Dental caries

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Abstract | Dental caries is a biofilm-mediated, sugar-driven, multifactorial, dynamic disease resulting in the phasic demineralization and remineralisation of dental hard tissues. Caries can occur throughout life, both in primary and permanent dentitions, and can damage the tooth crown and, in later life, also exposed root surfaces. The balance between pathological and protective factors influences the initiation and progression of caries. This interplay between factors underpins the classification of individuals and groups into caries risk categories allowing an increasingly tailored approach to care. Dental caries is an unevenly distributed, preventable disease with considerable economic and quality of life burdens. The daily use of fluoride toothpaste is seen as the main reason for the overall decline of caries worldwide over recent decades. This Primer aims to provide a global overview of caries, acknowledging the historical era dominated by restoration of tooth decay by surgical means, but it focusses on current, progressive and more holistic long-term, patient-centred, tooth-preserving preventive care.

[H1] Introduction

Dental caries involves interactions between the tooth structure, the microbial biofilm formed on the tooth surface (Figure 1) and sugars, as well as salivary and genetic influences [1]. The dynamic caries process consists of rapidly alternating periods of tooth demineralisation and remineralisation which, if net demineralisation occurs over sufficient time, results in the initiation of specific caries lesions at certain anatomical predaliction sites on the teeth. It is important to balance the pathological and protective factors which influence the initiation and progression of dental caries. Protective factors promote remineralisation and lesion arrest, whereas pathological factors shift the balance in the direction of dental caries and disease progression [1] (Figure 2). The daily use of fluoride toothpaste is seen by many authorities as the main reason for the overall decline of caries worldwide over recent decades; the mode of action of such toothpastes is concerned with shifting the balance of the oral biofilm towards health.

There is not a direct correlation between the extent of a caries lesion and whether or not pain and discomfort is felt. However, severe toothache, when it occurs, can be disabling and infection and sepsis arising as a consequence of caries spreading to involve the dental pulp can occasionally lead to serious systemic consequences (such as spreading local infection and, very rarelytreatment-related death (as a complication of anaesthesia), as well as to tooth loss.

The clinical detection of caries is traditionally made by detailed visual inspection of clean teeth by trained examiners. Although sharp pointed dental probes (or explorers) are still often used, they provide little additional diagnostic benefit and can do some damage. Dental radiographs or other supportive diagnostic methods are also needed in clinical practice to detect those lesions which remain hidden to visual assessment, particularly those situated on approximal tooth surfaces (that is, those surfaces that form contacts between adjacent teeth).

Although the ravages of caries can make teeth appear to be highly vulnerable to destruction by disease, from an evolutionary biology perspective human teeth are a high valued organ system involved in the prehension and processing of food, and can also function in defense, sexual attraction and phonetic articulation[2]. The outer surface of the tooth crown is composed of the hardest substance in the body (enamel) (Figure 1) with a specialized fluid (saliva) being secreted throughout the day to preserve its integrity. The morphology of the modern dentition has evolved mainly based on our dietary preferences, which have changed over the millennia[2]. Interestingly,

diets high in sugar tend to be soft and often liquid; teeth are not required for their ingestion, which may explain why teeth can be rapidly lost.

The aim of this Primer is to provide a balanced international overview of dental caries, both as a complex, multi-factorial disease and as a dynamically fluctuating disease process. The article covers the full range of perspectives from epidemiology to quality of life — via pathophysiology, diagnosis, risk assessment and prevention. Public health aspects are an important complement, but not covered in depth for reasons of space. Current research evidence is helping to chart the way forward to a more biologically-based way of planning and delivering caries prevention and care, at both the population and individual levels. These considerations underpin the development of science, practice and policy to optimise patient care and health.

[H1] Epidemiology

Epidemiological studies of caries have been undertaken for many decades and some of the data available through WHO and other organisations gives an impression that we have plentiful comparable global data. However, in order to evaluate and plan policy, epidemiology should provide data meeting the following specification: timely, accurate and understandable data for key age groups on the total amount of disease present (prevalence), the rate of disease progression (incidence) and disease trends over time. In addition, information on variations in disease levels between and within countries, including the estimates and trends in health inequalities (that is, differences in health status between groups within populations), are needed. However, we do not currently have accurate, up–to-date, clinically meaningful information across the globe that meets these specifications. Dental caries is still a neglected topic, despite the acknowledgment of the WHO that is still a major health problem in most industrialized countries, where 60-90% of children and the vast majority of adults are affected by dental caries[3]. Although caries has been considered a disease of childhood, in reality it continues into adulthood[4], where health inequalities remain[5].

Dental caries are considered to be the single most common chronic childhood disease, and its prevalence is thought to have increased recently in children ages 2-5 years globally, making this age group a global priority action area[6,7,8]. Census data from 2007 reported that for US children aged 2 to 5, caries prevalence in primary teeth showed an increase, from approximately 24% to 28% between 1988–1994 and 1999–2004 with caries rates being higher in children living in poor households or those from ethnic minorities [9]. In a more recent National Health and Nutrition Examination Survey (NHANES), from 2011-2012 approximately 23% of US children ages 2-5 years had dental caries in primary teeth. In addition, the same data revealed that approximately 10% of US children ages 2- 5 years had untreated dental caries. Dental caries prevalence shows marked differences in different regions of the US. In a recent study using the NHANES data from 1999-2004, children in LA County, one of the largest US counties, were more likely to experience dental caries than the average number across the US. Nearly 40% of preschool children residing in LA County had dental caries in primary dentition compared to 28% of same age children in the US. Children residing in LA County had less favorable oral health than children in the US in 1999-2004 with ethnic minorities having the worst [10] . Early childhood caries (ECC) – a very severe type of caries in children is a common bacterially-mediated and multifactorial disease characterized by marked decay of the teeth of children ≤6 years of age which is thought by some to be transmissible from caretakers to their children but is fully preventable. Representative international data is patchy on ECC, as most countries only report caries from age 5 or 6 years.

Traditionally, low caries prevalence has been observed in the developing countries, whereas the prevalence is higher in developed countries.[3] This geographic situation has become more complex due to speed of economic development and rapid changes in habits and diet in many countries. Although there might be gender or ethnic differences, they are minor compared with by sugar consumption, lifestyle and economic differences.

The traditional global index used to measure caries in epidemiological studies — but not clinical practice — is the DMF (Decayed, Missing and Filled) index, which is a numerical count of affected teeth per individual collected at either the Tooth (DMFT) or tooth Surface level (DMFS). The count of DMFT for an individual or group records their caries experience (that is, the total of both current and past caries). The index can be used at the different diagnostic thresholds which affect both mean DMFT and the proportion of individuals affected[11,12,13]. Depending on the criteria used, proportion of 15-year olds varies between 11-52% (Figure 3)[14].

Efforts are underway worldwide to improve our understanding of caries epidemiology by improving methodologies and optimising them for use in epidemiological field work, while also keeping compatibility with systems used in a fully equipped dental practice. In epidemiology, the International Caries Detection and Assessment System (ICDAS) "Epi modifications"[12], which can be used alongside the WHO basic reporting criteria[13], have now been used in many countries,[15] along with the more recent simplified merged-codes option[16] (Figure 3). The merged ICDAS codes, which are closer to those used in clinical practice, considers sound surfaces and three stages of caries as opposed to sound surfaces and six stages of caries in the full codes ICDAS option. It is also possible to combine clinical and radiographic findings to reveal the full prevalence of caries[17]. Recent work by a number of European organisations has shown — by way of a global example —that most of current national caries data for DMFT levels in 12-year-old children are not comparable across Europe[15]. This highlights the real challenges facing epidemiological studies on caries where apparently comparable results from across a number of countries have, in fact, been collected at different time-points with very variable levels of training and calibration and record caries at different thresholds.

When oral health topics were added to the ongoing Global Burden of Disease Study[18], oral diseases were found to be highly prevalent, affecting approximately 3.9 billion people worldwide. The methodology used in this major study is useful because it allows comparison with other diseases in terms of burden, but also novel from a caries epidemiology since it does not use the DMF Index

(which has been used globally for the last 60 years). Untreated caries in permanent teeth was the most prevalent condition evaluated across all medical conditions, with a global prevalence of 35% for all ages combined with 2.4 billion people affected. Note that some of these permanent teeth will have been in children and adolescents. Untreated caries in primary teeth in children ranked the 10th in prevalence, affecting 621 million children worldwide.

[H1] Mechanisms/pathophysiology

The mechanisms and pathophysiology underlying the development of dental caries are now increasingly well-understood and are best considered first from the hard tissue-related aspects (as the disease affects the calcified dental tissues) and then from the microbiology (biofilm)-related aspects (as these represent the driver of the caries process if homeostatic imbalance is maintained) (Figure 1). However, because of the multifaceted nature of the disease process, these factors are not independent. The dental hard tissues that are exposed to the oral environment (crowns and later roots following gingival recession) are the targets of the caries disease process and all tooth surfaces are susceptible throughout an individual's lifetime. However, caries will not occur in the absence of a cariogenic (pathogenic) dental biofilm and frequent exposure to dietary carbohydrates, mainly free sugars[19,20], and thus caries must be considered a dietary-microbial disease[21]. A modern concept of caries also includes consideration of how behavioural, social, and psychological factors as well as biologic factors are involved[22,23,24]. The importance of fluoride in modifying disease expression cannot be overemphasised[25] (Box 1). Perhaps dental caries can be best described as a complex biofilm-mediated disease that can be mostly ascribed to behaviours involving frequent ingestion of fermentable carbohydrate (sugars such as glucose, fructose, sucrose, and maltose) and poor oral hygiene in combination with inadequate fluoride exposure.

[H2] Demineralization and remineralization

Dental caries typically start at and below the enamel surface (the initial demineralisation is sub-surface) and is the result of a process where the crystalline mineral structure of the tooth is demineralized by organic acids produced by biofilm bacteria from metabolism of dietary fermentable carbohydrates, primarily sugars. Although a wide range of organic acids can be generated by dental biofilm microorganisms, lactic acid is the predominant end product from sugar metabolism[26] and is considered to be the main acid involved in caries formation. As acids build up in the fluid phase of the biofilm, the pH drops to the point where conditions at the biofilm-enamel interphace become undersaturated and acid demineralizes the tooth mineral so the surface layer of the tooth is partially demineralized[27]. The loss of mineral leads to increased porosity, widening of the

spaces between the enamel crystals and softening of the surface, which allows the acids to diffuse deeper into the tooth resulting in demineralization of the mineral below the surface (sub-surface demineralization). The build-up of reaction products, mainly calcium and phosphate, from dissolution of the surface and sub-surface raise the degree of saturation and can partially protect the surface layer from further demineralization. Also, the presence of fluoride can inhibit the demineralization of the surface layer[28]. Once sugars are cleared from the mouth by swallowing and salivary dilution, the biofilm acids can be neutralized by the buffering action of saliva. The pH of biofilm fluid returns toward neutrality and becomes sufficiently saturated with calcium, phosphate, and fluoride ions so that demineralization stops and re-deposition of mineral (remineralization) is favoured. Due to the dynamic nature of the disease process, the very early (subclinical) stages of caries can be reversed or arrested especially in the presence of fluoride.

