / n	p-Value
E. Bruzzesse, Italy (2009)	I			> 3 episodes: 28.33% 1 episódio: 63.83%	> 3 episodes: 0.06		
	C			> 3 episodes: 44.61% 1 episode: 59.63%	1 episode: 0.4		
T. J. Taipale. Finland (2015)	I	87%	0.033				
	C	100%					
T. J. Taipale. Finland (2010)	I	65%	0.014				
	C	94%					
I. Hojsak, Croatia (2015)	I	56.70%	0.905				
	C	57.50					
A S-Y Lau, Malasia (2018)	I	2.2	0.121				
	C	2.75					
G. Puccio, Italy (2007)	I	28%	0.140				
	C	42%					
J. Dekker, China (2022)	I			G1: 0% G2: 3.1%	P G1 and C =0.278 P G2 and C =0.029		
	C			9.40%			
R. Nocerino, Italy (2015)	I			Risk reduction comparing groups A and C: 22% Risk reduction comparing groups B and C: 12%	p A and C <0.001 p B and C =0.052 p A and B =0.021		
	C						

J. Maldonado, Spain (2012)	I	1.093 ± 1.00		0.969 ± 0.96		0.124 ± 0.33	
	C	1.470 ± 1.31	0.022	1.330 ± 1.23	0.021	0.143 ± 0.35	0.719
J. C. Picaud, France (2010)	I			22 %	> 0.05	5.2%	> 0.05
	C			26 %		4.3%	
A. Damholt, Scotland (2021)	I			1.4 ± 0.1			
	C			1.6 ± 0.1	0.164		
I. Hojsak, Croatia (2010)	I	43.2%		41.7%		2.9%	
	C	67.6%	< 0.001	66.9%	< 0.001	3.5%	0.759
J. S. Lin, Taiwan (2009)	I	Risk reduction comparing G1 and C: -0.352 (short term) -0.309 (long term)	P G1 and C: < 0.05				
	C	Other comparisons did not have significant reduction	Other P > 0.05				
H. Guo, China (2021)	I	30 days of intervention (i) : 14.89% 30 days in cold season (EF): 0%	30 days of (i) = 0.045				
	C	30 days of intervention (i):34% 30 days in cold season (EF): 12%	30 days (EF) = 0.025				
S. Sazawal, India (2010)	I					Risk reduction: 35%	0.05
	C						
S. Arslanoglu, Itay (2008)	I			2.1 ± 1.8	< 0.01	0.9 ± 1.1	< 0.05
	C			3.2 ± 2.2		1.3 ± 0.8	
S. Arslanoglu, Italy (2008)	I			14	0.07		
	C			30			
Z. Weizman, Israel (2002)	I	G1: 0.25 (0.15-0.35) G2: 0.17 (0.08-0.26)	0.457				
	C	0.24 (0.13-0.35)					
J. M. C. Sanz,	I					31.7%	

Spain (2006)	C					48.6%	< 0.05
K. Hatakka, Finland (2001)	I	39%	0.05				
	C	47%					
P. Cáceres, Chile (2010)	I	1.01 ± 1.07	0.89	0.45 ± 0.64	0.66	0.55 ± 0.76	0.97
	C	1.01 ± 1.11		0.44 ± 0.70		0.57 ± 0.80	
M. Cazzola. Italy (2010)	I	51.6%	0.045				
	C	68.5%					
T. T. Mai, Vietnan (2020)	I	15.9%	0.001				
	C	24.5%					
A. Prodeus, Russia (2016)	I			79%	>0.05		
	C			85%			
R. Agustina, Indonesia (2012)	I	G1: 2.36 ± 1.62 G2: 2.48 ± 1.56	>0.05				
	C	2.43 ± 1.61					
S. V. Gerasimov, Ukraine (2015)	I	57%	0.261				
	C	65%					
I. Shahramia, Iran (2018)	I	1.06 ± 0.58	0.01				
	C	1.63 ± 0.88					
Francesco Di Pierro, Italy (2020)	I			0.21	<0.01		
	C			1.28			
L. A. Conrad, USA (2023)	I			6m: 7.72 12m: 8.18 18m: 7.77 24m: 7.88	6m: 0.44 12m: 0.19 18m: 0.37 24m: 0.41		
	C			6m: 8.62 12m: 6.96 18m: 8.34 24m: 8.42			

Caption: I – intervention group; C – control group.

