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EVALUATION OF XYLITOL USE AND BITEWING RADIOGRAPHS AMONG SCHOOL-AGED CHILDREN IN A LOW-CARIES LEVEL POPULATION

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ABSTRACT

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Evaluation of xylitol use and bitewing radiographs among school-aged children in a low-caries level population

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The objective of the present work was to study, in a low-caries level population, the additional caries-preventive effect of xylitol/maltitol and erythritol/maltitol lozenges delivered at school, in comparison with the comprehensive routine prevention provided by the public dental health care. Also the literature on xylitol, considering the caries level of the population, as well as the *in vitro* mechanisms of action of xylitol and erythritol were evaluated. Further, the additional value of bitewing radiographic examination in the detection of caries was studied.

In a four-year, cluster-randomized, double-blinded clinical trial, 579 informed and consenting 10-year-olds were randomly assigned to receive xylitol or erythritol lozenges (one or two years) in addition to the comprehensive prevention, or to a control group receiving only comprehensive prevention. In the cross-sectional study, 363 pairs of radiographs obtained from these subjects at 14 years of age were analyzed.

The use of the lozenges did not result in caries reduction. A strong relationship between baseline caries level and the caries increment was observed. The conducted systematic review revealed that caries-preventive effect of xylitol was well shown in high-caries level populations. Both xylitol and erythritol decreased the adherence of polysaccharide-producing oral streptococci. Approximately half of the subjects benefited from the radiographic examination.

In a population with low caries occurrence the size of the caries-preventive effect of a polyol and the method required for reliable caries detection according to the contemporary caries management criteria seem to differ from those observed in a population with a high caries level. The observations on erythritol call for additional well-designed randomized clinical trials studying the properties of erythritol in varying levels of caries occurrence.

It can be recommended that in public dental health care the preventive methods used in addition to the comprehensive routine caries prevention should be targeted at children with clinical signs of dental caries or fillings.

Key words: caries, prevention, caries level, xylitol, erythritol

TIIVISTELMÄ

Aija-Maaria Hietala-Lenkkeri

Ksylitolinkäytön ja purusiiveketutkimusten vaikutusten arviointi kouluikäisillä lapsilla alhaisen kariestason väestössä

Turun yliopisto, Lääketieteellinen tiedekunta, Sosiaalihammaslääketieteen oppiaine

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Tämä työ pyrki selvittämään koulussa jaettavien ksylitoli/maltitoli- ja erytritoli/maltitolipastillien lisävaikutusta alhaisen kariestason väestön kariesehkäisyssä julkisen terveydenhuollon tarjoamaan tavanomaiseen ehkäisyyn verrattuna. Tutkimuksessa arvioitiin myös ksylitolin tehoa koskevaa kirjallisuutta, ottaen huomioon väestön kariestaso sekä ksylitolin ja erytritolin vaikutusmekanismeja *in vitro*. Lisäksi selvitettiin purusiivekekuvien tuomaa lisähyötyä kariesdiagnostiikassa. Nelivuotisessa, rypäs-satunnaistetussa kliinisessä kaksoissokkotutkimuksessa 579 informoidun suostumuksensa antanutta 10-vuotiasta satunnaistettiin ryhmään, joka sai terveyskeskuksen tavanomaisen kariesehkäisyn lisänä joko yhden tai kahden vuoden ajan ksylitoli- tai erytritolipastilleja tai verrokkiryhmään, jolle annettiin terveyskeskuksen tavanomainen kariesehkäisy. Poikittaistutkimuksessa analysoitiin samoista tutkittavista 14-vuotiaina otetut 363 purusiivekekuvaparia.

Pastillien käytöllä ei saavutettu lisätehoa karieksen ehkäisyssä. Tutkimuksessa todettiin voimakas yhteys tutkittavien lähtötilanteen kariestason ja neljän vuoden karieskertymän välillä. Tehty systemoitu kirjallisuuskatsaus osoitti ksylitolin kariesta ehkäisevän vaikutuksen korkean kariestason väestössä hyvin. Sekä ksylitoli että erytritoli vähensivät polysakkarideja tuottavien suun streptokokkien kiinnittymistä. Hieman yli puolelta tutkituista 14-vuotiaista löytyi röntgentutkimuksessa kariesvaurioita, jotka olivat jääneet toteamatta kliinisessä hammastarkastuksessa.

Alhaisen kariestason väestöissä sokerialkoholien ehkäisyteho ja karieksen diagnostiikkamenetelmien luotettavuus näyttävät eroavan korkean kariestason tilanteesta. Erytritolin vaikutusta koskevat havainnot on syytä varmentaa eri kariestasoa edustavien aineistojen kanssa tehtävissä, hyvin suunnitelluissa satunnaistetuissa kliinisissä tutkimuksissa.

Terveyskeskusten tarjoaman karieksen ehkäisyohjelman lisäksi käytettävät ehkäisymenetelmät tulisi kohdentaa lapsiin, joilla on jo kariesta tai paikattuja hampaita.

Avainsanat: karies, ehkäisy, esiintyvyys, ksylitoli, erytritoli

TABLE OF CONTENTS

ABBREVIATIONS

BW	Bitewing radiography
CAPP	WHO Oral Health Country/ Area Profile Project
CCT	Controlled clinical trial
DIFOTI	Digitized fiber optic transillumination
DMFS	Decayed, Missing and/or Filled Surfaces in permanent teeth
dmfs	Decayed, missing an/or filled surfaces in primary teeth
DMFT	Decayed, Missing and/or Filled permanent Teeth
dmft	Decayed, missing and/or filled primary teeth
ΔDMFS	Caries increment
EAPD	European Academy of Paediatric Dentistry
EC	Electrical conductance
ECM	Electronic caries measurement
FOTI	Fiber optic trans-illumination
ICDAS	International Caries Detection and Assessment System
ICW-CCT	International Consensus Workshop on Caries Clinical Trials
LF	Laser fluorescence
OCT	Optical coherence tomography
OR	Odds ratio
PF	Prevented fraction
QLF	Quantitative light-induced fluorescence
RCT	Randomized controlled trial
SBU	Statens beredning för medicinsk utvärdering - The Swedish Council on Technology Assessment in Health Care
SD	Standard Deviation
UniViSS	Universal Visual Scoring System
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following articles, which are referred to in the text by the Roman numerals I-IV.

I Lenkkeri AMH, Pienihäkkinen K, Hurme S, Alanen P. The caries-preventive effect of xylitol/maltitol and erythritol/maltitol lozenges: results of a double-blinded, cluster-randomized clinical trial in an area of natural fluoridation. International Journal of Paediatric Dentistry 2012;22:180-190.

II Hietala-Lenkkeri AM, Arpalahti I, Söderling E and Pienihäkkinen K. The additional effect of xylitol candies or chewing gum on dental caries in comparison with no gum or candies in subjects under eighteen years of age: a systematic review describing baseline caries level of the population. Manuscript 2016.

III Söderling EM, Hietala-Lenkkeri AM. Xylitol and erythritol decrease adherence of polysaccharide-producing oral streptococci. Current Microbiology 2010;60:25-29.

IV Hietala-Lenkkeri AM, Tolvanen M, Alanen P, Pienihäkkinen K. The additional information of bitewing radiographs in the detection of established or severe dentinal decay in 14-year olds: a cross-sectional study in low-caries population. The Scientific World Journal 2014; Article ID 175358, 8 pages.

1. INTRODUCTION

Dental caries is still a common oral disease in most industrialized countries, even though the occurrence has declined over the past decades. Prevention, early detection and treatment of carious lesions are relevant items in contemporary caries management. The slow progression of the disease enables the use of non-invasive treatment methods, provided the lesion is detected at an early stage of the disease process. On the other hand, the reliability of the clinical detection of lesions has been found to be limited. The sensitivity can, however, be increased by the combination of visual-tactile and radiographic methods. The understanding of the mechanisms of action regarding the non-invasive methods is of value in caries prevention.

The role of the oral environment is important in the etiology of caries. The selection of the bacteria and plaque acid production can be affected by preventive methods. Meticulous oral self-care, regular use of fluoride dentifrice and avoidance of frequent intake of fermentable carbohydrates are of crucial importance in caries management. In several studies, significant caries reduction has been reported following a regular consumption of xylitol. Erythritol is a sugar alcohol of the tetritol type. The evidence of its effect in cariology is scant but encouraging.

A gap in the understanding of possible special demands related to caries detection and prevention at low disease occurrence level has been identified on the basis of the findings reported in the literature. Therefore, it is of interest to investigate the eventual additional caries-preventive effect of xylitol and erythritol, as well as the mechanisms of reduction of mutans streptococci counts by them. Likewise, the value of bitewing examination in caries detection in a low-caries level population calls for additional studies.

2. REVIEW OF LITERATURE

2.1. Occurrence of dental caries

2.1.1. General

Dental caries is a chronic microbial disease affecting hard tissues of the teeth in all dentate age groups. It is still a major oral health problem in most industrialized countries, affecting 60-90% of schoolchildren and the majority of adults (Petersen 2003, Marthaler 2004). In Finland 14-37 % of women and 28-45% of males were reported to have a need for restorative treatment (Koskinen et al. 2012, Tanner 2013).

In the US, dental caries is the chronic disease most affecting children (Selwitz et al. 2007). Caries may cause pain and affect the quality of life as well as the individual's general health in a negative way. The treatment of caries is expensive and requires resources, which are unevenly distributed globally and may not necessarily be available for each individual in need (Petersen 2003).

There is variation in the distribution and severity of oral diseases between different parts of the world with only a minority of children benefitting from preventive measures and the use of fluorides. Likewise, differences exist within the same country or region (Petersen 2003, Marthaler 2004, Do 2012). In an area with endemic fluoride a significant inverse association between high fluoride content in the drinking water and the low mean DMFT was found in military recruits born in 1990 and 1992 in Finland (Kämppi et al. 2013). Numerous epidemiological surveys have indicated the significant role of socio-behavioral and environmental factors in oral disease and health (Petersen 2003).

In 1956, an oral health component of the World Health Organization (WHO), called Dental Health (DNH) was established. The establishment of the Global Oral Data Bank (GODB) providing caries data for a global map was initiated by the late Dr David Barmes in 1969. GODB served as a basis for the WHO Oral Health Country/ Area Profile Project (CAPP) initiated in Sweden in 1995. The object of CAPP was to present information on dental diseases and oral health services for various countries and areas. In CAPP the DMFT value of the 12-year-old age group is given, and the countries are listed according to alphabetical order or according to WHO regions: African region (AFRO), region of the Americas (AMRO), Eastern Mediterranean region (EMRO), European region (EURO), South East Asia region (SEARO) and Western Pacific Region (WPRO). (http://www.mah.se/CAPP/). In 2011 the global DMFT mean value for 12-year-olds of 189 countries was 1.67 http://www.mah.se/CAPP/Country-Oral-Health-Profiles/According-to-Alphabetical/Global-DMFT-for-12-year-olds-2011/). The WHO goal of DMFT 3 or less at 12 years of age by the year 2000 was achieved by seventy-eight percent of these countries (http://www.mah.se/CAPP/).

da Silveira Moreira (2012) reported an ecological study aiming at describing dental caries status of WHO member countries using data provided by WHO CAPP. In the study, the data were on average from the year 1997 and ranged between the years 1973 and 2008. The average worldwide DMFT index of twelve-year-olds of the 190 included countries was 2.11 (±1.32). Large differences in DMFT values between countries were indicated in the spatial distribution of caries (da Silveira Moreira 2012). Caries is a most prevalent oral disease in several Asian and Latin American countries, while it appears to be less common and less severe in most African countries (Petersen 2003).

High DMFT, that is, values of the highest quartile with values between 2.90 and 7.81 were reported in several South American countries of AMRO: e.g. Argentina, Bolivia and Peru; in eastern parts of EURO: Russian federation, Slovakia and Ukraine; in SEARO: India and Thailand and EMRO: Saudi Arabia. Low values were reported in most countries of AFRO; in North American countries of AMRO; in African countries belonging to EMRO: Egypt, Libya, Somalia and Sudan; in most countries in western EURO; in SEARO: Nepal and Sri Lanka and in WPRO: China and Australia (da Silveira Moreira 2012).

In da Silveira Moreira's study (2012), the DMFT value of the EURO countries ranged between 0.7 and 7.8 with a mean of 2.3 (±1.3). In half of the EURO countries the data were from the year 2000. The relative risk (RR) for dental caries in the EURO region consisting of fifty-three countries was 1.10. RR was used to show the deviation of each region from the world average, which served as the reference. In other words, the risk for caries in the EURO region was ten per cent higher than on average in the world. The EURO countries with RR higher than the average of the region were mostly countries of the former socialist republics called the Eastern bloc, that is, The Republics of the Soviet Union, Poland, German Democratic Republic, Czechoslovakia, Hungary, Romania and Bulgaria, as well as those of the other former socialist countries, Yugoslavia and Albania. This difference in the disease levels needs to be considered in the interpretation of the epidemiological data from Western European countries receiving increasing numbers of immigrants (Marthaler 2004). In comparisons with the regional average of EURO, most Western European countries had lower risks for caries (UK, Germany, Denmark the lowest) (da Silveira Moreira 2012). The uneven distribution of diseases between populations was also reported by Petersen (2003): "As for all diseases, the greatest burden of oral diseases is on disadvantaged and socially marginalized populations." Significant variations in mean caries experience between countries and between time periods were also observed in Do's (2012) analyses.

Recent statistics of WHO CAPP showed the weighted mean DMFT of 1.95 in EURO in 2008 and 2009. In Denmark, Finland and Sweden the DMFT value was less than one in 2008 and 2009: 0.7, 0.7 and 0.9, respectively. In the remaining two Nordic countries, Iceland and Norway, the DMFT values were higher: 1.4 and 1.7, respectively. The statistics of the two latter countries originated from the years 2005 and 2004, but were nevertheless higher than the values of the comparable time period in the other Nordic countries, yet below the weighted mean DMFT of EURO (www.mah.se/CAPP/Country-Oral-Health-Profiles/According-to-Alphabetical/Global-DMFT-for-12-year-olds-2011/).

2.1.2. Decline

The level of caries experience has declined over the past decades. The trend has been indicated by data of WHO regions ranging from the 1980's to the second decade of the 21st century (Petersen 2003, Marthaler 2004). Likewise, the reduction in caries experience was observed in an ecological study of da Silveira Moreira (2012), which used data provided by WHO CAPP, ranging from 1973 to 2008. No remarkable improvement had occurred in countries with a low economic and human development level; these are also the countries in which the majority of the world's population reside (Do 2012). The caries decline occurred mostly in countries with high economic and social development (Petersen 2003, Do 2012). It must be emphasized that dental caries is not eradicated but only controlled to a certain degree (Petersen 2003).

The reasons given for the caries decline in many developed countries include a number of public health measures, coupled with changing living conditions, lifestyles and improved self-care practices. In certain countries this positive trend could prevent the taking of action to further improve oral health, or from maintaining the achievements. It might also lead to the belief that caries problems no longer exist at least in developed countries. This, in turn, could result in the precious resources currently available for caries prevention being targeted to other areas (Petersen 2003, Marthaler 2004). Countries which have shown remarkable reduction in caries occurrence have been found to be those which in adults have had a high level to start with. In contrast, those with low occurrence among adults have started to show either increase or no additional decrease in caries level among children (von der Fehr and Schwarz 1994).

At a global level, caries was a disease of affluent countries in the pre-1980's, as was indicated by the high DMFT values in countries with a high standard of living at the time. Toward the beginning of the 21st century a major shift, resulting in caries as a disease of deprivation, has occurred (Do 2012). The countries with the high DMFT and high economic level have shown a steeper decline in DMFT compared with the countries with lower economic development and pre-1980 DMFT level (Do 2012).

Additionally, two countries with contrasting levels of standard of living/ social and economic development were investigated by Do (2012). The distribution of caries by income levels between these countries showed a strong contrast: in the country with low economic development the increase in income level resulted in increasing caries experience, whereas in the country with high economic development the increase in income level resulted in reduction in caries experience (Do 2012).

According to CAPP statistics, the global weighted mean DMFT value for 12-year-olds showed a mainly decreasing albeit fluctuating trend (Figure 1). In the pre-1980's the Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) showed high DMFT values for 12-year-olds, which was, as stated above, a typical phenomenon in high economic countries at that time. Likewise, the steep decline in the values over the following two decades was also typical. Since the early 1990's, a plateau with DMFT around value one has been established. (Figure 2).

The statistics for 12-year-olds starting in the mid 1970's showed that a decline in caries level had already begun in Finland (Figure 2). During this pre-1980's era, the initial DMFT started with a value as high as seven. The decline was rapid: by 1984 DMFT values of four and by 2009 of 0.7, had been achieved. Between 1975 and 1992 the proportion of caries-free children in Finland increased from nine to 38% (Tala 1992). The goal of WHO set in 1979 with a DMFT value of no more than three at the age of 12 by the year 2000 had been reached in Finland as early as before the mid 1980's.

The trend of caries count in relation to age seems to follow an s-shaped curve regardless of the severity of caries level. This indicates a cumulative character, "growth phenomenon", of caries with increasing age. It is only the slope of the curve which varies in relation to disease severity (Massler et al. 1954). In addition, different teeth are attacked in varying degrees of disease severity (von der Fehr and Schwarz 1994, Ruiken et al. 1986, Selwitz et al. 2007, Batchelor and Sheiham 2004). In very severe conditions nearly all teeth, excluding only incisors of lower jaw and all canines, are attacked. With decreasing severity the incisors, followed by the premolars, are no longer affected. The caries of the first molars seems to be reduced the least (Massler et al.1954, von der Fehr and Schwarz 1994, Ruiken et al. 1986, Batchelor and Sheiham 2004). Also changes occur on a tooth surface level. The caries of the smooth surfaces, excluding buccal and lingual pits and fissures, is diminished first (Ruiken et al. 1986). This reduction is followed by that of the proximal surfaces, and further of the buccal pits and fissures. The occlusal surfaces are affected the least. Even further, it has been documented that there are groups of tooth sites susceptible to caries in children. The most susceptible group of sites consists of occlusal surfaces of the 1st molars and buccal pits of the lower 1st molars, followed by the occlusal surfaces of the 2nd molars and 2nd premolars. The least susceptible of the five groups is the largest and consists of the majority of the lower anterior teeth and canines. Because not only one tooth or a site but all sites within the same group are affected simultaneously, alterations in caries levels become rapid and stepped in nature (Batchelor and Sheiham 2004). As a result, in low-caries children, caries is largely a phenomenon of the occlusal pits and fissures of the posterior teeth (von der Fehr and Schwarz 1994, Ruiken et al. 1986, Selwitz et al. 2007).

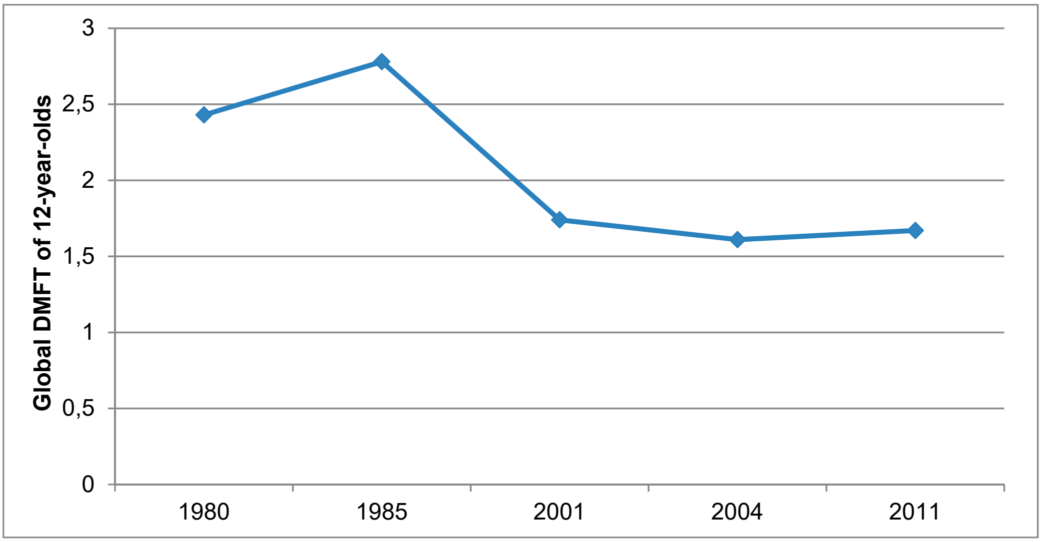


Figure 1. Trend of global dental caries (DMFT for 12-year-olds based on CAPP database).

