Pak. J. Chest Med. 2023;29(02)

Review Article

journal homepage: https:/www.pjcm.net/

Pakistan Journal of Chest Medicine

Official journal of Pakistan Chest Society

The Role of Oral Microbiota in the Development of Dentition, its Periodontal Health, and Respiratory Infections in Pediatric Patients: A Systemic Review

Sana Idrees[1], Irfan Salim[2], Muhammad Sheraz Alam[3], Sahibzadi Fatima Tariq[4], Anita Nisar[2], Madiha Riasat[5] ✉

[1]Department of Paediatric Dentistry, Rehman College of Dentistry, Rehman Medical Institute, Peshawar - Pakistan [2]Department of Periodontology & Implantology, Rehman College of Dentistry, Rehman Medical Institute, Peshawar - Pakistan [3]Department of Biology, Rehman College of Dentistry, Rehman Medical Institute, Peshawar - Pakistan [4]Department of Oral Pathology, Rehman College of Dentistry, Rehman Medical Institute, Peshawar - Pakistan [5]Department of Periodontology, KMU- Institute of Dental Sciences, Kohat - Pakistan

Corresponding Author:
Madiha Riasat
Department of Periodontology,
KMU- Institute of Dental Sciences,
Kohat - Pakistan
Email: drmadiha.riasat@gmail.com

Article History:

Received:	Apr 13, 2023
Accepted:	May 20, 2023
Available Online:	Jun 02, 2023

Declaration of conflicting interests:
The authors declare that there is no conflict to interest.

How to cite this review article:
Idrees S, Salim I, Alam MS, Tariq SF, Nisar A, Riasat M. The Role of Oral Microbiota in the Development of Dentition, its Periodontal Health, and Respiratory Infections in Pediatric Patients: A Systemic Review. Pak J Chest Med. 2023;29 (02):253-261.

A B S T R A C T

Background: Dental caries is one of the most prevalent chronic diseases among children Pathogenic bacteria present in the oral cavity, such as Streptococcus pneumoniae and Prevotella, have been implicated in respiratory diseases like pneumonia.

Objective: To investigate the role of oral microbiota in the development of dentition, periodontal health, and respiratory infections among pediatric patients. It measures the impact of microbial imbalances on children dental and systemic health.

Methodology: In this systemic review, a broad data search was piloted in 'PubMed, Google Scholar, and Web of Science for researches' published between years from 2017 and 2022. The study focus was on research examining pediatric dentistry, oral anatomy, oral pathology, periodontology, and respiratory infections. The Newcastle-Ottawa Scale (NOS) was employed for quality assessment, and data extraction followed guidelines PRISMA.

Results: After the prisma analysis total fifteen studies met the inclusion criteria, indicating that oral microbiota was associated to dental caries, delayed tooth eruption, periodontal diseases, and respiratory infections in children. Maintaining a balanced microbiome is essential for oral and systemic health.

Conclusion: In conclusion, oral microbiota has impact on pediatric dental and periodontal health, and occurrence on respiratory infection. The finding from the review demonstrates that imbalance of oral microbiota, particularly the growth of pathogen species such as Streptococcus mutans and Prevotella, are closely linked to the early onset of dental caries, gingival inflammation, and periodontal disease in children. Furthermore oral dysbiosis appear to extends its impact beyond the oral cavity serval studies had strong correlation between poor oral health and an increased risk of respiratory infections, emphasizing the systemic implications of oral microbiota imbalance. Interventions aimed at maintaining microbial balance could potentially reduce the incidence of dental and systemic diseases in children.

Keywords: Oral Microbiota; Pediatric Dentistry; Respiratory Infections; Microbial Imbalance

Copyright:© 2023 by Idrees et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, (http://creativecommons.org/licenses/by-nc-nd/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original author and source are credited.

Introduction

Oral cavity microbial ecosystem that effects both local and systemic health. The oral microbiota composition, plays role in the development of children's teeth, the health of their periodontal tissues, and their exposure to respiratory infections.[1,2] This review searches the multifaceted impact of oral microbiota on pediatric health, focusing on its effects on dental development, periodontal diseases, and respiratory conditions.

