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Salivary Microbiome in Caries Research: From Classical Concepts to Future Directions

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Abstract

Dental caries is a highly prevalent biofilm-mediated disease arising from complex interactions among oral microorganisms, diet, saliva, and host factors. Saliva is increasingly recognised as a practical and informative matrix for characterising oral microbial ecology and identifying biomarkers of caries risk. This narrative review synthesises historical and contemporary evidence on the salivary microbiome in caries research, with three aims: (a) to highlight early yet foundational work on salivary mutans streptococci and host factors, (b) to critically examine similarities and differences among recent 16S, metagenomic, and multi-omics studies linking salivary communities to caries, and (c) to discuss key future directions and translational potential. Early culture-based studies established strong associations between high salivary *Streptococcus mutans* counts, low pH, and elevated caries experience, supporting saliva-based microbial screening as a feasible risk assessment tool. More recent microbiome-era work reveals broader salivary dysbiosis in caries, involving shifts in community composition, functional pathways, and host–microbe interactions, although findings beyond *S. mutans* vary across age groups, populations, and methodologies. Metagenomic and metabolomic analyses demonstrate that specific taxa, pathways, and salivary proteins and metabolites can serve as candidate biomarkers, and that salivary parameters, including flow rate and pH, significantly modulate microbial signatures. Nevertheless, progress is limited by methodological heterogeneity, reliance on cross-sectional designs, and under-representation of multi-kingdom and multi-omics integration. Future research priorities include protocol standardisation, longitudinal cohort studies, mechanistic multi-omics, identification of protective taxa, and application of machine learning to multi-dimensional salivary datasets. Ultimately, salivary microbiome research holds promise for precision caries prediction and minimally invasive, microbiome-informed prevention strategies that can be applied in personalised care as well as in wider public health programmes.

INTRODUCTION

Dental caries is still among the most prevalent chronic diseases globally, affecting both children and adults and generating major health and economic impacts [1,2]. Historically, cariology centred on the role of particular acid-producing and acid-tolerant bacteria—most notably *Streptococcus mutans*—as the principal causative agents of enamel and dentine demineralisation in the presence of fermentable sugars [3,4]. In the last two decades, however, developments in sequencing methods and bioinformatics have shifted this view from a single-pathogen model to an ecological concept of caries as a dysbiotic disturbance of the oral microbiome shaped by host and environmental factors [5,6]. Saliva occupies a central position in this evolving framework. It acts as a medium for microbial dispersal, a reservoir reflecting the broader oral microbial

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community, and a key determinant of local ecological conditions through its buffering capacity, antimicrobial proteins, and flow [4,8,9]. Its non-invasive collection and suitability for repeated sampling make saliva an attractive substrate for epidemiological studies, longitudinal monitoring, and development of chairside diagnostic tools [10,11]. Subsequently, salivary microbiome research has expanded rapidly, encompassing 16S rRNA profiling, metagenomics, metaproteomics, and metabolomics to explore how salivary communities and host factors relate to caries risk, severity, and response to interventions [4, 5,12-14].

This narrative review synthesises the development of salivary microbiome knowledge in caries research, beginning with early, still influential studies linking salivary mutans streptococci and host factors to caries, and then evaluating more recent microbiome and multi-omics work in both children and adults. Particular attention is paid to consistencies and discrepancies across studies regarding caries-associated taxa, functional pathways, and host–microbe interactions, and to methodological features that may account for divergent findings. Finally, key research gaps and future directions are discussed, with emphasis on translational opportunities for salivary microbiome–based risk stratification, precision prevention, and public health implementation.

Classical perspectives: Saliva, mutans streptococci, and host factors

Early caries microbiology emphasised the central role of mutans streptococci and lactobacilli as "specific" cariogenic agents, supported by their acid tolerance, acid production, and ability to form extracellular polysaccharide-rich biofilms on tooth surfaces [3,15]. Salivary studies used selective culture methods and chairside tests to quantify *S. mutans* levels, demonstrating that very high salivary counts in preschool children predicted subsequent caries increment and could identify high-risk individuals before overt lesions developed [16,17]. These findings underpinned the use of salivary mutans streptococci tests in some risk assessment protocols and reinforced the conceptual link between salivary microbial load, sugar exposure, and caries experience [18,19].