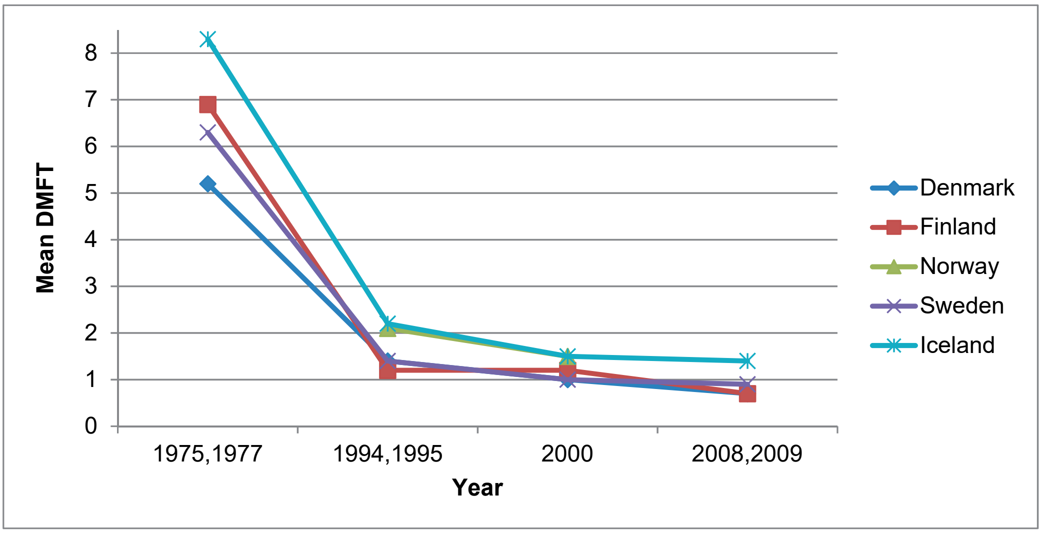


Figure 2. Trends of dental caries in Nordic countries DMFT for 12-year-olds based on CAPP database. (Values of Iceland represent years: 1981-1982, 1993-1994, 1996, 2005)

2.2. Detection of dental caries

2.2.1. Visual and visual-tactile

The principles of caries detection

The aim of caries detection is to assess the likelihood of a carious lesion, which calls for intervention long before the patient is experiencing any symptoms. The significance of a reliable diagnosis of a carious lesion at an early stage of the disease process has become relevant since the importance of early effective treatment of carious lesions is increasingly focused on (SBU 2007, Caries control: Current Care Guidelines, 2014).

The contemporary caries management focuses on prevention, early diagnosis and treatment (Ismail et al. 2007, Selwitz et al. 2007, SBU 2007, Chu et al. 2013) instead of focusing only on the level of cavitation (Pitts and Stamm 2004, SBU 2007) and the surgical treatment (Ismail et al. 2007). In individual caries management, meticulous examination of lesion depth and activity is required, in addition to the caries risk assessment (Caries control: Current Care Guidelines 2014). Recording only cavitated lesions is becoming outmoded, and differentiation between stages of the carious process is important also in future clinical caries trials. Additionally, the arrest or reversal of the progress of mineral loss should be considered as an outcome measure (Pitts and Stamm 2004). Today, the term caries-free can be considered inappropriate if only clinically visible dentine lesions have been registered. In such cases the term ‘no obvious decay’ could be used instead (Selwitz et al. 2007).

The relatively slow progression of carious lesions has resulted in a gradual change in the treatment philosophy, yielding a more prudent attitude towards restorative caries treatment, simultaneously favoring non-invasive treatment methods (SBU 2007). The new assessment techniques should, in the clinical context, be capable of measuring a wide range of lesion depths and changes in the degree of mineralization, either directly or indirectly. Ideally, a continuous scale should be used (Pitts and Stamm 2004). Moreover, the early diagnosis should be accompanied by a caries risk assessment (Chu et al. 2013, Selwitz et al. 2007) and assessment of the caries activity at the lesion site (Selwitz et al. 2007, Nyvad et al. 1999).

The most important diagnostic framing of a question is to decide whether a cavity exists or not, rather than determine whether the carious process has reached the dentine or not (SBU 2007). Accurate, objective and prompt detection of caries serves as an essential source of implementation of optimal prevention and an adequate treatment plan for the patient (Chu et al. 2013).

The earlier caries experience of a person is found to be the best single factor in predicting new carious lesions. The possibility to identify the children and adolescents having a low risk of caries occurrence over the coming two to three years has proved to be good. By contrast, it is difficult to accurately determine individuals at elevated risk for caries (Hausen et al. 2000). Likewise, the accuracy of precluding caries is in general higher than establishing a caries diagnosis (SBU 2007).

The methods of caries detection

The methods for the detection of carious lesions can be classified on several levels: by the method of the detection itself: visual, visual-tactile, radiographic, combination of visual and radiographic, fiber optic trans-illumination (FOTI), electrical conductance (EC), laser fluorescence (LF); by the surface: occlusal or proximal and by the extent of the lesion: enamel, dentinal or cavitated (Bader et al. 2001).

The most common methods for caries detection are visual and visual-tactile. These are often combined with bitewing radiographs (SBU 2007). In addition to visual and radiographic examination, the use of FOTI is recommended (Caries control: Current Care Guidelines 2014). The standard of caries diagnosis in Europe is clinical visual examination either with no probe (Pitts and Stamm 2004) or with gentle probing parallel to the surface (Caries control: Current Care Guidelines, 2014) due to the inherent risk of iatrogenic trauma (Selwitz et al. 2007).

The validity of diagnostic methods

The validity of the diagnostic methods commonly used in the detection of carious lesions has been reviewed both on the basis of studies on extracted permanent teeth and on the findings acquired in clinical or *in vivo* studies. The reliable and reproducible detection of dental caries by clinical examination has been recognized as a problem for decades, with very variable approaches being taken to recognize and stage lesions along the continuum of caries (Topping and Pitts 2009).

Based on the findings of twenty-two studies, mostly performed on extracted teeth, which had been published between 1985 and 2006 and systematically reviewed by the Swedish SBU (Statens beredning för medicinsk utvärdering - The Swedish Council on Technology Assessment in Health Care 2007), the visual-tactile examination was concluded to have limited reliability in the detection of enamel and early dentinal caries on the occlusal surfaces of the posterior teeth. The strength of the scientific basis of evidence was assessed as moderate. For visual-tactile examination of occlusal dentinal caries of permanent teeth, a remarkably wide distribution of sensitivity, that is, 10-95% percent and for specificity 38-98% cent were observed in a systematic review of nine studies on extracted teeth (SBU 2007). In another systematic review on dentinal lesions of occlusal surfaces of extracted permanent teeth, visual-tactile examination was again found to have a wide distribution of sensitivity, 19-92%, and a specificity of 85-97% (Bader et al. 2001).

In the *in vivo* studies on patients examined under clinical conditions for the dentinal caries of occlusal surfaces the sensitivity was found to be seventy-two and the specificity eighty-four per cent. Due to the limited number of studies, no conclusion on the ability of visual inspection to detect carious lesions on occlusal surfaces could be drawn (SBU 2007). In general, low sensitivity and high specificity in the visual-tactile detection of dentinal caries have been observed. In the detection of early enamel lesions of the occlusal surfaces the sensitivity is higher at the expense of specificity, which is significantly lower. Thus, the statement “no dentinal caries” is more likely to hold true than a diagnosis of “no enamel caries” (SBU 2007).

The diagnostic ability of visual examination on the proximal dentinal lesions of extracted teeth has, on the basis of three studies, shown to have low sensitivity of 21% and high specificity of 97%. In clinical /in vivo studies for the proximal surfaces the figures were 34 and 98%, respectively. The limited number of studies allowed no conclusion to be drawn on the ability of visual inspection to detect carious lesions on occlusal or proximal surfaces. In conclusion, with a sensitivity of less than 40% the visual-tactile method was considered insufficient in establishing the presence of dentinal carious lesions on the proximal surfaces of the posterior teeth. The strength of the scientific basis of evidence was assessed as moderate (SBU 2007).

In another article, 39 histologically validated diagnostic and 27 management studies published between 1966 and 1999 were systematically reviewed for the sensitivity and the specificity of the diagnostic methods commonly used in the detection of occlusal and proximal caries. The strength of evidence on the sensitivity and the specificity of these diagnostic methods was rated as poor. In other words, a remarkable amount of enamel, dentinal and cavitated caries on the occlusal and proximal surfaces on these teeth remained undetected. On the other hand, false positive diagnoses on healthy surfaces were assessed. In general, the sensitivity was lower than the specificity of the diagnostic method. In part, the low ratings resulted from a limited number of registrations instead of the low quality of the evaluated studies, per se (Bader et al. 2001).

Similarly, the clinical examinations alone were found by an International Consensus Workshop on Caries Clinical Trials to be relatively insensitive, although highly specific (Pitts and Stamm 2004).

Besides the sensitivity and specificity, a good evaluation of caries detection methods should take into consideration also the caries prevalence of the population studied, as well as the positive and the negative predictive values since they are affected by the prevalence. Because the true status of the tooth is not known in an *in vivo* situation not aiming at extraction of a tooth, the measurement of sensitivity and specificity as such provide no quantitative information on how likely the tooth is to be carious (Chu et al. 2013). The importance of reporting the caries prevalence of the population studied has been emphasized since it is of crucial significance in the results of the diagnostic methods and their generalizability (SBU 2007).

The poor evidence of the accuracy of visual inspection, bitewing radiographs, FOTI and lesion activity assessment have recently been documented in a systematic mapping of systematic reviews (Mejáre et al. 2015). Regardless of its eventual shortcomings, the importance of the visual and tactile examination has been emphasized by SBU (2007) as the basis of all caries detection for the individual clinician, the epidemiologist, and for the researcher as well (SBU 2007).

The diagnostic criteria systems

The 29 caries criteria systems published in the literature between 1966 and 2000 (Ismail 2004) is one indication of how numerous caries criteria systems are. The World Dental Federation reviewing seven systems also noted that several caries classification systems with different bases for classification have been developed over time (Fisher and Glick 2012).

The differences between the detection systems are related to the measurement of cavitated or non-cavitated stages; mere visual inspection; the use of probe; the assessment of active or inactive lesions and the cleaning as well as drying of the teeth (Ismail 2004). The existence of a large number of different diagnostic systems, using different definitions of caries detection thresholds, lesion staging and examination conditions has led to problems in comparing between studies and communicating across different dental domains (Topping and Pitts 2009).

The oldest is the Black's classification system, first introduced in the early 1900's. There, the division of cavitated carious lesions occurs on the basis of the site of the tooth (Fisher and Glick 2012). The DMF score was introduced by Klein, Palmer and Knutson in 1938, as cited by Pitts (2008). It summarizes the individual's caries experience by counting the number of decayed (D), missing (M) and filled (F) teeth (DMFT) or surfaces (DMFS) (Manji and Fejerskov 1994). The WHO Basic Methods Application, showing caries occurrence of an individual, has been widely used in epidemiological caries studies, in particular (Fisher and Glick 2012). The WHO coding system focuses on caries at a cavitation stage only.

The advantages of the WHO criteria have been listed by Chu et al. (2013), who considered them time efficient, yet having the accuracy required in field studies. The wide use of the criteria in previous studies has facilitated the inter-study comparison of the literature. Additionally, the high specificity of lesion detection and high inter- and intra-examiner agreement were mentioned as merits (Chu et al. 2013). In conditions with decreasing caries level and disease severity, a system sensitive enough to detect lesions prior to cavitation has become a necessity. That is, in a population with low caries occurrence, the detection of differences between subgroups requires the inclusion of early lesions in the analyses (Jablonski-Momeni et al. 2014). In systems not registering the non-cavitated lesions the caries occurrence becomes under-estimated (Fisher and Glick 2012).

The goal of early lesion detection aims at the arrest of the caries progression by treatment, or in the best case even at the re-mineralization of the lesion. That is why it is important to underline the fact that the diagnosis of caries is not only about detecting an existing lesion. An important point is to decide whether the lesion has progressed or if it has come to a halt (SBU 2007). In a sense, the principle of the early detection was introduced as early as in 1954 by the four-step scale of the European caries classification of Parfitt (1954), which according to a review by Ismail (2004) coded a slight discoloration with a loss of luster of the enamel surface no longer as sound but as a grade 1 lesion.

An improvement responding to the challenges of the modern caries detection has been brought about by the introduction of an International Caries Detection and Assessment System ICDAS (www.icdas.org/). It does not focus on cavities and on the need for restorative treatment but rather on improving the oral health through managing the dental caries process by prevention (Pitts 2004, Fisher and Glick 2012). The diagnostic criteria and recording system are crucial in guiding the most appropriate treatment and monitoring disease progress. ICDAS can be valuable in the detection of early enamel lesions, which is advantageous for contemporary caries management (Chu et al. 2013).

ICDAS is an evidence-based system integrating the best from different caries detection systems and definitions for the detection and classification of caries in dental education, clinical practice, dental research and dental public health. The carious process is divided into six stages: first visual change in enamel, distinct visual change in enamel, localized enamel breakdown, underlying dentine shadow, distinct cavity with visible dentine and extensive cavity within visible dentine. These dental terms are, in turn, placed under three lay terms: early stage decay, established decay, severe decay, with two terms in each. ICDAS can also be used in primary dentition. To be able to make an accurate assessment, the use of an over-head operating light, the cleaning as well as the drying of the tooth surfaces are considered essential. The system was first created in 2002 by an ICDAS multidisciplinary coordinating committee (www.icdas.org/) and revised and extended in 2005 to ICDAS II (Iranzo-Cortés et al. 2013). The revision included the addition of the assessment of the activity status of the lesion according to the criteria introduced by Nyvad et al. (1999).

There is a full protocol for examination to ensure that all conditions are specified in the ICDAS criteria (Ismail et al. 2007). The detection codes for primary coronal caries have been demonstrated to have the capability to record both the enamel and the dentinal caries in a reliable, valid and reproducible manner in both the permanent and the deciduous teeth. The codes are being adopted increasingly in the domains of research, epidemiology, clinical practice and education (Topping and Pitts 2009). However, ICDAS has been criticized for classifying the caries process with too few criteria in relation to the complexity of the clinical appearance of carious lesions (Kühnisch et al. 2008).

An attempt to patch up the shortcomings of existing adjunct caries detection methods was to systematize the carious lesions by an objective Universal Visual Scoring System (UniViSS), which is a three-step diagnostic procedure consisting of lesion detection and severity assessment, assessment of the discoloration and activity assessment (Kühnisch et al. 2009).

Caries lesion classifications should shift from a system that predominantly describes the current state of a lesion that needs to be restored to a system that assesses and quantifies the risk of progression of the disease; this will provide a more sensitive guide to care management (Fisher and Glick 2012). An attempt to determine the agreement between WHO criteria and the ICDAS scale and to overcome the main problem with using ICDAS in epidemiological studies was made by Iranzo-Cortés et al. (2013) in a study with three age groups. The cut-off point of three, that is, ICDAS codes zero to two classed as sound and codes three to six as caries, was found to be the strategy in comparison of the results acquired with the two criteria systems (Iranzo-Cortés et al. 2013).

2.2.2. Radiographic

Since the visual and the visual tactile examinations alone have proved to be relatively insensitive – although highly specific (Pitts and Stamm 2004) - with values of sensitivity depending on the dentinal extent of the lesion (Bader et al. 2001), they have often been supplemented in clinical trials with bitewing (BW) radiography (Pitts and Stamm 2004). The high underestimation of the prevalence of occlusal and proximal caries using clinical detection alone has been reported in several trials in adolescents (Poorterman et al. 1999, 2000, 2003a, 2003b). Combining the visual and the radiographic methods has increased the sensitivity but simultaneously decreased the specificity. As a result, the proportion of false positive diagnoses has increased (Bader et al. 2001). The additional yield of BW radiographs has also been shown in a systematic review of SBU, which concluded, although not unequivocally, that the combination of visual-tactile method and radiographs is more reliable than either method alone (SBU 2007). The poor accuracy of the radiographic examination has been reported in a systematic mapping of systematic reviews by Mejáre et al. (2015). The strength of the evidence for radiographs has likewise been rated as poor in a systematic review by Bader (2001) but this judgment was mostly due to the small number of assessments.

An International Consensus Workshop on Caries Clinical Trials (ICW-CCT) concluded in the final consensus statement that BW radiography may add information about many of the clinical stages of the carious process at proximal surfaces and, in the case of more advanced stages, at occlusal surfaces (Pitts and Stamm 2004).

In a systematic review of SBU (2007), radiographic examination was found to result in a moderate over-registration of occlusal dentinal caries with a specificity above 80%. The likelihood of false positive registrations in the dentine was found to increase significantly with the declining prevalence of caries. Radiographic examination yielded significant under-registration of occlusal enamel and dentinal caries with a sensitivity of less than 60%. The combination of visual and radiographic examinations increased the likelihood of a positive diagnosis being correct in comparison with either diagnostic method used alone. On the proximal surfaces the radiographic diagnostics resulted in a significant under-registration of carious lesions in enamel and dentine (sensitivity <60%). The high value of specificity (95%) indicates that no significant over-registration of dentinal caries occurred. In contrast with the proximal surface, the occlusal surface can be accessed directly. In the systematic review of SBU it became evident that in several studies on radiographic caries detection of occlusal lesions, actually uncertain clinical findings have been investigated. In other words, the material included several border-line (enamel-dentin) lesions. This, in turn, was likely to result in low sensitivity values regarding the value of radiography in the detection of occlusal lesions.

It can be questioned whether the exposure of children to recurrent X-ray examinations is ethically viable (SBU 2007). Dental X-ray examination causes a relatively small radiation dose to the patient but even a small dose of radiation increases the risk of developing cancer (STUK). A low-dose radiographic system and/ or subtraction radiography should be considered when radiography is used for caries trials (Pitts and Stamm 2004). The justification for radiographic caries examination was further questioned in the SBU review since the ability of bitewing radiographs to reliably detect carious lesions is known to be limited; a mere radiographic detection results in both false positive and false negative findings of caries. In Sweden and in several other European countries, BW radiographs are, however, routinely obtained annually or every two years. The frequency of BW examination shows, nevertheless, no correlation with dental health when different countries are compared. It has been suggested that instead of an individual risk assessment, geographic regions with known high risk for caries could be used as an entity for the intensified preventive actions (SBU 2007).

2.2.3. Additional methods of caries detection

As a complement to the visual-tactile and radiographic caries detection, several alternative methods have been introduced in recent years (Bader et al. 2001, Chu et al. 2013). Part of the diagnostic methods, which may become accessible for general clinical use in the future are based on different technical solutions and physical models like heat, ultra-sound, electrical conductance or fluorescence (SBU 2007). Laser fluorescence (LF) may be a useful adjunct in the monitoring of the progression of initial carious lesions on occlusal surfaces (Caries control: Current Care Guidelines 2014).