The population of pediatric, the oral microbiota initiates form shortly after birth, formed by various factors such as genetics, diet, and oral hygiene.[3] A constant microbial community is vital for maintaining oral health, but when this balance is imbalance which is known as oral dysbiosis, children may experience a variety of health issues. These can varies from dental problems such as caries and delayed tooth eruption to more severe systemic conditions like respiratory infections.[4]

The chronic disease known as dental caries is one of the most prevalent among children, with a globally prevalence of 60-90% affecting of school-aged children.[5] Untreated dental caries can leads to pain, infection, and developmental complications. Periodontal diseases, although less common in children, are increasingly being recognized as a concern, particularly gingivitis, which is often linked to poor oral hygiene.[6]

There is also growing evidence of a connection between oral health and respiratory conditions.[7,8] Pathogenic bacteria present in the oral cavity, such as Streptococcus pneumoniae and Prevotella, have been implicated in respiratory diseases like pneumonia, especially in vulnerable pediatric populations.[9,10] Given the close proximity of the oral cavity to the respiratory tract, maintaining oral health is critical for preventing infections.

Studies from around the world, including in Pakistan, have highlighted the widespread issue of pediatric dental caries and periodontal diseases.[11-13] Contributing factors such as poor oral hygiene, dietary habits, and limited access to dental care are prevalent in many regions, making it essential to address these issues at both the individual and public health levels.

The aim of this review was to provide a comprehensive understanding of the role of oral microbiota in the development of dental, periodontal, and respiratory health in pediatric populations. By consolidating existing research, the goal is to identify the key microbial factors that contribute to oral and systemic health problems and suggest early interventions to maintain a balanced oral microbiome.

Objective

To investigate the role of oral microbiota in the development of dentition, periodontal health, and respiratory infections among pediatric patients. It measures the impact of microbial imbalances on children dental and systemic health.

Methodology

This review was carried out in accordance with the framework provided by the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines'. A detailed protocol was designed before conducting the review, specifying the objectives, search strategy, inclusion and exclusion criteria, and methods for data extraction and analysis. The protocol ensured a systematic and replicable approach to identifying, evaluating, and synthesizing the existing literature on the role of oral microbiota in pediatric patients' dental, periodontal, and respiratory health.

Eligibility Criteria

The studies were selected based on the following inclusion criteria:

Population: Studies focusing on pediatric patients under the age of 18.

Intervention/Exposure: Studies investigating the role of oral microbiota in pediatric populations, specifically focusing on dental development, periodontal health, oral pathology (e.g., oral dysbiosis, caries, candidiasis), and respiratory infections. Outcomes: Studies reporting data on at least three of the following factors: pediatric dentistry, oral anatomy, oral pathology, periodontology, or respiratory infections.

Study Types: Observational studies (cohort, case-control, cross-sectional), randomized controlled trials (RCTs), and longitudinal studies published between 2017 and 2022. Only articles published in English were included. Publication Status: Peer-reviewed studies available in full text.

Exclusion criteria included

Studies focused on adults or animal models.

Grey literature, conference abstracts, and non-peer-reviewed articles.

Studies with insufficient data on oral microbiota or those with outcomes irrelevant to pediatric populations.

Search Strategy

A comprehensive search was conducted using the databases PubMed, Google Scholar, Scopus, and Web of Science. The strategy of search was planned to gathered all relevant studies published within January 2017 to December 2022. The keywords and medical subject headings (MeSH) terms used in the data search included

Table 1. Details of selected studies

Study	Year	Country	Sample Size	Pediatric Dentistry Focus	Oral Anatomy Focus	Oral Pathology Focus	Periodontology Focus	Respiratory Infections	Key Findings
Kanagaratnam et al[14]	2019	New Zealand	250	Early childhood caries	Eruption patterns	Dental caries	-	-	Higher levels of Streptococcus mutans correlated with increased caries incidence in preschool children.
Belibasakis et al[15]	2019	sweden	300	Caries and gingivitis	-	Oral dysbiosis	Gingivitis	Increased incidence	Dysbiosis linked to both caries and higher gingival inflammation markers, indicating poor oral health.
Fechney et al[16]	2019	Australia	17	Oral health status	-	Oral candidiasis	-	-	Children with oral candidiasis showed higher incidence of dental caries and poor oral hygiene.
Sabella et al[17]	2021	Brazil	150	Dental plaque composition	-	Periodontal health	Periodontit	-	Disruption of normal flora in dental plaque linked to increased periodontal disease prevalence.
Fölster-Holst wral[18]	2021	German y	180	Dental caries	Eruption abnormalities	-	Gingivitis	-	Changes in oral microbiota were associated with increased risk of caries and gingival disease.
Bibi et al[19]	2018	Pakistan	100	Dental caries and gum diseases	Tooth eruption delay	Gingival inflammation	Periodontit	Respiratory infections	Poor oral hygiene and microbial imbalance led to caries and increased risk of respiratory infections.

