Systematic Review Article

Efficacy and Safety of Probiotics for Dental Caries in Preschool Children: A Systematic Review and Meta-analysis

Abstract

Background: Early childhood caries is one of the most serious and high-priced oral health conditions among young children. With advancing dental sciences, the focus of dental caries treatment is shifted from restorative procedures to preventive measures, and a modality grabbing attention is probiotics. Probiotics exert their effects in many ways as chemical inhibition of pathogenic bacteria and stimulation of the immune response through the production of immunoglobulin A and many more. **Objective:** This systematic review aims to explore the efficacy and safety of probiotics in dental caries in preschool children. **Methodology:** The study was registered in the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42020159058). The search was done for randomized control trials in electronic databases such as Cochrane, PubMed, ClinicalTrials.gov, Medline, and Embase. It has further included manual searches of journals, conference abstracts, and books. Three reviewers done the selection of the study as per the criteria and also did the risk of bias assessment independently and wherever required, a fourth reviewer resolved the discrepancy in case of disagreement. **Results:** The nine randomized control trials were included in the study, and the pooled analysis revealed probiotics as an effective intervention in preschool children with dental caries. **Conclusion:** The results about the efficacy of probiotics in the prevention of dental caries are very encouraging, though the level of evidence is still inadequate.

Keywords: *Cariogenic microorganism, Decayed, Missing, and Filled Teeth/dmft index, dental caries, early carious lesions, Lactobacillus, probiotics, Streptococcus mutans*

Aarati S. Panchbhai[1], Mahalaqua Nazli Khatib[2], Rajiv M. Borle[1], Shravani S. Deolia[1], Vijay M. Babar[2], Anjali H. Vasistha[1], Ritika P. Parida[1]

[1]Dentistry, Sharad Pawar Dental College and Hospital, DMIHER (DU), Wardha, Maharashtra, India, [2]Research, Jawaharlal Nehru Medical College and Hospital, DMIHER (DU), Wardha, Maharashtra, India

Introduction

Literature suggests that the people who maintain oral hygiene and have caries-free dentition live an average of 10 years longer than those who lose their teeth. It is important to maintain or preserve natural teeth. Dental caries is the most common oral disease in adults and children in developed countries. Dental caries, if remained untreated, would cause discomfort, pain, and inability to eat or can cause nonvitality of the tooth and more serious consequences such as cysts, osteomyelitis, and facial space infections adding physical or financial burden for its treatment.[1-5]

It is estimated that oral diseases affect nearly 3.5 billion people, among which tooth decay or dental caries is the most common health condition (Global Burden of Disease, 2017).[6-8] The microorganisms that are mainly identified from carious lesions are *Streptococcus mutans, Lactobacillus acidophilus,* and *Actinomyces viscosus*. *S. mutans* is one of the most significant bacterial species involved in the early colonization and demineralization of tooth enamel to initiate dental caries. Improper brushing or inadequate exposure to fluoride may aggravate dental decay in children.[3,5,6] Early childhood caries (ECC) is defined as the presence of one or more decayed (noncavitated or cavitated lesions), missing (due to caries), or filled tooth surfaces in any primary tooth in a preschool-age child between birth and 71 months of age. The term "Severe Early Childhood Caries" refers to "atypical" "progressive" "acute" or "rampant" patterns of dental caries."[9] The reported prevalence rate of ECC is 1%–12% in developed countries and as high as 70% in developing countries making it a major health problem and economic burden, especially in the socially disadvantaged population.[1,10]

According to the WHO and FAO, probiotics are "live microorganisms which when administered in adequate amounts confer a health benefit on the host." Probiotics

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Address for correspondence:
Dr. Aarati S. Panchbhai, SPD College and Hospital, SRMMMTs Campus, DMIHER (DU), Sawangi (Meghe), Wardha - 442 001, Maharastra, India.
E-mail: artipanch@gmail.com

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are live microorganisms that are either the same or similar to microorganisms found naturally in the human body and beneficial to health.[6,11-13] Some examples of food products from which we can get probiotics are sourdough bread, yogurt, and pickles. Probiotics are also available in capsule, tablet, powder, and liquid form. The use of such advantageous bacteria has gained attention within dental research society with a focus on caries progression, periodontal disease, and oral malodor.[14] Many works of literature suggested uncertain results regarding the consumption of probiotics for dental caries in a pediatric population. A few studies found a reduction in *S. mutans*, while other studies reported no change; this could be due to dissimilarity in the methodology used in the studies, inadequate sample size, or duration of intervention.[15,16] Therefore, the aim of this systematic review was to investigate the effect of probiotic therapy in pediatric populations.

