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SYSTEMATIC REVIEW

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Oral cavity niche-derived probiotics and dental caries in children and adolescents: a randomized clinical trial-based systematic review

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Abstract

Background: Bacteriotherapy using oral cavity-derived probiotics has emerged as a promising adjunctive strategy for caries prevention. This systematic review aimed to assess the impact of oral cavity niche-derived probiotics on the colony-forming units (CFU) of aciduric bacteria and the reduction in caries incidence in children 0–18 years. **Methods**: Following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines, a search was conducted across PubMed, Virtual Library on Dental Health, Springer, Wiley, Science Direct, and SciELO databases. Only randomized controlled clinical trials published in English language during the last twenty years, involving humans aged 0–18 years without pre-established medical conditions, were included. Studies required at least 15 participants and adequate control groups. Quality assessment was performed using the Cochrane Collaboration tool, and only low-risk bias studies were included. **Results**: Twelve randomized controlled trials met the inclusion criteria after screening 1114 initial references. Eight studies demonstrated significant reductions in *Streptococcus mutans* counts and caries incidence. The probiotic strains were *Lactobacillus paracasei*, *L. reuteri*, and *Streptococcus* species. Administration intervals ranged from 15 days to 14 months (mean: 7.25 months), with follow-up periods varying from 15 days to 6 months. Powdered milk and tablets were the delivery vehicles. Significant bacterial count reductions were observed as early as 15 days, with sustained effects during follow-up periods. **Conclusions**: When administered appropriately, oral cavity-derived probiotics have demonstrated safety and efficacy in reducing cariogenic bacteria counts and caries incidence in children and adolescents. These findings support probiotics as valuable adjuncts to preventive measures in pediatric dentistry, particularly among high-risk populations. However, prolonged or repeated exposure appears necessary for optimal colonization and sustained benefits. **The PROSPERO Registration**: The present systematic review protocol was registered at the Open Science Framework (OSF) platform (registration DOI: https://doi.org/10.17605/OSF.IO/V3FB9).

Keywords

Oral probiotics; Dental caries prevention; Children

1. Introduction

Dental caries remains one of the most common chronic diseases in children worldwide, characterized by dysbiosis (a microbial imbalance favoring acid-producing bacteria that disrupts the natural oral microbiome homeostasis) and pathogenic biofilm formation. The etiology of the disease is multifactorial, including pathogenic microbiota, host and immune mechanisms, highly cariogenic diet, and deficient oral hygiene, among other factors [1–3]. The subsequent result is enamel demineralization and cavitation because of excessive acid production by cariogenic bacteria [4]. Despite diverse preventive measures and dental interventions, the own characteristics of dental caries disease often exhibit a high risk of recurrences, resulting in health and economic burdens [5].

Recent oral research studies have shown promising findings on dental caries prevention and control through a therapeutic strategy called bacteriotherapy, which employs beneficial bacteria known as probiotics [6, 7]. Probiotics are defined as live, harmless microorganisms that confer a health benefit on the host when administered in adequate amounts in foods or dietary supplements without adverse effects [3]. Traditionally, probiotics were developed to alter intestinal microflora. Implanted in the oral microflora of children, probiotics can

maintain or restore the natural local microbiome by interference and inhibition of other local microorganisms [7, 8]. Theoretically, certain harmless bacterial strains, such as species of *Lactobacillus* and *Bifidobacteria*, occupy a space in the dental biofilm that otherwise would be colonized by pathogenic microorganisms [6, 9, 10]. Thus, the oral microbiota is modulated and balanced due to a careful selection of acidogenic bacteria [11]. Therefore, oral health may be preserved for a long time, with significant reductions in dental caries incidence, particularly during the first years of life [10]. Dairy products supplemented with probiotics have been adopted as a natural means for easy oral administration in children [12, 13]. *In vitro* and clinical trials have been carried out with samples of children and adolescents of different age ranges and heterogeneity in their methodologies, so the reported outcomes are sometimes contradictory [12]. Furthermore, prior systematic reviews have primarily examined intestinal-origin probiotics and their impact on surrogate microbiological endpoints, including salivary *Streptococcus mutans* reduction and total bacterial load. These studies inadequately address the distinctive ecological adaptation, colonization capacity, and antagonistic characteristics of oral cavity-derived probiotic strains.

Some approaches suggest that the use of probiotics isolated from the dental plaque in the oral cavity, mainly *Lactobacillus* (LBC) species (*L. casei* and *L. paracasei*), some *Streptococcus* strains (*S. thermophilus* and *S. salivarius*), and *Bifidobacteria* can produce similar preventive anti-caries effects in children [1, 5, 8, 11]. The strategic implementation of biotics, including probiotics, prebiotics, synbiotics, and postbiotics, represents a promising low-cost therapeutic approach for dental caries prevention through the restoration of oral microbiome homeostasis, which may not be accomplished with traditional antimicrobial therapies alone [14]. These benefits are a result of several demonstrated bacteriotherapy properties, including safe administration, inhibition of *Streptococcus mutans* (SM) growth, less acid production from dietary sugars than other oral bacteria, synthesis of antioxidants, an increase in protective bacteria (*e.g.*, *Lactobacilli*) both in saliva and plaque, and good adherence to dental hard tissues [3].

