Caries prevention in Chile: An epidemiological, econometric, and economic evaluation

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Dedication

To my lovely wife Anakena for all the support given throughout this adventure of completing my PhD.

"Eternas gracias amada mía, no podría haber logrado esto sin ti".

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Abstract

In order to increase the proportion of caries-free preschool children, the Chilean Ministry of Health (MINSAL) proposed a fluoride varnish (FV) intervention program in the preschool setting. This thesis compares the costs and effects of such a proposal with alternative FV interventions in different socioeconomic scenarios.

A combinatory selection process was performed to define new FV interventions, for example, in the primary care setting during a well-child check-up. Epidemiological and econometric analyses were conducted and then used as data input into decision analytic models. Cost values, from a costing study, and the relative effectiveness of FV, obtained from a systematic review, were used as well.

Several Markov cycle decision models were created to simulate the performance of FV intervention over 2 years. The cost-effectiveness of the different interventions was compared and an incremental cost-effectiveness ratio (ICER) was estimated. The robustness of such estimations was tested using one-way deterministic sensitivity analyses and a Monte-Carlo simulation.

All FV interventions resulted in a small increase in the number of caries-free children. In the baseline scenario, FV application in the primary care setting without screening was more effective and less costly than the other interventions; this intervention increased the caries-free population by 3.7% at an extra cost of CLP 7,620 per child with an ICER of CLP 130,849 compared with counselling-only intervention. Increasing the starting age of FV application raised the incremental cost-effectiveness ratio. The ICER decreased when other health professionals, rather than dentists, provided the FV applications.

This thesis illustrates the simulation of the performance of FV in realistic scenarios incorporating important aspects of health and education policies. Also, this study demonstrates that MINSAL's proposal was not the least effective but was unequivocally the more costly intervention by far. The methodology and results of this thesis can be useful for both policy- and decision-makers.

Table of contents

Figures and Tables

Figures

Tables

Chapter 1. Introduction

The most recent epidemiological study conducted in Chilean children aged 6 years (Soto *et al.*, 2007a) showed that just 30% of them were caries-free. Aware of this, the Chilean Ministry of Health (MINSAL) has proposed as a public health objective increasing this caries-free rate by 35%, from 30 to 40% as a goal for the decade 2011-2020.

The evidence suggests that fluoride varnish (FV) has a positive effect on reducing the amount of dental decay or caries (Marinho *et al.*, 2013), and MINSAL has been interested in evaluating the effects and costs of using this technology in the last two years of preschool education (4 to 5-year-olds approximately). Personal communication between the author of this thesis and his colleagues at the Department of Oral Health of MINSAL ended in an agreement in which the possibility of a nationwide programme of FV would be explored in this thesis, with MINSAL providing the data required for the study.

However, aside from two studies (Weintraub et al, 2006; Tickle et al., 2016) there is no evidence on the effect of FV on caries-free populations. Also, due to the age range coverage proposed by MINSAL, there are doubts about the cost-effectiveness of a possible national programme of FV application. Despite a considerable and growing literature around the theme of cost-effectiveness studies in dentistry (Mariño, 2013), there are few studies about the cost-effectiveness of FV, as Quinonez et al. (2006) and Tickle et al (2016) for instance. Consequently, Chilean decision-makers would require more information to make the best decision about this technology.

As a result, the aim of this thesis was to evaluate the costs and effects of a nationwide FV application programme to increase the proportion of caries-free children in the preschool Chilean population, and to demonstrate, how health economics methodologies can help in decision-making in oral health. Performing a randomised controlled trial with a nested cost-effectiveness analysis was not possible due to both time and funding restrictions. Therefore, decision analytic models were used to perform several cost-effectiveness analyses of FV application.

This chapter describes briefly the contents of each chapter in this thesis. Chapters 2 to 4 contain a literature review describing the context and background of the thesis.

Chapter 2 contains the definition of dental decay or caries, where special attention is given to risk factors associated with caries; Chapter 3 analyses several interventions aimed at improving the oral health of preschool aged children and the feasibility of using such interventions in the Chilean context. Chapter 4 describes the Chilean context, explaining both the health and education systems; this chapter describes and critiques MINSAL's strategies as well. Chapter 5 describes the economics evaluations, particularly the cost-effectiveness analysis; in addition, it discusses decision analytics models and how to construct them.

Chapters 6 to 11 are the empirical chapters of the thesis with each chapter describing the methods and results for one study.

Chapter 6 describes an epidemiologic study that allowed a proxy of natural history of caries of the Chilean preschool population to be obtained. Due to differences in caries prevalence detected in Chapter 6 between Chilean regions, Chapter 7 evaluates through an econometric analysis, the relationship of caries prevalence and fluoridated water. Chapter 8, a systematic analysis, shows how the interventions to be compared were selected. The systematic review, performed in Chapter 9, gives efficacy values of FV in caries-free populations. Chapter 10, calculates the costs of the interventions under comparison. Chapter 11, the main study of this thesis contains a decision analytic models that give estimates of both the costs and effects of several FV interventions.

Finally, Chapter 12 summarises all empirical chapters, containing the general discussion and conclusions of this thesis as well.

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Chapter 2. Caries

2.1 Introduction

The term dental decay or dental caries or caries, can be defined as a localised bacterial-mediated chemical dissolution of any hard tissue of teeth (enamel, dentine, and cementum); also, the term is used to describe both the signs and symptoms produced by such chemical dissolution. Despite the fact that caries can be present on any surface of the tooth, this pathology is more frequent in those sites where dental biofilm (or dental plaque) can accumulate and mature (Fejerskov and Kidd, 2008).

This pathology can affect both primary and adult dentitions, having different behaviours and different risk factors depending on the age of individuals (Selwitz et al., 2007). For example, and regarding to socioeconomic factors, evidence suggests that people from lower socioeconomic status backgrounds are more prone to develop caries (Pitts et al., 2011).

Caries can be described as one of the most common preventable diseases in childhood that has reached epidemic proportions worldwide (Edelstein *et al.*, 2015), irrespective of the level of economic development in a society. For example, Vernazza *et al.* (2016) analysed data from the 2013 Children's Dental Health Survey and showed that 40% of 5-year-old children in England, Wales, and Northern Ireland had developed caries (defined as visual and cavitated caries into dentine, restorations, or teeth missing due to caries). In another example, the Colombian Ministry of Health (MINSALUD, 2014) showed that 62.1% of children aged 5-years in Colombia had developed caries (defined as advanced caries, restorations, or teeth missing due to caries).

The consequences of dental caries are significant because the cost incurred to treat these patients generates a significant financial burden on the health services (Cooper et al., 2013). Other consequences are related to the quality of life for children and their families that experience severe caries and pain (Casamassimo et al., 2009).

Given that this thesis is aimed at increasing the caries-free preschool population, this chapter defines caries and examines the epidemiology and consequences of caries in this age group. This chapter also covers the risk factors and preventive interventions that are related to the preschool population.

2.2 Definition of caries

Caries occur when oral bacteria in the mouth secrete acids that cause the dissolution of hard tissues of the teeth; this is the result of homeostatic balance alterations due to modification of local environmental conditions that favour the growth of dental pathogens, mostly Streptococcus and Lactobacillus species (Fejerskov and Kidd, 2008). These microorganisms produce weak organic acids, which are metabolites of bacterial fermentation of carbohydrates that can dissolve calcium phosphate and hydroxyl crystals (hydroxyapatite) that form dental hard tissue (Selwitz *et al.*, 2007;Harris *et al.*, 2009).

Even though caries is caused by microorganisms and can be transmitted from one person to another, it is not considered a highly communicable disease. Indeed, this pathology has been classified as a non-communicable chronic disease because it shares several risk factors with other such diseases (Petersen, 2009) and progresses slowly in most people (Selwitz *et al.*, 2007).

2.2.1 Caries process

The infection of the mouth with a cariogenic microorganism, such as *Streptococcus mutans*, may start early in life and occurs as a result of vertical transmission from mother to child during the first years of life (Laitala *et al.*, 2012). Microorganisms are able to form a biofilm that, as described by Fejerskov and Kidd (2008), is a community of microorganisms growing on the tooth surface. Such biofilms allow microorganisms to attach to any dental surface, even to smooth surfaces, such as enamel.

Microorganisms metabolise carbohydrates, especially highly refined sugars such as sucrose. As a result, the frequency and amount of sugar consumption play an important role in caries development. The role of sugar is so significant that the World Health Organization (WHO (2003) declared that sugars are the most important dietary factor in the development of caries.

Caries first appears in the enamel beneath the biofilm as small areas of subsurface demineralisation (Selwitz *et al.*, 2007), or white spot lesions. At this stage, the pathology is reversible, even in cases with some degree of cavitation. Under non-pathological conditions, the saliva can act as a buffer to neutralise the demineralisation process; also, saliva contains calcium and phosphate ions that can initiate the remineralisation process, forming a delicate demineralisation/remineralisation balance (Hurlbutt and Young, 2014). The remineralisation process can be enhanced by the presence of fluoride ions in mouth that form a much more acid-resistant hydroxyl crystal known as fluorhydroxyapatite (Harris *et al.*, 2004).

If the white spot lesion is not remineralised, microorganisms can penetrate further into the tooth and reach dentine. When the enamel that covers dentine is destroyed and dentine becomes visible, the lesion is considered as severe decay (Selwitz *et al.*, 2007). At this level of decay, the tooth requires curative treatment, which involves caries elimination and restoration (filling).

The caries process can penetrate even further within the dental tissue. It is possible that either microorganisms, their metabolites, or both reach the dental pulp, causing necrosis dental tissues. If the viability of dental pulp is affected, there is a risk that microorganisms can exit the apex (end of the tooth root) and affect the surrounding tissues. In a few cases, microorganisms reached other organs and caused death (Casamassimo *et al.*, 2009).

2.2.2 Treatment of caries

For several decades, the only treatment for caries, beside tooth extraction, was an operative or curative intervention; such treatment was based on surgical elimination of decayed dental tissue and placement of a restoration (filling). New evidence about the caries process has allowed the consideration of a different type of treatment; a non-operative treatment that relies on remineralisation. Such treatment can be applied during the first stages of caries and is based on biofilm (dental plaque) and diet control as well as the use of fluorides (Kidd, 2011). Nevertheless, if the caries process has advanced too far, operative treatment would still be required.

2.3 Measurement of caries

Several oral health indices have been developed to perform epidemiological studies that measure caries prevalence and its distribution in a specific population; in addition, such studies allow comparisons either of one population through time or between several populations. This section describes oral health indices, with particular emphasis on the DMF/dmf index, which is fundamental for this thesis.

2.3.1 DMF/dmf dental index

DMF is an oral health index that has been in use for 75 years, and is commonly used in dental epidemiology as a measure of caries severity. It is the summation of the numbers of decayed (D), missing (M), and filled (F) teeth either in an individual or in a population (Broadbent and Thomson, 2005). Consequently, this index is an ordinal variable at the individual level and a continuous variable at population level.

When it is used in the permanent dentition, it is written using uppercase letters (DMF); in the case of the primary dentition, it is written using lowercase letters (dmf) and can be found written as def, where the letter "e" means the extracted tooth. As DMF measures the number of teeth with caries history (DMFT), the score for an individual can range from 0 to 28 or, in cases that include third molars, the score ranges from 0 to 32. The same logic is applied for primary dentition where dmft/deft scores range from 0 to 20.

Another alternative is to use this index per tooth surface, considering that every tooth has 5 surfaces. Consequently, the number of dental surfaces affected by caries (DMFS) ranges from 0 to 128 or 148, depending on whether it includes third molars or not, and the dmfs/defs scores range from 0 to 88.

Independently of the measured unit (either tooth or tooth surfaces) and type of dentition, this index always records the caries experience or caries history; this means that for an individual, DMF/dmf scores increase over time (or remain constant), but do not decrease.

This index does not require any sophisticated technology and can be easily performed in almost any setting. Indeed, it can be performed while the patient lies down on a table or bench, using natural light (WHO, 2013).

DMF/dmf scores have different diagnostic or sensitivity criteria that allows the recording of different stages of caries. For example, the D_1/d_1 - D_3/d_3 criteria (or scale) classifies decayed components in three stages: D_1/d_1 for initial caries where there is no clinically detectable loss of substance, D_2/d_2 for enamel caries where there is detectable loss of tooth tissue but no softened floor of wall or undermined enamel, and D_3/d_3 for dentine caries where there is a detectable softened floor, undermined enamel, or a softened wall (Fejerskov and Kidd, 2008).

Other researchers have used different DMF/dmf scales depending on the type of diagnosis. For example, Amarante *et al.* (1998) used a the D_1/d_1-D_5/d_5 scale when the diagnosis was done using dental radiographs.

Limitations

As with all health indices, this index has some limitations, as described in this paragraph. For example, the simplest and least sensitive variant (D_3MFT/$d_3$mft) cannot differentiate the location and stage of caries; given that such an index is based on a clinical examination and does not use radiographs, it could underestimate the needs of treatment, as shown by Becker *et al.* (2007). Also, as DMF/dmf values are usually presented as the mean, the index does not reflect the skewed distribution of caries in a given population that could lead to interpretation mistakes (Ditmyer *et al.*, 2011); this is especially important in the youngest populations where significant percentages have no caries (dmf = 0). It does not consider the process of remineralisation of caries (Pitts and Stamm, 2004); hence, it is not a useful index to measure anti-caries efficacy of some treatments. Finally, the index weighs all of its components in the same way; therefore, calculating treatment need is difficult.

Despite its limitations, the DMF/dmf index is one of the simpler and more powerful tools in oral epidemiology. Furthermore, it has been used by WHO in the global oral surveillance system; this implies that there are several oral epidemiological studies that share the methodology proposed by WHO (WHO, 1997) and can be compared between them. For example, given that both surveys share the same age group (12-year-old adolescents) and the same methodology, the Chilean nationwide oral epidemiological survey performed by Soto *et al.* (2007b) can be compared with the Brazilian nationwide survey performed by the Brazilian Ministry of Health (2011); the former presented an average D_3MFT of 1.9 (95% confidence interval [CI], 1.81 to 1.99) and the latter showed an average of 2.1 (95% CI, 1.81 to 2.33).

Significant Caries Index

Another possibility is using DMF/dmf as an input to generate new indices. This is the case with the "Significant Caries Index" (SiC) that works with the subgroup of the population with higher DMF/dmf scores and allows the detection of high risk groups. This index is useful for patient populations with skewed distributions caused by a high number of caries-free individuals. To calculate this index, the individuals are first distributed according the DMF/dmf values, then the third with the highest scores are selected and finally, a mean DMF/dmf is calculated for this third only.

For example, Oulis *et al.* (2012) calculated in a Greek population aged 5 years with a $d_3$mft of 1.77 (95% CI 1.60 to 1.93) that the SiC index was 5.01. This allowed them to get a better picture of distribution of caries and conclude that despite the decrement of caries prevalence observed there were still disparities, for example, children in rural areas have more caries than those children that live in urban areas.

2.3.2 Diagnostic criteria

Knowledge about the caries process has grown over time, and this has altered the definition of caries. Such alterations have led to the identification of several diagnostic criteria; indeed, Ismail (2004) identified 29 criteria. The same author concluded that most caries detection criteria are ambiguous and do not measure the caries process during the different stages.

The main problem is not related to advanced lesions, where it is possible to determine almost immediately that a specific tooth is cavitated. The problem and subject of debate is related to initial lesions, where it is difficult to determine what stage the caries is in. This section of the chapter explains the diagnostic criteria that are significant to this thesis.

WHO

The WHO has defined caries, for epidemiological dental surveys, as a lesion present in a pit or fissure or on a smooth dental surface with a visible cavity, undermined enamel, or a wall or floor that is appreciably softened (WHO, 1997;WHO, 2013); consequently, they have established the use of a D_3MFT/$d_3$mf index. Given that the Chilean Ministry of Health (MINSAL) has chosen to work with the WHO methodology, this is emphasised in this thesis (see Chapter 6 for more details).

NIDCR

This diagnostic criterion was developed in 1987 by the oral health surveys at the National Institute of Dental and Craniofacial Research (NIDCR), part of the U.S. Department of Health and Human Services for epidemiological studies of caries. Such diagnostic criterion can be classified as a visuo-tactile system, where use of a dental explorer is required.

