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Karolinska Institutet, Stockholm, Sweden

**STOP CARIES STOCKHOLM:
A CARIES-PREVENTION PROGRAM FOR
CHILDREN LIVING IN MULTICULTURAL
AREAS WITH LOW SOCIOECONOMIC STATUS**

Maria Anderson



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STOP CARIES STOCKHOLM: A caries-prevention program for children living in multicultural areas with low socioeconomic status

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Η πρόληψις μείζόν ἐστι τοῦ θεραπεύειν (ancient Greek)

Η πρόληψη υπερβαίνει τη θεραπεία (Greek)

Prevention överträffar behandling (Swedish)

Prevention surpasses treatment (English)

ABSTRACT

Inequalities in oral health among children persist, despite more general improvements in recent decades. Dental caries still affects children in disadvantaged communities with a multicultural population, both more frequently and more severely. As caries is a disease that perseveres throughout life, it is important to prevent its development before it has begun. The present thesis describes effectiveness and costs of an expanded intervention program for toddlers in high-risk areas of Stockholm County. This thesis also investigates the effect of supplemental measures on surface level caries progression, and whether high-fluoride content supplements have any effect on select bacteria in the oral cavity.

Objectives: To evaluate the effectiveness of an expanded caries-preventive program in a 2-year, parallel cluster-randomized controlled trial on a cohort of toddlers living in multicultural areas of Stockholm County with a low socioeconomic status.

Patients and methods: Twenty-three dental clinics were stratified and randomized into one test group (n=1,652) and one reference group (n=1,751). Study participants began the intervention programs in 2011 at age 12 months and received the last intervention at age 36 months. The reference group received the standard caries-preventive program that was already in place once a year. The test group received the same and, in addition, supplemental measures that included fluoride varnish applications at 6-month intervals. The trial used the revised International Caries Detection and Assessment System (ICDAS II, hereafter referred to simply as ICDAS) to assess dental caries. Mean inter-examiner reliability based on clinical examination was $\kappa=0.61$ (first examination) and $\kappa=0.73$ (second examination) when an ICDAS score of 3 was used as the cut-off for cavitation.

At the final examination after 2 years, oral bacterial samples from a convenience sample of toddlers (n=507) in select dental clinics were analyzed using checkerboard DNA–DNA hybridization.

The health economic evaluation used predetermined intervention costs as well as costs retrieved from a systematic review of the dental records (n=1,346). The between-group difference in the 2-year increment of decayed, extracted, or filled surfaces (defs) was used in the cost-effectiveness calculations. Surfaces with ICDAS scores of 3–6 were considered decayed.

Results: At baseline (age 12 months), 5% of the toddlers had already developed signs of dental caries (ICDAS 1–6). One year later, we re-examined 80% (n=2,675) of all recruited study participants and 2 years later, 75% (n=2,536) when the toddlers were 36 months. At age 24

months, 7% of the children had developed initial stage decay (ICDAS 1–2) and 4%, moderate-to-severe decay (ICDAS 3–6). At age 36 months, dental caries (ICDAS 1–6) was seen in 23% and the prevalence of moderate-to-severe decay was 12%. No between-group differences occurred in prevalence or increment.

Except on the mandibular incisors, which were rarely affected, caries development followed the eruption pattern of the teeth. Most affected were the buccal surfaces of the maxillary incisors, which had a caries progression index (PI) of 26% between baseline and the 1-year examinations, and 21% between the 1- and 2-year examinations. The PI is an average of all changes or progressions to a more severe stage of decay according to ICDAS. Healthy surfaces and surfaces with initial stage decay (ICDAS 1–2) were less likely to progress. Of the maxillary incisor buccal surfaces rating ICDAS 6 at the 1-year exam, 21% were extracted 1 year later. No between-group differences occurred in progression on the buccal surfaces of the maxillary incisors or the occlusal surfaces of the first primary molars.

Biannual applications of fluoridated varnish with a high fluoride concentration had a minimal effect on the populations of oral microflora. Significant differences between the test and reference groups occurred only regarding *S. oralis*, which was less frequently seen in the reference group.

Overall tooth brushing frequency during the course of the trial increased from 55% to 91%, between ages 12 and 36 months.

Dental health care costs of the intervention were EUR 96 for the test group and EUR 72 for the intervention group. The difference in mean increment between the groups from baseline at 12 months to the follow-up at 36 months was 0.09 defs in favor of the test group, a number used as the base case in the incremental cost effectiveness ratio (ICER) calculations. From a dental health care perspective, the ICER was EUR 276; and from a societal perspective that also includes the parental investment in time, the cost per saved defs was EUR 464. Thus, the expanded intervention was not considered cost-effective.

Conclusions: Applications of fluoride varnish together with a standard caries-preventive program delivered every half year to toddlers between 12 and 36 months of age did not significantly reduce caries development compared with the caries-preventive program already in place. Application of fluoride varnish with a high concentration of fluoride did not affect surface level caries progression and had no significant effect on the composition of the oral microflora. The expanded program also increased costs from both health care and societal perspectives.

The trial outcome did benefit the patient in many ways, however. We gained knowledge that allowed children to avoid unnecessary dental visits and which indicated better alternatives for resource allocation. One goal of preventive dental interventions is to foster oral hygiene skills in individuals for themselves and their children. We established regular habits in the use of fluoridated toothpaste at a young age in most of the participants. This may explain why the fluoride varnish applications had no effect as a supplemental measure to the caries-preventive program already in place; without the new regular tooth brushing habits, we would have expected a higher prevalence of caries than we found in the reference group. In a caries-preventive approach, early caries assessment is essential in order to tailor preventive measures to the needs of the individual. In our study, we could show that dental caries occurs as early as age 12 months; this supports clinical examinations in a dental setting beginning with the emergence of the first primary teeth.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Karies, hål i tänderna, är den vanligast förekommande sjukdomen hos barn i stora delar av världen. Små hål blir ofta snabbt stora och barnen får ont i sina tänder som då behöver lagas eller tas bort. Det är något som små barn ofta upplever som obehagligt och många blir rädda.

I Sverige har tandhälsan blivit mycket bättre under de senaste årtiondena. Men det finns fortfarande barn som drabbas både allvarigare och oftare av karies. I vissa områden i Stockholm är karies vanligare bland barn än i andra områden. Typiskt för dessa *högriskområden* är att det finns fler familjer som har det sämre ställt ekonomiskt. Det är också vanligare att någon förälder i dessa områden är arbetslös och/eller har invandrat till Sverige.

Bland 3-åringar i högriskområden i Stockholms län år 2010 uppvisade 9 procent karies jämfört med 3 procent av 3-åringarna totalt i hela länet vid samma tidpunkt. Denna ojämlikhet i tandhälsa stämde inte överens med Tandvårdslagen, som anger att alla invånare ska ha en god

Tandkräm är bra för tänderna för att det innehåller något som kallas för <i>fluorid</i> , som motverkar karies. Fluorid finns också i fluorlack men då i högre koncentrationer än i tandkräm.

hälsa och tandvård på lika villkor. De tydliga skillnaderna i tandhälsan visade att något behövde göras och därför startades forskningsprojektet Stop Caries Stockholm (SCS) med syftet att förbättra tandhälsan hos de små barnen. Alla 1-åringar som bodde i högriskområden år 2011 bjöds in att delta. Totalt var 3 403 barn med i den vetenskapliga studien.

Hälften av barnen i studien lottades att ingå i en referensgrupp. De fick ta del av ett ordinarie program med kariesförebyggande insatser som ges till alla barn i länet. Programmet innehöll information till föräldrar om vad som var bra och dåligt för barnens tänder och instruktioner i hur de skulle borsta sina barns tänder. Dessutom fick alla barn efter besöket med sig varsin tandborste och tandkräm att ta hem. Dessa insatser gjordes en gång per år. När de var på besöket hos tandvården fick de också sina tänder undersökta.

Den andra hälften av barnen lottades till att ingå i testgruppen. Dessa barn fick samma program som barnen i referensgruppen, men fick gå till tandvården två gånger per år istället för en gång. Vid besöken hos tandvården fick de också fluorlack på sina tänder.

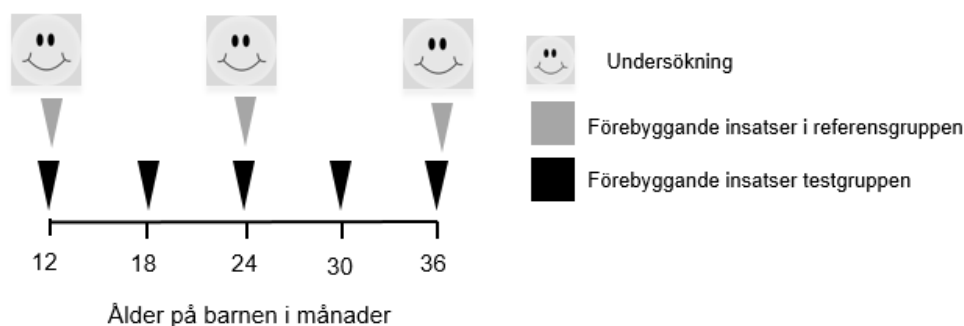


Bild som visar hur gamla barnen var när de kom till tandvården för undersökning och förebyggande insatser

Dessa förebyggande insatser gjordes när barnen var mellan 1 och 3 år gamla. När barnen var 3 år studerade man hur mycket karies barnen i referensgruppen hade jämfört med barnen i testgruppen. Av de barn som var med i studien från början var 75 procent kvar och kunde undersökas. Totalt hade 13 procent av barnen i referensgruppen fått karies jämfört med 11 procent i testgruppen. Denna skillnad var dock inte tillräcklig stor eller tillförlitlig för att det skulle gå att dra slutsatsen att extrabesöken eller fluorlacken låg bakom barnens förbättrade tandhälsa.

Utöver att undersöka hur stor andel av barnen som utvecklat karies studerade man också om det blev någon skillnad i hur snabbt hålen växte, från att vara små till att vara stora på olika tandtyper. Inga skillnader kunde påvisas. Vi tittade också på förekomsten av olika bakterier i munnen hos barnen vid 3 års ålder och inte heller här var det någon skillnad mellan de två grupperna.

De extra insatser som gjordes hos barnen i testgruppen var baserade på vetenskap med förväntat positivt resultat. Att de inte gav någon extra effekt var oväntat. Den troligaste orsaken till de små skillnaderna mellan referens- och testgrupp var att 91 procent av barnen borstade tänderna med fluortandkräm dagligen. Ett positivt resultat med denna studie är att barnen har fått mindre karies vid 3 års ålder jämfört med barn i andra liknande studier där de förebyggande insatserna startade vid en högre ålder.

Slutsatser från studien är att det är viktigt att göra rätt satsningar med de resurser som finns. De extra insatserna som testgruppen fick var mer kostsamma för tandvården och krävde mer tid av föräldrarna. Det bedömdes därför vara bättre att fortsätta med det ordinarie programmet, tills någon bättre metod utvecklats. Studien visar också att det är positivt att undersöka barnens tänder vid 1 års ålder. Tidpunkten gjorde det möjligt att dels följa utvecklingen av karies hos barnen under en längre tid, dels *lära föräldrar att borsta barnens tänder med fluortandkräm från det att första mjölkanden bryter fram.*

LIST OF SCIENTIFIC PAPERS

- I. Anderson M, Dahllöf G, Twetman S, Jansson L, Bergenlid AC, Grindefjord M (2016). Effectiveness of early preventive intervention with semiannual application of fluoride varnish application in Toddlers living in high-risk areas: a stratified cluster randomized controlled trial. *Caries Res*, 50:17-23. doi:10.1159/000442675
- II. Anderson M, Dahllöf G, Cunha Soares F, Grindefjord M (2017). Impact of bi-annual treatment with fluoride varnish on tooth surface level caries progression in children from 1 to 3 years of age. *J Dent*, 65:83-88. doi: 10.1016/j.jdent.2017.07.009
- III. Anderson M, Grindefjord M, Dahllöf G, Dahlén G, Twetman S (2016). Oral microflora in preschool children attending a fluoride varnish program: a cross-sectional study. *BMC Oral Health*, 16(1):130. doi: 10.1186/s12903-016-0325-6
- IV. Anderson M, Davidson T, Dahllöf G, Grindefjord M. Economic evaluation of an expanded caries-preventive program targeting toddlers in high-risk areas in Sweden. In manuscript.

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LIST OF ABBREVIATIONS

AAPD	American Academy of Pediatric Dentistry
CONSORT	Consolidated Standards of Reporting Trials
CCUG	Culture Collection, University of Gothenburg, Gothenburg, Sweden
DMFT(S)	Decayed, Missing, or Filled Teeth (Surfaces) – permanent teeth
dmft(s)	decayed, missing, or filled teeth (surfaces) – primary teeth
deft(s)	decayed, extracted, or filled teeth (surfaces) – primary teeth
ECC	Early childhood caries
ICDAS	International Caries Detection and Assessment System (unless otherwise noted, refers in this thesis to ICDAS II)
ICER	Incremental Cost-Effectiveness Ratio
HNA	Health Need Area
KI	Karolinska Institutet
OMGS	Oral Microbiology, Gothenburg, Sweden
PDS	Public Dental Service
PI	Progression index
RG	Reference group
S-ECC	Severe Early Childhood Caries
SCS	Stop Caries Stockholm
TG	Test group
WHO	World Health Organization

INTRODUCTION

Dental caries is a major public concern. Despite our increased knowledge on how to prevent its development, 621 million children have untreated primary teeth; dental caries is regarded as the most commonly occurring childhood disease (Pitts et al., 2017). There is also a prevailing inequality in oral health, which means that not all children are equally affected (Schwendicke et al., 2015). Disease development clearly follows a social gradient. Studies have found a strong relationship between the socioeconomic position of the family and the risk of developing dental caries (Hjern & Grindefjord, 2000; Vargas & Ronzio, 2006). We need to find ways of delivering dental care that will span these socioeconomic differences.

When children develop dental caries early in life, they may experience pain and infection, with ensuing anxiety, and their quality of life is disrupted. One study has shown that children with caries may fail to thrive, their mental development may be temporarily affected, and hospitalization sometimes becomes necessary (Finucane, 2012).

The disease often continues throughout life. Toddlers with dental caries often develop more caries during their preschool years (Grindefjord, Dahllöf, & Modéer, 1995). It is also well known that individuals who have had caries in their primary teeth tend to develop caries in their permanent teeth (Alm, Wendt, Koch, & Birkhed, 2007; Skeie, Raadal, Strand, & Espelid, 2006).

The primary challenge in managing young children with caries is their inability to cooperate. The emotional abilities, and cognitive and social skills, of toddlers and preschool children are insufficiently developed for handling dental treatment. Use of conscious sedation and general anesthesia is often necessary (Ismail, 1998).

Considering this, resource allocation for preventing caries development early in life becomes even more important. Caries that is not resolved at an early age risks becoming a chronic disease, requiring serial treatments that are stressful for the young patient and which consume resources.

Early childhood caries

Early onset caries in toddlers is often referred to as early childhood caries (ECC) (Tinanoff, 1998). One systematic review found that use of the term ECC varied (Ismail & Sohn, 1999). The American Academy of Pediatric Dentistry (AAPD) uses the definition “the presence of one or more decayed (noncavitated or cavitated lesions), missing (due to caries), or filled tooth surfaces in any primary tooth in a child under the age of six. In children younger than three

years of age, any sign of smooth-surface caries is indicative of severe early childhood caries (S-ECC)". S-ECC can also occur in later preschool years, depending on the location and extension of the caries (Council on Clinical Affairs, 2016).

In the first year of life, at about age 8 months, a child usually experiences the eruption of the first primary teeth. Primary tooth enamel is immature and thin, making these teeth more prone to cavity formation than permanent teeth (Kotsanos & Darling, 1991; Tinanoff & Douglass, 2001). A frequent intake of sugared beverages, such as drinks containing free sugar in baby bottles in the middle of the night, contributes to make ECC a fast progressing disease (Grindefjord, Dahllöf, Nilsson, & Modéer, 1995; Wendt & Birkhed, 1995). Lack of habitual tooth brushing and irregular use of fluoridated toothpaste further aggravate the situation (Wendt, Hallonsten, Koch, & Birkhed, 1994).

Caries epidemiology

Epidemiology is the "study of the distribution and determinants of disease frequency" (Rothman, 2012). Epidemiological determinations of dental caries are usually based on prevalence, that is, the presence of the disease at a given point of time or period in a specified population. How to define the presence of caries – according to tooth status – varies between studies.

The DMF index

Each year, the Swedish National Board of Health and Welfare [Socialstyrelsen] surveys the oral health of all Swedish children aged 0–19 years and publishes the results of two dental caries indices: the DMFT (capital letters, for permanent teeth) and the dmft (lowercase letters, for primary teeth). These indices describe the average occurrence of dental caries in an individual. Clinicians determine dental status on the tooth level according to WHO recommendations, using both clinical and radiographic findings (Swedish National Board of Health and Welfare, 2010a). In the indices, the D component denotes decayed teeth and describes caries that extends into the dentin; the crown of a tooth is considered decayed when there is an unmistakable cavity, undermineralized enamel, or a detectably softened floor or wall. The M component denotes missing teeth and describes the absence or presence of a tooth; and F, filled teeth, whether a tooth has a filling. WHO also publishes guidelines for determining dental status on the tooth surface level (World Health Organization, 2013).

ICDAS

In 2002 the coordinating committee for the International Caries Detection and Assessment System (ICDAS) presented ICDAS, a more comprehensive, evidence-based system for assessing dental caries status beyond the scope of the DMF indices. Aware that countries were using varying standards, the committee formed to develop a universally accepted system that would allow comparability between studies from various countries. The ICDAS committee comprises a wide range of recognized experts in dental research. The system has specific definitions. ICDAS expands on the DMF to include lesion *detection*, presence or absence of a lesion (disease); lesion *assessment*, characterization or monitoring of the detected lesion; and caries *diagnosis*, a human summation of the observed data.

The ICDAS committee and other participants continued to develop the system and introduced the current version of the ICDAS, the ICDAS II, in 2005. ICDAS II has one less code than the original ICDAS. To describe the severity of caries lesions, each tooth surface is assigned a separate code between 0 and 6. This code describes both the extension of the lesion along the surface and the depth of the lesion into enamel and dentin; a histological picture accompanies each code. The ICDAS system is preventively oriented and designed for use in dental education, clinical practice, and research and public health. It supports decision-making on both individual and public health levels (Pitts & Ekstrand, 2013; Shoaib, Deery, Ricketts, & Nugent, 2009).

The validity and reproducibility of the ICDAS II (hereafter referred to simply as ICDAS) is considered to be good and has been tested in several *in vitro* studies (Diniz, Rodrigues, Hug, Cordeiro Rde, & Lussi, 2009; Jablonski-Momeni, Stachniss, Ricketts, Heinzl-Gutenbrunner, & Pieper, 2008; Shoaib et al., 2009) and clinical studies (Braga, Oliveira, Bonini, Bonecker, & Mendes, 2009; Mendes et al., 2010; Mitropoulos, Rahiotis, Stamatakis, & Kakaboura, 2010).

