

Whole Mouth Health

The Next Generation of Everyday
Prevention for Oral Health



Copyright

Copyright © 2018 Colgate-Palmolive Company.

Commercial use of this work, or any portion thereof, is strictly prohibited without the express written permission of the Colgate-Palmolive Company.

Noncommercial use of tables, figures, or excerpts of this work with proper attribution is allowed.

Except for the noncommercial use of tables, figures, or excerpts referenced here, reproduction, modification, storage in a retrieval system or retransmission, in any form or by any means, electronic, mechanical or otherwise, for reasons other than personal use, is strictly prohibited without prior written permission.

Unless otherwise indicated, all materials on these pages are copyrighted by the Colgate-Palmolive Company.

Preferred Citation:

Colgate-Palmolive Company (2018), *Whole Mouth Health: The Next Generation of Everyday Prevention for Oral Health*, Colgate-Palmolive Company publication, New York.

Colgate-Palmolive Company
300 Park Avenue
New York, NY 10022

Foreword

Colgate is committed to offering everyone a future to smile about. We hold that such a future requires taking responsibility to improve oral health in the world. To realize this goal, Colgate not only continuously works to develop best-in-class oral care technologies, but also creates and promotes a broad framework of education, increased awareness and prevention activities related oral health.

The evolving understanding of mouth biology, modern patient demands and advances in oral care technology drive the need to consider what will be “the next generation of prevention” to achieve and maintain oral health. Colgate believes this need is best met by a Whole Mouth Health approach that elevates the importance of oral prevention and of achieving better oral health outcomes for all patients.

We define “Whole Mouth Health” as a holistic approach that brings together perspectives and insights from oral biology, behavioral sciences, practice management and public health coupled with advanced oral care technologies. Whole Mouth Health takes into consideration a new paradigm of adopting patient-centered dentistry, which can help dental practitioners yield personalized and participatory care focused on patient empowerment and everyday prevention.

A partnership between leaders in dental, medical and behavioral sciences and Colgate developed this white paper, *Whole Mouth Health – The Next Generation of Everyday Prevention for Oral Health* White Paper. These experts informed both the structure and content of this white paper.

We hope this White Paper will inspire dental teams to take a proactive approach about prevention in practice and empower all their patients to achieve Whole Mouth Health.

Whole Mouth Health

The Next Generation of Everyday Prevention for Oral Health

Abstract

Clinical studies well document that patients can prevent tooth decay and periodontal disease when engaged in good oral hygiene practices.¹ However, the continued high global prevalence of these oral diseases, with accompanying significant public health burdens, demonstrates that toothbrushing alone for most people may be insufficient intervention to achieve and maintain good oral health. Therefore, patients' comprehension of oral hygiene must go beyond tooth cleaning goals. Indeed, a more effective approach to everyday prevention of dental diseases may be achieved by the adoption of a Whole Mouth Health model. This model is consistent with the recognition that oral health is a component of overall systemic health and well-being, the adoption of patient-centered dentistry as a best-practice, and the prioritization of improved patient outcomes via prevention. This new paradigm also would involve the development and use of next-generation therapeutic oral care products that leverage the chemistry and biology of the mouth, particularly the management of the oral microbiome and control of biofilms on all mouth surfaces—the teeth, tongue, cheeks and gums—to augment the established effectiveness of routine mechanical oral hygiene practices. By encompassing these definitions, concepts, behaviors as well as evidence-based oral care products, Whole Mouth Health can become a new and holistic standard to achieve and maintain oral health.

Contents

	Page
Oral Health Diseases Remain a Public Health Burden	1
Oral Health is Integral to General Health and Well-being	2
Oral Health Requires Empowering All Patients	2
Oral Health Relies on Daily Self-Care	4
Oral Health Must Consider the Microbiome	5
Understanding the Oral Microbiome	6
Symbiotic and Dysbiotic Biofilms	6
Oral Health Needs Next-Generation Oral Care Products	7
Zinc: The Trace Element with Oral Health Benefits	8
Arginine: The Amino Acid with Proven Effects on pH and Biofilm Penetrability	9
Dual-Zinc plus Arginine: The Formulation with Abundant Oral Health Potential	9
Oral Health is Whole Mouth Health	10
References	11

Oral Health Diseases Remain a Public Health Burden

One in two: Around the world, about half of the population, some 3.5 billion people (48 percent), has tooth decay, periodontal disease or tooth loss.² This substantial public health burden has remained mostly static in the last 25 years,² despite known prevention practices and goals to reduce the impact of oral diseases by 2020 set by the World Health Organization (WHO), International Association for Dental Research and the Fédération Dentaire Internationale (FDI)³ World Dental Federation Assembly.

In 2012, WHO declared that almost all adults have dental caries, as did 60 to 90 percent of school-aged children.⁴ Untreated decay of permanent teeth is the most widespread noncommunicable global health condition – affecting about one in three people worldwide for a total of 2.52 billion, according to WHO’s 2015 Global Burden of Disease Study, which ranked 291 conditions.^{2,5} Decay of deciduous teeth affects 573 million globally (7.8 percent), severe periodontitis, 538 million (7.4 percent), and tooth loss, 276 million (4.1 percent) per the same 2015 study.² Notably, almost a fourth of adults older than 70 (23.7 percent) around the world lost some or most of their teeth.²

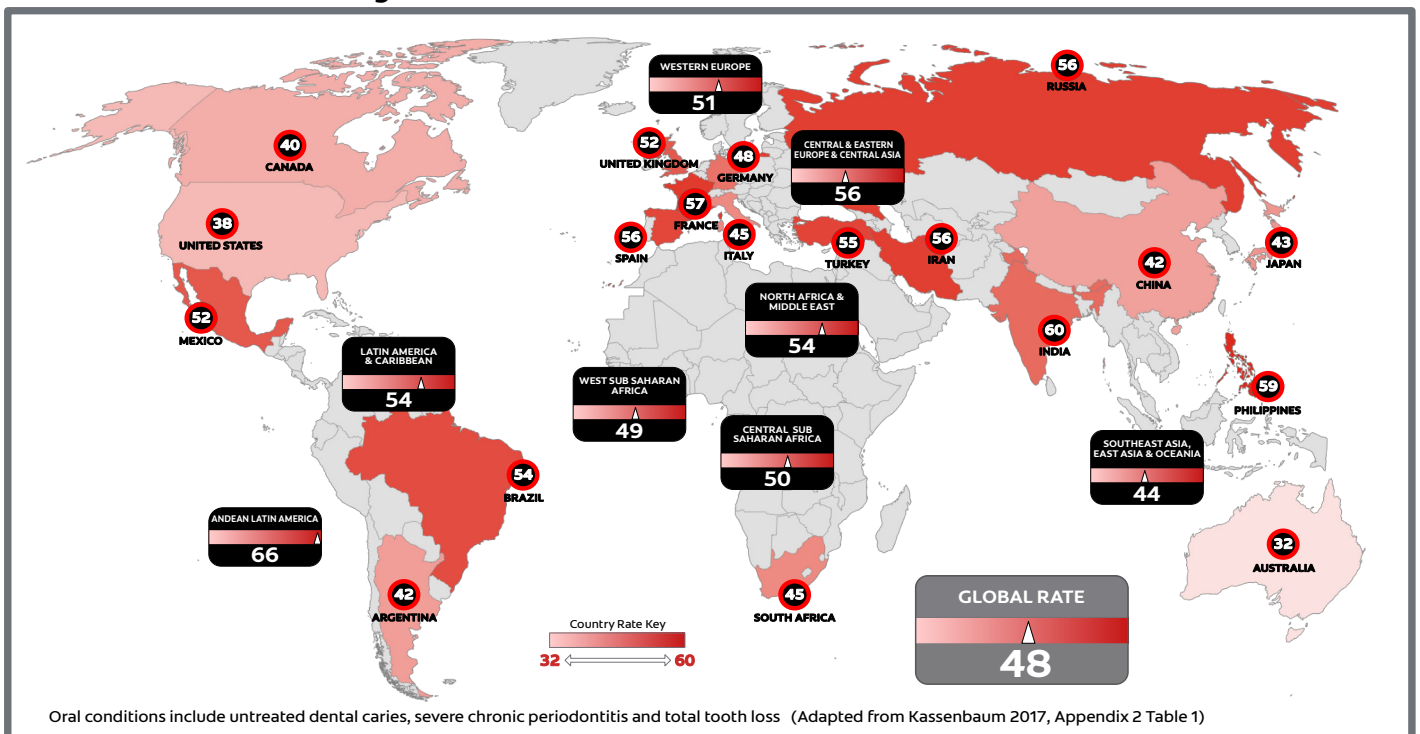
Because of these high rates, global health loss stemming from oral conditions outranks that of 34 types of cancer and is comparable to health loss due to schizophrenia, hypertensive heart disease and all maternal conditions together.² Country-level tallies of oral conditions vary because of several factors including social-economic circumstances, behavior and health risks, and deficiencies in data collection.^{5,6} While oral conditions are more prevalent in low- and middle-income countries, poor and disadvantaged population groups experi-