Frank lesions are detected as gross cavitations (d_2). Incipient lesions (d_1) may be subdivided into three categories depending on the location, each with special diagnostic considerations (Ismail, 2004). For example, regarding pits and fissures on occlusal, buccal, and lingual surfaces, these areas are diagnosed as carious when the explorer is retained after insertion with moderate to firm pressure and when the catch is accompanied by:

a. softness at the base of the area
b. opacity adjacent to the area, providing evidence of undermining or demineralization
c. softened enamel adjacent to the area which may be scraped away with the explorer.

This diagnostic criterion can be used along with dmfs, as was used by Weintraub et al. (2006) who assessed cavitated, decayed (d_{2+}), and filled surfaces on primary teeth ($d_{2+}fs$).

ICDAS

The International Caries Detection and Assessment System (ICDAS) is able to measure, among other things, the stage of the carious process, topography, location, restoration, or sealant status, if a tooth has a cavitation or not, and whether caries are active or not (Ismail *et al.*, 2007). This is the result of an international effort by a group of caries researchers, epidemiologists, and restorative dentists.

The ICDAS criteria for detection of caries on coronal tooth surfaces is a two-digit coding system. The first digit implies classifying each tooth surface on whether it is sound, sealed, restored, crowned, or missing. In the second digit, each tooth surface with caries must be classified using an ordinal scale (Table 2.1).

Code	Description	Lay term
0	Sound	Sound
1	First visual change in enamel	Early stage decay
2	Distinct visual change in enamel	
3	Localized enamel breakdown	Established decay
4	Underlying dark shadow from dentine	
5	Distinct cavity with visible dentine	Severe decay
6	Extensive distinct cavity with visible dentine	

Table 2.1. The ICDAS criteria for detection of caries on coronal tooth surfaces. Based on Ismail et al. (2007).

One important characteristic of ICDAS is that researchers can choose the stage of the caries process they want to research; for example, they can choose to research established decay (from codes 3 to 6) or severe decay (from codes 5 to 6). As was explained by Melgar *et al.* (2016), ICDAS can be transformed into the dmft index, where each tooth receives the worst ICDAS code of its five surfaces. Based on the literature, the same authors transform ICDAS codes 3-6 into the d component of dmft index; such a converted index can be written as $d_{(ICDAS\ 3\text{-}6)}$mft.

Regarding the use of both dmft and ICDAS, as Melgar et al. (2016) concluded, if the objective of the research is to determine the need of clinical care, dmft may be sufficient. By contrast, if more comprehensive research is required, ICDAS should be used.

2.3.3 Caries prevalence

Prevalence can be defined as the percentage of the population that have caries (Daly *et al.*, 2013). Thus, caries prevalence can be obtained from different oral health indices. For example, if the oral index used is $d_3$mft, the caries prevalence is calculated considering all of the individuals that have developed one tooth with caries, either decayed or filled or missing ($d_3$mft>0). Similarly, if the oral index is dmfs, caries prevalence is calculated including those children that develop at least one surface with caries ($d_3$mfs>0).

Using caries prevalence data, it is possible to determine the percentage of caries-free individuals ($d_3$mft/s=0). Such terminology is frequently used in epidemiological surveys; however, it must be remembered that the caries-free population includes also those individuals with initial caries and enamel caries defined as d_1 and d_2, respectively (Pine and Harris, 2007); therefore, the calculated caries-free population is not completely caries free.

Special attention must be given here to the other name used to describe a dmfs/t > 0 in children younger than 6 years of age; some researchers refer to this pathology as early childhood caries (ECC). The definition of ECC given by the Academy of American Pediatric Dentists is the presence of one or more decayed, missing, or filled tooth surface in primary dentition in children younger than 6 years of age (Evans *et al.*, 2013a). However, as was noted by Dye *et al.* (2015), despite the wide use of such terminology, the use of several diagnostic criteria and operational definitions limits comparability across studies.

To conclude, several ways to measure caries have been developed thus far, each one with advantages and disadvantages. Even though there is some degree of compatibility between them, researchers need to be cautious when they compare populations studied using different dental indices.

2.4 Epidemiology

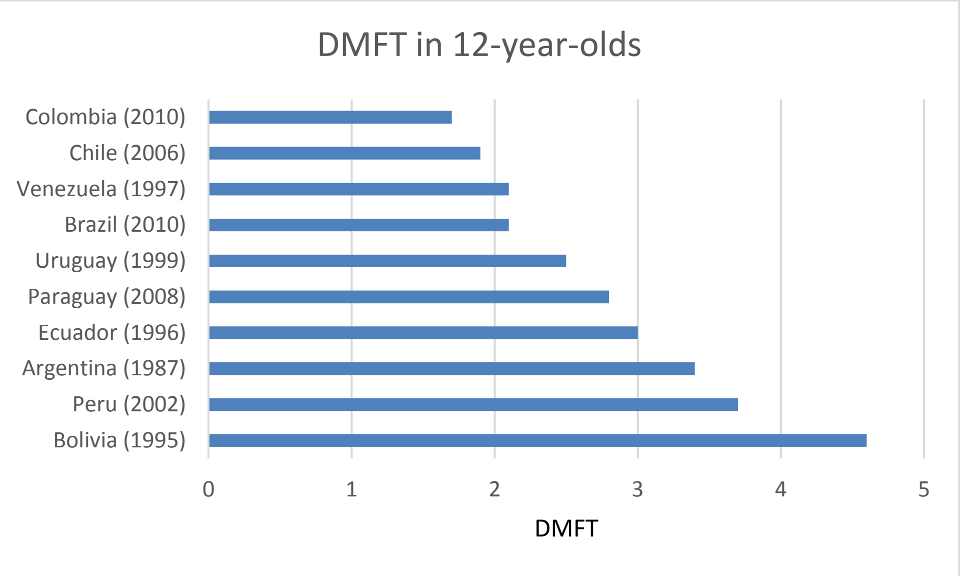
Most adults have experienced caries in most countries and, as Petersen *et al.* (2005) stated, this disease has been considered one of the most important global oral health burdens. Indeed, in a systematic review and meta-regression, Kassebaum *et al.* (2015) concluded that in the year 2010, untreated caries in adults (D component of DMFT) was the most prevalent disease worldwide, affecting 2.4 billion individuals. The same authors also concluded that untreated caries in primary dentition (d component of dmft) was the 10th most prevalent condition, affecting 621 million children worldwide.

The prevalence of caries varies among and within countries, and across every age group as well. As an example, Figure 2.1, which is based on data obtained from the Oral Health Country/Area Profile Project (CAPP) of Malmo University and the WHO, shows the variability of DMFT scores among South American countries in 12-year-old adolescents; it is possible to observe important differences among countries, and it should be noted that Chile has one of the lowest scores.

Furthermore, the distribution of caries is not homogenous among a given population and the evidence demonstrates that there are specific groups within populations with high levels of caries, even in high-income countries (Selwitz et al., 2007; Pitts et al., 2011). A high burden of disease within a population is usually related to poverty, low educational level, geographic isolation and other socioeconomic characteristics, all of them linked to oral health inequalities (Hobdell *et al.*, 2003;Pitts *et al.*, 2011).

Petersen *et al.* (2005) established in a WHO report that the pattern of caries prevalence is changing. Caries prevalence is decreasing in several developed countries, both in children and in adult populations; mainly due to public health measures and changes in living conditions, such as economic improvement for example. However, caries has not been eradicated, it has just been controlled (Petersen, 2003).

Unfortunately, such economic improvement also allows access to more refined sugar, which alongside with inadequate exposure to fluorides has had a negative impact in developing countries, where it is expected that caries will increase (Pitts *et al.*, 2011). However, this predicted increment in developing countries is controversial; a systematic review of epidemiological evidence performed by Cleaton-Jones *et al.* (2006) in 5 to 6-year-old children and 11 to 13-year-old children does not support such an increment.



In brackets, year of the last nationwide oral health survey.

Figure 2.1. DMFT at 12-year-olds in South America.

Additionally, there is strong evidence that caries is decreasing in South America. For example, in the Chilean context, Soto *et al.* (2007b) in a nationwide oral health survey concluded that prevalence of caries in 12-year-old adolescents has dropped from 84.4% in 1996-1999 to 62.5% in 2007. In the same age group, Brazil has showed a decrease in D_3MFT from 2.8 in 2003 to 2.1 in 2010 (Ministerio da Saude).

The evidence shows that both caries prevalence and caries extent are decreasing in South America. Based on this evidence, there is disagreement about whether more or less investment in prevention is required. Some governments might take advantage of this momentum and focus their efforts to reduce this pathology even more. Unfortunately, other governments might argue the opposite and decide not to invest in caries prevention.

2.5 Impact of caries in the primary dentition

2.5.1 Clinical impact

Clinically speaking, caries not only affects dental and oral tissues, as the breakdown in dental hard tissue could also form an entry point that would allow microorganisms to access the body more readily (Michael and Hibbert, 2014). This implies that individuals may suffer pain (sometimes extreme), have a reduction in the functionality of craniofacial structures (caused either by the pain or as a product of tooth extraction), and, in a few cases, may die as consequences of caries (Casamassimo et al., 2009).

Additionally, in childhood, caries influences general growth, psychological development, social interaction, self-image of children, and affects families; in other words, caries affects quality of life (Casamassimo et al., 2009). This was corroborated by Scarpelli *et al.* (2013) who, using an instrument to measure the oral health-related quality of life (OHRQoL), found in a Brazilian population of children aged 5-years that development of caries (dmft>0) had a negative influence on the quality of life of children and their families.

Caries pathology continues to develop during the entire lifetime of an individual, which means that susceptibility to caries continues into adulthood (Selwitz *et al.*, 2007). More importantly, onset of caries at an early age is related to the risk of developing more caries later on, as described by Andre Kramer *et al.* (2013) who found, in a Swedish cohort followed from 3 to 6 years of age, that in 6-year-olds, children that developed caries at 3 years of age had an increased risk of developing new caries compared to those who were caries-free at age 3.

Developing caries at an early age is highly associated with development of caries in the permanent dentition during adolescence and in adulthood as well. For example, Skeie *et al.* (2006) found, in a Norwegian cohort, a statistically significant difference (p = 0.004) in development of caries in 10-year-olds (D_{1-5}MFS > 0) between children with or without caries at 5 years of age (d_{1-5}mfs > 0), where the former had a prevalence of 81.4% and the later had a prevalence of just 61.4%.

A similar example was shown in a study by Peres *et al.* (2010) that compared the relationship between caries in primary dentition and adult dentition in a seminal Brazilian cohort study of Pelotas. They found that caries prevalence in 12-year-olds was 30.6% for those children who were caries-free children at 6 years of age, whereas caries prevalence was 70.9% in 12-year-old children who had dmft scores ranging from 4 to 19 at 6 years of age. Other similar findings have been identified in diverse populations, as demonstrated by Masood *et al.* (2012), Alm *et al.* (2012), and Isaksson *et al.* (2013).

2.5.2 Non-clinical impact

The nonclinical caries impact is related to the infrastructure and workforce (public or private) required to treat the disease (Casamassimo *et al.*, 2009), productivity loss of patients or family members, and school absences. For example, regarding school attendance of children and adolescents, Jackson *et al.* (2011) showed, in a study conducted in North Carolina-USA, that reduction in school performance was associated with school absences secondary to dental pain or infection. The same authors found that children missed an average of 0.5 days of school due to caries. In the case of adults, Hayes *et al.* (2013) estimated, in a study done in Canada, that a mean of 3.5 hours per year were lost from work, school, or normal activities; with potential productivity losses of over USD 1 billion.

All these consequences are undoubtedly linked to costs. For example, the traditional curative care approach is a significant economic burden even for industrialised countries that expend 5-10% of their public health expenditures on these kinds of treatments (Petersen *et al.*, 2005). This estimation is slightly higher than a study by Listl *et al.* (2015) who estimated that the global dental expenditure was USD 297.67 billion for year 2010, which corresponds to 4.6% of the global health expenditure.

The current data highlight the importance of reducing caries at early stages of life, by allowing a reduction in caries in adolescence and adulthood. From an economic perspective, investing in caries prevention would avoid productivity losses and reduce economic burdens related to oral health.

Summarising, caries in primary dentition has clinical and non-clinical effects. The clinical effects are strongly related to the quality of life of children and adult dentition and the non-clinical effects impact general development of children and also have economic implications. This evidence, lead us to think that the best alternative for improving children’s oral health related quality of life, reducing caries in adult dentition, and reducing the dental expenditure, is to prevent the onset of caries and its development in the primary dentition. Several strategies used to reduce the impact of caries on primary dentition will be described and analysed in Chapter 3.

2.6 Risk factors and determinants

Despite caries being an infectious disease, due to its unique characteristics, it is more comparable to chronic disease (Petersen, 2009). The pathology is influenced by multiple factors that are related to biological characteristics of the host, type and composition of microorganisms, change in the environment of populations, individual behaviour, and lifestyle (Fisher-Owens *et al.*, 2007;Selwitz *et al.*, 2007).

Undoubtedly, knowing which factor or combination of factors can be used as predictors of future caries is essential for both clinicians and policy-makers. As can be seen in this subsection, several researchers have tried to solve this question; however, the answer has never been simple. For example, Harris *et al.* (2004) performed a systematic review in order to detect which factors are associated with caries in preschool aged children and they concluded that 106 factors and determinants were related to caries in the 73 studies analysed. This very large number of factors reveals the complexity of caries.

The same authors also highlighted the difference between risk factors and risk indicators. Risk factors are related to exposure prior to the outcome. In other words, a proper definition of a risk factor must clearly establish that the exposure has occurred before the outcome (Burt, 2005); longitudinal studies are needed to prove such risk factors. On the other hand, exposure to risk prior to the outcome cannot be proven as risk indicators; they are more related to cross-sectional studies (Burt, 2005). Nevertheless, to give more fluidity to the text, this thesis uses the term risk factor to define both risk indicators and proper risk factors.

Furthermore, risk factors are not easily classified because they are intimately linked; this complexity can be observed in the different classification schemes used by different researchers (Harris *et al.*, 2004;Bramlett *et al.*, 2010;Borges *et al.*, 2012). Thus, in order to simplify the analysis, risk factors are classified here into five groups or areas: sociodemographic, socioeconomics, feeding habits, oral hygiene habits, and oral health services. The relationship between caries prevalence and the use of fluoride is discussed later in this chapter.

Describing all risk factors known to date is beyond the scope of this thesis; therefore, only those deemed significant for this thesis are included.

2.6.1 Sociodemographic factors

Caries is a chronic infectious disease, the legacy of which increases with age. As an example, in a study performed in Southern Italy, Nobile *et al.* (2014) found a relationship between the age of children (aged between 36 and 71 months) and caries prevalence. Similarly, Kramer et al. (2013) found that 6-year-olds children that developed caries at 3 years of age had a 2.29 times greater probability of developing new lesions (dmfs) than those who were caries-free. Unfortunately, these findings are not surprising given the chronicity of caries and the cumulative effects of the oral indices frequently used in these studies.

There is a good consensus among dentists that caries prevalence is not related to gender during early childhood. Several studies have demonstrated this fact such as Ferreira *et al.* (2007), for example, who studied children aged 0 to 5 years attending government nurseries in Canoas, Rio Grande do Sul-Brazil. Another study, by Piovesan *et al.* (2010) that evaluated children under 6-year-old in Santa Maria in Rio Grande do Sul, demonstrated this finding as well. Similar results were found in Lamezia Terme-Italy by Nobile *et al.* (2014).

Nonetheless, some studies show a difference in gender, such as Declerck *et al.* (2008) who found in a Belgian population of children aged 5 years that girls are less likely to develop caries (dmft > 0), which in a multivariate logistic regression model gave an odds ratio (OR) of 0.37 (95% CI, 0.19 to 0.71). However, in the same study, the authors did not find an association in children aged 3 years.