Studies have been done to determine how ICDAS criteria associate with the WHO recommended DMF indices and whether the results of studies using one method can be compared with a study using the other. The Braga et al. study (2009) on 252 children aged 36–59 months in Brazil found the prevalence of dental caries to be similar if clinicians used an ICDAS 3 as a cut-off score. Cut-off scores of 1 and 2 overrated prevalence, and a cut-off score of 4 underestimated prevalence. The Iranzo-Cortes et al. study, a similar study on older children and permanent teeth, supported this conclusion (2013).

Use of cavitation as a threshold for dental caries may be too inexact, especially for following progression or evaluating the effects of an intervention. ICDAS seems more appropriate for use in a clinical trial.

Unequal distribution

Dental caries is ubiquitous in all populations. Prevalence, however, varies, both within and between countries. Caries is more common in urbanized countries with a high consumption of sugar, especially of processed foods and soft drinks (Diehnelt & Kiyak, 2001). Data from the WHO Global Oral Health Data Bank show that dental caries affects 60–90% of school-aged children in industrialized countries; it is also common in Asia and Latin America. In contrast, it is both less common and less severe in most African countries (Petersen, 2003).

The prevalence of caries in toddlers varies as well. Reports suggest numbers between 0.5% and 56% in developed countries (Douglass, Tinanoff, Tang, & Altman, 2001). The Bourgeois & Llodra study (2014) analyzed the prevalence and severity of dental caries in 7,949 children from nine countries; the age span was 1–13 years. As expected, caries prevalence was lowest in the youngest children, with 89% of the 2-year-olds caries free compared with 27% of children 8 years and above. The mean dft of the study sample was 3.7; 94% of these lesions were untreated. ECC was defined as caries in children between 1 and 5 years of age; in this subgroup of 2,160 children, 52% had decayed or filled teeth. Greece had the lowest prevalence of ECC, 19%, and the Philippines the highest, 98%. Most of the affected children had more than one decayed tooth .

Since the late 1960s, the oral health status of Swedish children has been steadily improving (Folkhälsovetenskapligt centrum i Östergötland, 2009; Nordenram, 2012; Stecksén-Blicks, Kieri, Nyman, Pilebro, & Borssén, 2008). Despite this improvement, however, oral health disparities remain pervasive. A Swedish study found that 59% of 4-year-old children in Umeå with an immigrant background had dental caries compared with 32% of the rest of the children in the 2007 year cohort (Stecksén-Blicks et al., 2008). A similar discrepancy had been reported in Stockholm in 1995 where caries prevalence in 3.5-year-old children with an immigrant background was found to be 63% compared with 26% in children with a non-immigrant background (Grindefjord M, 1995). Similar patterns occur in other countries, where dental caries affects children from disadvantaged communities and minority ethnic groups more frequently and more severely than other children (Do, 2012; Vargas & Ronzio, 2006).

Social determinants

Social determinants such as income, education, and occupation influence the outcome of most health measures and several specific diseases (Bradley & Corwyn, 2002; Hollander, 2013). One of these is dental caries (Grindefjord, Dahllöf, & Modéer, 1995).

Educational level. The educational level of the parents, in particular of the mother, has been recognized as an important risk indicator of dental caries in children (Grindefjord, Dahllöf,

Nilsson, & Mod  r, 1996; Verrips, Kalsbeek, & Eijkman, 1993). Lower use of dental services and more severe caries experience have been noted in the children of parents with low educational levels, inappropriate eating habits, and poor oral health-care routines (Kim Seow, 2012). Sanders et al. (2009) found that child health information often exceeds the literacy skills of the parents. Lee et al. (2012) found health literacy to function as a mediator between socioeconomic factors and health behaviors and outcomes, including oral health status. Clinicians must take into account the importance of health literacy when managing factors related to ill-health. Maternal literacy skills have also been linked to maternal depression (Sanders, Shaw, Guez, Baur, & Rudd, 2009), and depression in mothers is a sign of stress and a parenting risk (Kim Seow, 2012).

Socioeconomic position. Parental socioeconomic position may influence caries experience, and this association can be stronger in highly developed countries. Determining exactly how socioeconomic status affects the well-being of children is difficult as several factors are most likely involved in the interaction. Indicators can include minority and immigrant status, single parenthood, and mental illness (Bradley & Corwyn, 2002). The Swedish National Board of Health and Welfare (2013) found that children are more likely to miss dental appointments if they live in single parent households, live in families that receive financial support, have young parents, or have parents with a low educational level. The Christensen et al. study (2010) found that immigrants more often live under low socioeconomic conditions than native-born citizens. These discrepancies diminish with time, but it may take 10 years or more for a newcomer in Sweden to achieve the same living standards as the rest of the population (Hjern, 2012). Recently, researchers have begun to study the relation between the physical and social environments of the neighborhoods where patients live. Results suggest that patterning of the residential environment may contribute to the rise and maintenance of health inequalities (Diez Roux & Mair, 2010). Thus, the increasing ethnic residential segregation and immigration in recent years (Biterman & Franz  n, 2007) means that Sweden may experience a rise in ECC.

Immigrant status. In preschool children, immigrant status by itself has been found to be an independent variable associated with dental caries (Grindefjord et al., 1996). A Norwegian questionnaire study found that parental attitudes concerning oral hygiene, diet, indulgence, and caries-related behaviors differed between the immigrant (mother of non-western origin) group and western-born natives group (Skeie, Riordan, Klock, & Espelid, 2006).

Knowledge gaps exist concerning how to best implement preventive measures in high-risk groups (Swedish Agency for Health Technology Assessment, 2002).

Prevention

Fluoride

Dental caries is a preventable disease. Several epidemiological studies have established the important role that fluoride plays in the control of caries.

Fluoride is a chemical element that occurs naturally in a wide variety of minerals, rock, and soil. It also occurs naturally in water (O'Mullane et al., 2016). Dean (1938) was the first to document the caries-preventive effect of fluoride when he studied caries prevalence among children in different areas of the United States and found that a higher percentage of children were caries free when domestic drinking water had a higher concentration of fluoride.

The major action of fluoride was not systemic, as first believed when it was introduced into water supplies in the 1940s; rather, fluoride has a local topical effect with three major modes of action. If fluoride is present during an acid challenge to the teeth, the surface of the teeth absorbs the fluoride and remineralization accelerates. In the remineralization process, a less soluble surface of fluoride apatite instead of hydroxyapatite is formed; fluoride apatite is more resistant to reductions in pH. Fluoride also has antimicrobial properties (Buzalaf, Pessan, Honório, & ten Cate, 2011). Although the effect of fluoride is not curative, it partially compensates bad eating habits.

Today drinking water and fluoridated toothpaste are the main sources of fluoride ingestion (de Maria, 2013). Drinking water is not fluoridated in Sweden, though it has been shown to be effective and is supported by dental organizations working with pediatric dentistry. Some authors claim that it is the most convenient way to administer fluoride and that it is socially equitable; that is, equally available to all social groups and ages (EAPD, 2009). The Swedish National Food Agency has set limits of 1.5 mg/l for fluoride that is naturally present in drinking water (IPCS, 2002; National Food Agency, 2001).

Fluoride toothpaste

Daily use of a fluoride toothpaste is an effective way of preventing dental caries (Mejäre et al., 2015). Optimal anti-caries concentration of fluoride in dentifrice has not been determined, although it is well known that the caries-prevention effect of fluoride is a dose-response effect: the higher the concentration of fluoride, the greater the prevention. The anti-caries effect of 500 ppm fluoride is unsatisfactory, but concentrations of 1,000–1,500 ppm fluoride have a well-documented preventive effect. Because ingested fluoride may give rise to fluorosis in the developing permanent dentition, the amount of toothpaste that children swallow must be regulated by limiting the amount of toothpaste placed on the toothbrush (Twetman, 2009). To

minimize the risk of developing dental fluorosis, a daily fluoride intake of more than 0.05–0.07 mg/bodyweight should be avoided (Burt 1992). The AAPD recommends a “smear” of toothpaste (about the size of a grain of rice) for children under 3 years and a pea-sized amount of toothpaste for children between 3 and 6 years of age (Council on Clinical Affairs, 2016). The recommendation in a Swedish knowledge database is similar but differs in age limits for the pea-sized amount of toothpaste. Figure 1 presents an extract of the recommendations that many dentists follow; pictures were added for this thesis (Twetman, 2015).


Age	Fluoride concentration (ppm)	Amount	Image	Frequency (daily)
6–24 months	1000	Smear		1–2 times
2–6 years	1000–1450	Pea size		2 times

Figure 1. Swedish recommendations on toothpaste use in preschool children.

Taking care in measuring the amount of toothpaste for younger children is important, not only because of their lower weight. Younger children are less likely to spit out the toothpaste, which they need to learn to do as soon as possible. A recent study found that 1.5–2.5-year-old children swallowed an estimated average of 64–84% of the toothpaste placed on the toothbrush (Cochran et al., 2004). One way to reduce the bioavailability of ingested fluoride is to brush after a meal. This possibly reduces the amount of fluoride reaching the blood (Trautner & Einwag, 1989). The toxic dose of fluoride is 5 mg/kg bodyweight. For a 1-year-old child of 10 kg, this corresponds to 50 ml of a 1000 ppm fluoride (1mg/ml) toothpaste (Whitford, 1987). If a normal-sized tube of toothpaste contains 75 ml, a toxic dose would be 2/3 of the tube. Thus for safety reasons, a parent should supervise tooth brushing.

Tooth brushing frequency varies among children. Stecksén-Blicks et al. (2008) found in their cohort of 4-year-olds that 71% had their teeth brushed twice a day or more with 98% using fluoridated toothpaste. Brushing only once a day was more common among children with an

immigrant background; although 94% brushed their teeth once a day or more, only 47% regularly brushed their teeth twice a day or more. Another Swedish study found similar frequencies in daily tooth brushing among 3-year-olds, where 93% had their teeth brushed at least once a day (Alm, Wendt, Koch, & Birkhed, 2008). Swedish data on tooth brushing habits in 1-year-olds are limited. A recent study in Boston, MA, USA, reported that 73% of 1–2-year-olds had their teeth brushed daily. Of these children, 71% came from low-income families and the parents of 46% had only a high school level education or lower (Johansson, Holgerson, Kressin, Nunn, & Tanner, 2010).

Fluoride varnish

Fluoride varnishes are another source of fluoride that are considered effective in reducing dental caries. A recent updated systematic review found that applications of a fluoride varnish two to four times a year reduce the average number of dmft surfaces by 37% and of DMFT, 43%. The included studies, however, were of moderate quality (Marinho, Worthington, Walsh, & Clarkson, 2013). Because varnishes are professionally applied and do not rely on patient compliance, they are suitable for high-risk individuals (Petersson et al., 2004)

Due to its composition, a fluoride varnish adheres to the tooth surface for longer periods than toothpaste and acts as a slow-release reservoir of fluoride (Ögard, Seppa, & Rölla, 1994). Varnishes have been shown to be safe to use in children; most likely due to the slow release of fluoride, serum fluoride values do not rise substantially after application. No acute toxic reactions have been documented (Chu & Lo, 2006).

Duraphat[®] is a commonly used fluoride varnish in Swedish dental practice. The varnish contains 5% sodium fluoride (NaF) or 22,600 ppm fluoride ions (ppm F⁻). Twetman et al. (1999) found that in whole saliva, fluoride concentrations reached peak concentration 1 hour following application, after which they slowly dropped. In plaque, fluoride concentrations reached their highest levels around 3 days following application. The Sköld-Larsson et al. (2000) study also found elevated concentrations of fluoride in plaque after 7 days. After 30 days, concentrations had returned to baseline levels.

The AAPD recommends use of fluoride varnish, even in the youngest children (Council on Clinical Affairs, 2016). Although fluoride varnish is considered to be effective and useful in at-risk children, its preventive effect as a non-invasive treatment of dental caries is unknown (Mejàre et al., 2015).

Diet control and restriction of sugar

In countries with moderate-to-extensive fluoride exposure, the relationship between sugar and dental caries is weaker than before fluoride was introduced as a supplement in drinking water and dental care products (Burt & Pai, 2001). *Frequency* rather than *quantity* seems to be important (Anderson, Curzon, Van Loveren, Tatsi, & Duggal, 2009). A recent study found a significant association between the frequency of consumption of sweetened beverages and dental caries. The impact of higher frequencies was stronger in the primary dentition than in the permanent dentition (Armfield, Spencer, Roberts-Thomson, & Plastow, 2013).

Seen over a lifetime, quality and quantity of ingested sugar become exceedingly important. Because caries is a cumulative disease, the detrimental effects of sugars continue to accumulate throughout life (Sheiham & James, 2015). Despite the use of fluoride and its ability to postpone cavitation, fluoride does not completely prevent dental caries, and the progressive nature of the disease becomes apparent.

The WHO guideline “Sugars intake for adults and children”(2015) shows that caries development varies with the intake of free sugars. If free-sugars intake is less than 10% of total energy intake, caries prevalence seems to be lower. Thus, WHO strongly recommends that the intake of free sugars be reduced to under 10% of total energy intake.

Caries prevention in Stockholm County

In Sweden, health services have a high priority, are widely available, and are tax financed (Virtanen, Berntsson, Lahelma, Köhler, & Murtomaa, 2007). The country has a long tradition of preventive dental health care, and the oral health status of the population has been regularly monitored. Since the introduction of preventive dental care for children in the 1970s, dental caries has decreased substantially (Hugoson, Koch, Helkimo, & Lundin, 2008).

Various preventive strategies have been used side by side. When prevention targets the individual, it is usually a matter of secondary prevention as the disease has often had time to develop. Preventive measures may also target a high-risk group, or with basic prevention, target an entire population (Koch, Poulsen, & Twetman, 2013). Geo-maps of caries risk are useful when allocating resources and preventive efforts (Strömberg, Magnusson, Holmen, & Twetman, 2011).

Stockholm County Council has mapped neighborhoods based on caries prevalence. The neighborhoods are grouped into four health need areas (HNA): HNA 1, 2, 3, and 4. Children in HNA 1 and 2 have the best dental health with approximately 22,900 children in each age. Children in HNA 3 and 4 have a higher prevalence of caries and more decayed teeth; there are

approximately 4,300 children in each age. A multicultural population with a predominance of families with medium or low socioeconomic status characterize HNA 3 and 4 (Stockholm County Council, 2010).

In 2004, the PDS introduced a new caries-prevention program in Stockholm County (Folktandvården Stockholms län AB, 2004). In 2002, the Swedish Agency for Health Technology Assessment and Assessment of Social Services had published “Preventing dental caries: a systematic review” (Swedish Agency for Health Technology Assessment, 2002). The review found no evidence for parts of the then-current prevention strategies, which included many measures designed for high-risk individuals. Based on this review, the core of the 2004 program directed a major part of prevention efforts toward the Stockholm County child population as a whole. The base program includes outreach activities at child health centers and schools and activities at the dental clinics. Children begin receiving standard preventive intervention when new teeth begin to erupt and are examined at dental clinics at at-risk ages. Aside from the core program, additional prevention strategies target groups at risk of developing dental caries; in particular, HNA 3 and 4. This new dental program neglects no child who has a higher risk of developing dental caries. Each child is assessed for caries risk during the routine dental check-ups to determine the timing of the next dental visit (Folktandvården Stockholms län AB, 2004).

Since 2004, annual reports on the dental health of children in Stockholm County began to improve. Differences between the HNAs remained, however, particularly among younger children. Further, in 2010, the County still failed to meet the WHO dental health recommendation for children aged 6 years overall (Stockholm County Council, 2010).

A guiding principle of Swedish dental health care is equal access to dental health (TL 1985;125 2 §) (Socialdepartementet) this means, based on the latest reports, focusing efforts on areas at high risk of developing dental caries in order to reduce disparities (Marinho, Higgins, Logan, & Sheiham, 2002; Marinho, Higgins, Sheiham, & Logan, 2003; Swedish Agency for Health Technology Assessment, 2002; Twetman, 2008).

A clinical trial in a high-risk area in Malmö tested a new program. Although it significantly reduced dental caries among the targeted 2-year-olds, many children had already developed dental caries (Wennhall, Matsson, Schröder, & Twetman, 2008). This implies that interventions should start at earlier ages.

Is it possible to halt caries development and reduce inequalities in dental health by introducing an expanded preventive program that *(i)* begins when the primary teeth erupt, *(ii)* is directed toward high risk areas, *(iii)* focuses on establishing regular tooth brushing habits with use of

fluoride toothpaste, and (iv) offers professional application of fluoride varnish twice year? And will Stockholm County be able to reach the WHO goal of oral health in 6-year-olds by doing so?

Distribution and progression of dental caries

Intervention influences presence *and* development of a disease.

On the individual level, analyses of dental caries reveal disease distribution in the dentition, disease onset and change over time, and which teeth and surfaces are affected. Analyses on the individual level also allow comparisons of one tooth or surface with another and studies of disease progression on each surface.

On the surface level, various approaches assess caries progression. *Caries rate (incidence rate)* incorporates time at risk for a surface to become carious. It can be calculated as a ratio: number of new lesions/100 tooth surface-years at risk. *Survival time* expresses how long a surface survives in one stage before progressing to the next stage. Survival time may be presented as median survival time in years (Mejäre, Raadal, & Espelid, 2013). In this thesis, we calculate the proportion of the total number of surfaces that progress or regress from one stage to another within a specified time period.

The progression of dental caries in children follows the eruption pattern of the primary dentition. In almost all 1–2-year-old toddlers with dental caries, the disease occurs on the maxillary incisors and, most commonly, on the buccal surfaces (Wendt, Hallonsten, & Koch, 1991). As the child grows older and new teeth erupt, the occlusal surfaces of the first primary molars frequently become affected instead. Depending on the age of the child, different teeth are more or less commonly affected. One Swedish longitudinal study found that in children aged 2.5 years, 72% of the caries in the dentition were located on the maxillary incisors (Grindefjord, Dahllöf, Ekström, Höjer, & Modéer, 1993). In children aged 3.5 years, this figure had decreased to 42% with a higher proportion of the cavities located on the primary molars. The distribution of new lesions varied depending on whether dental caries was present at 2.5 years or not. In children who were caries free at 2.5 years, 67% of the dentin lesions were located on the molars at 3.5 years. (Grindefjord, Dahllöf, & Modéer, 1995). A more recent longitudinal study on somewhat older children found that at age 3 years, children with caries lesions (with or without cavitation) were more likely to have developed new caries lesions at age 4 in comparison to children who had been caries free at 3. Among children with caries, the most frequently affected tooth for both enamel and dentin caries between ages 3 and 6 years

was the occlusal surface of the second primary molar (Kramer, Skeie, Skaare, Espelid, & Östberg, 2014).