This review tries to address the current knowledge gap by evaluating the clinical efficacy of oral cavity-derived probiotic strains on both microbiological and patient-centered clinical outcomes in children, thus offering more clinically applicable evidence for pediatric dental practice. So, the aim of the present systematic review of randomized controlled clinical trials was to assess the impact and influence of the administration of probiotics isolated from oral cavity niches on the count of colony-forming units (CFU) of acidogenic bacteria and the clinical reduction of dental caries incidence in children aged 0–17 years. The study hypothesis was: oral cavity-derived probiotic strains, when administered to pediatric populations, provide an adequate modulation of the oral microbiome and a great clinical reduction in dental caries incidence. Primary objective: to systematically evaluate the clinical efficacy of oral cavity-origin probiotics in reducing both the CFU of cariogenic bacteria and the incidence of dental caries in children and adolescents. Secondary objectives: (1) to compare the effectiveness of different oral-derived probiotic strains, delivery vehicles, and treatment durations on clinical outcomes; (2) to assess the safety profile and reported adverse events associated with oral probiotic interventions in pediatric patients; and (3) to identify methodological gaps and suggest directions for future research on biotic therapies for caries prevention in children.

2. Methods

The present systematic review of the published literature was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and checklist [15] (**Supplementary material 1**). This systematic review intended to answer the following focused Population, Intervention, Control, and Outcome (PICO) question: In pediatric patients (0–17 years old), does the administration of oral cavity-niche probiotics reduce the colonization of cariogenic bacteria and hence the incidence of carious lesions in primary and permanent teeth? According to this, a protocol including all aspects of a systematic review methodology (formulation of a research question, search strategy, selection criteria, study location and selection, data extraction, quality assessment, and result interpretation) was initially developed.

2.1 Protocol and registration

The present systematic review protocol was registered at the Open Science Framework (OSF) platform (registration DOI: https://doi.org/10.17605/OSF.IO/V3FB9).

2.2 Selection criteria

The studies included in this systematic review were original randomized controlled clinical trials evaluating (a) the role of the administration of oral probiotics (exclusively those obtained from the oral cavity niches) in decreasing the counts of CFU of aciduric bacteria and (b) the clinical reduction of caries incidence. Only those studies published in the English language during the last twenty years, performed on humans aged 0–18 years without any pre-existing medical conditions, were considered. The eligible trials had to include at least 15 participants and a placebo control group. Studies performed with patients with gingivitis, periodontal disease, and halitosis were discarded. Observational studies (cohort, case-control, cross-sectional), narrative reviews, clinical case reports, *in vitro* or animal studies, grey literature, conference/meeting proceedings, and opinions or letters to the editor were also excluded.

2.3 Database search strategy and data extraction

Potential references were screened from the following electronic databases or metasearch engines: PubMed (Medline), Virtual Library on Dental Health, Springer, Wiley, ScienceDirect, and SciELO. The first step was to describe the relationship between the main Medical Subject Headings (MeSH) terms: “Dental Caries”, “Oral Probiotics”, “Children”, and “Adolescents”. Boolean operators (AND/OR) were used for the interaction between the keywords and to determine the search conditions. The search strategy included the use of the following

entry-free terms and keywords: "caries lesions" OR "dental decay" OR "dental caries" OR "cavities"; AND "oral health"; AND "probiotics" OR "oral probiotics" OR "bacteriotherapy" OR "probiotic *lactobacilli*"; AND "children" OR "infants" OR "toddlers"; AND "adolescents" OR "teenagers". Different combinations of MeSH terms, keywords, and free text words were applied during the searching process in each electronic database to identify relevant references. The complete detailed search strategy per database can be seen in **Supplementary Table 1**.

The systematic literature search was conducted between 16 June and 18 July 2025, across all selected databases. In addition, automatic search alerts and manual updates were monitored during the subsequent months to consider any newly published or indexed relevant studies. No additional eligible trials were identified during this post-search update period.

Two authors/reviewers (JND and SAR) independently screened all potential titles and their abstracts according to the selection criteria. Most relevant studies were then obtained in full-text format. A further careful hand-searching based on the included studies' reference list was also conducted. These same reviewers performed data extraction from each article using pre-designed forms to record relevant information. The following data were collected: (a) year of the study and author, (b) number, age, and gender of participants, (c) study group characteristics, (d) interventions, and (e) clinical outcome assessment. Cohen's kappa coefficient (κ) was calculated to determine the level of inter-rater agreement. When necessary, the reviewers contacted study authors through e-mail to request missing data or unavailable relevant information on the method of randomization, blinding, and withdrawal management. Any disagreement was resolved by discussion and consultation with the other authors (AM, APG, JAGR) until a consensus was reached.

2.4 Quality assessment

Another two authors (JAGR and APG) critically and independently evaluated the level of evidence from the eligible studies for the final selection. A quality analysis of internal validity (risk of bias) of the selected studies was performed, and the sources were classified according to the problems in the investigation to determine if the obtained results produced consistent and valid results. For these purposes, the Risk of Bias 2.0 tool [16] was used with the Review Manager software, V. 5.3 (RevMan; The Cochrane Collaboration; Copenhagen, Denmark), which is considered adequate to evaluate potential biases in randomized controlled studies. This tool evaluates the risk of bias in randomized trial results with an emphasis on internal validity, assessing potential bias domains, such as selection bias (sequence generation and allocation concealment), performance bias (blinding of participants and researchers), detection bias (blinding of outcome evaluators), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other biases. All domains were judged "low risk of bias", "high risk of bias", or "unclear". Studies were rated as "high risk of bias" if one or more domains were judged "high risk". If none of the domains were of "high risk" and one or more domains were "unclear", the study was assessed as "unclear". If all domains were of "low risk", the overall judgment was "low risk". Disagreements between the authors were resolved in a consensus meeting with a third author (SAR). Only studies with a low risk of bias were finally included in the present systematic review. The whole process of study searching and eligibility is detailed in the PRISMA flow diagram (Fig. 1).