As demineralization progresses into the subsurface of the enamel and dentin in the case of root caries, with a continuing acid challenge and pH drop the rate of mineral loss becomes greater in the subsurface than at the surface, resulting in the formation a subsurface lesion. When sufficient mineral is lost, the lesion appears clinically as a white spot. This is a clinically important stage of the caries process, since the lesion can be arrested or reversed by modifying the causative factors or applying preventive measures; however, the repair process is typically mostly restricted to the surface layer.

At this stage in its development, initial-stage caries (ICDAS codes 1 and 2) are considerably demineralised, they may with changes in the local ecology, dietary practices and fluoride availability arrest and remain as they are (inactive lesions which do not progress but remains still recognisable as a scar because of the changes in the optical properties of the enamel), remineralise and effectively heal (re-precipitation of mineral in the lesion and possibly some superficial surface wear resulting in an apparently sound surface), or remain active and progress to a more extensive stage of destruction.

If the caries process progresses further, the surface porosity increases with the formation of microcavitations in enamel (ICDAS code 3) or in root caries — a progressive softening of the surface dentine layer. In caries of the tooth crown the surface layer of the lesion may eventually collapse, resulting in physical cavitation (a macroscopic hole – ICDAS code 5 or 6). Even at this more extensive stage of caries severity, a lesion may in optimal circumstances still arrest, although the biofilm retaining cavity will persist. When an irreversible stage of lesion extent is reached (typically in most

developed countries ICDAS 5&6), combined with symptoms and/or considerations of the functional or aesthetic needs of the patient, operative intervention is indicated. If the caries process continues eventually the dental pulp will be compromised and either a root canal treatment or tooth extraction will be necessary.

For optimal tooth health, the main goal is to maintain the mineral homeostasis of tooth surfaces. Since teeth are frequently exposed to acidic conditions either from biofilm or dietary acids, the ability to remineralize is essential to maintaining tooth integrity. Saliva is essential for preservation of tooth health by providing the minerals necessary for remineralization. Low levels of fluoride greatly enhance this process, which largely explains the remarkable effectiveness of fluoride in multiple delivery forms in reducing dental caries (Box 1)[28].

Dental caries is a dynamic disease process involving repeated cycles of demineralization and remineralization throughout the day[27,29].Teeth are most susceptible to caries when they first erupt in the mouth and over time become more resistant to subsequent acid challenge. The clinical implication is that there should be greater focus on monitoring the caries status of teeth and delivering preventive care during the periods when teeth are erupting.

[H2] Microbiology and dental biofilms

[H3] Oral microbiota in health. The mouth, such as other surfaces of the body, is colonized from birth by a diverse array of microorganisms (the oral microbiota)[30]. The most common group of microorganisms are bacteria, but yeasts, viruses, mycoplasmas, protozoa and *Archaea* can be present. The oral microbiota has a symbiotic or mutualistic relationship with the host. The resident oral microorganisms benefit from a warm and nutritious habitat provided by the host and, in return, act to repel invading microbes, contribute to the host defences, and engage in cross-talk with the host to down-regulate potentially excessive pro-inflammatory responses to commensal bacteria[31]. Saliva plays a critical role in maintaining this beneficial microbiota by buffering the oral environment at a neutral pH (optimal for the growth and metabolism of most of the oral microbiota), while providing proteins and glycoproteins as nutrients.

[H3] Dental biofilms. The oral microbiota grows on surfaces as structurally and functionally organised communities of interacting species, termed dental plaque[32,33]. Dental plaque is an

example of a biofilm, the formation of which involves a number of stages[34]. Tooth surfaces are covered by a conditioning film of proteins and glycoproteins (the acquired pellicle) that are derived mainly from saliva , but also contains components from bacteria and their products, gingival crevicular fluid (that seeps from the junction between the gum and the tooth), blood, and food[35] (Figure 1). The acquired pellicle provides binding sites for adherence by early bacterial colonizers of the tooth surface leading to dental biofilm formation, and also acts as physical barrier preventing acid diffusion[36].

Bacteria can be held weakly and reversibly near the surface by long-range van der Waal forces (force that do not involve covalent or ionic bonds) between the external layers of the bacterium and this conditioning film. Attachment becomes stronger and more permanent if interactions occur between molecules on the bacterium (adhesins) and complementary receptors in the conditioning film[32]. Secondary colonising species attach to the early colonisers (coadhesion), and the complexity of the biofilm increases. The biofilm undergoes maturation, and numerous synergistic and antagonistic microbial interactions occur[37]. A matrix is formed, composed of bacterial exopolymers (polymer secreted in the external environment), including polysaccharides derived from sugar metabolism and DNA; the matrix helps to retain the biofilm on the surface and can influence the penetration and movement of molecules within the biofilm[37,38]. The biofilm protect the bacteria against antimicrobial agents. The composition of these biofilms varies on different surfaces of the tooth due to subtle differences in the local environmental conditions.

[H3] Microbial aetiology of dental caries. The normally synergistic relationship between the resident microbiota and the host is dynamic and can be perturbed by changes in lifestyle or alterations to the biology of the mouth; these changes can predispose sites to disease. Risk factors for caries include the frequent consumption of fermentable dietary carbohydrates (especially sucrose)[39] and/or a reduced saliva flow[40] . Numerous cross-sectional and longitudinal epidemiological studies have reported a shift in the balance of the microbiota at sites with caries compared with sites with sound surfaces. Early studies of caries lesions found higher proportions and incidence of *Streptococcus mutans* and *S. sobrinus* compared with sound enamel; lactobacilli were isolated from advanced lesions[40]. These observations led to the proposal that caries are only caused by a limited subset of the many species found in dental biofilms (the 'specific plaque hypothesis') [41]. However, as more epidemiological studies were performed, caries were observed in

the apparent absence of these bacteria, whereas these organisms could persist on other surfaces that remained sound.

Subsequent laboratory studies confirmed that other bacteria found within dental biofilms could also generate a low pH from sugars, whereas others could reduce the potentially damaging effect of lactic acid by using it as a nutrient source and converting them to weaker acids, or by generating alkali from the metabolism of arginine or urea in saliva. These findings provided support for the 'non-specific plaque hypothesis', in which caries is a consequence of the net metabolic activity of the biofilm[41]. More recently, studies using classical culture or molecular approaches have found associations between caries and other groups of acid-producing and acid-tolerating bacteria, including a range of *Bifidobacterium*, *Actinomyces* and *Propionibacterium* species, and *Scardovia wiggsiae*.

Subsequently, alternative concepts have been proposed based on ecological principles that describe the events associated with caries[42,43]; these ecological plaque hypotheses are now generally accepted as the most plausible explanations of the microbial aetiology of caries (Figure 4). The original 'ecological plaque hypothesis' recognized the consistency of bacterial function (that is, rapid acid production and tolerance of the acidic conditions generated) in the absence of specificity in bacterial name, and emphasized the essential requirement of a caries-conducive environment (that is, sugar-rich diet and/or low saliva flow). Microorganisms with traits that are relevant to caries can be present in biofilms on sound enamel, but at a level or activity that is too low to be clinically relevant[42]. Caries is a consequence of an unfavorable shift in the balance of the resident microbiota driven by changes in the dental environment. The regular exposure of plaque to fermentable dietary sugars results in repeated conditions of low pH in the biofilms which will favour the growth and metabolism of acid-tolerating bacteria while inhibiting beneficial organisms that preferentially grow at neutral pH. Implicit in this hypothesis is the concept that disease can be controlled not only by directly inhibiting the implicated bacteria but also by interfering with the factors that drive the deleterious shifts in the microbiota (that is, reducing the amount and frequency of sugar intake to prevent acidic conditions, or promoting the use of snacks containing alternative sweeteners that cannot be metabolized to acid by oral bacteria)[42]. The ecological plaque hypothesis has recently been developed further to reflect the ability of some oral bacteria to adapt to acid stress during regular and prolonged conditions of low pH [the 'extended caries ecological hypothesis'][43]. Again, acidification of the plaque acts as the main factor selecting an acid-generating and acid-tolerating bacterial community, the development of which will increase the risk of caries[43] .

Dental caries, therefore, is not an example of a classic infectious disease but is a consequence of an ecological shift in the balance of the normally beneficial oral microbiota, driven by a change in lifestyle and oral environment. An appreciation of these principles opens up new avenues for caries prevention.

[H2] Environment and dental caries

Although biofilm formation is a natural process and is an essential step for caries formation, the presence of a biofilm on a tooth surface is not in and of itself an indication that disease is present. It is only after a complex interaction of host factors, including the tooth surface, acquired pellicle and saliva, and free sugars in the diet that the presence of the dental biofilm can lead to disease expression over time.

The unique environmental conditions that exist of each tooth site explain the highly localized and complex nature of the caries process whereby caries can occur at a specific location of the tooth surface and not on an adjacent tooth surface even when both appear to be covered by biofilm[27]. These include tooth-related factors that impact acid solubility (for example, tooth composition (imperfectly formed structure as in hypoplasias) and structure, and pre-eruptive and post-eruptive fluoride exposure, post-eruptive age of the tooth), and those that influence biofilm thickness and pathogenicity by creating areas of plaque stagnation (for example, tooth morphology, arch form, occlusion and tooth position) [36,37]. Development defects (for example, enamel hypoplasia, a condition characterized by thin enamel) may lead to increase acid solubility and loss of surface structure creating sites of plaque stagnation and increased risk of caries in primary teeth[44]. Caries susceptibility can also be affected by proximity of teeth to salivary gland orifices, and salivary film thickness and velocity at specific tooth sites[36,37]. Dental appliances (such as orthodontic appliances and dentures) and faulty restorations can also increase caries susceptibility at specific tooth sites by creating areas of stagnation encouraging biofilm formation[27].

[H1] Diagnosis, screening and prevention

Diagnosis, risk assessment, screening and prevention are all vitally important considerations for the successful understanding and control of dental caries at both the individual and population levels. In many countries screening has a specific public health meaning discrete from clinical practice, but this topic is beyond the scope of this Primer. The focus here is on what happens at the individual patient level, where high numbers of patients interact with oral health professionals around the world on a daily basis. It must be emphasised that, in order to prevent and control caries, both public health and individual level interventions need to be optimised and aligned.

The International Dental Federation (FDI)[1,45] and dedicated meetings[46] have reviewed the caries systems that are available. Although excellent work has been carried out in some countries in developing a range of assessment systems (Box 3), there is a shortage of comprehensive, internationally applicable, evidence-informed, holistic clinical systems, let alone ones developed by formal consensus processes. Therefore, whilst fully acknowledging that there are a range of other systems for undertaking some parts of the clinical tasks required to inform modern caries management, we will use the International Caries Classification and Management System (ICCMS [47-50]) as a unifying framework to illustrate the key points (Figure 5). In ICCMS, the elements of caries risk assessment at both the patient and intra-oral levels, together with the classification of caries by staging lesion severity and assessing lesion activity based on the ICDAS system are brought together with decision making. This information is used to produce a personalised care plan which can then be undertaken with an emphasis on tooth-preserving caries prevention and control, followed by risk based follow-up plan (dental recall). [47-50] The four key elements of the system (simplified for general practice as the "4D ICCMS Caries Management") allows a comprehensive assessment and formulation of a personalised caries care plan Figure 5.

