



The Impact of Research and Development on the Prevention of Oral Diseases in Children and Adolescents: An Industry Perspective

Diane Cummins, PhD¹

Abstract

Significant progress has been made globally in reducing dental caries and periodontal disease through adoption of safe and effective methods of prevention. Nonetheless, there are profound oral health disparities in the population and this necessitates further improvement.

This review provides an industry perspective of the impact of research and development on the prevention of oral disease in children and adolescents. It also provides an overview and discussion of the key routes that are currently under investigation in academic research, together with an outline of what it will take to develop a major new therapeutic and bring it into clinical practice and individual self care. The key challenges and opportunities are summarized. (*Pediatr Dent* 2006;28:118-127)

KEYWORDS: DENTAL CARIES, PLAQUE, GINGIVITIS, PERIODONTAL DISEASE, CHILDREN, ADOLESCENTS, PREVENTION

Introduction

The application of scientific knowledge to the prevention of oral disease has resulted in significant declines in dental caries and periodontal disease. Children are most often affected by dental caries. As they develop into adolescents, their risk of gingivitis also increases. Both diseases are complex, multifactorial conditions that have dental plaque and host tissues at the heart of their etiologies. Genetic and environmental factors also play a role in disease susceptibility or resistance.

These two oral diseases have stimulated much research and development over the past 50 years. Academic research has focused on developing new understanding of the epidemiology, etiology, and pathogenesis of these diseases, as well as identifying potential new routes to intervention. Industrial research has focused on the development and clinical validation of professional and consumer products for their treatment and prevention.

This paper provides a perspective of the impact of research and development on the prevention of oral disease in children and adolescents. It reviews significant advances in oral health and new scientific approaches to prevention, and summarizes the key challenges and opportunities in bringing new oral health measures into practice.

Oral health in the United States of America

The US Surgeon General's Report on Oral Health¹ focused attention on the importance of oral health to general health

and well-being. It recognized the progress made in reducing dental caries and periodontal disease through the adoption of safe and effective methods of prevention. Nonetheless, it made clear that a significant burden of oral disease still remains as a result of profound oral health disparities in the population. As oral health and general health are not independent, the mouth may provide an opportunity for early diagnosis of systemic disease. Further, oral disease, in particular periodontal disease, may be linked to systemic problems, such as diabetes and heart disease. The report provided a framework for further improvement in oral health, recognizing the need to change existing perceptions of oral health, to build an effective health care infrastructure, to remove known barriers between people and health services, to build the science base and develop new knowledge, and to increase collaboration to improve the oral health of those that suffer most.

The importance of translational research to the prevention of oral disease

The goal of translational research is to turn advances in scientific knowledge into improved dental care of patients. The focus is on practical validation of knowledge - applied research focused on developing and validating a product- or procedure-based therapeutic intervention. The schematic shown in Figure 1 is a useful representation of the process. Driven by a fundamental research hypothesis, basic research is focused on acquisition of new knowledge. Knowledge is validated through a hierarchy of research steps to deliver an intervention with sufficient clinical evidence to predicate a new clinical practice. As shown in Figure 2, basic research

¹Dr. Cummins is Worldwide Director, Oral Care Research and Development, Colgate-Palmolive Company, Piscataway, NJ. Correspond with Dr. Cummins at diane_cummins@colpal.com

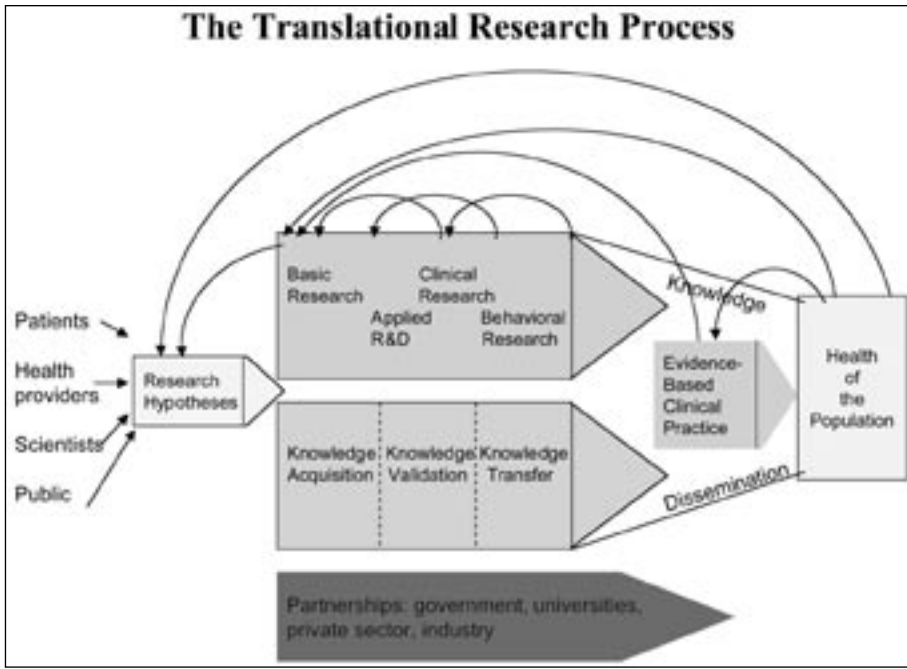


Figure 1. The translational research process.