Knowledge of progression time is important for planning follow-ups and operative treatment. However, there are several interacting factors, and prediction is difficult. Investigations of progression patterns provide some guidance. Compared with permanent teeth, progression in primary teeth is about twice as fast: Schwartz et al. measured a medium survival time of between 1.9 and 2.7 years on proximal surfaces for progression through the enamel in primary teeth. In permanent teeth, progression on proximal surfaces was between 3.4 and 8.1 years. In five study groups from the U.S. and Sweden, the progression rate varied depending on study group. High-risk individuals, those who had the highest number of lesions, exhibited the highest progression rate through the enamel (1984). Peyron et al. (1992) found that in children aged 3–6 years, 45% of carious lesions progress from the enamel to the dentin within 1 year.

Presence of dentin caries on the proximal surfaces of the primary molars increases the risk of caries on the mesial surfaces of the primary first molars. Dentin caries on the proximal surfaces of the primary molars also affects the caries rate. Mejàre et al. studied caries progression in children aged 6–12 years on radiographs. They found a caries rate (from a surface with no visible lesion to a lesion extending through the inner half of the enamel) of 1.32 new lesions/100 tooth surface–years on the mesial surface of the permanent molar, if the neighboring distal surface was sound. However, the caries rate was 15 times higher if the distal surface of the secondary primary molar had enamel caries that had reached the dentin border (Mejàre, Stenlund, Julihn, Larsson, & Permert, 2001).

A recent study using ICDAS followed caries development in primary teeth for 4 years. The study found that the location of the lesion influenced caries progression and that occlusal surfaces were more prone to cavitation. Further, the study found that cavitation increased with higher ICDAS scores. After 4 years, the proportion of teeth that became cavitated according to ICDAS was as follows: score 1, 19%; score 2, 32%; score 3, 68%; and score 4, 66% (Ferreira Zandona et al., 2012).

Cavitation on tooth surfaces at baseline was found to be more likely to progress to a more severe stage than sound surfaces at baseline were to develop a caries lesion (Ismail, Lim, & Tellez, 2015). A clinical trial administering fluoride varnish every 6 months in 4-year-old children found that surfaces, sound at baseline, received the greatest benefit (Divaris, Preisser, & Slade, 2013). Early intervention makes it possible to monitor caries progression; however, there are still gaps in knowledge about the best way to slow progression in primary teeth (Mejàre et al., 2015).

Dental biofilm

Recent years have witnessed a paradigm shift in how dental professionals and researchers view dental caries. The literature now considers it to be a complex and multifactorial disease: there is no one pathway of disease development, and both host specificity and environmental variables are disease factors. Rather than viewing caries as a transmittable and infectious disease caused by specific bacteria, the dental field now views caries as a disturbance of homeostasis in the dental biofilm (dental plaque) and a microbiological shift; with time clinically measurable symptoms develop (Fejerskov, 2004).

The biofilm, and its structural composition, varies between individuals, between sites in the mouth, and with patient age. Independent of where it occurs in the mouth, biofilm formation is similar. Initially, bacteria adhere to the pellicle-covered tooth surface. The pellicle is a protein film that forms directly after cleaning or chewing. These bacteria then begin to build microcolonies that produce an extracellular matrix, which is made up of proteins, extracellular polysaccharides, and nucleic acids. The entire process is regulated and includes lysis of cells that escape from the microbial colonies. The mature three-dimensional structure, known as plaque, is more resistant to the immune system and pharmaceuticals than are bacteria in the planktonic stage (Dahlén, 2012).

Cavity formation

Chemical interactions between salivary properties, sugar consumption patterns, preventive behaviors such as tooth brushing, and fluoride exposure all affect the natural equilibrium between the biofilm covering the teeth and the mineralized tooth structures in the mouth of the individual. Biofilm nutrients derive mainly from food and sugars that contain fermentable carbohydrates. When acids produced by endogenous bacteria as bi-products of the metabolism of fermentable carbohydrates lower the oral pH below a critical level, mineral depletion of the tooth enamel occurs. If the process stops, minerals begin adhering to the tooth surface, which eventually re-mineralizes. If the process continues, there will be a net loss of minerals from the tooth enamel; eventually, due to masticatory forces, a cavity develops (Selwitz, Ismail, & Pitts, 2007).

Oral microflora in children

It is known that an organism's ability to produce acids and tolerate a low pH environment is fundamental to the development and progression of tooth decay. Increasing frequencies of exposure to sugar increase the acidogenic bacteria in the biofilm as well as their acidogenicity. A high acidogenic ratio has been associated with active lesions on recently restored teeth. *Lactobacillus* and *S. mutans* were long considered the primary pathogens of dental caries, but

other acidogenic and aciduric bacteria are now thought to be involved (Beighton, 2005). Recent molecular-based studies have shown that *Actinomyces* and *Veillonella* contribute to the development of dental caries in children (Chalmers et al., 2015; Tanner et al., 2011).

In children, the oral ecosystem changes during the first years of life when a stable microflora is being established. Not all early presenting bacterial species will remain, but numbers as well as versatility increase with age. A recent study found presence of lactobacilli at 3 months of age to be associated with dental caries at age 3 years. At 3 years of age, *S. mutans* was more prevalent in children with dental caries. Further, the study found an association in the 3-year olds between dental caries and the presence of species/phylotypes belonging to *Actinobaculum*, *Atopobium*, and *Aggregatibacter*. The study also found that some bacteria support the absence of dental caries (Lif Holgerson, Öhman, Rönnlund, & Johansson, 2015). Is it possible that caries-preventive interventions affect the prevalence of some caries inhibiting species?

In the past, determinations of oral bacteria were based on cultivating methods. Today's molecular methods have opened new windows for studying bacterial action and diversity. This thesis used the deoxyribonucleic acid (DNA)-based technique "Checkerboard DNA-DNA hybridization" to identify bacteria presence in oral samples. Identification of microorganisms with this method is based on specific DNA probes against either species-specific nucleotide sequences (gene probe) or the entire bacterial genome (whole genomic probes) (Socransky et al., 2004).

More advanced methods have now been developed, and the leading method for identifying microorganisms today is 16S rDNA sequencing. The basis of this technique is that some sections of 16S rDNA are conserved and unique for each organism and can thus be used to identify bacteria. Approximately 280 bacterial species in the oral cavity have been cultivated and named. Cultivation-independent methods, mainly cloning-based methods using the 16s RNA gene, have identified over 600 oral phylotypes or species (Dewhirst et al., 2010).

Do caries-prevention programs, which include fluoride varnish and are introduced at an early age, influence the composition of oral microflora?

Health economics

Sweden spends SEK 25 billion annually on dental health care. Of these monies, the Swedish government makes a general public contribution of SEK 5 billion for the adult population. For the dental health care of children and adolescents, the elderly, and grown-ups with special needs; Swedish county councils spend about SEK 4 billion a year (The Dental and

Pharmaceutical Benefits Agency, 2017). Of these patients, only the dental care of children and adolescents is fully subsidized.

Due to limited public resources, economy plays an integral part. Besides higher health-care demands in the population, the gap between what can be offered and what the population demands is widening. Health economic evaluations are valuable tools when deciding policy. Such tools compare costs and consequences of two or more diagnostic methods or interventions in a structural manner, providing policymakers guidance (Swedish Agency for Health Technology Assessment, 2014).

Swedish health policy relies heavily on an ethical platform in decisions on use of public resources. The platform embodies three principles: the principle of human dignity, which states that all people have equal value and should therefore be treated equally; the need and solidarity principle, which states that resources should be directed toward those in greatest need; and the cost-effectiveness principle, which states that we should strive to maintain a reasonable balance between different health technologies and their effect on the quality of life (Government Offices of Sweden, 1995).

Economic evaluation methods

Sweden uses four main forms of economic evaluations. Although each method considers costs, the methods differ in how they measure the consequences of health-care programs.

Cost-minimization analysis assumes that the consequences of the programs are identical. This method only considers costs in comparisons of the alternatives.

Cost-effectiveness analysis measures the consequences of the programs in the most appropriate physical units of natural effects such as “life-years gained” or “cases correctly diagnosed”. In a program comparison, only one physical unit is used (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 2005). Oral health outcomes may, for example, be averted caries or number of tooth-years gained (O'Connell & Griffin, 2011).

To determine which of two methods is most cost effective, information concerning both costs and effects is needed. Cost-effective analysis often presents the results as an incremental cost-effectiveness ratio (ICER).

$$\text{ICER} = \frac{\text{Cost A} - \text{Cost B}}{\text{Effect A} - \text{Effect B}}$$

Cost A and Cost B are the costs that follow methods A and B, while Effect A and Effect B are the effects of methods A and B, respectively. Thus, ICER analyzes the cost of attaining an additional unit of effect, such as the costs to attain one more life-year or tooth-year (Swedish Agency for Health Technology Assessment, 2014).

Cost-utility analysis measures the consequences of a health-care program using health-state preference scores or utility weights; that is, the states of health associated with the outcomes are valued relative to one another. For instance, the analysis values not only the number but also the quality of the life-years gained. Consequences are measured as healthy years, usually quality-adjusted life-years (QUALY) (Drummond et al., 2005). Oral health outcomes may be measured as quality-adjusted tooth-year, oral health-related quality of life (OHRQoL), and when parents report on behalf of their children, Pediatric OHRQoL (O'Connell & Griffin, 2011).

Cost-benefit analyzes value outcomes in monetary terms in order to make them commensurate with the costs (Drummond, Meldrum, & Boyd, 2013).

Calculating costs

These four economic evaluations include measures of (O'Connell & Griffin, 2011):

- a) intervention costs – the value of resources used to deliver the intervention; b)*
intervention savings – averted treatment and other costs attributable to the
intervention; and c) net costs – the intervention costs netting out intervention savings.

In research it is important to document the costs associated with the study and to distinguish research costs from those associated with the costs of the intervention being evaluated. Calculations of the costs and savings for the intervention include measuring direct and indirect costs. *Direct costs* may include, for instance, salaries of the intervention personnel, medical supplies, and travel costs. *Indirect costs* are productivity losses and may include costs associated with the time spent traveling to providers' offices, for time spent waiting for intervention services, and due to absence from work (O'Connell & Griffin, 2011). Which costs to include in economic evaluations depends on the question to be answered. Different approaches are possible. In Sweden, the Dental and Pharmaceutical Benefits Agency guidelines regarding health economic analyses recommend use of the societal perspective in favor of the health-care perspective (The Dental and Pharmaceutical Benefit Agency, 2017).

Health economic analyses in dentistry

A 2003 review on economic evaluation of caries prevention found no support for any economic benefits of caries prevention. Lack of well-conducted studies and contradictory evidence made it problematic to judge health economic effects (Källestål et al., 2003).

A 2015 systematic review analyzed the overall quality of economic evaluation in dentistry. Electronic searching of Ovid MEDLINE, the Cochrane Library, and the NHS Economic Evaluation Database from 1975 to 2013 were undertaken to identify publications that included costs and outcomes in dentistry. In total, 8410 titles and abstracts were screened, but after removing 8235 due to unmet inclusion criteria and 61 for meeting exclusion criteria, 114 studies remained for analysis. After assessing the articles according to the Drummond 10-item checklist, it was concluded that most economic evaluation studies in dentistry fail to comply with all aspects of this checklist. Only 40% of the studies discounted health benefits and 39% of the studies showed no discounting for outcomes. Further, insufficient details of measurement and valuation of outcomes and costs were found in 9–11% of the included studies, while the studies were often inconsistent, tended to confuse terminology, and exhibited a lack of sound research methodology (Tonmukayakul, Calache, Clark, Wasiak, & Faggion, 2015).

In economic evaluations of caries-preventive programs, the literature has pointed to a need for collaboration between health economists and oral health researchers, both to improve the quality of the programs and to explore the considerations that must be made when interpreting the results (Marino, Khan, & Morgan, 2013).

THESIS AIMS

General aim

The general aim of the present research project was to improve the oral health of children living in vulnerable areas in Stockholm County, Sweden, and to evaluate the increased cost of an expanded caries-preventive program in relation to its impact on caries development in the children.

Specific aims

Study I

To test the hypothesis that caries prevalence is significantly lower in children between 1 and 3 years of age receiving a standard oral health program supplemented with biannual fluoride varnish applications compared with those receiving the standard oral health program only.

Study II

To test the hypothesis that caries progression in the buccal maxillary incisors is lower in children receiving a biannual fluoride varnish program than in those receiving a standard preventive program. Further, to analyze and describe caries progression on the surface level between 1 and 3 years of age with the International Caries and Detection System (ICDAS).

Study III

To test the hypothesis that there is a difference in the composition of the oral microflora between children receiving an expanded preventive program that included application of highly concentrated fluoride varnish and children receiving a standard intervention program solely. Further, to investigate the oral microbial composition in children who had developed early childhood caries at the age of 3 years and in those who remained caries free.

Study IV

The aim of this study was to make an economic evaluation of the expanded caries-preventive program and compare it with the standard program already in place.

MATERIALS AND METHODS

The present thesis is a randomized controlled trial (RCT) with two parallel arms conducted in the field and with a prospective longitudinal study design. An entire cohort of children was invited to participate; they were cluster randomized into two groups. Study I was based on the entire cohort while Studies II, III, and IV had differing study populations. The RCT was performed in Stockholm County, Sweden, between March 2011 and March 2014. We registered the trial at www.controlled-trials.com, where it was assigned an International Standard Randomized Controlled Trial Number: ISRCTN35086887.

Study groups

Study I

All children born in HNA 3 and 4 between 1 January and 31 December 2010 in Stockholm County were invited to participate. When the study began, 20 public and 3 private dental clinics treated the children. The clinics were invited to join the study, and all accepted. Only clinics with at least 10 children from the HNAs were invited to participate. One clinic in HNA 3 had only 4 children and was not invited to participate. The distribution of children in HNA 3 and 4 differed between the clinics. Four clinics only had children from HNA 4, 16 had children from HNA 3, and 3 had a mixture of children from HNA 3 and 4. Participating clinics were stratified into two clusters and then randomly selected to receive one of the two treatment groups.

The dental clinics allocated to the test group were from the following Public Dental Service (PDS) clinics in Stockholm County (an incorporated entity: Folktandvården Stockholms Län AB): Danvikstull, Hallunda, Jakobsberg, Märsta, Rinkeby, Saltsjöbaden, Skärholmen, Södertälje, Väsby; and from District Dental [Distriktstandvården] Jordbro. The dental clinics allocated to the reference group were from the following PDS clinics in Stockholm County (Folktandvården Stockholms Län AB): Farsta, Hallonbergen, Handen, Högdalen, Kista, Nynäshamn, Rosenlund, Sollentuna, Tensta, Tumba, Vällingby; and from the following PDS clinics in District Dental: Alby, Hallstavik.

The flowchart in Figure 2 presents the number of children eligible for examination each year.

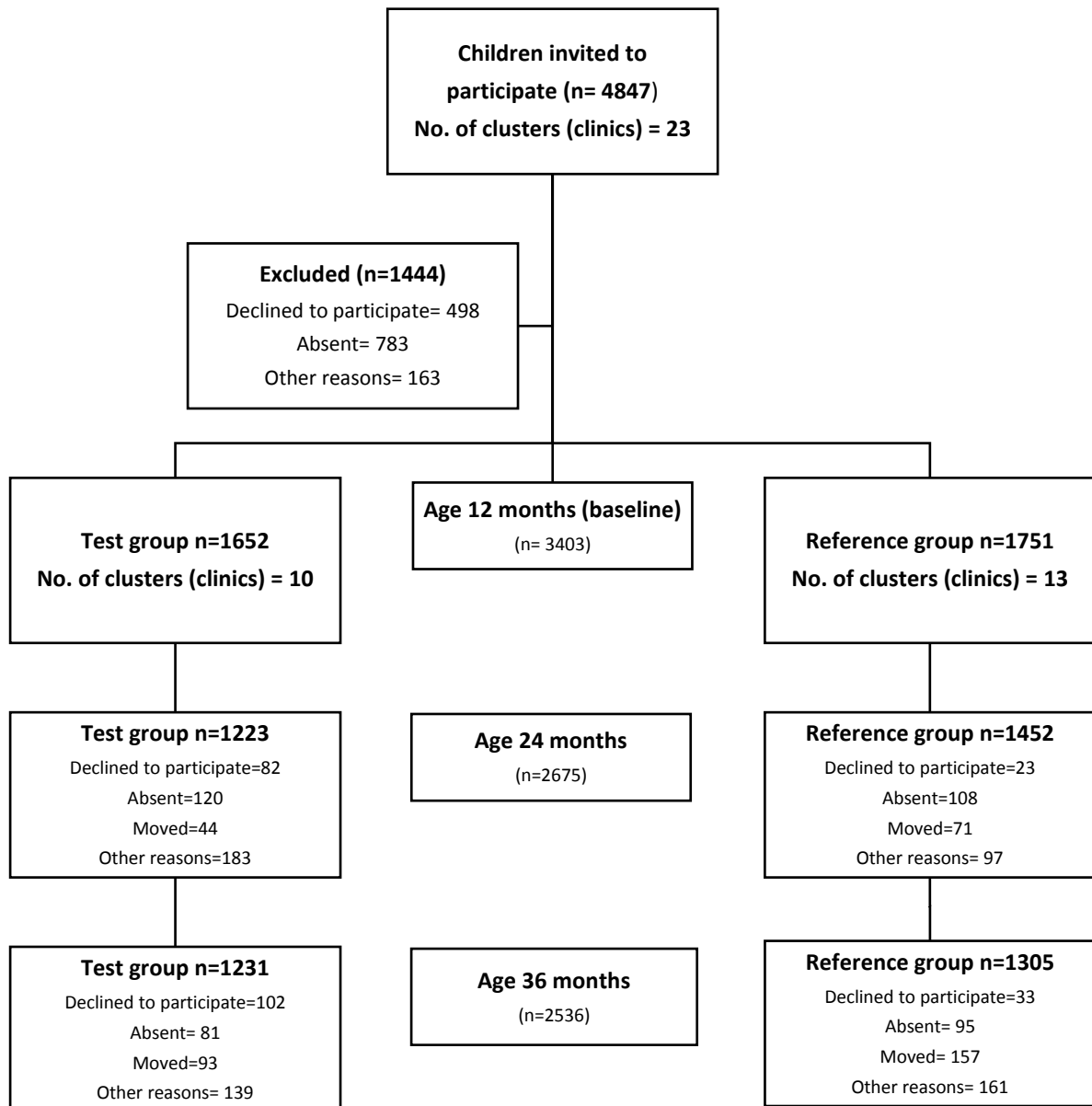


Figure 2. Flowchart of randomized children and reasons for dropping out. No clusters (clinics) dropped out.

Study II

The study population comprised the children in Study I who had developed dental caries (ICDAS 1–6) in any of the yearly examinations at ages 12, 24, and 36 months (n=801).