[H2] Prevention

[H3] Public health management. The goal of dental caries prevention is to preserve sound tooth structure, prevent demineralization of enamel and promote natural healing processes[46]. Interventions can be implemented at the population level with health policy, legislation, regulation and public health approaches to promote healthy behaviours and

impact broader social determinants of health[51,52]. Prevention approaches may target an entire population (for example, water fluoridation and sugar taxes) to assure equity, or higher-risk groups to seek to increase cost-effectiveness. The subject of fluoride and caries is considered in Box 1, while there is further consideration of fluorides and caries prevention in Box 2. Some caries risk factors at the population level include low family income, restricted dental care access, low fluoride exposure, low oral health literacy and high caries prevalence. Research is ongoing to find the best ways to target high caries-risk individuals. Prevention programmes can be targeted at groups with medical or special health care needs such as those with compromised immunity (for example, HIV and leukemia), cognitive or developmental disabilities that can make oral hygiene difficult, genetic disorders that are associated with oral conditions (for example, cleft lip and palate, ectodermal dysplasia), salivary dysfunction from Sjögren syndrome, diabetes, or frequent use of some medications that cause dry mouth (for example, antihistamines).

Since dental caries is a multi-factorial disease, complementary interventions may be more effective than single interventions. The WHO's oral health action plan emphasizes the need for oral health prevention programmes to be combined with other chronic disease prevention and educational programmes and policies sharing common risk factors[53]. In the future shared electronic health records, mobile smart devices and social media may assist in these efforts[54]. The Alliance for a Cavity-Free Future (an international public health advocacy charity) has chapters worldwide promoting a comprehensive agenda of activities and resources to prevent caries initiation and progression. Advocacy and education efforts include increasing public awareness and behaviour change to improve oral hygiene and decrease sugar consumption, advancing research and clinical caries management[55.56].

Many water supplies contain naturally occurring amounts of fluoride. Community water fluoridation, the adjustment of fluoride to community water supplies to obtain optimal levels for caries prevention, is a cost-effective, equitable, population-approach that best meets public health criteria and benefits all age groups (Box 2)[57]. The United States Public Health Service recommends the concentration of 0.7 mg/l to maximize caries prevention while minimizing the risk of dental fluorosis[58]. This approach is likely to provide societal cost-savings[59]. The WHO recommends a higher concentration (1.5 mg/l) but flags that the expected volume of water consumed and intake of fluoride from other sources should be considered when setting national standards[60].

Salt fluoridation, often combined with iodized salt, is an effective, frequently used population-based method of caries prevention. It is used primarily in Europe, Central and South America where fluoride in the drinking water is low, community water fluoridation is not feasible, and other forms of fluoride are used less frequently[61]. The fluoride concentration in salt is usually 250-300part per million (ppm). It is the least expensive method of caries prevention[62]. Milk fluoridation programmes have been used in some countries such as Hungary and the UK.[63.64]

Dental sealants are professionally applied resin material brushed onto the caries-prone pit and fissured grooves of the occlusal chewing surfaces of children's molars (back teeth) to prevent disease in sound teeth or arrest progression of initial non-cavitated carious lesions[65]. The application does not require local anaesthesia and sealants can be applied in school-based programmes with portable equipment. Sealant programmes are an effective community approach[66] that can be cost-effective when applied to children at higher caries-risk or from low-income families[67]. In the United States, schools with many children enrolled in the Free and Reduced Price Meal Program are targeted for school-based interventions[68].

Although preventive strategies should be cost effective and result in societal cost saving, prevention programmes incur many up-front costs, whereas the savings gained by averted disease and treatment may take years to accrue [69]. The impact of dental pain and infection on quality of life also needs to be considered. Economic assessments of preventive strategies depend on many factors including caries prevalence, personnel and material costs, intervention effectiveness and time frame. Examples of results from two different populations follow for comparison (Box 4)[70, 71].

[H3] Individual patient level. Many of the same approaches and technologies used at the population level are also appropriate for use in the dental office or community clinic level. A range of evidence based toolkits[72,]. clinical guidelines[73,74] Cochrane systematic reviews[75] , taken together with the WHO Guideline on sugar consumption[76], provide a rich evidence base to support caries prevention in individuals presenting at the dental office. This is built around advice to limit amount and frequency of sugar intake (also linked also to obesity and diabetes prevention) as well as the frequent use of fluoride containing toothpastes, supplemented according to caries risk status by fissure sealants and more intensive preventive interventions.

[H2] Diagnosis

[H3] Risk assessment

The first element in assessing an individual for caries according to the ICCMS system is to determine patient-level caries risk by taking a comprehensive history asking a series of questions known to be associated with increased caries risk or caries protective factors. This includes assessment of the medical history, and the relevant social history, for example where the patient is born and raised, the present residence, education level, and occupation. Finally, the patient is asked about diet conditions in terms of amount of sugar intake and frequency per day, number of in between meal snacks and the type of toothpaste used; all information important to assess the caries risk at the individual level[77].

A wide range of risk assessment tools can be used and are compatible with the ICCMS System. One such risk assessment is Cariogram[78] , for which there is more evidence than for many alternative systems; studies have shown moderate accuracy on children and young adults[79]. Others include CAMBRA and other risk factors questionnaires from a number of Universities are alternatives. The Cariogram uses 9 predicators in its full form: DMFT, related diseases, diet content, diet frequency, amount of plaque, levels of mutans streptoccocci, fluoride use, saliva secretion, and buffer capacity. A low score (0,1) indicates that a particular predictor contributes to low risk, whereas a high score (2,3) to high risk, an overall risk can be estimated, if the patient's profile remains stable[78].

The risk assessment (independent of how it is derived) can be built later into the ICCMS caries risk likelihood matrix[49,50] , which combines clinical caries activity with risk level assessment. Eventually, it is possible to assess if the patient is in low, moderate or high risk of getting more new lesions or progression of the existing caries lesions, within the next few years. The risk of developing dental caries can be lowered by effective dietary advice, improved plaque control and increased use of fluoride, for example by using 1450 ppm fluoridated toothpaste instead of 1050 ppm toothpaste[80], assuming that the patient is compliant.

[H3] Clinical assessments

In order to find and assess any caries lesions on individual tooth surfaces, a clinical examination is performed (the detect and assess element of the ICCMS 4D methodology). The goal is to find any caries lesions present and assess their severity, activity and the risk factors at the tooth level. Assessments can include saliva secretion (and in some countries buffer capacity and the presence of mutans streptococci is measured). Whilst these latter tests are deemed to have some value in

patient motivation, increasing knowledge as to the complexity of the biofilm is making such tests less clinically relevant. The level of plaque present is assessed clinically as it helps in assessing caries activity. Professional tooth cleaning then allows the identification of initial-stage lesions[81] and later-stage lesions which are best detected on clean (plaque free) dry teeth. Location of gingival bleeding due to gentle probing is also noted as a further indicator of lesion activity. Clinical examination alone will, for many patients, be insufficient in making a complete assessment of caries. This is because using visual examination alone the dentist/dental hygienists may miss a great number of initial and even some more severe lesions (Figure 6A).[82,83]

Then the mouth is dried by means of cotton rolls, and the individual tooth is examined by using the dental compressed air syringe. Lesion severity is then assessed according to the clinical appearance of the tooth surfaces [47, 48, 49, 50]. Although for many years and in many countries dentists have used a sharp explorer of dental probe to press into tooth fissures, it is now accepted that there is little diagnostic benefit from the tactile element and it may convert an inactive lesion into an active one.

An assessment of caries activity of the detected and staged lesions can then be made. In the ICDAS classification system [48,84,85], several predictors are used: the location of the lesion (plaque stagnation area or not); the colour of the lesion (whitish versus brownish); tactile feeling (rough, smooth) when a blunted probe is run over the lesions, whether the lesion is matte or shiny, cavitated or non-cavitated; and finally, if the lesion is located along the gingival line and whether the gingiva bleeds after probing or not. If the lesion has more of the following characteristics (plaque stagnation area, whitish, rough tactile feeling, matted, cavitated, and gingiva bleeding) versus the other characteristics, the lesion is categorized as active and the final diagnosis of the lesion will be initial, moderate or extensive active. If not, lesions are classified as initial, moderate or extensive arrested (inactive)[47].

[H3] Radiographic assessment

Radiographic examinations have been an important part of caries assessments ever since diagnostic radiography became available (Figure 6B). However, there is a delicate balance to be struck in balancing the diagnostic benefit against the small but real risks of using ionizing radiation electively. Therefore decisions as to when and how often to take dental radiographs for caries detection will depend upon factors such as the result of a thorough clinical examination, the patient's caries risk status, their age and when radiographs were last taken. The so-called bite wing radiograph provides

valuable information for caries in the tooth crowns, but these must be supplemented by additional views for some patients.

Although the dose of ionizing radiation has reduced with improvements in X-ray generation and the speed and sensitivity of films and sensors, there is still a responsibility to keep exposures as low as reasonably achievable and to use other diagnostic information where available to minimize radiographic exposures. Examples of clinical indications for a radiograph could be: suspicion of a caries lesion for a surface that is not easily inspected visually and assessment of the depth of a lesion which is, at least partly, visible clinically.

It should be appreciated that clinically for some surfaces, particularly approximal surfaces where the site of caries attack cannot be visualized directly, radiographic information can be pivotal in assessing the extent of caries lesions in terms of depth towards the dental pulp. However, this information has to be combined with knowledge about caries activity status and overall caries risk when integrating all information into a personalized care plan including decisions to treat non-operatively or operatively (the D for Decide in the 4D System). Other situations where the radiographic information can be invaluable include suspicious occlusal fissures where, in a high fluoride environment, an apparently small lesion may on occasion extend radiographically into the inner dentine. These examples highlight the importance of combining and integrating the clinical and the radiographic information in order to be able to make accurate diagnoses from which to build appropriate care plans. Recall frequency for both clinical and radiographic examination should be decided on an individualised basis, according to caries risk.

At the end of the clinical and then the radiographic examination information on lesions visually detected and/or radiographically detected can be combined in order to make a diagnosis (Figure 6).

[H1] Management

Management of inactive and active (with various degree of severity is outlined below and in Figure 7.

[H2] Initial lesions

The initial lesion (even when active) is managed through non-operative care using remineralization therapy, involving behavioural changes and promotion of mineralization over demineralization, typically by using fluoride-containing procucts.[1] Remineralization is aimed at stopping progression of the lesion or ideally, reversing it. As part of the mineralization therapy, management should involve reviewing the dietary and oral hygiene behaviours (plaque control) of the patient, followed by education and encouraging behavioural changes[86].

Fluoride is able to increase the rate and magnitude of remineralization of initial lesions[87],[88]. Fluoride can be delivered topically either as paste, gel or varnish by a dental professional or in the form of toothpaste, gel or mouthwash at home settings [89] (Box 1) . The acidulated fluoridated products have a low pH 3.0-4.0. Reducing the pH of the fluoride vehicle has been demonstrated in the laboratory to prolong the ingress of mineral ions into the lesion by preventing the blockage of superficial enamel pores, precenting access to the deeper areas of the lesion[86, 90]. Ideally, full recovery of an initial caries lesion would be achieved when calcium and phosphate are penetrating at high enough concentrations in the presence of slightly elevated concentrations of fluoride[91]. Saliva is the most important source of ions around teeth and its flow can be enhanced through chewing sugar-free gums[92]. Fluoridated drinking water has proved to be effective by increasing the local concentration of this ion in saliva and plaque[93]. More recently, attempts have been made to further enhance the remineralization potential by incorporating water-soluble bioavailable calcium and fluoride into topical products such as sugar-free gums, dental creams and varnishes. These formulations include casein phosphopeptide-stabilized amorphous calcium phosphate and phosphoryl oligosaccharides of calcium and their fluoride containing variations [94, 95, 96]. Early research works suggest that these formulations may beneficial anti-cariogenic effects; however, evidence is yet to build up. [94, 95, 96].