Several articles have evaluated the effect of probiotics in reducing the occurrence of certain types of ARI. Regarding otitis, 11 articles[10,11,16-18,24-26,28,30,37] analyzed the effects of probiotics in relation to this disease. The first study,[10] by Taipale, evaluated children aged 1 and 2 months until they reached 8 months. When using the probiotic in the intervention group, an incidence of otitis of 26% was observed, and in the control group the incidence was 17%, with *p = 0.455*. The same author conducted another study,[11] in 2015, in which he analyzed children aged 1 month until they reached 2 years. The intervention group presented an incidence of otitis of 61%, and the control group of 64%, with *p = 0.846*.

The article by Nocerino[16] studied children aged 1 to 2 years, using two forms of probiotic presentation: fermented cow's milk (A) and fermented rice (B). Group A presented an incidence of otitis of 2.2%, group B of 4.2%, and the control group of 14.85%. Thus, the p-value when comparing group A with the control was *p < 0.01*; when comparing group B with the control, *p = 0.006*. In the study by Maldonado,[17] children aged 6 to 12 months were analyzed. With the use of the probiotic, the intervention group presented a mean and standard deviation of 0.072 ± 0.26 for otitis, and the control group presented 0.132 ± 0.34, with *p = 0.177*. Picaud conducted a clinical trial[18] with children aged 4 to 6 months. The intervention group presented an incidence of otitis of 5.2%, and the control group, 8.3%, with a *p > 0.05*. Corsello's study[24] analyzed children aged 1 to 2 years. The incidence of otitis in the intervention group was 12.1%, while in the control group it was 21.7%, resulting in a *p = 0.151*.

Another author, Arslanoglu, conducted two studies.[25,26] In the first,[25] newborn children were analyzed over a period of 2 years. The intervention group presented a mean and standard deviation of 0.5 ± 1.0, and the control group of 0.7 ± 1.2, with *p < 0.05*. In the second,[26] newborns up to 6 months of age were analyzed; the intervention group using the probiotic had 4 cases of otitis, while the placebo group had 6 cases, with *p = 0.60*. Di Pierro's article[28] selected 3-year-old children, but the author analyzed the intervention group with 6 months of probiotic use, followed by another 3 months of follow-up. In the first 6 months, both the intervention and control groups had 111 participants. The incidence of otitis in the intervention group was 44.1%, and in the control group, 80.2%, with *p < 0.01*. Only 29 participants from each group were followed for another 3 months after probiotic use, and the incidence of otitis in the intervention group was 13.8%, and in the control group 41.3%, with *p > 0.05* in this additional period. Hatakka's clinical trial[30] recruited children aged 1 to 6 years. In the intervention group, the incidence of otitis was 31%, and in the control group it was 39%, with *p = 0.08*. The last article on otitis,[37] by Rautava, analyzed 1-year-old children over a period of 20 months. When using probiotics to prevent infections, the intervention group had a 22% incidence of otitis, and the control group had 50%, resulting in *p = 0.04*.

For pharyngitis, only four articles[9,16,24,28] addressed the disease. The first refers to the clinical trial by author Andaloro[9] in which the disease analyzed was streptococcal pharyngitis in children aged 6 to 11 years. The intervention group presented a mean and standard deviation of 1 ± 0.92, while the control group presented 2.39 ± 1.05, with *p < 0.01*. Nocerino's clinical trial,[16] in addition to addressing cases of otitis, analyzed episodes of pharyngitis in children aged 1 to 2 years. Group A presented an incidence of pharyngitis of 15.3%, group B of 34.7%, and the control group had an incidence of 43.4%. The *p-value* when comparing group A with the control was *p < 0.01*; when comparing group B with the control, *p = 0.168*. Corsello's study[24] recruited children aged 1 to 2 years. The incidence of pharyngitis in the intervention group was 19.7%, while in the control group it was 41.7%, with *p = 0.007*. Finally, Di Pierro's article (2016),[28] in addition to analyzing otitis, also evaluated episodes of pharyngitis. The intervention group, in the first 6 months, presented an incidence of pharyngitis of 16.2%, and the control group an incidence of 48.6%, with *p < 0.01*. In the following 3 months, the incidence of pharyngitis in the intervention group was 17.2%, and in the control group 27.6%, presenting *p > 0.05*.