Probiotics provide a health benefit when administrated in appropriate amounts. Exposure to probiotic bacteria from early in life may have a more positive impact on general and oral health than adults.[17,18] There are various mechanisms by which probiotics exert their effects on the host. Probiotics may act by chemical inhibition of pathogenic bacteria through decreasing luminal pH, production of certain inhibitory compounds, or reducing the availability of substrate to other bacterial populations. Moreover, it has been reported to stimulate nonspecific immune response leading to host resistance to microbial pathogens, immune elimination through the production of immunoglobulin A and cytokines, downregulation of hypersensitivity reactions, and decreased production of metalloproteinase.[19-22] Claudia *et al*., 2017, revealed that probiotics can produce antimicrobials, compete for cell adhesion sites, modulate the immune system, and degrade toxins.[19] The adhesion and colonization of the probiotics in the oral cavity is also of paramount importance since adhesion may increase the retention time of a probiotic on the host surfaces leading to prolonged action.[20-22]

Introducing a nonpathogenic microbial strain into the microflora of host not only aids in restoring oral health but also generates conditions that serve the dominance of nonpathogenic bacteria and inhibition of pathogenic microorganisms in the oral cavity. The probiotics will promote the diversity of health-associated microbes in the oral biofilm. Consequently, it seems rational to observe the effect of probiotics which have a positive influence on oral flora to help in the reduction of dental caries.[23]

Methodology

The protocol of the present systematic review was designed according to the PRISMA guidelines 2009 and was registered in the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42020159058).[24]

Search methodology for inclusion of studies

This systematic review and meta-analysis included detailed search strategies for identification of the studies. Search terms included MeSH or equivalent terms and text words from databases such as PubMed, Scopus, Cochrane, Google Scholar, and ScienceDirect databases from inception till 2019, while Medline and CENTRAL from inception till date. The search also included additional resources such as www.ClinicalTrials.gov, conference proceedings, and abstracts. Additionally, reference lists of the selected studies and reviews were scanned manually to identify the articles missed by electronic search. The Google search engine was also used to do an all-inclusive search on the World Wide Web to ensure completeness. Besides, the manual library search and the communication with experts were done.

Criteria for considering studies for this review

This systematic review and meta-analysis have included the studies with randomized controlled trials having full journal publications; the *in vivo* studies in humans were selected.

Eligibility criteria

Eligibility criteria for inclusion of the studies according to PICO format (participant, intervention, comparator, and outcome), is as mentioned:

- Participants (P): Healthy children in the age group 1–6 years
- Intervention (I): Probiotic in any form
- Comparator (C): Placebo/alternative treatment/as an adjunct
- Outcomes (O): Main and additional outcomes.

Inclusion criteria

- Healthy children in age group 1–6 years with or without dental caries
- Exposure: Probiotics, in any form/preparation, frequency, or duration.

Ice creams or dairy foods such as cheese, yogurt and milk, lozenges, toothpaste, tablets, drinks, and syrups

- Randomized controlled trials (*in vivo* studies)
- Years of search: Inception to 2019.

Exclusion criteria

- Elderly children/children above 6 years of age
- The children with a history of dental treatment, systemic antibiotics 3 months before baseline, habitual use of dairy probiotics, xylitol chewing gums, severe medical conditions, and who are allergic to dairy products
- Use of agents other than probiotics or other therapeutic or preventive modalities
- Animal studies, *in vitro* studies, systematic reviews or meta-syntheses, and observational studies.

Outcomes to be measured

Outcomes are categorized under

- Main outcomes
  - Reduction of dental caries: Using visual and tactile detection of lesions of dental caries and its severity is depicted by various standard criteria

such as ICDAS (International Caries Detection and Assessment System)/WHO Criteria (Decayed, Missing, and Filled Teeth and Decayed, Missing, and Filled surfaces, [DMFT]/dmfs/dmft)
    - Reduction in salivary *S. mutans* level/counts: The number of *S. mutans* levels in saliva was measured before and after the intervention
    - Observed/associated adverse effects/side effects/ complications.
- Additional outcomes
    - Reduction in Biofilm formation: Measured as visible plaque index
    - Increase in pH.