In parallel, the physicochemical characteristics of saliva came to be viewed as key determinants of caries susceptibility. A more acidic salivary environment and diminished flow favour bacterial adhesion and heightened metabolic activity of cariogenic organisms, whereas increased salivary flow and stronger buffering capacity help neutralise acids and promote remineralisation, thereby maintaining oral health [8,20]. Salivary proteins—for instance immunoglobulins, mucins, antimicrobial peptides, and enzymes—were also implicated in modulating microbial colonisation, biofilm structure, and host–microbe equilibrium [9, 21]. Taken together, these studies positioned saliva not only as a key ecological driver of caries risk but also as a convenient and informative sample source, providing the groundwork on which current salivary microbiome research has been built [5,10].

From single pathogens to salivary microbiome ecology

High-throughput 16S rRNA gene sequencing opened the way to detailed profiling of salivary bacterial communities without reliance on culture-based methods, revealing a much richer microbial diversity than previously recognised [22,23]. Early investigations using these approaches compared salivary community structures between individuals with differing caries experience or oral hygiene status, and frequently reported shifts in both composition and diversity [24,25]. In many of these studies, saliva from caries-active subjects was enriched in *Streptococcus*, *Veillonella* and various anaerobic taxa, whereas caries-free saliva more often contained higher proportions of *Neisseria*, *Haemophilus* and other taxa typically linked to oral health [13,26]. Later studies extended and refined these findings across different age groups. Among children, several reports identified particular salivary genera and species associated with early childhood caries, although the specific taxa differed between study populations [14,27]. In adults, salivary communities related to active dentine or root caries showed a more pronounced dysbiosis, with increased representation of proteolytic and anaerobic organisms, implying that caries progression in permanent dentitions may involve a broader functional repertoire than carbohydrate metabolism alone [28,29]. Despite variation between studies, a common ecological pattern emerges: caries tends to coincide with a transition from a diverse, functionally balanced salivary microbiome to one dominated by acid-producing, acid-tolerant and often proteolytic taxa under conditions of frequent sugar exposure and compromised host defences [5,13,26].

Salivary versus site-specific microbiomes

A long-standing question is how well saliva represents site-specific biofilms at caries-prone surfaces. Caries is fundamentally a local process, with lesion-associated plaque often exhibiting steep ecological gradients and distinct micro-niches not necessarily mirrored by saliva [5,30]. Studies comparing salivary and dentinal microbiomes in children with caries indicate that dentine lesions are dominated by particular anaerobic and proteolytic taxa, while saliva captures overlapping but less extreme compositional shifts [31,32]. These findings suggest that saliva serves as an integrative but somewhat diluted reflection of local dysbiosis, useful for screening and risk assessment but less suited to precise lesion-level characterisation [13,28].

Systematic work synthesising microbiome studies that measured *S. mutans* within broader communities has, however, shown that the association between *S. mutans* abundance and caries remains robust even when only pooled plaque or saliva samples are analysed [33]. This implies that, at least for key species with strong ecological footprints, salivary sampling can capture clinically relevant signals despite its non-localised nature [5,16]. Nevertheless, interpretations must consider that some dysbiotic changes are site-specific, and that combining salivary with plaque or dentinal data may offer a more complete picture of caries-associated ecology [26,34].

The persisting and evolving role of *S. mutans*

Recent microbiome-era research has partly rehabilitated, rather than discarded, the classical emphasis on *Streptococcus mutans*. A synthesis of oral microbiome and caries studies found that *S. mutans* was the only species consistently associated with caries in adults when saliva samples were analysed, while a broader set of taxa showed associations in plaque and in children [26]. A 2025 systematic review focusing on *S. mutans* within microbiome datasets similarly reported that higher prevalence and relative abundance of *S. mutans* reliably tracked with caries status across heterogeneous methodologies and populations [33]. These findings support the view that *S. mutans* remains a central member of the cariogenic consortium, even if not solely responsible for disease [5,26].

Contemporary reviews of *S. mutans* biology highlight its unique combination of acidogenicity, aciduricity, extracellular polysaccharide synthesis, and biofilm-forming capacity, all of which confer competitive advantages in low pH, sugar-rich environments [3,4]. Genome resequencing and comparative

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genomics have also revealed substantial strain-level variation in virulence traits, suggesting that salivary detection at the species level might overlook important functional heterogeneity relevant to individual risk [35,36]. Thus, while *S. mutans* remains a key target in salivary microbiome-based risk assessment, future work may need to incorporate strain- or gene-level markers to improve specificity and predictive performance [26,33].