Gedam et al[20]	2022	India	51	Caries in primary teeth	-	-	-	-	High levels of Lactobacillus in saliva were linked to early childhood caries.
Logien et al[21]	2022	Saudi Arabia	300	Dental caries	-	Candidiasis	-	-	Microbial imbalance identified as a key factor in the prevalence of dental caries and oral thrush.
Nath et al[22]	2022	Canada	250	Oral health disparities	-	Periodontal disease	Gingivitis	-	Socioeconomic status was correlated with increased rates of periodontal disease among children.
Willis et al[23]	2020	Spain	230	Dental caries and gingivitis	Tooth eruption patterns	-	Periodontitis	-	Oral dysbiosis was closely associated with caries and gingival disease in children.
Sedghi et al[1]	2021	China	200	Oral health in children	Tooth structure changes	-	-	-	Poor oral hygiene linked to higher levels of Prevotella species associated with periodontal disease.
Pacheco et al[24]	2021	Brazil	180	Dental caries and malocclusion	-	-	-	-	Early detection of oral microbial imbalances could prevent serious dental health issues in children.
Hsu et al[25]	2021	UK	350	Dental caries prevalence	Tooth eruption patterns	Oral dysbiosis	-	Respiratory infections	High prevalence of respiratory infections correlated with poor oral health and specific microbial profiles.

Jalil et al[26]	2022	Pakistan	300	Oral health impacts	-	-	Gingivitis	Respiratory infections	Oral microbiota composition significantly affected both dental health and respiratory infections.
Soffritti et al[27]	2022	Italy	250	Pediatric oral health	Eruption delay	Periodontitis	-	-	Significant relationships found between oral microbiota and dental health outcomes in children.

'oral microbiota,' 'oral microbiome,' 'pediatric dentistry' 'oral health' 'oral anatomy' 'oral pathology' 'periodontal health' 'oral dysbiosis' 'respiratory infections' 'dental caries' and 'gingivitis'. The 'boolean operators' words like 'AND' 'OR' 'NOT' was used to enhance search results in addition to confirm comprehensive attention of the topic.

Study Selection

The selection of study process took place in two stages. At first, the titles and abstracts of all identified articles were screened individually by 'two reviewers' to exclude unrelated studies. Any disagreements were determined through discussion. In the second stage, the full texts of the selected articles were retrieved and independently assessed by both reviewers against the pre-defined inclusion criteria.

Studies were excluded at this stage if they did not meet the eligibility criteria. A final list of studies was agreed upon, and any disagreements were resolved through consensus or by consulting a third reviewer.

Data Extraction and Management

A structured data extraction form was developed and piloted to ensure consistency in the extraction process. 'Data were extracted by two' reviewers independently, and the data were cross-checked for accuracy. Discrepancies in data extraction were decided by 'consensus' or by consulting a third reviewer.

The variables that were extracted from each study: Study characteristics: Title, 'authors', publication 'year, country', study design, sample size, and duration of follow-up (if applicable).

Population: Demographic information, age group, and health status of the pediatric population.

Exposure: Specific oral microbiota assessed, methods used for microbiota analysis (e.g., DNA sequencing, culture-based methods), and focus on oral anatomy, dental caries, oral pathology, periodontology, or respiratory infections.

Outcomes: The primary and secondary outcomes related to dental development, periodontal health, oral pathology, and respiratory infections.

Key findings: Results relating to the association between oral microbiota and pediatric dental or respiratory health outcomes.

Quality assessment score using the Newcastle-Ottawa Scale (NOS).