Although a non-surgical approach to the management of initial lesions appears to be the most beneficial, minimal intervention therapy can be used as well. Pit and fissure sealants have been applied using resin based material and glass ionomer cement. A newly developed resin based product with surface pre-reacted glass-ionomer filler is expected to release fluoride sustainably

because of its ability to recharge fluoride ion[97]. These fillers release other ions enhancing tooth mineral formation[98].

When an initial lesion is found, long-term monitoring along with managing the caries risk factors is an option to consider. A surgical intervention can be considered only if the initial lesion advances[99, 100,101].

[H2] Moderate lesions

The goal of non-invasive management of moderate lesions (Figure 7) is to arrest further progression and regain lost minerals. Two options are available.

[H3] Mechanical blocking. Clinical evidence shows that non-cavitated lesions on occlusal surfaces can be arrested with resin-based fissure sealants[102]. Extrinsic substrates are blocked as acids produced by the biofilm cannot reach the enamel and the number of bacteria in the carious dentine is reduced. The procedure requires strict dry conditions and the sealants must be regularly checked and maintained. A related technology to arrest proximal lesions is resin infiltration of the dentin layer [103]. Lesions limited to the outer third of the dentin are treated with a resin that penetrates and repairs subsurface pores. Although long-term results are lacking, it seems clear that the micro-invasive treatments display lower long-term costs than invasive therapy[104, 105].

[H3] Fluorides. Self and professionally applied fluorides can remineralise and arrest caries lesions (Box 1). Topically applied silver diamine fluoride is a cost-effective alternative to arrest early childhood caries and root caries lesions in frail elderly, especially when other options are absent[106, 107].

In the near future, novel nanotechnologies based on peptides and hydroxyapatite crystals together with biofilm engineering are expected to advance the noninvasive restorative options for moderate caries lesions[108,109].

[H2] Extensive lesions

Extensive lesions are still most commonly subjected to classical standard care; the demineralized tissues are completely removed and replaced with a filling material. However, the development of adhesive techniques without need of mechanical retention (that is, composite resins or tooth-

coloured mixtures of plastic and glass) has allowed dentists to adopt a more tooth-preserving approach. Yet low-quality evidence suggests that resin composites lead to higher failure rates and risk of secondary caries than amalgam (metal-coloured mixture of mercury and other metals) restorations.[110]

A recent development is the stepwise or partial caries removal in which only the superficial layers of the lesions are removed. Systematic reviews have concluded that this approach reduces the incidence of pulp exposure and favor caries arrest and tertiary dentin formation (that is, laying down new protective dentine in response to an advancing caries lesion in both primary and permanent teeth)[100,111]. Although these techniques show clinical advantage over complete caries removal, it is too early to recommend certain clinical strategies. It must also be underlined that the decayed teeth must be vital and free from symptoms. Furthermore, the success depends on an appropriate restoration that completely seals the tooth and keeps remaining bacteria in the deeper dentin layers dormant. A disputed mode of managing advanced asymptomatic lesions in primary molars is the Hall-technique[112]. The tooth is not prepared in the conventional way, but is covered by a preformed stainless steel crown with a superior clinical performance when compared with traditional conventional restorative care[113].

[H2Children with a very high caries risk
To prevent caries and have successful management of oral diseases, perinatal and infant oral health care are essential aspects of early intervention, which facilitate behavioural changes and allow for good oral health[114]. An essential step is to start educating caregivers and their healthcare providers on the importance of dental care during pregnancy and infancy, with the development of child-specific oral health measures and methods to prevent oral diseases[115]. This is especially important for children who are at high risk of Early Childhood Caries (ECC) development. Although there is no mechanistic difference in the pathology and principles of care between ECC and other forms of caries in children or adults, the issues related to ECC have more to do with specific behavioural risk factors, most importantly night time bottle use with sugary beverages and juices. Although anatomical differences between primary and permanent teeth (such as the enamel is much thinner in primary teeth and thus caries can progress faster into dentin) exist, the mechanisms, pathophysiology and treatment approaches are not different between both types. However,

clinical management for the younger patient and the involvement of carergivers brings its own challenges.

Caries Management by Risk Assessment (CAMBRA) is an evidence-based approach adapted to the specific needs of the subset of the child population with ECC who experience a very aggressive caries challenge.[115,116] CAMBRA for ECC assists providers in a structured manner to firstly assess caries risk and risk on progression at an early age in a patient-centered approach, based on age and dental status and risk factors ; secondly tailor a specific individualized care or preventive management plan, before deciding on a surgical modality; thirdly formalise a follow-up plan based on risk and age of the child; and fourthly ensure specific guidance for the caretakers with targeted self-management goals based on the age, risk and need of each individual patient at any given time. This version of CAMBRA provides the information to assess the risk of caries development and disease progression in young children as low, moderate, or high risk.

Assessments can also be done through the use of this risk assessment technique on three specific domains: risk and/or biological factors such as continual bottle use, sleeping with a bottle, frequency and types of snacks, child taking any medications and some other risk factors; protective factors with questions such as the use of fluoridated tap water, use of fluoridated toothpaste or the use of xylitol (recommended by some but with mixed evidence) on a continuous basis; and clinical findings where providers can assess the presence of early demineralized caries enamel surfaces, or cavities at very early age, presence of plaque biofilm, lack of salivary flow, among others[117,118].

Through these guidelines for children provided by CAMBRA, early intervention can be conducted in primary care settings by any qualified pediatric health care provider. Furthermore, providers are recommended to use minimally invasive treatments such as fluoride varnish[119]. At home, the caregiver should be guided and supported to adopt good oral health behaviours for their children and themselves and to use fluoridated toothpaste as soon as the first tooth appears with a small amount no more than a grain of rice to protect the teeth from developing caries[120]. Ultimately, these practices will benefit in the prevention and self-management of ECC and have the potential to deliver better practice, improve clinical outcomes and reduce the overall burden of disease in young children[121].

[H2] Follow up / Recall

The final element of continuing caries care is to estimate when the patient needs to come to the clinic again, and this depends on the patient's age and actual caries-risk status. It is no longer deemed appropriate that all patients should be recalled every six months. If the risk-assessment indicates low risk, the next visit can be postponed more than one year for adults, moderate to high risk imply that the recall should be shorter. After a suitable risk-based recall interval the caries management cycle starts again (Figure 5).

[H1] Quality of life

Having considered the scientific, clinical and public health aspects of caries it is important to appreciate the impact that the disease has on quality of life across the life-course. The demographic transition towards ageing societies and the oral health transition with considerably more people keeping their natural teeth into old age has resulted in a relative shift in the burden of untreated caries towards adults [122]. Caries is still a highly prevalent condition among adults (18-65) and older adults (>65)[122,123, 124], but also in children, even among very young children affecting their primary dentition [122,125].

Toothache is still prevalent among children and adolescents, and is strongly associated to dental caries, particularly among lower socioeconomic position groups with an estimated 5-6% increase in probability of toothache for each additional primary tooth with caries experience[126]. In the most recent national study in the UK, 18% of 12-year-olds and 15% of 15-year-olds reported toothache[127]. Despite the fact that dental caries can be asymptomatic, particularly at its initial stages, caries is associated with diminished quality of life for people affected and their families[128]. Among children, caries is associated with negative impacts on a range of daily life activities [129,130] and this was the case also among very young children where caries was associated with worse oral health related quality of life in terms of perceptions of both children and their parents [131]. Similarly, toothache and tooth decay are the conditions most commonly associated with worse oral health related quality of life on adults. Among adults in England, Wales and Northern Ireland, 16% reported frequent and 17% severe impacts on their daily life due to their oral conditions, but the respective prevalence for both frequent and severe oral impacts was 24% among those with decay and 38% among those with experience of severe caries as expressed through the PUFA (pulpitis, ulceration, fistula or abscess) index [123]. Globally, untreated caries accounted for almost 5 million disability adjusted life years (DALYs) in 2010, with a further 4.5 million DALYs attributed to excessive tooth loss. Caries contributed to DALYs across the different ages but more so for children and young and middle-aged adults. Indeed, caries are the predominant oral health cause of DALYs among people aged ≤35 years.

On the other hand, extensive tooth loss, was prevalent and an important contributor to DALYs among middle aged and older adults [18].

The impact of dental caries is not limited to oral symptoms and the detrimental influence on the quality of life. Caries in primary dentition is associated with malnutrition[132]; children with severe early childhood caries have relatively poor nutritional health for a range of nutrients compared to caries-free controls[133,134]. Other studies have shown a link between caries experience and poor child growth and low weight gain[135-138]. The evidence on whether treatment for caries considerably enhances growth is inconclusive[139-142] and further methodologically robust studies with longer follow-up periods are needed in that respect. However, treating severe dental caries in children resulted in significantly reduced toothache and sepsis, and improved satisfaction with teeth and smile as well as appetite compared with children in whom dental caries were not treated.[142] Apart from growth and development, caries also negatively affects schooling, as children with poorer oral health were more likely to have higher rates of school absence and also perform poorly in school compared with children with better oral health. [143,144] Finally, excessive dental caries has been linked with considerably increased risk of hospitalisation and therefore also has cost implications.[128,145]

The aforementioned impacts of caries disproportionately affect the more deprived groups in the society [123,126,127,131,146], in line with the evidence on clear socioeconomic inequalities with higher risk of caries lesions or experience among those in lower socioeconomic positions[147]. This highlights the importance of focussing not only on behavioural and biological risk factors but also on the broader social and environmental determinants of the disease[148].

[H1] Outlook

Dental caries remains one of the most prevalent global chronic diseases.[9,149] For at least a century, dental caries has been managed surgically. Public health measures, such as water fluoridation and topical fluorides, have had considerable impact on the burden of dental caries in developed countries. However, the failure to eradicate or halt the burden of this disease in many parts of the world, as well as vulnerable population groups in developed countries, means that dental caries remains a major public health problem.

In the emerging era of health outcomes and value-based healthcare systems[150], the success and payment for the provision of health care will be determined not only by the type and number of procedures provided to patients but also by the final health outcomes achieved. Management of dental caries should move forward to a model where health outcomes form the basis for compensation and are the focus of dental care. Accordingly, the major outcome of caries management clinically, personally or at a community level is the preservation of tooth structure and maintenance of teeth in a healthy state (outcome 1). A second outcome would be to control initial stages and arrest their progression or reverse the caries process towards health (outcome 2). These two outcomes precede the outcome of restoring lost tooth structure and function of decayed teeth (outcome 3), which is the current major outcome that is being reimbursed by third party payers or patients all over the world. In order to achieve these three outcomes, process outcomes must be evaluated throughout the care cycle and be reimbursed accordingly.

Dentists and other dental professionals must stage the caries progress, assess risk factors (on the dental, medical, biological, behavioural, and social level), develop comprehensive management plans to prevent new caries based on risk status of patients, control initial lesions, restore cavitated lesions, rehabilitate the dentition, and develop a follow-up plan[54]. Assessing and reimbursing dentists to evaluate all these process outcomes is as important as reimbursing them for achieving the health outcomes through procedures because it is through these outcomes that dental health is achieved. There is no doubt that valuing the newly proposed outcomes represents a revolutionary change in dental care globally, which as stated before has so far been focused on delivery of procedures. A procedure-focused system of reimbursement is not obsolete but rather it must become part of a larger model of health promoting system of care. Implementation of a new paradigm in dental practice and education, as expected, will not be easy and will take time.