Beyond S. mutans: broader salivary dysbiosis

Beyond *S. mutans*, a wide range of other salivary microbial taxa have been linked to caries in both paediatric and adult populations, although the evidence across studies remains variable and inconsistent [26]. Narrative and systematic reviews collating taxa across studies have identified species such as *Scardovia wiggsiae*, *Streptococcus sobrinus*, *Actinomyces* spp., various *Prevotella* and *Veillonella* species, and certain *Neisseria*, *Haemophilus*, and *Rothia* taxa as differentially abundant between caries-active and caries-free individuals [25,29,37]. For example, metagenomic analyses of children with varying caries severity have reported increased relative abundance of *Prevotella*, *Veillonella*, *Actinomyces*, and *Mogibacterium* in high-caries groups [13,27].

However, not all studies converge on the same non-mutans taxa, and some report minimal diversity differences between caries and non-caries salivary microbiomes, instead highlighting specific shifts in relative abundance of selected species [12,24]. Such inconsistencies likely reflect differences in sampling strategies, sequencing platforms, read lengths, reference databases, and analytic thresholds, as well as population-level differences in diet, fluoride exposure, and socio-behavioural factors [26,38]. Consequently, while a picture of broader salivary dysbiosis is emerging, definitive consensus on a stable panel of non-mutans caries-associated taxa has yet to be achieved [26,29].

Salivary environment, host factors, and multi-omics

Salivary microbiome patterns cannot be fully understood without considering the host environment in which these communities reside. Recent studies that integrate microbiome profiles with salivary clinical parameters show that factors such as diet, salivary pH and flow, fluoride exposure, and previous caries experience exert a significant influence on the overall composition of the oral microbial community [12,24,38]. High intake of sugars and other fermentable carbohydrates is closely linked to lower microbial diversity and a community shift toward acid-producing taxa such as *Streptococcus*, and mediation analyses indicate that changes in the oral microbiome partially account for the association between sugar consumption and reduced salivary Ph [38]. Salivary pH and flow rate themselves influence microbial composition, while fluoride application exerts a suppressive effect on the abundance of many genera, consistent with its known antimicrobial properties [20,38].

Multi-omics approaches have begun to reveal the functional consequences of these ecological shifts. Metagenomic and metaproteomic studies in children have shown that some salivary bacterial species and pathways differ between caries-active and caries-free groups, and that salivary proteins such as lactoferrin, mucins, matrix metalloproteinases, cystatins, immunoglobulins, and S100 proteins are differentially expressed in relation to caries status [12,39]. Parallel metabolomic analyses in severe early childhood caries have identified altered salivary metabolites and pathways—including amino acid, nucleotide, and transport-related metabolism—that correlate with specific salivary taxa and may serve as biomarker candidates [14,27]. These findings underscore that caries-associated salivary dysbiosis is fundamentally a functional, not merely taxonomic, phenomenon involving complex host–microbe metabolic interactions [13,26].

Virome, mycobiome, and non-bacterial components

Most salivary microbiome work has focused on bacteria, but emerging studies highlight the importance of non-bacterial community members in caries. Studies examining the "salivary virome" in children with severe caries have shown that viral communities, including bacteriophages, differ between caries-active and caries-free subjects, suggesting that phage–bacterium interactions can influence both the abundance and metabolic behaviour of oral bacteria [33]. Metagenomic analyses of phageomes associated with early childhood caries also suggest distinct ecological and functional signatures, pointing to potential contributions of viruses to caries susceptibility and progression [27].

Fungal communities, particularly *Candida* species, have long been implicated in caries, especially in high-sugar, low-pH environments, but comprehensive, standardised "multi-kingdom" salivary studies are relatively scarce compared with bacterial-focused work [26]. Preliminary evidence suggests that interactions among bacteria, fungi, and viruses in saliva may influence biofilm robustness, acidogenicity, and host immune responses, but systematic exploration of these relationships remains a key research gap [13,26]. Addressing this gap will require multi-kingdom sequencing, integrative analysis, and experimental validation of cross-kingdom interactions in relevant caries models [34].

Methodological evolution and study heterogeneity

Methodological advances have both enriched and complicated the interpretation of salivary microbiome–caries research. Earlier 16S rRNA sequencing studies mostly used short-read platforms (e.g., Illumina MiSeq) targeting variable regions such as V3–V4, providing genus-level resolution but often limiting species-level discrimination and potentially misclassifying closely related taxa [23,24]. Differences in DNA extraction methods, primer sets, sequencing depth, and bioinformatics pipelines introduced additional variability, making cross-study comparisons challenging [22,26].