2.6.2 Socioeconomic factors

The prevalence and severity of caries is highly related to socioeconomic factors such as income, educational level, and socioeconomic status (Fisher-Owens et al., 2007). A good example concerning the relationship between caries prevalence and family income was discussed by Peres *et al.* (2003) who studied a preschool population in Southern Brazil, the Pelotas cohort, and found that those families with incomes below the minimum wage were 7.7 (95% CI, 2.5 to 23.2) times more likely to develop caries than a family with an income greater than 6 times the minimum wage. In another Brazilian study, Ferreira et al. (2007), also using minimum wages, determined that those children (aged 0-5 years) whose families earned less than two times the minimum wage had more caries than those families with 3.5 or more times the minimum wage (OR 1.36; 95% CI, 0.96 to 1.93).

In addition, caries prevalence is highly related to the educational level of the parents, particularly with that of the mother, as was demonstrated by Peres *et al.* (2003) who detected that those children whose mothers had 8 or less years of education were 2.6 (95% CI 1.6 to 4.2) times more likely to develop caries than those whose mothers had more than 8 years of education. Along the same lines and in the same country, Piovesan *et al.* (2010) found that those children whose mothers had less than 8 years of education were more likely to have dmft > 0 than those whose mothers have 8 or more years of education, and presented a prevalence ratio (PR) of 1.42 (95% CI, 1.11 to 2.13). Similar findings were published by Tanaka *et al.* (2013) who found in a Japanese population that 15 or more years of education of the mother had a protective factor, with an OR of 0.32 (95% CI, 0.14 to 0.70), compared to those children whose mothers had less than 13 years of education.

Some authors have studied the influence of socioeconomic status (SES) on the prevalence and severity of caries. This approach causes problems, given that different definitions of SES are used in different studies (Petersen, 1990). For example, Pieper *et al.* (2012), in a German population, used educational level, vocational training, and occupational status of parents to categorise children into low, medium, and high SES; they found that children of low SES had almost twice the incidence of caries (dmft = 2.46) than those from high SES (dmft = 1.33). In a Brazilian study, Piovesan *et al.* (2011) used the type of school as a proxy of SES and found that those preschool children who attended public schools (low SES) had a 1.99 times (p = 0.008) greater probability of developing caries compared with those who attend private schools (high SES).

These studies support the conclusion that the poorest children have a higher caries prevalence and larger numbers of carious teeth. Such children usually have less educated parents, worse eating habits, poor oral hygiene habits, and less access to dental services. Undoubtedly, all of these factors cause health inequality; the existence of such inequalities is a universal phenomenon (Sisson, 2007) that affects more deprived populations, no matter the age of individuals.

2.6.3 Factors related to dietary habits

Consumption of processed sugars

Caries in preschool aged children is related to the consumption of foods and drinks rich in added sugar, which are all mono- and disaccharides added to food by the manufacturer, person preparing the food, or consumer (Sheiman and James, 2015). Several studies have explored this relationship. For example, Evans *et al.* (2013a) found that the consumption of more than 150 ml of sugar-sweetened beverages per day increases the likelihood of having severe early childhood caries (ECC), up to 4.6 times more than children that do not drink sugary drinks. Similarly, Pieper *et al.* (2012) found that when children consume 3 or more sugary drinks per day, the risk of caries increases by 53%. Similar results were obtained by Han *et al.* (2014) in a South Korean population, where they found a relationship between the frequency of snack and sugary drinks and severe ECC.

Use of baby bottles

Evidence suggests that there is no relationship between being bottle fed and caries prevalence. For example, Congiu *et al.* (2013) showed, in an Italian study of children aged 18-60 months, that the use of a bottle for feeding had no effect on caries prevalence (OR = 1.74; p = 0.06). Nobile *et al.* (2014), also in an Italian population, found that children fed with a baby bottle developed more caries (dmft = 0.89) than those who were not bottle fed (dmft = 0.41); however, they did not find an association between being bottle fed and caries prevalence (p = 0.23). Similar findings related to a lack of association between caries prevalence and baby bottle use were obtained by Declerck *et al.* (2008) in a Flemish population aged 3 years.

Feeding opportunity

An important point related specifically to the youngest age groups is the concept of feeding opportunity. There is a suggestion that feeding the child while he/she is going to sleep can affect caries development. This can be observed in a study performed by Pieper *et al.* (2012) who found that the use of bottle feeding during night-time increased the risk of caries 2.05 times (95% CI, 1.25 to 2.85) in children aged 8 months or more, compared with children aged less than 8 months. The same effect was obtained when other food as in the oral cavity while child is asleep; Congiu *et al.* (2013) found that the use of sweetened baby pacifiers at night increased the risk of caries.

2.6.4 Factors related to oral hygienic habits

The start date of oral hygiene habits plays a significant role in caries development. For example, Declerck *et al.* (2008) showed that those children who started brushing their teeth after the age of 2 years had a 3.22 greater probability of developing caries than those who started brushing at age one year or younger. Similarly, Pieper *et al.* (2012) showed that children that began brushing their teeth at age 2 or later were 53% more likely to develop caries at older ages (5 to 7 years).

Related to the question about who should brush a child's teeth, it is broadly accepted that the probability of having caries decreases when the parents perform the brushing. For example, Pieper *et al.* (2012) showed that when parents do not brush to the teeth of their 3-year-old, the probability of developing caries is 1.75 times greater than when they do.

As with other risk factors, other research has shown that this factor is not statistically significant. An example of this was given by Declerck *et al.* (2008) who found that helping with teeth brushing was not statistically significant for 3-year-olds nor 5-year-olds.

How many times tooth brushing is performed per day is also considered significant. This fact was demonstrated by Peres *et al.* (2003) who found, in a univariate logistic regression model, that those children who brushed their teeth once or twice a day were 1.5 (95% CI 1.0 to 2.4) times more likely to develop caries (dmft > 0), compared with children that brushed their teeth more than 3 times per day.

On the other hand, Nobile *et al.* (2014) found no statistical difference ($p=0.58$) when children brushed their teeth less than once a day, once a day, or more than once a day. Similar results were found by Declerck *et al.* (2008) whose results did not reach significance at a level of 5%.

2.6.5 Dental health services

In general, it is accepted that most preschool children do not have access to dental services unless they develop symptoms. This phenomena has been demonstrated by Naidu *et al.* (2013) who found that 28.7% of caries-free children had already visited a dentist or dental nurse between the age of 3 and 5, comparatively less than 51.4% of those children with caries ($p < 0.01$). Similar logic was described by Nobile *et al.* (2014) who found that 39.3% of children with caries had already accessed dental services between 36 and 71 months of age, compared with 15% of caries-free children ($p < 0.001$).

2.6.6 Predictive value of risk factors at population level

It is possible to conclude, from the previous paragraphs, that several factors are related to caries prevalence and caries severity, either as protective factors or as risk factors; however, depending on the population being analysed, such factors may or may not be statistically significant (Harris et al., 2004). Consequently, the findings in one population might not be easily extrapolated to another population.

Trying to find which factor truly is either a protective factor or risk factor is difficult. This is mainly due to the fact that most studies performed to find caries predictors are cross-sectional studies (Harris et al., 2004). However, such a type of study is not the ideal type of study design for such a purpose because the temporal association usually cannot be specified (Burt, 2005). Also, researchers may overspecify the regression models with irrelevant variables, thereby producing bias in the models (Wooldridge, 2009). Or it simply may be due to the fact that development of caries has different behaviour depending on population (Selwitz *et al.*, 2007). It has been suggested that the association of these factors should be investigated in future studies.

In the end, no single risk factor has a high level of predictive value, except for previous development of caries (Skeie et al., 2006, Andre Kramer et al., 2013). Unfortunately, this predictive factor is not useful when the objective is to increase the number of caries-free children ($d_3$mft = 0).

Consequently, more studies are required to identify which risk factors, or combinations of them, would specifically affect the Chilean preschool population.

2.6.7 Predictive value of risk factors at individual level

Since the early 1990s, dentists have tried to develop a predictive model of caries based on individual risks, or caries risk assessment (CRA). The objective of this approach has been to guide the practitioner in clinical decision making. CRA has been defined by Hurlbutt and Young (2014) as a formalized process where the probability of change in caries lesions (number, size, or activity) over a specific period of time can be obtained.

Several CRAs have been developed since then. For example, one of the first was published CAMBRA, developed by the California Dental Association (Featherstone *et al.*, 2003). This would be defined as an evidence-based approach to prevent or treat caries at an earlier stage. This methodology has a questionnaire with 24 items including risk indicators, risk factors, and protective factors and it can classify a child as having low, moderate, or high risk of caries.

However, despite their good intentions, there is no statistically valid and reliable method of CRA (Tellez *et al.*, 2013). The same authors highlight that the main evidence, which the predictability of CRA is based on, comes from cross-sectional studies; such studies, as was noted earlier in this chapter, only determine relationships and not causal mechanisms.

2.7 Summary

This chapter covered the basic concept of caries, its formation process and the fact that caries is preventable and completely reversible during the first stages of development. The epidemiology of caries was also discussed, highlighting the impact/burden of such pathology and the relationship between caries in primary dentition and caries in adult dentition. Oral health indices were also commented on, particularly DMF/dmf and caries prevalence.

Risk factors were analysed as well, concluding that caries prevalence is highly associated with socioeconomic inequalities and that those risk factors that are statistically significant in one population cannot be necessarily extrapolated to other populations.

Chapter 3. Caries prevention in preschoolers

3.1 Introduction

As will be explained in more detail in Chapters 4 and 6, Chile has a high rate of caries prevalence in the preschool population; indeed, the official figures show that only 30% of children aged 6 years are caries-free. Aware of this problem, as was commented in Chapter 1, the Chilean Ministry of Health (MINSAL) established increasing this caries-free rate by 35%, from 30 to 40% as a goal for the decade 2011-2020 (MINSAL, 2011).

In order to reach such a goal, MINSAL has launched a national community-school-based tooth brushing programme and has been evaluating a FV application programme (MINSAL, 2012c). Both interventions have pros and cons, to be analysed in this chapter.

However, the interventions proposed by MINSAL are not the only alternatives available. Given that caries is a multifactorial disease (Chapter 2), there are several other options for their prevention. Such options vary, for example, from modifying behaviours related to both oral hygiene and dietary habits to improving the enamel surface using fluoride treatments.

This chapter analyses caries preventive approaches available to preschool populations and explains why each approach may or may not be suitable for Chile, giving special emphasis to all those strategies associated with national programmes (MINSAL, 2012c) and their possible enhancements; a deeper analysis of all possible caries prevention interventions is out of the scope of this thesis.

3.2 Interventions

3.2.1 Fissure sealants

Pit and fissure sealants are an intervention that prevent and arrest the progression of non-cavitated carious lesions in which a thin layer of an adhesive material (either resins or glass ionomer based materials) is placed on molar occlusal surfaces. This technique works as a mechanical barrier between pits and fissures and the oral cavity; the material avoids both the colonization of microorganisms and the access of microorganisms to food particles. This intervention is highly recommended to be used in both school children and adolescents based upon the result of systematic reviews performed by health related governmental agencies

(CADTH, 2016;Wright *et al.*, 2016). However, there is insufficient quality evidence in young children, as was shown by Twetman and Dhar (2015) in another systematic review.

3.2.2 The uses of systemic fluoride

Two models of fluoride administration, systemic and topical, have an effect on caries prevention. Systemic administration prevents caries by modifying the developing enamel and producing fluorapatite crystals. However, evidence suggests that the best caries preventive approach is through topical administration during the remineralization process (Cameron and Widmer, 2013).

Systemic availability of fluoride ions relies on fluoride passing from the blood to the oral cavity through the saliva secretion from the salivary glands. This way allows a constant flow of very low quantities of fluoride into the oral cavity. Given that the main effect is post-eruptive, systemic fluoride would only be active and effective after tooth eruption. Furthermore, it needs to be constantly present in the oral cavity. The constant presence of fluoride ions, at very low concentrations in the interphase between tooth and dental film (or plaque) provides the most effective way to remineralise demineralized enamel (MINSAL, 2008).

Fluoridated water

Fluoridated water is the most important systemic method of caries prevention and it has been in use for almost 70 years (Mullen, 2005). Chile adopted this method during the middle of the 1980s. However, despite huge amounts of evidence and experience that confirms fluoridated water as a safe method, the global coverage is low. For instance, only 10% of population in UK has an optimally fluoridated water (1 ppm) (BFS, 2013). According to Cobiac and Vos (2012), only a 69% of Australia's population receive fluoridated water at the recommended minimum concentration (0.7 ppm).

Several studies show the benefits of fluoridated water in younger populations. Armfield (2010), using data from an Australian national surveillance survey of children's dental health, studied children aged 5 years with concentrations of fluoride equal or higher than 0.7 ppm or with concentrations with less than 0.3 ppm and found that the former demonstrated a dmft = 1.56 and a prevalence of 38.4%; in the latter, they obtained a dmft = 2.25 and a prevalence of 49.5%. Both caries prevalence and severity were statistically significant with a p-value less than 0.001. Further studies are reported in Chapter 7.

With this method, every single person in a community can access the benefits of fluoride and use of fluoridated water is considered an excellent way to reduce differences in oral health caused by socioeconomic factors (Yeung, 2008). For example, Riley *et al.* (1999) established that the introduction of water fluoridation reduced inequalities in dental health in a substantial way; the same authors also showed that fluoridated water reduced development of caries more effectively in populations of low socioeconomic compared to populations of high socioeconomic status. Nevertheless, there are some discrepancies related to this point. For example, Iheozor-Ejiofor *et al.* (2015) found, in a Cochrane systematic review which analysed prospective observational studies, that there is insufficient evidence to show that fluoridated water can alter disparities in caries development between groups with different socioeconomic status.

Several studies show that fluoridating water is cost-effective, for instance, Cobiac and Vos (2012) in an Australian study using Monte Carlo simulations (see Chapter 5), stated that extending the coverage of fluoridated water to all Australian communities (of at least 1,000 people) can avert 3,700 DALYs (95% uncertainty interval [UI] from 2,200 to 5,700) in children and adolescents, over the lifetime of the water treatment plant. Fluoridated water is cost-effective in the Chilean context as well. In a study about 12-year-olds Chilean adolescents, Mariño (2013) concluded that when no fluoridated water is compared with fluoridated water, the cost effectiveness ratio (see Chapter 5) showed that on average fluoridated water saved CLP 8,931 (95% UI from 7,950 to 10,121) per cavity-affected tooth (DMFT).

The history of fluoridated water in Chile began in 1953 with the first national programme; however, this programme was officially cancelled in 1977. A second programme started in 1985 in the Valparaiso Region expanded incrementally until it covered approximately 82.3% of the population (Mariño, 2013). Currently, due to opposition from a section of the population, the only non-fluoridated region is the Biobío Region (MINSAL, 2013a).

Fluoridated salt

Fluoridated salt has been used as an alternative to fluoridated water when the latter is not possible due to technical or legal reasons (Marthaler, 2013). Salt is commonly fluoridated at 250 ppm (ranging between 200 to 250 ppm); this means that an adult would on average ingest 1 mg of fluoride per day, given that an adult consumes around 4 grams of salt per day (Gillespie *et al.*, 2007). At the preschool level, Pieper *et al.* (2012) found in a cross-sectional study that children that did not consume fluoridated salt had more caries than those that did (OR = 1.33, 95% CI, 1.03 to 1.72).

Regardless the positive effects of fluoridated salt, there is not a national programme using this technology in Chile. A possible explanation for this could be due to the priority given to fluoridated water as the main systemic way of fluoride delivery (MINSAL, 2008). Another possible explanation may be related to the fact that Chilean consumption per capita of salt is 9.8 g/day, almost the double than the maximum (5 g/day) suggested by the WHO (PAHO, 2013); hence, support for a fluoridated salt programme may be seen as counterproductive.

Fluoridated milk

Since the fifties, several studies have been performed to analyse the effect of fluoridated milk on caries prevention. For example, in a Chilean community trial, Mariño *et al.* (2001) found that fluoridated milk reduced dmfs by 41% ($p < 0.01$) in children aged 3 to 6 years. In another example, Petersen *et al.* (2015), in a Bulgarian parallel arm 5-year cohort study of 3-year-old children, concluded that caries development in primary dentition was 46% ($p < 0.001$) and 30% ($p < 0.01$) lower in the fluoridated milk group compared with the non-fluoridated milk group in intervention and control communities, respectively. Nevertheless, despite the positive effect found in some studies, Yeung *et al.* (2015) reported in a Cochrane systematic review that there is not enough evidence to conclude that fluoridated milk is beneficial for school children.