A positive correlation between increase in visually detected fissure caries lesions and increase in laser fluorescence device (DIAGNOdent) values has been reported in a follow-up study in children (Anttonen et al. 2004). The device showed relatively good performance in lesion depth and activity estimations when used by dental students in sound teeth and in lesions extending into inner third of dentine but detection of borderline lesions extending to middle-third of dentin showed great variation (Parviainen et al. 2013). Kühnisch (2008) considered the performance of adjunct diagnostic methods (electrical resistance measurement, LF and its quantitative modification QLF) unsatisfactory in non-cavitated occlusal lesions (Kühnisch 2008).

2.3. Prevention of dental caries

2.3.1. Etiology of caries

Several hypotheses attempting to explain the role of plaque bacteria in the etiology of dental caries have been suggested over time. The association between acids and dental decay was introduced as early as in the late 19th century by W.D. Miller who, as cited by Hiremath (2011), linked the microbial acid production from dietary substrates to the etiology of dental decay in the chemo-parasitic theory. It was postulated that it was the quantity of plaque that determined the pathogenicity without discriminating between levels of virulence of bacteria.

In the specific plaque hypothesis, Loesche (1979) proposed that overgrowth of only a few actively involved indigenous species of plaque microflora results in the disease. Consequently, the disease was controlled by focusing the prevention against a limited number of species (Loesche et al. 1975, 1986). The non-specific plaque hypothesis, in turn, proposed that the disease is a result of the overall interaction between different combinations of indigenous bacteria present at inactive sites, as well. The concept of plaque as an active microbial community was recognized (Theilade 1986).

The ecological plaque hypothesis of Marsh (1994) was an attempt to combine the specific and the non-specific hypotheses. Plaque is a homeostatic and stable composition of several interacting bacterial species. The collapse of this balanced state, which results in an increase in previously minor acidogenic and aciduric species, can be caused by a significant perturbation in the conditions maintaining the stability. A diet rich in carbohydrates, low pH of the surroundings or decrease in saliva flow can present such ecological pressure. The changes in the oral environment resulting in an increase of Gram-positive bacteria capable of fast production of acids from the dietary carbohydrates (mutans streptococci and lactobacilli) and in a decrease of acid-sensitive species were considered essential in a shift from health to dental decay, where the balance is shifted to a de-mineralization state. The resulting low pH in the environment further enhances the excessive growth and metabolism of these acid-producing (acidogenic) and acid-tolerating (aciduric) species at the cost of acid-sensitive species predominating in enamel health (Marsh 1994, 2006, 2010). The extended ecological plaque hypothesis (Takahashi and Nyvad 2011) was reconsidered to explain the relation between dynamic changes in the properties of plaque bacteria and the de-mineralization/re-mineralization balance of the caries process. The caries process is then explained by three reversible stages: dynamic stability stage with mild and infrequent acidification; acidogenic stage presenting moderate and aciduric acidification, and aciduric stage in severe and prolonged acidic conditions.

This understanding of the etiology of caries has opened up another approach analogous to the principles of the ecological plaque hypothesis in caries prevention. Thus, not only is the putative pathogen focused on but also the ecology of the oral cavity affecting the selection of the microbes can be intervened in (Marsh 2003, 2006, 2010). The plaque acid production can be inhibited by fluoride-containing products or other inhibitors of bacterial metabolism (van Loveren 2001, Marsh 2003, 2006), as well as by avoiding the use of fermentable sugars between meals. The replacement of fermentable carbohydrates by non-fermentable sugar substitutes also reduces the conditions of low plaque pH and stimulates the flow of saliva, which in turn increases the buffering capacity of saliva and assists in returning the pH to a level promoting re-mineralization of the enamel. Again, the enamel chemistry can be consolidated by fluorides (Marsh 2003, 2006).

In practice, the prevention of dental caries includes good oral hygiene, the use of fluoride and adherence to regular meals, as well as the avoidance of frequent use of rapidly fermentable carbohydrates such as sucrose, fructose and glucose syrup (Dean 1938 cited by the Division of Oral Health (2000), Campain et al. 2003, Marshall et al. 2005). Likewise, the prevention of the colonization of mutans streptococci early in childhood is essential. The effect of tooth brushing twice a day using fluoridated toothpaste with a minimum concentration of 1 000 ppm has been undeniably shown in systematic reviews (SBU 2002, Walsh et al. 2010, Mejáre et al. 2015). In addition, it has been systematically documented that the preventive effect of fluoride increases with increasing fluoride concentration of the paste (Ammari et al. 2003, Walsh et al. 2010).

Starting from the Vipeholm dental caries study in the late 1940’s, evidence of moderate quality has been accumulated on the association between both the frequency (Gustafsson 1954) and the amount (Sheiham and James 2015) of sugars intake and the development of dental decay (Moynihan and Kelly 2014, Bernabé et al. 2016). This association has been emphasized to the extent that caries is not considered multifactorial but rather a disease with dietary sugars as the only single cause (Sheiham and James 2015). Frequent intake of fermentable carbohydrates, constant snacking and drinks are common vehicles of sugars today. Frequent sugar-sweetened beverage consumption has been documented to be significantly associated with caries (Armfield et al. 2013). This association can be modified by good fluoride exposure (Burt and Pai 2001, Armfield et al. 2013, Bernabé et al. 2016) and use of sugar alcohols (Deshpande et al. 2008, Antonio et al. 2011, Rethman et al. 2011).

It is considered that caries can be effectively prevented and controlled through a combination of individual, professional and community action (Petersen 2003). Regardless of that, an optimal intervention in relation to oral disease is not universally available or affordable due to discrepancy between costs and resources, as well as the inadequate value given to primary prevention in developing and economically less developed countries (Petersen 2003, Marthaler 2004, ten Cate 2013). Dental decay of today is a disease of children and adolescents in families with a poor socio-economic status and those with a low maternal educational level (Meurman and Pienihäkkinen 2010, Kim Seow W 2012, ten Cate 2001, 2013).

An association between teeth and the chemical element fluorine – often referred to by its negative ion called fluoride – was first discovered in the early 1900´s when mottled enamel was found to be related to the ingestion of toxic amounts of fluoride in the drinking water (Dean and Elvove 1936). Long-term exposure to an optimal level of fluoride has been shown to result in a decreasing caries occurrence in children and in adults (Dean 1938 cited by the Division of Oral Health (2000), SBU 2002, Petersen 2003, Walsh et al. 2010). For most other methods, despite their wide and common use in caries prevention, the evidence of their effect is scarce and equivocal. A recent systematic mapping of eighty-one systematic reviews covered the clinically-relevant topics in the field of pediatric dentistry. These included prevention, non-operative and operative treatment of caries. Strong evidence was shown only for the efficacy of daily use of fluoridated dentifrice (Mejáre et al. 2015).

Contemporary caries control should include prevention, an early diagnosis and intensive intervention of the eventual lesions (Chu et al. 2013). The aim of the non-invasive caries treatment is to get the early lesions to re-mineralize, arrest or slow down the progression (SBU 2007, Chu et al. 2013). Additionally, the causal factors leading to the condition should be recognized by the clinician (Marsh 2003). In a systematic review evaluating five trials on the efficacy of the approaches of the management of these non-cavitated lesions no conclusions could be drawn on the effect, however (Bader et al. 2001). The scientific basis was likewise not considered sufficient for any conclusions to be drawn about the possibilities to effectively treat the early carious lesions with non-invasive methods (SBU 2007). For the effect of fissure sealants the quality of the evidence was moderate only in high caries-risk children but the evidence of the effect in varying levels of caries is lacking (Ahovuo-Saloranta et al. 2013).

Besides the scarce evidence on their effect, the early detection and arrest of the lesions is challenged by the lack of adequate methods for the detection of these early lesions. Poor evidence of the accuracy has been found for traditional visible inspection and FOTI, LF (laser fluorescence) and lesion activity assessment on a visual basis in a comprehensive mapping of systematic reviews (Mejáre et al. 2015).

2.3.2. High- and low-caries populations

There is documentation that the efficacy of the prevention is related to the caries level of the population investigated (Burt et al. 2001, Mariño et al. 2009, Ahovuo-Saloranta et al. 2013). The susceptibility of groups of teeth and sites to caries makes it possible to achieve remarkable caries reduction in high caries conditions if the tooth resistance can be increased or the exposure to risk factors reduced. This also means that in low caries conditions more effort is required in order to achieve further caries reduction (Batchelor and Sheiham 2004). In a low caries population the size of the additional reduction in caries occurrence may not be of the same magnitude as observed in conditions with high caries level (Burt and Pai 2001, Seppä 2001, Mariño et al. 2009, Ahovuo-Saloranta et al. 2013).

The efficacy of fluoride tooth paste in children and adolescents has been documented to increase with increasing baseline levels of caries occurrence. If there is a general addition of 2.6 DMFS per one year in a population, tooth-brushing over three years by 1.6 children is required in order to prevent one DMF surface from developing, whereas with that of 1.1 DMFS per one year, tooth-brushing by 3.7 children is required (Mariño et al. 2009).

Another attempt to quantitatively estimate the occurrence-related efficacy of prevention was made by Ahovuo-Saloranta et al. (2013) with sealants. Due to missing data on baseline caries level in several publications, no true estimation could be performed and the authors made calculations on different caries levels. An assumption was made that forty per cent of tooth surfaces would decay over a follow-up period of two years. The placing of a resin-based sealant would then reduce the proportion of the decayed surfaces to approximately six per cent. If the probability of decay were 70%, the proportion would be reduced to 19%, respectively (Ahovuo-Saloranta et al. 2013).

No additional gain of the effect has been found in low-caries populations with an intensive preventive program targeted at high-risk individuals in comparison to high-risk subjects receiving only the comprehensive basic prevention (Hausen et al. 2000, Källestål 2005). One reason for the lack of success with the conventional high-risk approach may have been that the unfavorable conditions resulting in caries have simply been too strong to be overcome (Seppä 2001). If the caries level is already low, a preventive method or a program can also have reached its maximum effect and no additional reduction will be achieved by increasing the intensity or only by repeating the same method. Instead, another approach can be applied in high-risk individuals. Significant caries reduction has been achieved by a multiple approach regimen, which included not only individually tailored, heavily-intensified multiple caries-controlling measures in caries-active children but also a community level program aiming at the promotion of oral health in Pori, Finland (Hausen et al. 2007).

The good health achieved by previous preventive measures may also serve as a buffer against the disadvantageous factors and, thus, indirectly affect the caries increment in a favorable way even further. A prerequisite is, however, that the good exposure to fluoride and other measures, which have resulted in the present favorable state of health, are continued also in low-caries conditions. Thus, also restriction of sugar consumption is still of importance for a person assessed to be at high risk for caries (Burt and Pai 2001).

One phenomenon associated with the decline of caries is an accumulation of the disease. This means that a majority of the subjects have a low number of carious lesions and most of the lesions are found in a relatively small proportion of subjects in the society (Seppä 2001, ten Cate 2013).

The transference of knowledge and experiences gained from previous prevention programs into working in today's altered real life conditions is one major challenge (Petersen 2003). If an effect of a preventive method has been attained in a population with higher caries occurrence than that of the population which will use it, the effect cannot be compared to real life (Reich 2001).The distribution of oral health services to the public, as well as people's varying attitudes towards self-care are affected by social, economic and cultural circumstances and dynamic demographics (Petersen 2003).

In addition, there is evidence that the decline of caries has plateaued out (Suni et al. 1998) and even a slight increase of caries has been observed in Finnish and Swiss schoolchildren (Seppä 2001, Waltimo et al. 2016). As a result, the population-based health education is by no means losing its significance even in nations considered to have low caries occurrence (Seppä 2001). Further, there is variation in occurrence within a society. This calls for tailored programs for high-risk individuals and those in need of intensive professional care. Adolescents with practically no previous restorative treatment but who unexpectedly manifest several deep dentinal lesions can be seen as a reminder of a fact that each individual is at risk of caries (ten Cate 2001).

2.3.3. Xylitol and erythritol

The non-cariogenicity of a natural five-carbon polyol, xylitol, was first discovered in the 1970s in the Turku Sugar Studies (Scheinin et al. 1975). Another turning point in xylitol research was the Ylivieska field study (Isokangas et al. 1988), which showed significant differences in caries increments between xylitol gum and non-gum control groups of schoolchildren. In addition, a long-term effect of xylitol was documented in post-trial re-examinations of the same children (Isokangas et al. 1989, Isogangas et al. 1993).

Xylitol has been demonstrated to affect caries risk factors by decreasing the counts of mutans streptococci (MS) and the amount of plaque (Söderling 2009, Milgrom et al. 2012). A dose-response relationship in this reduction of MS has been observed by Milgrom et al. (2006) who found a decrease in MS levels in plaque with increasing daily exposure to xylitol. Also the synthesis of insoluble polysaccharides by MS contributing to plaque accumulation has been found to decrease with xylitol consumption.

The non-fermentability by the bacteria and the reduction in plaque adherence have been considered important mechanisms of action of xylitol in caries prevention (Söderling 2009). The effect of bacterial adherence of erythritol is not known.

Several xylitol caries studies (Scheinin et al. 1985, Kandelman et al. 1988, 1990, Mäkinen et al. 1995, 1996, Hujoel et al. 1999, Alanen et al. 2000, Machiulskiene et al. 2001) have been carried out in high risk populations. Many of these have shown a significant caries-reducing effect. The evidence of the caries-preventive effect of xylitol has also been assessed in a number of systematic reviews (Lingström et al. 2003, Mickenautsch et al. 2007, Deshpande et al. 2008, Antonio et al. 2011, Rethman et al. 2011). By contrast, in a novel Cochrane systematic review no conclusion could be drawn on the effect of xylitol (Riley et al. 2015).

In addition to saliva stimulation and chewing, the absence of fermentable sucrose has been considered an important determinant in caries prevention with xylitol (Mickenautsch et al. 2007). The view emphasizing chewing and saliva stimulation has been challenged by studies on mother-child transmission of salivary mutans streptococci, in which children themselves used no xylitol. As a result of maternal consumption the transmission of MS and possibly the caries level of the child were reduced (Söderling et al. 2000, Laitala et al. 2013, Lin et al. 2015). The effect of chewing can likewise be questioned by studies documenting caries reduction following use of topical oral syrup (Milgrom et al. 2009) and the use of xylitol wipes or swabs (Zhan et al. 2012 and Mäkinen et al. 2013). In the study of Zhan et al., no decline in salivary MS but a decline in caries occurrence was observed. In the study of Mäkinen et al. (2013) declines in both the plaque and the salivary MS, as well as in the caries incidence were observed.

A dose-response relationship has been assessed between xylitol chewing gum and caries (Deshpande et al. 2008). A statistically significant caries reduction following the use of sucrose-free polyol gum consumption was found in another systematic review, likewise performing a meta-analysis (Rethman et al. 2011). Caries reduction by xylitol was greater than by the other polyols analyzed, but the strength of recommendation was weak (Rethman et al. 2011). A systematic review (Antonio et al. 2011), which also performed a meta-analysis could not find strong evidence of the effect of xylitol candies in the prevention. In a systematic review of Lingström et al (2003), the evidence for the use of xylitol in chewing gum was found to be inconclusive. A novel Cochrane systematic review on xylitol included randomised and cluster-randomized caries prevention studies in both the children and the adults with consumption of any form of xylitol-containing product for a minimum of one year. The evidence on xylitol was regarded as being of low to very low quality, and not sufficient to determine whether xylitol has a caries-preventive effect. The only exception to this was xylitol-containing fluoride toothpaste, which may have a better caries-preventive effect than fluoride dentifrice without xylitol (Riley et al. 2015). Even though the review was technically well done, the inclusion and exclusion criteria used left only ten studies to be evaluated. These studies did not represent the "best" xylitol studies. For example, in five studies, the daily xylitol doses were far below the five to seven grams a day considered effective (Hayes 2001, Caries control: Current Care Guidelines, 2014). All systematic reviews performing a meta-analysis have shown a high level of statistical heterogeneity and none of them has considered general caries occurrence of caries as a modifying factor in the estimation of the effect of xylitol (Deshpande et al. 2008, Antonio et al. 2011, Rethman et al. 2011, Riley 2015) (Table 1).

Erythritol is a safe, well-tolerated and low-caloric four-carbon polyol. The evidence of the effect of erythritol on risk factors of caries and in caries reduction is very scarce in relation to that of xylitol (Mäkinen et al. 2001, 2005, Honkala et al. 2014). There is evidence that growth of several strains of mutans streptococci may be inhibited by erythritol (Kawanabe et al. 1992, Mäkinen et al. 2001, 2005). Also the plaque and salivary levels of MS, as well as the amount of plaque, have been shown to decrease following the use of erythritol (Mäkinen et al. 2005). The above-mentioned properties provide one with a motive for additional studies on caries-preventive properties of erythritol.

The decline in the occurrence of dental caries calls for the detection and prevention of dental caries to be brought up to date. The methods used in contemporary caries control and detection need to be analogous to our current understanding of the etiology and distribution of the disease in the population. In order to make use of the preventive methods and programs meaningful for the individual and the society they need to be effective in the particular population in which they are implemented. Thus, there is an obvious need for a careful evaluation of the clinical relevance of xylitol and diagnostic measures in a low-caries population.

Table 1. Systematic reviews of controlled or randomized clinical trials on the caries preventive effect of xylitol.