More recent work utilising full-length 16S rRNA sequencing with long-read platforms, such as Oxford Nanopore Technologies, has demonstrated improved species- and subspecies-level resolution from salivary DNA, enabling more precise detection of clinically relevant taxa [40]. Comparative evaluations show that full-gene approaches can reveal species overlooked by conventional short-amplicon methods, underscoring how technical choices shape apparent associations between salivary microbes and caries [40]. Shotgun metagenomics, while more costly and data-intensive, offers the added benefit of functional insight, allowing identification of genes and pathways associated with carbohydrate metabolism, acid production, and stress responses in caries-associated salivary communities [27,41]. Methodological heterogeneity, however, continues to limit the ability to synthesise findings quantitatively across studies, reinforcing the need for protocol standardisation and transparent reporting [26,38].

Salivary microbiome as a biomarker source

One of the most promising translational applications of salivary microbiome research is the development of biomarkers for caries risk prediction, early detection, and monitoring [26]. Classical work showed that extremely high salivary mutans streptococci counts predict future caries increment in young children, albeit with moderate sensitivity and specificity, supporting their use as

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early microbiological risk indicators [16]. Contemporary studies seek to enhance predictive performance by leveraging multi-taxa patterns, diversity metrics, functional pathways, and host parameters in multivariate models for caries risk stratification [12,28,41]. Metagenomic analyses of childhood caries have identified novel bacterial markers, functional pathways, and gene sets related to carbohydrate metabolism and biofilm formation that discriminate between children with varying caries severity [13,41]. Concurrent metabolomics and metaproteomics have revealed salivary metabolites and proteins that correlate with both caries status and specific microbial taxa, suggesting the feasibility of multi-omics biomarker panels [12,39,42]. Nevertheless, most candidate markers require validation in independent, larger cohorts and evaluation of clinical utility, including cost-effectiveness and ease of integration into existing care pathways [26,28].

Future methodological directions

Future directions in salivary microbiome and caries research increasingly emphasise moving beyond descriptive taxonomic comparisons toward mechanistic and clinically actionable work [26]. A key priority is to harness the practicality of saliva—non-invasive, easy to standardise, and suitable for repeated sampling—to support longitudinal, multi-site studies that can clarify causality and temporal dynamics in caries development [11,28]. By combining stronger study designs with modern sequencing platforms and more sophisticated analytical workflows, future research will be better positioned to separate microbial patterns that genuinely precede lesion formation from those that merely mirror established disease, thus enhancing the clinical utility of salivary biomarkers [38,41].

A key priority moving forward is the establishment and widespread use of rigorously standardised protocols for saliva collection, handling, and sequencing across different centres and populations [22]. Current variation in factors such as stimulated versus unstimulated saliva, timing in relation to toothbrushing or food intake, and storage conditions makes it difficult to compare findings between studies and limits the feasibility of formal meta-analyses [23,24]. Aligning these pre-analytical and analytical procedures—including agreement on DNA extraction methods, primer sets, and bioinformatic pipelines—would facilitate data pooling, support large-scale analyses, and improve confidence in identifying robust microbial and functional markers of caries risk that are reproducible across diverse settings [26,38].

Longitudinal cohort studies, particularly those following infants, preschool children, and adolescents, represent another crucial direction for advancing salivary microbiome research [7, 28]. Tracking participants from a caries-free state through the onset of initial lesions and into phases of progression or arrest can uncover temporal trajectories in salivary community structure and function that are invisible in cross-sectional snapshots [41]. These longitudinal designs also allow investigators to examine how modifications in diet, fluoride exposure, oral hygiene practices, and dental treatments reshape the salivary ecosystem and influence the probability of developing new lesions, thereby helping to separate causal pathways from secondary changes and to detect early microbial shifts that could serve as practical warning signals [26,38].

Multi-omics integration represents an additional, important avenue for deepening mechanistic insight. While 16S rRNA surveys describe which bacteria are present, shotgun metagenomics, metatranscriptomics, and metabolomics can indicate what those microbes are doing, including carbohydrate metabolism, acid production, biofilm formation, and stress responses in the salivary environment [33,41]. Combining microbial profiles with salivary proteomics—encompassing host immune factors, enzymes, and peptides—could reveal functional networks linking microbial activity, host defence, and biochemical milieu to caries onset and progression, ultimately identifying candidate pathways for targeted ecological therapies [12,39].