Prevention in Focus

The FDI notes that for reductions in oral conditions and the related expenditures, oral health must be fully integrated into disease prevention and health promotion strategies addressing entire populations who also require access to care.⁶

Recognizing what oral health is and its relationship to systemic health as well as having a strong focus on preventative oral health measures are vital to such initiatives and changing the oral disease continuum.

Age-standardized per-capita rate for all oral conditions (selected countries & regions)



ence higher oral health burdens in all countries, notes the WHO.⁵

The burden is particularly notable in children because early caries experience has life-long consequences. More than one in four surveyed countries, 27 percent of 209 nations, reported average DMFT* scores in 12 year-olds of greater than 3 to the WHO in 2015, some 245 million teeth.⁷ Regionally, DMFT ranged from a high 2.97 in South-East Asia to a low of 1.06 in Western Pacific in 2015,⁸ but SCI* scores reveal greater ranges in severity, such as 3.7 in Germany, 3.6 in the US, 4.3 in South Africa, 7.5 in Honduras and 7.1 in China.⁹

With such considerable oral disease burden, the impact on health care budgets is significant. Caries can account for 5 to 10 percent of healthcare budgets in industrialized countries.⁵ Worldwide dental diseases cost \$356.80 billion directly and another \$187.61 billion indirectly in 2015.¹⁰ Regionally, high-income North America, Australasia, Western Europe, High-income Asia Pacific and East Asia spend the most on dental expenses, while productivity losses related to dental disease are highest in Western Europe, Australasia, High-income North America, High-income Asia Pacific, and Central Europe.¹⁰ Because of such a substantial public health burden, modifying current approaches to preventive oral health care is necessary.

Oral Health is Integral to General Health and Well-being

In 2000, the U.S. Department of Health and Human Services stated oral disease and conditions can “...undermine self-image and self-esteem, discourage normal social interaction, cause other health problems and lead to chronic stress and depression as well as incur great financial cost. They may also interfere with vital functions such as breathing, food selection, eating, swallowing and speaking, and with activities of daily living such as work, school, and family interactions.”¹³

Moreover, untreated tooth decay and periodontal disease have follow-on health effects that can cause harm beyond the oral cavity. Tooth loss impacts the ability to eat and, hence, nutrition, which, for example, in children can be detrimental to growth.⁶ Periodontal disease can increase the

risk of complications in people with diabetes and may be associated with cardiovascular disease, gastrointestinal and pancreatic cancers, and, in pregnant women, with increased risk for preterm or low-birth-weight babies.⁶

These implications are addressed by the breadth of a new definition of oral health. In 2016, FDI received global approval and acceptance for their effort to bring precision and clarity to the diverse aspects of defining oral health, including related research, education, practice, policy and advocacy.¹² The definition states: “Oral health is multifaceted and includes the ability to speak, smile, smell, taste, touch, chew, swallow, and convey a range of emotions through facial expressions with confidence and without pain, discomfort, and disease of the craniofacial complex.”

“Whole mouth health is the absence of oral disease, which is good for your general health, too.”

—Mariano Sanz, MD, DDS
Professor of Periodontology,
Complutense University, Spain

Significantly, this definition also notes the importance of oral health as “a fundamental component of health and physical and mental well-being. It reflects the physiological, social, and psychological attributes that are essential to quality of life; [and] it is influenced by the person’s changing experiences, perceptions, expectations, and ability to adapt to circumstances.”¹² This specificity, while recognizing the different aspects of oral health, reinforces that oral health is not isolated from overall health.¹³ The description also enables dentistry to consider and support patients in their entirety while striving to preserve and maintain health.¹

Oral Health Requires Empowering All Patients

To succeed in improving patients’ adoption of preventive oral care, dental health professionals can and should go beyond providing just routine care and instead engage patients as coaches helping to motivate and optimize their behavior. This approach is a hallmark of patient-centered care (PCC), which is “providing care that is respectful of and

*The DMFT index records the number of decayed (D), missing (M) and filled (F) teeth (T) and is a measure used to calculate population-based estimates of oral health status, frequently among children aged 12 years. A point is added for each of the 32 adult teeth that is either decayed, missing or filled. The Significant Caries Index (SCI) represents an estimate of severity that averages the DMFT score for the third of a country’s population with the highest DMFT scores.¹¹

responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions.”¹⁴ PCC arose from the field of medicine and is gaining adoption as a best-practice in dentistry, as it’s foundation of good communication and shared decision making leads to high-quality care and improved oral outcomes in patients.^{15,16}

“We know that drilling and filling cavities is only relieving the symptoms, not really curing the disease. Prevention of caries and periodontal disease, or their progression, are the keys to maintaining health”

—Elmar Reich, DDS, DMD, PhD,
Professor,
ZAHNprofiLAXE-Praxis, Germany

PCC is fueled by what is known as the P4 approach to health care, so named for its four attributes: predictive, preventive, personalized and participatory.¹⁷ To be predictive, P4 uses data analytics and the resulting insights into health can lead to preventive care designed to improve patient health, rather than a sole focus on treating acute illness. Personalized and participatory care means a customized approach to informing the patient and enabling his or her decision making to optimize care.

“The modern patient wants to build a relationship with the dentist, hygienist, the assistant and receptionist, so he or she can ask questions and have open communication with the healthcare professional, whomever it is on the team”

—Lisa Knowles, DDS
Consultant and Founder,
Beyond 32 Teeth, USA

In adapting PCC for dentistry, several models have developed fundamental principles that address respectful interactions with patients for both their physical and emotional support and in consideration of how information is relayed, understood and acted upon.¹⁸ In general, these can be summarized as:^{19,20}

The disease context: What is the nature of the oral disease and how is the patient experiencing it?

The patient as a whole person context: How is the oral disease manifesting within the patient’s own biosocial circumstance?

The dental team-patient relationship: How is the empathy and compassion expressed by the dental team developing a long-term trusting relationship with the patient that will enhance decision-making?

The dental team-patient shared responsibility: How do both the dental team and patient conceptualize the patient’s oral health experience?

Understanding these principles helps dental practices enlist every employee as a member of a coaching team that can surround and engage a patient. Through thoughtful discussions and active listening, dental professionals can understand their patients better, meet their information needs and address related concerns while supporting their adoption of preventive care that can ultimately improve their oral health and well-being.

One key area of preventive care in dentistry is focused on supporting the patient to adopt and maintain an effective daily oral care routine. To address this, the dental team can use proven behavioral approaches to help their patients realize why they might want to change or optimize with their self-care routines to achieve and maintain oral health.²¹ This engagement can lead to patients setting and agreeing to commit to personal goals. Decision-making that resides with patients is a known motivator in aiding oral care compliance. Such positive communication outcomes lead to patient empowerment and feeling valued.¹⁶ Also, dental professionals who incorporate understanding, empathy and non-judgmental interactions into their conversations build a trusting relationship

What is P4?

P4 is named for its four attributes: predictive, preventive, personalized and participatory.