Aim	Studies included	Conclusion
Lingström et al. 2003		
To evaluate the effect of dietary changes in the prevention of dental caries.	RCT, CCT, xylitol gum, xylitol candy Alanen 2000, Isokangas 1988, Kandelman 1988, 1990, Machiulskiene 2001, Mäkinen 1995, 1996, Scheinin 1975	***Evidence for the use of xylitol in chewing gum is inconclusive (on the basis of the studies with moderate evidence).***
Mickenautsch et al. 2007		
To appraise existing evidence for a therapeutic/ anti-cariogenic effect of sugar-free chewing gum.	RCT, xylitol/ xylitol-sorbitol gum Machiulskiene 2001 and Scheinin 1975, Peng 2004 and Petersen 1999	***The anti-cariogenic effect can be ascribed to saliva stimulation through the chewing process, the lack of sucrose and the inability of bacteria to metabolize polyols into acids but not to any therapeutic action of polyol.***
Deshpande et al. 2008		
To assess the impact of polyol-containing chewing gums on dental caries compared with the effect with no gum.	RCT, CCT, xylitol gum Alanen 2000, Isokangas 1988, Kandelman 1990, Kovari 2003, Machiulskiene 2001, Mäkinen 1995,1996 Post trial: Hujoel 1999, Isogangas 1993, Isokangas 1989, 1991	***The use of polyol-containing gum as part of normal oral hygiene to prevent caries is supported by research evidence.***
Antonio et al. 2011		
To assess the caries preventive effect of consuming xylitol-based candies and lozenges.	RCT, CCT, xylitol candy Alanen 2000, Honkala 2006, Stecksén-Blicks 2008	***The use of xylitol-based candies and lozenges could favor a reduction in caries increment. Their consumption did not seem to be effective on the proximal surfaces. Findings are not supported by strong evidence, however.***

Aim	Studies included	Conclusion
Rethman et al. 2011		
To present evidence–based clinical recommendations on non-fluoride caries preventive agents on the market in the U.S.	RCT, CCT, polyol gum Alanen 2000, Machiulskiene 2001 (Good quality); Alanen 2000, Honkala 2006, Mäkinen 1995, 1996 (Fair quality); Isokangas 1988, Kandelman 1990, Kovari 2003, Oscarson 2006 and Stecksén-Blicks 2008 (poor quality)	***The panel concluded with moderate certainty that in children aged 5-16 years, supervised consumption of chewing gum sweetened with sucrose-free polyol (xylitol only or polyol combinations) for 10-20 minutes after meals marginally reduces incidence of caries*** The panel noted that it is biologically plausible that the act of chewing itself increases the rate of food clearance from the mouth, increases saliva production and more quickly neutralizes plaque acids, thereby potentially lowering the incidence and progression of caries. **Recommendation:** parents and caregivers of healthy children older than 5 years and at high risk of experiencing caries are advised to give the children sucrose-free polyol chewing gum after meals. **Strength of recommendation:** weak. (Evidence suggests implementing this intervention only after alternatives have been considered.)
Rethman et al. 2011		
To present evidence–based clinical recommendations on non-fluoride caries preventive agents on the market in the U.S.	Polyol candy Four studies on xylitol: Alanen 2000 (fair quality), Honkala 2006 (poor quality), Stecksén-Blicks 2008 and Oscarson 2006 (good quality)	***Based on the limited number of studies, the panel concluded with low certainty that: In children reporting caries experience, consumption of xylitol containing lozenges or hard candy reduces incidence of coronal caries.*** **Recommendation:** A majority of the panel recommended the use of xylitol lozenges after meals for children older than 5 years and a dose of 5 to 8 grams /day divided into two or three doses to maximize clinical benefits. **Strength of recommendation:** Expert opinion **(**Evidence is lacking)
Riley et al. 2015		
To assess the effects of different xylitol-containing products for the prevention of dental caries in children and adults.	RCT, xylitol/ sorbitol/ erythritol candy, xylitol topical oral syrup, xylitol sucking tablets, xylitol/ xylitol plus fluoride toothpaste, BB-12+ xylitol tablet, pacifier, xylitol wipes Bader 2013, Honkala 2014, Lenkkeri 2012, Milgrom 2009, Oscarson 2006, Petersson 1991, Sintes 1995, 2002, Taipale 2013, Zhan 2012	***The authors found some low quality evidence to suggest that fluoride toothpaste containing xylitol may be more effective than fluoride-only toothpaste for preventing caries in the permanent teeth of children. The remaining evidence was found to be of low to very low quality and is insufficient to determine whether any other xylitol-containing products can prevent caries in infants or older children.***

3. AIMS OF THE STUDY

The aim of the study was to investigate the prevention of dental caries using xylitol and erythritol lozenges and the detection of dental caries in a low-caries level population, and to systematically evaluate the available literature on xylitol, in relation to the caries level of the subjects studied. The specific objectives were:

- To investigate, in a low-caries level population, the additional effect of xylitol/maltitol and erythritol/ maltitol lozenges delivered at school, on dental caries, relative to a control group receiving comprehensive routine prevention provided by the public dental health care (I). We hypothesized that the prevented fraction of xylitol/maltitol lozenges would be of the same magnitude as in earlier xylitol studies and that the preventive effect of erythritol/maltitol would be seen when compared with no polyol and no saliva-stimulating intervention.
- To evaluate the literature on xylitol in caries prevention and the caries level of the population investigated (II). The hypothesis was that in a low-caries level population the effect of xylitol may vary from that observed in a high-caries level population.
- To compare the effects of xylitol and erythritol on glass adhesion of polysaccharide-producing oral streptococci, and to relate these effects to the growth inhibition found for these polyols (III). The hypothesis was that both xylitol and erythritol decrease the adherence of polysaccharide-producing mutans streptococci.
- To investigate the eventual additional value of bitewing radiographic examination in the detection of occlusal and proximal caries in low-caries conditions (IV). We hypothesized that in low-caries conditions radiographic examination is needed in addition to clinical observation in caries detection.
- To compare the occurrence of the clinically undetected dentine caries between adolescents with and those without clinically observed dentinal caries (IV). The hypothesis was that the hidden obvious dentinal decay calling for restorative treatment is found both in subjects with and those without clinically detected dentinal caries or fillings.

4. MATERIALS AND METHODS

4.1. Study subjects, designs and characteristics of the studies

Study I was a four-year double-blinded clinical trial conducted in initially 10-year-old children randomly assigned as clusters into one of the five study groups (Figure 3). In study II, the available literature covering the randomized controlled and controlled clinical trials on xylitol in caries prevention was systematically reviewed. Study III was an *in vitro* study on polysaccharide-producing oral streptococci. Study IV was a cross-sectional study using bitewing radiographs obtained from the subjects in study I (Table 2).

All grade four pupils (n=589) of the town of Kotka in autumn 1999 were eligible to be included in study I. Before the study, the personnel of the health center were informed of the study (March 1999) and the teachers were sent an informative letter (May 1999), in which also the willingness of the schools to participate and serve as the distributors of the lozenges was explored.

In study I the required sample size was calculated on the basis of the DMFT and DMFT=0 statistics of 15-year-olds in Kotka where the proportion of DMFT=0 subjects was between 55 and 60 %. To avoid the type II error and for the test to have a 90% power to detect a statistically significant difference, one hundred subjects per group were required. Attrition was estimated to be 10 % or less per year. The 21 participating schools were randomly assigned as clusters into five groups (n=579). Only then were they given a role as one of the four groups receiving the color-coded lozenges. This was done to ensure the concealment of the allocated intervention.

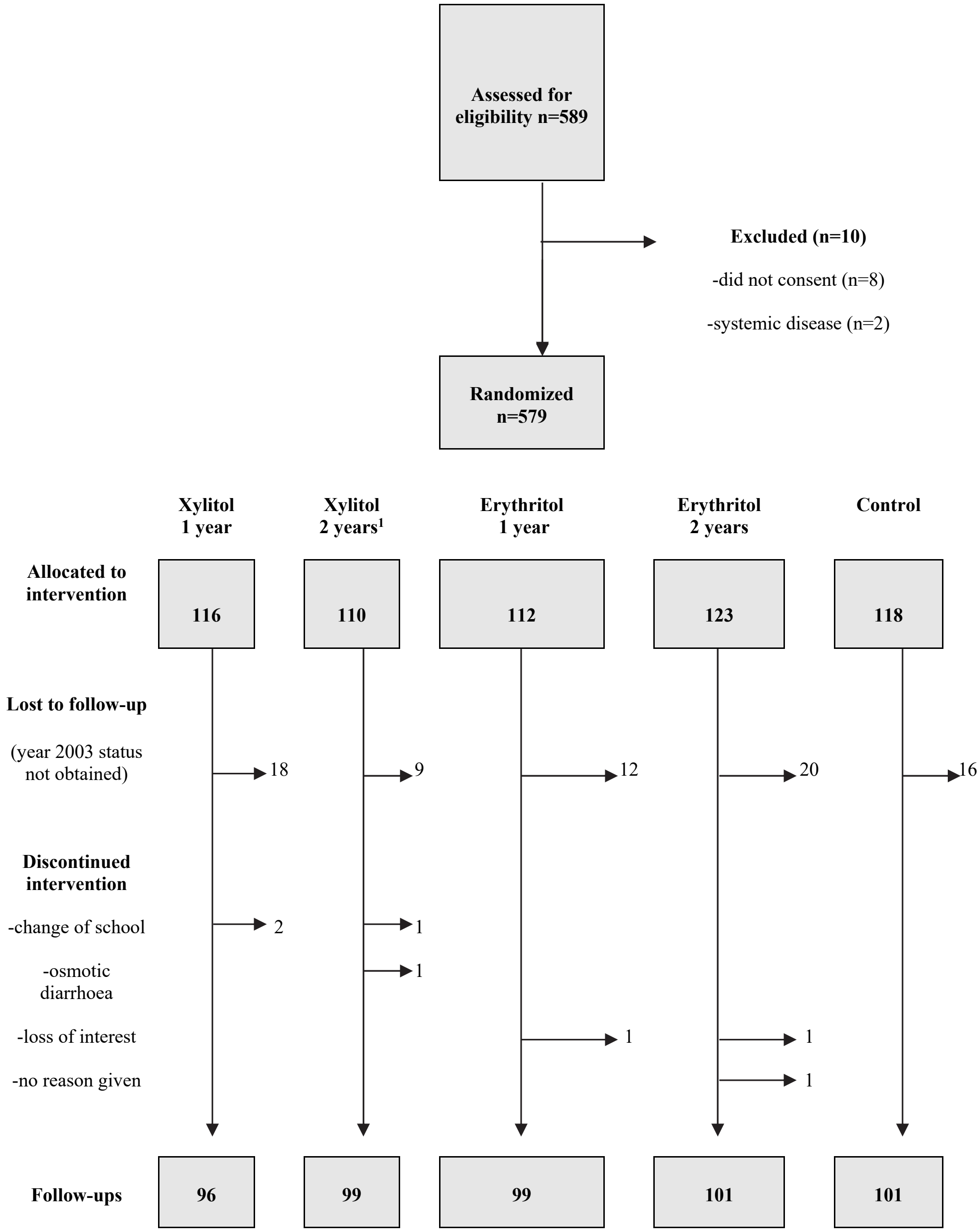
Clinical and radiographic data of 363 subjects whose clinical and radiographic registrations were performed by the same person in study I were included in the cross-sectional study (IV). In the systematic study II, trials with subjects below eighteen years of age were included. They had to be exposed to xylitol lozenges or chewing gum and the outcome measure ought to be a caries-related one. The minimum follow-up time for children under seven years of age was one year, and for the remaining children and adolescents two years.

4.2. Ethical aspects

The ethics board of Kotka Health Center approved study I before its onset. An informative letter (May 1999) was sent to all families (n=589) involved and their consent was solicited. Eight families did not consent and two subjects were excluded due to a systemic disease. It was made clear to each participant that participation was fully voluntary and one had the right to leave the study at any time with no explanation. The bulk agents of the lozenges (erythritol, maltitol and xylitol) have been considered safe. With the relatively low daily dose (4.2-4.7 g) of these sugar alcohols no laxative effect was expected. It was strongly emphasized to the subjects that the use of the lozenges by no means replaced tooth brushing with fluoridated dentifrice twice a day. The dose of radiation in obtaining a pair of bitewing radiographs (studies I and IV) was kept as low as possible and was likely to cause no health hazard to the children. A safety collar was used. Study IV used merely data collected in study I and no other data from any other record were combined.

Table 2. Characterization of the studies.

Study	Design	Material	n	Object of the study	Analysis
I	Double-blinded randomized clinical trial	Children using xylitol or erythritol lozenges for 1 year or 2 years. Control group children	Randomized/ analyzed 579/496 (85.7%)	4-year dentin caries increment	ANOVA, Kruskal-Wallis, Pearson chi-square, hierarchical logistic regression modelling,
II	Systematic review	Literature on caries-preventive effect of xylitol	16 articles	Caries-preventive effect of xylitol in relation to caries level of the population	
III	*In vitro*	Seven type strains of oral streptococci grown in 4% xylitol or erythritol	-	Adherence of oral streptococci	Independent samples *t*-test, Spearman's Rank Correlation
IV	Cross-sectional study	Bitewing radiographs from study I subjects	363 pairs of radiographs	Yield from radiographs	Crosstabulation, Mann Whitney *U* test,



[1)] In the Xylitol 2 years' group, 90 subjects received and 20 subjects did not receive the allocated intervention.

Figure 3. Flow of the subjects in study I (retrieved from Study I).

4.3. Test products and their administration (I)

In study I, the xylitol/maltitol lozenge (49% xylitol/ 47.46% maltitol, coconut oil, malic acid, polishing powder, emulsifier, flavor and color; weight 1.2 g) was Leaf Dents Lakerol plus strawberry, which is commercially available. The erythritol/maltitol lozenges (49.43% erythritol/ 47.04% maltitol, coconut oil, polishing powder, flavor, color and menthol; weight 1.0 g) were especially formulated for the study. The color-coded lozenges were made and donated to the study by CSM Leaf (Turku, Finland) where the code was kept unopened until all the statistical analyses had been performed. They were delivered to the schools in coded boxes from the manufacturer and consumed in three daily sessions supervised by the teacher. The daily amount was 4.7 g/4.6 g xylitol/maltitol and 4.5 g/4.2 g erythritol/maltitol, for on average 190 days per year either for one (1999-2000) or for two school years (1999-2001).

4.4. Data collection

The clinical data of studies I and IV were collected in annual clinical examinations of the teeth in September or October over the years 1999-2003 (study IV, year 2003 only). Bitewing radiographs were obtained in 2003 (studies I and IV). Additionally, two questionnaires were sent to the teachers (October 2000 and 2003) and one to the study subjects (April 2004). One dentist assisted by one dental nurse clinically examined the teeth of the study sample children in Kotka, which is a town with 55, 000 inhabitants in an area of natural fluoridation in south-eastern Finland. The average DMFT of 12-year-olds in Kotka was approximately 0.8 in comparison to the Finnish average of 1.2.

For the systematic review (II) the author (AH-L) and an information specialist at Turku university library (HT) conducted an original literature search through December 16, 2011. In the report, the period up to June 15, 2015 has also been covered (EJ). The internet sources searched were ProQuest –Health & Medicine, Cochrane (for systematic reviews), Web of Science, PubMed, CINAHL and Embase (excluding the original search). The following terms were used in the search strategy: all("dental caries" OR "dental health" OR anticaries OR "caries prevention" OR "caries prophylaxis") AND all(xylitol). The limits were: peer reviewed, English, Finnish, Swedish. The flow chart of the review selection is presented in Figure 4.

4.5. Analytical methods (II, III)

For study II the identified papers were independently screened by the reviewers (AH-L, IA and KP). Titles and abstracts were screened first (AH-L and IA). Following that, the full text articles of the accepted abstracts were ordered and screened for inclusion or exclusion (AH-L and KP). The reviewers discussed any disagreement regarding the inclusion or exclusion of each particular paper until a consensus was achieved. The eligibility criteria followed the PICO principle, in which patients (P) were human subjects under eighteen years, intervention (I) was an experimental group exposed to xylitol in a form of lozenge or chewing gum, control intervention (C) indicated inclusion of a no-treatment arm and the outcome measure (O) had to be dental caries –related. To be accepted the study had to be a randomized controlled trial (RCT), a controlled clinical trial (CCT) or a systematic review (SR). Other eligibility criteria included the study to be published in a peer-reviewed journal in English, Swedish or Finnish. The length of follow-up was a minimum of one year for children under 7 years or a minimum of two years for 7-18-year-olds. If the eligibility criteria were met, data extraction was performed. Due to the heterogeneity of the studies included in the systematic review (II), no quantitative meta-analysis was performed, and the study is merely a descriptive one. The caries level of each individual study population was assessed in relation to the DMFT values of 12-year-olds given in the WHO oral health report (2003). Values below 1.2 were regarded as very low, 1.2 to 2.6 as low, 2.7 to 4.4 as moderate, and values above 4.4 as high. The included papers were independently evaluated (AH-L and KP). The flow chart of the review selection is presented in Figure 4.

In study III the cells were cultured in 5 ml BHI overnight at +37°C from stocks kept frozen to produce log-phase cells, and then transferred to fresh BHI supplemented with 1% sucrose the following morning. The growth media contained 2% (0.13 mol/l) or 4% (0.26 mol/l) xylitol (Oriola, Espoo, Finland), or 2% (0.16 mol/l) or 4 % (0.33 mol/l) erythritol (Sigma, St. Louis, MO, USA). The polyols were added to the sterile media using filter sterilization. The control medium contained no added polyols. The cells were cultured in a shaking water bath at +37°C. Growth was followed by measuring the absorbance at a wavelength of 550 nm. The inhibition percentages were calculated from the growth curves at late log-phase. The ability of cells to adhere to a smooth glass surface was determined according to Mattos-Graner et al. (2000). We estimated the adhesion percentage from the cell density of adherent cells. The adherence tests were performed in triplicate.

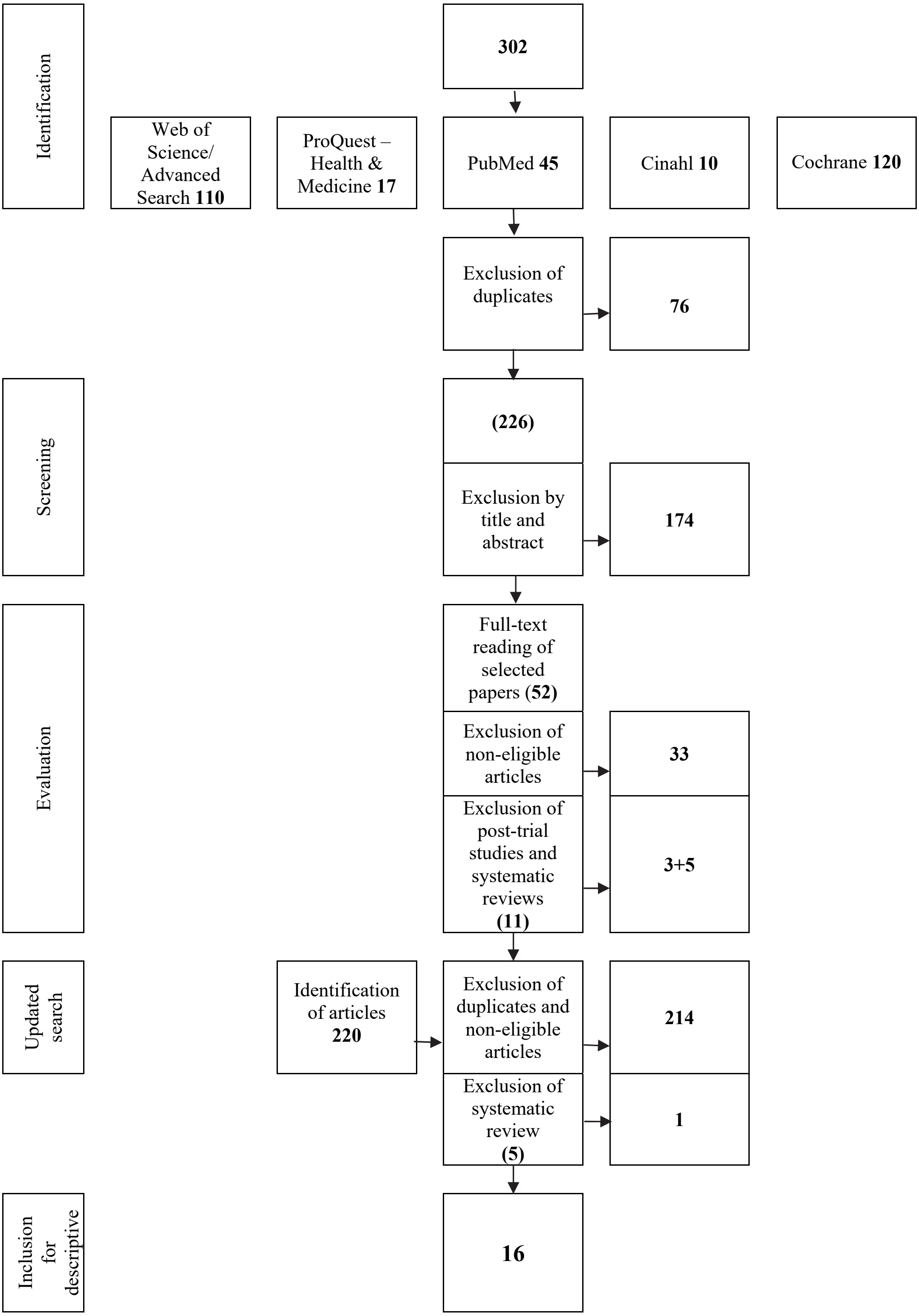


Figure 4. Flow chart of review selection.

