

# The Role Of Microorganisms In The Development Of Caries

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## Abstract

According to the World Health Organization, half of the world's population is infected with caries. In 2021, the population of the United States spent \$162 billion on dental care, and this amount is increasing every year. Dental caries is a noninfectious but preventable and treatable disease and the cause of its occurrence and development. Streptococcus, Lactobacillus, Actinomyces and Candida generation and the cariogenic properties of microorganisms present in the oral cavity have been studied extensively, but which of the microorganisms found in caries are cariogenic, the mechanism of caries formation, and the specific blocking of GTF enzymes are not understood. Therefore, conducting new research on the importance of microorganisms in caries and organizing existing data are important problems facing modern science. It is a sad situation that dental caries is widespread in developing countries in the form of early childhood caries in young children. In this article, we will try to collect information about caries and ECC microorganisms from the NCBI, Scopus and Google Scholar databases.

**Keywords:** pathogen microorganisms, biofilm, dental caries, oral health, ECC, gtf.

## Introduction

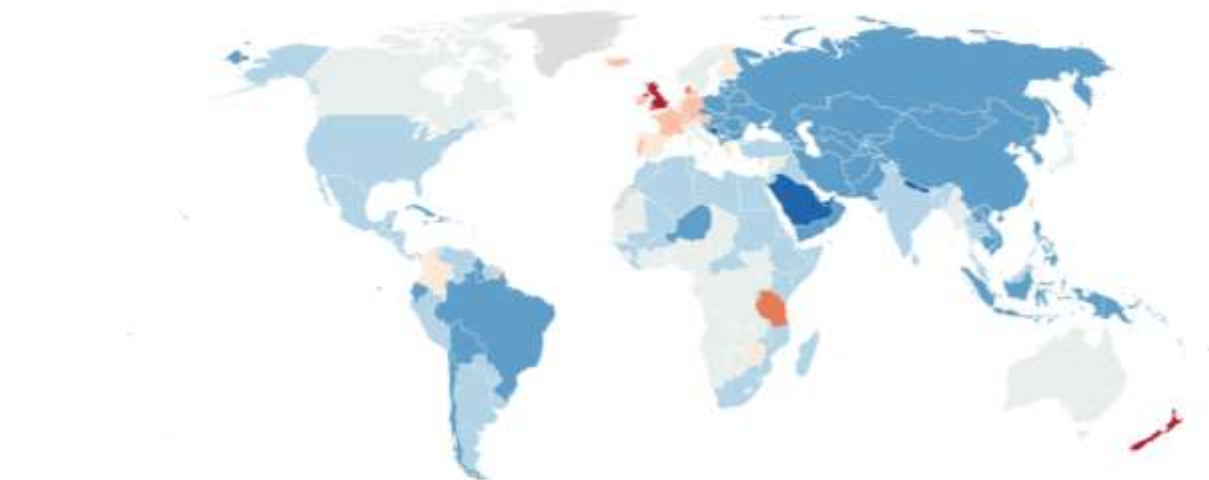
The human mouth contains 774 bacterial species. Of these, 58% have official names, 16% have been discovered but not named, and the remaining 26% are phylotypes not yet isolated from the mouth (1). Caries is a multifactor disease caused by microorganisms, malnutrition, the environment, genetics, and other factors (2). Under the influence of these factors, dental caries can occur because of changes in the permanent microflora in the oral cavity, especially in the teeth, and because of the dysbiosis effect of the changed microorganisms on a person (3). According to the World Health Organization, in 2022, more than 2 billion adults will be diagnosed with permanent dental caries, while 514 million children will be diagnosed with untreated dental caries (4).

Figure 1

## Global Oral Health Countries Profile

Prevalence of untreated dental caries in children aged 1 to 9 (%)

< 20 20-25 25-30 30-35 35-40 40-45 45-50 ≥ 50



Source: The choropleth was created basing WHO statistics in 2022. - Created with Datawrapper

Figure 1. Untreated caries is characterized as a lesion in a pit or fissure or on a smooth tooth surface that has an unmistakable cavity, weakened enamel, or a detectably softened, floor or wall (coronal caries) or feels soft or leathery to probing (root caries) The above Choropleth map was created based on statistics from 191 countries from the studies of the World Health Organization and the Institute of Health Metrics and Evaluation (IHME) Global Burden of Disease Study 2019 (GBD2019) (4, 5) . To view more complete statistics visit; [Global\\_database\\_2022](#)