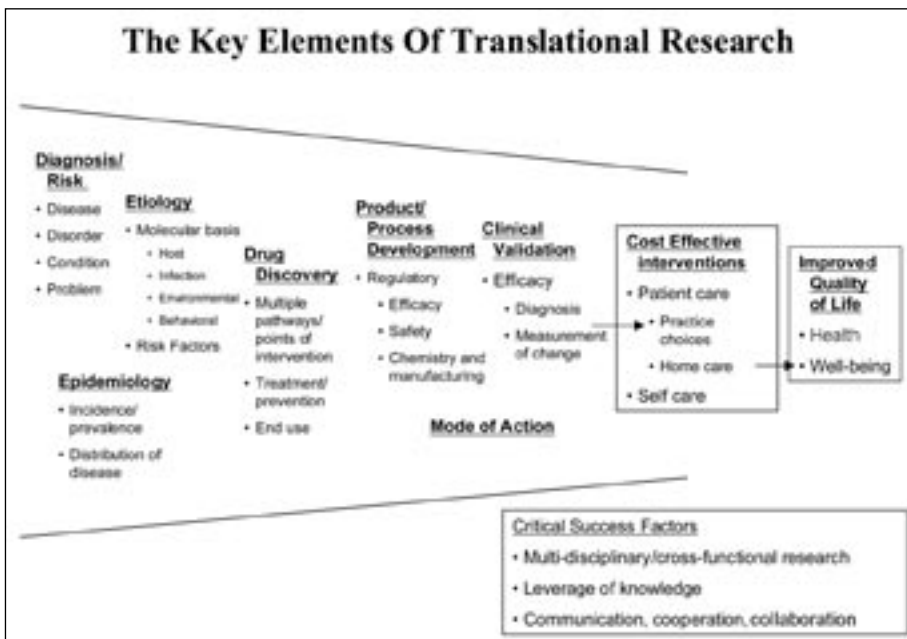


Figure 2. The key elements of translational research.

encompasses disease diagnosis, the molecular basis of disease and its risk factors, and the prevalence and incidence of disease. The etiology provides the mechanistic basis for drug discovery for treatment and prevention. Development of a product is complex; it must fully comply with regulatory requirements for safety and efficacy, and chemistry and manufacturing. Clinical validation of product efficacy and mode of action are critical. A multidisciplinary, cross-functional approach, together with effective leverage of expertise and acquired knowledge, are critical factors to successful translational research.

There have been relatively few truly significant breakthroughs in oral health care. The first, without question, was the development of topical fluoride products to prevent caries.²⁻⁴ Products to prevent calculus^{5,6} and to relieve dentinal hypersensitivity^{7,8} followed. Most recently, products to prevent plaque and gingivitis,⁹ such as toothpastes with triclosan¹⁰⁻¹², have been introduced. In each case, the translational research process took more than 20 years from demonstrating the potential of each technology in "proof of concept" studies to seeing the impact of specific products on dentistry. It is clear that translational research will be more important than it has ever been, if scientific knowledge is to contribute fully to the 2010 US Oral Health goals.

Significant advances impacting the oral health of children and adolescents

Dental caries varies widely in the US¹³ and globally¹⁴ among children and adolescents. Divergent trends in caries experience are correlated with sugar consumption and personal health behaviors.^{15, 16} Now concentrated in a subset of the young population, 80% of caries experience is found in 25% of children in the US.¹³ In the children's dentition, caries is manifest in a predictable manner rendering dental-stage specific, protocol-driven interventions appropriate.¹⁷

Periodontal disease in children and adolescents is less well documented. Nonetheless, 50% of high school students in the US have reported gingivitis.¹ The potential link between periodontal and systemic disease suggests that the prevention of early periodontal disease in children and adolescents is worthy of attention.

Recognition that dental caries and periodontal disease are chronic infections caused by the indigenous oral flora has had important consequences for prevention and treatment.¹⁸ Dental plaque is a complex, highly diverse, multispecies biofilm that develops over time on the tooth surfaces and adjacent to the gingival margin.¹⁹ Plaque bacteria create the highly hydrated exopolysaccharide matrix

in which they are enmeshed.²⁰⁻²² Sugar promotes matrix and acid formation, thus playing a dual role in plaque pathogenicity and virulence in dental caries.²³ Tooth enamel and the periodontal tissues play a critical role in response to dental plaque in caries and periodontal disease, respectively. Genetic and environmental factors are additional determinants of risk.²⁴

Means to preventing and treating oral disease are driven by understanding of disease processes. Because children and adolescents are most affected by dental caries, disease prevention in the young has been primarily focused on caries.²⁴ Good oral hygiene is a key strategy for the prevention of both dental caries and periodontal disease.²⁵⁻²⁸ Observation of the caries-protective effects of water-borne fluoride focused caries research on the validation of fluoride treatments. In contrast, the clinical observation that periodontal disease could be prevented by meticulous plaque control has directed research in chemical plaque control and antimicrobial therapies.

The contribution of consumer products and the oral care industry to the prevention of dental caries and periodontal disease in children and adolescents

Consumer products have contributed to the oral health of children and adolescents in three areas: oral hygiene implements for mechanical plaque removal, topical fluoride treatments for caries prevention, and topical antimicrobial treatments for the prevention of early periodontal disease.

The toothbrush design features can improve brushing technique and enhance individual motivation. The Colgate Smiles range was designed with this knowledge (Figure 3). Clinical studies have shown that the “Junior” and “Youth” brushes effectively remove plaque around and between teeth and along the gum line. Further, consumer research has shown that these brushes are well liked by children and their parents. The “Junior” brush addresses the dexterity challenges of its target age group, while the tongue cleaner on the “Youth” brush is a valued additional feature. Based upon parental observation, there was a clear association between the child’s liking the toothbrush and increased brushing compliance.²⁹

The dramatic decline in caries prevalence and severity over the last several decades has been attributed to the widespread use of fluoride. Initially, fluoride was thought to affect tooth development and mineralization, and that systemic fluoride administration was necessary for optimum benefit. A paradigm shift in understanding of the action of fluoride drove development and validation of topical treatments for the prevention of dental caries.¹⁸ Today, consumer and professional products encompass over-the-counter (OTC) toothpastes and mouthrinses for self care, prescription products, such as high fluoride toothpastes and mouthrinses for home care, and professional products, such as varnishes and gels for in-office treatment.