4.6. Clinical and radiological examination (I, IV)

The examining dentist was instructed by one of the supervisors (PA) before the onset of study I. The subjects were clinically examined annually in September or October over 48 months by the examining dentist (AH-L) who also took bitewing radiographs at the final visit. If a child was absent from school on a scheduled day of the examining dentist, the local health center dentist was asked to carry out the examination with no delay (1999: 21 examinations; 2000: 12; 2001: 8; 2002: 13 and 2003: 24, respectively). These findings were included in the analyses.

The children were asked to brush their teeth before the examination, which took place in a dental chair with good illumination. A mouth mirror, dental explorer, fiber optics and an air syringe were used. The bitewing radiographs were obtained using Kodak Ultra-Speed D safety one film and a Kwik-Bite film holder (Hawes-Neos Dental, Bióggio, Switzerland) using one of the six X-ray units of Kotka health center. The processing of the films was performed manually by one experienced dental nurse (studies I and IV).

Caries was diagnosed according to modified WHO criteria. WHO codes zero and one were considered sound surfaces. An enamel lesion with a loss of substance was coded as an enamel lesion. Dentin caries calling for filling was diagnosed as a dentinal lesion (D_3). The registrations were made at surface level. No clinical double examinations were carried out.

The radiographs were analyzed by the examining dentist (AH-L 296 pairs) and a senior dentist (KP 143 pairs) and by both (74 pairs) in a dark room with an illuminator and a 1,5-fold magnification blind to the clinical score and allocation. A calibration of the examiners preceded the analysis of the radiographs. Modified Mejáre criteria (1998), in which also the deep lesions on occlusal surfaces were diagnosed was used (studies I and IV). The bitewings analyzed in study IV (363 pairs) had been obtained from study I and re-coded to ICDAS with the exception that the activity of the lesions could not be judged in the radiographs. WHO codes zero and one corresponded to ICDAS codes 0 to 2. An enamel lesion with a clinically detectable loss of substance but with no obvious spread in the dentine (ICDAS 3) was regarded as an established enamel decay. Dentine caries obviously spreading in the dentine (ICDAS 4 to 6) was considered an established and severe dentinal decay calling for filling. The subjects were categorized into those with and those without clinically observed dentinal caries.

The occlusal surfaces of the 1st and the 2nd molars, the mesial surfaces of the 2nd premolars and the 1st and the 2nd molars, and the distal surfaces of the 1st and the 2nd premolars and the 1st molars were included in the radiographic analyses. The data input in annual Excel files was carried out by the examining dentist (studies I and IV).

4.7. Outcome measures

The clinical four-year dentin caries increment of the permanent teeth (ΔD_3MFS) was the main outcome measure (study I). It was measured individually as the difference between the final and the baseline D_3MFS values. The groups were compared using a dichotomized response variable in relation to the proportion of children with $\Delta D_3MFS=0$. The secondary outcome included clinical and radiographic information. In the additional analyses, the comparison of groups with continuous response variable was performed. No changes were made to the outcomes after the onset of the study.

In study III the inhibition of glass surface adhesion of oral streptococci in relation to inhibition of growth by xylitol or erythritol was the study outcome.

The additional diagnostic yield from the radiographs was the outcome measure in study IV. The detection of established or severe decay (ICDAS 4-6) on a surface clinically registered ICDAS 0-2 (yield 1) or ICDAS 3 (yield 2) was measured on a tooth, on a surface, and on an individual level.

Study II was a descriptive systematic review seeking to provide information about the xylitol effect on dental caries and the associated caries level of the population. The study outcome was prevented fraction (PF), measured if the incidence of dental caries was reduced following the use of xylitol lozenges or gum in comparison to no use of xylitol.

4.8. Statistical methods

In all studies, probability values of <0.05 were considered statistically significant.

In study I, data handling and statistical analyses were performed using an intention to treat approach. ANOVA (differences in age between drop-outs and follow-ups), Kruskal-Wallis test (differences in baseline D_3MFS between drop-outs and follow-ups), and Pearson chi-square test (differences in gender and differences in dichotomized baseline D_3MFS between drop-outs and follow-ups) were used. Hierarchical logistic regression modeling was used for analyses of dichotomous response variables to adjust for potential clustering. The results were quantified using OR (95% CI). For continuous response variables between the groups, the Kruskal Wallis test was used. For dichotomous response variables, the Glimmix procedure of the SAS software for Windows version 9.2 (SAS Institute Inc., Cary, NC, USA) and for other analyses, the SPSS software for Windows version 14 (SPSS Inc., Chicago, IL, USA) were used.

Independent samples *t*-test (SPSS 14.0 for Windows) was used for comparison of growth in study III. The associations between different variables were investigated using Spearman's Rank Correlation.

In study IV, the yield on a tooth surface and on an individual level were described using crosstabulation. The independent samples nonparametric Mann-Whitney U test was used to test the significance of differences between subjects with and subjects without clinically detected caries in relation to the occurrence of yield. The level of significance, set to 0.05. PASW Statistics Data Editor Software for Windows version 18 (SPSS Inc., Chicago, IL, USA), was used for analyzing the data.

5. RESULTS

5.1. Clinical trial: participant flow, protocol deviations, adverse events and baseline characteristics (I)

All but ten of the 589 children assessed as eligible for participation in the trial were randomized (Figure 3). Of all subjects randomized, 85.7% (n=496) were available in the final examination and included in the analyses according to the intention to treat principle, that is, in groups they were originally allocated to. The protocol deviations included additional prophylaxis (n=33) and discontinuation of one school (n= 20) during the first year of intervention due to problems in the logistics of the lozenges and the opinion of the class being in favor of stopping the intervention. One subject (Xylitol/maltitol 2 years group) reporting osmotic diarrhea withdrew from the study during the first year of the intervention. No differences were observed in the baseline characteristics (age, mean D_3MFS, DMFS=0 or proportion of boys and girls) between the follow-ups and the dropouts (Table 3).

5.2. Caries preventive effect of xylitol and erythritol lozenges in low-caries-population (I)

The additional use of xylitol/maltitol or erythritol/maltitol lozenges did not result in further caries reduction in a low-caries level population (I). Tables 4 and 5 present the main finding of the study: no significant differences were observed between any polyol group and the control group in relation to the proportion of ΔD_3MFS=0 in the modeling.

5.3. Relationship between baseline caries level and the four-year caries increment (I)

In the hierarchical logistic regression modeling for dichotomized ΔD_3MFS response variables, the relationship between the baseline caries level and the four-year caries increment was found to be strong (OR = 7.38; 95% CI: 3.78-14.41). This observation is shown in Table 5.

Table 3. The number and mean age (in months) of subjects, the number and proportion of boys and of subjects with $D_3MFS=0$, and mean D_3MFS value in follow-up subjects and dropouts. Baseline information for each group given at individual level. Comparisons between follow-up and dropout subjects by group, and between groups of follow-up subjects (modified from Study I).

	Group	Total N	Age Mean (SD)	Boys n (%)	$D_3MFS=0$ n (%)	D_3MFS Mean (SD)
Follow-up			1	2	3	4
	Xylitol/maltitol 1yr	96	123.5 (4.8)	50 (52.1)	74 (77.1)	0.46 (1.2)
	Xylitol/maltitol 2 yrs	99	123.4 (4.2)	45 (45.5)	79 (79.8)	0.35 (0.8)
	Erythritol/maltitol 1yr	99	122.6 (4.5)	53 (53.5)	89 (89.9)	0.23 (0.8)
	Erythritol/maltitol 2yrs	101	123.2 (4.1)	38 (37.6)	85 (84.2)	0.31 (0.8)
	Control	101	122.6 (3.6)	48 (47.5)	83 (82.2)	0.27 (0.7)
	Total	496	123.1 (4.2)	234 (47.2)	410 (82.7)	0.32 (0.9)
Dropout						
	Xylitol/maltitol 1 yr	18	124.1 (5.2)	11 (61.1)	11 (61.1)	0.94 (1.6)
	Xylitol/maltitol 2 yrs	9	125.4 (7.5)	4 (44.4)	5 (55.6)	0.56 (0.7)
	Erythritol/maltitol 1 yr	12	124.7 (4.7)	4 (33.3)	9 (75.0)	0.33 (0.7)
	Erythritol/maltitol 2yrs	20	123.7 (3.7)	8 (40.0)	14 (70.0)	0.60 (0.9)
	Control	16	121.8 (4.8)	4 (25)	15 (93.8)	0.06 (0.3)
	Total	75	123.8 (5.0)	31 (41.3)	54 (72.0)	0.52 (1.0)

Stat. sign.:

Differences between follow-ups and dropouts not significant in any group (age: ANOVA; gender: chi square test; $D_3MFS=0$: chi square test; D_3MFS: Mann-Whitney U test)
Differences between groups not significant (follow-up)
1) $p= 0.375$ ANOVA
2) $p= 0.174$ Pearson chi-square test
3) $p=0.168$ Pearson chi-square test
4) $p= 0.226$ Kruskal Wallis test

Table 4. Number and percentage of children with no caries increment ($\Delta D_3MFS=0$) at final examination clinically, and clinically and radiographically (modified from Study I).

Group	**N**	**$\Delta D_3MFS=0$**	
		Clinical n (%)	Clinical and Radiographical n (%)
Xylitol/maltitol 1 year	96	40 (42)	18 (19)
Xylitol/maltitol 2 years	99	46 (47)	20 (20)
Erythritol/maltitol 1 year	99	38 (38)	19 (19)
Erythritol/maltitol 2 years	101	52 (51)	27 (27)
Control	101	43 (43)	23 (23)
Total	496	219 (44.2)	107 (21.6)

Table 5. The results of the hierarchical logistic regression for dichotomized ΔD_3MFS response variables at clinical examination and combined clinical and radiographic examination. Cluster (School)-adjusted effect size (odds ratio, OR) and its 95% confidence interval (CI) for the variables in the model (retrieved from Study I).

Factors	*Clinical*			*Clinical and radiographical*		
	Adjusted OR	95% CI	*P*-value	Adjusted OR	95% CI	*P*-value
Control *versus* Xylitol/maltitol 1year	1.04	0.57-1.90	0.887	0.89	0.35-2.27	0.802
Control *versus* Xylitol/maltitol 2years	1.25	0.69-2.25	0.462	0.99	0.39-2.49	0.980
Control *versus* Erythritol/maltitol 1year	0.73	0.41-1.32	0.298	0.81	0.32-2.07	0.655
Control *versus* Erythritol/maltitol 2years	1.46	0.81-2.61	0.212	1.32	0.55-3.18	0.533
Girls *versus* Boys	1.11	0.76-1.62	0.583	1.03	0.66-1.62	0.892
Baseline $D_3MFS>0$ *versus* $D_3MFS=0$	7.38	3.78-14.41	<0.001	5.42	2.11-13.91	<0.001

5.4. Review of caries-preventive effect of xylitol with caries in different caries levels (II)

The original search in December 2011 identified three hundred and two papers. The abstracts and further the full text articles not fulfilling the pre-defined selection criteria were excluded. Four randomized (Alanen et al. 2000, Machiulskiene et al. 2001, Kovari et al. 2003 and Oscarson et al. 2006) and seven controlled clinical trials (Scheinin et al. 1985, Isokangas 1988, Kandelman et al. 1988, Kandelman et al. 1990, Mäkinen et al. 1995, 1996 and Stecksén-Blicks et al. 2008) were included for assessment of relevance, quality and data extraction. In the updated search in June 2015 two hundred and twenty (220) titles and abstracts were identified. After exclusion of non-eligible papers and duplicates, five additional randomized trials (Lenkkeri et al. 2012, Alamoudi et al. 2012, Campus et al. 2013, Honkala 2014 and Lee et al. 2015) fulfilling the inclusion criteria were included for the evaluation. Thus, 16 original trials were evaluated in the present descriptive systematic review.

The included trials were heterogenic in many respects (Table 6). For instance, the studies included subjects between the ages of two and twelve years. Likewise, the baseline caries levels of the subjects, as well as the country DMFT levels, showed significant heterogeneity. Only one study investigating permanent teeth was carried out in a low-caries level population (Lenkkeri et al. 2012). Seven studies had subjects with high caries levels (Scheinin et al. 1985, Kandelman et al. 1988, Kandelman & Gagnon 1990, Mäkinen et al. 1995, Machiulskiene et al. 2001, Campus et al. 2013, Honkala et al. 2014) and the remaining three studies moderate (Isokangas et al. 1988, Alanen et al. 2000, Stecksén-Blicks et al. 2008).

The results of the review with the related prevented fractions (PF) are presented in Table 7. Of the eleven studies analyzing permanent teeth, ten had been performed in populations with a high or moderate caries level. A statistically significant preventive effect was observed in eight trials with a high caries level (prevented fraction between 25.6% and 114%). In these studies, the daily consumption of xylitol was considered sufficient with a dose varying between 3 and 20 grams. One study (Honkala et al. 2014) showed a negative prevented fraction (-17.6%). This study was a placebo-controlled clinical trial comparing the relative preventive effect of three polyols rather than a measurement of the clinical significance.

Primary teeth were analyzed in five trials. Two of them represented low-caries level populations and three high level populations. A statistically significant preventive effect was reported in one study carried out in a low-caries level population, whereas the other one showed no significant effect. Two of the studies in high-caries level populations showed a significant caries-preventive effect of xylitol with a prevented fraction varying between 37.4% and 63.3%. Again, a study showing a negative prevented fraction (-25.0%) was a placebo-controlled study measuring the plain xylitol effect when added to comprehensive prevention.

5.5. Effect of xylitol and erythritol on adherence of polysaccharide-producing oral streptococci (III)

Reduction in the adherence and inhibition of growth of the polysaccharide-producing oral streptococci were observed in the presence of both the xylitol and the erythritol. With 4% xylitol and with 4% erythritol the growth inhibition for clinical *S. mutans* isolates was between 13 and 73%. There was no association between the reduction in the adherence and the growth inhibition for either polyol.

Table 6. The mean DMFS/DMFT at baseline and the DMFT level of the country investigated (modified from the manuscript of Study II).

Author, Year, Country and Time of study	**Age**	**Baseline DMFS of subjects**	**Country DMFT level[1]**
PERMANENT TEETH			
Scheinin et al. 1985 Hungary 1981-84	7 to 10 yrs	DMFS: 7 yrs: X 1.4, C 0.8,8 yrs: X 3.4, C 2.3 9 yrs: X 4.2, C 2.5, 10 yrs: X 5.6, C 3.3 ***High***	High (1985: 5.0)
Isokangas et al. 1988 Finland 1982-85	11 and 12 yrs	DMFS : C: 4.8; X: 4.1: ***Moderate***	Moderate (1982: 4.0)
Kandelman et al. 1988 French Polynesia 1981-84	6 to 12 yrs	DMFS given by age. The values vary between 2.2 (6-yr-olds) and 16.4 (12-yr-olds) ***High***	Moderate (1982: 3.2)
Kandelman&Gagnon 1990 Canada 1985-	8 and 9 yrs	DMFS: X65: 6.33 C: 5.67 ***High***	Moderate (1982: 3.2)
Mäkinen et al. 1995 Belize 1989-	10.2 yrs	DMFS: Xstick3: 6.6; Xstick5: 6.1; Xpellet3: 3.4; Xpellet5: 5.1; C: 4.3 ***High***	High (1989:6.0)
Alanen et al. 2000 Estonia 1994-99	10 yrs	DMFS: Xgum: 1.78; Xcandy12: 2.86; Xcandy13: 1.64; Xcandy22: 1.48; Xcandy23: 1.78; C: 2.18 ***Moderate***	Moderate (1992: 4.1)
Machiulskiene et al. 2001 Lithuania 1994-97	11.6 yrs	DMFS: X: 5.0; C:6.4 ***High***	High (1993-1994: 4.9)
Stecksén-Blicks et al. 2008 Sweden 2003-05	10 to 12 yrs selected high-risk	DMFS proximal:X: 0.5; C: 0.7 ***Moderate***	Very low (2002: 1.1)
Lenkkeri et al. 2012 Finland 1999-2003	10 yrs	DMFS: X: 0.35; C: 0.27 ***Low***	Low (2000: 1.2)
Campus et al. 2013 Italy 2007-	8.3 yrs selected high-risk	C_6FS: X 57.14%; Placebo 56.41% ***High***	Low (2004: 1.1)
Honkala et al. 2014 Estonia 2008-2011	8.7 yrs	dmft+DMFT: X 5.65; S-placebo 6.02 ***Moderate/High***	Moderate (1998: 2.7)
PRIMARY TEETH			
Mäkinen et al. 1996 Belize 1990-92	6 yrs	dmfs of primary teeth: Xstick: 11.0; Xpellet: 12.2; C: 12.8 ***High***	High (1989:6.0,)
Kovari et al. 2003 Finland 1993-95	3 yrs	Average dmf in 3-year-olds 0.3[2] ***Low***	Low (1994: 1.2)
Oscarson et al. 2006 Sweden 2002-04	2 yrs	dmfs X: 0.4, C: 0.4 ***Low***	Very low (2002:1.1)
Alamoudi et al. 2012 Saudi Arabia	2 to 6 yrs, selected high-risk	dmft: X: 8.37; C: 10.27 ***High***	High (2002:5.9)
Lee et al. 2015 USA 2007-	5 to 6 yrs	dmfs: X 6.3, Placebo 4.3, statistically significant difference between groups ***High***	Very low (1999-2004: 1.19)

[1] WHO CAPP: WHO Oral Health Country/ Area Profile Programme (CAPP), [2] Kovari Helena (Thesis 2002)

Table 7. The results of the included clinical trials and the related prevented fractions (PF) (modified from the manuscript of Study II).