P4 medicine proactively uses systems biology and digital technology to gather and analyze data from and for clinical practice, with an emphasis on “quantifying wellness and demystifying disease for the well-being of the individual.”¹⁷ Because these explorations involve the calculation and modeling of health and disease at population and patient levels, practitioners can apply and translate the resulting learnings and insights to their individual patients. Moreover, because P4 considers the complex biological interactions underlying health and disease states, its practice is holistic, comprehensive and requires a focus on the entire patient, not just his or her symptoms.

with patients.¹⁵ Praise from dental professionals can help patients experience feelings of positive accomplishments, which acts as a reinforcement and links their time in the dental chair to rewarding interactions with the dental team, rather than feelings of dread or failure.

“An important aspect of behavioral reinforcement is having a reward directly linked to the behavior that you’re trying to reinforce. Like people realizing that tooth brushing takes away the fuzzy teeth feeling, which is the biofilm, and creates a clean mouth feeling, a reward itself that reinforces the desired oral care behavior”

—**Eleanor Putnam-Farr, PhD, MBA**
Assistant Professor of Marketing,
Rice University, USA

When successful, the use of PCC principles in chair-side connections helps patients become open to the dental team sharing and reinforcing prevention-based oral hygiene standards and behaviors, beyond the basic “tooth brushing conversation.” Helping patients to recognize that both hard (teeth) and soft (tongue, cheeks and gums) tissue surfaces play roles in the mouth’s complex ecosystem can increase their understanding of the value of preventative oral care. Dental professionals can further share information on oral health risks and disease, assist in real time with optimized techniques and instruct on oral care product benefits. They should also be prepared to provide further knowledge resources, such as a website link, as part of the visit. In this age of immediate information, many patients want instant access to explanations or statistics while pursuing answers to their questions.

Through this dialogue, the dental team can readily evaluate whether patients fully grasp the importance of a daily self-care routine, while also helping patients assess if they can execute related tasks with precision or completeness.¹ Additionally, patients should be helped to develop a fuller appreciation of the impact of behavioral factors on their oral health, such as the need to reduce dietary sugar, tobacco smoking or unhealthy use of alcohol or improve a poor diet.^{1,6}

In sum, such discussions help patients in two major ways: they become open to investing in their oral health every day to benefit their overall health and they improve their health literacy, which influences their ability to comply with guidance and engage in effective self-care practices.¹ Of note, these con-

versations and general PCC approaches should extend to all types of patients because of the strong effects that the “expert” information transferred by the dental team can have on future, long-term behavior.²²

When successful, patient-centric care results in dental patients who recognize the importance of oral health in their general well-being, comprehend how their overall health and behaviors influence their oral health, and adopt good preventive oral care as part of their everyday health.^{15,16} Long-term clinical studies document that PCC activities and communications combined with regular professional dental cleanings and effective plaque removal through improved self-care with appropriate oral care products do result in improved oral health.²³



Oral Health Relies on Daily Self-Care

Twice-daily tooth brushing, and maybe flossing, for some patients is just a cleaning behavior – food debris is cleared, teeth feel cleaned and breath is freshened. Their greater recognition of the role of daily oral care as prevention against common oral diseases may not be significant let alone their appreciation of its impact on their overall health and quality of life.

Patients’ daily self-care to manage oral biofilms, and simultaneously prevent common oral diseases like caries and periodontal diseases, should entail brushing with fluoride toothpaste supplemented by additional effective antimicrobial agents.²⁹ Toothpastes are ideal because of their ubiquitous availability in a variety of formulations devised to deliver actives and employ features patient expect, such as a pleasant taste, that also aid compliance.^{24, 25}

How to Engage Patients in their Daily Oral Health

- 1 Ask questions to elicit patient's personal oral health goals.
- 2 Provide one or two specific personalized recommendations.
- 3 Explain clear and perceptible benefits of these recommendations.
- 4 Work to gain the patient's commitment to his or her oral health goals.
- 5 Provide appropriate oral care product samples that relate to patient needs.

The evolution of toothpastes has incorporated ingredients to improve oral health and provide a variety of functions. Ancient toothpastes, dating to 5000 BC Egypt, varied in ingredients from powdered ox hooves' ashes to burnt eggshells to pumice to crushed oyster shells.²⁶ Modern toothpastes and mouthwashes add ingredients to help prevent or treat specific oral diseases and conditions beyond keeping teeth and gums clean, such as decreasing tooth sensitivity or enhancing tooth whiteness.²⁶

Fluoride has been added to toothpastes to help prevent dental decay since 1914.²⁶ Fluoride inhibits formation and halts progression of caries and helps reverse those at an early stage.²⁷ Successful studies of fluoride-enhanced water supplies in the US and Canada led to recommendations for fluoride incorporation into public water supplies by the U.S. Public Health Service in the 1940s and 1950s.²⁷ The efficacy of water fluoridation in preventing and controlling dental caries spurred a variety of fluoride-incorporating oral care products.²⁷ Studies document that fluoride concentrations of 1,000 to 1,500 parts per million in toothpaste renders tooth enamel less susceptible to the deleterious cavity-causing oral bacteria in dental plaque, reducing caries by 20 to 30 percent.²⁸

Augmenting toothpaste formulations with antimicrobial actives has aided in reducing the growth and metabolic activity of gum dwelling harmful bacteria to thwart biofilms and dental disease.²⁹ For example, a toothpaste containing fluoride and an antibacterial has been shown in clinical studies to significantly reduce plaque, gingivitis, bleeding gums and tooth decay³⁰ as well as the regrowth of plaque biofilm.^{31,32}

Since the incorporation of fluoride and antimicrobials into toothpastes, new research of the oral bacterial population's diversity and function has added to the understanding of the oral microbiome and revealed the opportunity for optimized use of antibacterials. Today, many mechanisms might explain why agents have limited efficacy in controlling the mouth's microbes when formed into biofilms vs floating more freely in the oral cavity. These mechanisms include the microbe's slow growth rates, their responses to stress and their biological development to tolerate agents, as well as the ability of the biofilm structure to prevent the agent's penetration.^{42,45}

New knowledge about the oral microbiome is informing the development of next-generation oral care products aimed at sufficiently reducing the bacteria to control the risk of dental disease while creating and supporting their beneficial functions consistent with health. Such antibacterial product designs, when successful, would likely control biofilm and promote oral health through subtle, more targeted effects.

Oral Health Must Consider the Microbiome

The human microbiome is the community of microorganisms that exist on and within the human body, usually harmoniously.³³ These organisms obtain food or other benefits from people via a symbiotic and commensal relationship and in return play a defining role in overall human health,³⁴ including digestive track maintenance, host defense and anti-inflammation activity among other tasks.³³

Human microbial cohabitants comprise a very large community, almost the same in number as the body's cells. Overwhelmingly, these corporal residents are different strains of bacteria,³⁵ but also include varieties of fungi, viruses, protozoa and other microorganisms.³⁶

Recent studies, newer technologies like genetic sequencing and mapping, and data analytics esca-

late both the amount of data available about the dynamic nature of the human microbiome as well as the understanding of its participation in human health status.³³ For example, the large public-private collaboration of several U.S. federal agencies, academic institutions and nonprofit organizations participating in the National Microbiome Initiative supports interdisciplinary studies addressing the fundamental questions about microbiomes in humans and other ecosystems.³⁷ The Initiative also develops platforms to analyze large data sets and share the information and resulting insights,³⁷ revealing new perspectives of the dynamic role of the microbiome in health and disease.