Of the available vehicles, toothpaste is the most studied. Several comprehensive clinical reviews have shown



Figure 3. The Colgate Smiles range of children's toothbrushes.

that regular brushing with fluoride toothpaste reduced the development of new caries by 24% to 25% compared to brushing with nonfluoride paste. The effects increased in “high risk” individuals with higher initial caries levels and with higher fluoride level, by 5% to 10% for 1,500 over 1,000 ppm fluoride. Effectiveness also increased with higher frequency of use and with supervised brushing.³⁰⁻³³ Based upon risk/benefit and compliance, it is evident that toothpaste is the most appropriate vehicle to deliver fluoride on a routine daily basis. This reinforces the importance of daily tooth brushing with fluoride toothpaste to prevention of dental caries in children and adolescents. OTC toothpastes vary in their fluoride source and in other functional ingredients, such as the cleaning and polishing agent and the flavor. These differences are largely driven by consumer preference, especially mouth feel and taste. The fluoride source is not critical to effectiveness in cavity prevention, as clinical evidence has shown, at equal fluoride dose, that toothpastes formulated with sodium fluoride (NaF), sodium monofluorophosphate (MFP), and stannous fluoride (SnF₂) are equally effective.³³

OTC mouthrinses have shown similar efficacy to toothpaste.^{34,35} High fluoride rinses may provide additional caries protection as adjuncts to daily brushing with toothpaste in “high risk” children when used on a periodic (4 x annual) basis under professional supervision. Mouthrinse may also help prevent white spot lesions in orthodontic patients.³⁶⁻³⁸ Likewise, high fluoride gels^{37, 39} and varnishes^{37, 40-43} have been shown to be effective, used periodically, as an adjunct in “high risk” individuals. Few data are available comparing one vehicle to another; all fluoride treatments appear to be effective, but there is no clinical basis for superiority.⁴⁴ There are also insufficient data to determine the clinical effectiveness of combinations of fluoride treatments.^{45,46} Based upon apparent risk/benefit, varnishes may be preferred over gels and rinses.³⁷

In contrast to fluoride, the use of antimicrobial therapies in children and adolescents has been limited. Many antimicrobial agents have been screened in basic research, but

few have been successfully reduced to clinical practice.⁴⁷ Chlorhexidine mouthrinse, considered to be the gold standard for antiplaque efficacy,⁴⁸ is approved by the US Food and Drug Administration (FDA) as a prescription treatment, whereas mouthrinses based upon the essential oils and on cetyl pyridinium chloride (CPC) are pending approval as OTC products for the prevention of plaque and gingivitis.⁴⁹

The antiplaque and antigingivitis toothpaste, Colgate Total®, has been clinically proven to be effective during routine daily use. Based upon triclosan, an antibacterial agent, a specially designed vehicle containing a copolymer as the delivery agent,⁵⁰ and fluoride, it is arguably the most comprehensively tested consumer product available today. More than 40 controlled clinical studies have documented superior efficacy versus regular fluoride dentifrices.^{11, 51-55} Interestingly, while Colgate Total® is not marketed for the prevention and treatment of periodontal disease, its effects have been demonstrated in three clinical studies.⁵⁶⁻⁵⁹

In summary, the oral care industry has provided safe and effective oral care products that are clinically proven to help prevent oral diseases in children and adolescents. Toothbrushes that encourage compliance are fundamental to establishing good oral hygiene practices at an early age. Fluoride toothpaste has played a major role in the dramatic decline in caries. Professionally applied topical fluoride treatments can provide additional benefit to “high risk” individuals. Toothpastes and mouthrinses that prevent plaque and gingivitis provide valuable oral health benefits beyond cavity prevention. Specific “at risk” individuals, such as orthodontic and diabetes patients, may find their use particularly beneficial.

In addition to professional and consumer products, the oral care industry has made significant contributions to the dental research science base and to new knowledge. Specifically, through basic and clinical research, industry has impacted knowledge of the epidemiology and etiology of caries and periodontal disease, the mechanism of action of fluoride and antimicrobials, and the factors influencing the clinical performance of toothpaste, mouthrinse, gels, and other delivery vehicles. Through behavioral research, the importance of consumer habits and attitudes, consumer preference, product usage and compliance has been appreciated. Equally important has been the industry’s contribution to education and knowledge transfer. Dental health awareness has been raised through global activities, such as Oral Health Month. Schools programs, such as Bright Smiles, Bright Futures, have brought dental services to the underrepresented. Targeted publications and symposia have brought advances in science, including advances in prevention of oral disease in children and adolescents, to the dental professional. Last, but not least, through sponsorship, industry has provided funding for basic research and clinical training.⁶⁰

New therapeutic approaches to prevention of oral diseases in children and adolescents

The divergent trend in caries experience calls for a new focus on high risk groups and risk-based, individualized therapies. At present, the detection methods used routinely by most clinicians are not sufficiently sensitive to detect caries at an early stage. Furthermore, risk assessment at the individual level is not well developed.⁶¹ The validation of new methods may reveal new biology-based tailored approaches to caries prevention. These include digital fiber-optic transillumination (DIFOTI)^{62, 63} and quantitative light-induced fluorescence, QLF,⁶⁴⁻⁶⁶ which are currently in development for the detection of early caries. Other technologies include new multifactor tools to assess disease risk and activity.⁶⁷⁻⁶⁹

Shifts in scientific paradigms advance new scientific knowledge and stimulate exploration of new scientific approaches to disease prevention. Complex, dynamic, multifactorial diseases, such as dental caries and periodontal disease, are subject to multiple technical approaches to potential new therapeutics. The literature on the science and IP pertinent to the development and validation of new therapeutics is dominated by approaches to dental plaque control and the prevention and control of dental caries. For this reason, and because children and adolescents are most affected by dental caries, this section focuses on the key concepts and approaches to dental plaque control and the prevention and control of dental caries.

Table 1 summarizes new approaches to caries prevention that target the host defense of tooth enamel. Underpinning these approaches is a strong knowledge of the mechanisms of action of fluoride. Two theoretical approaches to enhance calcium incorporation into tooth enamel are: (1) to increase the delivery and retention of topical fluoride; and (2) to deliver and retain exogenous calcium and phosphate. Both present a significant challenge, as salivary composition limits calcium uptake and salivary flow predisposes fluoride clearance.