Reference	**Xylitol**	**Control**	**Age** (years)	**Follow-up** (months)	**Baseline caries**		**Caries increment**		**PF**
					X	**C**	**X**	**C**	
PERMANENT TEETH									
Scheinin et al. 1985	Sweets & Paste	No	7	36	1.4	0.8	1.7	2.9	41.4%
			8		3.4	2.3	2.2	3.6	38.9%
			9		4.2	2.5	2.6	3.7	29.7%
			10		5.6	3.3	2.9	3.9	25.6%
Isokangas et al. 1988	Gum	No gum	11-12	24	4.1	4.8	1.1	2	45.0%
Kandelman et al. 1988	Confection-ery	No	6-12	32	6.5*	6.5*	4.58	7.19	36.3%
Kandelman & Gagnon 1990	Gum	No	9	24	6.33	5.67	2.09	6.06	65.5%
Mäkinen et al. 1995	Gum stick3	No	10.2	40	6.6	4.3	0	5	100.0%
	Gum stick5				6.1	4.3	0.5	5	90.0%
	Gum pellet3				3.4	4.3	0.8	5	84.0%
	Gum pellet5				5.1	4.3	-0.7	5	114.0%
Alanen et al. 2000	Gum	No	10	36	1.78	2.18	1.87	4.42	57.7%
	Candy1,2				2.86	2.18	2.5	4.42	43.4%
	Candy2,2				1.48	2.18	1.68	4.42	62.0%
	Candy1,3				1.64	2.18	1.72	4.42	61.1%
	Candy2,3				1.78	2.18	2.77	4.42	37.3%
Machiulskiene et al. 2001	Gum	No	11.6	36	5.0	6.4	3.4	5.3	35.8%
Stecksen-Blicks et al. 2008	Tablet	No	11.3	24	0.5**	0.7**	0.7**	0.7**	0.0%
Lenkkeri et al. 2012	Lozenge	No	10	48	0.32	0.27	1.63	1.52	-7.2%
Campus et al. 2013	Gum	Placebo	8.3	24	57.14%	56.41%	1.43%	10.26%	86.0%
Honkala et al. 2014	Candy	Sorbitol placebo	8.7	36			2%	1.7%	-17.6%
PRIMARY TEETH									
Mäkinen et al. 19966	Gum stick	No	6	24	11	12.8	2.6	4.9	46.9%
	Gum pellet				12.2	12.8	1.8	4.9	63.3%
Kovari et al. 2003	Gum	Tooth-brushing	3	48	6%***	6%***	25% ***	37% ***	32.4%
				72	6%***	6%***	33% ***	45% ***	26.7%
Oscarson et al. 2006	Tablet	No	2	24	0.4	0.4	0.38	0.80	52.5%
Alamoudi et al. 2012	Chewable table	Counsel-ing	2-6	18	8.37#	10.27#	9.19 ##	14.69##	37.4%
Lee et al. 2015	Gummy bears	Placebo	5-6	30	6.3	4.3	5.0	4.0	-25.0%

*calculated as a geometric mean of given subgroups, **dentinal proximal caries, calculated based on given data, ***% of subjects having obvious decay or fillings, and additional proportion of subjects having obvious decay or fillings, calculated based on data in the Thesis (Kovari 2002), # average dmft-scores given for subjects at baseline # and for those at final examination,=follow-ups##

5.6. Additional information of bitewing-radiographs in detection of established or severe dentinal decay in low-caries population (IV)

In 44% of the subjects (*n*=363) no caries was detected in the clinical examination. The registrations of the clinical examination by tooth and surface are given in Table 8. The yield on an individual level, measured as the proportion of subjects with more established and severe dentinal decay detected in the radiographs than in the clinical examination, was nearly 50% in DMFS=0, and nearly 60% in DMFS>0 subjects (yield 1, *P*= .005) (Table 9). On a tooth surface level, the yield was greatest on the occlusal surfaces of the first molars. On these surfaces, established and severe dentinal decay (ICDAS 4-6) was registered in radiographs in 40% of the clinically registered established cavitated enamel lesions (ICDAS 3), and on 11% of ICDAS 0-2 surfaces (Table 10). On the proximal surfaces, the yield was greatest on the mesial surfaces of the first molars.

Table 8. Number and percentage of surfaces with different stages of decay in clinical examination by tooth and surface (retrieved from Study IV).

			ICDAS 0-2[a]	ICDAS 3[b]	ICDAS 4-6[c]	Filled	Surfaces excluded
			n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Maxilla							
	1st premolar						
		Distal	662 (91.2)	10 (1.4)	2 (0.3)	1 (0.1)	51 (7.0)
	2nd premolar						
		Mesial	687 (94.6)	6 (0.8)	0 (0.0)	0 (0.0)	33 (4.5)
		Distal	678 (93.4)	0 (0.0)	0 (0.0)	1 (0.1)	47 (6.5)
	1st molar						
		Occlusal	575 (79.2)	46 (6.3)	30 (4.1)	69 (9.5)	6 (0.8)
		Mesial	617 (85.0)	59 (8.1)	9 (1.2)	15 (2.1)	26 (3.6)
		Distal	691 (95.2)	3 (0.4)	0 (0.0)	5 (0.7)	27 (3.7)
	2nd molar						
		Occlusal	590 (81.2)	57 (7.9)	32 (4.4)	13 (1.8)	34 (4.7)
		Mesial	689 (94.9)	2 (0.3)	1 (0.1)	0 (0.0)	34 (4.7)
Mandibula							
	1st premolar						
		Distal	710 (97.8)	0(0.0)	0 (0.0)	0 (0.0)	16 (2.2)
	2nd premolar						
		Mesial	678 (93.3)	0 (0.0)	0 (0.0)	1 (0.1)	47 (6.5)
		Distal	670 (92.2)	8 (1.1)	1 (0.1)	0 (0.0)	47 (6.5)
	1st molar						
		Occlusal	507 (69.8)	68 (9.4)	48 (6.6)	97 (13.4)	6 (0.8)
		Mesial	636 (87.6)	55 (7.6)	10 (1.4)	14 (1.9)	11 (1.5)
		Distal	705 (97.1)	1 (0.1)	1 (0.1)	7 (1.0)	12 (1.7)
	2nd molar						
		Occlusal	545 (75.1)	67 (9.2)	39 (5.4)	52 (7.2)	23 (3.2)
		Mesial	690 (95.0)	12 (1.7)	0 (0.0)	2 (0.3)	22 (3.0)

Sum of surfaces in each row =726. Total number of surfaces analyzed = 11 616.[a] WHO 0, 1; [b] established enamel lesion with a clinically detectable loss of substance;[c] established and severe dentinal decay calling for filling

Table 9. The number and proportion of subjects with yield from the radiographic examination in relation to the clinical findings (retrieved from Study IV).

Subjects		Yield 1[a]	Yield 2[b]	Yield 1 and 2
	N	n (%)	n (%)	n (%)
DMFS=0	161	76 (47.2)	25 (15.5)	77 (47.8)
DMFS>0	202	117 (57.9)	57 (28.2)	119 (58.9)

[a)] ICDAS 0-2 in clinical examination, ICDAS 4-6 in bitewing radiographs
[b)] ICDAS 3 in clinical examination, ICDAS 4-6 in bitewing radiographs

Table 10. Number of ICDAS 0-2 surfaces in both clinical examination and with BW included, and number of surfaces with yield from radiographs (retrieved from Study IV).

		ICDAS 0-2[a] in both clinical examin. and BW	ICDAS 0-2[a] in clinical examin., ICDAS 4-6[c] in BW (Yield 1)	ICDAS 3[b] in clinical examin., ICDAS 4-6[c] in BW (Yield 2)
		n (%)[1]	n (%)[1]	n (%)[2]
1st premolar				
	Distal	1324 (96.5)	12 (0.9)	0 (0.0)
2nd premolar				
	Mesial	1324 (97.0)	5 (0.4)	0 (0.0)
	Distal	1269 (93.3)	18 (1.3)	0 (0.0)
1st molar				
	Occlusal	963 (89.0)	114 (10.5)	45 (39.5)
	Mesial	1110 (88.6)	40 (3.2)	22 (19.3)
	Distal	1308 (93.7)	11 (0.8)	0 (0.0)
2nd molar				
	Occlusal	1032 (90.9)	98 (8.6)	42 (33.9)
	Mesial	1324 (96.0)	3 (0.2)	0 (0.0)

[1)] % of surfaces registered clinically ICDAS 0-2
[2)] % of surfaces registered clinically ICDAS 3
[a] ICDAS 0-2, WHO 0, 1
[b] ICDAS 3, enamel lesion with a clinically detectable loss of substance
[c] Established or severe dentine decay = ICDAS 4-6, dentine caries obviously spreading in the dentine

6. DISCUSSION

6.1. Main findings

No additional preventive effect was observed as a result of school-based use of xylitol or erythritol lozenges in the present four-year randomized clinical trial of low-occurrence children. This showed the difficulty in attempting additional caries prevention in children of a low-caries level population. The incidence of additional caries seemed to be strongly related to one's previous caries experience, instead.

The descriptive systematic review of clinical xylitol trials demonstrated relatively well the caries-preventive effect of xylitol in high or moderate caries level populations and in permanent dentitions, whereas in a population with low occurrence of the disease it seemed difficult to show the evidence for the effectiveness of xylitol unless selection of high-risk subjects was carried out. This difficulty did not, however, preclude the possibility of the health-maintaining effect of xylitol. Instead, it showed that the effect might be related to the occurrence of caries in the population.

The *in vitro* comparison of xylitol and erythritol showed growth inhibition of polysaccharide-producing oral streptococci by both polyols, but also revealed that this inhibition did not depend on the size of the reduction in adherence. This may have been the reason why xylitol reduced plaque and MS counts also in subjects with xylitol-resistant MS as a result of long-term use of xylitol.

The cross-sectional study of the 14-year-olds of a low-caries level population with practically no history of prior radiographic examination demonstrated that both subjects with and without clinically detected caries may have benefitted from bitewing radiographs as an adjunct to clinical examination in the detection of occlusal dentinal lesions in need of restorative treatment. In this age group, most of the yield from bitewings is obtained on the occlusal surfaces of the first permanent molars and nearly as frequently on the occlusal surfaces of the second permanent molars. On the other hand, in a low-caries level population, both the yield and the occurrence of caries on the newly erupted premolars was very low, with more than 90% of proximal surfaces showing no signs of caries clinically or radiographically. In addition, the distribution of gain surfaces per subject differed between clinically healthy and non-healthy subjects. In the former, the number of yields from the radiographs was either one or two per subject, whereas in the latter the number of lesions seemed to accumulate: nearly 20% had three yields or more per subject.

6.2. Methodological aspects, validity and reliability of the results

6.2.1. Randomization

Randomized controlled clinical trial (RCT) is regarded as the gold standard in studies investigating the efficacy of a treatment (Ryan et al. 2013). Randomization by subject instead of clusters would be the method of choice in relation to the validity of the results. Judging by the previous sugar substitute studies (Isokangas 1988, Kandelman et al. 1988, 1990, Mäkinen et al. 1995, 1996), none of them being randomized by subject, this goal has clearly proven a difficult one to achieve in clinical trials. The present study was no exception to this, but used schools as the units of randomization for practical reasons. If used, the effect of cluster setting on the validity of the data needs to be recognized and the data handled accordingly. That is why the hierarchical logistic regression modeling was used in the present study.

6.2.2. Blinding, study sample

The double-blinded study setting and the similar treatment of the study groups apart from the polyol intervention were likely to decrease the risk of performance bias in the present RCT. The subjects of the whole age cohort of the ten-year-olds in the selected region were candidates for the study. Since most families (581/ 589) consented and only two subjects were excluded for other reasons, the sample was likely to be a representative one.

There were no socio-economic differences and no ethnic diversity in the study population. Likewise, there were no imbalances in baseline variables between different groups or between boys and girls. On the other hand, the external validity may be affected by the low caries level and the fact that the region belongs to the Wiborg rapakivi granite area enriched with fluorine and its negative ion fluoride, which may have affected the dental health of the subjects.

6.2.3. Sample size

The original calculations for group sizes were made for pair wise comparison of each intervention group with the control group. The data were, regardless of this, analysed using hierarchical logistic regression in order to adjust for its eventual clustering. In the original power calculations, an odds ratio (OR) of approximately 2.3 was considered clinically relevant. In the results of the present study, the highest cluster-adjusted effect size, that is, the OR of control versus erythritol 2-year group was, however, not more than 1.46 (95%

CI 0.81-2.61). This indicates that the result of no difference between the groups was not due to lack of power in the tests used, but, instead, a true finding.

6.2.4. Intention-to-treat principle, methodological quality

The RCT was reported following the Consolidated Standards of Reporting Trials (CONSORT) and analyzed by the intention-to-treat (ITT) principle accordingly. In this approach, the deviations and withdrawals are ignored and all randomized subjects are analysed (Gupta 2011). Accordingly, one school of twenty subjects (Xylitol/maltitol 2 years), which did not finish the intervention as planned, was analysed as if they had not ended the use of lozenges too early. The treatment effect may become under-estimated because also noncompliant subjects are included in the analyses (Gupta 2011). The result of no difference between the groups in the present RCT cannot, nevertheless, be interpreted as resulting from the use of the ITT approach. In general, the compliance was likely to be good since the lozenges were delivered in sessions supervised by the teachers in the classrooms. Neither were there significant problems reported in the questionnaires by the subjects. Due to relatively equal attrition between groups and the altogether relatively low attrition rate of fourteen per cent over the period of four years, the risk of attrition bias was not likely to be high. In the present study the daily xylitol dose was slightly below the level which has been considered effective. However, in previous studies on permanent teeth, statistically significant preventive effect has been reported with doses even smaller than used in the present trial (Kandelman 1990, Mäkinen 1995, Machiulskiene 2001). Thus, the low xylitol dose, *per se*, does not automatically preclude the possibility to obtain caries preventive effect. In particular, since the deficit was marginal, the low dose of xylitol is not a likely explanation to the lack of additional xylitol effect. Moreover, the present study was of equal length and likely to be long enough in comparison with earlier xylitol trials, which have reported up to significant caries reductions. On the other hand, in the prevailing low-caries conditions the rate of caries progression may be slower. Thus, more time for caries to develop than in high-caries level may be required. Consequently, the follow-up of four years ought to be enough to detect the caries-preventive effect of the intervention, if it existed.

Due to the heterogeneity of the xylitol trials no quantitative meta-analysis was performed in the present review (IV). On the other hand, a possibility for another approach to study and describe the diverse features related to the occurrence of dental caries was therefore opened up for us. As a result, not only randomized controlled trials (RCT), which are considered the gold standard of experimental studies, but also controlled clinical trials (CCT) could be included in the present review. The reliability of the clinical evidence of CCT's is weaker than that of RCT, and separate criteria for grading the evidence were used for these study types. This was done to avoid the CCT's from being punished twice for their inherent shortcomings such as a greater chance of a bias, which is already taken into consideration by placing the CCT's behind RCT's in the hierarchy of research evidence.

6.2.5. Examination of caries

The clinical examinations were carried out in several different dental units and the radiographic examinations were obtained using six different X-ray units (I, III). Even though this inevitably meant variation in the facilities, each unit had the same pieces of equipment required for the examination. Also no significant difference in the quality of radiographic images obtained using different units was noted. The nurse assisting in the registrations and in the manual processing of all the radiographs was an experienced one.

The performance of the clinical examination by only one calibrated dentist reduced examiner-based variation and can be regarded as a strength of the study. However, the lack of intra- and inter-examiner calibration may be a potential source of bias (I and III). On the other hand, the radiographic analyses were in part performed by two examiners, which may have partially compensated for this eventual limitation. In addition, with the concordance of 93% of all these examined surfaces the accuracy of diagnoses could, however, be considered satisfactory (I). The routine application of fissure sealants on the occlusal surfaces of the first molars before the onset of the trial and the regular exposure to fluoride products, as well as to a high natural fluoridation, may be factors related to the high number of hidden lesions in conjunction with this particular population. This calls for prudence in the generalization of the results to populations other than those of low occurrence.

The WHO procedure for caries classification has gained wide use in earlier clinical trials as a time-efficient, yet accurate enough method (Chu et al. 2013). This also facilitated the comparison of the present study with the earlier ones. However, one major shortcoming of the WHO method is its focus on cavitated stages of caries, which is no longer in line with the goals of modern cariology aiming at early detection and even arrest of non-cavitated lesions. Consequently, the study investigating the detection of caries in low-caries level conditions (III) was brought up to date by transforming the radiographic codes of WHO to ICDAS (International Caries Detection and Assessment System). By doing so, information on the earliest stages of enamel caries has possibly been disregarded. On the other hand, this did not affect the registrations of the crucial point of the study regarding the established and severe lesions and, further, the assessment of need for restorative treatment of caries.

The Mejáre scoring system has been created for the detection of proximal lesions (1998). In the present study, the registration of proximal lesions was complemented with that of the severe occlusal dentine lesions. For morphological and anatomical reasons, the detection of early dentinal lesions on occlusal surfaces was not considered possible in the present study, either.

One challenge of bringing together and drawing a novel and compact conclusion of the original publications in the present thesis was related to the fact that different study designs had been used in obtaining the findings. In a low-occurrence population not only the prevention but also the detection of caries seemed to have special features differing from those in a high-occurrence one. In addition, regardless of numerous systematic reviews on xylitol, to our knowledge, none had focused exactly on the caries occurrence as an eventual factor modifying the caries-preventive effect of the polyol. Further, we became interested in the mechanisms of action of xylitol and that of erythritol, which is a novel, potentially caries-preventive polyol. Consequently, it became a natural and an obvious continuum to us to step by step discover some different aspects related to caries prevention in low-occurrence conditions.

6.3. Results in relation to previous research

6.3.1. The additional caries-preventive effect of xylitol and erythritol in low-caries level conditions in relation to previous research

Unlike in several previous xylitol trials, no difference was found between the study and the control groups in the present cluster-randomized clinical trial. Many xylitol trials showing a caries-preventive effect have been randomized (Machiulskiene et al. 2001) and controlled clinical trials (Isokangas 1988, Kandelman et al. 1988, 1990, Mäkinen et al. 1995, 1996) carried out in populations showing a higher baseline caries level than the present one. The finding of no additional effect is, however, in line with the trials of Oscarson (2006) in very low-occurrence children, and Bader (2013) in adults even at elevated risk of caries. Those studies observed no statistically significant reduction in caries increment following the use of xylitol lozenges.

The low baseline level of caries, presumably as a result of comprehensive free prevention given in health centers, and the high fluoride content in the region were the likely reasons for not attaining additional caries reduction in the present clinical trial of ours. In such a low-caries population there may not have been space for xylitol to have effect, and the statistical power in the comparison of groups was weakened.

Even though no caries reduction in relation to controls was obtained with the use of erythritol in the present study, erythritol is without a doubt an interesting sugar alcohol from the cariologic point of view. This was documented in a fairly novel three-year randomized controlled trial (Honkala 2014) on 10-year-olds using 7.5 grams erythritol, xylitol or sorbitol a day in the form of lozenges. The number of decayed teeth and surfaces was significantly lower in the erythritol in comparison with the sorbitol and xylitol groups. In addition, the time for a dentine caries lesion to develop was longer in the erythritol than in the sorbitol or xylitol group. It is, however, worth pointing out that these results were not obtained in a low-occurrence population. At baseline, the combined dentin caries indices of a mixed dentition on tooth and surface levels (dmft+ DMFT and dmfs+ DMFS) were approximately six and twelve, respectively in this Estonian population.

6.3.2. The level of caries and the caries-preventive effect of xylitol

Several systematic reviews on xylitol have been published over the past years (Lingström et al. 2003, Mickenautsch et al. 2007, Deshpande et al. 2008, Antonio et al. 2011, Rethman et al. 2011, Riley et al. 2015). However, in those studies, the caries-preventive effect of xylitol has not been related to the caries occurrence of the population, but rather the quantification of the effect size, *per se,* has been the main focus. In addition, the selection criteria have been strict, yet allowing heterogeneous but a very limited number of studies to be included. In the present descriptive systematic review, the field of assessment was broadened beyond the randomized clinical trials to include the controlled clinical trials as well. Even though in a CCT the grade of evidence is lower than in a RCT, the post-trial examinations have clearly indicated that findings of the caries-preventive effect of xylitol have not been biased even with the incomplete blinding and randomization (Virtanen et al. 1996). In a population with moderate or high caries level, to some extent all tooth surfaces are likely to be affected by tooth decay. It is in these circumstances that the caries-preventive effect of xylitol has been relatively well shown. This preventive fraction in favor of using xylitol was likewise shown in our systematic descriptive analysis. Then again, in a low-occurrence population, the number of potential sites for xylitol to affect is far smaller and mostly limited to the occlusal surfaces, in which the effect of xylitol has proved to be difficult to demonstrate.

6.3.3. The effects of xylitol vs. erythritol on adherence of mutans streptococci

Even though the significance of mutans streptococci as a risk factor of caries may in all stages of the disease no longer be considered as important as earlier, MS remain, however, very virulent bacteria from a cariologic point of view (Parisotto et al. 2010, Takahashi and Nyvad 2011).

The microbial adhesion to tooth surface, promoted by the extracellular polysaccharides produced from MS, is an important virulence factor in the pathogenesis of caries (Koo et al. 2013). In our study, this adhesion was reduced and also the growth of the polysaccharide-forming streptococci was inhibited by both xylitol and erythritol. What is interesting in our results is the finding that even though the polyols (4%) did reduce both the adhesion and the growth of the streptococci, these changes were not associated with one another. For xylitol, in particular, the decrease in adhesion, that is, more shedding bacteria, was not associated with an increase in growth inhibition. For erythritol, however, a non-significant trend was observed. Thus, it seems that the mechanisms of inhibition of adherence and that of growth may differ between xylitol and erythritol.