Study III

To avoid disrupting the ongoing RCT, we chose a convenience sample of 507 children (test group: 263; reference group: 244) from 7 of the participating PDS clinics for Study III. Besides the clinical examination at 36 months, bacterial sampling was done in these children.

Study IV

In Study IV, we retrieved data from the dental records of children in 6 of the PDS clinics participating in Study I. The clinics were consecutively selected as they finished the 36-month examination, thus all records for the participating toddlers in both intervention groups at each of the 6 clinics were analyzed ($n = 1346$).

Information, agreement, and ethical permission

Studies I and II

Before the examination, the dental clinics sent an information letter about the project to the parents of the selected children. During the first clinic visit, dental staff informed the parents verbally about the project; the study authors encouraged clinicians to use an interpreter when necessary. During the visit, parents could request a copy of the translation of the information letter in 1 of 10 languages. Parents signed informed-consent forms before the examination and understood that they could withdraw from the study at any time with no consequences for their children's oral health care. The Regional Ethics Committee in Stockholm approved the study (daybook no. [Dnr] 2010/1956).

Study III

Parents received a letter and verbal information about the bacterial sampling. All parents of participating children signed informed-consent forms for Study III participation. The Regional Ethics Committee in Stockholm approved the study (daybook no. [Dnr] 2013/143-32).

Study IV

The Regional Ethics Committee in Stockholm approved a supplementary ethics application (daybook no. [Dnr] 2016/1240-32).

Methods

Project management (Study I)

A steering group was created at the start of the study. This group included members from Stockholm County Council, management representatives from participating PDS clinics, representatives from academia, and members of the project group. The group was tasked to monitor the progress of the project as well as function as a sounding board for issues that emerged in the course of the study. A project group was responsible for managing and conducting the study. At each clinic, a dentist, a dental hygienist, and a dental nurse were chosen to form the clinic's study team. The steering group launched a website (www.stopcariesstockholm.se) to disseminate information about the project to the parents,

media, and other interested parties. The author of this thesis was a member of the steering group, the project group, and headed and educated the clinic study teams.

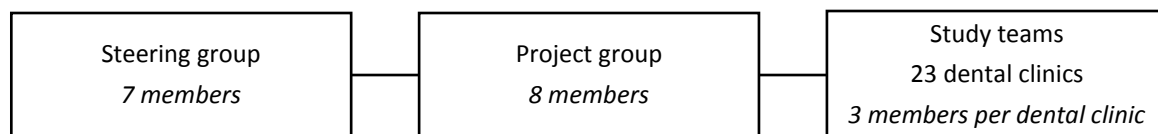


Figure 3. Management structure of the RCT.

Before the start of the study, all study teams attended lectures on the background of the project and on how to implement the clinical and administrative routines into their practice. Communication between the study teams and the project group was via e-mail, telephone, and an intranet-based network accessible to all PDS clinics that was open for questions and discussion concerning different project topics. Members of the project group visited the dental clinics when necessary. At least once a year, the project group called meetings with the clinics to discuss progress.

Education and calibration in ICDAS II (Study I)

All dental personnel assigned to examine the children attended a course in ICDAS, which included a 90-minute e-learning program developed by ICDAS group members (Topping, Hally, & Bonner, 2008). All study team personnel also attended a half-day course that included a lecture, a small group exercise, and a calibration exercise using an audio response system (mentometer). Upon course completion, all examiners (24 dental hygienists and 25 dentists) took a test comprising 25 images, each an image of a single tooth with a caries-affected surface, to be scored according to ICDAS. Reliability was calculated for each examiner using a criterion standard determined by two skilled examiners (one was the author of this thesis). To determine inter- and intra-rater reliability, one skilled examiner (the author of the thesis) and one newly trained examiner examined 20 children, 3–5 years of age, twice at a 2-week interval; intra- and inter-reliability were calculated for each study team member.

Intervention (Studies I–IV)

The RCT comprised two treatment groups: a reference group (RG) and a test group (TG). All participating children received a standard caries-preventive program for oral health that included hands-on tooth brushing instructions to the parents with feedback from the dental team, information about the importance of brushing the child's teeth twice daily with fluoride toothpaste, and dietary counselling focusing on drinking water as a healthy alternative to other thirst-quenchers and reducing the frequency of between-meal snacking. Upon completion of the intervention, the parents received a toothbrush and a tube of toothpaste (1,000–1,450 ppm

fluoride) free of charge. The PDS introduced this program in 2004 (Folk tandvården Stockholms län AB, 2004).

The RG received the standard caries-preventive program at their 12-, 24-, and 36-month visits. The TG, in addition to the standard program, received supplemental measures comprising topical applications of fluoride varnish (Duraphat®, 22.6 mg of fluoride/ml) on the buccal surfaces of their primary teeth at ages 12, 18, 24, 30, and 36 months (Appendix 1).

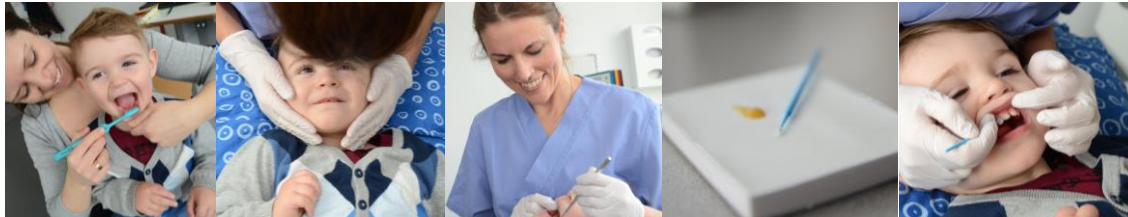


Figure 4. Illustration of a dental setting in the test group for carrying out a standard oral health program, examination, and application of fluoride.

Examination (Study I)

The project group sent all participating dental clinics lists of which children were to receive the intervention. Each clinic was assigned a project code number from 1 to 23. The children were also given unique code numbers that included the code number of the dental clinic where they were enrolled. This code was then used to track study data of the child; data were recorded on a specially designed form. At the examination, ICDAS II was used to score dental caries (Figure 5). The examiners also recorded whether a tooth was unerupted, had been extracted due to dental caries, was missing for other reasons, or had been filled. Examinations followed ICDAS II guidelines, but with some modification for age and ability to cooperate. At the end of each visit, the examiner rated the child's degree of acceptance of the schedule as positive, reluctant, negative, or impossible to examine (Holst, Hallonsten, Schröder, Ek, & Edlund, 1993).

At the dental visit, the examiners also registered whether the children showed any clinical sign of gingivitis and their gender.





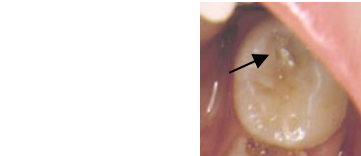


CODE	PICTURES		CRITERIA
0			Sound tooth surface
1			First visual change in enamel (seen after prolonged air drying)
2			Distinct visual change in enamel
3			Localized enamel breakdown due to caries with no visible dentin
4			Underlying dark shadow from dentin
5			Distinct cavity with visible dentin
6			Extensive distinct cavity with visible dentin

Figure 5. Illustration of an abridged ICDAS II manual, showing codes, pictures, and descriptions that the examiners could refer to during caries determination.

Questionnaire (Study I)

At the dental visit, the examiner interviewed the parent, completing a survey questionnaire comprising seven questions. The same survey questionnaire was used in interviews at the 12-, 24-, and 36-month examinations (Appendix 2).

Stratification and randomization (Study I)

The study was cluster randomized and the children were allocated to one of the two treatment groups before study start. Stratification was done by merging all clinics into one of two groups where the number of children in each group was as equal as possible; an administrator not involved in the RCT stratified the clinics. In the stratification process, a matching at the clinic level concerning whether the children at the clinic belonged to HNA 3, HNA 4, or both was done; in addition, efforts were also made to achieve an equal distribution concerning the geographical location of the dental clinics to the northern or the southern sections of Stockholm. Randomization was done by drawing lots to determine which group would be the test group and which the reference group (Figure 6).

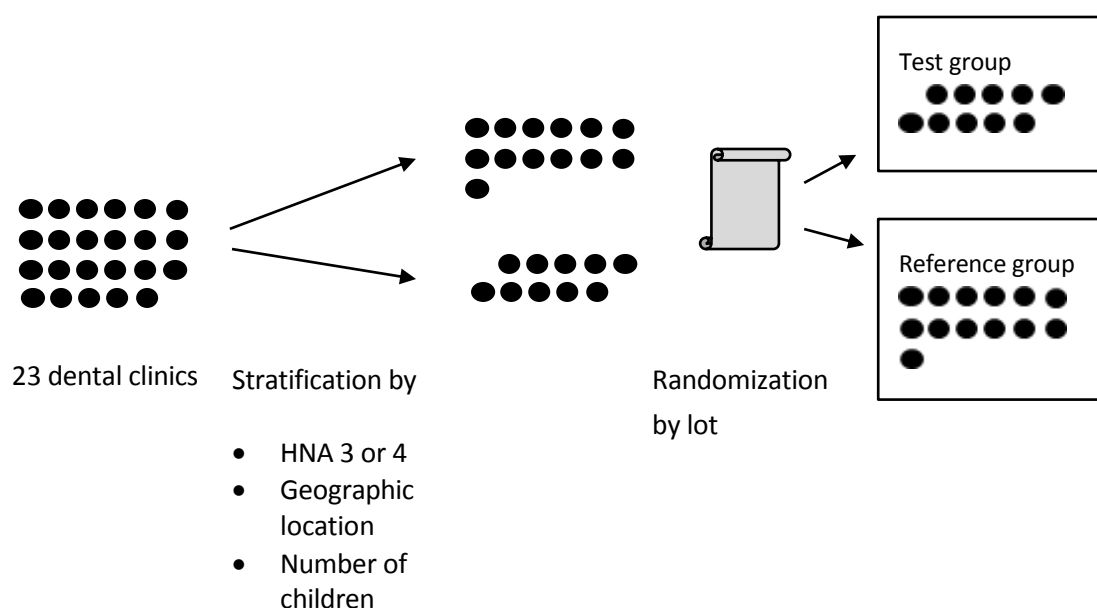


Figure 6. Illustration of the stratification and randomization procedure in the SCS trial.

Data (Study I)

The results of the examinations registered in in the specially designed form (Appendix 2) and the questionnaires (Appendix 3) were sent for scanning to a researcher not involved in the study in any other way. The scanned data were then imported into Excel and SPSS.

Bacterial collection and analysis (Study III)

Bacterial sampling

Before sampling began, participating clinics were trained in bacterial sampling procedures, which included a slideshow (PowerPoint®).. The dental personnel collected samples during the examination at age 36 months , using one sterile swab per child (Sarstedt®), which was carefully rotated on the inside of the cheeks and lips, and on the teeth and tongue of the child (Figure 7). The swab was then put into a tube that was marked with the code for the child and the date of the sampling, sent by mail, marked with the date of storing, frozen, and stored at -20°C for 3–15 months in a biobank, until further processing.



Figure 7. Bacterial sampling with a sterile swab.

Checkerboard DNA-DNA hybridization

The Department of Oral Microbiology and Immunology, University of Gothenburg, Gothenburg, Sweden, analyzed the samples using checkerboard DNA–DNA hybridization according to the recommendations of Wall-Manning for analysis of cariogenic bacteria (Wall-Manning, Sissons, Anderson, & Lee, 2002). A short description of the technique follows.

The first step was to prepare whole genomic probes for the 12 bacterial strains to be analyzed in the saliva samples. These species were precultivated to provide a source of purified DNA for use in probe preparation. After the DNA was extracted from the bacteria, the quality of the DNA was evaluated. Each DNA probe was then labelled with a digoxynigenin (DIG) marker. Subsequently, the DNA was quantified and probes for each species prepared. The next step

involved preparation of the stored bacterial samples, which included releasing DNA from the samples. Mixed standards equivalent to 10^5 and 10^6 cells were prepared from cultured cells of each of the 12 bacterial species in the panel. Samples and standards were then applied to a positively charged nylon membrane using a Minislot device (Immunetics, Cambridge, MA, USA) (Figure 8) in horizontal lanes. Using a Miniblotter device (Immunetics) (Figure 8), the DIG-marked DNA probes were then added to the membrane at one end and absorbed by capillary action to orthogonal strains opposite the lanes of the saliva samples. The DNA was fixed using a UV crosslinker. At this point, only single-stranded DNA resided on the membrane. The membranes were then enclosed in plastic bags hybridization buffer and the probes were left to hybridize in a 37°C water bath overnight, allowing homologous DNA strands from the saliva sample and the probes to anneal.

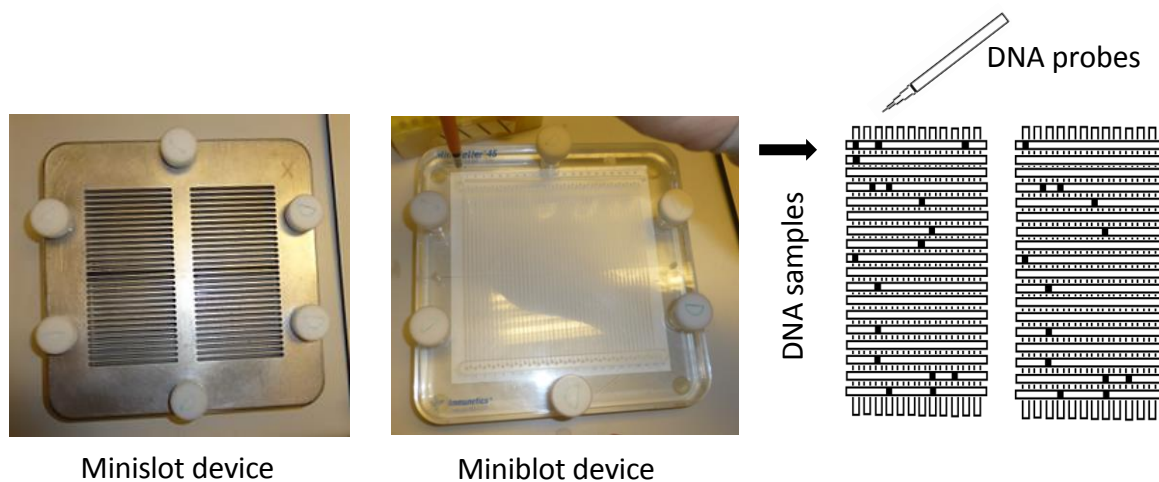


Figure 8. Checkerboard DNA-DNA technique used to detect bacterial species in saliva samples. A Minislot device (Immunetics) was used to transfer the salivary samples to a nylon membrane in horizontal parallel lanes. The membrane was then moved to a Miniblot device (Immunetics) where the DNA probes for each bacteria to be analyzed was added to the membrane in separate, vertical slots. Through capillary action, the probes were absorbed into orthogonal strains opposite the lanes containing the saliva samples. In this way, all samples were exposed to each probe. If any single-stranded DNA was present in the sample and homologous with the single-stranded DNA in the probe, hybridization occurred. The DNA probe was marked with an antibody, and if any hybrids were formed, they were detected with an enzyme targeting the antibody. By adding the substrate of the enzymes, hybrids are visualized.

On the following day, excess DNA probe was washed from the membrane in several washing cycles. A phosphatase-conjugated DIG antibody to the DIG marker on the probe was added and allowed to react with the DIG, and the bound enzyme activated an applied chemiluminescent substrate (CDP-Star®, Roche Diagnostics). The chemiluminescent signal intensities were assessed in biomedical light units (BLU) in a LumiImager Workstation (Boehringer Mannheim) which digitalizes a photo of the membranes and the BLU signals so

that they can be visualized on a computer screen. The intensity of each hybridization signal is converted to an equivalent number of cells by comparison with the DNA standards. Figure 9 shows the black signals on the screen from a digitalized photo using the LumiImager Workstation. The detection level was $>10^4$ cells per ml sample (Dahlén, Preus, & Baelum, 2015).

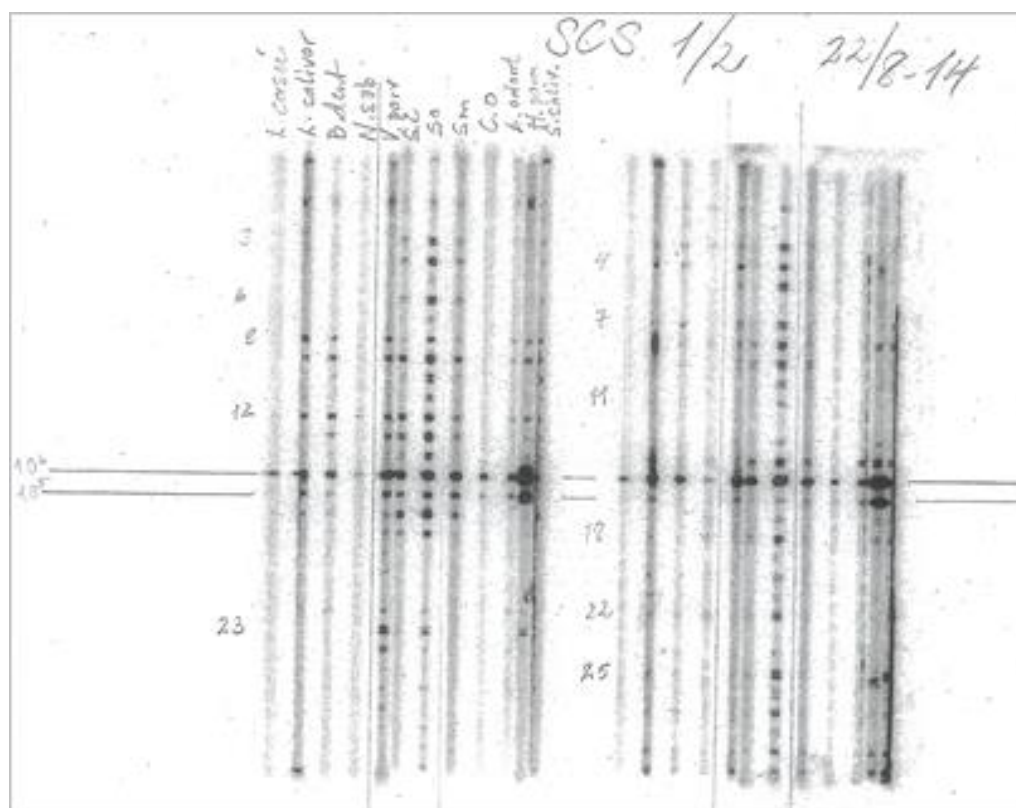


Figure 9. Chemiluminescent signals generated during analysis of each patient sample. The signals were visually analyzed on a computer screen. The vertical lanes show the reactions to the DNA probes in this order: *Lactobacillus casei* OMGS 3184; *Lactobacillus salivarius* OMGS 3830; *Bifidobacterium dentium* OMGS G174; *Neisseria subflava* CCUG 23930; *Veillonella parvula* OMGS G186; *Streptococcus intermedius* CCUG 17827; *Streptococcus oralis* OMGS 2470; *Streptococcus mutans* OMGS 2482; *Capnocytophaga ochracea* OMGS 1233; *Actinomyces odontolyticus* OMGS G67; *Haemophilus parainfluenzae* CCUG 12836 and *Streptococcus salivarius* OMGS 2473. In the middle, the results for the reference samples are seen including 10^6 (high standard) and 10^5 (low standard) cells per ml sample.