2.5 Planned meta-analysis methodology

A meta-analysis was originally planned to synthesize the extracted data when sufficient homogeneity existed among the included studies. For dichotomous outcomes, we planned to calculate Risk Ratios (RR) with 95% confidence intervals (CIs), using the Mantel-Haenszel method under a fixed-effect model, or the random-effects model if significant heterogeneity was detected. For continuous outcomes, we considered calculating Mean Differences (MD) or Standardized Mean Differences (SMD) with 95% CIs, depending on the measurement scales used across studies. Heterogeneity assessment was planned using the I^2 statistic (values of 25%, 50%, and 75% would represent low, moderate, and high heterogeneity, respectively), supplemented by the Chi-square test ($p < 0.10$ indicating significant heterogeneity), and forest plots. Publication bias assessment was planned using funnel plots and Egger's regression test. All meta-analyses were planned to be conducted using RevMan 5.4 software (The Cochrane Collaboration, Copenhagen, Denmark).

However, after thorough evaluation by two independent and pre-calibrated reviewers (SAR and AM), substantial methodological heterogeneity among the included studies (differences in study populations, probiotic strains, concentrations, administration protocols, outcome measurement methods, and follow-up periods) precluded reliable quantitative synthesis, leading to the decision to perform a descriptive qualitative analysis instead.

3. Results

After discarding duplicates, the initial electronic and hand search yielded 1114 references/abstracts in total. Then, 1022 of them were eventually excluded as duplicates (n=773) or non-relevant (n=249), leaving 92 potentially eligible studies in full text for further evaluation. Overall, twelve prospective clinical trials were included after the qualitative analysis, and their findings were reported in the present systematic review. The most common reasons for exclusion were studies performed with adult patients, observational designs, and case reports. Details of the publication screening process are shown in Fig. 1. At the first phase of selection, the inter-reviewer agreement was significant ($\kappa = 0.91$); then, a value of kappa for study selection, after the full-text assessment, was 0.864, also indicating a substantial level of agreement.

3.1 Methodological evaluation

The results of the quality assessment of the included studies are detailed in **Supplementary Table 2** (Ref. [1, 3, 5, 7, 8, 10, 11, 13, 17–20]). The total quality score among these studies, according to the used scales, ranged between 10 and 16. The

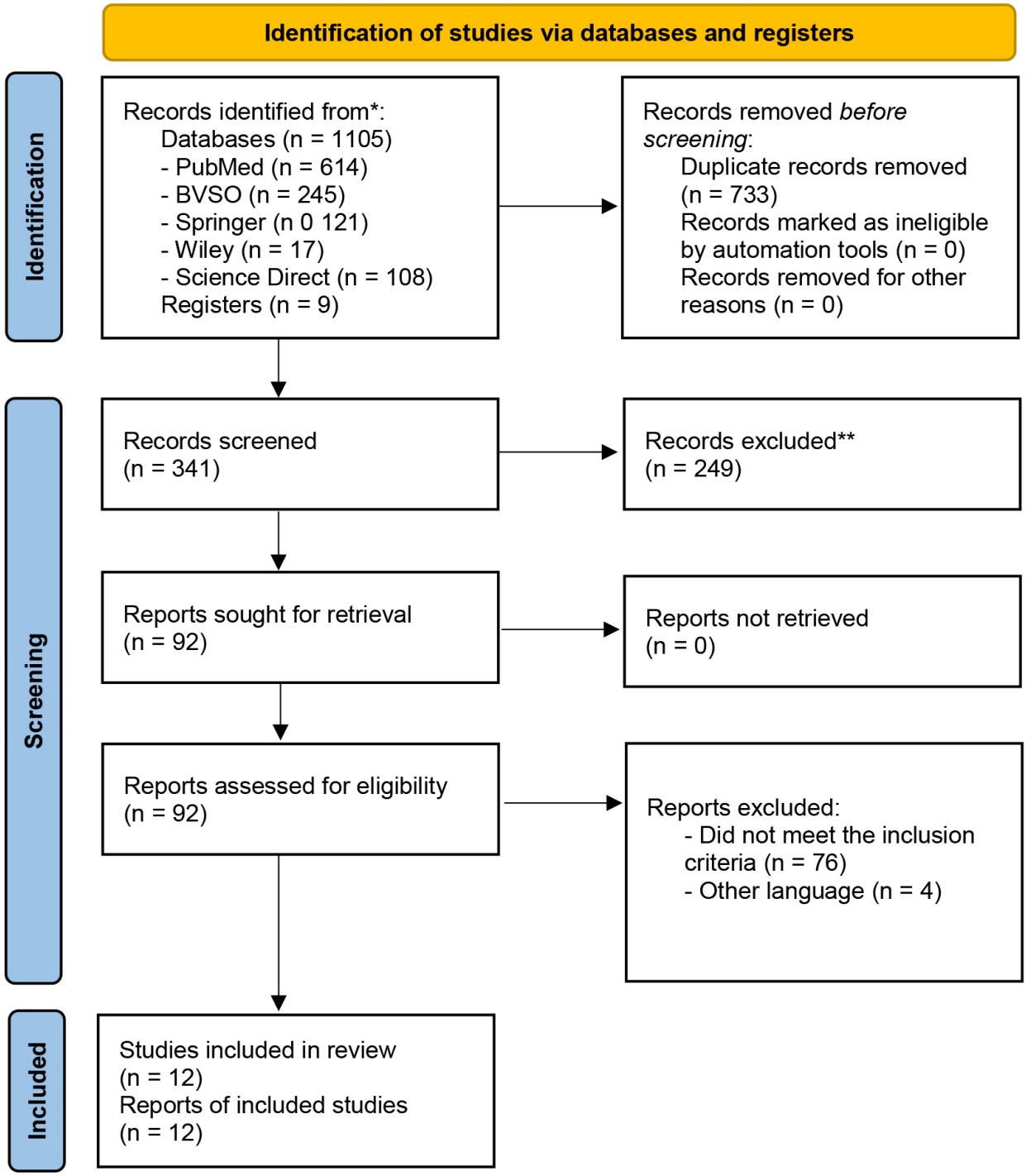

FIGURE 1. PRISMA flow diagram for obtaining the included articles. BVSO: Virtual Library on dental health.