Fortunately, there are a few practical examples of success in changing paradigms of care in dentistry. For example, in the 1970s and 1980s, a series of clinical trials compared non-surgical and surgical periodontal therapies and found that for most levels of severity of periodontal diseases both modalities produced similar outcomes [151]. While there was vociferous reaction from supporters of the surgical modalities of care, the emergence of evidence led to a radical shift over two decades towards non-surgical care. It may be that similar changes to a less interventional approach to caries management can change practice[152]. Another pragmatic model for implementation is the development and dissemination of guidelines and policies that direct dentists into adopting the desired behaviours. Dentists are used to adopting, though with some hesitation, standards dictated

by dental insurance companies, government agencies, licensing boards or health authorities. The prime example of the change in behaviour due to policies is the adoption of infection control measures and standards for occupational health and radiation safety.

Other than those two pragmatic experiences, there is dearth of evidence on implementation of changes in dental practice[153]. Continuing education and articles in dental journals, while necessary, are by themselves insufficient in their effectiveness to influence change in practices of practitioners. The case to support this conclusion is clear in the adoption of pit-and-fissure sealants. Although sealants are based on the same materials as resin composite fillings, their adoption has been slower than the rapid growth in use of tooth coloured filling materials[154]. The reason for this may be because when sealants are promoted, based upon the evidence[155], as a procedure of choice for non-surgical management of initial caries lesions, they replace a standard operative procedure that dentists have adopted as the norm. By contrast, tooth-coloured restorative materials replaced amalgam "silver" filling materials, which dentists and patients started to abandon as a norm because of concerns about the exposure to mercury and aesthetics.

It is expected that the proposed integrated caries management system and value-based dental care require for many, but not all, changes in the current norms of practice. The way to move forward in implementation will require a multi-pronged strategy, collective engagement of all dentists, educators, and policy makers, and research studies that assess the outcomes of the new proposed paradigm of caries management, and refine it as needed. It should be appreciated that timescales and tipping points in implementation are notoriously unpredictable.

The burden of dental caries in the world is considerable in terms of cost, loss of time from work and school, in some cases severe facial and systemic infections, and rarely death. Hence, it is imperative that the new approach described in this Primer is implemented now. A collaboration among dental schools, clinics, and professional and government agencies must be formed to create a learning organization that share experiences and assist in conducting research of the previously described outcomes. The initial steps of this work are underway with a consensus production of a Guide in caries management for practitioners and educators[49]. Fortunately, there are today new tools that can aid and empower changing norms of practice and collecting outcome data. The use of computerized reminders, electronic audit and feedback, and stop-and-go decision algorithms in electronic health records, provide new venues to help in changing practitioner behaviours. Audit and feedback have been found to be modestly effective in changing healthcare behaviours[156].

Incorporation of instantaneous audit and feedback in electronic health records could provide reminders to practitioners to follow standards of care during the care process.

The task ahead will be to develop new tools and reimbursement incentives as well as form a collaboration to coordinate the implementation of the new caries management system across fields. The collaboration will also design and assist partners in conducting research on outcomes of the new caries management system. It is time now to start the process of moving towards preserving tooth structure, rather than retorting it with artificial materials.

Text boxes

Box 1 | Fluoride and caries

The benefits of fluoride on caries prevention and arrest are generally accepted by dental researchers and practicing professionals worldwide. These include community-based methods of fluoride delivery (water, milk and salt fluoridation) and a broad range of fluoride agents (paste, gel, foam, rinse, solution, varnish, drops, tablets). The use of fluorides in toothpoastes is credited with the overall global reduction in caries in many countries over recent decades as toothbrushing with toothpaste is so widely accepted as a behavioural norm associated with both health and grooming. The preventive contribution of the fluoride toothpaste outweighs that from brushing per se. Flossing is practiced to a very variable extent and the evidence for a caries preventive effect is limited.

Fluoride can come in various formulations mainly sodium fluoride (NaF), acidulated fluorophosphates (APF) or stannous fluoride (SnF_2). Fluoride toothpaste is the most widely used form of fluoride delivery worldwide. Fluoride dentifrices (fluoride containing paste) have shown in numerous clinical trials to be effective anticaries agents. The benefit is seen to be derived from the frequent low dose applications.

Topical fluoride use at high concentrations (>2,500ppm) provides the driving force to penetrate the dental biofilm adjacent to the tooth surface, delivering fluoride to tooth surface and more importantly concentrates it in incipient lesions. At these levels, fluoride is shown to decrease rate of enamel demineralization and increased rate of enamel remineralization. There is also a relationship between higher fluoride concentration and prolonged retention of fluoride in the oral cavity. High fluoride levels are necessary for the formation of fluoride reservoir (calcium fluoride-like deposits) on the tooth surface and in dental plaque. Very high fluoride levels can also have a transient bactericidal effect, but this would require repeated frequent applications of professionally applied high concentration fluoride which is not practical.

References Box 1: 87, 157-163.

Box 2| Fluorides and caries prevention: evidence and controversial aspects.

Fluoride has a key and widespread role in caries prevention and control which has been demonstrated by a range of evidence for decades. The evidence for effectiveness for the protection and treatment of specific individuals through fluoride toothpastes, gels and varnishes is clear and has been demonstrated convincingly in a number of Cochrane Systematic Reviews. Use of fluoride in this way is largely uncontroversial, although in some countries environment lobbies have voiced concerns at a philosophical as opposed to a scientific level.

Despite the long history of successful use of water fluoridation as a public health intervention (where the concentration of fluoride in drinking water is either maintained or modified to a level between 0.7 mg/l1.5 mg/l to maximize caries prevention while minimizing the risk of dental fluorosis. The WHO recommends that water volume consumed and intake from other sources should be considered when setting national standards[60], but this subject has in some countries been, and in many countries continues to be, controversial. In countries where controversy exists, the central argument is around the balance between public benefit on one hand and the perceived medication of individuals without their consent on the other. Also, if young children swallow too much fluoride at an age during which their permanent teeth are forming, there is a risk of marks developing on those teeth. This is called 'dental fluorosis'. Most fluorosis is very mild, with faint white lines or streaks visible only to dentists under good lighting in the clinic. More noticeable fluorosis, which is less common, may cause aesthetic concerns. Despite the vociferous arguments and scare stories about the dangers of water fluoridation, it has been supported in many countries for decades and is still supported by a wide range of medical, public health and dental bodies worldwide. There is a paucity of recent high quality studies of the magnitude of the benefit achievable by water fluoridation – which may not be as high as was estimated before the widespread use of fluoride in the diet and in toothpastes and before considerable lifestyle changes. However, the benefit is still judged to be substantial for caries in children [164]. There are also influential critiques of the systematic review methodology used in the recent Cochrane review that maintain the potential benefits of using wider eligibility criteria for studies in such reviews in order to achieve a fuller understanding of the effectiveness of water fluoridation.[165] Alternatives at the community level include both salt and in some places milk fluoridation; however the evidence for these interventions is more limited.

Box 3| Protocols to risk assess and classify dental caries

Risk assessment protocols: for example, Cariogram and Caries Management by Risk Assessment

- Research tools for example the Nyvad criteria for assessing caries with a focus on activity.
- Epidemiological caries "indices" such as: WHO Basic Methods, International Caries Detection and Assessment (ICDAS) and the Caries Assessment Spectrum and Treatment (CAST) Index.
- Operative dentistry based classifications: Black's Classification System (early 1900s), American Dental Association Caries Classification System (incorporates ICDAS), Mount-Hume Classification System and Site-Stage (SI/STA) Classification System.

Box 4| Economic assessments of preventive measures.

Compared to many diseases, health economic assessments of caries prevention at both the public health and individual levels are scarce. Traditional studies have focussed on short term comparisons of different types of restorative materials, or comparing a fissure sealant against a conventional filling, but not taking into account the long terms costs and consequences of repeated replacement of restorations when the disease is not controlled, nor patient preferences. Few robust studies looking at the costs and benefits of using behavioural change techniques to modify caries risk or of using anticipatory guidance or modifying oral health literacy exist. These topics need further research across disciplines – as do health economic evaluations of the integrated use of preventive management systems at the Individual, dental practice and regional levels. Two case reports are outlined below.

- The estimated cost-effectiveness of caries prevention programmes for children in Chile compared to no intervention were evaluated using economic models[70]. Salt fluoridation, community water fluoridation and school-based milk fluoridation provided the most cost-savings from a societal perspective, followed by school-based fluoride mouth rinse programmes. School-based programmes using fluoride-gel application, dental sealants, and supervised tooth brushing using fluoride toothpaste were effective, but did not yield societal savings within a six-year time frame. Dental sealant programmes would be cost-saving if applied to children at high caries risk.

- Dynamic modelling to compare different approaches for preventing ECC in a low-income Medicaid enrolled population in New York[71] found net savings from community water fluoridation, motivational interviewing especially if implemented for caregivers of children younger ≤2 years, and tooth brushing programs with fluoride toothpaste within a 10-year time frame. Fluoride varnish programmes were recommended for the youngest children at high risk, such as done by paediatric medical providers in North Carolina's Into the Mouths of Babes Program[166].

Figure 1: Normal tooth anatomy and developing dental biofilm. The tooth's hard tissue consists of enamel, dentin and cementum. Enamel is a hard material composed almost exclusively of mineral (mainly composed of hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$]) and covers the dentine on the crown of the tooth. Cementum is a bone matrix like substance composed of mineral and collagen; it covers the root of the tooth. The dental pulp forms the central part and contains connective tissue, blood vessels and nerves. Teeth are covered by a salivary pellicle layer consisting of proteins and glycoproteins, which facilitates binding of the oral microbiota to the teeth; this structure is called the dental biofilm (also known as dental plaque). The biofilm shuts off the surface enamel from the saliva and oral cavity and produces a protected micro-environment at the tooth surface. Gums (gingiva) surround the teeth. In humans, primary teeth erupt around 6 months of age; these are gradually replaced by permanent teeth from around 6 years of age.

Figure 2: Balancing pathological and protective factors in dental caries. A focus on optimising the protective factors (those favouring healthy teeth) will promote remineralisation and shift the dynamic balance of the caries process in the direction of health and lesion arrest. A failure to mitigate the effects of the pathological factors will promote demineralisation and shift the dynamic balance in the direction of disease initiation and disease progression.

Figure 3: Impact of different disease detection thresholds on epidemiological surveys. Whichever classification systems are used in epidemiological research on dental caries, results depend on the detection threshold employed. The so-called iceberg metaphor for caries is illustrated graphically. The tip of the iceberg is represented by the 11% of children with obvious cavitated dentine decay (which is the WHO Basic Surveys convention). As lesions with obvious visual decay in dentine, clinical cavitated decay in enamel and clinical visual decay in enamel are added the proportion of children with dental caries is seen to increase [12,13 ; in this example] to 21%, 25% and 52% respectively[14]. Data are based on 15 year-old children examined in the National Child Dental Health Survey (CDHS) of England, Wales and Northern Ireland undertaken in 2013[14]. Radiographs (if they can be taken) would reveal even more of the total iceberg of disease[17].