Early childhood caries (ECC) is a disease that damages teeth in children under 72 months. It is caused by caries from internal and external factors on primary teeth, leading to tooth damage, fillings, and loss (5). ECC is a multifactor disease similar to caries, the origin of which is mainly caused by microorganisms, fermentable carbohydrates, and hereditary factors (6). A report presented at the 2018 International Conference on Pediatric Dentistry on Early Childhood Caries concluded that 72 studies published between 1998 and 2018 summarized the results and found that, accordingly, early childhood caries ranged from 12% to 98% in children (7). ECC is not given sufficient attention by parents due to the fall of primary teeth in young children, resulting in a decrease in the child's appetite due to pain during feeding time, along with aesthetic effects on the child that cause it to lag in development, causing the child's innate immunity to drop (8)(9). Severe ECC can result in jaw dysplasia, chewing dysfunction, temporomandibular problems, and abnormal pronunciation (10). In addition, the surgical procedure performed in a severe form of ECC causes psychological trauma to the child (11).

### The importance of microorganisms in the appearance of caries

The oral cavity was in direct contact with the external environment, and protection from sudden changes in the external environment was required for the development of microorganisms there. Approximately 1,000 microorganisms, exopolysaccharides and various other organic and inorganic substances are involved in the formation of biofilms by accumulating in tooth surfaces and cracks(12). As a result of the long-term presence of biofilm on the surface of a human tooth, the resistance of pathogenic bacteria in its composition to the human immune system and the external environment of microorganisms increases, causing diseases of caries, periodontitis, and gingivitis not only in the tooth but throughout the oral cavity(13).

Due to the mould of food residues in the oral cavity after eating, they metabolize the monosaccharide and disaccharide carbohydrates contained by some microbes (e.g.) on the enamel surface to form an acid that demineralizes teeth and causes cavities (14, 15). These cavities are Streptococcus mutans, considered favourable for the deposition of other microorganisms (Actinomyces, Bifidobacterium, Eubacterium, Lactobacillus, Parvimonas, and Rothia) (16), and some of them, for example, bacteria of the Lactobacillus order, cause the stronger development of caries or the development of other cariogenic bacteria (17). Three main factors in the development of caries are teeth, carbohydrates, and microorganisms. Although their interactions are considered important, even more factors influence the formation of caries, but the general mechanisms of their occurrence have not been fully revealed (14). The

formation of biofilms by microorganisms is crucial in the development of caries and its associated properties (18). This poses a challenge in controlling and treating microorganisms in diseases related to biofilms (19).

### Streptococci

Streptococci are the main cariogenic pathogens that cause caries in the tooth, the most common being *Streptococcus mutans* and *Streptococcus sobrinus* (20, 21). The cariogenic properties of *S. mutans* and *S. sobrinus* are ensured by sugar metabolism, adhesion, resistance to an acidic environment, signaling, competence, and bacteriocins and genes protecting against the oxidative and immune systems of the host organism in their genomes (21). *Streptococcus* species play an important role in forming biofilms and creating a favourable environment for other bacteria, leading to the development of caries (22). While the biofilm acts as a substrate for other cariogenic bacteria, it protects them from the external alternative environment (23) and reduces the pH of the dentin layer from 6.0–7.4 to 5.4 (24). Biofilm formation consists of three stages, and with tooth cleaning, mucin, glycoproteins, proline-rich acidic proteins, sialic acid, bacterial cell residues, and other exoproducts adhere to tooth enamel and form a pellicle (23). *Streptococcus sanguis*, *Actinomyces viscosus* and other similar bacteria colonize the pellicle layer under the influence of carbon sources, pH and osmotic concentration (25). In the final step, *S. mutans* attaches to the surface of primary colonized bacteria (26). Streptococci attach to the tooth surface through the glucan-binding region of the enzyme glucosyltransferase (GTF) in the cell wall, antigen I/II and glucan-binding proteins (21). According to research, the glucan layer delays the neutralization of acids produced by cariogenic bacteria and causes tooth decay (27). Several different GTFs are required for glucan formation (21). GTF-S synthesizes soluble dextrin with an  $\alpha$ -(1-3) bond, and GTF-I synthesizes insoluble D-mutan with an  $\alpha$ -(1-6) bond (20, 28). According to previous research, *S. mutans* should work in cooperation with *S. sobrinus* to rapidly produce glucan (21).