most common drawbacks among the studies were the lack of an adequate methodology for sample size calculation and deficiencies in the description of the randomization method used for assigning the participants to the study groups.

3.2 Characteristics of included studies

At the end of the selection and evaluation process, a total of twelve studies were included. These studies were classified according to the following evaluation assessment criteria: (a) decrease in the amounts of aciduric bacteria only, (b) clinical reduction of caries incidence only, and (c) both variables. The general characteristics of these twelve included trials are shown in three independent **Supplementary Table 3a** (Ref. [3, 7, 8, 13, 19, 20]); **Supplementary Table 3b** (Ref. [10, 17]); **Supplementary Table 3c** (Ref. [1, 5, 11, 18]). Also, the studies were classified according to their corresponding endpoint (decrease of aciduric bacteria, reduction of carious lesions, or both) and quantitatively described in detail in **Supplementary Table 4** (Ref. [3, 7, 8, 13, 19, 20]); **Supplementary Table 5** (Ref. [10, 17]); and **Supplementary Table 6** (Ref. [1, 5, 11, 18]).

Of the total of the articles included here, eight studies obtained statistically significant results (within each individual study), favoring the oral cavity niche-probiotic therapy in the reduction of SM—and other cariogenic bacteria—and in the clinical decrease in dental caries incidence at the time of administration [3, 5, 8, 10, 11, 13, 17, 18]; one study did not show significant differences at that time, but they reported lower SM derived counts when the probiotic strain established itself within the child's oral microbiota [7]. Finally, only one study reported no significant long-term differences in the incidence of dental caries lesions [1]. The probiotic administration time ranged from 15 days to 14 months, with a mean of 7.25 months. The follow-up period varied from 15 days to 6 months, during which probiotic strain samples were obtained from the mouth after suspending the administration. Only one study, with a follow-up of up to 8 years, did not exhibit significant evidence of reduction of carious lesions or permanent probiotic colonization [1]. The most widely used vehicles for probiotic administration were powdered milk—in four trials [3, 5, 8, 20], and tablets—also used in four trials [7, 10, 13, 19], as well as mouthwashes [17] and cereals [1] were also employed. The probiotic strains used in the included trials were *L. paracasei*, being the most used in five studies; *L. reuteri* PTA5289, *S. uberis* KJ2™, *S. oralis* KJ3™, and *S. rattus* JH145™ were applied in two studies, and *S. salivarius* M18 in a single study.

3.3 Potential reduction of aciduric bacteria

The present review included six randomized controlled clinical trials [3, 7, 8, 13, 19, 20] involving children with an age range from 1 to 14 years. Three of these trials had two study groups (probiotics *vs.* placebo) with an established dose and time of administration; instead, Manmontri and coworkers [3] presented only one control group (placebo) and two experimental groups (probiotics): the first one with a daily probiotic administration and the second one with a probiotic administration three times a week. The probiotic strains used in these studies were *S. salivarius* [7], *L. paracasei* [3, 8], and a combination of *S. uberis*, *S. oralis*, and *S. rattus* [13]. SM samples were obtained from saliva and bacterial plaque [3]. The outcomes were measured in CFU (105 CFU/mL), except by Cortés-Dorantes and colleagues [13], who measured the luminescence scores with the CariScreen® system. The time of probiotic administration varied from 15 days to 6 months, with a mean of 95 days, as did the follow-up period. In the probiotic group, the first evidence of a significant reduction of SM could be observed at 15 days, 3 months, and 6 months. During the follow-up period, the levels of SM were maintained at low counts even after the suspension of the probiotic administration [3, 8, 13]. Similarly, Kamble *et al.* [19] compared the effectiveness in decreasing SM count among an oral probiotic (EvoraPlus/ProBiora Plus™, which comprises a blend of three *Streptococcus* species) against 0.2% chlorhexidine digluconate, Hexidine®, and Himalaya Herbals Hiora® as control groups. After 14 and 21 days, EvoraPlus probiotics showed a higher reduction of SM compared with chlorhexidine and Hiora, even though the differences were not statistically significant.

In contrast, Burton *et al.* [7] did not find any significant difference regarding the placebo group in the overall reduction rates of SM at the time of administration; however, in the group treated with *S. salivarius* M18, a subgroup of participants retained populations of this strain, showing consistent inhibition profiles over pure M18 cultures and lower SM counts regarding their respective baseline values. The characteristics of the clinical trials with significant reductions in aciduric bacteria amounts are shown in **Supplementary Table 4**.