A tiny intra-oral device attached to the tooth surface, which contains a reservoir to constantly and slowly release fluoride, has been shown to be effective in “proof of concept” clinical trials,^{70, 71} but it has not yet found a place in clinical practice. A number of approaches to deliver exogenous calcium, through protein- and peptide-based carriers^{72, 73} and silicate-based carriers⁷⁴, have shown some promise in early “proof of concept” studies. Encapsulation of fluoride and/or calcium in microcapsules that adhere to the mucosa offers attractive possibilities. In principle, encapsulates derived from biodegradable materials that act as substrates for enzymes in saliva and plaque could be slowly activated *in situ*. Though supplier companies have expertise in encapsulation technologies, this approach has not yet been validated as a practical route to caries prevention. The approach that has shown greatest potential to date is a dual component dentifrice containing dicalcium phosphate dihydrate (dical) and 1,000 ppm sodium fluoride. In two

long-term caries clinical studies, this toothpaste provided 11% and 14% reductions in cavities compared to a regular sodium fluoride dentifrice.^{75, 76}

Table 2 summarizes new approaches that target bacteria to control dental plaque formation. The knowledge that dental caries is a chronic infection caused by an imbalance in the normal endogenous flora led to the first conceptual approach: the evaluation of topical antimicrobial systems to reduce the total burden of infection. Chlorhexidine varnishes have shown some promise, but to date the evidence for their long-term effectiveness in preventing cavities is inconclusive.^{77, 78} In contrast, as indicated previously, the triclosan/copolymer toothpaste has been clinically proven in a 2 year caries clinical trial to provide superior prevention of cavities compared to regular fluoride toothpaste.⁵²

The knowledge that specific organisms are primary etiologic factors in caries formation has led to the second conceptual approach: the development and evaluation of methods to eliminate specific caries causative organisms, especially *Streptococcus mutans*. Several long-term investigations are in progress. Vaccines and other immunogenic routes to reduce specific oral pathogens have received significant attention. Passive immunization, using *S mutans* targeted antibody or antibody fragment, is reported to offer promise.⁷⁹ Replacement therapy is an alternative route to the same benefit. *S mutans* replacement by a genetically modified benign *S mutans* strain has been shown feasible in animal studies. Clinical trials are in progress to assess the potential of this route to prevent caries.⁸⁰ Introduction of a benign endogenous species, such as *Streptococcus salivarius*, that excludes *S mutans* by producing antimicrobial peptides *in situ* may also offer promise.⁸¹ The probiotic approach of regularly introducing an innocuous exogenous bacterial species to suppress outgrowth of normal oral pathogens has been disclosed in the patent literature.⁸² Likewise, interest has been demonstrated in the potential of antimicrobial enzymes and peptides that target and kill specific plaque pathogens.⁸³

Table 1. New approaches to caries prevention that target tooth enamel to boost the host defense

Target	Scientific paradigm	Technical approach	Potential new therapeutic
Tooth enamel	Topical fluoride modulates calcium incorporation into tooth enamel	Increase delivery and retention of fluoride	Dual component calcium/ fluoride dentifrice Slow release F systems Device Encapsulation
		Deliver additional calcium (and phosphate)	Ca delivery systems Protein/peptide carriers Silicate/glass carriers

Table 2. New approaches to caries prevention that target bacteria to control dental plaque formation

Target	Scientific paradigm	Technical approach	Potential new therapeutic
Plaque bacteria	Infection caused by endogenous flora	Reduce burden of infection	Topical antimicrobials Chlorohexidine Triclosan
		Eliminate causative organisms, especially <i>S mutans</i>	<i>S mutans</i> targeted vaccine Replacement therapy GMO Probiotics Targeted antimicrobial enzymes and peptides
	Biofilm is a highly complex entity that behaves differently from its individual constituents	Prevent bacterial adhesion	Coat enamel surface Agents Sealants Block bacterial adhesion Bacterial surface GTF and matrix formation Cell-cell signaling
		Modulate biofilm physiology	Control plaque pH Xylitol Arginine/bicarbonate buffer Upregulate arginine deaminase
		Disrupt plaque matrix	Glucan hydrolase enzymes

The recognition that dental plaque is a bacterial biofilm and that it is a highly complex entity that behaves quite differently from its individual constituents has led to exploration of several novel routes. The concept of controlling plaque formation by preventing bacterial adhesion to the tooth surface has been investigated on several fronts. Physical approaches include coating the enamel surface with a polymer,⁸⁴ whereas biological approaches to prevent initial colonization include inhibition of plaque matrix formation⁸⁵ and inhibition of the bacterial signaling mechanisms.⁸⁶ The concept of modulating biofilm physiology is also of some interest. Particular attention has been paid to routes to modulate and control plaque pH. The potential

of xylitol to inhibit acid production and, thereby, to reduce demineralization is well recognized. In long-term caries clinical studies, two toothpastes containing 10% xylitol as an adjunct to fluoride provided 12% and 14% reductions in cavities compared to their respective fluoride controls.^{87, 88} An arginine/bicarbonate system has shown initial promise in a “proof of concept” clinical trial as an alternative to fluoride.⁸⁹ On a further horizon is the possibility to up-regulate the natural pH regulation system in *S sanguis*. The arginine deiminase system, which breaks down arginine to ammonia, is triggered when plaque pH is reduced below 5.5.⁹⁰ The concept of disrupting the plaque matrix has found favor on a periodic basis. Research in the 1970s on the effects of two enzymes, mutanase and dextranase, showed early promise, but clinical effects were not forthcoming.⁹¹⁻⁹³ Significant subsequent effort is apparent from the scientific and IP literature, focused on enhancing enzyme activity, stability, and retention in the mouth. Of interest is a novel glucanhydrolase, with both mutanase and dextranase activity, that has been shown to reduce plaque formation in a short term “proof of concept” clinical study.⁹⁴

The introduction of phage display offers the possibility of developing biotechnologies that express protein-based therapeutics in the mouth. The concept of cloning genes into an oral microorganism to express a therapeutic active and re-implanting the modified organism into the mouth has recently attracted attention. The first principle, that oral microorganisms can be genetically modified to produce active agents, has been demonstrated through the expression of a single chain antibody to *S mutans* antigen 1/11 in *Lactobacillus zeae*.⁹⁵

In summary, there are numerous exciting scientific approaches being pursued in basic dental research to identify and evaluate new routes to prevent oral diseases in children and adolescents. Rapid progress is being made in biotechnology, especially genomics, proteomics, and nutrigenomics, and in materials science, especially nanotechnology, that may enable effective biology-based interventions and “smart” delivery systems to be turned into practice. Early “proof of concept” studies show that there are some promising avenues to new interventions. Whether they can be fully validated in human clinical trials and developed into meaningful therapies remains to be determined.