Understanding the Oral Microbiome

Awareness of the human oral cavity microbiome traces back to van Leeuwenhoek's 1683 report of observing animalcules in his tooth plaque, "white matter, which is as thick as if 'twere batter."³⁸ Since then, nearly 5,000 peer-review publications have shared the results of oral microbiome research, more than 40 percent of which have appeared since 2011.³⁶

Catalyzing such investigations are a variety of efforts, notably the Human Microbiome Project (HMP) of the U.S. National Institutes of Health, which is characterizing the microbiomes of the oral cavity and four other body areas of healthy people.³⁹ Data from the HMP and other programs has informed the Human Oral Microbiome Database, a project of the U.S. National Institute of Dental and Craniofacial Research (NIDCR), which already has tallied more than 770 species in the human upper digestive and upper respiratory tracts, including that dwelling in the oral cavity, pharynx, nasal passages, sinuses and esophagus.⁴⁰

In the human oral cavity, billions of microbes comprise an ecosystem that colonizes both the hard tooth surfaces as well as the soft mucosa tissues.³³ When this ecosystem is in balance, health usually prevails. However, hygiene, diet, tobacco use, stress and other factors can lead to imbalances, a state

called dysbiosis, with associated detrimental health effects.^{33,41}

Symbiotic and Dysbiotic Biofilms

Most oral bacteria exist in a complex community called a biofilm, which plays a significant role in dental disease. Biofilms occur when heterogeneous bacteria weave into an integrated matrix by attaching to each other or oral surfaces and adhering to the polymer-like substances they produce.⁴²

The properties of biofilms are more than just the sum of their constituent species. These properties result from the synergistic or antagonistic effect of their multi-species bacterial communities and can be helpful or harmful to oral health. Biofilms possess their own rate of growth, genetic activity and functionality⁴¹ different from other planktonic oral microbiome occupants. Bacteria in biofilms are influenced by their specific, residential environment, and their communal signaling ability can influence the human immune system's inflammatory response.^{33,41,43-45}

Mouth movements, like those during talking and eating, as well as saliva flow can move shreds of plaque, a tooth-surface biofilm,⁴¹ within the mouth.³³ Biofilm fragments in saliva and the fluid within crevices between teeth and gums serve as reservoirs to recolonize teeth.¹ Both the composition and functionality of biofilms on the hard and

<h2>The Oral Microbiome</h2> <p>When the oral microbiome is in balance, health usually prevails</p> <p>Hygiene, diet, tobacco use, stress & other factors can yield imbalance, with detrimental health effects</p>	<h3>Symbiosis</h3>  <h3>Health</h3>	<h3>Dysbiosis</h3>  <h3>Disease</h3>
--	---	---

soft tissues of the mouth can vary significantly within a person based on oral niche, timepoint or life stage, as well as from person to person.

In a healthy state, biofilms form on the teeth and soft tissues from benign, “friendly” bacteria that include those of the genera *Neisseria*, *Streptococcus*, *Veillonella*, *Granulicatella*, *Gemella*, *Prevotella*, *Rothia*, *Fusobacterium* and *Actinomyces*.^{41,43} Beneficial biofilms shield against non-oral microbes and restrict the growth of pathogenic microorganisms associated with common oral diseases like caries and periodontal diseases. By maintaining a neutral pH that balances acid and alkali production, for example, symbiotic biofilms help create a balance between the microbiome and oral cavity tissues.^{33,41,43-45}

However, if a healthy oral microbiome is perturbed by changes in an individual’s physiology or behavior, dysbiosis can occur. In milder detrimental states, dysbiotic oral biofilms contribute to common concerns like oral malodor, generated when certain bacteria metabolize the proteins and amino acids left behind after eating and drinking into air-borne sulfur compounds such as hydrogen sulfide and methyl mercaptan.¹

“In a healthy mouth, ‘good’ bacteria are predominant with a sparse population of ‘bad’ bacteria. But when bad bacteria actually reign over good bacteria, this microbiome is in a state of dysbiosis, which is harmful to oral health”

—**Lakshman Samaranayake, DDS, Hon DSc**
Professor Emeritus of Oral Microbiology,
The Hong Kong University, Hong Kong

In an enduring state of dysbiosis, biofilm progression at the gingival margin can lead to gingivitis inflammation and changes in the bacterial population, favoring *Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia* and *Aggregatibacter actinomycetemcomitans*. These bacterial strains undermine and inhibit the response of the immune system, further increasing bacterial diversity^{33,41,43-45} and resulting in infection and possible destruction of the bones and tissue supporting teeth.^{41,46}

More deleterious dysbiotic states may also promote cariogenic bacteria. For example, frequent contact with dietary sugars prompts ongoing bacterial-enabled conversion to acid, shifting the oral environment to favor growth of decay-causing bacteria such as *Streptococcus mutans*.⁴¹ Moreover, some

Periodontal Disease Diversity

Periodontal disease may not be a single disorder. Rather, it may be a group of harmful conditions, each with a distinct genetic, bacterial and inflammatory signature, according to NIDCR-funded genome-wide association study, which analyzed DNA from about 1,000 people with different severities of periodontal disease.⁴⁶

Despite this diversity, effective biofilm control through daily oral hygiene remains a key strategy towards preventing occurrence and progression of periodontal disease.

bacteria decrease their production of acid-neutralizing alkalis,⁴⁷ reducing their protective effect on dental caries.⁴⁸⁻⁵⁰

Because dysbiosis propels disease development and progression,¹ preventing it is a key goal of proactive oral care. Dental professionals need to help patients understand that overall biofilm control—removing the “fuzzy coating” from their teeth—via brushing paired with the use of appropriate oral care products is an accessible and effective way to control and manage bacteria throughout the whole mouth, specifically on teeth, tongue, cheeks and gums. Newer oral care products formulated to optimize the whole mouth’s microbiome should help patients sustain ideal oral health conditions throughout life.^{33,41,43-45,51}

Oral Health Needs Next-Generation Oral Care Products

Numerous studies support that decreasing bacteria in the whole mouth correlates with significant reductions in plaque, gingivitis, and other harmful biofilm-related oral diseases. Further benefits associated with bacterial control of antimicrobial formulations containing additional components to provide positive effects on enamel leading to whiter teeth or fresher breath.⁵²⁻⁵⁷

But given the recent advances in understanding the role of microbiome oral health, as well as the various factors that may lead to a dysbiotic state, the demands for new oral care products with im-

proved effectiveness are expanding. The action of dentifrice ingredients now must be broader than simply enhancing mechanical plaque control.

For example, antimicrobial ingredients for oral care products could better safeguard the mouth microbiome on all mouth surfaces. The design of such products could seek to subtly control the overall mix and amount of bacteria through more targeted action, enabled by more effective penetration of antimicrobial active into biofilm.

“I like the idea of a product that could address biofilm on all mouth surfaces, not just the teeth or gingival, but also on the cheeks and the tongue.”

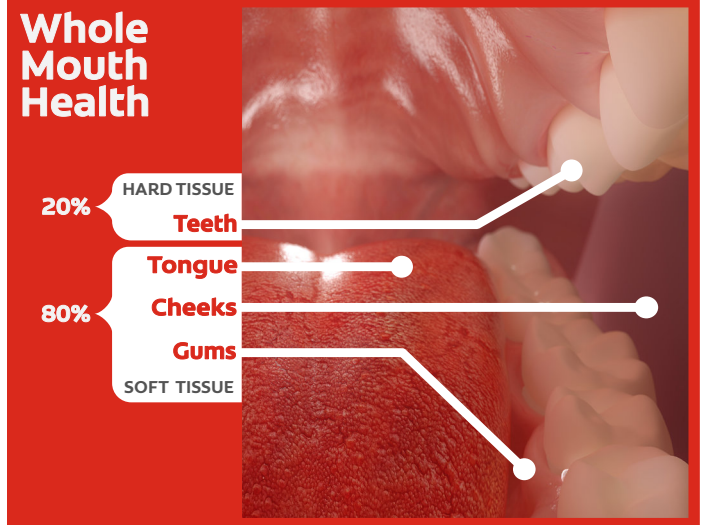
—Ann Eshenaur Spolarich, PhD, RDH
Professor of Clinical Medicine and Pharmacology,
Director of Research,
A.T. Still University
School of Dentistry and Oral Health, USA

Moreover, antimicrobial ingredients should be made available beyond the tooth structure to address the diverse microbes that occupy the 80 percent of the mouth comprised of soft tissues.⁵⁸ Even patients who routinely brush and floss effectively harbor soft tissue biofilms reservoirs¹ in the oral mucosa. Oral care products must also retain two baseline performance criteria: efficient delivery of active agents to both hard and soft tissues in the mouth during brushing and sustained action and retention on these surfaces.^{24,25,59}

A recently developed formulation with promising performance against these criteria contains a specifically designed combination of dual zinc and arginine in a fluoride toothpaste.