3.4 Potential reduction of incidence/new carious lesions

Two controlled clinical trials were evaluated, which included children with an age range of 2 to 17 years. Keller and coworkers [17] administered probiotic strains of *L. reuteri* PTA5289 in tablets for 12 weeks. The assessments were made directly on the carious lesions, using light fluorescence with a QLF™ (Quantitative Light-induced Fluorescence; Inspektor Research Systems B.V.; Amsterdam, The Netherlands). This equipment consists of a special intraoral handpiece designed to detect changes in enamel fluorescence (ΔF) and measures the lesion extension with different images through the Inspektor Pro program (in mm^2). The authors concluded that there was a significant decrease ($p < 0.05$) in the time of fluorescence in the probiotic group, but there were no significant differences in the changes of the lesion extension. In contrast, Hedayati-Haijkand and colleagues [10] administered commercial ProBiora tablets containing a combination of three oral probiotic strains (*S. uberis*, *S. oralis*, and *S. rattus*) for 3 months plus another 12 months of follow-up. The dental caries incidence was determined using the Carious, Lost, and Filled Surfaces (CPO-D) index. They found significant differences in the increase in dental caries lesions at three months and one year after suspending the administration in the test group. The authors also reported a 75% prevention rate, with a more effective probiotic intervention in those children with a high risk of dental caries. The characteristics of the clinical trials assessing the reduction of the incidence of dental caries lesions are shown in **Supplementary Table 5**.

3.5 Potential decrease of aciduric bacteria and reduction of incidence/new carious lesions

Three double-blind randomized controlled clinical trials were evaluated, in which participants in an age range of 4 months to 14 years were included [1, 5, 17, 18]. All studies employed *L. paracasei* as the experimental probiotic strain. Only one study was conducted to verify the effect of the early administration of probiotics on the oral colonization of SM [1]; here, the probiotic strain was administered to 4-month-old children for 14 months, with a subsequent 8-year follow-up period. They assessed the prevalence of dental caries using the CPO-D index at 3, 6, and 9 years of age. The authors concluded that early intervention with *L. paracasei* did not affect the frequency or incidence of dental caries. Regarding the count of SM and *L. paracasei* CFU/mL, they did not find any significant differences, since the levels of colonization were similar in both groups. On the contrary, Wattanarat *et al.* [5] and Teanpaisan

et al. [11] administered probiotic strains in powdered milk for 6 months. They evaluated and recorded relevant information on the children of both groups at baseline and 3, 6, and up to 12 months. Regarding the counts of SM, they found significant reductions at 3 and 6 months; at 12 months (6 months after discontinuation of probiotics), they found no significant differences compared with the baseline levels. The *lactobacilli* count remained constant during the initial administration of the probiotic and 6 months later in both studies, indicating the ability of *L. paracasei* to be retained in the oral cavity, despite the cessation of the intervention at 6 months. To evaluate the incidence of carious lesions, Teanpaisan and coworkers used the Decayed, Missed, and Filled surfaces (DMFS) index to evaluate the prevalence of caries, finding a significant difference at 12 months, favoring probiotics [11]. Wattanarat and colleagues [5] employed the International Caries Detection and Assessment System (ICDAS) system (the detection codes for coronal caries ranged from 0 to 6 depending on the severity of the lesion) and evaluated the increase in dental caries in "all surfaces", "pits and fissures", and "smooth surfaces", as well as the appearance of new cavities in the same three areas. No significant differences were found in the smooth surfaces, but they were in the occlusal pit-and-fissure area. Finally, all studies coincided with the idea that prolonged or repeated exposure to probiotics is necessary for adequate probiotic colonization in the oral cavity. The characteristics of these clinical trials focused on the decrease in aciduric bacteria counts (CFU) and caries lesions are shown in **Supplementary Table 6**.

4. Discussion

According to the findings retrieved in the present systematic review, in general, human oral probiotic supplements, when administered appropriately, are capable of decreasing the counts (CFU) of cariogenic/aciduric bacteria, particularly SM and other *streptococci* species, or inhibiting them in saliva and dental biofilm of children aged 0–17 years, in comparison with placebo controls. In contrast, Mayta-Tovalino and coworkers [21] developed a meta-analysis with 19 clinical trials, with a follow-up up to 108 months. Probiotics did not reduce the dental caries experience (Mean Difference or MD: −0.24 carious pieces; 95% CI: −0.72 to 0.23) or *Lactobacillus* count (MD: −0.78 CFU/mL; 95% CI: −1.65 to 0.09) *vs.* control; no effect on bacterial plaque index (MD: 0.21 units; 95% CI: −0.55 to −0.96), gingival index (MD: 0.04 units; 95% CI: −0.18 to 0.27), and salivary pH (MD: −0.12 pH units; 95% CI: −0.72 to 0.48) *vs.* control. However, probiotics reduced SM count *vs.* control (MD: −0.40 CFU/mL; 95% CI: −0.57 to −0.24).

Furthermore, this type of probiotics has demonstrated a noticeable reduction in the incidence of caries lesions during childhood and young adolescence. Regarding this, important clinical and further research implications can be drawn from the present systematic review. The use of oral niche probiotics represents a safe potential addition to regular oral preventive methods in children and young adolescents. Oral probiotic ingestion constitutes a pioneering area of research in pediatric dentistry, which includes the association between nutrition and oral cavity health. The included studies in the present review can help the pediatric dentistry practitioner identify not only the best-suited oral probiotic supplement, but also the optimal vehicle for its delivery. Proper tooth hygiene, topical fluorides, and reduced sugar consumption are nowadays considered the most effective methods to prevent and control dental caries. Probiotic therapy can be a valuable adjunct to increase the effectiveness of pediatric preventive care programs designed to improve oral health, especially among vulnerable populations.