Addressing other diseases, such as laryngitis, tracheitis, and rhinitis, two articles were analyzed.[16,24] The study by Nocerino,[16] already mentioned, addressed these diseases in children aged 1 to 2 years. Group A presented an incidence of laryngitis of 6.6%, tracheitis of 26.3%, and rhinitis of 13.9%. Group B presented an incidence of laryngitis of 9.3%, tracheitis of 27.1%, and rhinitis of 26.3%. The control group presented an incidence of laryngitis of 18%, tracheitis of 4.2%, and rhinitis of 28.7%. The *p-values* when comparing group A with the control were: laryngitis, *p = 0.005*; tracheitis, *p = 0.018*; rhinitis, *p = 0.003*. When comparing group B with the control group, the values were: laryngitis, *p = 0.05*; tracheitis, *p = 0.033*; rhinitis, *p = 0.675*. Corsello's article[24] also addressed these three diseases in children aged 1 to 2 years. The incidence

in the intervention group was laryngitis, 9.1%; tracheitis, 16.7%; rhinitis, 33.3%. In the control group, the incidences were: laryngitis, 23.3%; tracheitis, 31.7%; rhinitis, 40%. The *p-values* were laryngitis, *p = 0.029*; tracheitis, *p = 0.048*; rhinitis, *p = 0.438*.

Considering other conditions addressed, Hatakka[30] brought results on the use of probiotics in the prevention of sinusitis, bronchitis, and pneumonia. In this clinical trial, children aged 1 to 6 years were analyzed over a 7-month intervention period. For sinusitis, the incidence in the intervention group was 3%, and in the control group, 4%, with p = 0.69. For bronchitis, the incidence was 6% in the intervention group and 7% in the control group, with p = 0.43. When analyzing pneumonia, the incidence in the intervention group was 1%, and in the control group, 2%, with *p = 1*. Another study, by Sazawal,[23] analyzed children aged 1 to 3 years and addressed only pneumonia. The intervention group presented 90 cases of the disease, while the control group had 115 cases, resulting in *p = 0.05*.

The prevention of the common cold was addressed in only one article,[34] which analyzed children aged 3 to 6 years. The average number of cases in the intervention group was 0.217, while in the control group it was 0.266, resulting in *p = 0.017*.

DISCUSSION

Based on the reading of the 33 reviewed articles,[8-40] different types of probiotics were addressed, mostly administered orally, in various presentations. The comparison was carried out in children and pre-adolescents, addressing a variety of respiratory diseases, which were separated into upper respiratory tract infections (URTIs) and lower respiratory tract infections (LRTIs).

In the clinical trials evaluated, some investigated previously healthy children, while others included those with a history of recurrent infections or variable atopy. This heterogeneity in the samples made it difficult to analyze the data to conclude the effectiveness of the use of probiotics in the prevention of infectious diseases of the respiratory tract in the pediatric population.

Regarding respiratory tract infections in general, 17 articles were analyzed.[10-14,17,20-22,27,30-33,35,36,38] Of these, eight studies[10,11,17,20,22,32,33,38] presented analysis with statistical significance. A specific trial[21] proposed the use of 3 different types of probiotics. However, only the group that received *L. casei rhamnosus* showed a significant reduction in infections, compared to the control group, while the other strains tested did not show relevant effects. This suggests that the use of probiotics, in this context, does not favor the prevention of respiratory tract infections in children, or that there is a difference in efficacy between the different probiotics.

Regarding URTIs, 13 articles were obtained,[8,15-20,25,26,31,34,39,40] of which seven [8,18,19,26,31,34,40] did not show statistical significance. We can highlight one study[15] with discrepant results when using different probiotics, in which the use of *Bifidobacterium animalis subsp*. *Lactis HN019* did not reduce the occurrence of URTIs *(p = 0.278)*, while the use of *Lacticaseibacillus rhamnosus HN001* had statistical significance in reducing URTI episodes *(p = 0.029)*.

In addition to the issue of the type of probiotic, another article[16] presented different results for the same bacterium (*Lactobacillus paracasei CBA L74*), but in different samples (cow's milk "A" and fermented rice "B"). In relation to the control, "A" presented *p < 0.01* and "B" *p = 0.052*.[17] Thus, it should be considered whether the form of presentation of the product may influence the result of the prevention investigated or whether it is related to chance.