Zinc: The Trace Element with Oral Health Benefits

The element zinc is found in trace amounts in the human diet yet has an array of health benefits. Zinc is essential for many aspects of general body metabolism.⁶⁰ When formulated and dosed appropriately, zinc has proven therapeutic applications, such as reducing the length of the common cold and enhancing the healing of wounds.⁶¹⁻⁶³ As an antioxidant, Zinc has defensive roles to counter oxidative stress, including protecting against aging and supporting regenerative processes such as DNA and protein production.^{63,64} Zinc also impacts all three primary enzymatic functions: catalysis, regulation and structural integrity.⁶³⁻⁶⁵



The teeth make up only 20% of the total surface area of the mouth

About 95 percent of human cells contain zinc,⁶⁵ including skin tissues and tooth enamel and dentin, and it is found in plaque biofilms and saliva.⁶⁶ Zinc is therefore also present in the oral mucous membranes and soft tissues.⁶⁷

As an antimicrobial, zinc ion [Zn²⁺] is the most effective form.⁶⁷⁻⁷⁰ Research suggests the zinc ion's mechanisms of antibacterial action may include inhibiting or suppressing bacterial metabolism, and their nutrition, as well as co-adherence with neighboring organisms or human cells.^{67,71-75}

Zinc combined with citrate is readily available in fluoride toothpastes. Zinc-citrate imparts a certain stability in the dentifrice but is easily broken down in the mouth to elevate zinc levels in saliva and plaque.^{60,76} Zinc-citrate fluoride toothpastes have been shown able to prevent, control and reduce plaque,^{77,78} significantly reduce gingivitis and malodor,⁷⁹⁻⁸² inhibit the crystal growth that builds dental calculus,^{83,84} and maintains gingival health.^{85,86}

While zinc is generally known to be effective as an antibacterial, its inclusion in oral care formulations has been beset with a number of drawbacks. To utilize zinc most effectively, it is necessary to provide sustained release to allow the metal to build up on the targeted oral tissues and bacterial plaque, a considerable challenge for a product that is present in the oral cavity on average two minutes per usage.

At the same time, because zinc is naturally present in the human body, soft tissue surfaces are able to rapidly utilize the amount of available zinc.


Mode of Action

Works in two ways

Weakens to kill bacteria in plaque biofilms and saliva – on hard & soft tissue

Fortifies the soft tissue's natural defense by creating a protective barrier on the whole mouth

Dual Zinc Plus Arginine



community together.^{87,88} By helping to unravel biofilm structure, arginine can increase penetrability of other actives, and enhance, for example, the effectiveness of their activity.^{89,89}

Dual-Zinc plus Arginine: The Formulation with Abundant Oral Health Potential

Because of zinc's numerous health benefits and arginine's known direct and indirect activity on biofilm, combining the two in a fluoride toothpaste could benefit patients more comprehensively than fluoride toothpaste alone. The combination of Dual-Zinc plus Arginine delivers new advances towards controlling the oral biofilm, optimizing delivery and bioavailability of zinc to the oral biofilm, and supporting the natural defense

mechanisms against oral pathogens.¹ Dual-Zinc plus Arginine is designed to inhibit bacterial nutrient uptake, metabolism and aggregation, which weakens the organisms and biofilm architecture while permitting natural clearance of the biofilm⁹⁰. This novel formulation also generates a protective mineral shield on both hard and soft tissue, further

However, zinc's substantivity as well as retention are common formulation challenges, along with product taste attributes that could prevent patients' acceptance as a product for daily use.

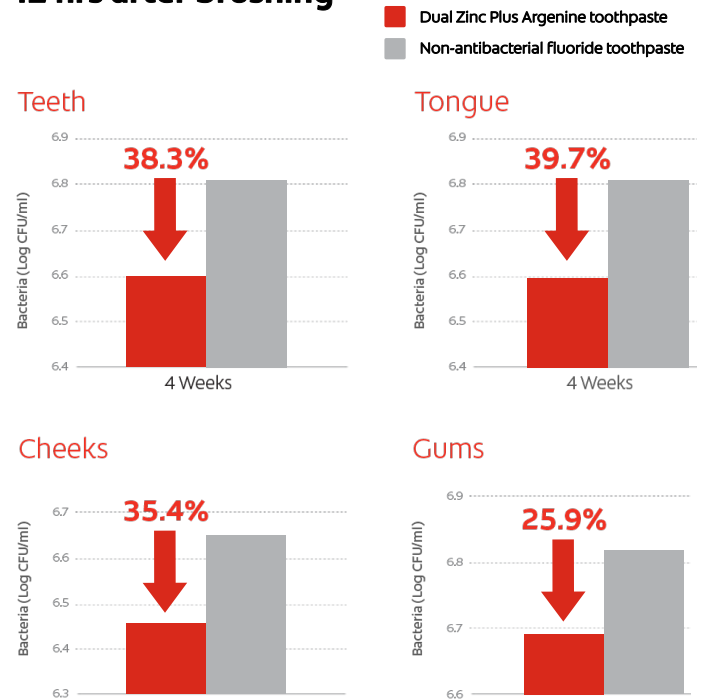
Hence, considering the acknowledged properties of zinc and recognizing its untapped potential to deliver effective and targeted antimicrobial efficacy on multiple oral surfaces, using this naturally occurring element in a toothpaste designed for the next generation of every-day oral care appears as an obvious option.

Arginine: The Amino Acid with Proven Effects on pH and Biofilm Penetrability

Arginine (L-arginine) is a natural amino acid the body needs to construct its proteins. The substance also has a documented added ability to enhance the delivery and functionality of zinc in in toothpaste.¹

Arginine alone may provide benefits in the oral cavity in two ways: adjusting local pH and enhancing biofilm penetration. Increasing the availability of arginine in the oral cavity, via certain toothpaste formulations with insoluble calcium compounds, means more is available for the biofilm bacteria to metabolize, which in turn produces the weak base ammonia, and a consequent increase in the pH of plaque. This subtly enhanced environment supports tooth remineralization. Arginine also disturbs the development of biofilms by interfering with the bacterial production of the exopolysaccharide, a glue-like substance necessary to hold the matrixed

Superior reductions in bacteria 12 hrs after brushing^{91*}



*Statistically significant greater reduction of cultivable bacteria on teeth, tongue, cheeks, and gums with Dual Zinc Plus Arginine toothpaste vs. non-antibacterial fluoride toothpaste at 4 weeks, 12 hours after brushing.

limiting bacteria adherence and regrowth, and strengthening all mouth surfaces (teeth, tongue, cheeks and gums) against day-to-day bacterial challenges.

The Dual-Zinc plus Arginine formula has been proven to deliver comprehensive benefits and improve patient outcomes. A clinical study indicated the efficacy of the combination of a Dual-Zinc plus Arginine fluoride toothpaste to reduce whole mouth bacteria after 12 hours. The bacterial load was reduced significantly by up to 38.3 percent on teeth, 39.7 percent on the tongue, 35.4 percent on cheeks, and 25.9 percent on gums, compared to ordinary fluoride toothpaste, for 12 hours after four weeks of use.⁹¹

In a six-month clinical study, the Dual-Zinc plus Arginine formulated fluoride toothpaste significantly reduced plaque and gingivitis by 30.1 percent and 26.3 percent, respectively, when compared to ordinary non-antibacterial fluoride toothpaste.⁹² Moreover, in addition to its potential to prevent caries and gingivitis, the new formulation has been shown to: reduce gum bleeding⁹², dentine hypersensitivity⁹³ tartar⁹⁴, stains⁹⁵, and oral malodor.⁹⁶

By working with the biology and chemistry of the mouth, the Dual-Zinc plus Arginine fluoride toothpaste goes beyond just teeth cleaning to protect against common oral diseases. As part of a twice-daily regimen, it could become the cornerstone of oral care helping patients be proactive about achieving and maintain whole mouth health.

Oral Health is Whole Mouth Health

The ongoing unmet global need for improved oral health requires a proactive approach to prevention that includes optimized oral care products. The improved understanding of mouth chemistry and biology and the principle that oral health is essential to an individual's general health and well-being are driving a new holistic standard-of-care focused on whole mouth prevention.