Data collection and analysis

Selection of studies

The studies were selected as per the criteria. Firstly, titles and abstracts of the studies which were appropriate to the review were screened and a complete text of eligible studies was extracted. There was no language barrier in the selection process of studies. The PRISMA flow diagram illustrated the entire selection process as per recommended guidelines.

Data extraction and management

A complete text of the included studies was extracted and assessed. Any discrepancy or confusion therein was discussed among review authors for mutual settlement, and wherever required, a fourth review author was requested to resolve the inconsistency. The risk of bias (RoB) assessment was done to resolve any discrepancy. The selected randomized control trials were summed up into a "summary table." [Tables 1-3].[25-32]

Assessment of risk of bias in included studies

The RoB assessment was done for included studies; any ambiguity or differences were discussed to reach a common conclusion. Whenever needed, a third review author brought the terms to a mutual decision.

A domain-based evaluation for RoB was done for each study; accordingly, studies were judged for seven domains and assigned either "low risk," "high risk," or "unclear risk" of bias [Figures 1-3].

Data synthesis

This systematic review has provided the narrative synthesis of the findings from the included studies, structured around the target population characteristics, type of intervention, type of outcomes, and intervention content. It has provided summaries of intervention effects for each study by calculating the risk ratios (for dichotomous outcomes) or standardized mean differences (for continuous outcomes). However, where studies have used the same type of intervention and comparator with the same outcome measure, we have pooled the results using a random-effect meta-analysis and calculated 95% confidence intervals and two-sided *P* values for each outcome.

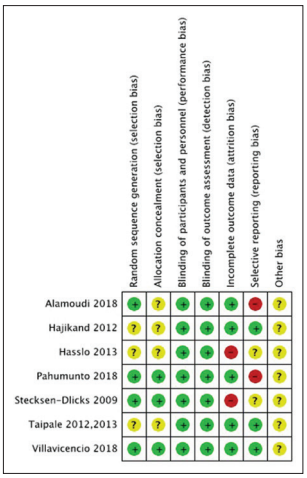

Figure 1: Risk of bias summary

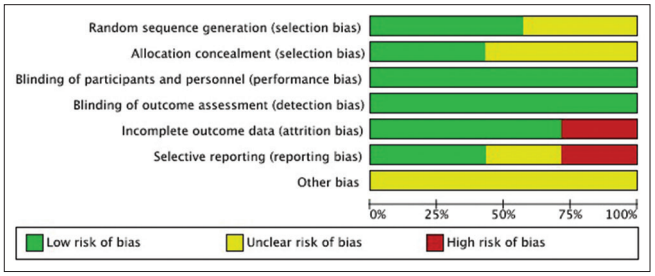

Figure 2: Risk of bias graph

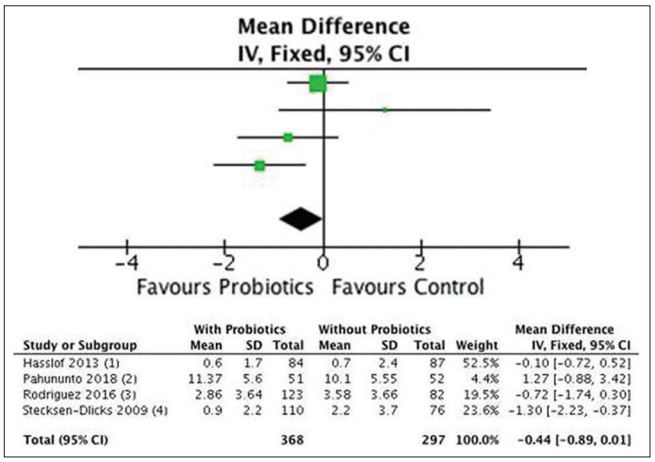

Figure 3: Forest plot for cavitated lesions

In this study, the subgroup analysis according to the type of probiotic strain was not done. The studies rather focused on the effect of probiotics on the reduction in dental caries and associated adverse effects if any. Heterogeneity in the studies was assessed by using the Chi-square test and I^2 statistics.