So, what will it take to develop a major new therapeutic for the prevention of oral disease in children and adolescents and bring it into clinical practice and individual self care? There is no doubt that improved diagnostics for early caries detection and for composite risk assessment will be invaluable. In common with medical research and the development of pharmaceuticals, a robust and predictive hierarchy of screening tools, which include laboratory (mechanism-based) and human (*in vivo* and *in situ*) protocols, will enhance the “hit” rate in the drug discovery phase. Cost effective product delivery systems are essential to “put the science into practice.” Efficient clinical research is vital to ensure that truly effective measures are readily validated.

Finally, regulatory approval for a new therapeutic requires significant investment.

Challenges and opportunities

There are challenges ahead in the quest to deliver excellent oral health to all sectors of society. The paradigm that dental caries and periodontal disease may not truly be prevented is one. At this time, there certainly are no “magic” bullets; based on available evidence, the best that may be accomplished is disease control through judicious use of multiple interventions. A second challenge, given the divergent trends in caries experience, is the alignment of both research and clinical practice with the “real” target population. What is the right balance between further implementation of current measures and the development of new interventions? A third challenge is the cost effectiveness, cost/benefit, and risk/benefit of disease prevention to society and to the individual. Focus on these challenges should help in placing research bets and driving research investment through to implementation.

Likewise, opportunities will arise from advances in science and technology outside of dental research, from investment in core capabilities to support research priorities, and from increased effectiveness of translational research. Together, they will enable new therapeutic approaches to prevention of oral diseases in children and adolescents to be explored more effectively and the most promising approaches to be reduced to practice faster and smarter.

References

1. US Department of Health and Human Services. Oral Health in America: A Report of the Surgeon General. Rockville, MD: US Department of Health and Human Services, National Institute of Dental and Craniofacial Research, National Institutes of Health, 2000.
2. Scheie AA. Dentifrices in the control of dental caries. In: Embery G, Rolla G, eds. Clinical and biological aspects of dentifrices. Oxford Medical Publications; 1992:29-40.
3. Stamm JW. The value of dentifrices and mouth rinses in caries prevention. *Int Dent J* 1993;43:517-527.
4. O’Mullane D. Contribution of fluoride toothpastes to oral health. *Int Cong Symp Series* 1995; 209:3-8.
5. White DJ. Tartar control dentifrices: Current status and future prospects. In: Embery G, Rolla G, eds. Clinical and biological aspects of dentifrices. Oxford Medical Publications 1992:277-292.
6. Netuveli GS, Sheiham A. A systematic review of the effectiveness of anticalculus dentifrices. *Oral Health Prev Dent* 2004;2:49-58.
7. Kanapka J. Over-the-counter dentifrices in the treatment of tooth hypersensitivity. *Dent Clin N Am* 1990;34:545-560.

8. Jackson RJ. Dentifrices for the treatment of dentine hypersensitivity. In: Embery G, Rolla G, eds. *Clinical and biological aspects of dentifrices*. Oxford Medical Publications 1992:337-344.
9. van der Ouderaa FJG. Human clinical studies of anti-plaque and anti-gingivitis agents dosed from a dentifrice. In: Embery G, Rolla G, eds. *Clinical and biological aspects of dentifrices*. Oxford Medical Publications 1992:181-204.
10. van der Ouderaa FJG, Cummins D. Anti-plaque dentifrices: Current status and prospects. *Int Dent J* 1991;41:117-123.
11. Volpe AR, Petrone ME, DeVizio W, Davies RM, Proskin HM. A review of plaque and gingivitis, calculus and caries clinical studies with a fluoride dentifrice containing triclosan and PVM/MA copolymer. *J Clin Dent* 1996;7(Suppl);S1-S14.
12. Cummins D. Zinc citrate/triclosan: a new anti-plaque system for the control of plaque and the prevention of gingivitis: Clinical and mode of action studies. *J Clin Periodontol* 1991; 18:455-461.
13. Vargas CM, Crall JJ, Schneider DA. Sociodemographic distribution of pediatric caries: NHANES III, 1988-1994. *J Am Dent Assoc* 1998;129:1229-1238.
14. Peterson PE. *The World Oral Health Report, 2003*. Geneva, Switzerland: World Health Organization; 2003. Available at: www.who.int/oral_health/media/en/orh_report_03_en.pdf. Accessed February 8, 2005.
15. Bratthall D, Hansel-Petersson G, Sundberg H. Reasons for the caries decline: what do the experts believe? *Eur J Oral Sci* 1996;194(4pt2):416-432.
16. Diehnelt DE, Kiyak HA. Socioeconomic factors that affect international caries levels. *Comm Dent Oral Epidemiol* 2001;29: 226-233.
17. Edelstein BL. Pediatric caries worldwide: Implications for oral hygiene products. *Compend Contin Educ Dent* 2005;26 No 5(Suppl 1):4-9.
18. Fejerskov O. Changing paradigms in concepts on dental caries: Consequences for oral health care. *Caries Res* 2004;38:182-191.
19. Marsh PD. Dental plaque as a microbial biofilm. *Caries Res* 2004;38:204-211.
20. Critchley P, Wood JM, Saxton CA, Leach SE. The polymerization of dietary sugars by dental plaque. *Caries Res* 1967;1:112-129.
21. Bowen WH, Velez H, Aquila M, Velásquez H, Sierra LI, Gillespie G. The microbiology and biochemistry of plaque, saliva and drinking water from two communities with contrasting levels of caries in Columbia, SA. *J Dent Res* 1977;56: C32-C39.
22. Hotz P, Guggenheim B, Schmid R. Carbohydrates in pooled dental plaque. *Caries Res* 1972;6: 103-121.
23. Caufield PW, Li Y, Dasanayake A. Dental Caries: An infectious and transmissible disease. *Compend Contin Educ Dent* 2005;26 No 5(Suppl 1):10-16.
24. Slayton R. Oral health promotion in children and adolescents. *Compend Contin Educ Dent* 2005;26 No 5(Suppl 1):30-35.
25. Lindhe J, Nyman S. The effect of plaque control and surgical pocket elimination on the establishment and maintenance of periodontal health: A longitudinal study of periodontal therapy in cases of advanced tissue disease. *J Clin Periodontol* 1975;2:67-69.
26. Axelsson P, Lindhe J. Effect of controlled oral procedures on caries and periodontal disease. *J Clin Periodontol* 1978;14:524-527.
27. Attstrom R. Does supragingival plaque removal prevent further breakdown? In: Guggenheim B, ed. *Periodontology Today* Karger, Basel. 1988;251-259.
28. Cummins D. Routes to chemical plaque control. *Biofouling* 1991;4:199-207.
29. Surma D. Consumer assessment of toothbrushes designed for children of different ages. *Compend Contin Educ Dent* 2005;26 No 5(Suppl 1):36-39.
30. Topping G, Assaf A. Strong evidence that daily use of fluoride toothpaste prevents caries. *Evid Based Dent* 2005;6:32.
31. Chaves SC, Vieira-da-Silva LM. Anticaries effectiveness of fluoride toothpaste: A meta-analysis. *Rev Saude Publica* 2002;36:598-606.
32. Twetman S, Axelsson S, Dahlgren H, Holm AK, Kallestal C, Lagerhof F, Lingstrom P, Mejare I, Nordenram G, Norlund A, Petersson LG, Soder B. Caries-preventive effect of fluoride toothpaste: a systematic review. *Acta Odont Scand* 2003;61:347-355.
33. Marinho VCC, Higgins JPT, Logan S, Sheiham A. Fluoride toothpastes for preventing dental caries in children and adolescents. *The Cochrane Database of Systematic Reviews* 2005;Issue 3:Cochrane Library, ISSN 1464-780X.
34. Marinho VCC, Higgins JPT, Logan S, Sheiham A. Fluoride mouth rinses for preventing dental caries in children and adolescents. *The Cochrane Database of Systematic Reviews* 2005;Issue 3:Cochrane Library, ISSN 1464-780X.
35. Twetman S, Petersson LG, Axelsson S, Dahlgren H, Holm AK, Kallestal C, Lagerhof F, Lingstrom P, Mejare I, Nordenram G, Norlund A, Soder B. Caries-preventive effect of sodium fluoride mouth rinses: a systematic review of controlled clinical trials. *Acta Odont Scand* 2004; 62:223-230.
36. Adair SM. The role of fluoride mouth rinses in the control of dental caries: a brief review. *Pediatr Dent* 1998;20:101-104.
37. Newbrun E. Topical fluorides in caries prevention and management: A North American perspective. *J Dent Educ* 2001;65:1078-1083.
38. Benson PE, Parkin N, Millett DT, Dyer FE, Vine S, Shah A. Fluorides for the prevention of white spots on teeth during fixed brace treatment. *The Cochrane Database of Systematic Reviews* 2005;Issue 3:Cochrane Library, ISSN 1464-780X.