Representatives of the genus *Streptococcus* produce lactic acid by breaking down glucose and fructose in food residues (29). At the same time, other bacteria that colonize biofilms, such as streptococci, can produce acid that lowers the pH level on the enamel surface (30, 31). A decrease in the pH level is one of the main factors in the demineralization of the enamel layer of the tooth (32).

*S. sobrinus* is often found together with *S. mutans* in severe cases of caries (33). *S. sobrinus* uses glucans to adhere to the tooth surface (21). In particular, GTFs secreted by *S. mutans* promote the adhesion of *S. sobrinus* to the tooth surface (34, 35). The Medical University of Lublin in Poland conducted a study in 2022, which showed that *S. sobrinus* contributes to the beginning of dental caries or the cariogenic process (36). According to other studies, *S. mutans* phenotypically mainly secretes GTF-S, while *S. sobrinus* synthesizes GTF-S and GTF-I (20).

In an animal model of biofilm formation, the activity of the GTF enzyme under slow growth conditions of *S. sobrinus* was mainly composed of GTF-S (28), while under fast growth conditions, the ratio of GTF-I increased and produced more insoluble dextran (28). Based on these studies, Conrads G. and others found that *S. sobrinus*, together with *S. mutans*, participates in the destruction of the smooth surface of the tooth (21).

The "conditional competition" between them is important for causing tooth root caries by streptococci. Due to caries-causing factors, the increase in *S. mutans* in the biofilm showed a decrease in *S. sanguinis* (37). In vivo and in vitro studies have observed the occurrence of tooth root caries by disrupting the mutual balance of *S. mutans* and *S. sanguinis* species in the tooth (38-40).

### Lactobacilli

Lactobacilli are gram-positive, facultative anaerobic bacteria (41). When a person is born, the oral cavity becomes germ-free (42) and has shaped in infants under one year (9). Until 1950, lactobacilli were seen as the main microorganisms for dental diseases; then, in the literature, *S. mutans* occupied dominance (43, 44). Lactobacilli require three factors for stable colonization of teeth: a source of glucose, free from mechanical influences, and low pH conditions (45). This condition is fully manifested in the period of deep caries and causes lactobacilli to develop caries in the dentine layer of the tooth. Lactic acid produced by lactobacilli, similar to other organic acids, causes tooth demineralization (16). The cell surface of lactobacilli contains S-layer proteins with a special crystal structure, and these proteins provide hydrophobicity on the cell surface of lactobacilli, making them resistant to high ion and pH changes (46). Genes that produce GTF enzymes are also found in lactobacilli, such as *S. mutans*. This means that lactobacilli produce glucan throughout the biofilm synthesis process (47). In situations of caries lacking *S. mutans*, lactobacilli can also be identified (48).

*L. fermentum* is one of the most common lactobacilli in caries, and its presence during the disease indicates a high caries index (48). *L. casei*, *L. rhamnosus*, *L. gasseri*, and *L. crispatus* species are most common in the period of caries (49).

Lactobacillus is found in mothers of children of different ages.

### Table 1

Bacterium's scientific name	From the extracted teeth of children (ages 3-5) with a severe ECC	From the saliva of caries-prone children (ages 2-5).	From dental biofilms of children (ages 2-6) with severe form of ECC	From the Saliva of mothers who have caries	Mother and child pairings (ages 2–5) at risk for caries.	Species are dominant in dental caries in adults
<i>L. fermentum</i>	+	+	+	+	+	+
<i>L. casei/paracasei</i>		+	+		+	+
<i>L. plantarum</i>	+				+	+
<i>L. rhamnosus</i>	+	+			+	+
<i>L. mucosae</i>		+			+	
<i>L. oris</i>		+		+		
<i>L. salivarius</i>	+	+		+	+	+
<i>L. vaginalis</i>				+		
<i>L. gasseri</i>		+	+	+		+
<i>L. brevis</i>	+					
<i>L. buchneri</i>	+					
References	51	52	53	48	54	55

The table was compiled and completed based on Badet and Thebaud's 2008 research.

In the above table and several other studies, *L. casei/paracasei*, *L. fermentum*, *L. rhamnosus*, *L. gasseri*, *L. salivarius* and *L. plantarum* species have been identified as the dominant species in caries of adults and children, including ECC (45, 50).

Probiotic components and extensive research have been conducted on bacteria from the genus *Lactobacillus* in fighting against various opportunistic pathogens, food pathogens (51), oral cavity diseases, and caries. For instance, it has been found that lactobacilli promote the development of *S. mutans* by secreting antibacterial compounds such as protein or hydrogen peroxide (52). In an additional study, children who drank milk supplemented with *L. rhamnosus* GG had a lower chance of developing cavities (53).