Observations

Cavitated lesions [Figure 3]

For cavitated lesions, the study showed that the intervention was effective with a reduction in cavitated lesions. All the studies favored the outcome except for

Table 1: Characteristics of studies included in meta-analysis

Parameters	Rodriguez 2016		Pahumunto 2018		Stecksen-Dlicks 2009		Villavicencio 2018		Hasslöf 2013	
Outcomes	Continuous data									
	Mean of intervention±SD	Mean of control±SD	Mean of intervention±SD	Mean of control±SD	Mean of intervention±SD	Mean of control±SD	Mean of intervention±SE	Mean of control±SE	Mean of intervention±SD	Mean of control±SE
	Probiotics +	Probiotics −	Probiotics +	Probiotics −	Probiotics +	Probiotics −	Probiotics +	Probiotics −	Probiotics +	Probiotics −
Caries increment measurement (cavitated)	BL (*n*=123): 1.62±2.51 12 months (*n*=123): 2.86±3.64	BL (*n*=82): 1.69±2.75 12 months (*n*=82): 3.58±3.66	BL (*n*=59): 10.61±5.81 6 months (*n*=51): 11.37±5.60	BL (*n*=52): 8.85±6.09 6 months (*n*=52): 10.10±5.55	BL (*n*=133): 0.5±1.7 21 months (*n*=110): 0.9±2.2	BL (*n*=115): 0.6±1.6 21 months (*n*=76): 2.2±3.7	BL (*n*=136): 2.23±3.57 9 months (*n*=119): 2.22±32.32	BL (*n*=227): 2.22±3.49 9 months (*n*=202): 1.88±30.57	BL (*n*=89): 0±0 6 years (*n*=84): 0.6±1.7	BL (*n*=90): 0.2±1.0 6 years (*n*=87): 0.7±2.4
Caries increment measurement (noncavitated)	BL (*n*=123): 0.67±1.71 12 months (*n*=123): 1.30±2.31	BL (*n*=82): 0.69±1.56 12 months (*n*=82): 1.68±2.69					BL (*n*=136): 0.71±1.64 9 months (*n*=119): 0.60±1.65	BL (*n*=227): 0.65±1.81 9 months (*n*=202): 0.70±1.80		
SM counts					BL (*n*=133): 0.6±3.4 21 months (*n*=110): 0.2±1.7	BL (*n*=115): 0.6±2.4 21 months (*n*=76): 0.8±5.5	BL (*n*=136): $0.84×10^5±3.13×10^5$ 9 months (*n*=119): $0.16×10^5±0.80×10^5$	BL (*n*=227): $1.02×10^5±3.89×10^5$ 9 months (*n*=202): $0.42×10^5±2.86×10^5$		

SD: Standard deviation; SE: Standard error; BL: Basal Level; SM: Streptococcus Mutans

Pahumunto *et al*.'s study which showed the intervention was ineffective.[26]

The mean difference was found to be −0.44 (−0.89, 0.01), with significant overall effect. The heterogeneity test suggests that there were insignificant differences in the studies. All the studies favored the outcome except for Pahumunto *et al*. which showed that the intervention was ineffective and was given only for 6 months.[26] While, for studies by Rodríguez *et al*. and Stecksén-Blicks *et al*., the findings were significant with 12 months and 21 months of intervention, respectively.[25,32]

Caries prevalence

Hedayati-Hajikand *et al*., 2012, studied and compared the caries prevalence in participants taking probiotics and not on probiotics.[29] It was demonstrated that the intervention was effective and there was a reduction in the prevalence of carious lesions in participants on probiotics. The mean difference was found to be 0.52 (0.30 0.90), and the overall effect was found to be significant (0.02). Being a single study that mentioned caries prevalence, the heterogeneity test was not applicable.

Streptococcus mutans count

Stecksén-Blicks *et al*. studied and compared the *S. mutans* count in participants taking probiotics and not on probiotics.[32] For *S. mutans* count, the study showed that the intervention was effective with the reduction in *S. mutans* count.

The mean difference was found to be −0.60 (−1.88, 0.680), and the overall effect was found to be nonsignificant. Being a single study that mentioned *S. mutans* count*,* the heterogeneity test was not applicable.[32]

Discussion

The present systematic review and meta-analysis were carried out to evaluate the effect of probiotics on dental caries anticipating outcomes such as a reduction in dental caries, salivary *S. mutans* count and biofilm formation, and an increase in pH. Additionally, the present work has also assessed adverse/side effects or complications of probiotic use.

The articles included in the present review work were subjected to the RoB assessment; overall, the risk was found to be low for selection bias, allocation, and blinding. The results about the efficacy of probiotics in the prevention of dental caries as an intervention were very encouraging, although the level of evidence is still inadequate.