The efficacy of probiotics in children's dental caries prevention depends on their origin. Oral cavity niche-derived oral probiotics are safe and able to decrease SM counts and the incidence of new carious lesions in children [18, 22]. According to Seminario-Amez and colleagues [23], the oral cavity is considered a microbiological environment that requires homeostasis. When certain risk factors, such as acidogenic and enamel-adhesive microbiota, prolonged exposition time, poor oral hygiene, a fermentable carbohydrate-rich diet (sugared food/drinks), saliva with deficient secretion rate and buffering capacity, and some immunodeficiencies, are present in the oral cavity, local balance is altered [9]. Under these unfavorable conditions, cariogenic/aciduric microorganisms and their toxins can colonize the adhesive biofilm on the dental firm tissues; therefore, local infectious polymicrobial diseases, such as dental caries, are developed [12].

Further, bacterial profiles change with caries stages and differ between primary and permanent dentitions [24, 25]. *Streptococcus mutans* and *Streptococcus sobrinus* have been historically related to dental caries in children [20–22]. That is why most of the included studies in the present review mainly focus on the probiotic antimicrobial effects against these cariogenic pathogens. However, recent microbiome-based studies have involved a much wider variety of acidogenic microorganisms. Bacterial species, such as non-*mutans streptococci*, *Veillonella* spp., *Actinomyces* spp., *Bifidobacterium* spp., *Propionibacterium*, and *Lactobacillus fermentum*, have also been associated with caries initiation and progression [20–23].

Therefore, different preventive measures should be implemented to control the different dental caries risk factors, mainly based on dietary changes (*e.g.*, sugar intake reduction and enhancing host resistance) through diverse clinical procedures, such as topical fluoride therapies. Other interventions, including bacteriotherapy through probiotic intake, are not yet widely accepted, but emerging evidence make this therapy promising and encouraging [8, 12]. The mechanisms of probiotic action in children are not fully clear, but they depend on local events [17, 22–26]. According to published evidence, probiotic bacteria strains can act in several ways: (a) preventing cellular adhesion and invasion and co-aggregation of pathogenic bacteria by competitive inhibition and antagonization, (b) producing substances such as lactic acid, hydrogen peroxide, and bacteriocins (antimicrobial agents produced by lactic acid bacteria, whose action provides them with the probiotic effect), (c) modifying the local environment by a reduction in pH as a result of fermentation products, and (d) interacting and modulating the local and systemic inflammatory immune responses (humoral and cellular) [3, 4, 6, 9, 10, 16, 17, 20, 25, 26].

LBC species are some of the most used probiotics in children

and adolescents [1, 3–5]. There is wide evidence that LBCs are strongly influenced by sugar consumption. For instance, *L. salivarius* is considered a strong acid-producing bacterium that has been associated with high dental caries in children [3]. However, oral-derived LBC probiotics also provide beneficial preventive effects against dental caries disease, including the reduction of SM counts, dental caries risk, and initial dental caries development. The effect is particularly higher in 3- to 4-year-olds. This effect might be attributed to the "window of infectivity" in these children [4]. LBC produces low molecular weight bacteriocins, which possess an inhibitory and competitive/antagonist activity against a wide range of bacterial species, including oral SM and *S. sobrinus*, in plaque and saliva. They also synthesize different antimicrobial substances such as organic acids, hydrogen/carbon peroxide, diacetyl, and adhesion inhibitors against acidogenic bacteria. Thus, LBC probiotics can inhibit SM *in vitro* growth and control the multiplication of these regular resident acidogenic microorganisms [13, 19]. Additionally, a dairy-based vehicle for *L. paracasei* and *L. reuteri* has proven to be favorable because of its buffering effects, which may hamper intra-oral bacterial acidogenicity [2, 10, 13]. Further, *L. paracasei*, *L. rhamnosus*, and *L. reuteri* do not ferment sucrose and exhibit a significantly increased capacity to suppress the growth of SM in children without active caries [2, 10, 16, 27–29]. However, Hasslöf and colleagues [1] found no significant differences in dmfs and DMFS scores between the probiotic and placebo groups in a clinical study with 9-year-old children; SM and LBC colonization levels and frequency of carious lesions were similar in both groups.

Güngör *et al*. [30] assessed the adhesive capability of 70 lactic acid bacteria. They observed a significant diversity in the ability of these bacteria to adhere to the enamel and reported that all strains could reduce the quantity of SM on the surface of the saliva-covered tooth. Some of these findings were corroborated by Samot and coworkers [31] in their *in vitro* study; these authors concluded that saliva probiotic strains of the genus LBC exhibited potentially useful adhesive capacity, which may constrain the growth of some oral pathogenic bacteria. Thereby, probiotics possess the ability to compete with pathogenic bacteria for adhesion surfaces and nutrients, causing their displacement [20]. It has also been proven that *L. paracasei* exhibits antibacterial capabilities, inhibiting the presence of different pathogens, such as SM, *S. salivarius*, *S. sanguis*, *Staphylococcus aureus*, *Actinomyces viscosus*, and some *Candida* species [32]. Additionally, LCB probiotics stimulate the modulation of immune effects; in other words, probiotic supplementation increases the local innate host immunity through the enhanced production of salivary immunoglobulin A (IgA) [8] and HNP1–3 (human neutrophil peptide, a small cationic antimicrobial peptide present in the saliva produced by the submandibular salivary glands) [5]. Keller *et al*. [17] reported a propensity for less hard tissue demineralization on early enamel carious lesions after a 3-month protocol of daily consumption of LBC probiotic tablets. The authors theorize that probiotic supplements contribute to the control of the acid stress within the biofilm; they also state that LBC probiotics have a lower ability to co-aggregate with SM than any other bacteria.