Costing (Study IV)

Societal and health-care perspectives were both considered in cost estimations. The direct costs that mirror the cost of dental care were extracted from clinical trial data. All indirect costs, however, had to be estimated.

Direct-cost analysis comprised two parts. The first part analyzed intervention costs and included costs for the fluoride varnish; for the toothpaste and toothbrush each child received at

the intervention; for the invitation postage; for the time of the dental staff at each intervention; and for overhead. Estimations of staff costs were based on the median salary for dental personnel in the Stockholm County PDS and included social taxes and fees. Overhead costs were calculated using the method described in the Swedish Dental Care Reform of 2008 (Government Offices of Sweden, 2008).

The second part analyzed different cost variables using the dental records of a subgroup of the clinical trial participants. Data included visits related to caries development but not the SCS intervention programs. Data collection included all time between the 12-month and the 36-month examinations. The dental records were reviewed systematically and predetermined variables were recorded on a reply form (Appendix 4). The monetary value of the visits was calculated using the 2011 Stockholm County PDS price lists for pediatric dental care: one for general dental care and one for specialist dental care. If a child missed an appointment, the cost was assigned a predetermined standard value not covering the true cost of the dental personnel as they were assumed to use the time for other activities connected to their work.

Indirect costs were calculated using estimates of the parental costs: time off from work to accompany the child, including waiting time, intervention time, and travel time. Waiting time data reported in a health economic study from the Netherlands (Vermaire, van Loveren, Poorterman, & Hoogstraten, 2011) were used as no Swedish data were found. Intervention times were calculated from trial data, excluding the dental staff time used for administrative routines. An earlier Swedish study (including dental clinics around the country) had calculated a median round-trip travel time to the dental office of 30 minutes, which we found reasonable, also for Stockholm (Oscarson, Källestål, Fjelddahl, & Lindholm, 2003). Evaluating the true time costs of the accompanying parents is always difficult. Some parents may have been on parental leave, had a part-time job, scheduled the dental visit for after-work hours, or been without work, while others had full-time work. Unpaid work was used as a proxy for the costs of the accompanying parent, and we valued this similar to Vermaire and coworkers (2014).

All costs were discounted by 3% annually from the second year of the intervention period, according to Swedish government guidelines (The Dental and Pharmaceutical Benefit Agency, 2017)

Costs due to project management were not included in the costing analysis. All costs were calculated separately for the test and the reference groups, and an average cost per child for dental treatment during the intervention time was calculated.

Intervention program costs were calculated in Swedish Crowns (SEK). Euro (EUR) was determined using the 19 May 2017 exchange rate: SEK 1 = EUR 0.10 (Sveriges Riksbank,

2017). All costs were adjusted to 2011 year price levels and discounted by 3% annually from the second year of the intervention period, as recommended by official Swedish government guidelines (The Dental and Pharmaceutical Benefit Agency, 2017).

In the cost-effectiveness analysis, number of prevented defs was used as a measure of effectiveness. An ICER was calculated from both the societal and the health-care perspective. A sensitivity analysis was then done to test how various scenarios would influence the ICERs.

Statistical analyses

All data were processed with IBM SPSS software (version 22.0, Chicago, IL, USA). The descriptive analyses of the variables included calculations of measures of central tendency (mean) and dispersion (standard deviation). The descriptive analysis of variables measured on nominal or ordinal scales was the frequency distribution. We considered a *p*-value less than 0.05 to be statistically significant.

Study I

Sample size

Sample size was determined from information obtained from PDS sources on caries prevalence in various areas of Stockholm County (Stockholm County Council, 2010). Sample size was based on detecting a 4% reduction in caries prevalence at the age of 3 from 11% to 7%. The relatively low prevalence of caries in the study group and the cluster design contributed to the need for quite a large sample. A power analysis conducted before study start calculated that a minimum of 1,264 children for the TG and the RG – a sample of 2,528 children – had to be recruited to the study in order to identify the expected reduction with 80% power and a significance level of 5%. In addition to this, however, we estimated an informed-consent return level of 75% and an annual drop-out fraction of 10% a year, which increased the needed sample size.

Calibration of examiners

Cohen's kappa was used to estimate inter- and intra-examiner reliability.

Comparison of outcome variables

Between-group comparisons of the test and reference groups according to outcome variables were done: for dichotomous variables, multiple logistic regression analyses and for numerical variables, multiple linear regression analyses. The observations comprised a two-level hierarchical data structure, and the clusters (clinics) were included in all regression analyses as

covariates to compensate for dependency within clusters (calculated intraclass correlation coefficient, $\rho = 0.023$).

Study II

ICDAS score 3 was used as a threshold for cavitation (Braga et al., 2009). Cross-referenced tables show caries progression. The chi-square test assessed between-group differences in caries progression.

Study III

Sample size

The prevalence of *S. mutans* was used as a criterion standard in the power calculations. Systematic reviews have shown that *S. mutans* is a strong biomarker for caries development in young children (Parisotto, Steiner-Oliveira, Silva, Rodrigues, & Nobre-dos-Santos, 2010; Thenisch, Bachmann, Imfeld, Leisebach Minder, & Steurer, 2006). Further, we made an assumption that a 50% difference in prevalence of high counts ($\geq 10^5$ cells) would be relevant for the clinician. Based on this, we calculated that we would need about 170 participants in each group to reach 80% power with a significance level at 5%.

Comparison of outcome variables

Chi-square tests calculated between-group differences in the percentage distribution of bacterial growth.

Study IV

We used effect data from the clinical trial in Study I and ICDAS score 3 as a threshold for cavitation (Braga et al., 2009) in the deft index in the ICER calculations. Health economic data were processed using Microsoft Excel 2013 and IBM SPSS software (version 22.0, Chicago, IL USA).

RESULTS

Participants (Study I)

Characteristics and prevalence of dental caries at baseline

Study participants were recruited between 1 March 2011 and 31 March 2012. In HNAs 3 and 4 were 4,847 eligible 1-year-old children; of these, 498 declined to participate, 783 missed their appointment, and 163 children were excluded for other reasons. Thus, the total study population comprised 3,403 children (Figure 1). Boys and girls were evenly distributed. Baseline participant characteristics were collected using a structured survey questionnaire. No

significant between-group differences in baseline variables occurred (Table 1). We compared baseline caries data in the test and reference groups and found more caries (ICDAS 1–6) in the RG; when clustering was taken into account in the analyses, there was no significant differences. At 12 months, 0.6% of the children had developed caries (ICDAS 3–6).

Table 1. Baseline characteristics of the test and reference groups, at age 12 months (n=3403).

Variable	Test group (n = 1,652) (%)	Reference group (n = 1,751) (%)
Girls/boys	53/47	50/50
Home language other than Swedish	81	76
Gingivitis	5	4
Mothers' education (< 9 years)	23	20
Family income (< SEK ¹ 20,000/month)	40	37
Tooth brushing (≥ 1 /day)	53	57
Sweet drinks (> 2/day)	11	11
Candy (> 1/week)	10	8

¹ Swedish crowns

Examiners (Study I)

Calibration of examiners

Examiner reliability of the clinic examiners, as determined against a standard decided by two skilled examiners and using 25 images of single teeth to be scored was good: For ICDAS scores 0–6, mean kappa among the examiners was 0.66 (range 0.38–1.0). When an ICDAS score 3 was used as a cutoff, mean kappa was 0.85 (range 0.48–1.0).

To further evaluate reliability, we clinically examined 20 children (3–5-year-olds) and recorded dental caries according to ICDAS. One skilled and one newly trained examiner made separate examinations of the children. The same two examiners re-examined the children 2 weeks later. Intra-examiner reliability was $\kappa = 0.62$ and $\kappa = 0.49$, and inter-examiner agreement was $\kappa = 0.42$ (first examination) and $\kappa = 0.60$ (second examination). When we used an ICDAS score of 3 as a cutoff, intra-examiner reliability was $\kappa = 0.72$ and $\kappa = 0.73$, and inter-examiner reliability was $\kappa = 0.61$ (first examination) and $\kappa = 0.73$ (second examination).

Prevalence of dental caries (Study I)

Prevalence of dental caries increased in both intervention groups between ages 12 and 36 months. At 12 months, most children were caries free. With an ICDAS score 3 as a cutoff for dental caries, less than 1% were affected. Initial stage decay (ICDAS 1–2) was more common at 12 and 24 months but at 36 months, the largest share of caries was moderate to extensive decay (ICDAS 3–6). At 24 months, 4% of the children had developed caries (ICDAS 3–6) and at 36 months, 12%. Adding in initial stage decay at 36 months, 23% of the children in total had developed dental caries (ICDAS 1–6, Figure 10).

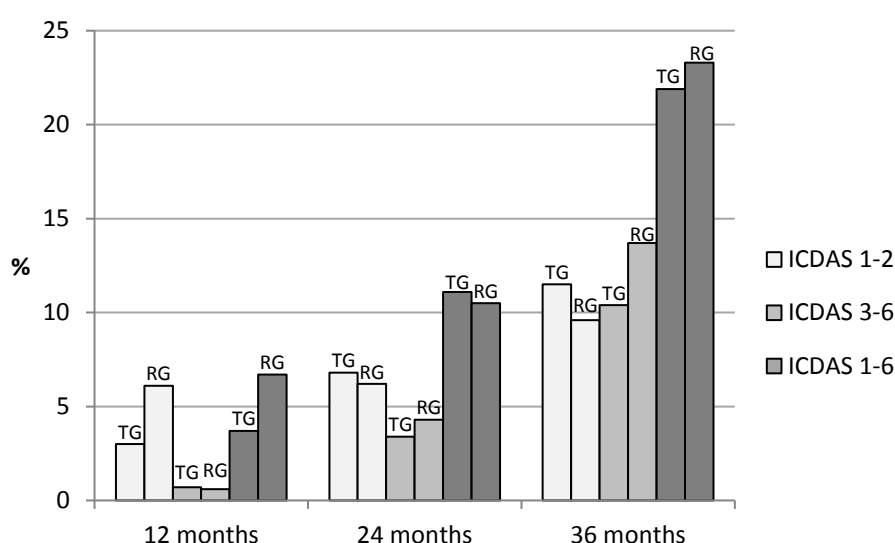


Figure 10. Graph showing the proportion of children with dental caries at ages 12, 24, and 36 months, grouped as initial stage decay (ICDAS 1–2), moderate-to-extensive decay (ICDAS 3–6), and the sum of both (ICDAS 1–6). Prevalences for the test group (TG) and the reference group (RG) are shown separately (12 months: n=3,403; 24 months: n=2,675; and 36 months, n=2,536).

Effectiveness of intervention (Study I)

No significant between-group differences in the prevalence of dental caries occurred at any ICDAS scoring level at ages 24 or 36 months. We also compared the increment of dental caries and found no significant difference between the intervention groups. This means that applications of fluoride varnish twice yearly between 12 and 36 months of age, together with one extra visit for the standard intervention, were unable to decrease caries development.

Tooth brushing habits (Study I)

At 12 months, 53% of the children in the TG and 57% in the RG had their teeth brushed at least once a day with fluoridated toothpaste. This figure increased as the children grew older. At 36 months, 90% of the children in the TG and 92% of the children in the RG brushed their teeth

daily, with no significant difference between the two intervention groups. Further, we found that 35% of the children had their teeth brushed twice a day at 12 months, 58% at 24 months, and 67% at 36 months (unreported results).

Compliance and harm (Study I)

No serious adverse events following varnish application were reported, although a few children vomited directly after the procedure due to the smell, texture, or taste of the fluoride varnish. Compliance was good. At 36 months of age, 75% of the children showed a positive acceptance of the program with no significant difference between the TG and the RG.

Caries distribution and progression on the surface level (Study II)

Sample caries prevalence and distribution

In the study sample, 3% of the children had developed cavitation (ICDAS 3–6) at 12 months, 16% at 24 months, and 42% at 36 months. Overall, caries development followed the eruption pattern of the primary teeth with the exception of the mandibular primary incisors, which were almost totally unaffected by caries. The maxillary primary incisors were the teeth that first and most frequently throughout the study developed cavitation (ICDAS 3–6) and especially the buccal surfaces. As Figure 11 shows, cavitation (ICDAS 3–6) of primary molar occlusal surfaces appeared from 24 months.

Caries progression on the buccal maxillary incisors

We studied caries progression on the buccal maxillary incisors in cross-reference tables showing the change in ICDAS score for each tooth surface between the 12–24-month and the 24–36-month examinations.

Least progression occurred on initially healthy surfaces where only about one-fifth showed any signs of progression. Caries progression on healthy surfaces and surfaces with initial stage decay (ICDAS 1–2) more commonly remained within the initial decay score interval (ICDAS 1–2). Moderate decay lesions (ICDAS 3–4), more so than healthy surfaces or initial stage lesions (ICDAS 1–2), progressed to extensive lesions (ICDAS 5–6). This occurred in both the 12–24-month and the 24–36-month intervals. The more severely decayed a surface was at 24 months, the more likely the tooth would be extracted at 36 months. Of surfaces with a score of ICDAS 6 at 36 months, 21% were extracted at 36 months.

To determine the proportion of buccal surfaces on the upper maxillary incisors that progressed to a more severe stage (ICDAS 0–6) from between the 12–24-month to the 24–36-month periods, we calculated a summarizing progression index (PI) (Figure 12). No significant difference between the two time periods occurred ($p=0.95$).

	12 months	24 months	36 months
Buccal maxillary incisors	1.5%	6.4%	9.3%
Occlusal first primary molars	0%	1.7%	7.5%
Occlusal second primary molars	-	0.9%	5.3%

Figure 11. Distribution and average prevalence of cavitated lesions (ICDAS 3–6) on the surface level at 12, 24, and 36 months. Only the most commonly affected surfaces are shown.

Impact of intervention on caries progression

To evaluate the effect of the intervention, we calculated a PI for the buccal surfaces of the maxillary incisors in each intervention group. The only significant difference occurred during the 12–24-month interval, when the 12–24-month PI was 29% in the TG and 23% in the RG; in the 24–36-month interval, both groups had a PI of 21%.

Appendix 5 presents unpublished data on caries progression on the buccal surfaces of the maxillary incisors. It shows the proportional change for each ICDAS score, 0–6, between the 12- and 24-month examinations and the 24- and 36-month examinations for the test and reference groups. As the two graphs show, progression differed between the test and the reference groups, and regression from a higher to a lower ICDAS score also occurred.

No comparison of caries progression on the occlusal surfaces of the first primary molars between the two intervention groups was made between 12 and 24 months as only a few of these surfaces were decayed. With ICDAS 3 as a threshold for cavitation, 6.0% of the surfaces in the TG and 7.3% of the surfaces in the RG became cavitated between 24 and 36 months. Progression was lower in the TG, but the difference was not significant ($p=0.17$).



Figure 12. Progression index (PI) of caries on the buccal surfaces of the upper maxillary incisors between 12 and 24 months (m) and between 24 and 36 m.

Oral microflora (Study III)

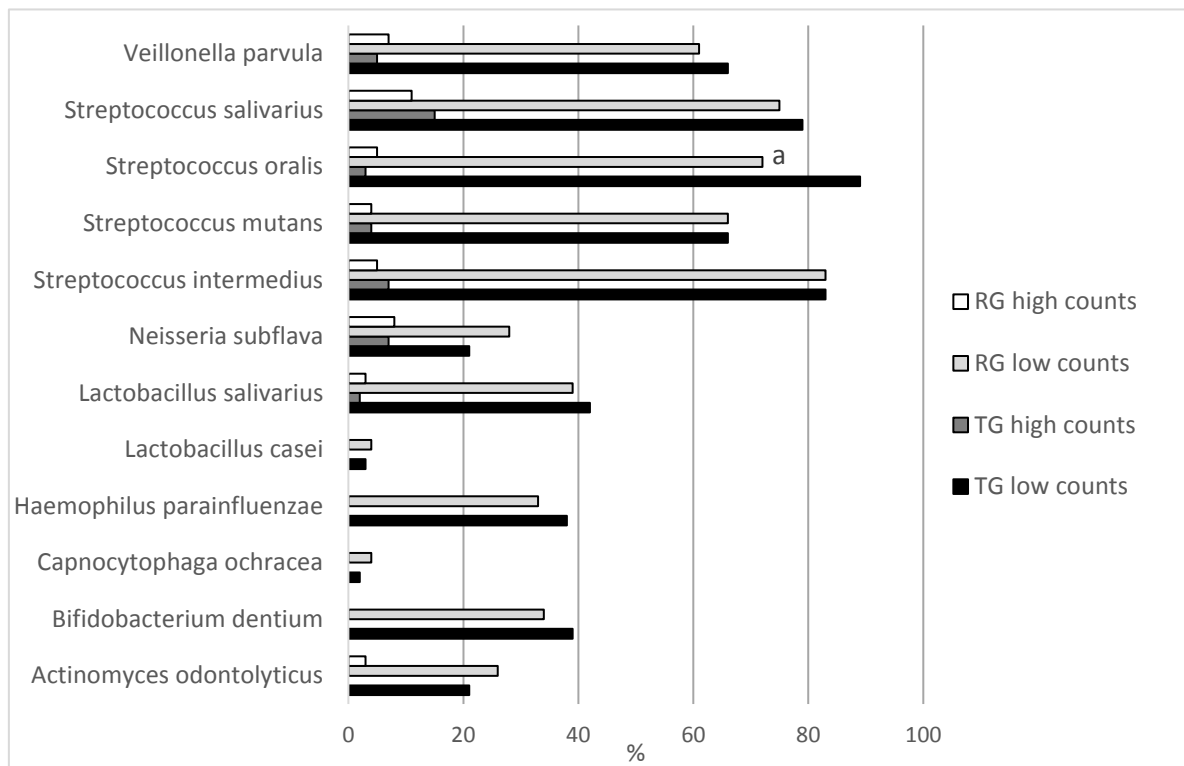
Effect of intervention

In this study sample, background data for the test and reference groups diverged somewhat. In the TG, significantly larger proportions of the toddlers spoke a language other than Swedish at home, had at least one smoking parent, and had more dental caries (ICDAS 1–6, ICDAS 3–6) than in the RG ($p<0.05$).

We compared the TG and the RG concerning presence of the predefined bacteria species. As Figure 13 shows, gram positive streptococci were the most prevalent species in both interventions groups. We found no difference concerning *S. intermedius*, *S. salivarius*, and *S. mutans*, but *S. oralis* seemed to occur less frequently in the RG ($p<0.05$). *V. parvula*, *L. salivarius*, *B. dentium*, and *H. parainfluenzae* were commonly found in low counts. *S. salivarius* and *N. subflava* were most commonly found in high counts.