Chile has undertaken important research related to fluoridated milk (Villa *et al.*, 1989;Mariño *et al.*, 2001;Marino *et al.*, 2004;Weitz *et al.*, 2007). Such investigations led to MINSAL, in those rural schools where fluoridated water is not available, to initiate a programme of fluoridated milk in 2000. This programme covers children attending public school from the age of 6 to 14 years old (MINSAL, 2008;Banoczy *et al.*, 2013). However, due to the expansion of the availability of fluoridated water sources, coverage of this programme is reducing. This reduction could be due to the priority given to fluoridated water programmes.

3.2.3 The use of topical fluorides

Topical fluoride acts as catalyst for the diffusion of calcium and phosphate into the tooth and rebuilds tooth surfaces due to formation of fluoridated hydroxyapatite and fluorapatite crystals, which are more resistant to acid attack than hydroxyapatite (Selwitz *et al.*, 2007). Also, topical fluoride has an effect on the glycolytic cycle of oral microorganisms, thus reducing the production of acid and affecting metabolism of intracellular carbohydrates (MINSAL, 2008).

Topical administration of fluoride allows fluoride ions, at very high concentrations, to directly reach the interface between the tooth and dental biofilm, without having to pass through the circulatory system. This avoids fluoride ions reaching other parts of the organism. However, given the high concentrations used, the risk of acute fluoride intoxication through ingestion increases. The probable toxic dose, defined as the dose that requires therapeutic intervention and hospitalization, has been calculated to be 5 mg F/kg (Shulman and Wells, 1997). Such information is extremely important for children under the age of 6 who have less control of deglutition or swallowing reflexes. Topical fluorides come in various forms such as toothpaste, gels, mouthwashes, FV, etc. They will be discussed in the following sections.

Fluoride toothpastes

In a systematic review, dos Santos *et al.* (2013) compared fluoride toothpastes associated with oral health education against no intervention. This review included individual or cluster randomized or quasi-randomized controlled trials in children with primary dentitions not older than 7-year-olds at the end of the eligible studies. They found that children who used standard fluoride toothpaste (1,000-1,500 ppm) had significant caries reduction at surface levels with a prevention fraction or PF (defined as the measure of treatment effect presented for caries increment) of 31% (95% CI, 18 to 43), as well as at the level of the tooth (PF = 16%; 95% CI, 8 to 25). The effect of toothpastes with fluoride concentrations over 1,000 ppm was similar to that reported by a Cochrane systematic review performed by Walsh *et al.* (2010) who compared different concentrations of fluoride and showed that the pooled estimate was statistically significant (RR 0.87; 95% CI ,0.81 to 0.93) in favour of a higher fluoride concentration (>1,000 ppm).

The same authors (dos Santos *et al.*, 2013), found that low concentration fluoride toothpastes (<600 ppm) compared with no interventions, were not statistically significant (RR = 0.87; 95% CI 0.65 to 1.17) at reducing the percentage of children that developed caries. On the other hand, they found that a standard fluoride toothpaste (1,000-1,500 ppm) resulted in a statistically significant reduction in the percentage of children that developed caries (RR = 0.86; 95% CI, 0.81 to 0.93). Nevertheless, the use of such toothpastes was associated with mild but not aesthetically objectionable fluorosis (or enamel defects during the tooth formation).

Based upon the evidence discussed above, the suggestion made by MINSAL (2012c) to use toothpastes with fluoride concentrations less than 600 ppm should be re-evaluated.

Fluoride gels and mouthwashes

Marinho *et al.* (2015) conducted a Cochrane systematic review about the use of fluoride gels, including randomised or quasi-randomised controlled trials where 'blind outcome assessment' was stated or indicated. They found a prevention fraction of 20% (95% CI 1 to 38; p = 0.04) at the surface level (dmfs) in children aged 2 to 6.5 years. The authors highlighted the wide CI and recommended that the results should be viewed with caution, given that standard deviations of two of the three studies were imputed. At the same time, they found scarce evidence about the frequency of accidental swallowing of the gel during treatment.

Fluoride gels typically used contain acidulated phosphate fluoride with a concentration of 12,300 ppm. The Chilean Ministry of Health has used this technology in non-water-fluoridated schools for more than 15 years. However, given that most of the Chilean population can access fluoridated water at the moment, this fluoride application is hardly used in caries preventive programmes. Also, given the risk of ingestion and possible fluoride overdose (Ripa, 1990), MINSAL has contraindicated the use of such gels in children under 6 years old (MINSAL, 2008).

Fluoride mouthwashes contain 0.2% sodium fluoride. Such a solution is used in Chile in supervised weekly rinsing programmes in non-fluoridated school communities, due to the positive effect found in the literature in which a pooled estimate by Marinho *et al.* (2016) resulted in D(M)FT prevention fraction of 23% (95% CI, 18 to 29; p < 0.0001). However, given the risk of accidental intake, MINSAL has stated that its use is contraindicated for children under the age of 6 years (MINSAL, 2008;MINSAL, 2009b).

Despite the positive effects on caries reduction for some highly concentrated topical fluoride applications such as fluoride pastes, gels, and mouthwashes, the American Dental Association in their updated clinical recommendations on topical fluoride for caries prevention (Weyant *et al.*, 2013) concluded that only 2.26% FV is recommended for children younger than 6 years of age. This was based on the high risk of nausea and vomiting associated with gel and mouthwashes, as well as the risk of fluorosis due to the ingestion of fluoride.

Fluoride varnish

Fluoride varnish (FV) was initially developed in 1964 with the objective of prolonging the contact time between fluoride and dental enamel (Seppa, 2004). FV contains a highly-concentrated fluoride active ingredient (i.e., a high concentration of fluoride ions), in a base that allows the product to adhere to the tooth surface even in presence of saliva. The fluoride ion can form fluorapatite crystals during the remineralisation process and interact with saliva, forming calcium fluoride (CaF_2) that releases fluoride ions when the pH drops.

The oldest and best studied product is Duraphat (Colgate Oral Pharmaceuticals by Pharbil Waltrop GmbH, Waltrop, Germany), which contains sodium fluoride at 50 mg/ml or 22,600 ppm of fluoride ion in a natural colophony base. Others product based on the same active ingredient at the same concentration include, amongst others, Fluoridin, Durofluor, and Cavity Shield. Another product, Fluor Protector, has a different composition containing fluorsilane in a polyurethane polymer. No matter the brand of the product, FV must be applied on teeth surfaced using a microbrush, probe, or swab. There are two methods of administration, single and multiple-doses.

Efficacy

Several systematic reviews and meta-analyses have been performed in order to determine the effect of FV on the preschool population, among them, Carvalho *et al.* (2010) who included randomized, controlled clinical trials, and quasi-randomized studies. They compared FV application and no intervention or placebo and calculated the prevention fraction (PF) of dmfs. The target population were preschool aged children (up to 6 years old). They concluded that the studies analysed in this systematic review suggest that FV can reduce caries incidence, but they did not find conclusive scientific evidence to support this.

In another Cochrane systematic review, Marinho *et al.* (2013) compared FV application versus either no intervention or placebo. This review included randomised and quasi-randomised controlled trials with blind outcome assessment used or indicated; in children with primary dentition aged 1 to 8 years. They found that FV caused a significant reduction in caries (37%; 95% CI, 24 to 51) at the surface level (dmfs); however, at an individual level, despite finding a caries reduction (RR = 0.81), the difference was not statistically significant in the meta-analysis (95% CI, 0.62 to 1.06). Despite the fact that there is evidence to suggest that FV has a positive effect on primary dentition, this finding must be taken into consideration carefully because the target population included children with mixed dentitions, which is beyond the objective of this thesis.

There are no systematic reviews that analyse the effect of FV on caries prevalence in a caries-free preschool population; there are only two studies that were designed to evaluate this question, the studies of Weintraub *et al.* (2006) and Tickle *et al.* (2011). Recently, the results of the latter one, the Northern Ireland Caries Prevention in Practice Trial or NIC-PIP (see 3.6.4), which was ongoing during the development of this thesis, have recently been published (O'Neill *et al.*, 2017;Tickle *et al.*, 2017).

Few studies can be found about the cost-effectiveness of FV, for instance, Quinonez et al. (2006), evaluated the cost-effectiveness of FV during attendance at a Medicaid well-child appointment in North Carolina, USA. In this programme, FV was applied by physicians to children aged 9 to 42 months. The study included clinical data only and used the number of months without cavities per child as the outcome. The authors concluded that FV is not cost saving in the 42 first months of life. Unfortunately, given both the difficulties of measurement and the lack of clinical significance, the outcome is very difficult to apply in a public health programme.

The pilot study (NIC-PIP), published at the beginning of 2017 (O'Neill et al.) found no statistically significant difference ($p = 0.81$) in caries prevalence (at dmft>0 or caries-free level) between intervention group (FV) and control group (no FV). However, Tickle et al. (2017) found statistically significant differences ($p = 0.007$) between both groups at surface level (dmfs level), where the intervention group had in average 1.3 fewer carious surfaces than control group. The mean cost per carious surface avoided after a follow-up of 3-years was £251 (95% CI from £ 79.52 to £ 454.39).

In summary, very little is known about the cost-effectiveness of FV and, even less is known about the effect on caries-free populations. Therefore, this thesis will enhance our understanding of the effect of FV on such population.

Furthemore, information related to both the efficacy and costs of FV on caries-free populations would be extremely useful to evaluate MINSAL's goal of increasing the caries-free population by 2020. Due to the importance of determining the correct value of efficacy of FV for this thesis, a systematic review of the effects of FV on caries prevalence in preschool populations was performed and is presented in Chapter 9.

Safety

Related to safety, Duraphat (Colgate-Palmolive, 2014) is contraindicated when the patient is allergic to one of its ingredients (sodium fluoride, colophony, or other ingredients) or when the patient has stomatitis, mouth ulcers, gum disease, or asthma. Unfortunately, the systematic review performed by Marinho *et al.* (2013) did not provide information about the side effects and acceptability.

However, Milgrom *et al.* (2014) who studied the pharmacokinetics of FV application in young children, concluded that sporadic application of FV is safe for young children. They measured urinary fluoride levels of children aged 12 to 15 months five hours after application of FV, following guidance by the American Academy of Paediatrics. These findings are consistent with Weintraub *et al.* (2006) and Salazar (2008) whose studies reported no adverse effects.

Clinical procedure

In general, the procedure of application is very simple and requires a dose up to 0.25 ml (or 5.65 mg fluoride) for primary dentition (Colgate-Palmolive, 2014). The following sequence of application is based on the Chilean protocol of FV application (MINSAL, 2012c).

- Toothbrushing without toothpaste must be supervised by professional or an assistant (educator or technical). Given the age of the children, there is a need for the professional or an assistant to double-check the molar sector, where there is greater accumulation of plaque and caries risk.
- Ask the child to swallow saliva and then open the mouth.
- Use gauze to remove excess saliva and to keep teeth partially isolated and dry. It is not advisable to use cotton wool because it adheres to FV.
- Apply a thin coat of varnish on all tooth surfaces, thicker layers do not protect more and only lead to a loss of material. Apply the varnish by quadrants.

Post-application instructions, also based on Chilean guideline of FV application

- It is desirable to wait at least 3 hours from the application of varnish before the child eats food, and the child should also try to avoid hard foods or hot liquids after application. Only if it is critical, after a half an hour has elapsed, children can drink water, cold milk, or yogurt.
- Do not brush your child's teeth during the rest of the day.

To summarise, FV intervention is safe for use in preschool children, easy to apply, and highly effective. However, the evidence about the efficacy of FV on caries-free populations is scarce. It could be the option of choice for public health programmes, but more studies are required.

3.2.4 Complex interventions

It is important to highlight here that are a significant number of caries preventive techniques not used as unique interventions, but rather as part of a complex intervention, where two or more preventive interventions (or technologies) are used simultaneously. For example, the programme proposed by MINSAL includes three preventive strategies: oral health education, the use of toothbrush with toothpaste, and the application of FV.

Theoretically, a complex intervention has a positive outcome, as the total effect of all strategies would be better than the effect of each strategy on its own. However, a negative aspect is that we do not know what the real effect of each intervention is. This implies that for research proposes, such of complex interventions can only be compared with similar studies.

Two complex interventions, whose components include the use of FV, will be discussed in the following section.

Childsmile

This scheme originated in Scotland due to the high prevalence of caries and inequalities seen between socioeconomic groups. This programme was initiated in 2006 and is composed of several parts: Childsmile Practice, Childsmile Nursery and Childsmile School, and Childsmile Core.

Childsmile Practice is focused on infants under 2 years of age, where dental health professionals work closely with dental health support workers to focus on community-based oral health improvement, provide one-on-one family support, and liaison between health care services. Childsmile Nursery and Childsmile School programs provide clinical preventive activities to children living in the most deprived quintiles such as FV application. Finally, Childsmile Core provides free tooth-paste/toothbrush kits to every child in Scotland at least six times before children turn 5 years old. Also, Childsmile offers free daily toothbrushing to all 3- and 4-year-old children attending nursery school in Scotland (Macpherson *et al.*, 2010).

Two major studies have been published related to the evaluation of such programmes. Macpherson *et al.* (2013) used secondary data (at the country scale) and found a correlation between the initiation of toothbrushing (start of Childsmile) and a reduction in the $d_3$mft; however, as was highlighted by the authors, this study lacked individual school- and child-level data related to the participation in the tooth-brushing programme. In another publication, a research protocol, Wright *et al.* (2015) explained how the tooth-brushing program (Smile Core) and the application of FV (Smile nursery) would be evaluated through a randomised controlled trial.

Northern Ireland Caries Prevention in Practice Trial (NIC-PIP)

This study is part of a pilot study that discusses a possible nationwide programme aimed at reducing caries prevalence in Northern Ireland (Tickle et al., 2011). The trial objectives, in the author's words are:

"To compare over a 3 year period the effectiveness of fluoride varnish, fluoride toothpaste, toothbrush and standardised health education, provided twice a year, as a preventive package, with standardised health education alone provided twice a year in preventing the conversion of 2 to 3 year old children from caries-free at baseline to caries-active state in the primary dentition, reducing the number of carious surfaces (caries into dentine) in the primary dentition in children who convert from caries free to caries active states and preventing episodes of pain and extraction of primary teeth".

As was commented earlier, this is one of few studies designed exclusively to detect the effect of FV on caries-free populations. Nevertheless, given the complexity of such a study, establishing the effect of FV alone is difficult to estimate, as well as comparing this programme with others programmes. On the other hand, this programme is very similar to the Chilean proposal (MINSAL, 2012c); therefore, they may be compared once the results are published.

3.2.5 Settings

School-based

Essentially, this approach is mostly related to those interventions concerning toothbrushing habits and consumption of cariogenic food and drinks. The main objective of these strategies is to achieve behavioural change in children, their families, and their school-communities. Even though there are countless experiences with these kinds of strategies, there is limited evidence about their effects. This was concluded by Cooper *et al.* (2013), in a Cochrane systematic review, as follows:

"Based on this review there is limited evidence that primary school based behavioural interventions that promote twice daily toothbrushing and reduce snacking on sugary foods can prevent caries by improving children's oral hygiene".

This review included RCTs of behavioural interventions in schools with a focus on toothbrushing and cariogenic food and containing skills, instructions, and educational components. The review analysed studies performed in children aged 4 to 12 years. They suggest that behaviour at home play a pivotal role in clinical outcomes and further studies should consider this point, as well as the influence of social determinants of health. In addition, there is limited evidence about the cost-effectiveness of oral health preventive programmes intending to alter the behaviour of people (Watt, 2007).

Undoubtedly, the conclusion of Cooper *et al.* (2013) is controversial and is not shared by many other researchers. For example, Macpherson *et al.* (2013) concluded that a significant improvement in oral health detected in Scottish preschool aged children was likely to due to the nursery toothbrushing program implemented across Scotland. Similarly, Pieper *et al.* (2015), in an RCT performed in Germany in children aged 2-4 years, concluded that a supervised daily toothbrushing programme had a positive effect on high risk preschool populations; where the dmft increment in the test group (intensive daily dental hygiene provided by special personnel) was 21% ($p = 0.043$) lower compared to the control group (visit of dentists to kindergarten once a year).