Figure 4 Ecological plaque hypothesis to explain the aetiology of dental caries. The ecological plaque hypothesis describes the differences seen in the microbiota from sound and carious sites as a consequence of a change in oral environmental conditions. An increased frequency of fermentable sugar intake results in the biofilm spending more time at a low pH, which will select for bacteria that

grow preferentially under acidic conditions. The growth of bacteria associated with sound surfaces is then disadvantaged, which over time results in an increase in the proportions and activity of cariogenic species at a site and a heightened risk of caries. This risk is raised in individuals with impaired saliva flow and sugar-rich diet, but reduced in those with appropriate oral hygiene and exposure to fluoride.

Figure 5: Overview of the ICCMS™ system with its four key elements. The International Caries Classification and Management System (ICCMS) is a health outcomes focused system that aims to maintain health and preserve tooth structure. It uses a simple form of the "ICDAS" caries classification model to stage caries severity and assess lesion activity in order to derive an appropriate, personalised, preventive, risk-adjusted, tooth preserving management plan. The four key steps in this 4D model are: determine patient level caries risk through a targeted history; detect and assess caries lesion severity and activity; decide on a personalised caries care plan with elements at both the whole patient and at the specific tooth levels; and then do the appropriate tooth-preserving and patient level caries prevention and control interventions. The cycle then re-starts after a risk-based follow-up interval.

Figure 6: Clinical and radiographic appearance of the stages of severity of tooth decay. Clinical appearance (part a) and bitewing radiograph (part b) of the same tooth. Examples of sound and Extensive caries surfaces are shown on the biting (or occlusal) surfaces, which contain developmental depressions and grooves (pits and fissures) that collect dental biofilm and are caries predilection sites. The initial and moderate stage lesion examples show approximal surface (where adjacent teeth are in contact). Caries also develops on the free smooth surfaces (adjacent to cheeks, lips and tongue).

Figure 7: ICCMS™ caries management plan. ICCMS™ proposes a comprehensive assessment and personalised caries care plan based on integrated information derived from assessing both the caries lesions and their activity at a tooth surface level as well as the likelihood for new caries and for caries lesion progression. Based on lesion extent, activity and risk, the personalised care is divided into specific items for preventing new caries on sound surfaces, providing non-operative (that is, non-surgical) care for some lesions to control the caries process and providing minimally invasive tooth preserving operative (surgical) care only where this is unambiguously indicated. Risk reduction and management is also a continuing feature of the care plan.

References

1. Pitts N. B. & Zero, D. T. White Paper on Dental Caries Prevention and Management. *FDI World Dental Federation* http://www.fdiworlddental.org/sites/default/files/media/documents/2016-fdi_cpp-white_paper.pdf (2016).

2. Koussoulakou, D.S., Margaritis, L.H. & Koussoulakos, S.L. A curriculum vitae of teeth: evolution, generation, regeneration. *Int J Biol Sci* 5, 226-43 (2009).

3. Petersen. P-E., Bourgeois, D., Ogawa, H., Estupinan-Day, S. & Ndiaye, C. The global burden of oral diseases and risks to oral health. *Bulletin of the World Health Organization.* 83, 661-669 (2005).

4. Broadbent, J.M., Thomson, W.M. & Poulton, R. Trajectory patterns of dental caries experience in the permanent dentition to the fourth decade of life. *J. Dent. Res*. 87, 69–72 (2008).

5. Pitts, N. et al. Global Oral Heath Inequalities Dental Caries Task Group - Research Agenda. *Adv. Dent. Res*. 23, 98-200 (2011).

6. American Academy of Pediatric Dentistry. American Academy of Pediatric Dentistry reference manual 2014-2015. *Pediatr. Dent.*, 36 (6 reference manual), 1-140. (2014).

7. US Department of Health and Human Services. Oral Health in America: A Report of the Surgeon General. *National Institute of Dental and Craniofacial Research.* https://www.nidcr.nih.gov/datastatistics/surgeongeneral/report/executivesummary.htm (2000).

8. Dye, B.A. *et al*. Trends in pediatric dental caries by poverty status in the US. *Int. J. Paedi. Dent.* 20(2), 132-43 (2010).

9. Dye, B. A. *et al.* Trends in oral health status: United States, 1988-1994 and 1999-2004. *Vital Health Stat. 11*(248), 1-92 (2007).

10. Dye, B. A., Vargas, C. M., Fryar, C. D., Ramos-Gomez, F., & Isman, R. Oral health status of children in Los Angeles County and in the United States, 1999-2004. *Community Dent Oral Epidemiol. 45, 135-144* (2016)

11. Pitts, N. B. Discovering Dental Public Health: from Fisher to the Future. *Community Dental Health* 11, 172-178 (1994).

12. Topping, G.V. & Pitts, N. B. in *Monographs in Oral Science vol 21-Detection, Assessment, Diagnosis and Monitoring of Caries: Clinical visual caries detection.* (ed. Pitts, N.) 15-41 (2009).

13. Kühnisch, J. *et al.* Occlusal caries detection in permanent molars according to WHO basic methods, ICDAS II and laser fluorescence measurements. *Community Dent. Oral Epidemiol.* 36 (6), 475-84 (2008).

14. Pitts, N. B., Chadwick, B. & Anderson, T. *Children's Dental Health Survey 2013 Report 2: Dental Disease and Damage in Children in England, Wales and Northern Ireland.* (London: Health and Social Care Information Centre, 2015).

15. Patel, R.N. *et al.* Variability of Methodologies Used to Determine National Mean DMFT Scores for 12-Year-Old Children in European Countries. *Community Dental Health 2016,* 33, 286-291 (2016).

16. Pitts N, Melo P, Martignon S, Ekstrand K, Ismail A. Caries risk assessment, diagnosis and synthesis in the context of a European Core Curriculum in Cariology. *Eur. J. Dent. Educ.* 15 (Suppl. 1) 23–31, (2011).

17. Agustsdottir, H. *et al.* Caries prevalence of permanent teeth: a national survey of children in Iceland using ICDAS. *Community Dent. Oral Epidemiol.* 38, 299-309 (2010).

18. Marcenes, W. *et al.* Global burden of oral conditions in 1990-2010: a systematic analysis. *J. Dent. Res.* 92, 592-7 (2013).

19. Moynihan, P.J. & Kelly, S.A. Effect on caries of restricting sugars intake: systematic review to inform WHO guidelines. *J. Dent. Res.* 93, 8-18 (2014).

20. Sheiham, A. & James, W.P. Diet and Dental Caries: The Pivotal Role of Free Sugars Reemphasized. *J. Dent. Res.* 94(10), *1341-7.* (2015).

21. Zero, D.T. *et al.* The biology, prevention, diagnosis and treatment of dental caries: scientific advances in the United States. *J. Am. Dent. Assoc.* 140 Suppl 1, 25S-34S (2009).

22. Reisine, S. & Litt, M. Social and psychological theories and their use for dental practice. *Int. Dent. J.* 43, 279-87 (1993).

23. Fejerskov, O. Concepts of dental caries and their consequences for understanding the disease. *Community Dent. Oral Epidemiol.* 25, 5-12 (1997).

24. Selwitz, R.H., Ismail, A.I. & Pitts, N.B. Dental caries. *Lancet* 369, 51-9 (2007).

25. Zero, D.T. Sugars - the arch criminal? *Caries Res.* 38, 277-85 (2004).

26. Takahashi, N. Microbial ecosystem in the oral cavity: metabolic diversity in an ecological niche and its relationship with oral diseases. (ed. Watanabe M, T.N., Takada H) (Elsevier, Oxford, 2005).

27. Zero, D.T. Dental caries process. *Dent. Clin. North Am.* 43, 635-64 (1999).

28. ten Cate, J.M. & Featherstone, J.D. Mechanistic aspects of the interactions between fluoride and dental enamel. *Crit. Rev. Oral Biol. Med.* 2, 283-96 (1991).

29. Featherstone, J.D. The continuum of dental caries--evidence for a dynamic disease process. *J. Dent. Res.* 83, Spec. No C, C39-42 (2004).

30. Wilson, M. in *Microbial inhabitants of humans. Their ecology and role in health and disease.* (Cambridge University Press, Cambridge, 2005).

31. Devine, D.A., Marsh, P.D. & Meade, J. Modulation of host responses by oral commensal bacteria. *J. Oral Microbiol.* 7, 26941 (2015).

32. Nobbs, A.H., Jenkinson, H.F. & Jakubovics, N.S. Stick to your gums: mechanisms of oral microbial adherence. *J. Dent. Res.* 90, 1271-8 (2011).

33. Zijnge, V. *et al.* Oral biofilm architecture on natural teeth. *PLoS One* 5, e9321 (2010).

34. Wright, C.J. *et al.* Microbial interactions in building of communities. *Mol. Oral Microbiol.* 28, 83-101 (2013).

35. Scannapieco, F.A. Saliva-bacterium interactions in oral microbial ecology. *Crit. Rev. Oral Biol. Med.* 5, 203-48 (1994).

36. Hara, A.T. & Zero, D.T. The caries environment: saliva, pellicle, diet, and hard tissue ultrastructure. *Dent. Clin. North Am.* 54, 455-67 (2010).

37. Jakubovics, N.S., Yassin, S.A. & Rickard, A.H. Community interactions of oral streptococci. *Adv. Appl. Microbiol.* 87, 43-110 (2014).

38. Klein, M.I., Hwang, G., Santos, P.H., Campanella, O.H. & Koo, H. Streptococcus mutans-derived extracellular matrix in cariogenic oral biofilms. *Front. Cell. Infect. Microbiol.* 5, 10 (2015).

39. Sheiham, A. & James, W.P. A reappraisal of the quantitative relationship between sugar intake and dental caries: the need for new criteria for developing goals for sugar intake. *BMC Public Health* 14, 863 (2014).

40. Loesche, W.J. Role of Streptococcus mutans in human dental decay. *Microbiological Reviews* 50, 353-380 (1986).

41. Rosier, B.T., De Jager, M., Zaura, E. & Krom, B.P. Historical and contemporary hypotheses on the development of oral diseases: are we there yet? *Front. Cell. Infect. Microbiol.* 4, 92 (2014).

42. Marsh, P.D. Are dental diseases examples of ecological catastrophes? *Microbiology* 149, 279-294 (2003).

43. Takahashi, N. & Nyvad, B. Caries ecology revisited: microbial dynamics and the caries process. *Caries Res.* 42, 409-18 (2008).

44. Hong, L., Levy, S.M., Warren, J.J. & Broffitt, B. Association between enamel hypoplasia and dental caries in primary second molars: a cohort study. *Caries Res.* 43, 345-53 (2009).

45. Fisher, J. & Glick, M. FDI World Dental Federation Science Committee (2012). A new model for caries classification and management: the FDI World Dental Federation caries matrix. *J. Am. Dent. Assoc.* 143(6):546–551 (2012).

46. Ismail, A. *et al.* Caries management pathways preserve dental tissues and promote oral health. *Community Dent Oral Epidemiol.* 41, e12–e40 (2013)*.*

47. Pitts, N.B. & Ekstrand, K.R. International Caries Detection and Assessment System (ICDAS) and its International Caries Classification and Management System (ICCMS) - methods for staging of the caries process and enabling dentists to manage caries. *Community Dent. Oral Epidemiol.* 41, e41-e52 (2013).

48. ICDAS Foundation. International Caries Detection and Assessment System (ICDAS). What is ICDAS. https://www.icdas.org/what-is-icdas (2017).