Oral microflora in relation to caries prevalence

We also compared the results of the microbial analyses with the prevalence of dental caries among the children. In the study group ($n=500$), 23.4% showed dental caries (ICDAS 1–6). Children with dental caries (ICDAS 1–6) more frequently had *V. parvula* and children that were caries free (ICDAS 0), *B. dentium*, *L. casei*, *L. salivarius*, and *N. subflava* ($p<0.05$). We found no significant differences in *A. odontolyticus* or any of the streptococci strains.



^aSignificantly lower than the TG ($p < 0.05$; chi-square test).

Figure 13. Graph showing the prevalence of low counts ($\geq 10^4$ cells) and high counts ($> 10^5$ cells) of selected oral bacteria in the test group (TG) ($n=263$) and the reference group (RG) ($n=237$).

Health economic evaluation

Treatment effect

We calculated the mean increment of defs between the two intervention groups from baseline at 12 months to the follow-up at 36 months. The increment value was 0.09 lower in the TG. Discounting second-year effects by 3% did not change the value, and we used 0.09 as the base case effective measure in the cost-effectiveness calculation.

Costs

Table 2 presents a summary of the costs. Average supplemental intervention costs per child were EUR 29.16 higher. The retrieved information from the dental records increased costs during the intervention period and costs from a dental health care perspective; total per-child costs in the supplemental intervention group were EUR 97.08 and in the standard intervention group, EUR 71.22. According to the costs retrieved from the dental records, costs for standard intervention were slightly higher as costs for non-intervention visits and treatment at a specialist clinic for pediatric dentistry were included. Adding the indirect costs to the dental health care

perspective costs, per-child costs from a societal perspective were EUR 41.79 higher for the expanded intervention program.

Table 2. Average dental costs per child in the two intervention groups, ages 12 to 36 months.

Costs	Expanded intervention (EUR)	Standard intervention (EUR)	Difference
Intervention	80.92	51.77	29.16
Additional costs (dental records)	15.15	19.46	-4.30
Dental health care perspective	96.08	71.22	24.86
Indirect costs	43.50	26.57	16.93
Societal perspective	139.58	97.79	41.79

Cost effectiveness

We calculated an ICER and found that the supplemental intervention program added EUR 276.22 from a dental health care system perspective and EUR 464.33 from a societal perspective. A sensitivity analysis using a discount rate of 0% instead of 3% (as used in the calculations of the costs) increased the ICER by EUR 4.78, while a discount rate of 5% lowered the ICER by EUR 3.11. The standard program dominated when no effect was assumed or when a worst-case scenario was tested. A best-case scenario considering the effect lowered the ICER by EUR 193.35 from a dental health care perspective. If no travel time was assumed, the ICER decreased program costs by EUR 117.44 from a societal perspective.

The economic evaluation of the expanded caries-prevention program, compared to the standard program already in place, showed that the expanded program was not cost effective, was not more effective in preventing caries, and in addition, was more costly.

GENERAL DISCUSSION

The four papers in this thesis analyze various aspects of a prospective, cluster-randomized controlled field trial – the Stop Caries Stockholm (SCS) trial – that evaluated the effectiveness of an expanded caries-preventive program designed to improve the oral health of 1–3-year-olds living in multicultural areas of Stockholm, Sweden, with a low-socioeconomic status. Study I showed that the expanded program failed to reduce the prevalence or the increment of dental caries. Study II exposed the inability of the expanded program to reduce the progression of dental caries on the surface level. Study III revealed that applications of highly concentrated fluoride varnish twice a year had no effect on the composition of the oral microflora in the children. The cost analysis in Study IV, the last study, found that the expanded program was more costly than the standard intervention already in place, and since oral health was not substantially improved, could not be considered cost effective.

Caries prevalence (Study I)

The timing of this longitudinal SCS trial, from the period of eruption of the first primary teeth at age 1 year to age 3, is a strength; this type of early information is not commonly reported. We found existing dental caries at baseline, when the cohort was only 1 year old. Initial stage lesions (ICDAS 1–2) dominated the picture, and only a few children had developed cavitation (ICDAS 3–6). Study I found a 0.6% prevalence of dental caries (ICDAS 3–6). This is in line with the Wendt et al. study, an older Swedish study that reported a caries prevalence of 0.5%; in our trial, 78% of the children had an immigrant background, while the cohort in the Wendt et al. study, 19% had an immigrant background (1991).

Compared to a study on African-American children (n=96) in the state of Alabama, USA, Study I found a considerably lower presence of cavitation. Among 1-year-olds, the Alabama study reported a 1.1% prevalence of cavitated surfaces (d) (six children with no erupted teeth excluded). An international oral health promotion program reported even higher dft prevalences in 1–2-year-old children: 14% in Greece and 9% in Morocco (Bourgeois & Llodra, 2014).

Study I observed how dental caries continued to develop, both in severity as well as in number of children and number of teeth and surfaces per child. At the 1-year examination when the children were 24 months old, initial dental caries affected more children, 9.4% compared with 4.6% at baseline, while 3.9% percent of the children had developed dental caries (ICDAS 3–6), compared with the 0.6% at baseline. This is lower than the 6.4% that Grindefjord and co-

workers reported in 1993 for 2.5-year-olds living in the southern suburbs of Stockholm (Grindefjord et al., 1993). In that study, 56% of the children had an immigrant background.

Our caries data for the 3-year-olds are interesting to compare with other Swedish studies and national data. At the 2-year examination when the toddlers were 3 years old, the proportion with dental caries (ICDAS 3–6) exceeded the number with initial stage decay (ICDAS 1–2) for the first time. Compared with the Grindefjord et al. (1993) study, Study I observed a prevalence of 23% (ICDAS 1–6), lower than the 37% (initial and manifest lesions) reported in that study with 3.5-year-old children.

However, the preventive strategies used in the 1980s and 1990s differ from the current standard intervention. Before 1987, fluoride toothpaste was not recommended for children under the age of 4. Instead, fluoride tablets were recommended from age 6 months. After 1991, tooth brushing with fluoride toothpaste was recommended from when the first molar erupted, when the children were around 18 months of age (Swedish National Board of Health and Welfare, 1991), which is still later than for the toddlers in our study.

If we compare the data for our 3-year-olds with the same in the Wennhall et al. study – many times referred to as the “Rosengård” trial – it is clear that those children had worse dental health than ours: 85% of the children in their test group and 63% in their reference group had developed dental caries (2005). But, preventive interventions started later than in ours. When the children were 3 years old, they had participated in an intervention for only 1 year compared with 2 years in our study.

Our trial found a defts of 0.64 in the test group and of 0.69 in the reference group at age 3 years. The Rosengård trial found a dmfs of 3.0 in the intervention group at the 3-year examination. At the 3.5-year examination in the Grindefjord et al. study (1995), the ds at 3.5 years was 1.5, which is twice what Study I found. Caries development at the age of 3 in Study I, where both the proportion of children with caries and the number of defts/dmfs were lower compared to the other two studies described above, implies that beginning regular use of fluoride toothpaste when the teeth erupt has a positive effect on caries development.

It is also of interest to compare our caries data for the 3-year-olds with the data reported by Stockholm County for the same. In Study I, 12% of the children had developed dental caries (ICDAS 3–6), which is a bit higher than what the County reported for cavitated surfaces in HNAs 3 and 4 in 2012 (9%) and 2013 (10%) (Stockholm County Council, 2013). The somewhat higher values in Study I are difficult to fully explain. Although the cohorts differ between the years and are not fully comparable, the most likely explanation is that our children

were enrolled in a clinical trial and the trial examiners used ICDAS, which yields a more precise assessment than the dmfs system that the PDS uses. Thus, the quality of the caries diagnosis is important for accurate data. In general practice, we recommend examiner calibration on a regular basis.

Effectiveness of the expanded intervention (Study I)

We found no additional effect of the expanded caries-preventive program on the development of dental caries. The study design was based in part on knowledge of the efficacy of fluoride varnish (Marinho et al., 2002; Marinho et al., 2003; Swedish Agency for Health Technology Assessment, 2002; Twetman, 2008). But there were knowledge gaps concerning effectiveness in this particular group of high-risk individuals (Petersson et al., 2004; Swedish Agency for Health Technology Assessment, 2002; Twetman, 2008). A recent meta-analysis of 10 trials suggested a prevented d(e/m)fs fraction of 0.37 (95% CI: 0.24–0.51) in the primary dentition with bi-annual use of fluoride varnish. To consider, though, is that the meta-analysis included 10 trials that were judged to have both high and low risks of bias (Marinho et al., 2013). Since this Cochrane review, several studies reporting results similar to ours have appeared.

A study similar to ours in design but done in Northern Ireland was unable to show any significant difference between test and reference groups concerning prevalence of dental caries. They did, though, find a significant difference in dmfs at the 3-year follow-up with somewhat lower values among those children who had received fluoride varnish (Tickle et al., 2016). In contrast, in a school-based prevention program targeting preschool children in Greece, where the children received supervised tooth-brushing with 1000 ppm fluoride among other measures, the children in the test group that had also received applications of fluoride varnish had no significant reduction in dmfs (Agouropoulos, Twetman, Pandis, Kavvadia, & Papagiannoulis, 2014). Further, a study on native American Indians in the United States that included high-risk children (baseline dmfs 19.9–22.8) found that a 3-year intervention program including fluoride varnish applications four times a year did not change the caries increment of the children (Braun et al., 2016).

In Study I, daily tooth brushing increased from 55% to 91%, and as fluoride toothpaste has been shown to be the most effective way of preventing dental caries (Mejàre et al., 2015), the significant increase in fluoride exposure may explain why the biannual fluoride varnish applications failed to have an effect.

A recent study on a fluoride varnish program found that when both test and control groups received oral health information, varnish had no effect on ECC prevalence (Memarpour,

Dadaein, Fakhraei, & Vossoughi, 2016). Thus, the access to oral health information that we provided both groups in Study I may explain why little to no effect of fluoride varnish occurred. At the same time, whether we gave information once or twice a year was inconsequential. Nevertheless, the results of Study I are important. They show the value of evaluating interventions in the population for which they are intended as it is risky to assume a positive result based solely on research reports.

Reporting of non-significant results

The lack of any significant effect in our study was unexpected. Dissemination of such results, however, when the study is well-designed and based on the findings of basic research, is always important. The Dickersin et al. study (2011) found that lack of significant findings to report often delays publication of a study and makes acceptance in a scientific journal more difficult, and by a high-impact journal even more difficult, compared with studies reporting significant findings.

This issue, where publication of quality research also requires significant findings in line with the hypotheses, is known as publication bias, and it has its risks. Misleading conclusions may be drawn when clinical trials are selectively reported. Relevant, unpublished data that surface at a later date sometimes alter general views created by previously reported significant results (Dickersin & Chalmers, 2011). In view of this problem, the International Committee of Medical Journal Editors (ICMJE) began to require in 2005 that unregistered trials not be considered for publication (De Angelis et al., 2005). Trial registration should include basic findings and be available to the public through the WHO International Clinical Trial Registration Platform (Gulmezoglu, Pang, Horton, & Dickersin, 2005).

Reporting bias is another issue associated with unexpected results. Studies with significant results are more likely to be over-reported and studies with non-significant results, under-reported. Publically available study protocols increase transparency (Dickersin & Chalmers, 2011). Thus, many journals today require adherence to reporting guidelines. For RCTs, these guidelines are the Consolidated Standards of Reporting Trials (CONSORT) statement which has been further developed for cluster-randomized controlled trials (Campbell, Elbourne, Altman, & group, 2004). The guidelines advocate that harm arising during a clinical trial be reported.

Harm and compliance

Trial examiners reported no serious adverse events after fluoride varnish applications; minor adverse events, however, included gastrointestinal reactions, and a few children vomited

directly after treatment. This is in line with a recent study on fluoride varnish in young children in Northern Ireland. The minor adverse reactions reported, such as gastrointestinal disorders and administration site conditions; such as redness or rash, were likely associated with the intervention itself, with no bearing on the safety of the intervention (Tickle et al., 2016, 2017).

Study I also showed that children may have experienced the dental examination and intervention as stressful; at the 2-year examination, examiners reported that one-fourth of the 3-year-old toddlers showed negative acceptance of the program. Published data report that this is common for this young age group. A Swedish study on 3-year-old children found that 76% cooperated well during dental examinations (Holst et al., 1993). This should be kept in mind when developing dental interventions.

Surface level analysis (Study II)

Study II did not find that the expanded intervention was helpful in preventing dental caries. However, because the study was longitudinal, we thought it was of interest to examine caries progression on the surfaces that had developed caries and see if the supplemental measures had any effect. This was especially interesting in view of our use of ICDAS. Study II included all toddlers who already had or developed any level of dental caries (ICDAS 1–6) during the trial.

The distribution of dental caries mimicked the eruption pattern of the primary teeth, as other studies have shown (Douglass 2001, Wendt 1991): the buccal surfaces of the maxillary incisors were affected first and exhibited the highest progression throughout the study. Analyses of the buccal maxillary incisors found that initially sound surfaces which developed caries were the least likely to undergo caries progression. The proportion of surfaces displaying progression to severe decay (ICDAS 5–6) was less for surfaces with initial decay (ICDAS 1–2) than for moderate decay (ICDAS 3–4) at baseline. Ismail and co-workers (2015) observed this same tendency.

Study II introduced the progression index (PI), an expression we coined to summarize the total proportion of surfaces that progressed in severity of cavitation between examinations. We found a trend for a higher PI between 12 and 24 months than for between 24 and 36 months, but the difference was not significant. To expect, though, is that progression on maxillary incisors slows down as toddlers age. Reasons for this include the reduced consumption of beverages in baby bottles and an increased use of fluoridated toothpaste.

One important goal of early detection of dental caries is to reduce progression and avoid cavitation of surfaces with initial states of decay. We examined whether highly concentrated

fluoride varnish applications twice a year could do this. Study II found no difference in caries progression on the buccal maxillary incisors between the test and the reference groups. Analyses of the occlusal surfaces of the primary first molars between the examinations at ages 24 and 36 months found no differences either.

In contrast, an RCT on 2–4-year-old Aboriginal children in Australia reported different results. Fluoride varnish was applied twice a year in the intervention group but not at all in the control group. Otherwise, oral health behavior was the same in both groups. The study found a 25% reduction in risk of surface level caries due to fluoride varnish. Efficacy was greatest on surfaces that were sound at baseline; in particular, the varnish had most effect on anterior maxillary facials (Divaris et al., 2013).

Microbial analyses (Study III)

Study III found no differences in the oral microflora of children who received a fluoride varnish compared with those who did not. This mirrors the main results of Studies I and II, which found no caries-preventive effect of the supplemental measures. In the planktonic stage, many bacteria are sensitive to high fluoride concentrations, but in a complex biofilm community, bacteria may be more resistant (Mannaa et al., 2014; Marquis, Clock, & Mota-Meira, 2003). Fluoride has been suggested to lower bacterial production of acids, but the clinical effects of fluoride have not been confirmed (Buzalaf et al., 2011). Too low frequency of varnish application may have contributed to the lack of effect, as well as the daily use of fluoride toothpaste in both groups by over 90% in each group. This fact may have reduced the impact of the highly concentrated fluoride varnish.

Today, dental caries is viewed as the net activity in the biofilm, independent of microorganism composition. Bacteria associated with disease might be present, but at too low level to cause any symptoms (Pitts et al., 2017). This might explain why Study III found no differences in the prevalences of *Streptococcus mutans*, *Actinomyces*, and *Veillonella* between children with and without dental caries. Other studies have shown these bacteria to be important in the development of severe ECC (Chalmers et al., 2015; Jiang, Zhang, & Chen, 2013; Tanner et al., 2011). The oral environment has a direct effect on the presence of various bacteria. And the bacteria that are present may, in turn, affect the environment of the region where they reside. Some are acidophilic and others are rapid producers of acids (Pitts et al., 2017). Thus, it was interesting to observe higher prevalence of *Lactobacillus*, *Neisseria*, and *Bifidobacterium* in the caries-free children. These bacteria could possibly be beneficial concerning caries development (Corby et al., 2005; Wade, 2013).

Health economic analyses (Study IV)

The outcomes of the economic evaluations were expected. A costly program that had little or no caries-preventive effect could not be cost effective. Today, health economic analyses have become increasingly important, with an attendant knowledge gap in the management of dental conditions and cost effectiveness (Mejàre et al., 2015). Limitations in public resources for dental health care mean resources must be used wisely. Study IV presents the increased costs that would have followed an expansion of the standard program already in place. Exploring these costs gives policy-makers valuable information.

If we compare our intervention costs (direct costs) with the Swedish Rosengård study in 2005, direct costs per child in our trial must be considered lower. The 2005 study was conducted on 2-year-old children in a multicultural area with a low socioeconomic status. Direct costs per child for 3 years of intervention were EUR 310. This cost must be considered higher than our yearly intervention costs of EUR 51.77–80.92 per child (Wennhall, Norlund, Matsson, & Twetman, 2010).

Our analysis of the incremental costs for each saved dmfs used the insignificant difference in caries increment between the test and reference groups at age 36 months. The Northern Ireland study tested a similar program for 3 years on somewhat older children than in our study. This study reported a 34% relative reduction in dmfs with a mean cost per avoided tooth surface of EUR 296.18 (exchange rate £1=€1.18) (O'Neill et al., 2017). That cost was higher than our mean cost of EUR 267.70, to consider though is that they included cumulative cost for 3 years.

The above is an attempt to compare our costs and cost-effectiveness values with those reported in other studies; however, this is difficult as calculations differ. A systematic review of 63 studies identified a need for methodological quality improvements in reporting economic evaluations of caries-preventive programs (Marino et al., 2013). To support researchers, standards for economic evaluations have been developed (Husereau et al., 2013).

Methodological considerations

The trial was a cluster-randomized, controlled field trial with two parallel arms and non-blinded.

Cluster level randomization

Randomization on a cluster level was the method chosen to reduce the risk of contamination between the two intervention groups. Before randomization, the dental clinics were stratified in order to balance the test and reference groups for confounding factors. Analysis of the

baseline characteristics that emerged in the structured interview showed that the groups were balanced considering gender, some social variables, tooth brushing habits, and intake of sweet drinks and candy. In the clinical examination, however, the RG exhibited higher values of initial stage decay (ICDAS 1–2). One dental clinic in the RG stood out from the other clinics considering number of initial stage decays that were recorded at 12 months, but this number had reversed at 24 months. We tested the results of Study I with and without the data from this clinic and found no influence in any direction concerning the effectiveness of the intervention.

Non-blinding

Lack of blinding in the study design is problematic, but how to blind study participants is a difficult question. Applying a placebo varnish in the reference group to enable blinding would only have ensured partial blinding; the test group made a second visit to the clinic while the reference group did not. Regardless, not blinding a trial always increases the risk of biased results. Selection bias may have been introduced as the parents knew which treatment their children would receive, possibly affecting compliance and retention. However, we observed no significant differences in retention between the test and reference groups. Two years after introduction of the two interventions, dropout rates between the two groups were equal.