Cavitated lesions

For cavitated lesions, the study showed that the intervention was effective with a reduction in cavitated lesions. All studies favored the outcome except for Pahumunto *et al*. which showed the intervention of 6 months as ineffective.[26] While, for studies by Rodríguez *et al*. and Stecksén-Blicks *et al*., the findings were significant with the intervention of 12 months and 21 months, respectively.[25,32] Cagetti *et al*., 2013, mentioned the therapeutic effect of probiotics in the

Table 2: Characteristics of studies included in meta-analysis

Parameters	Hajikand 2012		Alamoudi 2018		Taipale 2012, 2013		
Outcomes	Continuous data						
	Mean of intervention SD % Probiotics +	Mean of control SD % Probiotics −	Mean of intervention SD % Probiotics +	Mean of control SD % Probiotics −	Mean of intervention SD % Probiotics +	Mean of control SD% Probiotics −	
						Xylitol	Sorbitol
DMFT					BL (*n*=32): NA 2 years (*n*=32): 0% 4 years (*n*=32): 9%	BL (*n*=35): NA 2 years (*n*=35): 0% 4 years (*n*=33): 21%	BL (*n*=29): NA 2 years (*n*=29): 0% 4 years (*n*=28): 7%
SM counts			BL (*n*=90): 90 (100%) 28 days (*n*=90): 46 (51.1%)	BL (*n*=88): 88 (100%) 28 days (*n*=88): 79 (89.8%)	BL (*n*=32): NA 2 years (*n*=32): 6% 4 years (*n*=32): 56%	BL (*n*=35): NA 2 years (*n*=35): 31% 4 years (*n*=32): 70%	BL (*n*=29): NA 2 years (*n*=29): 10% 4 years (*n*=32): 46%
Caries prevalence	BL (*n*=54): 13 (24%) 12 months (*n*=54): 13 (24%)	BL (*n*=56): 15 (27%) 12 months (*n*=56): 26 (47%)					
Visible plaque index	BL (*n*=54): 18 (34%) 12 months (*n*=54): 29%	BL (*n*=56): 22 (40%) 12 months (*n*=56): 25%					

NA: Not available; SD: Standard deviation; DMFT: Decayed, Missing, and Filled Teeth; BL: Basal Level; SM: Streptococcus Mutans

prevention of dental caries. Additionally, they studied the risk factors associated with caries for instance acid production by cariogenic microbials concerning probiotic administration. The probiotics were effective against *S. mutans* reducing their counts; however, the randomized controlled trials need to be conducted in humans to generate enough scientific evidence.[10]

Caries prevalence

The study by Hedayati-Hajikand *et al*., 2012, compared the caries prevalence in participants taking probiotics and not on probiotics where the intervention was effective with a reduction in the prevalence of carious lesions. The overall effect was found to be significant (0.02).[29] Poorni *et al*., 2019, evaluated the role of probiotics and *streptococcus* strains on the incidence of carious lesions doing systematicreview, the included clinical studies showed a high RoB. Although *in vitro* studies showed promising results, clinical studies have not demonstrated clear clinical outcomes. Thus, there is a vast scope for future research in this field.[4]

Streptococcus mutans count

The study by Stecksén-Blicks *et al*. compared the *S. mutans* count in participants taking and not taking probiotics. For *S. mutans* count, the study showed that the intervention was effective with the reduction in *S. mutans* count. The overall effect was found to be nonsignificant.[32] Dhawan R *et al*., 2013, examined the effect of probiotics on plaque, salivary *S. mutans* levels, and gingival index in cases of gingivitis.[33] The baseline evaluations were made followed by two posttreatment evaluations for 2 weeks, and there was a significant reduction in plaque index, *S. mutans* level, and gingival index.[33] Chuang *et al*., 2011, could not observe any difference between *S. mutans* levels in placebo and probiotic groups using *Lactobacillus paracasei* containing probiotics. However, the *in vitro* studies mentioned that *Lactobacillus paracasei* could restrain the growth of *S. mutans*.[21] Coqueiro *et al*., 2018, reviewed the therapeutic effects of probiotics containing *Bifidobacterium* and *Streptococcus* on levels of salivary *S. mutans* and found reduced incidence of dental caries and *S. mutans* levels. It was concluded that the effects of combined therapy using fluoride and probiotics would be more effective.[34]

Ahola *et al*., 2002, and Taipale *et al*., 2012, have demonstrated that specific probiotic strains can affect oral pathogens by reducing the counts of *S. mutans* and lactobacilli in the saliva and biofilm.[5,35] The scientific origin of oral probiotics makes use of genetically altered competitive microbes or a mixture of probiotics containing inhibitory oral microbes.[36-38] Streptococcal salivaris and thermophilus have been widely studied *in vitro*.[36-38] Schwendicke *et al*. revealed streptococcal thermophilus be capable to compete against cariogenic bacterial species in oral flora owing to its aciduric nature, although with limited efficiency as compared to Lactobacilli.[39,40] At similar, Lee and Kim showed that *Lactobacillus* strains formed wider