The literature on the mechanisms of action of erythritol is scarce. It has been suggested that the mechanism of inhibition of several strains of mutans streptococci by erythritol may differ from that of xylitol, which affects the growth at all phases, whereas erythritol seems not to affect the early phases of mutans streptococci growth (Mäkinen et al. 2005). However, this view was not supported by our results.

In one study, which used wipes as the mode of delivery of xylitol the salivary counts of mutans streptococci did not decrease. However, reduction in caries occurrence was observed in relation to mere mechanical sweeping (Zhan et al. 2012). This finding may be in line with ours, in which the reduction of glass surface adherence was not related to growth inhibition of mutans streptococci. Thus, caries reduction can be obtained by xylitol even though the mutans cell counts *per se* may not necessarily be reduced by the polyol consumption. A common factor in both these studies may be the interference of cell adherence on a surface, which further prevents plaque from accumulating, and the onset of the demineralization of a tooth surface.

6.3.4. The additional value of bitewing radiographs in the detection of caries

Also the previous literature has reported on the yield from the radiographs when used as an adjunct to a clinical caries examination in low-caries level populations as observed in the present study (Poorterman et al. 1999, 2000, 2002, 2003a, 2003b). In other words, this means overestimation of the proportion of caries-free subjects (Poorteman et al. 1999), high underestimation of the prevalence of caries (Poorterman et al. 2002), failure to notice even large lesions (Poorterman et al. 2003b) and a delay in the diagnosis and the application of preventive measures (Poorterman et al. 2003a), when clinical examination is used alone. The percentage of subjects benefitting from the radiographs has likewise been approximately of the same magnitude in the present and the previous studies (Lillehagen et al. 2007, Mestriner et al. 2006). Also our findings on the tooth surface level are in line with those observed in previous studies investigating the hidden caries on occlusal surfaces of adolescents (Weerheijm et al. 1997 and Hintze 1993). It needs to be taken into account, however, that the differences in counting the yield, as well as in the ages (Poorterman 1999, 2003a, Richardson 1996) and caries levels between the populations studied, narrow down the possibility to compare the studies.

6.3.5. The clinically un-detected caries in healthy and non-healthy subjects

The strong relationship between earlier caries experience and the likelihood of getting more caries, which was observed in the present study has also been described in the previous literature (Forgie et al. 2000, SBU 2007). A randomized clinical trial investigating the caries-preventive effect of chlorhexidine varnish in high-risk adolescents also found no difference between the study groups. Instead, earlier caries experience was found to be a stronger explanatory factor for variation in caries increment than whether chlorhexidine varnish was used or not (Forgie et al. 2000). The present findings regarding the subjects with earlier experience, in other words, those in whom more disease could be expected as a whole, along with more hidden lesions, did yield more from the radiographs than those without previous experience of the disease; this can be understood as a logical consequence of the relationship.

On the other hand, the high occurrence of severe caries lesions in subjects regarded as healthy in the clinical examination was an unexpected, yet noteworthy finding. It may, however, be an exaggeration of the true state of affairs and, in part, be explained by the fact that the present radiographs were the first ones obtained from most of the subjects. The caries has thus had time to accumulate since the eruption of these teeth. This accumulation was harvested as one entity at this one cross-sectional point, which in addition gave no information about the activity of the lesions or the process of caries progression as a whole.

6.4. Scientific and clinical relevance of the study

The present clinical trial (I) and the systematic review (II) suggest that when the level of caries in a given population is relatively low, the addition of saliva-stimulating polyol lozenges to the comprehensive routine caries prevention of dental public health care may not reduce caries, and thus not be worthwhile as a population strategy. As noted above, in low-caries adolescents, the decay of buccal and lingual or proximal surfaces is, however, no longer as frequent as before. Regardless of the eventual exposure to the xylitol the subjects with previous caries experience seem to be more prone to additional caries than those without.

When the level of caries decreases, the numbers of decayed tooth surfaces, teeth and dentitions also decrease. Simultaneously, the proportions of healthy subjects and those with no new decay increase, and the clinical trials may face several challenges. For example, the DMF values are not normally distributed and the mean value is not a representative way to describe a population with more and more subjects having no disease at all. The accumulation of the decay in a small proportion of subjects may also call for a new approach to the measurement of the disease. Thus, it needs to be considered whether caries ought to be measured on an individual or on a tooth level considering different stages.

It is also important to realize that if the possible polyol effect is the main focus of a study, conclusions should not be drawn regarding the clinical significance on the basis of the results of such a study. Likewise, it must always be borne in mind that if the focus is on the clinical significance of the method, the no-treatment arm should be included in the study design. In other words, the inclusion of a control group receiving placebo is essential in providing scientifically proven evidence, but if the clinical significance is estimated, the study setting should likewise include the no-treatment arm.

The findings of the clinical trial in this thesis suggest that it may be unprofitable to deliver additional xylitol to the whole low-occurrence population. When the occurrence of a disease has reached a fairy low level, a small further increase in total amount of usefulness may be reached by this additional prevention. However, in relation to the size of the investment made, the addition in usefulness no longer increases to the extent which had been observed on a high level of the disease. In other words, when the level of the disease was high a remarkable additional gain in health was achieved even with only a relatively small investment or addition to the previous prevention. With declining occurrence, the size of the additional usefulness decreases and finally reaches a plateau. The plateau can be seen as a positive sign reflecting an effect of the previous preventive measures taken. Thus, an ever-increasing intensity of the same actions is not required, nor justified. The level of health which can be acquired by these particular methods and by using a meaningful amount of effort has obviously been reached at this point. The remaining resources ought to be directed to the prevention and treatment of disease and to the subjects who are in urgent need, and in particular to those still manifesting a severe disease in a population with a low occurrence in general.

The reasons for the accumulation of the disease with declining occurrence and the optimal methods for improving the health of this small proportion of subjects still manifesting a high occurrence of the disease are crucial. At this point, a new approach and perspective, as well as a consideration of methods differing from those previously used and no longer showing a satisfactory effect, are called for. Thus, one must not ignore the subjects with an abundance of disease even though the general occurrence of the disease in a population has declined to a satisfactory level. On the contrary, this proportion of the population with an accumulation of the disease should be placed in the center of active measures, and the reasons behind the persistent disease identified. Dental caries is also related to the social situation of the subject. Its prevention is thus not only a mission of dental health care personnel but also of actors in different fields in the society, not to mention the oral self-care. Another reason for advocating the change of perspective is the fact that once the occurrence of a disease has achieved a certain level and plateaued, the additional investment in further reduction of the level of the disease does not result in an additional reduction of the same magnitude as has been achieved in a high level of the disease. Additional reduction of the disease calls for a change of scope in the aiming of the resources, not stopping them altogether.

The clinical relevance of the *in vitro* study on the two polyols is that both xylitol and erythritol seemed to have an effect on the adherence of polysaccharide-producing oral streptococci, which is a phenomenon contributing to plaque accumulation.

The clinical significance of the work on the detection of caries (III) is that a significant amount of established and deep hidden dentinal lesions in need of restorative treatment would have remained undetected and untreated if a decision had been made on a clinical basis only in the present low-occurrence population of children aged 14 years. The mere clinical detection of caries or the knowledge of a previous caries experience may not be sufficient criteria when assessing the likelihood of the need for a restorative treatment or the need to obtain the first pair of bitewing radiographs. It is important to point out that the study was carried out in a country with strict instructions on radiograph use in children. There is great variation in practice regarding the use of radiography in children between different countries. In Sweden and several other European countries, for example, the bitewings have been routinely obtained annually or every two years (SBU 2007). On the other hand, in Finland, the use of radiography is permissible with a treatment-related justification only (Caries control: Current Care Guidelines, 2014), and routine screening is not a practice. This standard is even more prudent than the guidelines for use of radiography in children given by EAPD, which gives two age-based recommendations (at 8-9 and 12-14 years) for radiographs and an additional one regarding bitewing controls on the basis of individual risk assessment (Espelid et al.2003). In Finland, the clinical dental examination (carried out by a dentist or a dental hygienist) is routinely supplemented by FOTI (Caries control: Current Care Guidelines, 2014). This combination may still not be sensitive enough, and more frequent use of radiographs might be advisable in adolescents, in particular.

6.5. Recommendations for actions

All children should have their teeth examined and an individual prevention program ought to be designed for each person based on the findings of the clinical examination. In a low-occurrence population, the additional caries-preventive measures should be targeted at children with clinical signs of dental caries and high risk of developing caries. On the other hand, the lack of these signs by no means precludes the possibility of the presence of severe caries calling for restorative treatment. Instead, a remarkable portion of both the clinically healthy and the non-healthy 14-year-olds seem to benefit from radiographic examination of the permanent molars. Thus, obtaining radiographs of adolescents with no prior radiographic examination ought to be seriously considered at the age of fourteen to fifteen at the latest. That would enable the early detection and management of caries and serve as a safety net for both those with no clinically detected caries and those with no prior radiographic examination. It would also aid in the decision to target the preventive measures at those in need.

7. CONCLUSIONS

On the basis of the results presented in this thesis, the following conclusions can be drawn:

- Both xylitol and erythritol are able to inhibit the adherence of polysaccharide-producing oral streptococci, but the effect on the adherence does not seem to be associated with the growth inhibition found for these polyols.
- In a low-caries level population the school-based use of xylitol or erythritol lozenges may not have an additional caries-preventive effect when compared with a control group receiving comprehensive routine prevention.
- In relatively low-caries conditions the future caries increment is strongly related to past caries experience
- In populations with high and moderate caries levels the caries-preventive effect of xylitol has been reliably and repeatedly demonstrated in the literature.
- A remarkable portion of adolescents both with and without clinically detected dentine caries or previous fillings may benefit from radiographic examination in a low-caries level population.
- The yield is obtained regardless of FOTI in the clinical examination, and mainly on the occlusal surfaces of the first and second permanent molars.

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REFERENCES

Ahovuo-Saloranta A, Forss H, Walsh T, Hiiri A, Nordblad A, Mäkelä M, Worthington HV (2013). Sealants for preventing dental decay in the permanent teeth. (Review). *The Cochrane Library*; Issue 3.

Alamoudi NM, Hanno AG, Masoud MI, Sabbagh HJ, Almushayt AS, Masoud IM (2012). Effects of xylitol on salivary mutans streptococcus, plaque level, and caries activity in a group of Saudi mother-child pairs. *Saudi Med J* 33:186-192.

Alanen P, Isokangas P, Gutmann K (2000). Xylitol candies in caries prevention: results of a field study in Estonian children. *Community Dent Oral Epidemiol* 28:218-224.

Alanen P, Holsti ML, Pienihäkkinen K (2000). Sealants and xylitol chewing gum are equal in caries prevention. *Acta Odontol Scand* 58:279-284.

Ammari AB, Bloch-Zupan A, Ashley PF (2003). Systematic review of studies comparing the anti-caries efficacy of children's toothpaste containing 600 ppm of fluoride or less with high fluoride toothpastes of 1,000 ppm or above. *Caries Res* 37:85-92.

Antonio AG, Pierro VS and Maia LC (2011). Caries preventive effects of xylitol-based candies and lozenges: a systematic review. *J Public Health Dent* 71:117-124.

Anttonen V, Seppä L, Hausen H (2004). A follow-up study of the use of DIAGNOdent for monitoring fissure caries in children. *Community Dent Oral Epidemiol* 32:312-318.

Armfield JM, Spencer AJ, Roberts-Thomson KF, Plastow K (2013). Water fluoridation and the association of sugar-sweetened beverage consumption and dental caries in Australian children. *Am J Public Health* 103:494-500.

Bader JD, Shugars DA. Bonito AJ (2001). Systematic reviews of selected dental caries diagnostic and management methods. *J Dent Educ* 65:960-968.

Bader JD, Vollmer WM, Shugars DA, Gilbert GH, Amaechi BT, Brown JP, Laws RL, Funkhouser KA, Makhija SK, Ritter AV, Leo MC (2013). Results from the Xylitol for Adult Caries Trial (X-ACT). *J Am Dent Assoc* 144:21-30.

Batchelor PA, Sheiham A (2004). Grouping of tooth surfaces by susceptibility to caries: a study in 5-16 year-old children. *BMC Oral Health* 28;4:2.

Bernabé E, Vehkalahti MM, Sheiham A, Lundqvist A and Suominen AL (2016). The shape of the dose-response relationship between sugars and caries in adults. *J Dent Res* 95:167-172.

Burt BA and Pai S (2001). Sugar Consumption and Caries Risk: A Systematic Review. *Journal of Dental Education* 65:1017-1023.

Campain AC, Morgan MV, Evans RW, Ugoni A, Adams GG, Conn JA, Watson MJ (2003). Sugar-starch combinations in food and the relationship to dental caries in low-risk adolescents. *Eur J Oral Sci* 111:316-325.

Campus G, Cagetti MG, Sale S, Petruzzi M, Solinas G, Strohmenger L, Lingström P (2013). Six months of high-dose xylitol in high-risk caries subjects – a 2-year randomised, clinical trial. *Clin Oral Invest* 17:785-791.

CAPP. http://www.mah.se/CAPP/Country-Oral-Health-Profiles/According-to-Alphabetical/Global-DMFT-for-12-year-olds-2011/ (accessed May 10, 2016)

Chu CH, Chau AM, Lo EC (2013). Current and future research in diagnostic criteria and evaluation of caries detection methods. *Oral Health Prev Dent* 11:181-189.

Caries (control) (online). Current Care Guidelines. Working group appointed by the Finnish Medical Society Duodecim and Finnish Dental Society Apollonia. Helsinki: The Finnish Medical Society Duodecim, 2014 (referred April 27, 2016). Available online at: www.kaypahoito.fi

da Silveira Moreira R (2012). Epidemiology of Dental Caries in the World, Oral Health Care - Pediatric, Research, Epidemiology and Clinical Practices, Prof. Mandeep Virdi (Ed.), ISBN: 978-953-51-0133-8, InTech, Available from: http://www.intechopen.com/books/oral-health-care-pediatric-research-epidemiology-andclinical-practices/epidemiology-of-dental-caries-in-the-world.

Dean HT and Elvove E (1936). Some epidemiological aspects of chronic endemic dental fluorosis. *Am J Public Health Nations Health* 26:567-575.

Deshpande A, Jadad AR (2008). The impact of polyol-containing chewing gums on dental caries: a systematic review of original randomized controlled trials and observational studies. *J Am Dent Assoc* 139:1602-14.

Div of Oral Health, National Center for Chronic Disease Prevention and Health Promotion, CDC (2000). Achievements in public health, 1900-1999: Fluoridation of drinking water to prevent dental caries. *JAMA* 10:1283-1286.

Do LG (2012). Distribution of caries in children: variations between and within populations *J Dent Res* 91:536-43.

Espelid I, Mejáre I, Weerheijm K (2003). EAPD guidelines for use of radiographs in children. *Eur J of Paediatr Dent* 4:40-8.

European Commission Health & Consumer protection directorate-general. Opinion of the scientific committee on food (SCF) on erythritol. (opinion expressed on 5 March 2003). http://ec.europa.eu/food/fs/sc/scf/out175_en.pdf

Fisher J and Glick M (2012). FDI World Dental Federation Science Committee A new model for caries classification and management: The FDI World Dental Federation Caries Matrix. *J Am Dent Assoc* 143:546-551.

Forgie AH, Paterson M, Pine CM, Pitts NB, Nugent ZJ (2000). A randomised controlled trial of the caries-preventive efficacy of a chlorhexidine-containing varnish in high-caries risk adolescents. *Caries Res* 34:432-439.

Gupta SK (2011). Intention-to-treat concept. A review. *Perspect Clin Res* 2:109-112.

Gustafsson BE (1954). The Vipeholm dental caries study: survey of the literature on carbohydrates and dental caries. *Acta Odontol Scand* 11:207-231.

Hausen H, Kärkkäinen S, Seppä L (2000). Application of the high-risk strategy to control dental caries. *Community Dent Oral Epidemiol* 28:26-34.

Hausen H, Seppä L, Poutanen R, Niinimaa A, Lahti S, Kärkkäinen S, Pietilä I (2007). Noninvasive Control of Dental Caries in Children with Active Initial Lesions. *Caries Res* 41:384-391.

Hayes C (2001). The effect of non-cariogenic sweeteners on the prevention of dental caries: a review of the evidence. *J Dent Educ* 65:1106-9.

Hintze H (1993). Screening with conventional and digital bite-wing radiography compared to clinical examination alone for caries detection in low-risk children. *Caries Res* 27:499–504.

Hiremath SS (2011). Textbook of Preventive and Community Dentistry, 2nd edition. Chapter 30: Dental caries, pp 323-324.

Honkala S, Runnel R, Saag M, Olak J, Nommela R, Russak S, Mäkinen PL, Vahlberg T, Falony F, Mäkinen K, Honkala E (2014). Effect of Erythritol and Xylitol on Dental Caries Prevention in Children. *Caries Res* 48:482-490.

Hujoel PP, Mäkinen KK, Bennett CA, Isotupa KP, Isokangas PJ, Allen P, Mäkinen PL (1999). The optimum time to initiate habitual xylitol gum-chewing from obtaining long-term caries prevention. *J Dent Res* 78:797-803.

ICDAS (International Caries Detection and Assessment System) 2013. www.icdas.org

Iranzo-Cortés JE, Montiel-Company JM, Almerich-Silla JM (2013). Caries diagnosis: agreement between WHO and ICDAS II criteria in epidemiological surveys. *Community Dent Health* 30:108-111.

Ismail AI. Visual and visuo-tactile detection of dental caries (2004). *J Dent Res* 83 Spec No C:C56-66.

Ismail AI, Sohn W, Tellez M, Amaya A, Sen A, Hasson H., Pitts NB (2007). The International Caries Detection and Assessment System (ICDAS): an integrated system for measuring dental caries. *Community Dent Oral Epidemiol* 35:170-178.

Isogangas P, Mäkinen KK, Tiekso J, Alanen P (1993). Long-term effect of xylitol chewing gum in the prevention of dental caries : follow-up 5 years after termination of a prevention program. *Caries Res* 27:495-498.

Isokangas P, Alanen P, Tiekso J, Mäkinen KK (1988). Xylitol chewing gum in caries prevention: a field study in children. *J Am Dent Assoc* 117:315-320.

Isokangas P, Tiekso J, Alanen P, Mäkinen KK (1989). Long-term effect of xylitol chewing gum on dental caries. *Community Dent Oral Epidemiol* 17:200-3.

Isokangas P, Tenovuo J, Söderling E, Männistö H, Mäkinen KK (1991). Dental caries and mutans streptococci in the proximal areas of molars affected by the habitual use of xylitol chewing gum. *Caries Res* 25:444-448.

Jablonski-Momeni A, Winter J, Petrakakis P, Schmidt-Schäfer S (2014). Caries prevalence (ICDAS) in 12-year-olds from low caries prevalence areas and association with independent variables. *Int J Paediatric Dent* 24:90-7.

Kandelman D, Bär A, Hefti A (1988).Collaborative WHO xylitol field study in French Polynesia. I. Baseline prevalence and 32-month caries increment. *Caries Res* 22:55-62.

Kandelman D, Gagnon G (1990). 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.

Kawanabe J, Hirasawa M, Takeuchi T, Oda T, Ikeda T (1992). Noncariogenicity of erythritol as a substrate. *Caries Res* 26: 358–362.