Interestingly, despite MINSAL's promotion of such behavioural interventions (through the protocol of toothbrushing and community-based application of FV) in the preschool population (MINSAL, 2012c), they did not analyse existing evidence on the effects of both toothbrushing and dietary interventions in school-based communities on making decisions to use these interventions.

Dental surgery

Preschool populations have access to caries prevention interventions, as an alternative to school-based programmes, through the use of dental health services; as was done in NIC-PIP study (see 3.2.4). However, there are some limitations; this section discusses the special characteristics of this age group, which makes the contact between children and dentists difficult, and analyses the participation of non-dental personnel.

It is easy to assume that children have access to preventive caries interventions if they attend routine dental check-ups. Regardless, this age population does not regularly attend routine dental check-ups. Camargo *et al.* (2012), in a Brazilian cohort (Pelotas cohort, see Chapter 3), concluded that the utilization of dental services was low. The same authors explained that one aspect of this phenomenon could be explained as a policy-related issue due to the prioritization given to this school population (from 6 to 14-year-olds) and the emphasis on curative procedures. Similar problems were found in the Chilean context, as was commented by Monsalves (2012), where the priority is given to other dental programmes (e.g., school children) rather than preschool programmes.

In addition, Camargo *et al.* (2012) concluded that those children whose mothers had higher education levels ($p < 0.001$) and economics status ($p < 0.001$), among other factors, attended more routine dental check-ups. This phenomenon is highly related to health inequality, because poor economic status is linked to disparities in access to dental health services (Biordi *et al.*, 2015). Decreased utilization of dental services was demonstrated by Machry *et al.* (2013), who found in a Brazilian study that just 23.68% of children aged between 1 and 5 years had visited the dentist.

Goettems *et al.* (2012), in another Brazilian study, highlighted another phenomenon observed in this age group that is related to the fact that children are taken to the dentists only when they already have caries and/or pain. Similar findings can be observed in an analysis based on Chilean data (Hoffmeister dataset, see Chapter 7) from children aged 4 years. This analysis showed that 57.04% of children who had caries had already visited the dentist, compared with just a 39.44% of caries-free children ($p < 0.001$). As Nobile *et al.* (2014) commented, the fact that children arrived with caries at their first dental visit, showed that dentists do not play an effective role at preventing caries in this age group.

Based on the previous paragraphs, the use of regular check-ups for preventing caries is of limited use in the Chilean context. Better alternatives where young children already access to health care systems must be explored.

Other settings

In recent years, there has been a change in the way that caries is treated and several organizations have highlighted the importance of preventive care in young children. Some organizations, recognizing that caries is a complex disease and requires a great deal of input, have even started to involve non-dental health professionals in caries prevention (AAPD, 2013;MINSAL, 2013d). This approach includes the participation of physicians, nurses and other health personnel in activities such as counselling, screening, and even application of FV (Sams *et al.*, 2013).

A clear example of this new approach is the Into the Mouths of Babes Program (IMBP), which has been running in North Carolina since 2001 and includes preventive dental care during medical office visits (Achembong *et al.*, 2014). This programme is directed towards the preschool population enrolled in Medicaid, which is a national social health care programme for disadvantaged and poor people in the Unites States.

There are several arguments for the inclusion of such professionals in oral preventive care that can be summarized in one point: earlier access to children by non-dental health professionals. As was explained before in this chapter, a characteristic cultural phenomenon in early childhood caries (ECC) is that children are not taken to dentist until they have symptoms; in other words, they are taken to dentist when it is too late. Such a phenomenon occurs to a lesser extent with other professionals, especially in those health systems that have well-child programmes. Another possible reason for the earlier access to such professionals is that, in some countries, there are difficulties in access to dental professionals either because they are expensive, scarce, or both (Quinonez *et al.*, 2006).

Therefore, to take advantage of earlier visits to non-dental health professionals, some organizations such as the American Academy of Paediatrics and the American Academy of Paediatric Dentistry (Chou *et al.*, 2014) have developed specific guidelines and protocols for non-dental health professionals in order to prevent and treat caries, especially in those populations who have less access to dentists (Taylor *et al.*, 2014).

The Chilean Ministry of Health (MINSAL), through the integrated national health programme for children with integral approach (MINSAL, 2013d), included participation of non-dental health professional such nurses and nutritionists. Therefore, expanding the roles of non-dental health professionals might be beneficial.

3.3 Summary

In summary, it is possible to say that there is limited evidence about the effects of behavioural changes in school-based interventions. Using dental check-ups as a preventive caries intervention is unlikely to be useful in the Chilean context due to limited access by preschool aged children to dental care. Although, access to dental care by younger populations, from a health system perspective, may be possible through the participation of non-dental health professionals.

Highly concentrated fluoride interventions, such as mouthwashes and gels, are not indicated in children less than 6 years old. Fluoridated water reduces both caries prevalence and caries severity in younger populations, and almost every Chilean population has access to fluoridated water. Finally, FV may be the option of choice as a public health programme because it is safe, easy to use, and is an effective product to reduce caries; however, very little is known about the effect of FV on preschool populations, especially in children that are caries free.

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Chapter 4. The Case of Chile

4.1 Introduction

The Chilean Ministry of Health (MINSAL) has decided to employ the use of topical fluorides as a specific preventive measure against caries. Given that the lowest percentage of caries-free children was found in those populations that attend public institutions (MINSAL, 2012a), MINSAL has been interested in exploring a nationwide application of FV to all preschool aged children that attend public institutions. This way, in theory, MINSAL hopes to increase the number of caries-free children and, at the same time, reduce the gap in inequality based on socioeconomic status (MINSAL, 2012b).

This decision was based on several unpublished studies commissioned by MINSAL. Soto *et al.* (2007a), for example, established that only 30% of 6-year-old children in Chile were caries-free, measured as $d_3$mft = 0, in primary dentition (MINSAL, 2009a). Similarly, a consolidated report compiled by MINSAL (MINSAL, 2012b) showed that the percentage of caries-free children was 83% and 50% among 2- and 4–year-olds, respectively. They concluded that inequality in oral health was visible in children in as early as 2 years of age among different socioeconomic groups, as well as by different geographic zones.

Given this oral health situation, MINSAL has set a target for the period 2011-2020 (MINSAL, 2011) to increase the number of 6-year-old caries-free children by 35% (a move from the current level of 30% to 40%). In order to reach the target, MINSAL has considered implementing three strategies (MINSAL, 2012c). The first strategy is to reinforce and expand the model of promotional and preventive interventions at the preschool and school levels; including a possible nationwide FV programme. A second strategy involves strengthening the components of a comprehensive oral health care model with a family and community approach in the primary care setting. The third strategy aims at improving the availability of a recording system and epidemiological data.

As commented on in the introduction of this thesis (Chapter 1), personal communications with the Department of Oral Health of MINSAL (MINSAL, 2012b) produced an agreement in which the possibility of a nationwide programme of FV would be explored in this thesis, with MINSAL providing the data required for the study. It was agreed that the intervention studied should be based on the "protocol of teeth-brushing and community-based application of fluoridated varnish for interventions in preschool population" and would focus on children attending public preschool education (MINSAL, 2012b). Similarly, MINSAL proposed to explore incremental incorporation of socioeconomic groups (from low to high) into the FV programme; this means L (low), ML (medium and low), and HML (high, medium, and low) socioeconomic statuses.

To determine how a nationwide preventive programme could affect the preschool population, it is necessary to understand both the Chilean education and health systems. In addition, an analysis of the FV protocol is required to properly define MINSAL's proposal. Subsequently, this chapter analyses the FV protocol and describes both the Chilean health and education systems in the preschool setting.

4.2 Health system

The Chilean health system is mixture of mainly two subsystems, public and private. The Chilean State has a leadership and regulatory role over both subsystems through the Ministry of Health. The system is funded principally by the State, worker's contributions, and out of pocket payments (PAHO, 2012).

There are two main systems of health insurance, a unique public system called the National Health Fund (FONASA) and a private health insurance system, composed of several private health insurance institutions (ISAPREs). FONASA covers around 81.8% of the population, mostly those of low income, including the poorest populations and those unable to pay, which are classified as FONASA A. On the other hand, ISAPREs cover 10.6% of the population and their affiliates have the highest incomes (MIDEPLAN, 2013).

For those affiliated with ISAPREs, or the private subsystem, both private and public institutions provide primary care and non-primary care health interventions. In the case of FONASA, almost all health interventions are provided by public institutions. Non-primary care interventions are almost entirely provided by the National Health Services System (SNSS), which is a network of public hospitals. Primary care interventions are provided mainly in public primary care institutions including basic hospitals, urban health centres, family health centres, rural health centres, etc. Most primary care institutions belong to city councils (90.1%) and SNSS owns just 8.3% of them (ISAGS, 2014).

The model adopted by MINSAL to deliver primary care interventions is a model of comprehensive health care with a family and community approach, which is executed through council health services and SNSS for FONASA affiliates only.

Such a primary care model establishes that health care is a continuous process focused on the comprehensive care of families, with an emphasis on people's health before disease appears, providing them with the tools necessary for self-care. Its emphasis is on promoting healthy lifestyles, encouraging multisector actions, and strengthening family and community responsibility for improving health conditions (MINSAL, 2013d). In concordance with the model's logic, there are several promotional and preventive oral health interventions for preschool children in the primary care setting.

4.2.1 Control of child's health or well-child programme

Control of the children's health programme, also known as the "well-child programme" (WCP), has been defined by MINSAL (2013d) as the comprehensive, systematic, and regular care provided to children in order to monitor normal growth and development. This programme provides basic health interventions based on promotion and prevention for children aged 0 to 9 years. This activity is performed by physicians and/or nurses and contains several sub-activities, for example, taking of histories, physical exams, assessments of nutritional status, and evaluations of integral development. Also, it looks for the development of parenting skills, detects health risk factors, delivers milk, and gives immunizations.

Similarly, this programme has a dental component given by non-dental health professionals (MINSAL, 2013d):

- Physician or Nurse, evaluates oral health habits and gives advice about them for those 1.5-year-olds
- Nutritionist, evaluates oral health habits and provides counselling on topics related to feedings habits for those 3.5-year-olds.

The national socioeconomic characterization survey (CASEN) done by the Chilean Ministry of Social Development (MIDEPLAN) in 2013 showed that coverage of the WCP, defined as the number of children that attend the WCP divided by the population of the correct age in Chile, decreases by age.

For example, coverage decreased significantly from the age of 2 years (59.24%) to 6 years (15.55%), see Figure 4.1, which is based on CASEN survey (MIDEPLAN, 2013). Also, there is a clear difference in coverage between the types of health insurance groups the children belong to, which is a proxy of socioeconomic status. For example, at 4 years of age, the WCP coverage was 51% and for FONASA A and 33% for ISAPRE (MIDEPLAN, 2013).

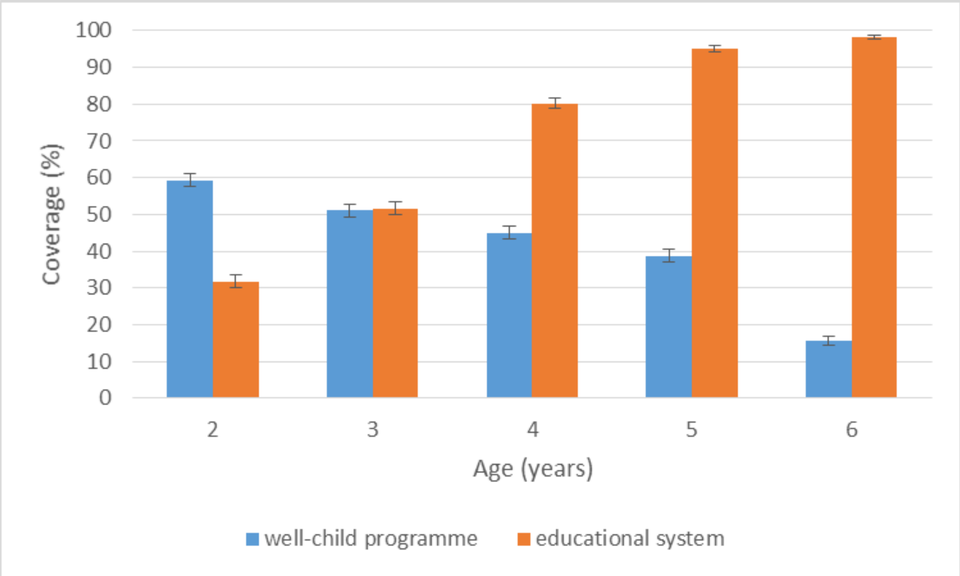


Figure 4.1. Coverage of well-child programme and educational system.

4.2.2 Control of oral child's health or dental well-child programme

As part of the WCP, there is a procedure performed by dentists and dental teams known as the dental well-child programme (DWCP). The DWCP includes a complete oral health evaluation of the child performed by a dentist who gives oral health advice and, depending on his/her availability and skills, gives treatment if necessary (MINSAL, 2013d). The coverage of this programme is 33% in 2-year-olds and 32% in 4-year-olds (Letelier, 2010).

4.2.3 Comprehensive oral health programme at 6-year-olds

In 2005, the Chilean Government established a nationwide health programme called "Garantías Explícitas en Salud (GES)" – explicit guarantees in health. This programme looks to improve the quality of life of Chilean people and reduce health inequality gaps between socioeconomic groups. The programme guarantees access, quality, financial protection, and opportunity (defined as waiting time to be treated) for treatment of 80 pathologies and health conditions. Under the programme, FONASA and ISAPREs should automatically ensure such guarantees to their respective beneficiaries (MINSAL, 2005).

A comprehensive oral health programme was included in GES at this age because eruption of permanent teeth begins around age 6. The objective of the programme is to provide oral health care to all 6-year-old Chilean children. The estimate, by the year 2015, of the size of the preschool population that must be compulsorily treated was 251,066 children, which corresponded to 1.4% of the entire Chilean population (INE, 2010).

Oral health interventions, mostly focused on caries, are provided irrespective of children's oral health diagnosis; consequently, there are two types of interventions. Educative and preventive treatment (T1) is performed in all children. Furthermore, according to MINSAL (2013e), 65% of children receive T1 plus a restorative intervention (T2). Dental emergencies are included in another GES programme that guarantees, at least, emergency treatment for individuals that require such interventions.

Given that this programme is compulsory, any savings is important. Unfortunately, there are few studies about the real costs of health interventions in the public health system (see Chapter 10). MINSAL (2017b) published the expected cost of a comprehensive oral health programme (valid for both public and private health sectors), where T1 was 32,160 Chilean pesos (CLP) and T2 CLP 27,990. Such costs are based on FONASA's tariff and are not based on micro costing (PUC, 2012); hence, the real costs of such interventions are unknown. Without a clear understanding of the real cost of a comprehensive oral health programme for 6-year-olds, we are unable able to estimate the savings (in a short-term analysis) that a possible nationwide programme of FV would bring. Therefore, more research is needed in this area.

In summary, the Chilean health system delivers to preschool children both basic dental and non-dental health interventions (such as clinical evaluations and counselling). Also, the delivery of dental emergency treatment is assured. Operative treatments (dental fillings) are mostly focused on school children.

To better understand the preschool Chilean context, the Chilean education system is described in the next section.

4.3 Education system

Preschool education is provided by both public and private institutions in two cycles, the first cycle covers 0 to 4-year-olds and the second cycle covers 4 to 6-year-olds; where preschool education is offered at three levels: nursery, for 0 to 2-year-olds; middle level, for 2 to 4-year-olds, and transitional level, for 4 to 6-year-olds. Simultaneously, every level is subdivided into two stages. For example, the transition level is divided into the first transition level, or pre-kinder, and the second transition level, or kinder (see Table 4.1).

The education in the first cycle is mainly provided by two public institutions: "Junta Nacional de Jardines Infantiles" (JUNJI) and "Fundación Integra" (INTEGRA), and supplemented by some private institutions; both public institutions provide services either directly or through a third party. The second cycle is quite different in the public sector, where education is principally given by both public and subsidised schools, and by JUNJI and INTEGRA to a lesser extent. Subsidised schools are those private schools that are publicly funded, where parents must pay part of the annual fee.