This approach requires state-of-the-science tools, such as next-generation therapeutic oral care products capable of maintaining a healthy oral microbiome, particularly the control of bacteria and biofilms on all mouth surfaces. A dentifrice containing Dual-Zinc plus Arginine was shown to be efficacious in clinical studies and provides multi-faceted biofilm management for the prevention of common oral diseases.⁹⁰⁻⁹⁶ By adopting such

toothpastes into daily oral hygiene regimens, patients should achieve better whole mouth protection resulting in clinically meaningful reductions in common oral diseases, tooth sensitivity, whiter teeth, fresher breath and food acid neutralization.

This new paradigm will be effective by shifting the focus of dentistry from a “cure” approach centered on teeth to a “care” approach centered on prevention and patients, recognizing their health, behaviors and beliefs. Practices that team together to coach patients enable their comprehension of the relationship between preventive care and preserved health and encourage their empowerment to make adequate self-care decisions. Joint professional-patient prioritization of improved long-term oral outcomes over immediate delivery of routine cleanings and acute oral care will also sustain and grow mutual efforts toward durable oral health goals.

With prevention as a defining direction, this approach is well positioned to make health of the whole mouth—teeth, tongue, cheeks and gums—an achievable new and holistic standard of everyday prevention in oral health.

Elements of Whole Mouth Health

- Whole Mouth Health is an achievable holistic standard for oral health.
- Oral health is a component of overall, systemic health and well-being.
- Oral hygiene means preventive care for the whole mouth—the teeth, tongue, cheeks and gums.
- Preventive oral care improves patient outcomes.
- Patient-centered dentistry is effective to empower patients to enhance their oral care.
- New oral product technologies should help control bacteria and biofilm on all mouth surfaces.

References

- 1 Cummins D, Marsh, D. Changing the paradigm of daily prevention to achieve whole mouth health in the 21st century. *J Clin Dent* 2018;29 (Spec Iss A):A1-9 .
- 2 Kassebaum NJ, Smith AGC, Barnabe E, Fleming TD, Reynolds AE, Vos T, Murray CJL, Marcenes W. Global Burden of Disease 2015 Oral Health Collaborators. Global, regional, and national prevalence, incidence, and disability-adjusted life years for oral conditions in 195 countries, 1990-2015: A systematic analysis for the global burden of disease, injuries and risk factors. *J Dent Res* 2017;96:380-87.
- 3 Fédération Dentaire Internationale. <https://www.fdiworlddental.org/about-fdi/history> World Health Organization. Oral Health Factsheet. <http://www.who.int/news-room/fact-sheets/detail/oral-health>, retrieved September 2018.
- 4 World Health Organization. Sugars and dental caries. WHO Technical Information Note October 2017. <https://www.who.int/nutrition/publications/nutrientrequirements/sugars-dental-caries-keyfacts/en/>, retrieved September 2018.
- 5 FDI World Dental Federation. The Challenge of Oral Disease – A call for global action. The Oral Health Atlas. 2nd ed. Geneva: the Federation; 2015 https://www.fdiworlddental.org/sites/default/files/media/documents/complete_oh_atlas.pdf.
- 6 World Health Organization. Global burden of caries disease. Country Oral Health Country/Area Profile Programme. https://www.mah.se/CAPP/Country-Oral-Health- Profiles/Global_burden_of_caries_disease/, retrieved September 2018.
- 7 World Health Organization. Significant Caries Index. Country Oral Health Country/Area Profile Programme. https://www.mah.se/CAPP/Country-Oral-Health- Profiles/Global_burden_of_caries_disease/, retrieved September 2018
- 8 World Health Organization. SIC (selected countries). Country Oral Health Country/Area Profile Programme. <https://www.mah.se/CAPP/Methods-and-Indices/for-Measurement-of-dental-diseases/Significant-Caries-Index/Significant-Caries-Index-selected-countries/>, retrieved September 2018
- 9 Righolt AJ, Jevdjevic M, Marcenes W, Listl S. Global-, Regional-, and Country-Level Economic Impacts of Dental Diseases in 2015. *J Dent Res* 2018;97(5):501-07.
- 10 World Health Organization. Methods and Indices. [https://www.mah.se/CAPP/Methods-and- Indices/](https://www.mah.se/CAPP/Methods-and-Indices/), retrieved September 2018
- 11 FDI World Dental Federation. FDI unveils new universally applicable definition of 'oral health' <https://www.fdiworlddental.org/news/press-releases/20160906/fdi-unveils-new-universally-applicable-definition-of-oral-health>, retrieved September 2018
- 12 U.S. Department of Health and Human Services. Oral Health in America: A Report of the Surgeon General. Rockville, MD: U.S. Department of Health and Human Services, National Institute of Dental and Craniofacial Research, National Institutes of Health, 2000. Accessed at https://oralcancerfoundation.org/wp-content/uploads/2016/09/oral_health_in_america.pdf. retrieved September 2018
- 13 Institute of Medicine. Crossing the quality chasm: a new health system for the 21st century. Washington, DC: National Academy Press, 2001.
- 15 Mills I, Frost J, Cooper C, Mole DR, Kay E. Patient-centred care in general dental practice – a systematic review of the literature. *BMC Oral Health* 2014;14:64.
- 16 Mills I, Frost J, Kay E, Moles DR. Person-centred care in dentistry the patients' perspective. *Br Dent J* 2015;218:407-13.
- 17 Hood L, Flores M. A personal view on systems medicine and the emergence of proactive P4 medicine: predictive, preventive, personalized and participatory. *N Biotechnol* 2012;29:613– 24. ¹⁸ Picker Institute: The Eight Principles of Patient-Centered Care. <https://www.picker.org/about-us/picker-principles-of-person-centred-care/> retrieved September 2018
- 19 Scambler S, Gupta A, Asimakopoulou K. Patient-centred care--what is it and how is it practised in the dental surgery? *Health Expect* 2014;18(6):2549-58.
- 20 Scambler S, Delgado M, Asimakopoulou K. Defining patient-centred care in dentistry? A systematic review of the dental literature. *Br Dent J* 2016;221(8):477-84.
- 21 Yevlahova D, Satur J. Models for individual oral health promotion and their effectiveness: a systematic review. *Aust Dent J* 2009;54:190-97.
- 22 Butterworth G. Principles of developmental psychology: an introduction. New York: Psychology Press, 2014.
- 23 Axelsson P, Nyström B, Lindhe J. The long-term effect of a plaque control program on tooth mortality, caries and periodontal disease in adults: Results after 30 years of maintenance. *J Clin Periodontol* 2004;31:740-57.
- 24 Cummins D, Creeth JE. Delivery of antiplaque agents from dentifrices, gels and mouthwashes. *J Dent Res* 1992;71:1439-49.
- 25 Cummins D. Vehicles: How to deliver the goods. *Periodontol* 2000 1997;15:84-99.