Non-blinding also induces risk of observer bias. The harder (i.e. death) the outcome is, the less likely it is biased (Schulz & Grimes, 2002). The primary outcome measure of our trial was dental caries, and some subjectivity is involved, despite well-defined criteria. Observation bias in a non-blinded trial should be less when, as in our trial, randomization is done on a cluster level instead of the individual level.

Non-participation in a randomized controlled trial

Thirty percent of the children invited to participate in our trial were not enrolled at baseline, mainly because they declined to participate or did not show up for the examination. Of the participating children, 75% completed the study. If we consider that the areas the trial was performed in had a low socioeconomic status, that the cohort included parents who were 20–30 years of age and had a high rate of resettlement, and that the majority of the parents had an immigrant background which also is linked to a higher rate of movement (Statistics Sweden, 2008; Swedish National Board of Health and Welfare, 2010b), retention must be considered good.

Studies have examined the impact of non-participants. An RCT study of caries-preventive strategies performed in three larger cities in the Netherlands asked parents who declined to allow their child participate to fill in the same questionnaire as the parents of the study participants. Although the socioeconomic status of the non-responders was somewhat lower,

their children had fewer dental caries (dmfs) than the participating children. Thus, non-participation does not necessarily give rise to a non-participation bias (Vermaire et al., 2011). In contrast, a study in Germany on 8-year-olds found that the children who declined to participate had higher dmft levels, and the study suggested that they might cooperate less well on preventive oral health measures (Splieth, Steffen, Welk, & Schwahn, 2005). It seems that non-participation may or may not contribute bias.

The drop-outs in our trial did not differ concerning baseline data. Thus, non-participants and drop-outs should not have affected of the outcome. Participation was high enough to be considered informative as calculated.

ICDAS in clinical trials (Study I and II)

We used ICDAS to diagnose dental caries in our clinical trial. Our hope was a more precise assessment that would allow us to follow changes on the tooth surface before cavitation.

Misclassification bias is always a risk in clinical trials. Study I found inter-examiner reliability for ICDAS scores 3–6 ($\kappa=0.61$ and 0.73) to be satisfactory, but unsatisfactory ($\kappa=0.42$ and 0.60) for the ICDAS score range 0–6. Inter-examiner differences in scoring have a larger impact in longitudinal studies than in short-term studies. Warren et al. (2015) have shown that decayed surfaces are more easily classified than initial lesions. This can be problematic when interpreting results, which Figures 3 and 4 in Study II, as well as the graphs in Appendix 4 of this thesis, illustrate.

Study II, which followed surface level progression on the buccal surfaces of the maxillary incisors, found that most regression occurred when an initial caries decay (ICDAS 1–2) became a sound surface. Biologically, this must be considered likely. Among the toddlers, use of compressed air was irregular, which may also have interfered with the outcome. Further, we found regression on surfaces that were considered cavitated, particularly from ICDAS 4 to ICDAS 3, thus showing the difficulties in discriminating between such scorings longitudinally.

Authors have suggested complicated transitional scoring systems, with weightings for transitions, to differentiate between biologically possible reversals and reversals that arose due to examiner error in longitudinal studies (Ismail, Lim, & Sohn, 2011). Use of such systems, however, leads to modulation of the results, making them less reliable, especially in comparisons between interventions.

Study II exposed changes in the scoring of surface level progression between examinations. The calculated progression incidence shows a tendency for these young ages.

Checkerboard hybridization (Study III)

The checkerboard DNA-DNA hybridization technique may be used to distinguish clinically significant complexes of bacteria and is a useful tool for the enumeration of bacteria. The method has been criticized, as it may increase the risk of cross-reactions due to similarities in DNA regions between closely related species. Before starting Study II, we tested for cross-reactions between the probes and chose 12 probes that would minimize any cross-reactions.

Another concern has been that checkerboard DNA-DNA hybridization may not detect all strains of the species to be analyzed and that a high number of species are required for detection. As investigators at The Forsyth Institute who first developed the method point out, many such concerns may be adjusted for in the procedure (Socransky et al., 2004).

The technique offers many advantages. In contrast to culture-based microbiology methods, checkerboard DNA-DNA hybridization is insensitive to loss of organism viability. The technique is also rapid and relatively inexpensive. It is possible to identify 40 species and analyze 28 samples simultaneously on a single membrane (Nascimento, Issa, Watanabe, & Ito, 2006).

We decided to use swabs to collect samples because of the low age of the children and found this method to be suitable for the field trial design of the study. The clinics involved in the trial confirmed this.

The reason we decided to use checkerboard hybridization and specific whole genomic DNA probes in Study III was to detect and semi-quantify a high number of bacterial species in a limited number of samples. Other, more advanced and more sensitive methods are available. But to answer our research question, we considered the method to be sufficiently rigorous. Significant differences in our selection of species would have been detected, if present. Furthermore, the 12 species we chose are early colonizers of the oral cavity (mucosal membranes and teeth) likely to be representative for this age group.

Health economic evaluation (Study IV)

In the cost-effectiveness analyses, we included an insignificant difference for the defs increment. This might be an undesirable methodological consideration, but this was necessary in order to analyze intervention costs and cost effectiveness.

Further we reported no measurements of quality of life, as is generally recommended (Drummond et al., 2005). This is because we did not collect this information in the SCS trial. As the expanded intervention yielded no gain, it is unlikely that this measure would have added anything to the conclusion.

Relevancy of findings

The inevitable, always justified question is whether our results are relevant. Relevancy determines quality. We have already touched on some of these aspects in this Discussion.

The quality of our study design adds to these aspect of our results. The RCT design is well suited to test differences between two interventions. Randomization minimizes selection bias. In our case, clustering before randomization was advantageous as the baseline characteristics, which we collected in the questionnaire and could have been considered risk factors or confounders, were evenly distributed between the test and the reference groups.

The power analysis before the trial started ensured a large enough sample size would be enrolled for the result to be significant if the expanded program was effective.

A few systematic errors, as mentioned above, lowered the quality of the study to some extent. The non-blinded design added selection bias to some degree, and observation bias was also a concern.

Misclassification bias was also present. But considering the results of the caries development comparisons between the test and the reference groups based on ICDAS 3–6, reliability was better than for the whole range of ICDAS scores; thus, effectiveness of the intervention must be considered reliable.

The trial might have underestimated the effectiveness of the supplemental measures since in the analysis, all toddlers in the TG who completed the study, independent of the number of fluoride varnish applications they had received, were included. We did, however, estimate the effect size, both adjusted and unadjusted, for the clustering without observing a change in outcome. We also checked if there were any differences in effectiveness between children receiving 2, 3, or 4 fluoride varnish applications, but we found nothing that would affect the outcome.

The external validity of Study I showed that the results are applicable in toddlers living under the same circumstances as ours, that is, living in high-risk areas due to a skewed distribution of dental caries commonly seen in the Western world, and with a majority of the children using fluoride toothpaste.

A recent publication rated Study I according to the quality of evidence using the LEVEL OF EVIDENCE grading system. For level of evidence (possible rated levels 1–3), our study received a 2 (Oliveira & Dos Santos, 2016). Had Study I been blinded and achieved 80% retention, a rated level 1 should had been possible (Newman, Weyant, & Hujoel, 2007).

Study designs should strive to achieve the best possible quality. Some factors, difficult to control practically – like the missed appointment and imperfect reliability – serve to make the results realistic. Our results might not be fully applicable on the individual level, but in relation to the hypothesis to be tested, the trial outcome is valid: adding fluoride varnish to the standard caries-preventive program already in place in Stockholm County does not reduce the development of dental caries in the studied cohort of high-risk children from HNAs 3 and 4.

Ethical reflections

The SCS trial raises potential issues in the area of scientific ethics. This includes, for instance, the preventive intervention itself – a clinical examination that might be stressful to young children – and language difficulties, where study information may have been difficult to understand because the home language was not Swedish.

To start with, I would like to underline that the preventive efforts made to avoid the development of dental caries in children are of great importance and that the general moral principles of both doing good (*beneficence*) and not to harm (*non-maleficence*) support these efforts. When dental caries is prevented, children avoid the consequences of oral disease, which include pain, infection, and dental fear. Beneficence includes not only for the child but also for society itself as we reduce the use of antibiotics and slow the development of resistance. Further, we reduce the use of anesthetic gases as toddlers with ECC often need general anesthesia during treatment.

Science involving young children challenges the principle of *autonomy* as children cannot decide for themselves. In line with general praxis, parents decide on behalf of their children. In our trial, the parents gave written informed consent for their toddler to participate. Something worth considering, though, is that as the SCS trial is ongoing, the children will develop, and at age 7 years, when the last follow-up is scheduled, the children should be given an opportunity to understand their involvement in the trial.

Information must be given in a way that the receiver can interpret. Because the trial is being conducted in a multicultural area, it was expected that the parents would be more comfortable with and commonly speak another language than Swedish. For this reason, we recommended that the examiners use a professional translator when needed. We also made the information letter for the study available in 11 different languages: Arabic, Bosnian/Serbian/Croatian, English, French, Persian, Russian, Somali, South Kurdish, Spanish, Swedish, and Turkish.

Experiences of the trial also vary among children. Some might experience the examinations and fluoride varnish treatments as unpleasant. The mouth is a sensitive part of the body of the

child, and it is not unusual that children do not like having their teeth brushed. But by examining the children's teeth early, signs of dental caries can be found; topical application of fluoride and brushing the teeth of the children allow us to spare children the consequences of dental caries. The benefits outweigh the slight feeling of discomfort that might arise. And because not only the TG but also the RG received preventive treatment, the study takes the principle of *justice* into account.

Because we focused the preventive interventions in high-risk areas, some high-risk individuals living in other areas will gain no direct benefit from the study, but they will indirectly, from the trial outcome. A further question is whether the risk of stigmatization increases since the study focused on multicultural areas with a low socioeconomic status. My opinion, rather, is that the opposite occurred. As Swedish society is segregated to a larger extent today than it was a few decades ago, it is highly important to show and try to deal with the consequences of segregation. Working with intervention and becoming involved in people's lives, trying to influence them in one way or another, is a delicate issue. How far can we go and still ensure that we respect the *integrity* of the parent and child, and where does the responsibility of society end? In our study, we approach that border as the use of fluoride varnish in the dental office in one way is done to compensate for home care routines that have broken down.

This study was commissioned by the Stockholm County Council, and there is a plan to provide extra resources for the prevention of dental caries in children. As the resources are limited, it is important to use them in an efficient way and to evaluate the results of the interventions that are made. Delivering the information on dental caries to those who need the information most is not an easy task. And the skewed picture of prevalence today emphasizes the need for new approaches and actions. Concerning the study, however, the moral principle of doing good is paramount, and the benefits outweigh the risks.

MAIN FINDINGS AND CONCLUSIONS

Study I

The expanded caries-preventive program with more regular dental visits than the standard program and biannual application of fluoride varnish between 1 and 3 years of age did not reduce the prevalence or increment of early childhood caries in children living in multicultural areas with a low-socioeconomic status.

Study II

(i) The expanded caries-prevention program did not reduce dental caries progression in the buccal maxillary incisors.

(ii) Caries development followed the tooth eruption pattern, and progression of dental caries was most prominent on the maxillary buccal incisors.

(iii) Healthy surfaces or surfaces with initial stage decay were less likely to progress.

(iv) It is possible to use ICDAS to follow the progression of dental caries. Regression and discrepancies between examinations occur when ICDAS is used in a clinical field trial.

Study III

(i) The composition of oral microflora in preschool children did not differ between those who had received applications of highly concentrated fluoride biannually and children who had received a standard intervention program solely.

(ii) No differences in the *S. mutans* or *A. odontolyticus* counts were found between children with or without dental caries.

(iii) In children who had remained caries free, higher prevalences of *Lactobacillus*, *Neisseria* and *Bifidobacterium* species were found. This finding supports the concept that caries is more due to absence or under-abundance of beneficial bacteria rather than linked to specific pathogens.

Study IV

The economic evaluation of the expanded caries-prevention program, compared to the standard caries-prevention program, showed that the expanded program was not cost effective. The expanded program was not more effective, and it was also more costly.

CLINICAL IMPLICATIONS

Studies of this size in toddlers, to evaluate the effect of caries-preventive interventions longitudinally, are rare in Sweden. The SCS trial was large enough to allow reliable conclusions to be drawn. The project placed substantial demands on dental personnel to organize the examinations and intervention sessions and to obtain written informed consent from the parents for the participation of the toddlers. It was likely also a challenge to conduct a structured interview with the parents that included personal, possibly sensitive issues. The dental personnel managed it well, though, and the study could be completed.

The interventions were conducted on premises where the supplemental interventions supposedly would be permanently implemented, had they been shown to be effective and had an economic evaluation supported the expanded program.

In the SCS trial, we found some level of dental caries (ICDAS 1–6) in 5.2% of the toddlers at the age of 1 year, and caries development was continuous throughout the study. A preventive rather than an operative approach to managing dental caries was important in these early examinations so that we could follow disease development. Early intervention was essential. The development of dental caries was lower in our study compared to in other similar populations in other studies in Sweden, as discussed earlier. This advocates that children should be examined and given detailed oral hygiene instructions that include the introduction of fluoridated toothpaste when the first teeth emerge. Receiving a first summons to the dental clinic at the age of 1 seems appropriate. Currently, caries prevention is part of the standard caries-preventive program in Stockholm, but not a clinical examination at the age of 1.

Dental healthcare resources are limited, so they must be used wisely. Thus, among others, one important consideration is which of the dental personnel should perform these interventions and examinations. The dental team responsible for treating children should comprise a dentist, a dental hygienist, and a dental nurse. Dental hygienists are permitted to diagnose dental caries, and the delivery of the preventive message is an important part of their profession (Swedish National Board of Health and Welfare, 2005). Thus, hygienists seem to be ideal for examining 1- and 2-year-old toddlers and give information to the parents. Hygienists, however, are recommended to always work in collaboration with a dentist, in case they would encounter dental diseases or other issues of concern would arise. The dental teams in the SCS trial involved the same numbers of hygienists and dentists, but it was the dental hygienist who, to a large extent, performed the examinations. When toddlers are 3 years old, a dentist should be present at the examination, due to the need for more in-depth knowledge of dental development.

Working with toddlers requires particular skills. So, before becoming responsible for the dental health of 1- and 2-year-old of children, the dental team will need further education. This training should involve several skills specific for working with young children. Managing young children in the dental setting is one of them and in-depth knowledge of ECC another. The dental personnel involved in the study perfected their skills, both in caries diagnosis and in the management of toddlers, through practice accrued by participation in the trial.

When ECC occurs in a 1-year-old in Stockholm County today, the general dentist has no clear guidelines to refer to (Mejäre et al., 2015). A structured program is needed for an appropriate caries investigation that includes anamnestic data, risk assessment, and detailed instructions on how to perform interceptive treatment (secondary prevention) of toddlers with early signs of or an already established disease. The program should include how to create working home-care routines that include the use of fluoridated toothpaste.

When we reviewed the dental records in Study IV, we found that the clinics did not routinely use interpreters. This may have been due to the multicultural origin of the dental personnel. However, it has been shown that language difficulties can reduce the benefit of the preventive message (Ekman, Holm, Schelin, & Gustafsson, 1981), so use of an interpreter should not be underestimated. Thus, dental clinics should perhaps consider using an interpreter more often, when language difficulties impair communication, as it would benefit both themselves and their patients.

The study yielded other important information, on study participation rates, which might indicate what could be expected in the PDS system for this age group. Of the 30% of the total cohort that were excluded from the study, 54% were no-shows, that is, the parents did not bring the toddlers to the baseline examination when they were 1 year old. This means that 16% of the toddlers selected for participation did not attend their first dental examination and, possibly, that this figure might approximate dental clinic attendance at this age.

But society wishes all children to attend their scheduled dental appointments. All children are entitled to good health, which means that they should be examined and assessed concerning risk. Check-ups and treatment are, as far as possible, evidence based, to avoid unnecessary expenditure in time and resources on the parts of patients and society. It is known that some children in the group who do not attend their dental appointments need special attention. Among these are children with chronic diseases, such as congenital heart disease (Saunders & Roberts, 1997), who have been shown to have a higher risk of developing dental caries (Foster & Fitzgerald, 2005). These children, obviously, are in contact with child health care in other ways, and their oral health is sometimes neglected in the face of other, seemingly more serious,

health issues. It is important to find ways of discovering these children so that they, too, may have their teeth examined and receive health care information. In the long run, these children will gain much from timely examinations and treatment.

One solution could be to expand collaboration between the nurses at the Child Health Centers who meet the children regularly during the preschool years. If the nurses asked whether the children had been to the dental clinic and received oral hygiene instructions, and if they lifted the upper lip of the child to look at the buccal surfaces of the maxillary teeth, they would be able to spot more advanced lesions. When there are signs of dental disease, or the child has not been to the dental clinic, the nurses could send a dental referral. Possibly, children with chronic diseases might be in need of dental care at a pediatric dental clinic (Grahn, Wikstrom, Nyman, Rydberg, & Stecksén-Blicks, 2006).

When the children are 1 month old and sometimes when they are 8 month old, all families receive an invitation for a home visit by a nurse from the local Child Health Center (Swedish Association of Local Authorities and Regions, 2017). The home visit is a chance to discuss caries-preventive measures such as tooth brushing; fluoridated toothpaste; and when the teeth emerge, avoidance of sugary beverages in the baby bottle, especially at night time.

Not only children with chronic disease are at risk of missing dental appointments. One Swedish study conducted in-depth interviews with parents who regularly failed to take their children to the dentist. The main finding was that the families did not prioritize the dental examinations because they felt overloaded by the demands of their daily living and survival (Hallberg, Camling, Zickert, Robertson, & Berggren, 2008). Social factors interact with dental health behavior and nonattendance may be a sign of maltreatment (Bradbury-Jones, Innes, Evans, Ballantyne, & Taylor, 2013). Children subjected to abuse or neglect have been shown to have eight times more untreated decayed teeth (Greene, Chisick, & Aaron, 1994). Repeated failures of children to attend dental appointments or to complete planned treatment, tooth pain, and requiring several sessions of general anesthesia during treatment may be indicators of dental neglect. Here, the dental team must be observant and ready to attempt counter-measures for the best of the child (Cairns & Welbury, 2009).

We often talk about risk factors for dental caries, such as social status and the educational level of the mother (Grindefjord et al., 1996; Julihn, Barr Agholme, Grindefjord, & Modeer, 2006). Life-style factors of the mother such as fat and sugar intake during pregnancy have also been associated with dental caries in the later preschool years of children (Wigen & Wang, 2011), as have low weight at birth and mothers who smoked during pregnancy (Bernabe, MacRitchie, Longbottom, Pitts, & Sabbah, 2017).