#### Actinomycetes

Actinomycetes are polymorphic microorganisms that account for a sizable portion of the oral microbiota in all mammals (54, 55) and play a significant role in the beginning phase of dental caries while participating in root caries (56-60). Actinomycetes *A. oris*, *A. naeslundii*, and *A. viscosus* are found in the oral cavity (61, 62). *A. viscosus* plays a significant role in root caries and early colonization of the tooth surface (62). Because the *A. viscosus* cell surface has a substantial adhesive property (63), it metabolizes starch, sucrose, glucose, and fructose from carbohydrates to produce acid and participate in tooth demineralization (64). *Actinomyces viscosus* and *Actinomyces naeslundii* produce the specific lectin substance  $\beta$ -N-acetyl galactosamine, which selects the attachment of *S. mutans* to the tooth surface, promoting caries development in *S. sanguis* (65, 66). *Actinomyces viscosus* and *Actinomyces naeslundii* produce the specific lectin substance  $\beta$ -N-acetyl galactosamine, which selects the attachment of *S. mutans* to the tooth surface, promoting caries development in *S. sanguis* (65, 66).

Experiments conducted by Chen Ma, Feng Chen, and others proved that actinomycetes are related to ECC (67), and two times more actinomycetes were found in children with congenital heart disease with ECC (68). Patients diagnosed with cardiac endocarditis

since 1939 have been diagnosed with actinomycetes from *A. graminis*, *A. bovis*, *A. viscosus*, *A. funkei*, *A. israelii*, *A. naeslundii*, *A. neuii*, and *A. odontolyticus*, which have been found to infect patients through dental diseases and other dental-related factors (69-74) .

## Candida

*Candida* belongs to the world of fungi and is one of the most common fungi in the environment and the human body, and it is important to create a polymicrobial biofilm in the oral cavity while causing candidiasis in humans (75, 76). *Candida* was found in 31% of people without caries in the oral cavity (77). They are a genus of medically important fungi (78, 79). *Candida* representatives are regarded as cariogenic pathogens due to their acidic nature, the production of acids by breaking down carbohydrates, the production of biofilms, and the production of collagenolytic proteinases (80) (81). Although their relation to caries has not been fully clarified, *Candida* has been isolated from root and dentin caries. *Candida* was detected in 56.1% of the caries-affected population (77). *C. albicans* is widely distributed throughout the oral cavity and can be found in any part of the oral cavity (82). In particular, among those with weak immunity, diabetes mellitus and immunodeficiency virus infection are common in elderly individuals and children (83-87). *C. albicans* hyphal structure and the ability to thrive in low pH environments are important in the caries process (88, 89), and oral bacteria such as *Streptococcus*, *Actinomyces*, and *Fusobacterium* are seen as interrelated in their interactions and nutrition during disease pathogenesis (90-94). Its significant amount causes microbial dysbiosis, creates conditions for the abundance of *S. mutans* in the dental biofilm in tooth root caries, and creates a cariogenic environment in the tooth root (95). *C. albicans* was found in 97% of children with dentinal caries (96). *Candida* has also been implicated in ECC, with a 2016 study by Xiao et al. showing young children infected with *C. albicans* (97). In other studies, *C. albicans* has been associated with an abundance of *S. mutans* in the dental microflora in severe ECC (98).

## Conclusion

According to the most recent microbiome study, a large number of bacteria, fungi, archaea, and viruses that have not been isolated and examined in the oral cavity have been discovered and live in a balanced condition with other bacteria and humans. As a result of the imbalance, numerous medical conditions occur in the human oral cavity. Caries and their types, such as early childhood caries, are difficult and expensive diseases to treat among oral cavity diseases, and their prevalence in developing countries is a major problem. Microorganisms have a critical role in the incidence and progression of caries. At a time when antibiotic resistance is increasing, it is essential to study the relevance of each bacterium in caries and its types in a specific way. As a result, it may be more beneficial to take advantage of protein compounds that block glucan-producing genes in microbes, control the actions of GTFs, and substitute antibiotics in the treatment of caries.

To that end, it is critical to determine the specific functions of microorganisms involved in caries, in addition to understanding their complete genome, and to investigate their dysbiosis and bios relationships to restore the environmental balance in caries.

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