An important aspect to highlight here is that school entry age for the first stage of transition level (pre-kinder) is 4-year-olds by March 31st and 5-year-olds by March 31st for the second stage of transition level or kinder (MINEDUC, 2011). In practical terms, this means that if a child has not reached the required at these specific dates, he or she must wait until the next academic year to enter. Therefore, the academic year does not coincide with the calendar age of children.

Cycle	First				Second	
Level	nursery		middle		transition	
Stage	junior	senior	junior	senior	pre-kinder	kinder
Age (years)	0 to 1	1 to 2	2 to 3	3 to 4	4 to 5	5 to 6

Table 4.1. Classification of Chilean preschool educational system by age.

4.3.1 Coverage

Despite the fact that coverage, defined as the number of children that attend school divided by the eligible population, has increased during recent years, there is still a clear difference between ages (Arzola and Camhi, 2013) and the biggest differences were detected between cycles. For example, the latest national socio-economic characterization survey (CASEN) conducted by MIDEPLAN (2013) showed that the educational coverage of 5-year-olds (second cycle) was 95.1%, which is much higher than coverage of 31.8% observed in the first cycle of 2-year-olds (see Table 3.1). At 4-year-olds, the Chilean coverage (for the year 2012) estimated by the Organisation for Economic Co-operation and Development (OECD, 2014) was 79%, lower than OECD average (84%).

4.3.2 Attendance

Given that MINSAL has proposed sending personnel to perform the FV application in schools, it is important to be aware of the daily attendance of children. Arbour *et al.* (2014) measured the daily attendance of children in both pre-kinder and kinder settings following 1868 children during a complete academic year in public schools in Santiago of Chile. They concluded that children at pre-kinder and kinder levels, on average, do not attend 21.7% and 20.8% of the academic days, respectively.

It is then reasonable to assume that the second cycle of preschool education, on which this thesis is based, covers an important percentage of the preschool population; however, the daily attendance is around 80%.

4.4 Description of fluoride varnish protocol

In 2012, MINSAL published a FV protocol that contains, among other topics, evidence on which the protocol was based on and indications and contraindications for FV application.

As evidence of FV efficacy, the protocol uses the Cochrane systematic review completed by Marinho *et al.* (2003) who found a preventive fraction of 33% (95% CI , 22% to 44%; $p < 0.01$) in primary dentition. Similarly, a systematic review performed by Cardiff University (2008) showed that FV application every 6 months in low and medium-risk populations can prevent caries. For high-risk populations, the study suggested that FV application every 3-6 months can prevent between 66% and 69% of decayed surfaces.

The protocol states that application of FV can be performed by either a dentist, a dental nurse, or a dental hygienist; similarly, it can be done by a dental assistant (another type of dental auxiliary personnel in the Chilean workforce) under a dentist's supervision. Also, the protocol establishes that FV should be applied after an oral health examination.

The oral health examination must be executed by a dentist and is performed to detect those children with moderate or high risk of caries in which FV will be applied. Thus, such an examination acts like a screening test.

According to the protocol, a child is considered at risk (or is indicated for FV) if he/she:

- Has or has had any carious lesion, incipient or cavity, in the last 3 years.
- Has at least one of the following factors, which may increase the risk of caries:
    - poor oral hygiene
    - a family group with a high dental damage
    - dental enamel defects
    - sleeps with baby bottle with liquids other than water or breastfeeds at night on demand
    - during the day, drinks constantly, juices, soft drinks, or sugary liquids
    - frequent intake of either sugary or flour based foods.
    - uses regularly, oral medications high in sugar
- Has a physical or mental disability
- Belongs to a low socioeconomic status group
- Has a decreased salivary flow or xerostomia

Also, the protocol describes the contraindications of FV application as the following:

- Children who receive professional fluoride treatments periodically
- Children with low risk of caries
- Presence of ulcerative gingivitis and stomatitis
- Known allergies or reactions to rosin (from natural coniferous resin) or related ingredients
- Teeth with pulp exposure possible (deep caries). The application is contraindicated on those teeth only

All elements required to perform FV application with screening (e.g., human resources, instruments, and consumables) are described in more detail in Chapters 8 and 9. Chapter 3 contains a description of the application process proposed by MINSAL.

4.5 Critique of fluoride varnish protocol

After considering all factors explained in this chapter, MINSAL's proposal was defined as FV application in the preschool setting (pre-kinder and kinder), every 3-6 months depending on caries risk, with prior screening performed by dentists. As expected, there are arguments for and against MINSAL's proposal; those that are relevant to this study are discussed in this section.

A possible argument for MINSAL's proposal is given by the high pre-kinder and kinder coverage. The high rate would facilitate access to children who are gathered together in schools; however, due to the attendance rates shown, caution needs to be exercised and multiple visits to schools may need to be considered. At the same time, the fact that children are being seen in their natural environment would, hypothetically, increase children's cooperation.

Another argument for the chosen setting is that there would be no extra costs for parents compared to, for example, if they had to take their children to other settings. This would, therefore, improve the opportunity of access to the entire population, as well as reduce the influence of economic variables, such as household income. Potentially, use of the school setting might help to reduce oral health inequalities.

However, given that a considerable percentage of the population is not caries-free at these ages, especially those more deprived populations (MINSAL, 2012c), it is possible that FV impact may be small. An alternative would be to start the FV programme at an earlier age. MINSAL, unfortunately use unpublished data to make its recommendations, thus making it difficult to determine the proportion of caries-free children by socioeconomic group. Undoubtedly, to fully understand caries prevalence, more studies are required.

It must also be recognised that there are some uncertainties related to the evidence given by MINSAL about FV efficacy. The evidence presented in the FV protocol was based on the prevented fraction of FV published by Marinho et al. (2003), where studies included children both with and without caries. This study was not based solely on the caries-free population, thus FV efficacy argued may not justify a nationwide programme that seeks to increase the percentage of caries-free children.

Furthermore, the FV effects argued by MINSAL are based on dmfs, and such an index cannot be compared directly with dmft (which is the caries index used by MINSAL) and caries prevalence (dmft > 0). This was described in more detail in Chapter 2. In other words, it is unclear whether the positive results shown previously to justify the programme can be replicated in a programme that attempts to increase the percentage of caries-free children.

Based on the FV protocol, it can be deduced that MINSAL would not provide FV to the entire population, adopting a medium and high-risk approach instead. Unfortunately, the same document does not give a clear difference between both risk classifications and, given the lack of evidence of FV in caries-free populations, the frequency of application to be used is also not clear.

Given that MINSAL's goal is to increase the percentage of caries-free children in the entire preschool population, the question that arises here is whether the high-risk approach is the best alternative to reach such a goal, i.e., would treating the high-risk only population be enough to improve the oral health of the entire population?

The high-risk approach is based on the use of methods to detect children at high-risk such as a clinical examination as screening; this could be performed knowing the main risk indicators and predictors (Masood *et al.*, 2012). Though, as explained in Chapter 2, the main predictor of caries is past caries experience; consequently, a screening would not be very useful if MINSAL wants to increase the percentage of caries-free children (dmft = 0).

There is, therefore, a need to analyse what might happen if the low-risk population is treated and/or how the untreated low-risk population would influence the entire population. The evidence gives some indication about this, for example, Batchelor and Sheiham (2006) analysed the occurrence of new caries lesions over a 4-year period in children aged 7 years; they found that more than 50% of new lesions (DMFS) occurred in children initially classified as caries-free, and those children classified as highest-risk (with 7 or more lesions) generated just 6% percent of all new lesions.

A controversial point of the FV protocol is the use of low socioeconomic status (SES) to identify high-risk children. Given that belonging to a public school has been used by MINSAL as a proxy of low SES (Ceballos *et al.*, 2007;Soto *et al.*, 2007a;Soto *et al.*, 2009), there is no sense in performing a screening when all children are considered high-risk because they belong to a public school. In other words, how useful is performing a screening when all children have an indication for FV application?

The application of FV is a very simple process that involves painting the tooth surface with either a special brush or a gauze (Colgate-Palmolive, 2014). This means that application would not require a highly qualified professional to perform it. Therefore, the question arises about

MINSAL's proposal: what is the opportunity cost of sending highly qualified (and highly expensive) personnel to do a very basic procedure?

The previous question is important in the Chilean context due to scarcity of dentists in the public subsystem; there are 4,000 dentists, according to Goic (2015), that must treat around 80% of the Chilean population. This is even more important when the demand for the public dental workforce is analysed, as with the explicit warranties on health programme (GES) for example; Monsalves (2012) argued that due to the high demand and the fact that most working hours are dedicated to treating GES pathologies and other priority groups, the coverage of dental care has been reduced to a small section of the population. Therefore, taking dentists (and dental staff) out of surgeries and sending them to schools to do a simple job may not be advisable.

As MINSAL is already using non-dental professionals in oral health education, it is reasonable to evaluate possibly less expensive alternatives such as nurses, for example. This could also expand the role of other health professionals during the WCP and allow them to perform the application. This approach is consistent with the opinion of Selwitz *et al.* (2007) who argued that prevention of dental caries cannot be achieved by reliance only on dental care teams and suggested that we need to incorporate other health professionals. Also, this approach would be compatible with MINSAL's strategic line of strengthening the components of a comprehensive oral health care model, with a family- and community-based approach (MINSAL, 2012c).

4.6 Summary

This chapter described the Chilean health and education context and analysed the FV programme proposed by Chilean Ministry of Health (MINSAL) at the pre-kinder and kinder grades to increase the percentage of caries-free 6-year-olds. The preschool population is covered by both health and education systems with different rates depending on the child's age.

Evidence of the percentage of caries-free children, used by MINSAL, is based on unpublished data. The FV protocol lacks conclusive evidence about the effects of FV on caries-free children. More research is required to obtain reliable information on these topics.

There are uncertainties about the use of screening to target the high-risk population and the impact that such high-risk populations could have on the entire population; further studies regarding the possible impact would be worthwhile. There are concerns about sending highly qualified and scarce personnel to perform a very simple task; other alternatives should be explored.

Chapter 5. Economic Evaluations

5.1 Introduction

As was explained in Chapter 4, there are some reservations about whether a nationwide FV application programme can increase the number of caries-free children in the Chilean preschool population. This is because the measure of treatment effect chosen to justify such programme was not the most appropriate. MINSAL used the caries prevented fraction published by Marinho *et al.* (2003), which includes children with caries as well as caries-free children.

Due to the expected high cost of a national FV programme, which would cover, at least, children who attend preschool public education, it is necessary to determine whether a nationwide FV application would, or would not, effectively increase the number of caries-free children in the Chilean preschool population.

There are also some questions about the delivery method chosen by MINSAL (2012c) because of the high opportunity cost of sending highly qualified and expensive personnel to perform a relatively simple FV application procedure. Consequently, while aiming to maximise the caries-free population, it would be reasonable to explore other delivery alternatives and compare them with the interventions proposed by MINSAL (2012b).

A method to compare the cost and outcomes of other possible interventions involves the use health economics and, more specifically, economic evaluation methods. Such evaluations are frequently used to define the most efficient way to use scarce resources, and they can aid decision-makers in better allocating their resources (Soto, 2002).

Economic evaluations have been extensively used to inform decisions about which health care intervention to fund (Briggs *et al.*, 2011); however, their use in dentistry has been limited (Mariño *et al.*, 2013). Also, few studies (Quinonez et al, 2006; O'Neill et al., 2017) looking at cost-effectiveness of fluoride varnish are available. This chapter describes the basic concepts of economic evaluation to provide a theoretical framework for the main empirical research of this thesis.

5.2 Economic evaluations

Frequently, in order to improve population health or the delivery of services, decision-makers have to choose between two or more alternatives under conditions of uncertainty. As was proposed by Gray *et al.* (2011), such decisions require more than just data about effectiveness, decision-makers also have to consider the cost of their decisions. In health economics, the costs of any decision are the missed benefits if resources would have been used in the next best alternative – this is the economic notion of opportunity cost. Economic evaluation is a method of providing information to decision-makers about whether the benefits of a new intervention are worth achieving that is the benefits obtained from using resources to provide the new intervention outweigh the benefits that could have been provided had the resources been used in another way. Economic evaluation is defined by Drummond *et al.* (2005) as:

> "The comparative analysis of alternative courses of action in terms of costs and consequences".

It is important to highlight here that economic evaluations do not focus on identifying the cheapest alternative, their focus is on the most efficient alternative, even if that alternative is to 'do-nothing' (Guinness and Wiseman, 2011).

Depending on the unit that consequences are measured, economic evaluations can be divided into three main forms: cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis. These three forms are each briefly described below.

Cost-effectiveness analysis

This analysis compares two or more interventions using a single natural unit, such as the amount of caries or DMFT index, for example, as the measure of effectiveness. This type of analysis allows the comparison of health interventions that produce the same outcome (Gray *et al.* (2011), and can address questions of economic (productive) efficiency; i.e., how can a specific good or service be produced at the lowest cost?

Given that this type of economic evaluation is used in this thesis, a deeper description is given later in this chapter.

Cost-utility analysis

The concept of utility here is related to the preferences that an individual or society have for a particular set of health outcomes (Drummond *et al.*, 2005). It uses a generic health index, typically reported as quality-adjusted life-years (QALY) as a measure of effectiveness. This allows the comparison of different health interventions with different clinical outcomes. This method is described as a variation of cost-effectiveness analysis. However, while generic health indices have been developed, there are concerns that these indices may not detect small variations in utility that might occur with treatments for oral diseases (Vernazza *et al.*, 2012). Therefore, condition specific dental generic indices have been proposed. For example, the quality-adjusted tooth years, or QATY, was developed by Birch (1986), where one QATY represents a sound tooth over a 1-year period.

Cost-benefit analysis

Here, the effect of an intervention is translated into a unit of measurement that is commensurate with the unit of measurement of costs, typically a monetary measure of value (or benefit). The monetary valuation of benefits is compared with the cost used to estimate the cost-benefit of a treatment. Given that this analysis uses money as a common measure for costs and benefits, it allows the comparison of health interventions with interventions (or investment) of other areas of the economy. This methodology thus allows the consideration of how best to allocate resources within an economy, and so addresses allocative efficiency (i.e., how can we best use the resources we have available) as well as technical efficiency (i.e., how can we produce a given outcome at least cost or maximise outcomes for a set cost) (Guinness and Wiseman, 2011).

5.2.1 Economic evaluations in dentistry

In two different literature reviews about the use of economic evaluations in dentistry, Mariño *et al.* (2013) and Tonmukayakul et al. (2015) concluded that the use of economic evaluations in dentistry has increased in recent years. The systematic review done by Tonmukayakul *et al.* (2015), which included studies from 1973 to 2015, found that 53% (59 of 114) of economic evaluations were focused on caries prevention or its treatment and 30% of the studies were published between 2011-2013. The same authors, using the Drummond checklist as a way to evaluate the quality of the publications (see 5.9), concluded that most studies failed to satisfy some components of standard EE research methods, such a sensitivity analysis and discounting.

In the same line, the systematic review done by Mariño et al. (2013), which included only caries prevention programmes, established that economic evaluations in dentistry suffer from methodological problems related to how these studies deal with uncertainty (which is normally addressed within an economic evaluation using sensitivity analyses); see 5.8.

Several "dental" economic evaluations are discussed in the thesis, emphasising specific elements. A recently published economic evaluation of preventive interventions (Tickle *et al.*, 2011;O'Neill *et al.*, 2017;Tickle *et al.*, 2017) is closely related to the objective of this thesis and will be discussed later on.

As was commented on earlier, regarding FV (Chapter 3), there are just one study about cost-effectiveness of FV on caries-free populations (NIC-PIP). Hence, this thesis should make an important contribution about the cost-effectiveness of fluoride varnish in caries-free populations.

5.2.2 Using randomised controlled trials as a framework to generate the data used in economic evaluations.

In order to compare health interventions, economic evaluations require data about both costs and consequences. A source of such data comes from randomized controlled trials (RCTs), which, as was commented by Richards (2009), are powerful research tools that allow the separation and measurement of the effect of an intervention, reducing the systematic differences between baseline characteristics of the groups that are compared.