Next to LBC, *Bifidobacteria* and *S. salivarius* are the probiotics most commonly used in pediatric bacteriotherapy [4, 6]. In the child's oral cavity, *Bifidobacteria* are highly prevalent in deep caries lesions and may play an important role in their progression [12, 20]. But, as with LBC, *Bifidobacteria* administered as a probiotic provides anti-caries effects in children. Specifically, *Bifidobacterium* DN-173 010 has demonstrated a significantly diminishing effect on salivary SM. However, only a few studies administering this probiotic have been conducted in pediatric populations, so it is not possible to draw any conclusions on its benefits [9, 20]. On the other hand, *S. salivarius* has shown, both in human and animal studies, the capability of producing bacteriocin and two exoenzymes (dextranase and urease), which potentially help limit the progression of carious lesions by the reduction of plaque accumulation and acidification [7].

Evaluation of a suitable vehicle for oral probiotic administration is essential. Most of the natural probiotics are found in dairy products—*e.g.*, milk, cheese, yogurt, and infant formulas, *etc.* [4, 12]. Milk acts as a buffer to the produced acid, and itself contains calcium, calcium lactate, and other organic and inorganic anti-cariogenic compounds. Cheese and yogurt are thought to have more local effects, as they clear more slowly than milk from the oral cavity. On the other hand, non-dairy products, such as orally administered capsules, lozenges, gums, cereals, porridges, fruit juices, and even pacifiers, have demonstrated similar effects [4, 6, 12, 20].

4.1 Short-term versus long-term effects of probiotics in caries prevention

The studies included in this systematic review demonstrate clear distinctions between the short-term and long-term effects of probiotic supplementation in preventing dental caries in pediatric populations.

4.1.1 Short-term effects (immediate to 6 months)

Short-term effects of probiotics demonstrate consistently promising results. The majority of included studies documented immediate beneficial effects manifesting within days or weeks of intervention initiation. The most significant short-term effects include a notable reduction in *Streptococcus mutans* counts in both saliva and dental plaque, with improvements observed as early as 14 days of treatment. Additionally, enhanced local immune responses were documented, particularly elevated levels of antimicrobial peptides such as HNP1–3, which reached significantly higher levels during the initial 3–6 months of intervention. Studies also reported improvements in dental remineralization markers, with detectable changes in quantitative light-induced fluorescence, indicating reduced enamel demineralization [19].

Salim *et al*. [33] evaluated the effect of the oral probiotic *Streptococcus salivarius* M18 on salivary *S. mutans* counts, pH, and buffering capacity in preprimary children aged 3–6 years. Forty healthy children in full primary dentition were randomly allocated to an experimental group receiving *S. salivarius* M18 lozenges once daily for 7 days or to a control

group receiving unsweetened placebo lozenges. The probiotic group showed a statistically significant reduction in salivary *S. mutans* counts and a significant increase in salivary buffering capacity, with no significant change in salivary pH. A strong positive linear correlation was found between caries experience (def score) and salivary *S. mutans* counts, supporting the role of *S. mutans* in early childhood caries.

4.1.2 Long-term effects (beyond the intervention period)

In contrast, long-term effects present more variable and generally fewer durable outcomes. Evidence indicates that the beneficial effects of probiotics are typically temporary and tend to diminish following treatment discontinuation. However, several studies documented some persistence of effects for periods ranging from weeks to several months after intervention cessation. For instance, Manmontri *et al*. [3] demonstrated that effects on *S. mutans* reduction persisted up to 6 months after discontinuation, while Teanpaisan *et al*. [11] detected the probiotic strain up to 4 weeks after treatment cessation [1]. Evidence for permanent changes in the oral microbiota is limited. The longest follow-up study by Hasslöf *et al*. [1], which tracked children for 9 years following early intervention (4–13 months of age), found no long-term effects on caries experience at 3, 6, or 9 years of age. This suggests that early probiotic interventions do not necessarily confer permanent protection against dental caries [1]. Results for actual long-term caries prevention are mixed. While some studies reported significant reductions in caries increment during a one-year follow-up, other longer-term follow-up studies did not confirm these sustained benefits [5, 10].

4.2 Examples of clinical scenarios about probiotic therapy in children

In order to illustrate the potential and limitations of oral probiotic interventions in pediatric dentistry, three hypothetical practical situations are provided. The following examples reflect typical conditions encountered in clinical practice and are directly based on evidence synthesized in the present review.

4.2.1 Clinical scenario 1

A 5-year-old child with a high caries risk profile (multiple incipient lesions, frequent sugar intake, and suboptimal oral hygiene) is enrolled in a dental prevention program. In addition to standard interventions (fluoride varnish and dietary counseling), the pediatric dental team recommends a daily probiotic supplement containing *S. salivarius* M18 for six months. At follow-up, the child demonstrates a reduction in salivary *Streptococcus mutans* counts and improved remineralization of non-cavitated lesions, aligning with results from randomized trials showing probiotics' adjunctive efficacy in reducing new carious lesions in high-risk pediatric populations.

4.2.2 Clinical scenario 2

A 7-year-old male patient with special healthcare needs, who has difficulty maintaining adequate oral hygiene, is prescribed a probiotic-enriched yogurt as part of a home-care personalized program. Over the span of a school year, regular consumption is associated with a clinically observed decrease in active plaque and a stabilization in caries progression, consistent with recent evidence indicating the benefit of probiotics for caries-prone children, especially when administered in long-term, age-appropriate delivery vehicles.