Regarding URTI, we obtained seven articles[17,19,20,23,25,29,31] that express divergent results among themselves. Of these, two were favorable to the use of probiotics in prevention.[25, 29]

Analyzing the findings extracted in this review for the prevention of respiratory tract infections, we can see a greater number of articles that demonstrate insignificant results for the use of probiotics in the prevention of these diseases in children, considering the most diverse forms of presentation and bacteria analyzed. Furthermore, we have one article16 that expresses both results (*p > 0.05* and *p < 0.05*) in different phases of the study, as explained.

Regarding otitis and pharyngitis, 12 articles[9-11,16-18,24-26,28,30,37] analyzed the effects of probiotics in relation to these diseases. Regarding otitis, seven articles[10,11,17,18,25,26,30] did not present statistically significant values, indicating that the probiotics used in such studies do not effectively prevent otitis. Four articles[16,25,29,37] indicated efficacy in preventing otitis, with *p-values < 0.05*. For pharyngitis, only four articles[9,16,24,28] addressed the disease, however, 2 articles[9,24] showed statistical significance. However, there was one study[16] in which the values diverged in relation to the same probiotic, changing only the form of presentation with *p < 0.01* through one presentation and *p = 0.168* through another.

Another article[28] presented a long-term intervention, in which the control group with intervention for 6 months showed better results in the prevention of otitis and pharyngitis ($p < 0.01$), but at the 3-month follow-up time, showed efficient results only for pharyngitis ($p < 0.051$), while not for otitis ($p > 0.05$).

Addressing other diseases, such as laryngitis, tracheitis, and rhinitis, two articles were analyzed.[16,24] For laryngitis, one of the studies[24] showed a positive response, while another[16] was relevant when comparing only fermented cow's milk with the control group ($p=0.005$). However, when compared to fermented rice, it did not obtain statistical relevance, questioning the influence of the form of presentation of the probiotic. The results, in both articles, were positive for the prevention of tracheitis. Addressing rhinitis, one study[16] had a positive result, with $p=0.003$, when using fermented cow's milk; however, when using the other form of presentation, it had $p=0.675$. The other study[24] did not show statistical relevance for the disease.

Considering the conditions that were not widely addressed in the articles, only one study[30] presented results on the consumption of fermented milk *with Lactobacillus GG* in the prevention of sinusitis, bronchitis, and pneumonia; however, all diseases had an unfavorable outcome to the use of probiotics. Another study[22] addressed only pneumonia and showed negative results in the prevention of the disease. In contrast, the prevention of the common cold was addressed in only one article,[34] which presented a favorable outcome, with $p < 0.05$.

In the studies in question, limitations are noted, one of which is the use of different types of prebiotics, probiotics, and synbiotics, in their various forms of presentation, dose, and duration of use. In addition, being a multicenter review, each study expressed the results in its own way, addressing everything from respiratory tract infections in general to more specific forms, highlighting each disease, such as otitis, rhinitis, and sinusitis. Furthermore, parents with a history of atopy and recurrent infections were relevant in the analysis of the risk of bias, as these factors could hinder the interpretation of the results. The wide age range covered in certain articles, including children and pre-adolescents, may also influence the results, considering the maturation of the immune system throughout childhood, along with the response to infections. The articles presented different ways of expressing the results, from percentage, mean with standard deviation, or risk reduction, so it was not possible to find a pattern in the analysis of the results to try to homogenize the findings.

Considering what has been presented in this review, we suggest that future studies on the subject should be randomized clinical trials, controlling for the variables of atopy and recurrent infections in the studied population. The results should be expressed as
mean and standard deviation, and analyzed exclusively during the intervention period with probiotics. In addition, it is necessary to control the age range of the participants, establishing the ideal minimum age for conducting the study and considering whether the child attends daycare or not, which may increase exposure to the diseases analyzed.

CONCLUSION

The use of probiotics as a tool for preventing respiratory infections in children is still a controversial practice, with most of the evidence in the literature not supporting its use. However, further studies with satisfactory methodological rigor are still needed to control for confounding variables, in order to provide a more robust analysis.

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