Table 3: Study-wise risk of bias

	Pahumunto 2018	Villavicencio 2018	Alamoudi 2018	Hasslo 2013	Hajikand 2012	Taipale 2012, 2013	Stecksen-Dlicks 2009
Random sequence generation (selection bias)	L	L	L	U	U	U	L
Allocation bias: Allocation concealment	L	L	U	U	U	U	L
Performance bias: Blinding of participants and personnel	L	L	L	L	L	L	L
Detection bias: Blinding of outcome assessment	L	L	L	L	L	L	L
Attrition bias: Incomplete outcome data addressed	L	L	L	H	L	L	H
Reporting bias: Selective reporting	H	L	H	U	L	L	U

bacteria-free zones than streptococcal thermophilus.[40] The strains K12 and M18 streptococcal salivaris are mostly researched compared to other strains. The streptococcal salivarius M18 was more effective in the reduction of biofilm and caries risk *in vitro* with an inhibitory effect on *S. mutans* and *Streptococcus sobrinus*.[41-45] However, there are still doubts about which is the best bacterial strains, its dose and period of administration, Consequently, prospective extended research work is desired.[11]

Soldering mentioned commonly researched probiotics such as *Bifidobacterium lactis* BB-12 (BB-12), *Lactobacillus rhamnosus* GG, and *Lactobacillus reuteri*.[46] The coronal and root caries occurrence was reduced with the use of *Lactobacillus rhamnosus* with or without fluoride.[46,47] The *Bifidobacterium lactis* BB-12 when administered in infants reduced the occurrence of caries. However, longitudinal studies are required to ascertain the adverse effects of probiotics on oral health.[30]

Conclusion

Overall, the meta-analysis has proved that probiotic as an intervention is effective in the reduction of carious lesions in preschool children. No adverse effects were noted in the studies for the period of probiotics use. Although probiotic intervention in dental caries was found to be effective, the demonstrated level of evidence is inadequate. Considering that common oral diseases arise out of deranged microbial equilibrium, the recent research on probiotic focus on reducing virulent strain and restoring healthy microbiota. The prospective extended research with broader representation would be desired to identify the specific probiotic strains with anticariogenic activity. Probiotics may be a promising aid for the prevention of dental caries; however, the ideal dose forms and duration of probiotic intervention need to be determined through supplementary high-quality research.

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Conflicts of interest

There are no conflicts of interest.

References

1. Congiu G, Campus G, Lugliè PF. Early childhood caries (ECC) prevalence and background factors: A review. Oral Health Prev Dent 2014;12:71-6.
2. Baliga S. A vision for pediatric and preventive dentistry oral health policy in India. J Indian Soc Pedod Prev Dent 2018;36:223-4.
3. Shivakumar KM, Vidya SK, Chandu GN. Dental caries vaccine. Indian J Dent Res 2009;20:99-106.
4. Poorni S, Srinivasan MR, Nivedhitha MS. Probiotic *Streptococcus* strains in caries prevention: A systematic review. J Conserv Dent 2019;22:123-8.
5. Taipale T, Pienihäkkinen K, Salminen S, Jokela J, Söderling E. *Bifidobacterium animalis* Subsp. Lactis BB-12 administration in early childhood: A randomized clinical trial of effects on oral colonization by mutans streptococci and the probiotic. Caries Res 2012;46:69-77.
6. World Health Organization. Oral Health. World Health Organization. Available from: https://www.who.int/news-room/fact-sheets/detail/oral-health. [Last accessed on 2020 Aug 01].
7. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: A systematic analysis for the global burden of disease study 2017. Lancet 2018;392:1789-858.
8. Centres for Disease Control and Prevention. Oral Health Conditions. Available from: https://www.cdc.gov/oralhealth/conditions/index.html#:~:text=Someofthemostcommon,onecavitybyage2034. [Last accessed on 2023 Aug 03].
9. American Dental Association. Statement on Early Childhood Caries. Available from: https://www.ada.org/en/about-the-ada/ada-positions-policies-and-statements/statement-on-early-childhood-caries. [Last accessed on 2023 Aug 07].
10. Cagetti MG, Mastroberardino S, Milia E, Cocco F, Lingström P, Campus G. The use of probiotic strains in caries prevention: A systematic review. Nutrients 2013;5:2530-50.
11. Claudia F, Catalina A, Francisca L, Fernanda R. Role of probiotics as bacteriotherapy in dentistry: A literature review. J Pharm Bioalled Sci 2018;14:S34-8. DOI: 10.22592/o2017n30a2.
12. Singh VP, Sharma J, Babu S, Rizwanulla T, Singla A. Role of probiotics in health and disease: A review. J Pak Med Assoc 2013;63:253-7.
13. Sanders ME. Probiotics: Definition, sources, selection, and uses. Clin Infect Dis 2008;46 Suppl 2:S58-61.
14. Teughels W, Van Essche M, Sliepen I, Quirynen M. Probiotics and oral healthcare. Periodontol 2000 2008;48:111-47.
15. Aminabadi NA, Erfanparast L, Ebrahimi A, Oskouei SG. Effect of chlorhexidine pretreatment on the stability of salivary lactobacilli probiotic in six- to twelve-year-old children: A randomized controlled trial. Caries Res 2011;45:148-54.
16. Juneja A, Kakade A. Evaluating the effect of probiotic containing milk on salivary mutans streptococci levels. J Clin Pediatr Dent