39. Marinho VCC, Higgins JPT, Logan S, Sheiham A. Fluoride gels for preventing dental caries in children and adolescents. *The Cochrane Database of Systematic Reviews* 2005;Issue 3:Cochrane Library, ISSN 1464-780X.
40. Seppa L. Efficacy and safety of fluoride varnishes. *Compend Contin Educ Dent* 1999;20(1 Suppl):18-26.
41. Beltran-Aguilar ED, Goldstein JW, Lockwood SA. Fluoride varnishes. A review of their clinical use, cariostatic mechanism, efficacy and safety. *J Am Dent Assoc* 2000;131:589-596.
42. Strohmeier L, Brambilla E. The use of fluoride varnishes in the prevention of dental caries: a short review. *Oral Dis* 2001;7:71-80.
43. Weintraub JA. Fluoride varnish for caries prevention: comparisons with other preventive agents and recommendations for a community-based protocol. *Spec Care Dentist* 2003;23:180-186.
44. Marinho VCC, Higgins JPT, Sheiham A, Logan S. One topical fluoride (toothpastes, or mouth rinses, or gels, or varnishes) versus another for preventing dental caries in children and adolescents. *The Cochrane Database of Systematic Reviews* 2005;Issue 3:Cochrane Library, ISSN 1464-780X.
45. Marinho VCC, Higgins JPT, Sheiham A, Logan S. Combinations of topical fluoride (toothpastes, mouth rinses, gels, varnishes) versus single topical fluoride for preventing dental caries in children and adolescents. *The Cochrane Database of Systematic Reviews* 2005;Issue 3:Cochrane Library, ISSN 1464-780X.
46. Axelsson S, Soder B, Nordenram G, Pertersson LG, Dahlgren H, Norlund A, Kallenstal C, Mejare I, Lingsstrom P, Lagerhof F, Holm AK, Twetman S. Effect of combined caries-preventive methods: a systematic review of controlled clinical trials. *Acta Odontol Scand* 2004;62:163-169.
47. Cummins D. Mechanisms of action of clinically proven anti-plaque agents. In: Embery G, Rolla G, eds. *Clinical and Biological Aspects of Dentifrices*. Oxford University Press 1992:205-228.
48. Jones CG. Chlorhexidine: is it still the gold standard? *Periodontol* 2000 1997;15:55-62.
49. Advanced Notice of Proposed Rulemaking: 21 CFR Part 356: Oral Health Care Drug Products for Over-the-Counter Human Use; Antigingivitis/Antiplaque Drug Products: Food and Drug Administration. www.fda.gov/OHRMS/DOCKETS/98fr/03-21669.htm.
50. Nabi N, Mukerjee C, Schmid R, Gaffar A. In vitro and in vivo studies on triclosan/PVM/MA copolymer/NaF combination as an anti-plaque agent. *Am J Dent* 1989;2(Spec Issue):197-206.
51. Davies RM, Ellwood RP, Davies GM. The effectiveness of a toothpaste containing triclosan and polyvinyl-methyl ether maleic acid copolymer in improving plaque control and gingival health: a systematic review. *J Clin Periodontol* 2004;31:1029-1033.
52. Mann J, Vered Y, Babayof, Sintes J, Petrone ME, Volpe AR, Stewart B, DeVizio W, McCool JJ, Proskin HM. The comparative anti-caries efficacy of a dentifrice containing 0.3% triclosan and 2.0% copolymer in a 0.243% sodium fluoride/silica base and a dentifrice containing 0.243% sodium fluoride/silica base: A two-year caries clinical trial in adults in Israel. *J Clin Dent* 2001;12:71-76.
53. Zambon JJ, Reynolds HS, Dunford RG, DeVizio W, Volpe AR, Berta R, Temprow JF, Bonta Y. Microbial alterations in supragingival dental plaque in response to a triclosan-containing dentifrice. *Oral Microbiol Immunol* 1995;10:247-255.
54. Fine DH, Furgang D, Bonta Y, DeVizio W, Volpe AR, Reynolds H, Zambon JJ, Dunford RG. Efficacy of a triclosan/NaF dentifrice in the control of plaque and gingivitis and concurrent microflora monitoring. *Am J Dent* 1998;11:259-270.
55. Walker C, Borden LC, Zambon JJ, Bonta CY, DeVizio W, Volpe AR. The effects of a 0.3% triclosan-containing dentifrice on the microbial composition of supragingival plaque. *J Clin Periodontol* 1994;21:334-341.
56. Rosling B, Wannfors B, Volpe AR, Furuichi Y, Ramberg P, Lindhe J. The use of a triclosan/copolymer dentifrice may retard the progression of periodontitis. *J Clin Periodontol* 1997;24:873-880.
57. Furuichi Y, Rosling B, Volpe AR, Lindhe J. The effect of a triclosan/copolymer dentifrice on healing after non-surgical treatment of recurrent periodontitis. *J Clin Periodontol* 1999;26:63-66.
58. Cullinan MP, Westerman B, Hamlet SM, Palmer JE, Faddy MJ, Seymour. The effect of a triclosan-containing dentifrice on the progression of periodontal disease in an adult population. *J Clin Periodontol* 2003;30:414-419.
59. Ellwood RP, Worthington HV, Blinkhorn ASB, Volpe AR, Davies RM. Effect of a triclosan/copolymer dentifrice on the incidence of periodontal attachment loss in adolescents. *J Clin Periodontol* 2003;30:414-419.
60. Davies RM, Ellwood RP, Davies GM. The contribution of industry to the decline in dental caries. *Dent Update* 2001;28(3):140-142.
61. Berg JH. Early dental caries detection as part of oral health maintenance in young children. *Compend Contin Educ Dent* 2005;26 No 5 (Suppl 1):24-29.
62. Schneiderman A, Elbaum M, Schultz T. Assessment of dental caries with Digital Imaging Fiber-Optic Transillumination (DIFOTI): in vitro study. *Caries Res* 1997;31:103-110.
63. Young DA. New caries detection technologies and modern caries management: merging the strategies. *Gen Dent* 2002;50:320-331.