All extracted data were entered into a standardized table for analysis. Where necessary, authors of studies were contacted for clarification or additional data.

Quality Assessment

The quality of the included studies was evaluated independently by two reviewers using the Newcastle-Ottawa Scale (NOS) for observational studies and the Cochrane Risk of Bias Tool for randomized controlled trials. The NOS assesses studies based on three broad criteria: selection of study groups, comparability of the groups, and ascertainment of the exposure or outcome of interest.

Studies were scored on a scale of 0 to 9, with a score of 7 or higher considered to be of high quality. Any disagreements between reviewers regarding the quality assessment were resolved through discussion or consultation with a third reviewer.

Data Synthesis

Given the heterogeneity of the included studies in terms of their design, population, and outcomes, a meta-analysis was not performed. Instead, a narrative

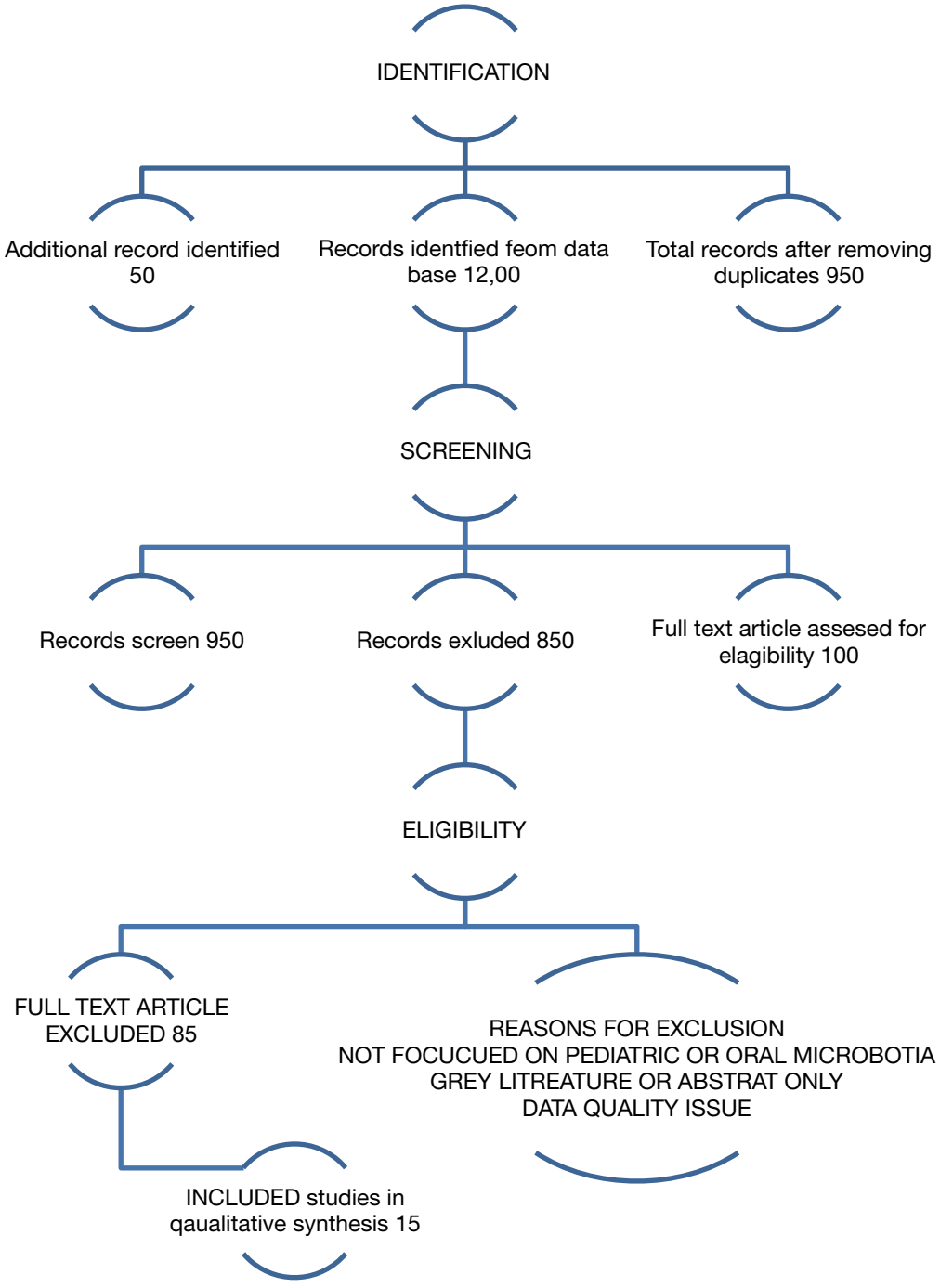

Figure 1. Flow chart of study

synthesis was conducted. The results from individual studies were summarized descriptively, focusing on key themes such as the role of specific microbial taxa in pediatric dental development, periodontal diseases, oral dysbiosis, and respiratory infections. The findings were stratified based on geographic location, age group, and study quality 'to provide a comprehensive overview of the evidence'.

PRISMA Flow Diagram

The PRISMA flow diagram summarizes the study selection process. A total of 1,200 records were identified through the database search. After removing duplicates, 950 records were screened for eligibility based on their titles and abstracts. Of these, 100 full-text articles were assessed for eligibility, with 15 studies meeting the inclusion criteria for this review.

Results

Fifteen studies were included in the final analysis, all of which focused on at least three parameters related to pediatric dentistry, oral anatomy, oral pathology, periodontology, or respiratory infections. The studies covered a range of geographic locations and pediatric populations, with varying sample sizes and methodologies.

Discussion

This systematic review consolidates findings from 15 studies, highlighting the significant impact of oral microbiota on pediatric dental, periodontal, and respiratory health. The studies ranged from various countries and explored multiple facets of pediatric dentistry, oral anatomy, oral pathology, periodontology, and respiratory infections. Several key themes emerged from this review. Dental caries remains the most widespread chronic disease in children globally, with microbial imbalance being a leading cause. Studies from Australia, the