2012;37:9-14.
17. Yli-Knuuttila H, Snäll J, Kari K, Meurman JH. Colonization of *Lactobacillus rhamnosus* GG in the oral cavity. Oral Microbiol Immunol 2006;21:129-31.
18. Twetman S, Stecksén-Blicks C. Probiotics and oral health effects in children. Int J Paediatr Dent 2008;18:3-10.
19. Wattanarat O, Makeudom A, Sastraruji T, Piwat S, Tianviwat S, Teanpaisan R, *et al.* Enhancement of salivary human neutrophil peptide 1-3 levels by probiotic supplementation. BMC Oral Health 2015;15:19.
20. Snel J, Marco ML, Kingma F, Noordman WM, Rademaker J, Kleerebezem M. Competitive selection of lactic acid bacteria that persist in the human oral cavity. Appl Environ Microbiol 2011;77:8445-50.
21. Chuang LC, Huang CS, Ou-Yang LW, Lin SY. Probiotic *Lactobacillus paracasei* effect on cariogenic bacterial flora. Clin Oral Investig 2011;15:471-6.
22. Teanpaisan R, Piwat S, Dahlén G. Inhibitory effect of oral *Lactobacillus* against oral pathogens. Lett Appl Microbiol 2011;53:452-9.
23. Philip N, Suneja B, Walsh LJ. Ecological approaches to dental caries prevention: Paradigm shift or shibboleth? Caries Res 2018;52:153-65.
24. Aarati P, Khatib MN, Deolia S, Borle R, Babar V, Vasistha A, *et al*. Efficacy and safety of probiotics for dental caries in preschool children: A systematic review and meta-analysis. PROSPERO; 2020.CRD42020159058.
25. Rodríguez G, Ruiz B, Faleiros S, Vistoso A, Marró ML, Sánchez J, *et al.* Probiotic compared with standard milk for high-caries children: A cluster randomized trial. J Dent Res 2016;95:402-7.
26. Pahumunto N, Piwat S, Chankanka O, Akkarachaneeyakorn N, Rangsitsathian K, Teanpaisan R. Reducing mutans streptococci and caries development by *Lactobacillus paracasei* SD1 in preschool children: A randomized placebo-controlled trial. Acta Odontol Scand 2018;76:331-7.
27. Villavicencio J, Villegas LM, Arango MC, Arias S, Triana F. Effects of a food enriched with probiotics on *Streptococcus mutans* and *Lactobacillus spp*. Salivary counts in preschool children: A cluster randomized trial. J Appl Oral Sci 2018;26:e20170318.
28. Alamoudi NM, Almabadi ES, El Ashiry EA, El Derwi DA. Effect of probiotic *Lactobacillus reuteri* on salivary cariogenic bacterial counts among groups of preschool children in Jeddah, Saudi Arabia: A randomized clinical trial. J Clin Pediatr Dent 2018;42:331-8.
29. Hedayati-Hajikand T, Lundberg U, Eldh C, Twetman S. Effect of probiotic chewing tablets on early childhood caries – A randomized controlled trial. BMC Oral Health 2015;15:112.
30. Taipale T, Pienihäkkinen K, Alanen P, Jokela J, Söderling E. Administration of *Bifidobacterium animalis* subsp. Lactis BB-12 in early childhood: A post-trial effect on caries occurrence at four years of age. Caries Res 2013;47:364-72.
31. Hasslöf P, West CE, Videhult FK, Brandelius C, Stecksén-Blicks C. Early intervention with probiotic *Lactobacillus paracasei* F19 has no long-term effect on caries experience. Caries Res 2013;47:559-65.
32. Stecksén-Blicks C, Sjöström I, Twetman S. Effect of long-term consumption of milk supplemented with probiotic lactobacilli and fluoride on dental caries and general health in preschool children: A cluster-randomized study. Caries Res 2009;43:374-81.