RCTs have been used more and more as frameworks to generate such costs and consequences (Gray *et al.*, 2011), because as well as the advantages of RCTs for comparative research, they allow prospective data collection about resources used concurrently and in the same people as data collection on outcomes. Therefore, they allow patient-specific data to be obtained, which are potentially useful for analysis of internal validity. Also, given that RCTs usually have a large fixed cost, adding an extra stage to collect economic data might only incur modest extra costs (Drummond *et al.*, 2005).

Nevertheless, RCTs have limitations and cannot be used in all economic evaluations. For example, it is possible that an RCT for a given health intervention to be evaluated simply does not currently exist or could not be readily designed. Another limitation is that the time horizon of an available RCT is typically not sufficiently long enough to capture all relevant costs and effects. This point is important in chronic pathologies that affect individuals during their entire lifetimes, as dental caries does.

In the author's view, there are two more important limitations. First, RCTs might not provide evidence about a particular setting or group of patients (Gray *et al.*, 2011) and, given the controlled nature of RCTs, they might not represent those patients or group of patients that an economic evaluation needs to analyse, i.e., those seen in clinical practice. The other prohibitive limitation is the cost of an RCT, which could be very large, especially for RCTs that need to study large populations over long periods of time.

These limitations have led researchers to employ other frameworks to gather costs and outcomes data to be used in economic evaluations.

5.2.3 Chilean guideline for economic evaluations

With the objective of establishing a standard methodological framework for the economic evaluations in Chile, the Chilean Ministry of Health MINSAL (2013c) published in 2013 a guideline titled "Methodological Guideline for Economic Evaluations of Health Intervention in Chile" (henceforth referred to as the Chilean guideline for economic evaluations). This guideline summarises basic aspects of economic evaluations and gives important recommendations related to the perspective to be considered including (in terms of target population) costs, outcomes, and time horizon.

This guideline was published with the objective of outlining a reference case; thus, it is considered mandatory for researchers that work on public health policies. Furthermore, it is requirement of work conducted for public institutions such as the Ministry of Health, National Health Fund, National Institute of Health, etc. (MINSAL, 2013c).

Given that this thesis analyses a national health programme and estimates the impact of Chilean public health policy, this research considers the Chilean guideline for economic evaluations in more detail.

5.3 Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) is typically used when decision-makers have to choose between a limited range of options in a very specific field (Drummond *et al.*, 2005) and under a given budget. Despite this limitation, it is the most common economic evaluation used to analyse preventive interventions in dentistry (Mariño *et al.*, 2013).

When the interventions are mutually exclusive, they could be compared directly, ordering them by costs (always from lowest to highest). Then, the difference in costs (incremental cost) and difference in effects (incremental effect) are calculated for each intervention, comparing such intervention with the previous less expensive alternative.

An intervention is dominated when it is both more costly and less effective than its comparator, and thus can be eliminated from further consideration. After having eliminated all dominated interventions, leaving the undominated interventions only, we can estimate the incremental cost-effectiveness ratio or ICER. Such a ratio is estimated by dividing the incremental cost by the incremental effect to give us the production cost of one more unit:

$$ICER = (cost_a - cost_b) / (effect_a - effect_b) = \text{incremental cost/ incremental effect}$$

The ICER gives the production cost of one extra unit of effect compared to the next less costly and less effective alternative. Consequently, the ICER also provides information about the opportunity cost of the total costs to provide an intervention; the higher the ICER, the less likely it is that resources could be reallocated without the loss of more benefits than could be obtained with the intervention.

5.3.1 Cost-effectiveness plane

The costs and effects of health interventions can be plotted in a graph called a cost-effectiveness plane. The y-axis on the graph represents the incremental cost of the interventions and the x-axis represents the incremental effect of such interventions, where the intersection of both axes represents either a do-nothing alternative or the current intervention.

Costs and effects can be brought together to inform judgements about efficiency, which can be illustrated using the incremental cost-effectiveness analysis plane (Figure 5.1). Considering the intersection of both axes as the centre, the graph can be divided into four quadrants. In the northeast quadrant, the interventions are more costly but more effective and, in the southeast quadrant the intervention is less costly and more effective. In the southwest quadrant, the intervention is less costly and less effective than the alternative and in the northwest quadrant, the intervention is more costly and less effective than the alternative.

Typically, one would pick those alternatives that fall in the south-east quadrant and discard those that are in the northwest quadrant. In practice, however, most interventions are placed in the northeast quadrant, i.e., they are more effective but more costly (Drummond *et al.*, 2005).

Here it is important to explain further the concept of dominance, which occurs when one intervention dominates another in terms of both costs and effect, which means it is more effective and less costly. Such a concept of dominance is observed in the CE plane as well; all undominated interventions can be connected by a line, called the cost-effective frontier, and all the interventions that are placed above the line are considered as dominated (Figure 5.2). As was commented on by Gray *et al.* (2011), for any given level of spending, health gain will be maximised by choosing any intervention on such a frontier. Similarly, the slope of the line represents the ICER, where the steeper the slope, the higher ICER.

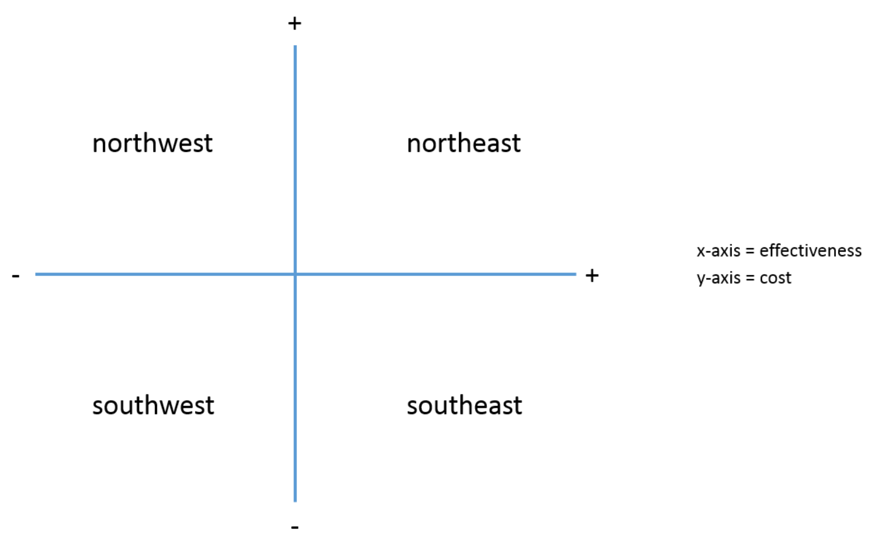


Figure 5.1. Cost-effectiveness quadrants.

5.3.2 Interpreting the cost-effective analysis results

The calculation of costs, consequences, and ICERs of interventions is not enough to determine whether an intervention is cost-effective or not. As was explained by Drummond *et al.* (2005), the result of a CEA can only be interpreted by reference to an external standard; that is the ICER has to be compared to some externally set threshold. When an ICER is above a certain value (or threshold), the intervention is considered as not cost-effective. This analysis is based on two assumptions, that the treatments are perfectly divisible and there are constant returns to scale (Drummond *et al.*, 2005), which means that the ICER does not change with the scale of the intervention.

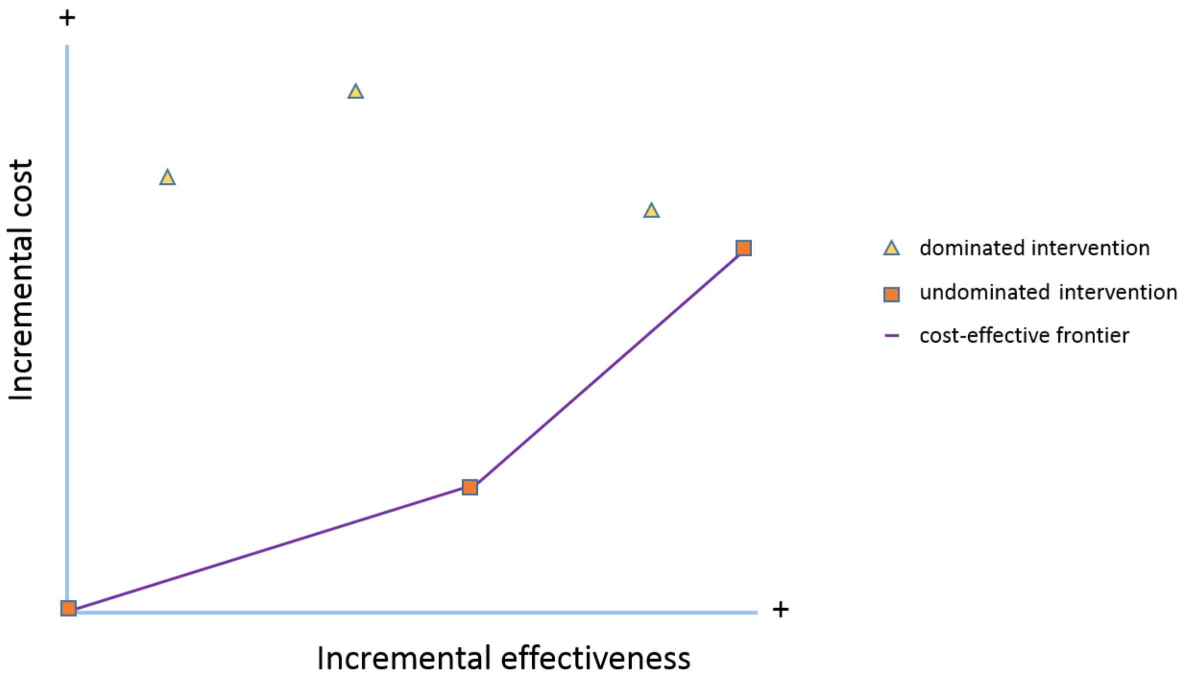


Figure 5.2. Northeast quadrant and cost-effective frontier.

Unfortunately, there is no evidence about how much the decision-makers are willing-to-pay for a caries-free preschool child, which is the outcome of the main study of this thesis. A way to get such a threshold would be, for example, through the use of willing-to-pay (WTP) methodologies (Oscarson *et al.*, 2007;Vernazza *et al.*, 2015); nevertheless, the use of such methods would represent future work beyond this thesis.

Another method, suggested by Drummond *et al.* (2005), is that in the absence of information, a legitimate reference or threshold could be that at which a programme is currently funded. This way would allow, at least, the determination of whether a new technology being evaluated is or is not more cost-effective than the currently provided intervention. This approach is directly related to the concept of productive efficiency.

5.4 Decision analytic models

As was previously discussed, economic evaluations require a framework that allows them to obtain the costs and outcomes being analysed. Such a framework can be given by randomised controlled trials (RCTs); however, RCTs have several limitations. Decision analytic models (DAMs) provide an alternative framework for economics evaluations.

A decision analytic model can be defined as a systematic approach to construct and structure decisions (Gray *et al.*, 2011). This approach uses mathematical relationships to define consequences from alternative options being evaluated (Briggs *et al.*, 2011). The likelihood of a consequence, which has both a cost and an outcome, is expressed as a probability; consequently, DAMs can give the expected costs and outcomes of decision options. Notably, DAMs can synthesise data from different sources (Petrou and Gray, 2011) and are able to incorporate and quantify uncertainties in a decision problem (Gray *et al.*, 2011).

DAMs have been used extensively in medicine and pharmacology and their use has increased in recent years (Philips *et al.*, 2006). While it is true that there are no reviews on the frequency of DAMs in dentistry, it is possible to deduce that this kind of study is scarce. This assertion is based on: (1) the fact that not all economic evaluations use DAMs as framework and (2) the relative scarcity of economic evaluations in dentistry (Mariño *et al.*, 2013).

As an example of the use of DAMs in dentistry, Pennington *et al.* (2009) evaluated different restoration pathways following an initial treatment decision (root canal treatment or tooth extraction with replacement). Using a Markov model, they were able to simulate the costs and effects of different treatment alternatives until patients reached 100-year-olds or until they died. In another example, Schwendicke *et al.* (2015) evaluated the cost-effectiveness of mineral trioxideaggregate (MTA) and calcium hydroxide for direct pulp capping in Germany. Through a Markov model, they determined that MTA was more cost-effective (over a long-time horizon) because such material could avoid expensive retreatments.

Several authors have given suggestions about what to include or not in DAMs (Weinstein *et al.*, 2003;Drummond *et al.*, 2005;Briggs *et al.*, 2011;Gray *et al.*, 2011). There is no agreement related to what constitutes a 'good model' or how models should be formally assessed (Philips *et al.*, 2006), although there have been efforts to reach a consensus on best practices. For this reason, some institutions have started to formulate their own recommendations to perform these models.

For example, the Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) published, in 2013, the Consolidated Health Economic Evaluation Reporting Standards (CHEERS). Such a consensus guideline merges existing opinions and provides recommendations to optimize the conduct and reporting of health economic evaluations, including model-based economic evaluations. In the Chilean context, the methodological guide for economic evaluations (MINSAL, 2013c) includes a chapter specifically dedicated to these mathematical models.

The present thesis considers the recommendations of these guidelines with an emphasis on the Chilean context.

5.4.1 Defining the decision problem

This part of the construction process of a DAM is related to the definition of the question to be analysed under conditions of uncertainty, also called defining the 'decision problem'. This concept is like the specification of the study question for economic evaluations (Drummond et al., 2005). The definition of the question should reflect data availability and the perspective of the institution that will make the decision (or that is assumed to be making the decision).

All alternative interventions and settings to be analysed must be clearly defined as well as the recipient population. It must include the time horizon to be evaluated and a clear definition of costs and outcomes. Finally, this section should specify the boundary of the model, meaning how far the model should go to capture all possible implications of an intervention (Drummond *et al.*, 2005).

5.4.2 Structuring a decision model

Several authors (Weinstein *et al.*, 2003;Barton *et al.*, 2004;Petrou and Gray, 2011;Siebert *et al.*, 2012) have proposed guidelines about the selection process of the structure of the models being used.

As an example, Gray *et al.* (2011) adapted an algorithm created by Barton *et al.* (2004) that also helps to define a possible decision model. This algorithm is based on sequential questions about what the model needs to represent.

First, they state that when an interaction (e.g. between individuals) is important, they recommend more complex models such as system dynamic models or discrete event simulations. A system dynamic approach models the state of a system in terms of changing, continuous variables over time and a discrete event simulations describes the progress of individuals, which pass through various processes that affect their characteristics and outcomes over time (Brennan *et al.*, 2006).

Then, when the events are not recursive, they suggest decision tree models, otherwise, they recommend the use of Markov models. Finally, they propose the use of individual sampling models when the models require the representation of many health states.

Some characteristics of both disease and intervention being evaluated help to answer the questions formulated by Gray *et al.* (2011). For example, when the disease is infectious, it would be necessary to evaluate the interaction among individuals. Also, when the disease is chronic, it is likely that one intervention or event might be repeated during the lifetime; thus, individuals should require multiple interventions or movement between several health states should be evaluated.

At the end, the selection of the structure of the model must be analysed case-by-case because there is not agreement about what is the most appropriate model structure in a given case (Briggs et al., 2011). Although several types of models are available, only decision trees, Markov models, and a combination of both (the Markov cycle tree model) will be discussed in more detail in this chapter because, following the algorithm proposed by Gray *et al.* (2011), there is no interaction between children, and the application of FV needs to be repeated several times; thus, these are the relevant models.

5.5 Models

As was explained in the previous section, only decision trees, Markov models, and Markov cycle tree models will be described in this section. Some concepts, needed to understand the logic of the models, will be explained in each type of model using examples.

5.5.1 Some previous concepts

Probabilities

Given the importance of the concept of probability in decision analysis modelling, this concept is going to be discussed here. In basic terms, a probability (in decision analysis) can be defined as a number indicating the likelihood of an event taking place in the future (Briggs *et al.*, 2012). Probabilities can be classified as follows (Drummond *et al.*, 2005):

- Joint probability: defined as the probability of two events occurring concomitantly. It is noted as P(A and B), where the events are independent P(A and B) = P(A) * P(B)
- Conditional probability: defined as the probability of an event A given that an event B is known to have occurred. The notation is P(AIB)
- Independence: when, events A and B are independent if the probability of event, or P(A), is the same as P(AIB).