64. Boersma JG, van der Veen MH, Lagerweij MD. Caries prevalence measured with QLF after treatment with fixed orthodontic appliances: influencing factors. *Caries Res* 2005;39:41-47.
65. Gonzalez-Cabazas C, Fontana M, Gomes-Moosbauer D. Early detection of secondary caries using quantitative light-induced fluorescence. *Oper Dent* 2003;28:415-422.
66. Pretty IA, Smith PW, Edgar WM. Detection of in vitro de-mineralization adjacent to restorations using quantitative light-induced fluorescence (QLF). *Dent Matter* 2003;19:368-374.
67. Featherstone JD, Adair SM, Anderson MH. Caries management by risk assessment: consensus statement. *J Calif Dent Assoc* 2003;31:257-269.
68. Featherstone JD. The caries balance: contributing factors and early detection. *J Calif Dent Assoc* 2003;31:129-133.
69. American Academy of Pediatric Dentistry. Policy on use of a caries risk assessment tool (CAT) for infants, children and adolescents. *Pediatr Dent* 2004;26:25-27.
70. Mirth D, Adderly DD, Amsbaugh SM, Monell-Torrens E, Li SH, Bowen WH. Inhibition of experimental dental caries using an intra-oral fluoride-releasing device. *J Am Dent Assoc* 1983;107:55-58.
71. C. Meyerowitz, G.E. Watson. The efficacy of an intra-oral fluoride-releasing system in irradiated head and neck cancer patients; a preliminary study. *J Am Dent Assoc* 1998;129:1252-1259.
72. Iijima Y, Cai F, Shen P, Walker G, Reynolds C, Reynolds EC. Acid resistance of enamel subsurface lesions remineralized by a sugar-free chewing gum containing casein phosphopeptide-amorphous calcium phosphate. *Caries Res* 2004;38(6):551-556.
73. Cai F, Shen P, Morgan MV, Reynolds EC. Remineralization of enamel subsurface lesions in situ by sugar-free lozenges containing casein phosphopeptide-amorphous calcium phosphate. *Aust Dent J* 2003;48(4):240-243.
74. Stoor P, Soderling E, Salonen JJ. Antibacterial effects of a bioactive glass paste on oral microorganisms. *Acta Odontol Scand* 1998;56(3):161-165.
75. Silva MF, Melo EV, Stewart B, DeVizio W, Sintes JL, Petrone ME, Volpe AR, Zhang Y, McCool JJ, Proskin HM. The enhanced anti-caries efficacy of a sodium fluoride and dicalcium phosphate dihydrate dentifrice in a dual-chambered tube: A 2-year caries clinical study on children in Brazil. *Am J Dent* 2001;14 Spec No:19A-23A.
76. Boneta AE, Neesmith A, Mankodi S, Berkowitz HJ, Sanchez L, Mostler K, Stewart B, DeVizio W, Petrone ME, Volpe AR, Zhang YP, McCool JJ, Bustillo E, Proskin HM. The enhanced anti-caries efficacy of a sodium fluoride and dicalcium phosphate dihydrate dentifrice in a dual-chambered tube: A 2-year caries clinical study on children in the United States. *Am J Dent* 2001;14 Spec No:13A-17A.
77. Baca P, Munoz MJ, Bravo M, Junco P, Baca AP. Effectiveness of a chlorhexidine-thymol varnish for caries reduction in permanent first molars of 6-7 year old children: 24 month clinical trial. *Comm Dent Oral Epidemiol* 2002;30(5):363-368.
78. De Soet JJ, Gruythuysen RJ, Bosch JA, van Amerongen WE. The effect of 6 monthly chlorhexidine varnish on the microflora and dental caries incidence in a population of children in Surinam. *Caries Res* 2002;36(6):449-455.
79. Kelly CG, Medaglini D, Younson JS, Pozzi G. Biotechnological approaches to fight pathogens at mucosal sites. *Biotechnology and Genetic Engineering Reviews* 2001;18:329-347.
80. Hillman JD. Principles of microbial ecology and their application to xerostomia-associated opportunistic infections of the oral cavity. *Adv Dent Res* 1996;10(1):66-68.
81. Tagg JR, Dierksen KP. Bacterial replacement therapy: adapting "germ warfare" to infection prevention. *Trends in Biotechnology* 2003;21(5):217-223.
82. Oh. Compositions containing lactic acid bacteria that inhibit the production of water insoluble glucan or inhibit GTF in dental plaque to prevent caries or inhibit the growth of anaerobic bacteria to reduce gingivitis, periodontitis and halitosis. World Patent application: WO9907826A1; US Patent application: US 20030077814A1.
83. Marshall RI. Gingival defensins: linking the innate and adaptive immune responses to dental plaque. *Periodontol* 2000 2004;35:14-20.
84. Arweiler NB, Sculean A, Auschill TM. Delmopinol—An alternative to chlorhexidine? *Schweiz Monatsschr Zahnmed* 2003;113(2):136-142.
85. Kruger C, Pearson SK, Kodama Y, Vacca-Smith A, Bowen WH, Hamanstrom L. The effects of egg-derived antibodies to glucosyltransferases on dental caries in rats. *Caries Res* 2004;38:9-14.
86. Wang BY, Kuramitsu HK. Interactions between oral bacteria: Inhibition of *Streptococcus mutans* bacteriocin production by *Streptococcus gordonii*. *Appl Environ Microbiol* 2005;71(1):354-362.
87. Sintes JL, Escalante C, Stewart B, McCool JJ, Garcia L, Volpe AR, Triol C. Enhanced anticaries efficacy of a 0.243% sodium fluoride/10% xylitol/silica dentifrice: 3-year clinical results. *Am J Dent* 1995;8(5):231-235.
88. Sintes JL, Elias-Boneta A, Stewart B, Volpe AR, Lovett J. Anticaries efficacy of a sodium monofluorophosphate dentifrice containing xylitol in a dicalcium phosphate dihydrate base. 30-month caries clinical study in Costa Rica. *Am J Dent* 2002;15(4):215-219.
89. Acevedo AM, Machedo C, Rivera LE, Wolff M, Kleinberg I. The inhibitory effect of an arginine bicarbonate/calcium carbonate Cavistat-containing dentifrice on the development of dental caries in Venezuelan school children. *J Clin Dent* 2005;16(3):63-70.