33. Dhawan R, Dhawan S. Role of probiotics on oral health: A randomized, double-blind, placebo-controlled study. J Interdiscip Dent 2013;3:71-8.
34. Coqueiro AY, Bonvini AA, Raizel R. Probiotic supplementation in dental caries: Is it possible to replace conventional treatment. Nutrire Rev Soc Bras Aliment Nutr 2018;43:1-9.
35. Ahola AJ, Yli-Knuuttila H, Suomalainen T, Poussa T, Ahlström A, Meurman JH, *et al.* Short-term consumption of probiotic-containing cheese and its effect on dental caries risk factors. Arch Oral Biol 2002;47:799-804.
36. Sanders CC, Sanders WE Jr. Enocin: An antibiotic produced by *Streptococcus salivarius* that may contribute to protection against infections due to group A streptococci. J Infect Dis 1982;146:683-90.
37. Roos K, Håkansson EG, Holm S. Effect of recolonisation with "interfering" alpha streptococci on recurrences of acute and secretory otitis media in children: Randomised placebo controlled trial. BMJ 2001;322:210-2.
38. Hillman JD, Mo J, McDonell E, Cvitkovitch D, Hillman CH. Modification of an effector strain for replacement therapy of dental caries to enable clinical safety trials. J Appl Microbiol 2007;102:1209-19.
39. Schwendicke F, Korte F, Dörfer CE, Kneist S, Fawzy El-Sayed K, Paris S. Inhibition of *Streptococcus mutans* growth and biofilm formation by probiotics *in vitro*. Caries Res 2017;51:87-95.
40. Lee SH, Kim YJ. A comparative study of the effect of probiotics on cariogenic biofilm model for preventing dental caries. Arch Microbiol 2014;196:601-9.
41. Cosseau C, Devine DA, Dullaghan E, Gardy JL, Chikatamarla A, Gellatly S, *et al.* The commensal *Streptococcus salivarius* K12 downregulates the innate immune responses of human epithelial cells and promotes host-microbe homeostasis. Infect Immun 2008;76:4163-75.
42. Di Pierro F, Donato G, Fomia F, Adami T, Careddu D, Cassandro C, *et al.* Preliminary pediatric clinical evaluation of the oral probiotic *Streptococcus salivarius* K12 in preventing recurrent pharyngitis and/or tonsillitis caused by *Streptococcus pyogenes* and recurrent acute otitis media. Int J Gen Med 2012;5:991-7.
43. Horz HP, Meinelt A, Houben B, Conrads G. Distribution and persistence of probiotic *Streptococcus salivarius* K12 in the human oral cavity as determined by real-time quantitative polymerase chain reaction. Oral Microbiol Immunol 2007;22:126-30.
44. Burton JP, Drummond BK, Chilcott CN, Tagg JR, Thomson WM, Hale JD, *et al.* Influence of the probiotic *Streptococcus salivarius* strain M18 on indices of dental health in children: A randomized double-blind, placebo-controlled trial. J Med Microbiol 2013;62:875-84.
45. Walker GV, Heng NC, Carne A, Tagg JR, Wescombe PA. Salivaricin E and abundant dextranase activity may contribute to the anti-cariogenic potential of the probiotic candidate *Streptococcus salivarius* JH. Microbiology (Reading) 2016;162:476-86.
46. Soldering E. Probiotic and dental caries. Microb Ecol Health Dis 2012;23:55-6. doi: 10.3402/mehd.v23i0.18582.
47. Näse L, Hatakka K, Savilahti E, Saxelin M, Pönkä A, Poussa T, *et al.* Effect of long-term consumption of a probiotic bacterium, *Lactobacillus rhamnosus* GG, in milk on dental caries and caries risk in children. Caries Res 2001;35:412-20.