49. Pitts, N.B. *et al*. ICCMS™ Guide for Practitioners and Educators. *ICDAS Foundation* https://www.icdas.org/uploads/ICCMS-Guide_Full_Guide_With_Appendices_UK.pdf (2014).

50. Ismail, A., Pitts, N.B. & Tellez, M. The international caries classification and management system (ICCMS^{TM}) an example of a caries management pathway. *BMC Oral Health* 15, 1.3 Suppl. 1 (2015).

51. Watt, R.G. Social determinants of oral health inequalities: implications for action. *Community Dent. Oral Epidemiol.* 40, Suppl 2:44-8 (2012).

52. Jürgensen, N. & Petersen, P.E. Promoting oral health of children through schools--results from a WHO global survey. *Community Dent. Health* 30, 204-18 (2013).

53. WHO World Health Organization*.* Oral health: action plan for promotion and integrated disease prevention*. WHO IRIS* http://apps.who.int/iris/bitstream/10665/21909/1/b120_10-en.pdf (2006).

54. Weintraub, J.A. Sustainable oral health interventions. *J. Public Health Dent.* 71, Suppl 1:S95-96 (2011).

55. Panagakos, F. Partners in prevention: A winning approach for communities and companies. J. *Evid. Base Dent. Pract.* 12, 58-61 (2012).

56. Alliance for a Cavity-Free Future. About us. Take a closer look at the Alliance. *The Alliance for a Cavity-Free Future (ACFF),* www.allianceforacavityfreefuture.org/en/us/about-us (2016).

57. Guide to Community Preventive Services. Dental Caries (Cavities): Community Water Fluoridation. *The Community Guide* www.thecommunityguide.org/oral/fluoridation.html (2013).

58. USDHHS federal panel on community water fluoridation. U.S. Public Health Service Recommendation for fluoride concentration in drinking water for the prevention of dental caries. *Public Health Reports*. 130, 1-14 (2015).

59. Griffin, S.O., Jones, K. & Tomar, S.L. An economic evaluation of community water fluoridation. *J Public Health Dent.* 61, 78-86 (2001).

60. WHO World Health Organization. *Guidelines for drinking-water quality, 4th ed*. 42. (World Health Organization, Geneva, 2011).

61. Pollick, H.F. Salt fluoridation: a review. *C.D.A.J.* 41, 395-404 (2013).

62. Marthaler, T.M. Salt fluoridation and oral health. *Acta. Med. Acad.* 42, 140-155 (2013).

63. Bánóczy, J., Rugg-Gunn, A. & Woodward. M. Milk fluoridation for the prevention of dental caries. *Acta Med Acad.* 42, 156-167 (2013).

64. Yeung, C.A., Chong, L.Y. & Glenny, A.M. Fluoridated milk for preventing dental caries. *Cochrane Database Syst. Rev.* 3(9), CD003876 (2015).

65. Wright, J.T. *et al.* Evidence-based clinical practice guideline for the use of pit-and-fissure sealants. A report of the American Dental Association and the American Academy of Pediatric Dentistry. *J. Am. Dent. Assoc*. 147, 672-682 (2016).

66. Guide to Community Preventive Services. Dental Caries (Cavities): School-Based Dental Sealant Delivery Programs. *The Community Guide* www.thecommunityguide.org/oral/schoolsealants.html (2013).

67. Griffin, S.O. *et al.* Centers for Disease Control and Prevention (CDC). Use of dental care and effective preventive services in preventing tooth decay among U.S. Children and adolescents--Medical Expenditure Panel Survey, United States, 2003-2009 and National Health and Nutrition Examination Survey, United States, 2005-2010. *MMWR Surveill. Summ.* 63, Suppl 2, 54-60 (2014).

68. Siegal, M.D. & Detty, A.M. Do school-based dental sealant programs reach higher risk children? *J. Public Health Dent.* 70, 181-7 (2010).

69. Weintraub, J.A., Stearns S.C., Rozier, R.G. & Huang, C.C. Treatment outcomes and costs of dental sealants among children enrolled in Medicaid. *Am J Public Health*. 91, 1877-1881 (2001).

70. Mariño, R., Fajardo, J. & Morgan, M. Cost-effectiveness models for dental caries prevention programmes among Chilean schoolchildren. *Community Dent. Health* 29, 302-8 (2012).

71. Edelstein, B.L., Hirsch, G., Frosh M. & Kumar, J. Reducing early childhood caries in a Medicaid population: a systems model analysis. *J. Am. Dent. Assoc.* 146, 224-32 (2015).

72. Public Health England. *Delivering better oral health: an evidence-based toolkit for prevention - Third edition.* (Public Health England, London, 2014).

73. SIGN Scottish Intercollegiate Guidelines Network (SIGN). *SIGN138 Dental interventions to prevent caries in children* (Healthcare Improvement Scotland, 2015).

74. Weyant, R.J. et al., Topical fluoride for caries prevention: executive summary of the updated clinical recommendations and supporting systematic review. *J. Am. Dent. Assoc.* 144(11):1279–1291 (2013).

75. Marinho, V.C.C. *et al*. Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries in children and adolescents. *Cochrane Database Syst Rev* 4(4):CD002782 (2003).

76. WHO World Health Organization. *WHO Guideline: Sugars intake for adults and children* (World Health Organization, Geneva, 2015).

77. Disney, J.A. *et al.* The University of North Carolina Caries Risk Assessment study: further developments in caries risk prediction. *Community Dent. Oral Epidemiol.* 20, 64-75 (1992).

78. Bratthall, D. & Hänsel Petersson, G. Cariogram--a multifactorial risk assessment model for a multifactorial disease. *Community Dent. Oral Epidemiol*. 33(4), 256-64 (2005).

79. Twetman, S., Ekstrand. K, & Keller, M. Caries – en biofilmmedieret sygdom. *Tandlægebladet* 17, 1-6 (English summary) (2013).

80. Walsh T, Worthington HV, Glenny A-M, Appelbe P, Marinho VCC, Shi X. Fluoride toothpastes of different concentrations for preventing dental caries in children and adolescents. Cochrane Database Syst. Rev. (1):CD007868 (2010).

81. Carvalho, J.C., Ekstrand, K.R. & Thylstrup A. Dental plaque and caries on occlusal surfaces of first permanent molars in relation to stage of eruption. *J. Dent. Res.* 68, 773-9 (1989).

82. Mejàre, I. Bitewing examination to detect caries in children and adolescents--when and how often? Dent. Update 32, 588-90 (2005).

83. Ridell, K., Olsson, H. & Mejàre I. Unrestored dentin caries and deep dentin restorations in wedish adolescents. *Caries Res.* 42, 164-70 (2008).

84. Ekstrand, K.R., Bruun, G. & Bruun, M. Plaque and gingival status as indicators for caries progression on approximal surfaces. *Caries Res.* 32, 41-5 (1998).

85. Ekstrand, K.R., Martignon, S., Ricketts, D.J. & Qvist, V. Detection and activity assessment of primary coronal caries lesions: a methodologic study. *Oper. Dent*. 32, 225-35 (2007).

86. Amaechi, B.T. Remineralization therapies for initial caries lesions. *Curr. Oral Health Rep.* 2, 95-101 (2015).

87. Zero, D.T. Dentifrices, mouthwashes, and remineralization/caries arrestment strategies. *BMC Oral Health* 6 Suppl 1, S9 (2006).

88. Ten Cate, J.M. & Fetherstone, J.D. Mechanistic aspects of the interactions between fluoride and dental enamel. *Crit. Rev. Oral Biol. Med.* 2, 283-296, (1991).

89. Newbrun, E. Topical fluorides in caries prevention and management: a North American perspective. *J Dent Educ* 65, 1078-1083, (2001).

90. Lee, Y.E. *et al*. Comparison of remineralization effect of three topical fluoride regimens on enamel initial carious lesions. *J Dent.* 38(2), 166-71 (2010).

91. Amaechi, B.T. & van Loveren, C. Fluorides and non-fluoride remineralization systems. *Monogr. Oral Sci.* 23, 15-26 (2013).

92. Kandelman, D. & Gagnon, G. A 24-month clinical study of the incidence and progression of dental caries in relation to consumption of chewing gum containing xylitol in school preventive programs. *J. Dent. Res.* 69, 1771-1775 (1990).

93. Featherstone, J.D. Prevention and reversal of dental caries: role of low level fluoride. *Community Dent. Oral Epidemiol.* 27, 31-40 (1999).

94. Reynolds, E.C., Cai, F., Shen, P. & Walker, G.D. Retention in plaque and remineralization of enamel lesions by various forms of calcium in a mouthrinse or sugar-free chewing gum. *J. Dent. Res.* 82, 206-211 (2003).

95. Kitasako, Y., Sadr, A., Hamba, H., Ikeda, M. & Tagami J. Gum containing calcium fluoride reinforces enamel subsurface lesions in situ. *J. Den. Res.* 91, 370-375 (2012).

96. Hamba, H., Nikaido, T., Inoue, G., Sadr, A. & Tagami, J. Effects of CPP-ACP with sodium fluoride on inhibition of bovine enamel demineralization: a quantitative assessment using micro-computed tomography. *J. Dent.* 39, 405-13 (2011).

97. Tay, F.R. *et al.* The glass-ionomer phase in presin-based restorative materials, *J. Dent. Res.* 80, 1808-1812, (2001).

98. Ito, S. *et al.* Effects of surface pre-reacted glass-ionomer fillers on mineral induction by phosphoprotein. *J. Dent.* 39, 72–9 (2011).

99. Holmgren, C., Gaucher, N., Decerle, N. & Doméjean, S. Minimal intervention dentistry II: part 3. Management of non-cavitated (initial) occlusal caries lesions – non-invasive approaches through remineralization and therapeutic sealants. *Br. Dent. J.* 216, 237-243 (2014).

100. Ricketts, D., Lamont, T., Innes, N.P., Kidd, E. & Clarkson, J.E. Operative caries management in adults and children. *Cochrane Database Syst. Rev.* 3:CD003808 (2013).

101. Kidd, E., & Fejerskov, O. Changing concepts in cariology: forty years on. *Dental Update* 40(4), 277-286 (2013).

102. Zandona, A.F. & Swift, E.J. Jr. Critical appraisal. Evidence for sealing versus restoration of early caries lesions. *J. Esthet. Restor. Dent*. 27(1), 55-8 (2015).

103. Meyer-Lueckel, H., Bitter, K. & Paris, S. Randomized controlled clinical trial on proximal caries infiltration: three-year follow-up. *Caries Res*. 46, 544-8 (2012).

104. Schwendicke, F., Meyer-Lueckel, H., Stolpe, M., Dörfer, C.E. & Paris, S. Costs and effectiveness of treatment alternatives for proximal caries lesions. *PLoS One*. 27, 9(1):e86992 (2014).

105. Schwendicke, F., Stolpe, M., Meyer-Lueckel, H. & Paris, S. Detecting and treating occlusal caries lesions: a cost-effectiveness analysis. *J. Dent. Res.* 94, 272-80 (2015).

106. Wierichs, R.J. & Meyer-Lueckel, H. Systematic review on noninvasive treatment of root caries lesions. *J. Dent. Res*. 94, 261-71 (2015).

107. Duangthip, D., Jiang, M., Chu, C.H. & Lo E.C. Non-surgical treatment of dentin caries in preschool children - systematic review. *BMC Oral Health*, 15:44 (2015).