Kim Seow W (2012). Environmental, maternal, and child factors which contribute to early childhood caries: a unifying conceptual model. *Int J Paediatr Dent* 22:157-68.

Koo H, Falsetta ML, Klein MI (2013). The exopolysaccharide matrix: A virulence determinant of cariogenic biofilm. *J Dent Res* 92:1065-1073.

Koskinen S, Lundqvist A, Ristiluoma N, eds. (2012). Health, functional capacity and welfare in Finland in 2011. National Institute for Health and Welfare (THL), Report 68/2012. 290 pages. Helsinki 2012. Helsinki 2012. ISBN 978-952-245768-4 (printed), ISBN 978-952-245-768-1 (online publication).

Kovari H, Pienihäkkinen K, Alanen P (2003). Use of xylitol chewing gum in daycare centers: a follow-up study in Savonlinna, Finland. *Acta Odontol Scand* 61:367-370.

Kühnisch J, Berger S, Goddon I, Senkel H, Pitts N.B, Heinrich-Weltzien R (2008). Occlusal caries detection according to WHO basic methods, ICDAS II and laser fluorescence measurements: results from an epidemiological study. *Community Dent Oral Epidemiol.* 36:475-484.

Kühnisch J, Goddon I, Berger S, Senkel H, Bücher K, Oehme T, Hickel R and Heinric-Weltzien R (2009). Development, Methodology and Potential of the New Universal Visual Scoring System (UniViSS) for Caries Detection and Diagnosis. *Int J Environ Res Public Health* 6:2500-2509.

Källestål C (2005). The effect of five years' implementation of caries-preventive methods in Swedish high-risk adolescents. *Caries Res* 39:20-26.

Kämppi A., Tanner T, Päkkilä J, Patinen P, Järvelin MR, Tjäderhane L and Anttonen V (2013). Geographical distribution of dental caries prevalence and associated factors in young adults in Finland. *Caries Res* 47:346-354.

Laitala ML, Alanen P, Isokangas P, Söderling E, Pienihäkkinen K (2013). Long-term effects of maternal prevention on children’s dental decay and need for restorative treatment. *Community Dent Oral Epidemiol* 41:534-540.

Lee W, Spiekerman C, Heima M, Eggertsson H, Ferretti G, Milgrom P, Nelson S (2015). The effectiveness of xylitol in a school-based cluster-randomized clinical trial. *Caries Res* 49:41-49.

Lenkkeri, AM, Pienihäkkinen K, Hurme S, Alanen P (2012). The caries-preventive effect of xylitol/maltitol and erythritol/maltitol lozenges: results of a double-blinded, cluster-randomized clinical trial in an area of natural fluoridation. *Int J Paediatr Dent* 22: 180-190. doi: 10.1111/j.1365-263X.2011.01182.x

Lillehagen M, Grindefjord M, Mejáre I (2007). Detection of approximal caries by clinical and radiographic examination in 9-year-old Swedish children. *Caries Research* 41:177–185.

Lin HK, Fang CE, Huang MS, Cheng HC, Huang TW, Chang HT and Tam KW (2015). Effect of maternal use of chewing gums containing xylitol on transmission of mutans streptococci in children: a meta-analysis of randomized controlled trials. *Int J Paediatr Den*t Feb 13.doi: 10.1111/ipd.12155. [Epub ahead of print].

Lingström P, Holm AK, Mejáre I, Twetman S, Söder B, Norlund A, Axelsson S, Lagerlöf F, Nordenram G, Petersson LG, Dahlgren H, Källestål C (2003). Dietary factors in the prevention of dental caries: a systematic review. *Acta Odontol Scand* 61:331-340.

Loesche WJ, Rowan J, Straffon LH, Loos PJ (1975). Association of Streptococcus mutans with human dental decay. *Infect Immun* 11:1252-1260.

Loeshe WJ (1979). Clinical and microbiological aspects of chemotherapeutic agents used according to the specific plaque hypothesis. *J Dent Res* 58:2404-2412.

Loesche WJ (1986). Role of Streptococcus mutans in human dental decay. *Microbiol Rev* 50:353-380.

Machiulskiene V, Nyvad B, Baelum V (2001). Caries preventive effect of sugar-substituted chewing gum. *Community Dent Oral Epidemiol* 29:278-288.

Manji and Fejerskov (1994). Textbook of Clinical Cariology, 2nd edition, eds. A. Thylstrup and O. Fejerskov, Chapter 7: An epidemiological approach to dental caries, p.170.

Mariño VCC, Higgins JPT, Logan S, Sheiham A (2009). Fluoride toothpastes for preventing dental caries in children and adolescents (Review). The Cochrane Library, Issue 1.

Marsh PD (1994). Microbial ecology of dental plaque and its significance I health and disease. *Adv Dent Res* 8:263-271.

Marsh PD (2003). Are dental diseases examples of ecological catastrophes? *Microbiology* 149:279-294.

Marsh PD (2006). Dental plaque as a biofilm and a microbial community – implications for health and disease. *BMC Oral Health* 15 (Suppl 1):S14.

Marsh PD (2010). Microbiology of dental plaque biofilms and their role in oral health and caries. *Dent Clin North Am* 54:441-454.

Marshall TA, Broffitt B, Eichenberger-Gilmore J Warren JJ, Cunningham MA, Levy SM (2005). The roles of meal, snack, and daily total food and beverage exposures on caries experience in young children. *J Public Health Dent* 65:166-173.

Marthaler TM (2004). Changes in dental caries 1953-2003. Review. *Caries Res* 38:173-181.

Massler M, Pindborg JJ and Mohammed C (1954). A compilation of epidemiologic studies in dental caries. *Dental Caries* 44:1357-1362.

Mattos-Graner RO, Smith DJ, King WF, Mayer MPA (2000). Water-insoluble glucan synthesis by mutans streptococcal strains correlates with caries incidence in 12- to 30-month-old children. *J Dent Res* 79:1371-1377.

Mejáre I, Källestål C, Stenlund H, Johansson H (1998). Caries development from 11 to 22 years of age: a prospective radiographic study. Prevalence and distribution *Caries Res* 32:10-16.

Mejáre IA, Klingberg G, Mowafi FK, Stecksén-Blicks C, Twetman SH, Tranaeus SH (2015). A Systematic Map of Systematic Reviews of Pediatric Dentistry - What do we Really Know? *PLoS ONE* 10(2):e0117537.doi:10.1371/journal.pone.0117537

Mestriner SF, Pardini LC, and Mestriner W Jr (2006). Impact of the bitewing radiography exam inclusion on the prevalence of dental caries in 12-year-old students in the city of Franca, São Paulo, Brazil. *Journal of Applied Oral Science*, 14:167–171.

Meurman PK., Pienihäkkinen K (2010). Factors associated with caries increment a longitudinal study from 18 months to 5 years of age. *Caries Res* 44:519-524.

Mickenautsch S, Leal SC, Yengopal V, Bezerra AC, Cruvinel V (2007). Sugar-free chewing gum and dental caries: a systematic review. *J Appl Oral Sci* 15:83-88.

Milgrom P, Ly KA, Roberts MC, Rother M, Mueller G, Yamaguchi DK (2006). Mutans streptococci dose response to xylitol chewing gum. *J Dent Res* 85:177-181.

Milgrom P, Ly KA, Tut OK, Mancl L, Roberts MC, Briand K, Bancio MJ (2009). Xylitol pediatric topical oral syrup to prevent dental caries: a double-blind randomized clinical trial of efficacy. *Arch Pediatric Adolesc Med* 163:601-607.

Milgrom P, Söderling EM, Nelson S, Chi DL, Nakai Y (2012). Clinical evidence for polyol efficacy. *Adv Dent Res* 24:112-116.

Moynihan PJ, Kelly SAM (2014). Effect on caries of restricting sugars intake. Systematic review to inform WHO guidelines. *J Dent Res* 93:8-18.

Mäkinen KK, Bennett CA, Hujoel PP, Isokangas PJ, Isotupa KP, Pape HR Jr, Mäkinen PL (1995). Xylitol chewing gums and caries rates: a 40-month cohort study. *J Dent Res* 74:1904-1913.

Mäkinen KK, Hujoel PP, Bennett CA, Isotupa KP, Mäkinen PL, Allen P (1996). Polyol chewing gums and caries rates in primary dentition: a 24-month cohort study. *Caries Res* 30:408-417.

Mäkinen KK, Isotupa KP, Kivilompolo T, Mäkinen PL, Toivanen J, Söderling E (2001). Comparison of erythritol and xylitol saliva stimulants in the control of dental plaque and mutans streptococci. *Caries Res* 35:129–135.

Mäkinen KK, Saag M, Isotupa KP, Olak J, Nõmmela R, Söderling E, Mäkinen PL (2005). Similarity of the effects of erythritol and xylitol on some risk factors of dental caries. *Caries Res* 39:207–215.

Mäkinen KK, Järvinen KL, Anttila CH, Luntamo LM and Vahlberg T (2013). Topical xylitol administration by parents for the promotion or oral health in infants: caries prevention experiment at a Finnish Public Health Centre. *Int Dent J* 63:210-224.

Nyvad B, Machiulskiene V and Baelum V (1999). Reliability of a new caries diagnostic system differentiating between active and inactive caries lesions. *Caries Res* 33:252-260.

Oscarson P, Lif Holgerson P, Sjöström I, Twetman S, Stecksén-Blicks C (2006). Influence of a low xylitol-dose on mutans streptococci colonization and caries development in preschool children. *Eur Arch Paediatr Dent* 7:142-147.

Parfitt GJ (1954). A standard clinical examination of the teeth. *Br Dent J* 96:296-300.

Parisotto TM, Steiner-Oliveira C, Duque C, Peres RC, Rodriques LK, Nobre-dos-Santos M (2010). Relationship among microbiological composition and presence of dental plaque, sugar exposure, social factors and different stages of early childhood caries. *Arch Oral Biol* 55:365-373.

Parviainen H, Vähänikkilä H, Laitala ML, Tjäderhane L, Anttonen V (2013). Evaluating performance of dental caries detection methods among third-year dental students. *BMC Oral Health* 13:70.

Peng B, Petersen PE, Bian Z, Tai B, Jiang H (2004). Can school-based oral health education and a sugar-free chewing gum program improve oral health? Results from a two-year study in PR China. *Acta Odontol Scand* 62:328-332.

Petersen PE, Razanamihaja N (1999). Carbamide-containing polyol chewing gum and prevention of dental caries in schoolchildren in Madagascar. *Int Dent J* 49:226-230.

Petersen PE (2003). The World Oral Health Report 2003: continuous improvement of oral health in the 21st century – the approach of the WHO Global Oral Health Programme. *Community Dent Oral Epidemiol* 31(Suppl.1):3-24.

Petersson LG, Birkhed D, Gleerup A, Johansson M, Jönsson G (1991). Caries-preventive effect of dentifrices containing various types and concentrations of fluorides and sugar alcohols. *Caries Res* 25:74-79.

Pitts N (2004). "ICDAS"—an international system for caries detection and assessment being developed to facilitate caries epidemiology, research and appropriate clinical management. *Community Dent Health* 21:193-198.

Pitts NB and Stamm JW (2004). International Consensus Workshop on Caries Clinical Trials (ICW-CCT)- Final Consensus Statements: Agreeing Where the Evidence Leads. *J Dent Res 83* Spec No C:C125-128.

Pitts N (2008). Dental Caries – The Disease and its Clinical Management, 2nd edition, eds. O. Fejerskov, E. Kidd, B. Nyvad and V. Baelum, Chapter 9: The impact of diagnostic criteria on estimates of prevalence, extent and severity of dental caries, p. 151.Poorterman JHG, Aartman IH, Kalsbeek H (1999). Underestimation of the prevalence of approximal caries and inadequate restorations in a clinical epidemiological study. *Community Dent Oral Epidemiol* 27:331-337.

Poorterman JHG, Weerheijm KL, Groen HJ, Kalsbeek H (2000). Clinical and radiographic judgment of occlusal caries in adolescents. *Eur J Oral Sci* 108:93-98.

Poorterman JHG, Weerheijm K, Aartman IHA, Kalsbeek H (2003a). Radiographic Dentinal Caries and its progression in occlusal surfaces in Dutch 17-year-olds: A 6-year longitudinal study. *Caries Res* 37:29-33.

Poorterman JHG, Aartman IH, Kieft JA (2003b). Approximal caries increment: a three-year longitudinal radiographic study. *Int Dent J* 53:269-274.

Reich E (2001). How to measure the effects of fluoride treatments in clinical trials? The role of caries prevalence and caries assessment. *Caries Res* 35 (Suppl. 1):34-39.

Rethman MP, Beltrán-Aquilar ED, Billings RJ, Hujoel PP, Katz BP, Milgrom P, Sohn W, Stamm JW, Watson G, Wolff M, Wright JT, Zero D, Aravamudhan K, Frantsve-Hawley J, Meyer DM (2011). American Dental Association Council on Scientific Affairs Expert Panel on Nonfluoride Caries-Preventive Agents. Nonfluoride caries-preventive agents: executive summary of evidence-based clinical recommendations. *J Am Dent Assoc* 142:1065-1071.

Riley P, Moore D, Ahmed F, Sharif MO, Worthington HV (2015). Xylitol-containing products for preventing dental caries in children and adults. *Cochrane Database of Systematic Reviews* 2015, Issue 3. Art. No.: CD10743. DOI: 10.1002/14651858.CD010743.pub2.

Ruiken R, König K, Truin GJ, Plasschaert F (1986). Longitudinal study of dental caries development in Dutch children aged 8-12 years. *Comm Dent Oral Epidemiol* 14:53-56.

Ryan R, Hill S, Prictor M, McKenzie J; Cochrane Consumers and Communication Review Group (2013). *Study Quality Guide.* May 2013 http://cccrg.cochrane.org/authorresources (accessed July 4, 2015)

SBU Att förebygga karies (2002).- En systematisk litteraturöversikt. Statens beredning för medicinsk utvärdering (SBU). The Swedish Council on

Technology Assessment in Health Care. SBU-rapport nr 161 (Fluor i tandkräm) 45-54.(Swedish).

SBU Karies - diagnostik, riskbedömning och icke-invasiv behandling (2007). En systematisk litteraturöversikt. Statens beredning för medicinsk utvärdering (SBU) The Swedish Council on Technology Assessment in Health Care. SBU rapport nr 188 (Swedish).

Scheinin A, Mäkinen KK, Tammisalo E, Rekola M (1975). Turku sugar studies XVIII: incidence of dental caries in relation to 1-year consumption of xylitol chewing gum. *Acta Odontol Scand* 33:269-278.

Scheinin A, Bánóczy J, Szöke J, Esztári, Pienihäkkinen K, Scheinin U, Tiekso, J, Zimmermann P, Hadas E (1985). Collaborative WHO xylitol field studies in Hungary. I. Three-year caries activity in institutionalized children. *Acta Odontol Scand* 43:327-347.

Selwitz RH, Ismail AI, Pitts NB (2007). Dental caries. *Lancet* 369:51-59.

Seppä L (2001). The Future of Preventive Programs in Countries with Different Systems for Dental Care. *Caries Res* 35:26-29.

Sheiham A and James WPT (2015). Diet and dental caries: The pivotal role of free sugars reemphasized. *J Dent Res* 94:1341-1347.

Sintes JL, Escalante C, Stewart B, McCool JJ, Garcia L, Volpe AR, Triol C (1995). Enhanced anticaries efficacy of a 0.243% sodium fluoride/10% xylitol/silica dentifrice: 3-year clinical results. *Am J Dent* 8:231-235.

Sintes J, Elias-Boneta A, Stewart B, Volpe AR (2002). Anticaries efficacy of a sodium monofluorophosphate dentifrice containing 10% xylitol in a dical base. (Abstract FDI World Dental Congress). *International Dental Journal* 51:374.

Stecksén-Blicks C, Holgerson PL, Twetman S (2008). Effect of xylitol and xylitol-fluoride lozenges on approximal caries development in high-caries-risk children. *Int J Paediatr Dent* 18:10-177. doi: 10.1111/j.1365-263X.2007.00912.x.

STUK (Radiation and Nuclear Safety Authority in Finland) http://www.stuk.fi/web/en/topics/use-of-radiation-in-health-care/dental-x-ray (accessed June 22, 2016).

Suni J, Helenius H, Alanen P (1998). Tooth and tooth surface survival rates in birth cohorts from 1965, 1970, 1975, and 1980 in Lahti, Finland. *Community Dent Oral Epidemiol* 26:101-106.

Söderling E, Isokangas P, Pienihäkkinen K, Tenovuo J (2000). Influence of maternal xylitol consumption on acquisition of mutans streptococci by infants. *J Dent Res* 79:882-887.

Söderling EM (2009). Xylitol, mutans streptococci and dental plaque. *Adv Dent Res* 21:74-78.

Taipale T, Pienihäkkinen K, Salminen S, Jokela J, Söderling E (2012). Bifidobacterium animalis subsp. lactis BB-12 administration in early childhood: a randomized clinical trial of effects on oral colonization by mutans streptococci and the probiotic. *Caries Res* 46:69-77.

Taipale T, Pienihäkkinen K, Alanen P, Jokela J, Söderling E (2013). Administration of Bifidobacterium animalis subsp. lactis BB-12 in early childhood: a post-trial effect on caries occurrence at four years of age. *Caries Res* 47:364-372,

Takahashi N, Nyvad B (2011). The Role of Bacteria in the Caries Process: Ecological Perspectives. *J Dent Res* 90:294-303.

Tala H. Oral health in Finland. Helsinki: National board of Health, 1989-92.

Tanner T, Kämppi A, Päkkilä J, Patinen P, Rosberg J, Karjalainen K, Järvelin MR, Tjäderhane L and Anttonen V (2013). *Acta Odontol Scand* 71:1436-1442.

ten Cate JM (2001). What dental diseases are we facing in the new millennium: some aspects of the research agenda. *Caries Res* 35 (suppl 1):2-5.

ten Cate JM (2013). Contemporary perspective on the use of fluoride products in caries prevention. *Br Dent J* 214:161-167.

Theilade E (1986). The non-specific theory in microbial etiology of inflammatory periodontal disease. *J Clin Periodontol* 13:905-911.

Topping GV, Pitts NB (2009). International Caries Detection and Assessment System Committee. Clinical visual caries detection. *Monogr Oral Sci* 21:15-41.

van Loveren C (2001). Antimicrobial activity of fluoride and its in vivo importance: identification of research questions. *Caries Res* 35(suppl1):65-70.

Virtanen JI, Bloigu RS and Larmas MA (1996). Timing of first restorations before, during, and after a preventive xylitol trial *Acta Odontol Scand* 54:211-216.

von der Fehr, Schwarz (1994). Textbook of Clinical Cariology, 2nd edition, eds. A.Thylstrup and O. Fejerskov, Chapter 8: Recording dental caries and health statistics in Europe, pp. 199, 205-206.

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

Waltimo T, Menghini G, Weber C, Kulik EM, Shilc S, Meyer J (2016). Caries experience in 7-, 12- and 15-year-old schoolchildren in the canton of Basel-Landschaft, Switzerland, from 1992 to 2011. *Community Dent Oral Epidemiol* 44:201-208.

Weerheijm KL, Kidd EAM, Groen HJ (1997). The effect of fluoridation on the occurrence of hidden caries in clinically sound occlusal surfaces. *Caries Research*. 31:30–34.

Zhan L, Cheng J, Chang P, Ngo M, Denbesten PK, Hoover CI and Featherstone JD (2012). Effects of Xylitol Wipes on Cariogenic Bacteria and Caries in Young Children. *J Dent Res* 91 (Suppl):85S-90S.