Future translational and equity-focused directions

The search for beneficial or protective taxa within the salivary microbiome is also likely to intensify. Rather than focusing solely on depletion of classic cariogenic organisms such as *S. mutans*, researchers are increasingly interested in organisms that consume lactic acid, produce alkali (for example via arginine or urea metabolism), or otherwise stabilise pH and inhibit overgrowth of harmful species [5,13]. Recognising and defining these potentially protective taxa, as well as clarifying their ecological functions, could underpin the development of next-generation probiotics, synbiotics, or other microbiome-supportive strategies that foster ecosystem resilience instead of focusing solely on the elimination of specific pathogens, in line with modern ecological concepts of caries [26,43].

A further key avenue for future work is the use of machine learning and related advanced analytical methods applied to rich, multidimensional salivary datasets. Predictive models that combine microbial composition, diversity metrics, functional pathway data, and host or behavioural variables (for example, sugar consumption, fluoride exposure, and socioeconomic indicators) have the potential to generate robust caries risk scores that surpass the performance of conventional predictors alone [38,41]. These approaches will need rigorous external validation and careful consideration of challenges such as overfitting, transparency, and bias, but they could ultimately form the basis of practical decision-support tools integrated into routine clinical care and public health settings [26].

Translationally, salivary microbiome research is well positioned to feed into the development of simple, low-cost, and minimally invasive diagnostic tools for caries risk assessment and monitoring [10,11]. Point-of-care platforms that detect combinations of microbial markers, functional genes, or host–microbe signatures could be deployed in schools, primary care clinics, and community settings to identify high-risk individuals before lesions become extensive, especially in resource-limited regions where access to restorative treatment is constrained [28,41]. Successful implementation of such tools will depend not only on technical performance but also on considerations of cost-effectiveness, ease of use, and integration with preventive interventions such as fluoride varnish applications, dietary counselling, and tailored recall intervals [26].

Finally, future work will need to address equity and global health dimensions by ensuring that salivary microbiome datasets and derived tools reflect the diversity of diets, cultural practices, and health systems worldwide [2]. Many existing studies are concentrated in high-income settings, yet caries burden is often highest in low- and middle-income countries that have differences in nutrition, fluoride access, and oral health care, all factors which can create distinct microbial and ecological contexts [6,7]. Expanding research to under-represented populations, co-designing interventions with communities, and evaluating microbiome-informed screening and prevention strategies in real-world conditions will be essential steps to realise the full potential of salivary microbiome science in reducing global caries inequalities [2,26].

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CONCLUSION

Research on the salivary microbiome in relation to dental caries has progressed from early, culture-based studies of mutans streptococci and salivary host factors to complex multi-omics analyses of bacterial, viral, fungal, and host components. Classical work established that high salivary *S. mutans* counts, low pH, and reduced flow are robustly associated with elevated caries risk, legitimising saliva as a clinically relevant matrix for risk assessment. Microbiome-era studies have broadened this picture, demonstrating that caries is typically accompanied by salivary dysbiosis, characterised by shifts in community composition, functional pathways, and host–microbe interactions that extend beyond single species. Despite variability across age groups, populations, and methods, several patterns recur: *S. mutans* remains a consistent salivary marker of caries; multiple genera show context-dependent associations; salivary parameters and diet significantly shape microbial signatures; and integrated metagenomic, proteomic, and metabolomic data can reveal candidate biomarker panels for early detection and personalised prevention. However, methodological heterogeneity, reliance on cross-sectional designs, limited multi-kingdom analyses, and under-representation of diverse populations constrain current understanding and translational application. Addressing these limitations through standardised protocols, longitudinal multi-omics cohorts, and advanced analytical approaches—including machine learning—will be critical to move from associative observations to mechanistic insight and evidence-based tools. Looking ahead, salivary microbiome research holds substantial potential to support precision oral health strategies, including minimally invasive, point-of-care diagnostics and microbiome-informed preventive interventions tailored to individual and population risk profiles. If coupled with efforts to ensure equity, accessibility, and integration into existing health systems, this work could meaningfully contribute to reducing the global burden of dental caries and improving oral health across the life course.

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