90. Marquis R, Bender GR, Murray DR, Wong A. Arginine deiminase system and bacterial adaptation to acid environments. *Appl Environ Microbiol* 1987;53:198-200.
91. Caldwell RC, Sandham HJ, Mann VW, Finn SB, Formicola AJ. 1. The effect of a dextranase mouthwash on dental plaque in young adults and children. *J Am Dent Assoc* 1971;82:124-131.
92. Lobene RR. 2. A clinical study of the effect of dextranase on human dental plaque. *J Am Dent Assoc* 1971;82:132-135.
93. Keyes PH, Hicks MA, Goldman BM, McCabe RM, Fitzgerald RA. 3. Dispersion of dextranous bacterial plaques on human teeth with dextranase. *J Am Dent Assoc* 1971;82:136-141.
94. Ryu SJ, Kim D, Ryu HJ, Chiba S, Kimura A, Day DF. Purification and partial characterization of a novel glucanhydrolase from *Lipomyces starkeyi* KSM 22 and its use for inhibition of insoluble glucan formation. *Biosci Biotechnol Biochem* 2000;64(2): 223-228.
95. Kuepper MB, Huhn M, Spiegel H, Ma J, Barth S, Fischer R, Finnern R. Generation of human antibody fragments against *Streptococcus mutans* using a phage display chain shuffling approach. *BMC Biotechnol* 2005;5(1):4.

Abstract of the Scientific Literature



Consistency of DIAGNOdent Instruments in Assessing Fissure Caries

The objectives of this study were to: (1) compare DIAGNOdent with visual examination and bitewing radiographs for clinical assessment of occlusal fissures; and (2) evaluate the consistency of 4 different machines. The authors also aimed to correlate DIAGNOdent readings with microbiological culture from the measured sites. Thirty-four occlusal lesions were examined in subjects between 18 and 30 years of age. Two examiners conducted visual and radiographic assessments. Each site was measured using 4 different DIAGNOdent instruments in random order. The fissure was opened and lesion depth was measured. Bacterial samples were taken from all lesions. The correlation between the DIAGNOdent readings and lesion depth was weak but significant. The level of infection showed a very weak correlation with DIAGNOdent readings. Inter-device correlation was significant, but a common cutoff point could not be determined.

Comments: Although the correlation between DIAGNOdent readings and lesion depth is weak, the instrument appears to be useful in detecting the presence of dentinal caries. The problem is that this cutoff point varies between instruments. The clinician should be aware of this fact and understand that recommendations of the manufacturer and others may need to be modified slightly for individual instruments. **SC**

Address correspondence to Dr. Alfheiður Ástvaldsdóttir, Department of Cariology and Endodontology, Institute of Odontology, Karolinska Institutet, PO Box 4064, SE-141 04 Huddinge, Sweden.

Ástvaldsdóttir Á, Holbrook WP, Tranaeus S. Consistency of DIAGNOdent instruments for clinical assessment of fissure caries. *Acta Odontol Scand* 2004;62:193-198.

27 references