- ²⁶ Colgate History of Toothbrushes and Toothpastes. 2006. <https://www.colgate.com/en-us/oral-health/basics/brushing-and-flossing/history-of-toothbrushes-and-toothpastes> retrieved September 2018.
- ²⁷ Centers for Disease Control and Prevention. Recommendations for using fluoride to prevent and control dental caries in the United States. MMWR Recomm Rep (2001) 50:1–42. <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5014a1.htm>, retrieved September 2018
- ²⁸ Marinho VCC, Higgins JPT, Logan S, Sheiham A. Fluoride toothpastes for preventing dental caries in children and adolescents. The Cochrane Database of Systematic Reviews 2003;(1). Cochrane Library. Art no: CD002278.
- ²⁹ Jepsen S, Blanco J, Buchalla W, Carvalho JC, Dietrich T, Dörfer C, Eaton KA, Figuero E, Frencken JE, Graziani F, Higham S,M, Kocher T, Maltz M, Ortiz-Vigon A, Schmoedel J, Sculean A, Tenuta LMA, van der Veen MH, Machiulskiene V. Prevention and control of dental caries and periodontal diseases at individual and population level: consensus report of group 3 of the joint EPR/ORCA workshop on the boundaries between caries and periodontal diseases. J Clin Periodontol. 2017; 44 (Suppl 18): S85-S93. .
- ³⁰ Riley P, Lamont T. Triclosan / copolymer containing toothpastes for oral health (Review). The Cochrane Database of Systematic Reviews 2013(12) Cochrane Library. Art no: CD010514.
- ³¹ Jenkins S, Addy M, Newcombe R. Toothpastes containing 0.3% and 0.5% triclosan. I. Effects on 4-day plaque regrowth. Am J Dent 1989;2(Spec No):211–14.
- ³² Jenkins S, Addy M, Newcombe R. The effects of 0.5% chlorhexidine and 0.2% triclosan containing toothpastes on salivary bacterial counts. J Clin Periodontol 1990;17:85–9.
- ³³ Kilian M, Chapple IL, Hannig M, Marsh PD, Meuric V, Pedersen AM, Tonetti MS, Wade WG, Zaura E. The oral microbiome - an update for oral healthcare professionals. Br Dent J 2016;221(10):657-66.
- ³⁴ Lederberg J, McCray A. Ome Sweet 'Omics – a Genealogical Treasury of Words. The Scientist 2001;17(7):9–10.
- ³⁵ Sender, R, Fuchs S, Milo R. Are We Really Vastly Outnumbered? Revisiting the Ratio of Bacterial to Host Cells in Humans. Cell 2016;164(3):337-40.
- ³⁶ Lloyd-Price J, Abu-Ali G, Huttenhower C. The healthy human microbiome. Genome Medicine 2016;8(1):51.
- ³⁷ White House Office of Science and Technology Policy. Fact Sheet: Announcing the National Microbiome Initiative. May 13, 2016.
- ³⁸ Dobell, Clifford. Antony van Leeuwenhoek and his Little animals; being some account of the father of protozoology and bacteriology and his multifarious discoveries in these disciplines. New York, Harcourt, Brace and company. 1932. ISBN132940017409138.
- ³⁹ NIH Common Fund Human Microbiome Project (HMP). <https://hmpdacc.org/hmp/>, retrieved September 2018
- ⁴⁰ Chen T, Yu WH, Izard J, Baranova OV, Lakshmanan A, Dewhirst FE. The human oral microbiome database: a web accessible resource for investigating oral microbe taxonomic and genomic information. Database (Oxford) 2010;2010:baq013.
- ⁴¹ Sanz M, Bighton D, Curtis MA, Cury JA, Dige I, Dommisch H, et al. Role of microbial biofilms in the maintenance of oral health and in the development of dental caries and periodontal diseases. Consensus report of group 1 of the Joint EFP/ORCA workshop on the boundaries between caries and periodontal disease. J Clin Periodontol. 2017;44 Suppl 18:S5– S11. 10.1111/jcpe.12682. DOI: 10.1111/jcpe.12682.
- ⁴² Donlan R M, Costerton J W. Biofilms: survival mechanisms of clinically relevant microorganisms. Clin Microbiol Rev 2002;15: 167–93.
- ⁴³ Mira A, Simon-Soro A, Curtis MA. Role of microbial communities in the pathogenesis of periodontal diseases and caries. J Clin Periodontol 2017; 44 (Suppl 18): S23-S38.
- ⁴⁴ Marsh PD. Contemporary perspective on plaque control. Brit Dent J 2012;212: 601-606.
- ⁴⁵ Marsh PD, Head DA, Devine DA. Ecological approaches to oral biofilm: control without killing. Caries Res 2015;49 (Suppl 1): 46-54.
- ⁴⁶ Department of Health and Human Services, National Institutes of Health, National Institute of Dental and Craniofacial Research. Congressional Justification for FY2018. <https://www.nidcr.nih.gov/sites/default/files/2017-09/nidcr-congressional-justification-2018.pdf>,
- ⁴⁷ Burne RA, Zeng I, Ahn SJ, Palmer SR, Liu Y, Lefebure T, Stanhope MJ, Nascimento MM. Progress in dissecting the oral microbiome in caries and health. Adv Dent Res 2012;24:77-80.
- ⁴⁸ Tagahashi CT. Oral microbiome metabolism: From “Who are they?” to “What are they doing?” J Dent Res 2015;94:1628-37.
- ⁴⁹ Reyes E, Martin J, Moncada G, Neira M, Palma P, Gordon V, Oyarzo F, Yevenes I. Caries-free subjects have high levels of urease and arginine deiminase activity. J Appl Oral Biol 2014;22:235-40.
- ⁵⁰ Nascimento MM, Liu Y, Kalra R, Perry S, Adewumi A, Xu X, Primosch RE, Burne RA. Oral arginine metabolism may decrease the risk for dental caries in children. J Dent Res 2013;92:604-8.

- ⁵¹ Zaura E, ten Cate JM. Towards understanding oral health. *Caries Res* 2015;49 (Suppl 1):55-62.
- ⁵² Riley P, Lamont T. Triclosan / copolymer containing toothpastes for oral health (Review). *The Cochrane Database of Systematic Reviews*. 2013;12. Cochrane Library. Art no: CD010514.
- ⁵³ Mankodi S, Wachs GN, Petrone DM, Chaknis P, Petrone M, DeVizio W, Volpe AR. Comparison of the clinical efficacy of a new manual toothbrush on gingivitis reduction and plaque removal. *Compend Contin Educ Dent* 2004;10(Suppl 2):28-36.
- ⁵⁴ Nathoo S, Chaknis P, Petrone M, DeVizio W, Volpe AR. A clinical comparison of gingivitis reduction and plaque removal efficacy of a new manual toothbrush. *Compend Contin Educ Dent* 2004;10(Suppl 2):37- 45.
- ⁵⁵ Williams M, Vazquez J, Cummins D. Clinical comparison of a new manual toothbrush on breath volatile sulfur compounds. *Compend Contin Educ Dent* 2004;10(Suppl 2):22-27.
- ⁵⁶ Fine DH, Sreenivasan PK, McKiernan M, Tischio-Beresci D, Furgang D. Whole mouth anti-microbial effects after oral hygiene: comparison of three dentifrice formulations. *J Clin Periodontol* 2012;39:1056- 64.
- ⁵⁷ Panagakos FS, Volpe AR, Petrone M, Morrison BM Jr, DeVizio W, Proskin HM. Advanced oral antibacterial/anti-inflammatory technology: A comprehensive review of clinical benefits of a triclosan/copolymer/fluoride dentifrice. *J Clin Dent* 2014;25(Suppl):S1-30.
- ⁵⁸ Mager DL, Ximinez-Fyvie LA, Hafferjee AD, Socransky SS. Distribution of selected bacterial species on intra-oral surfaces. *J Clin Periodontol* 2003;30:644-54.
- ⁵⁹ Duckworth RM. Pharmacokinetics in the oral cavity: Fluoride and other active ingredients. In: *Toothpastes. Monogr. Oral Sci.* van Loveren C (ed). Basel. Karger. 2013;23:125-39. ⁶⁰ King JC. Zinc: an essential but elusive nutrient. *Am J Clin Nutr* 2011;94(2):679S-84S.
- ⁶¹ Hemila H. Zinc lozenges and the common cold: a meta-analysis comparing zinc acetate and zinc gluconate, and the role of zinc dosage. *JRSM Open* 2017;8(5):2054270417694291.
- ⁶² Kogan S, Sood A, Granick MD. Zinc and wound healing: A review of zinc physiology and clinical applications. *Wounds* 2017;29:102-06.
- ⁶³ Lin PH, Sermersheim M, Li H, Lee PHU, Steinberg SM, Ma J. Zinc in wound healing modulation. *Nutrients* 2017;10(1):E16.
- ⁶⁴ Bhattacharya PT, Misra SR, Hussain M. Nutritional aspects of essential trace elements in oral health and disease: An extensive review. *Scientifica* 2016;2016: 5464373.
- ⁶⁵ King JC. Zinc: an essential but elusive nutrient. *Am J Clin Nutr* 2011;94(2):679S-84S.
- ⁶⁶ Fatima T, Rahim ZBHA, Lin CW, Qamar Z. Zinc: A precious trace element for oral health care. *J Pak Med Assoc* 2016;66: 1019-23.
- ⁶⁷ Cummins D, Jones S, Watson GK. The importance of the speciation of zinc to its activity as an anti-microbial agent. *Recueil des Travaux Chimiques des Pays-Basque* 1987;106:0-48.
- ⁶⁸ Cummins D, Watson GK. Computer modelling relating chemistry to biological activity of metal anti- plaque agents. *J Dent Res* 1989; 68 (Spec Iss):1702-05.
- ⁶⁹ Watson GK, Cummins D, van der Ouderaa FJG. Inhibition of acid production by *Streptococcus mutans* NCTC 10449 by zinc and the effect of metal speciation. *Caries Res* 1991;25:431-437.
- ⁷⁰ Coombes CC, Laing ME, Taylor DM, Vesey JA, Williams DR. Speciation of zinc and tin (II) in dentifrices with reference to availability in saliva. *Chemical Speciation and Bioavailability* 1994;6:33-51.
- ⁷¹ Cummins D. Zinc citrate/triclosan: a new anti-plaque system for the control of plaque and the prevention of gingivitis: short term clinical and mode of action studies. *J Clin Periodontol* 1991;18:455-61.
- ⁷² Phan TN, Buckner T, Sheng J, Baldeck JD, Marquis RE. Physiologic actions of zinc related to inhibition of acid and alkali production by oral streptococci in suspensions and biofilms. *Oral Microbiol Immunol* 2004;19:31-8. ⁷³ Sheng J, Nguyen PT, Marquis RE. Multi-target anti-microbial actions of zinc against oral anaerobes. *Arch Oral Biol* 2005;50: 747-57.
- ⁷⁴ Koo H, Sheng J, Nguyen PT, Marquis RE. Co-operative inhibition by fluoride and zinc of glucosyl transferase production and polysaccharide synthesis by mutans streptococci in suspension cultures and biofilms. *FEMS Microbiol Lett*. 2006; 254:134-140.
- ⁷⁵ Gu H, Fan D, Gao J, Zou W, Peng Z, Zhao Z, Ling J, LeGeros RZ. Effect of ZnCl₂ on plaque growth and biofilm vitality. *Arch Oral Biol* 2012;57:369-375.
- ⁷⁶ Saxton CA, Harrap GJ, Lloyd AM. The effect of dentifrices containing zinc citrate on plaque growth and oral zinc levels. *J Clin Periodontol* 1986;13:301-06.
- ⁷⁷ Harrap GJ, Saxton CA, Best JS. Inhibition of plaque growth by zinc salts. *J Periodontal Res* 1983;18:634-42.