Because dental caries is easily detected and documented, perhaps it is time to reverse our reasoning and use dental caries as a risk indicator that overall health behavior in the family is not functioning properly, especially in children who do not attend dental treatment?

We need to find ways to help these children. The PDS cannot do this alone, Social Services cannot do this alone, and the health care system cannot do this alone. One way may be to create a collaborative group comprising representatives from these three groups and to whom we can refer these children: a group that is better able to give these children and families the support they need. Investing time, effort, and money into children at young ages would likely lower the incidences of illness and disease later on.

In writing about our trial, we decided to introduce a new term: progression index (PI). The PI of the buccal surfaces on the maxillary incisors – 26% – means that one-fourth of the surfaces had experienced disease progression by the 1-year examination at age 24 months. But Study II reported that most surfaces at 24 months of age were healthy or in an initial stage of decay, which seldom progress to a more severe stage. However, 4% of the surfaces had progressed to extensive decay at the 1-year examination. This supports a proposal that the status of the buccal surfaces of the maxillary incisors – the teeth with the highest likelihood of developing caries at that age – could be used as an indicator for determining the timing of the next visit. If there are no visible caries on the incisors or only initial caries stage of decay in children living in high-risk areas, the timing of the next examination could safely be made for 1 year later. However, between the examinations at ages 24 and 36 months, surfaces with extensive decay increased compared to the preceding year, and 21% of the teeth with buccal surfaces presenting an ICDAS score of 6 were extracted during this time. A child who has any surfaces with a score of 6 should probably have a recall interval shorter than 1 year. This, together with other data from the examination, may provide guidance for when to examine the child next.

The SCS trial yielded information on the characteristics of the children in HNAs 3 and 4. Together with their caries data, we can now more precisely target the dental care they need. These figures can be used in deciding how to allocate resources to dental healthcare in these areas. “The inverse care law” (Hart, 1971) is always a risk in low-socioeconomic status areas where people with the heaviest economic burdens have fewer resources. Thus, we need to compensate these areas with more dental resources, larger clinics, more dental personnel, and higher pediatric competence in the dental personnel. The socioeconomic risk indicators emerging from our data point to a need for future allocation of extra resources in these high-risk areas.

FUTURE RESEARCH

Our study aimed to reduce social inequalities in oral health by using preventive measures at an early age directed towards children living in high-risk areas. As discussed before, implementation of the intervention at a young patient age was positive regarding tooth brushing habits in the cohort, but the supplemental measures did not substantially affect the oral health status of the study population. New methods are needed to manage the higher prevalence of caries among multicultural children in families with a low- or medium-socioeconomic status. As caries is a multifactorial disease, a single solution will not solve the problem. Preventive interventions are needed on both the patient and the community level.

On the patient level, incorrect oral hygiene is often the reason for the development of dental caries. When patients are young, interventions must target parents in order to effect changes in hygiene. The self-efficacy of the parents – a person's belief in their own competence – influences their tooth-brushing patterns and how likely they are to take their child to the dental clinic (Kakudate et al., 2010). Strengthening parental self-efficacy could be one way to achieve more successful results in caries-preventive work.

To effectively communicate a preventive message, parental health literacy – “the ability to perform basic reading and numerical tasks necessary to navigate the health care environment and on health care information” – is necessary (Lee et al., 2012). Health literacy skills have been associated with oral health. In the group of multicultural persons we are working with, language may be an obstacle contributing to low health literacy. Differences in health literacy levels depending on ethnic origin have been found (Lee et al., 2011). For us, to achieve success on both the individual and the broader societal level, we may need to begin here: to increase literacy, if it seems insufficient, and to communicate our preventive message in a way that facilitates learning in patients and parents. Caregivers must be familiar with effective ways of communicating their message (Sanders et al., 2009).

One Swedish study found that the social composition of the neighborhood where a child lived affected their oral health: the more deprived the area, the more caries they developed. In these areas where health need was greatest (HNA 3 and HNA 4), more than 80% of the inhabitants were immigrants (Swedish National Board of Health and Welfare, 2013). Low health literacy skills may be one explanation of this phenomenon. Actions on a community level are recommended. Although it does not address the age group we want to reach, one study that could be interesting to perform is to add health literacy to the educational curriculum. Health literacy would include oral as well as other health issues important for the age group but also

in a lifetime perspective. A side aspect would be to study how this influenced the rest of the family.

On the individual level, a cognitive behavioral technique that has been considered successful is motivational interviewing. One study using motivational interviewing as part of a preventive intervention toward parents of pre-school children found that the technique had changed oral health behaviors 2 years after the intervention. No effect on caries development, however, was seen (Ismail, Ondersma, Jelele, Little, & Lepkowski, 2011). Given more time, it is possible that motivational interviewing would have also had an effect on caries development.

From a societal perspective, we need more supportive actions. To improve the oral health of vulnerable children, we cannot depend solely on the actions of caregivers, we must set in other actions in parallel. One intervention that seemed to be effective in reducing dental caries as well as allow inequalities in the oral health of children to be monitored was the nursery tooth-brushing program in Scotland (Anopa et al., 2015; Macpherson, Anopa, Conway, & McMahon, 2013). But instead of using a toothbrush to apply fluoride toothpaste to the children's teeth, the children would receive fluoride toothpaste on their finger (after they had eaten lunch and washed their hands) to spread out on their own teeth. This is because use of a toothbrush has its own hygienic obstacles in the difficulties attached to storing and the risks of mixing the toothbrushes at the day-care centers. This would at least ensure that the children had their teeth exposed to fluoride toothpaste at least once a day. In the Scottish program, the parents also received tooth paste and toothbrushes for home use, which seems like a smart action together with the lubricating of fluoride toothpaste to be evaluated.

Preventive interventions in obesity studies have been cited for a lack of durability of effects (Haynos & O'Donohue, 2012). The same could occur with caries-preventive interventions. We need to determine the threshold for where the gain of various interventions becomes null. The threshold could comprise improved health and cost effectiveness.

As the SCS trial is a longitudinal trial, the effect of the intervention in the children will be assessed at age 7 years. We will also reassess our data regarding risk factors and factors that may further explain the links between immigrant status, low socioeconomic status and dental caries.

To sum up, we consider the SCS intervention program to have produced useful information, which points us in unexpected directions. And we are satisfied with the outcome of the trial, despite the somewhat disappointing results; we would have preferred to report that the program was both effective in preventing dental caries as well as cost effective. However, we feel that

our efforts directly benefit the patient: among other things, they will not be subjected to unnecessary dental visits.

Because one goal of preventive dental interventions is to foster oral hygiene skills in individuals for themselves and their children, our study must be considered successful. We established regular habits in the use of fluoridated toothpaste at a young age in most of the participants. And as Swedish society requires any treatment that is to be reimbursed to have scientific evidence-based support, we provided reliable results for the effectiveness of the program. Further, we showed that collaboration between public and private dental healthcare and academia is possible and is a promising way of conducting scientific projects.

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Appendix 1

Work flow

Before the appointment

- Send the information letter and an invitation to the scheduled appointment by land post.
- If the appointment is cancelled, offer a new appointment as soon as possible.
- If the child misses the appointment, offer a new appointment as soon as possible.
- If necessary, book an interpreter for the appointment.

Examination and intervention

12 months (dental hygienist, children in both the test and reference groups)

- Ask the parents if they have received the information letter concerning the study; then verbally inform them about the trial. Ask how they feel about their children participating in the study, if they are worried about anything, and if they have any questions. If the parents want their child to participate, the parents, on behalf of their children, together with the examiner, sign the informed-consent form.
- Complete the questionnaire together with the parent.
- Give the parents standard information (verbally and written) considering the oral health based on the recommendation in the “Caries prevention program”.
- Teach the parents how to brush the teeth of their children by letting them practice brushing their children’s teeth; correct them if necessary.
- Dry the teeth with a cotton roll, and air dry if possible and then examine, the teeth of the children; record your findings using ICDAS II in the 12-month examination form.
- For the children in the test group, apply fluoride varnish and admonish them not to eat for 4 hours; ask the parents not to brush the teeth of their child until morning.
- Give the parent a tooth brush and fluoridated toothpaste.

18 months (dental nurse, children in the test group)

- Give the parents standard information (verbally and written) considering the oral health based on the recommendation in the “Caries prevention program”.
- Teach the parents how to brush the teeth of their children by letting them practice brushing their children’s teeth; correct them if necessary.
- For the children in the test group, apply fluoride varnish and admonish them not to eat for 4 hours; ask the parents not to brush the teeth of their child until morning.
- Give the parent a tooth brush and fluoridated toothpaste.

24 months (dental hygienist, children in both the test and reference groups)

- Complete the questionnaire together with the parent.
- Give the parents standard information (verbally and written) considering the oral health based on the recommendation in the “Caries prevention program.”

- Teach the parents how to brush the teeth of their children by letting them practice brushing their children's teeth; correct them if necessary.
- Dry the teeth with a cotton roll, and air dry if possible and then examine, the teeth of the children; record your findings using ICDAS II in the 24-month examination form.
- For the children in the test group, apply fluoride varnish and admonish them not to eat for 4 hours; ask the parents not to brush the teeth of their child until morning.
- Give the parent a tooth brush and fluoridated toothpaste.

30 months (dental nurse, children in the test group)

- Give the parents standard information (verbally and written) considering the oral health based on the recommendation in the "Caries prevention program".
- Teach the parents how to brush the teeth of their children by letting them practice brushing their children's teeth; correct them if necessary.
- For the children in the test group, apply fluoride varnish and admonish them not to eat for 4 hours; ask the parents not to brush the teeth of their child until morning.
- Give the parent a tooth brush and fluoridated toothpaste.

36 months (dentist and dental nurse, children in both the test and reference group)

- Complete the questionnaire together with the parent.
- Give the parents standard information (verbally and written) considering the oral health based on the recommendation in the "Caries prevention program".
- Teach the parents how to brush the teeth of their children by letting them practice brushing their children's teeth; correct them if necessary.
- Dry the teeth with a cotton roll, and air dry if possible and then examine, the teeth of the children; record your findings using ICDAS II in the 36-month examination form.
- For the children in the test group, apply fluoride varnish and admonish them not to eat for 4 hours; ask the parents not to brush the teeth of their child until morning.
- Give the parent a tooth brush and fluoridated toothpaste.

After the appointment

- Scan the informed-consent form, and send it for archiving in the digital dental records.
- Send the questionnaires and ICDAS forms to the project group.

Appendix 2

Examination form

Child code:

Age in months:

☐ 12

☐ 18

☐ 24

☐ 30

☐ 36

Gingivitis: ☐ Yes

☐ No

Plaque: ☐ Yes

☐ No

Dental caries status (ICDAS II)

Surface	55	54	53	52	51	61	62	63	64	65
m	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
o	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
l	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Surface	85	84	83	82	81	71	72	73	74	75
m	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
o	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
l	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Cooperation examination: ☐ Positive ☐ Reluctant ☐ Negative ☐ Impossible to examine

Appendix 3

Questionnaire

Code number:

Age in months: ☐ 12 ☐ 18 ☐ 24 ☐ 30 ☐ 36

Intervention program: ☐ TG ☐ RG

Tick the box that suits best

What language is spoken at home/native language? (several options possible)

☐ Swedish ☐ Spanish ☐ Turkish ☐ Arabian ☐ Somali
☐ Persian ☐ Other _____

Does anybody in the family smoke? (several options possible)

☐ No ☐ Mother ☐ Father ☐ Another relative

What monthly income does the family have before taxes?

☐ < 20.000 SEK ☐ 21.000-30.000 SEK ☐ > 30.000 SEK

How often do you brush your child's teeth with fluoridated toothpaste?

☐ Never ☐ A few times a week ☐ 1 time/day ☐ 2 times/day ☐ >2 times/day

How often does your child drink anything sweet? (i.e. juices, sweetened tea, milk or gruel, soft drinks)

☐ Never ☐ A few times a week ☐ 1 time/day ☐ 2 times/day ☐ >2 times/day

How often does your child eat candy?

☐ Never ☐ 1 time/week ☐ A few times a week ☐ Every day

Does your child have any chronic/long lasting disease diagnosed by a medical doctor?

☐ Yes (for instance diabetes/asthma/blood disease) ☐ No

Appendix 4

Dental record data

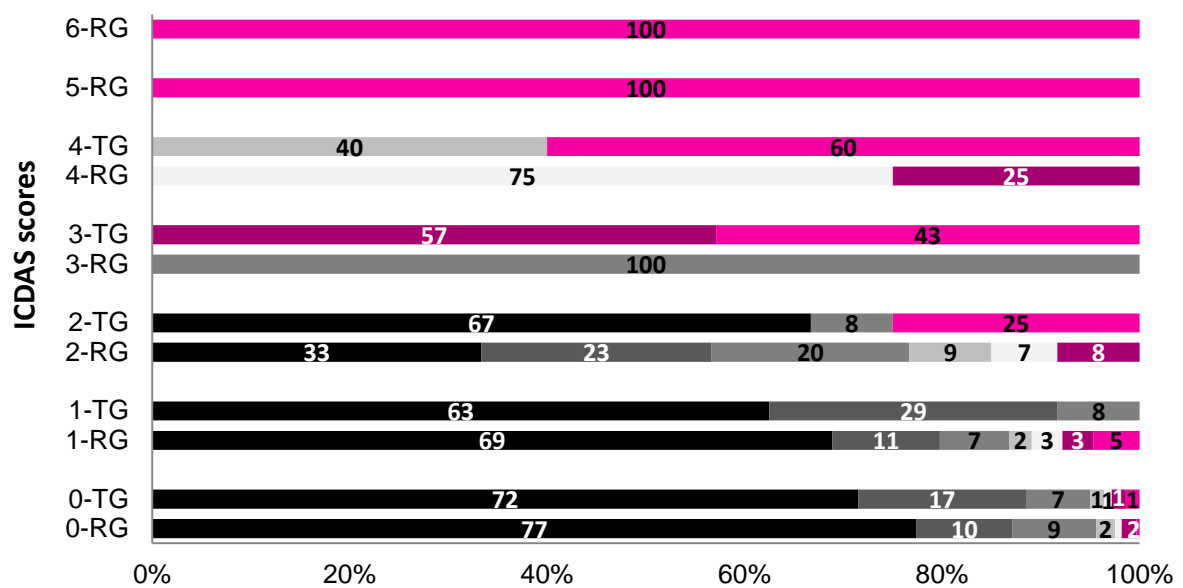
Variables extracted from the dental records of 1,346 children

Variable	Explanation
Clinic	Name of the clinic
ID	Code number in the Stop Caries Stockholm project
Prevention program	Test group <i>or</i> reference group
Gender	Boy <i>or</i> girl
Additional visits due to caries, 2011–2014	Number of visits per year
Time for additional visits, 2011–2014	Minutes per year
Cost for additional treatments, 2011–2014	Swedish crowns per year according to price list ^a
Dental caries	No caries <i>or</i> caries (ICDAS >0)
Absence from Stop Caries Stockholm examination, 2011–2014	Number of absences from examinations per year
Absence from treatment, 2011–2014	Number of absences from treatment per year
Time, missed treatment, 2011–2014	Total time in minutes per year
Interpreter present, 2011–2014	Number of visits with interpreter present per year
Referral sent	No <i>or</i> yes
Number of visits to a special clinic, 2011–2014	Total number of visits per year
Cost for the specialist treatment, 2011–2014	Swedish crowns per year according to price list ^b
Interpreter present, specialist treatment, 2011–2014	Number of visits with interpreter present per year
Missed specialist treatment, 2011–2014	Number of missed specialist treatments per year
Time, missed specialist treatment, 2011–2014	Total time in minutes per year
End date, general dental treatment	End date, general clinic dental records
End date, specialist treatment	End date, specialist clinic dental records

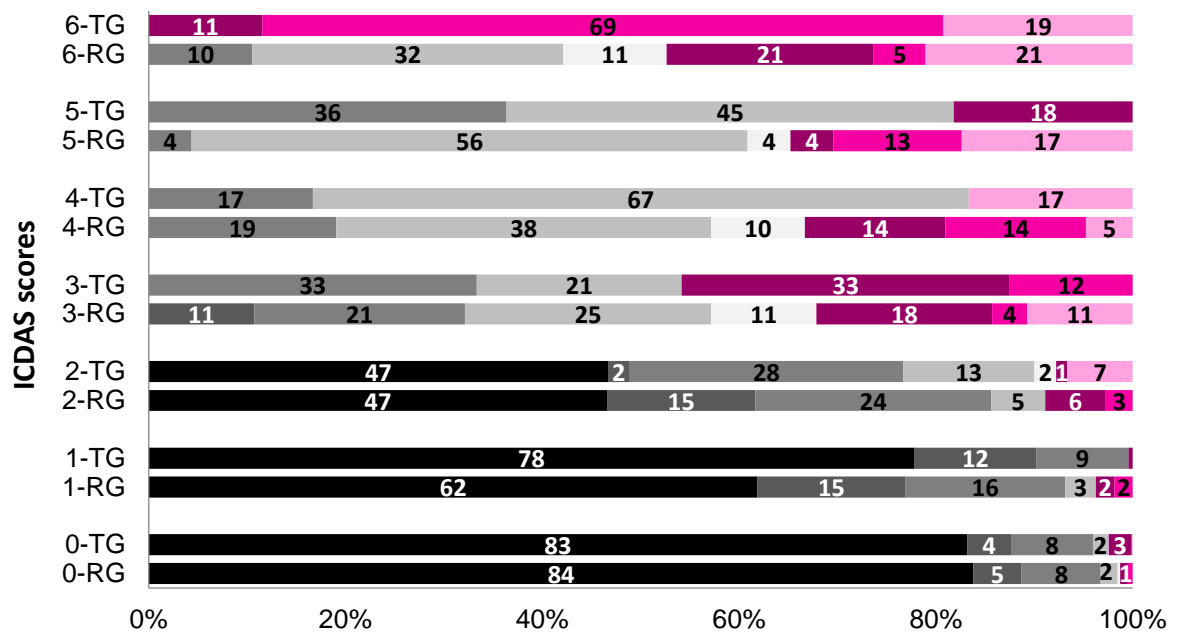
^a using the 2011 price list for children, PDS Stockholm

^b using the 2011 price list for pediatric specialist treatment, PDS Stockholm

Appendix 5



Graph 12–24 months showing the progression of dental caries on the buccal surfaces of the buccal maxillary incisors in the test group (TG) and the reference group (RG). Vertical lines show ICDAS scores at 12 months and the horizontal lines show the frequency (%) of the ICDAS scores at 24 months.



Graph 24–36 months showing the progression of dental caries on the buccal surfaces of the buccal maxillary incisors in the TG and the RG. Vertical lines show ICDAS scores at 24 months and the horizontal lines show the frequency (%) of ICDAS scores 0–6 and extracted (e) at 36 months.

ICDAS SCORES 0 1 2 3 4 5 6 e