108. Clarkson, B.H. & Exterkate, R.A.M. Noninvasive dentistry: A dream or reality? *Caries Res*. 49(suppl 1), 11-17 (2015).

109. Marsh, P.D., Head, D.A. & Devine, D.A. Prospects of oral disease control in the future - an opinion. *J. Oral Microbiol.* 6, 261-76 (2014).

110. Rasines Alcaraz, M.G. *et al*. Direct composite resin fillings versus amalgam fillings for permanent or adult posterior teeth. *Cochrane Database Syst. Rev*. 31, 3:CD005620 (2014).

111. Ferreira, J.M., Pinheiro, S.L., Sampaio, F.C. & de Menezes, V.A. Caries removal in primary teeth--a systematic review. *Quintessence Int.* 43, e9-15 (2012).

112. Innes, N.P., Evans, D.J. & Stirrups, D.R. The Hall Technique; a randomized controlled clinical trial of a novel method of managing carious primary molars in general dental practice: acceptability of the technique and outcomes at 23 months. *BMC Oral Health* 7:18 (2007).

113. Seale, N.S. & Randall, R. The use of stainless steel crowns: a systematic literature review. *Pediatr Dent.* 37, 145-60 (2015).

114. Gajendra, S. & Kuma, J.V., Oral health and pregnancy: a review. *N. Y. State Dent. J.* 70(1), 40-4, _2004).

115. AAPD Council on Clinical Affairs. Guideline on Caries-risk Assessment and Management for Infants, Children and Adolescents. (American Academy of Pediatric Dentistry, Council on Clinical Affairs; 2013).

116. Ramos-Gomez, F.J. A model for community-based pediatric oral health: implementation of an infant oral care program. *Int. J. Dent.* 156821 (2014).

117. Ramos-Gomez, F. & Ng, M.W. Into the future: keeping healthy teeth caries free: pediatric CAMBRA protocols. J. Calif. Dent. Assoc. 39(10), 723-33 (2011).

118. Institute of Medicine. *Oral Health Literacy. Roundtable on Health Literacy; Board on Population Health and Public Health Practice* (National Academies Press, Washington DC. 2003).

119. Karlinsey, R.L. & Pfarrer, A.M. Fluoride Plus Functionalized β-TCP: A Promising Combination for Robust Remineralization. (ed. ten Cate, J.M.) Advances in Dental Research. 24(2), 48-52 (2012).

120. ADA Report. Fluoride toothpaste use for young children. *The Journal of the American Dental Association,* 145(2), 190-191 (2014).

121. Ramos-Gomez, F. & Ng, M-W. Into the Future: Keeping Healthy Teeth Caries Free: Pediatric CAMBRA Protocols. *Journal of the California Dental Association* 39(10), 723-733 (2011).

122. Kassebaum, N.J. *et al.* Global burden of untreated caries: a systematic review and metaregression. *J. Dent. Res.* 94(5), 650-8 (2015).

123. White, D.A. *et al.* Adult Dental Health Survey 2009: common oral health conditions and their impact on the population. *BDJ* 213, 567-572 (2012).

124. Thomson, W.M. Epidemiology of oral health conditions in older people. *Gerodontology* 31(Suppl. 1), 9–16 (2014).

125. Vernazza, C.R., Rolland, S.L., Chadwick, B. & Pitts, N. Caries experience, the caries burden and associated factors in children in England, Wales and Northern Ireland 2013. *Br Dent J.* 221(6), 315-20 (2016).

126. Slade, G.D. Epidemiology of dental pain and dental caries among children and adolescents. *Community Dental Health* 18, 219-227 (2001).

127. Ravaghi, V., Holmes, R.D., Steele, J.G., Tsakos, G. The impact of oral conditions on children in England, Wales and Northern Ireland 2013. *Br Dent J.* 221(4), 173-8 (2016).

128. Casamassimo, P.S., Thikkurissy, S., Edelstein, B.L. & Maiorini E. Beyond the dmft: the human and economic cost of early childhood caries. *J Am Dent Assoc.* 140, 650–657 (2009).

129. Krisdapong, S., Prasertsom, P., Rattanarangsima, K. & Sheiham, A. Relationships between oral diseases and impacts on Thai schoolchildren's quality of life: evidence from a Thai national oral health survey of 12- and 15-year-olds. *Community Dent Oral Epidemiol.* 40, 550-9 (2012).

130. Montero, J. *et al.* Oral health-related quality of life in 6- to 12-year-old schoolchildren in Spain. *Int. J. Paediatr. Dent.* 26(3), 220-230 (2016).

131. Abanto, J. *et al.* Impact of dental caries and trauma on quality of life among 5- to 6-year-old children: perceptions of parents and children. Community Dent. Oral Epidemiol. 42, 385-94 (2014).

132. Psoter, W.J., Reid, B.C. & Katz, R.V. Malnutrition and dental caries: a review of the literature. *Caries Res.* 39, 441-447 (2005).

133. Schroth, R.J. *et al*. Vitamin D status of children with severe early childhood caries: a case-control study. *BMC Pediatr*. 13:174 (2013).

134. Schroth, R.J., Levi, J., Kliewer, E., Friel, J. & Moffatt, M.E. Association between iron status, iron deficiency anaemia, and severe early childhood caries: a case-control study. *BMC Pediatr*. 13:22 (2013).

135. Ayhan, H., Suskan, E. & Yildirim, S. The effect of nursing or rampant caries on height, body weight and head circumference. *J. Clin. Pediatr. Dent.* 20, 209–212 (1996).

136. Sheiham, A. Dental caries affects body weight, growth and quality of life in pre-school children. *Br. Dent. J.* 201(10): 625-6 (2006).

137. Oliveira, L.B, Sheiham, A. & Bönecker M. Exploring the association of dental caries with social factors and nutritional status in Brazilian preschool children. *Eur J Oral Sci* 116:37–43 (2008).

138. Alkarimi, H.A., Watt, R.G., Pikhart, H., Sheiham, A. & Tsakos, G. Dental caries and growth in school-age children. *Pediatrics.* 133:e616-23 (2014).

139. Acs, G., Shulman, R., Ng, M.W. & Chussid, S. The effect of dental rehabilitation on the body weight of children with early childhood caries. *Pediatr. Dent.* 21:109–113 (1999).

140. Malek Mohammadi, T., Wright, C.M. & Kay, E.J. Childhood growth and dental caries. Community Dent Health 26, 38–42 (2009).

141. Gemert-Schriks, M.C.M. *et al.* The influence of dental caries on body growth in prepubertal children. *Clinical Oral Investigations* 15, 141-149 (2010).

142. Alkarimi, H.A., *et al.* Impact of treating dental caries on schoolchildren's anthropometric, dental, satisfaction and appetite outcomes: a randomized controlled trial. *BMC Public Health.* 12, 706 (2012).

143. Jackson, S.L., Vann, W.F. Jr., Kotch, J.B., Pahel, B.T. & Lee, J.Y. Impact of poor oral health on children's school attendance and performance. *Am. J. Public Health.* 101, 1900–1906 (2011).

144. Krisdapong, S., Prasertsom, P., Rattanarangsima, K. & Sheiham, A. School absence due to toothache associated with sociodemographic factors, dental caries status, and oral health-related quality of life in 12- and 15-year-old Thai children. *J. Public Health Dent.* 73(4), 321-8 (2013).

145. Griffin, S.O., Gooch, B.F., Beltrán, E., Sutherland, J.N. & Barsley, R. Dental services, costs, and factors associated with hospitalization for Medicaid-eligible children, Louisiana 1996-97. *J. Public Health Dent.* 60, 21–27 (2000).

146. Moles, D. Epidemic of dental abscesses? Dental abscesses have increased most among poorer people. *B.M.J.* 336, 1323 (2008).

147. Schwendicke, F. *et al.* Socioeconomic inequality and caries: a systematic review and meta-analysis. *J Dent Res.* 94, 10-8 (2015).

148. Fisher-Owens, S.A. *et al.* Influences on children's oral health: a conceptual model. Pediatrics. 120, e510-20 (2007).

149. Bagramian, R.A., Garcia-D-Gody, F. & Volpe, R.A. *Am J Dent.* 22, 3-8 (2009).

150. Porter, M.E. *New Eng J Med.* 36,109-112 (2009).

151. Kaldahl, W.B., Kalkwarf, K.L. & Patil, K.D. A review of Longitudinal Studies that compared Periodontal Therapies. *J Periodontol.* 64, 243-253 (1993).

152. Innes, N. & Evans, D. Association between parental guilt and oral health problems in preschool children. *Br Dent J.*206, 549-50 (2009).

153. Eccles, M.P. *et al.* Developing clinical practice guidelines: target audiences, identifying topics for guidelines, guideline group composition and functioning and conflicts of interest. *Implementation Science*, 7, 60 (2012).

154. Tellez, M. Gray, S.L, Gray, S., Lim, S. & Ismail, A.I. Sealants and dental caries: dentists' perspectives on evidence-based recommendations. *JADA,* 142, 1033-40 (2011).

155. Beauchamp, J. *et al.* Evidence-based clinical recommendations for the use of pit-and-fissure sealants: a report of the American Dental Association Council on Scientific Affairs. *Dent. Clin. North Am*. 53(1), 131-47 (2009).

156. Phelan, M.P. *et al*.. A multifaceted intervention to improve electronic health record (EHR) nursing documentation for emergency department blood draws. *Academic Emergency Medicine*, 22(5 SUPPL. 1), S322 (2015).

157. Fejerskov, O., Thylstrup, A. & Larsen, M.J. Rational use of fluorides in caries prevention. A concept based on possible cariostatic mechanisms. *Acta Odontol. Scand.* 39(4), 241–249 (1981).

158. Fluoride Recommendations Work Group. Recommendations for using fluoride to prevent and control dental caries in the United States. *Centers for Disease Control and Prevention MMWR* https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5014a1.htm (2001).

159. Hellwig, E. & Lennon, A.´M. Systemic versus Topical Fluoride. *Caries Res.* 38, 258–262 (2004).

160. Margolis, H.C., Moreno, E.C. & Murphy, B.J. Effect of low levels of fluoride in solution on enamel demineralisation in vitro. *J. Dent. Res.* 65, 23-29 (1986).

161. Marinho, V.C., Higgins, J.P., Logan, S. & Sheiham, A. Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries in children and adolescents. *Cochrane Database Syst. Rev.* 4:CD002782 (2003).

162. ten Cate, J.M. Current concepts on the theories of the mechanism of action of fluoride. *Acta Odontol. Scand.* 57(6), 325-329 (1999).

163. ten Cate, J.M. & Featherstone, J.D. Mechanistic aspects of the interactions between fluoride and dental enamel. *CRC Crit. Rev. Oral Biol. Med.* 2, 283-296 (1991).

164. Iheozor-Ejiofor, Z., et al. Water fluoridation for the prevention of dental caries. *Cochrane Database of Systematic Reviews* Issue 6, CD010856 (2015).

165. Rugg-Gunn, A.J. *et al*. Critique of the review of 'Water fluoridation for the prevention of dental caries' published by the Cochrane Collaboration in 2015. *British Dental Journal* 220, 335 - 340 (2016).

166. Pahel, B.T., Rozier, R.G., Stearns, S.C. & Quiñonez, R.B. Effectiveness of preventive dental treatments by physicians for young Medicaid enrollees. *Pediatrics* 127, e682-e689 (2011).