- ⁷⁸ Saxton CA, Harrap GJ, Lloyd AM. The effect of dentifrices containing zinc citrate on plaque growth and oral zinc levels. *J Clin Periodontol* 1986;13(4):301-6.
- ⁷⁹ Williams C, McBride S, Mostler K, Petrone DM, Simone AT, Crawford R, Patel S, Petrone ME, Chaknis P, DeVizio W, Volpe AR, Proskin HM. Efficacy of a dentifrice containing zinc citrate for the control of plaque and gingivitis: A 6-month clinical study in adults. *Compend Contin Educ Dent*. 1998; 19 (2 Suppl):4-15.
- ⁸⁰ Barnes VM, Richter R, Bastin D, Lambert P, Xu T. Dental plaque control effect of a zinc citrate dentifrice. *J Clin Dent*. 2008;19:127-30.
- ⁸¹ Zhong Y, Li X, Hu DY, Mateo LR, Morrison BM Jr, Delgado E, Zhang YP. Control of established gingivitis and dental plaque using a 1450 ppm fluoride/zinc-based dentifrice: A randomized clinical study. *J Clin Dent* 2015;26(4):104-108
- ⁸² Navada R, Kumari H, Le S, Zhang J. Oral malodor reduction from a zinc-containing toothpaste. *J Clin Dent* 2008;19:69-73.
- ⁸³ Sowinski J, Petrone DM, Simone AJ, Crawford R, Patel S, Petrone ME, DeVizio W, Volpe AR, Proskin HM. Clinical efficacy of a dentifrice containing zinc citrate: A 12-week calculus clinical study in adults. *Compend Contin Educ Dent* 1998 19(Suppl): 16-19.
- ⁸⁴ Richter R, Jogun S, Won B, Zhang YP, Miller S. Long-lasting efficacy of an experimental 1450 ppm fluoride/zinc-based dentifrice as measured by calcium buildup on an in situ intra-oral device after 12 hours: A randomized clinical trial. *J Clin Dent*. 2015; 26: 91-95.
- ⁸⁵ Kakar A, Newby EE, Kakar K, Ghosh S, Targett D, Bosma ML. A randomized clinical trial to assess maintenance of gingival health by a novel dentifrice containing 0.1% w/w o-cymen-5-ol and 0.6% w/w zinc chloride. *Int Dent J* 2011;61 (Suppl 3):13-20.
- ⁸⁶ Kakar A, Newby EE, Ghosh S, Butler A, Bosma ML. A randomized clinical trial to assess maintenance of gingival health by a novel gel to foam dentifrice containing 0.1% w/w o-cymen-5-ol and 0.6% w/w zinc chloride. *Int Dent J* 2011;61(Suppl 3): 21-27.
- ⁸⁷ Hoiby N, Bjarnsholt T, Givskov M, Molin S, and Ciofu O. Antibiotic resistance of bacterial biofilms. *Int J Antimicrob Agents* 2010;35:322-332.
- ⁸⁸ He J, Hwang G, Liu Y, Gao L, Klipatril-Liverman L, Santarpia P, Zhou X, Koo H. L-arginine modifies the exopolysaccharide matrix and thwarts *Streptococcus mutans* outgrowth within mixed-species oral biofilms. *J Bacteriol* 2016;198:2651-661.
- ⁸⁹ Huang X, Zhang K, Deng M, Exterkate RAM, Liu C, Zhou X, Cheng L, Ten Cate JM. Effect of arginine on the growth and biofilm formation of oral bacteria. *Arch Oral Biol* 2017;82:256-262d.
- ⁹⁰ Manus L, Daep C, Begum-Gafur R, Makwana E, Won B, Yang Y, Huang K, Maloney V, Trivedi H, Wu D, Masters J, Enhanced In Vitro Zinc Bioavailability Through Rational Design of a Dual-Zinc plus Arginine Dentifrice, *J Clin Dent* 2018;29 (Spec Iss A):A10-19.
- ⁹¹ Prasad K, Sreenivasan P, Mateo L, Cummins D, The effects of two new Dual Zinc plus Arginine dentifrices in reducing oral bacteria in multiple locations in the mouth: 12-hour whole mouth antibacterial protection for whole mouth health, *J Clin Dent* 2018;29 (Spec Iss A):A 25-32.
- ⁹² Delgado E, Garcia-Godoy F, Montero-Aguilar M, Mateo L Zhang Y, A clinical investigation of a Dual Zinc plus Arginine dentifrice in reducing established dental plaque and gingivitis over a 6-month period of product use, *J Clin Dent* 2018;29 (Spec Iss A):A33-40.
- ⁹³ Seriwatanachai D, Mateo L. Data on File, Colgate-Palmolive Technology Center, Jan 2016.
- ⁹⁴ Seriwatanachai D, Mateo L, Data on File, Colgate-Palmolive Technology Center, Sept 2016.
- ⁹⁵ Delgado E, Mateo L. Data on File, Colgate-Palmolive Technology Center, Jan 2017.
- ⁹⁶ Hu D, Zhang X, Zhong Y, Mateo L, Delgado E, Zhang Y, A clinical investigation of the efficacy of a Dual Zinc plus Arginine dentifrice for controlling oral malodor, *J Clin Dent* 2018;29 (Spec Iss A) :A41-45.

Colgate[®]

The Colgate logo consists of the word "Colgate" in a white, italicized serif font, with a registered trademark symbol (®) to its upper right. Below the text is a white, upward-curving arc that resembles a smile.