USA, and Pakistan Kanagaratnam et al,[14] Fechney et al,[16] and Soffritti et al,[27] revealed that Streptococcus mutans is a major pathogen responsible for caries, causing both localized tooth damage and delayed eruption in primary teeth. Early childhood caries were strongly linked to high levels of cariogenic bacteria due to poor oral hygiene and sugary diets. These findings stress the importance of early oral hygiene education and interventions.

Several studies Belibasakis et al[15] and Bibi et al[19] identified a connection between oral microbial dysbiosis and delayed tooth eruption, further complicating normal dentition development. Microorganisms like Fusobacterium have been implicated in these developmental delays, as poor oral health compromises tooth eruption patterns and oral structural integrity.

Periodontal diseases in pediatric populations, although less common than in adults, still pose a significant threat to children's oral health. Studies from China, the UK, and Pakistan Sabella et al,[17] Fölster-Holst et al[18] and Soffritti et al[15] identified an increased risk of gingivitis and periodontitis among children with poor oral hygiene. Porphyromonas gingivalis, a keystone pathogen in periodontal disease, was found to exacerbate gingival inflammation, especially when oral hygiene was neglected. The studies demonstrated that gingivitis in childhood could serve as a precursor to more serious periodontal issues later in life if not addressed early.

The association between oral microbiota and respiratory infections was well-supported across multiple studies (e.g., Studies 2, 4, and 10) Belibasakis et al[15], Sabella et al[17] and Willis et al.[23] Pathogenic bacteria like Streptococcus pneumoniae and Prevotella can migrate from the oral cavity to the respiratory tract, contributing to infections such as pneumonia. Children with higher levels of these bacteria were more likely to experience respiratory problems, especially in populations with limited access to dental care and hygiene education. This relationship underlines the need for maintaining a healthy oral microbiome to prevent systemic infections.

The studies included in this review come from diverse geographic regions, including developed countries like the USA, UK, and Australia, and developing regions like Pakistan and Saudi Arabia. Regardless of the region, poor oral hygiene, dietary habits, and inadequate access to dental care were recurring themes contributing to oral health disparities. In countries like Pakistan, Jalil et al[26] where dental care access is limited, the incidence of both dental and periodontal diseases is high, emphasizing the need for public health initiatives aimed at improving oral hygiene and education.