4.2.3 Clinical scenario 3

A preschool female child with a history of early childhood caries and restorative treatment under general anesthesia completes 12 months of probiotic drops containing *L. reuteri* PTA5289. At the end of the intervention, recurrence of moderate or extensive new caries lesions is evaluated. Although some recent publications report no significant advantage of oral probiotics over placebo, this case illustrates both the potential for and the limitations of probiotic strategies in the real-world context of high caries recurrence and biological variability.

These scenarios emphasize that while probiotic therapy can be a valuable adjunct to conventional caries preventive measures—particularly for high-risk, special needs, and young pediatric patients—it must be tailored to individual dental caries risk profiles and used in conjunction with evidence-based primary interventions, rather than as a replacement.

4.3 Strengths and contributions to the knowledge of pediatric dentistry

The present systematic review provides a rigorous synthesis of randomized clinical trial evidence regarding the use of oral cavity niche-derived probiotics in pediatric dental patients, substantially expanding current knowledge on biologically targeted caries prevention strategies. By evaluating CFU reductions of aciduric bacteria and the incidence of dental caries across a broad pediatric age spectrum, the review offers clinically relevant insights into the safety and efficacy of specific probiotic strains, administration vehicles, and protocols most beneficial for children and adolescents. These findings not only reinforce the concept of bacteriotherapy as an effective adjunct to established preventive measures, but also inform evidence-based recommendations for individualized pediatric care, particularly in high-risk populations, thereby supporting the integration of probiotic therapy into contemporary pediatric dental practice [34–37].

4.4 Limitations

The important limitations of the present systematic review were:

(1) Most eligible studies basically focused on two outcomes: CFU counts of SM and the incidence of caries disease in pediatric patients after probiotic administration. However, even though several authors reported beneficial effects while probiotics were administered, the lack of long-term follow-up periods makes it unlikely to suggest that these effects continue after stopping bacteriotherapy. Furthermore, the included studies largely focused on SM counts and caries incidence. Pediatric dental caries is a multifactorial disease involving broader microbial communities (*e.g.*, *Actinomyces*, *Veillonella*, *Bifidobacterium* spp.) and host/dietary factors. Restricting

outcomes to CFU counts and caries lesions might oversimplify probiotic effects.

(2) Only twelve randomized controlled trials were included, which might make it difficult to generalize the results of this review, given the heterogeneity of interventions and outcomes. For instance: study design, participants' characteristics, probiotic therapy, probiotic strains and concentrations, administration vehicles, as well as the timing of outcome measurements/evaluations (most studies had short follow-up periods ($\leq$6 months), with only one extending to 8 years), and outcome reporting, among others. In this regard, the lack of consistent long-term follow-up, as mentioned above, prevents conclusions about sustained efficacy, colonization of probiotics, and long-term caries prevention. Also, the restricted sample sizes within individual studies weaken the power to draw strong conclusions from this review. This high heterogeneity made direct comparisons and pooling the studies' results quite problematic, making a meta-analysis impractical, with precise, crude effect estimates (risk ratios, mean differences, *etc.*), and limiting the clinical impact and strength of combined evidence. Therefore, the findings were presented descriptively only. Additionally, most clinical trials involved small sample sizes, which might limit the inference about the results and conclusions.

(3) The use of a quality assessment scoring system based on the Cochrane Collaboration tool, while appropriate for randomized controlled trials, may have introduced some subjectivity in the evaluation process. Although we employed independent reviewers and consensus-building procedures to minimize bias, the inherent limitations of any quality assessment framework—including potential inter-rater variability and the weighting of different bias domains—should be acknowledged as a methodological constraint. Furthermore, despite using the Cochrane tool, a few included studies showed some methodological deficiencies. So, their results might be prone to Type I and II errors. Publication bias could be ruled out, as only English-language studies were included. Future clinical trials should prioritize the long-term evaluation of these indigenous strains, as suggested by recent systematic assessments of oral-niche probiotics.

5. Conclusions

Despite its limitations, the present review can conclude that CFU counts of cariogenic pathogens in saliva and plaque and incidence of caries lesions could be reduced through the early, repeated, and long-term intake of oral probiotic supplements in children and adolescents, using different suitable vehicles. Oral probiotics are safe and play a role as antagonistic agents on acidogenic/aciduric bacteria that contribute to the dental caries process development. Timely provided, bacteriotherapy (as oral-niche probiotics) seems to have a positive influence on the prevention of dental caries in children. However, it should be considered only as an adjunct to conventional oral preventive measures for attaining the best results.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and analyzed during the current systematic review are derived from published primary studies cited in the reference list. All relevant data extracted from these sources are included within the article and its accompanying tables (**Supplementary Tables 3,4,5,6**). Any additional information regarding the search strategy or quality assessment is available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

JND, SAR and AM—conceived the research idea; collected and curated the data. AM and SAR—served as the pre-calibrated expert reviewers who performed the assessment of methodological heterogeneity and determined the final synthesis strategy. AM—also participated in the consensus meetings to resolve disagreements regarding study eligibility and data extraction. JAGR and APG—analyzed the data. JND, JAGR and APG—led the writing. All authors read, critically revised for intellectual content, and agreed with the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The present systematic review did not require any ethical approval.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Jose Arturo Garrocho Rangel and Amaury Pozos-Guillén are serving as members of the Editorial Board of this journal. We declare that Jose Arturo Garrocho Rangel and Amaury Pozos-Guillén had no involvement in the peer review of this article and no access to information regarding its peer review. Full responsibility for the editorial process of this article was delegated to HKH.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found in the online version, at https://oss.jocpd.com/files/article/2049721556945256448/attachment/Supplementary%20material.zip.

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