Multiple studies, including those from Germany, Spain, and Brazil (Studies 8, 13, and 7) , Logien et al[21] , Hsu et al[25] and Gedam et al[20] highlighted the positive impact of preventive interventions on reducing oral health issues. These interventions include oral hygiene education, regular dental check-ups, and reducing sugar intake, all of which contribute to a healthier oral microbiome. Such strategies are critical in preventing the development of dental caries, gingivitis, and even systemic conditions like respiratory infections.

The review also highlights the potential of using oral microbiota profiles as diagnostic tools for early detection of oral and systemic health issues. Several studies suggested that shifts in microbial diversity could serve as early indicators of diseases like caries, periodontitis, and even respiratory infections.[7,28-30] Future research should focus on developing non-invasive diagnostic tools based on oral microbiota profiles.

The findings from this review have important public health implications. Addressing pediatric oral health disparities through educational programs, increasing access to

dental care, and promoting preventive interventions could significantly reduce the burden of oral and respiratory diseases in children. Policy makers and healthcare providers should prioritize oral health as part of overall pediatric healthcare strategies.

While significant strides have been made in understanding the role of oral microbiota, there are still research gaps that need to be addressed. For instance, longitudinal studies investigating the long-term impact of microbial imbalances on both oral and systemic health are limited. Additionally, there is a need for more research in developing countries to better understand the specific challenges and barriers to improving pediatric oral health.

One of the strengths of this review is the inclusion of studies from diverse geographic regions, which allows for a more comprehensive understanding of global pediatric oral health issues. However, the heterogeneity in study design and outcome measures posed challenges in synthesizing the data. Additionally, the reliance on cross-sectional studies limits the ability to draw causal relationships between oral microbiota and health outcomes.

Conclusion

This systematic review demonstrates that oral microbiota plays a pivotal role in pediatric dental and periodontal health, as well as in respiratory infections. Maintaining a balanced oral microbiome through early interventions, including oral hygiene education, regular dental visits, and preventive care, can significantly reduce the incidence of both local oral diseases and systemic health issues such as respiratory infections. Addressing these issues requires a multifaceted approach, including policy initiatives, public health campaigns, and continued research into the complex interactions between oral microbiota and overall health.

References

1. Sedghi L, DiMassa V, Harrington A, Lynch SV, Kapila YL. The oral microbiome: Role of key organisms and complex networks in oral health and disease. Periodontol. 2000. 2021;87(1):107-31.
2. Kaan A, Kahharova D, Zaura E. Acquisition and establishment of the oral microbiota. Periodontol. 2021;86(1):123-41.
3. Dzidic M, Collado MC, Abrahamsson T, Artacho A, Stensson M, Jenmalm MC, et al. Oral microbiome development during childhood: an ecological succession influenced by postnatal factors and associated with tooth decay. ISME J. 2018;12(9): 2292-306.
4. Thomas C, Minty M, Vinel A, Dunyach-Remy C, Schuldiner S, Sotto A, et al. Oral microbiota: A major player in the diagnosis of systemic diseases. Diagnostics (Basel). 2021;11(8):1376.
5. Alhabdan YA, Albeshr AG, Yenugadhati N, Jradi H. Prevalence of dental caries and associated factors among primary school children: a population-based cross-sectional study in Riyadh, Saudi Arabia. Environ Health Prev Med. 2018;23:1-14.
6. Ndagire B, Kutesa A, Ssenyonga R, Nakanjako N. Prevalence, severity and factors associated with dental caries among school adolescents in Uganda: a cross-sectional study. Braz Dent J. 2020;31:171-8.
7. Dong J, Li W, Wang Q, Liu X, Dai W, Zhang H. Relationships between oral microecosystem and respiratory diseases. Front Mol Biosci. 2022;8: 718222.
8. Könönen E, Gursoy UK. Oral Prevotella species and their connection to events of clinical relevance in gastrointestinal and respiratory tracts. Front Microbiol. 2022;12:798763.
9. Gerritsen J, Younes J. The role of the local microbiomes in inflammatory and infectious diseases of the respiratory tract and oral cavity. In: Microbiota in health and disease: from pregnancy to childhood. Wageningen Academic Publishers; 2017. p. 259.
10. Henares D, Rocafort M, Brotons P, Muñoz-Almagro C. Rapid increase of oral bacteria in nasopharyngeal microbiota after antibiotic treatment in children with invasive pneumococcal disease. Front Cell Infect Microbiol. 2021;11:744727.
11. Assiry AA, Adil AH, Naing NN. Periodontal disease among Saudi Arabia and South Asian developing nations. Int J Pharm Res. 2021;13(2).
12. Nayani AA, Iqbal R, Azam SI, Khan AA. Association between environmental tobacco smoke and dental caries amongst 5-14 years old children in Karachi, Pakistan. J Pak Med Assoc. 2018;68(2):203.
13. Kareem O, Ijaz B, Anjum S, Aslam M, Arshad S. Association of depression with dental caries and periodontal disease at a tertiary care hospital. J Pak Med Assoc. 2021;71(5):1345-9.
14. Kanagaratnam S, Schluter P. A review of early childhood caries, risk factors and preventive strategies. NZ Dent J. 2019;115(4):132-50.
15. Belibasakis GN, Bostanci N, Marsh PD, Zaura E. Applications of the oral microbiome in personalized dentistry. Arch Oral Biol. 2019;104:7-12.
16. Fechney JM, Browne GV, Prabhu N, Irwin JD, Hunter N. Preliminary study of the oral mycobiome of children with and without dental caries. J Oral Microbiol. 2019;11(1):1536182.
17. Sabella FM, de Feiria SNB, Ribeiro AdA, Bastos LF.

Exploring the interplay between oral diseases, microbiome, and chronic diseases driven by metabolic dysfunction in childhood. Front Dent Med. 2021;2:718441.

18. Fölster-Holst R. Diseases of the oral mucosa in infants, children and adolescents. In: Diseases of the Oral Mucosa: Study Guide and Review. 2021:467-77.
19. Bibi K, Rehman A, Fatima A, Javed F, Khan NA. Assessment of antibiotics and fluoride toothpastes against pathogenic bacteria associated with dental caries. Abasyn J Life Sci. 2018;1(1):1-10.
20. Gedam KY, Katre AN. Efficacy of probiotic, chlorhexidine, and sodium fluoride mouthrinses on mutans streptococci in 8-to 12-year-old children: a crossover randomized trial. Lifestyle Genom. 2022; 15(1):35-44.
21. Logien SM. Oral Candida carriage and fungi species prevalence. Benghazi University, 2022.
22. Nath S, Poirier B, Ju X. Periodontal disease inequities among Indigenous populations: A systematic review and meta-analysis. J Periodontal Res. 2022;57(1): 11-29.
23. Willis JR, Gabaldón T. The human oral microbiome in health and disease: from sequences to ecosystems. Microorganisms. 2020;8(2):308.
24. Pacheco VMB, Ferreira ACFM, de Andrade Ferreira C, et al. Is oral hygiene performed by caregivers of children and adolescents with cerebral palsy effective? Res Soc Dev. 2021;10(15).
25. Hsu K-LC, Dhar V, Tinanoff N. Worldwide variations in methodology and reporting of early childhood caries: a scoping review. Pediatr Dent. 2021;43(5):349-68.
26. Jalil V, Khan M, Haider SZ, Hussain R, Qureshi H, Gilani MA. Investigation of the antibacterial, anti-biofilm, and antioxidative effect of Piper betle leaf extract against Bacillus gaemokensis MW067143 isolated from dental caries, an in vitro-in silico approach. Microorganisms. 2022;10(12):2485.
27. Soffritti I. Investigating the role of environmental and human microbiome in health and disease: focus on pathogen's monitoring and control. 2022.
28. Di Stefano M, Polizzi A, Santonocito S, Palazzo G, Giudice A. Impact of oral microbiome in periodontal health and periodontitis: a critical review on prevention and treatment. Int J Mol Sci. 2022;23(9):5142.
29. Jia G, Zhi A, Lai P, Wang G, Xie H, Wei F, et al. The oral microbiota–a mechanistic role for systemic diseases. Br Dent J. 2018;224(6):447-55.
30. Acharya A, Chen T, Chan Y, Alonaizan FA, Wang X, Joud H, et al. Species-level salivary microbial indicators of well-resolved periodontitis: a preliminary investigation. Front Cell Infect Microbiol. 2019;9:347.