5.5.2 Decision Trees

Decision trees are branching analytic structures in which each branch represent an event. A decision tree is composed of three types of nodes (decision, chance, and end) ordered, by convention, from left to right (Gray *et al.*, 2011).

The model starts with a decision node, which indicates a decision point between different interventions (shown as a square). Then, every decision node has two or more chance nodes (shown as circles), which represent the possible alternative events for a patient. Depending on the complexity of the tree, a chance node can end either in another chance node or in a terminal node (shown as a triangle); however, in economic applications, to obtain the estimates of costs and outcomes, all chance nodes must end in a terminal node.

The following example (Figure 5.3), shows a very schematic decision tree. The objective of this model, a cost-effectiveness model, was determining which type of mechanized endodontic system, either system A or system B, is more successful (producing an asymptomatic tooth from a tooth with no previous root canal treatment as outcome) with a less cost; considering a second intervention or retreatment, using the same system, in case the first intervention fails.

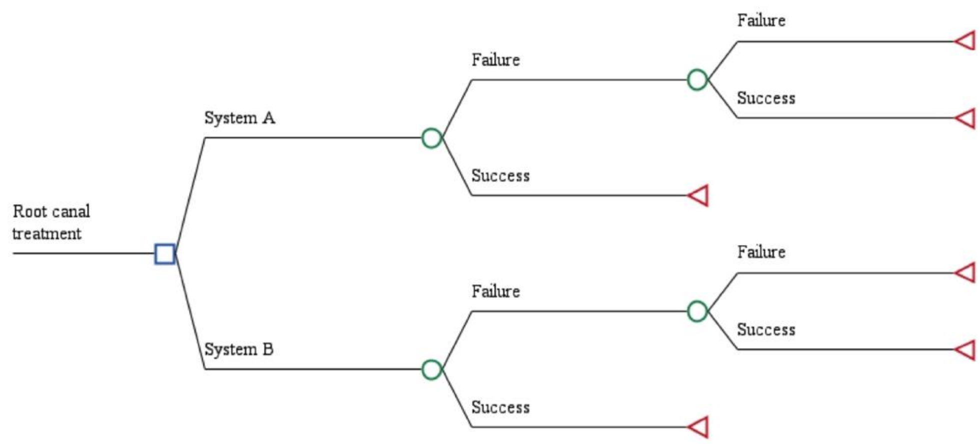


Figure 5.3. Schematic decision tree.

Probabilities

By convention, to represent the likelihood that an uncertain event occurs, the probabilities are entered under the branches (or branch probabilities) emanating from each chance node. Given that the events are mutually exclusive, the sum of all branch probabilities emanating from a chance node must be equal to 1.

In the example (Figure 5.4), the probability of system A fails in the treatment (T_{A1}-) is 0.1. However, the probability that the same system fails in the retreatment (T_{A2}-) is not the same, it is higher (0.4). In this case, two probabilities are being used, an independent probability or P(T_{A1}-) and a conditional probability or P(T_{A2}-I T_{A1}-). Also, P(T_{B1}-) = 0.05 and P(T_{B2}-I T_{B1}-) = 0.5.

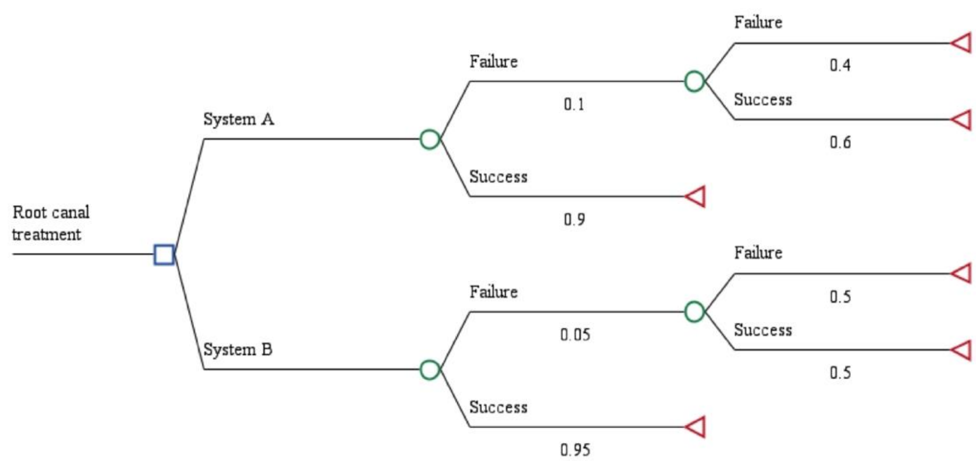


Figure 5.4. Decision tree with probabilities added.

Pay-offs

Once probabilities have been imputed in the model, the pay-offs can be identified and entered in the model (Gray *et al.*, 2011). The pay-offs include the cost of events in the model and the final outcomes at the end node; such outcome values take various forms depending on the type of evaluation (e.g., utilities or natural unit outcomes). In the example (Figure 5.5), the cost of a treatment (CT_{A1}) using system A is £ 800 and retreatment (CT_{A2}) is £ 1,000. Also, CT_{B1} = £ 1,000 and CT_{B2} = £ 1,000. At the terminal node, a failure is equal to zero because the model quantifies the number of successes only.

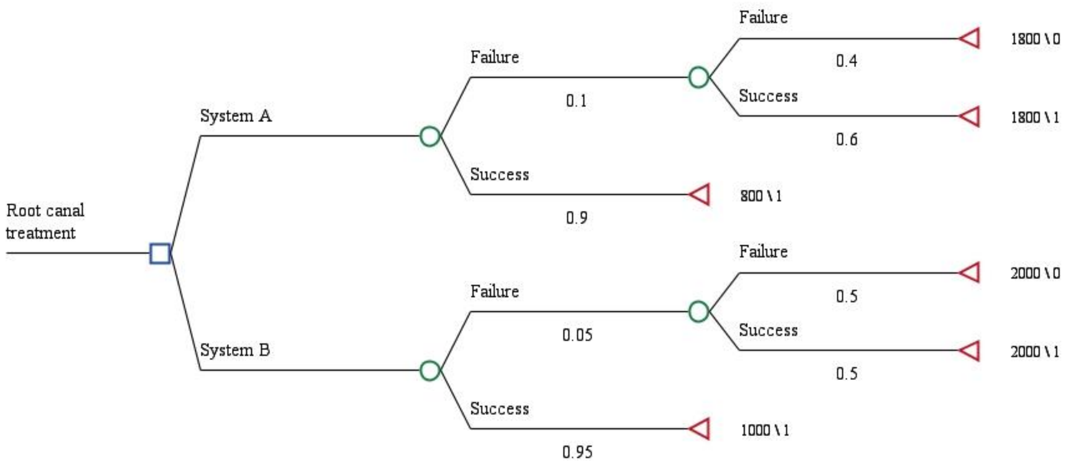


Figure 5.5. Decision tree with pay-offs added.

Expected values

Every end node represents a pathway or sequence of logic events that was followed by an individual (or cohort); therefore, it is possible to estimate the probability of a given pathway (end node) by multiplying all branch probabilities of such a pathway.

For example, the probability of the end node (as pathway) where system A fails twice should be obtained as follows:

$$P(T_{A1}-) * P(T_{A2}-\mathrm{I}\ T_{A1}-) = 0.1 * 0.4 = 0.04$$

Each pathway has a cost associated with it; this cost represents the sum of the costs of each event of such a pathway (Drummond *et al.*, 2005). Following with the example, the cost of the pathway where system A fails twice, should be:

$$CT_{A1} + CT_{A2} = £\ 800 + £\ 1{,}000 = £\ 1{,}800$$

To obtain the expected cost of each pathway (end node), the cost attached to each end node (or pathway) is multiplied by the pathway probability. Also, to obtain the expected cost of a given intervention (chance node), the expected costs of all pathways (end nodes) belonging to such an intervention are added. The same logic is used to obtain the expected outcome of an intervention. In the same example:

$$(P(T_{A1}-) * P(T_{A2}-I\ T_{A1}-)) * (CT_{A1} + CT_{A2}) = 0.04 * £\ 1{,}800 = £\ 72$$

Finally, Figure 5.6 shows the results of this cost-effectiveness analysis, where the system A was more cost-effective than system B because the former produced a successful treatment with less cost (£ 900) than the latter (£ 1050).

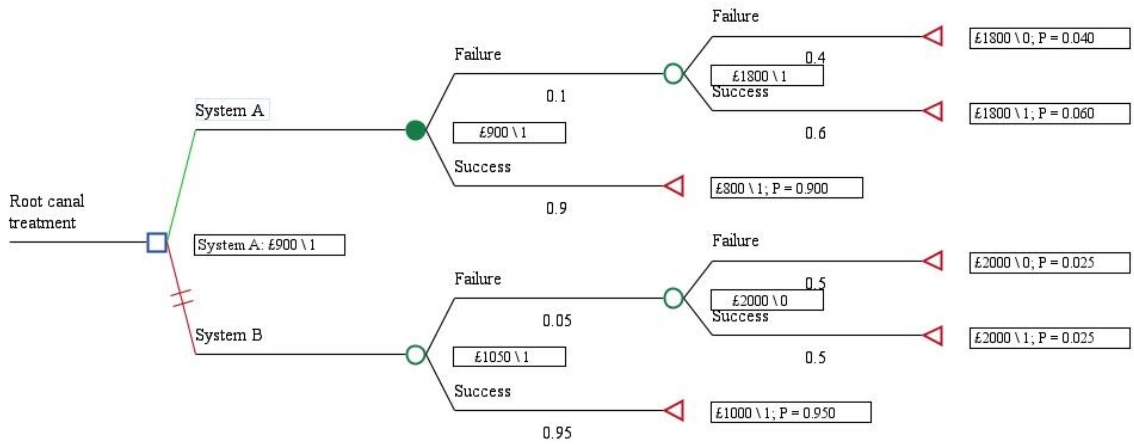


Figure 5.6. Complete decision tree.

This type of model is relatively simple to understand and is widely used in economic evaluations. However, it has some limitations (Drummond *et al.*, 2005). For example, these models do not consider a time variable; thus, decision problems that require consideration of a time element cannot be readily addressed using this type of model. A second limitation is that they are not often suitable for those studies considering chronic pathologies, such as dental caries; in part because such pathologies require ongoing treatment or involve movement between health states (e.g., whether the person is in an acute phase or in remission).

In very basic terms, the number of branches of the tree, which represent its complexity, is given by the nature of the decision problem to be answered, the natural history of the disease, and the availability of data.

5.5.3 Markov models

Markov models are analytic structures able to study interventions that are sequential or repetitive in nature. Thus, they are appropriate for long-term outcomes and especially suited for chronic diseases (Gray et al., 2011).

These models are composed of a finite set of health states or Markov states, in which an individual (usually a patient) or a cohort can be found at a given point in time. The number of states depends on the nature of the decision question and, they are sequential and mutually exclusive. There are three types of Markov states (MINSAL, 2013):

- Temporal states, in which individuals can be located just once during the analysis.
- Transitional states, where individuals can come back to the same state at different times.
- Absorbing states, in which the individual remains without possibility of moving to another state.

Using a dental example, Figure 5.7 shows the natural history of caries of a tooth (using DMFT index). A sound tooth (DMFT = 0) is considered to be in a temporal state. When a tooth is either filled or decayed, it is considered to be in a transitional state. Finally, when a tooth is extracted (missing), it is considered to be in an absorbing state.

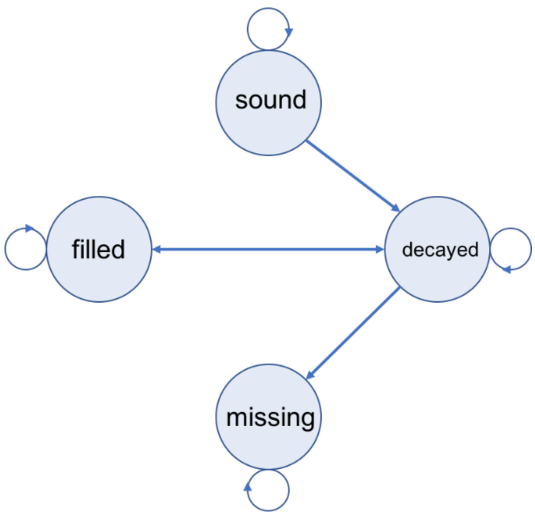


Figure 5.7. Markov model.

In simple terms, the initial distribution of individuals into the different Markov states is given by a set of initial probabilities. After a defined period or Markov cycle the individuals can either pass to another health state or remain in the same one. The likelihood of an individual moving between Markov states is defined and is known as the transition probability. When the transition probabilities are constant, this kind of model is called a Markov chain. In cases when the transition probabilities are not constant, for example, when the probabilities change during the lifespan of an individual, the structure is called a Markov process.

A Markov cycle represents the minimum amount of time that any individual will stay in any Markov state; the selection of the length of the cycle is closely related to the natural history of the disease being analysed (Gray *et al.*, 2011). Also, the cycle length must consider characteristics of the interventions and the availability of the data.

The outcomes estimated are obtained using rewards; there are several types of rewards in Markov models (Gray *et al.*, 2011) and they can be used depending on what is being estimated in the model. For example, the state reward is the value of cost and outcomes assigned to being in a Markov state. The transition reward is counted if there is a cost or outcome associated with the individual transiting to a new state. Finally, there is a one-time reward that can be used at the start of simulation (cycle zero) or at the final cycle; this reward is used to count the number of patients with a pathology at the end of a follow-up period for example.

One important characteristic of these models is that they are memoryless, a phenomenon called the Markovian assumption (Briggs *et al.*, 2011). This assumption means that all individuals in a specific Markov state are equal, regardless of what cycle they have been in before or how long they have been in a specific cycle. This characteristic could be problematic in some pathologies, when the prognosis depends on the history of the patient in the previous states.

Time-dependency

As was discussed earlier, two types of probabilities exist in Markov models, initial and transitional, where the former is the initial distribution of individuals (of a hypothetical cohort) and the latter is the probability to pass from one Markov transitional state to another. Also, a transitional probability can be either constant or variable. Variable transitional probabilities are linked to the concept of time-dependency of Markov models, where transitional probabilities vary depending on how long the cohort has been modelled (Briggs et al., 2011).

The concept of transitional probability is related to the concept of the natural history of disease as well, which describes how a chronic disease changes through the time (see Chapter 6). The natural history of a disease is studied using cohorts, where a group of individuals is followed over the course of the disease (often years).

Unfortunately, there are few longitudinal studies that show the development of caries over time (Andre Kramer *et al.*, 2013). Studies by Dunedin and Pelotas, the former performed in New Zealand since 1972 (Broadbent *et al.*, 2008) and the latter conducted in Brazil since 1982 (Peres *et al.*, 2011), are the best-known examples.

The data obtained from these kinds of studies have been used to determine the risk of a child developing caries over the time. For example, Kopycka-Kedzierawski and Billings (2006), using a maximum likelihood method to obtain the transition probabilities of passing from caries-free to caries in children 6 to 12 years of age, assessed the impact of salivary *Streptococcus mutans* levels on caries status.

In another example, Stephenson *et al.* (2010) used a multilevel competing risks survival analysis model to estimate the transition probability of passing from caries-free surface to surface with caries in primary dentition, in a British cohort that followed children aged 4-5 to 9-11 years.

Such data could be useful to model the effect of some preventive intervention, for example. However, as far as the author is aware, there are no studies that link caries transition probabilities from primary to adult dentition. Consequently, the effect of a specific preventive intervention would be estimated in either primary or adult dentition; in the case of this thesis, primary dentition is the selected aspect.

Based on the previous paragraph, the time horizon, or time where both costs and outcomes of an economic evaluation are estimated, would be short and based on primary dentition.

5.5.4 Markov cycle tree model

Decision trees and Markov models are not mutually exclusive and, can be used jointly; indeed, Markov models are considered as a form of a recursive decision tree (Briggs *et al.*, 2011). The models that combine both Markov and decision tree models have been called Markov cycle tree models (Sonnenberg and Beck, 1993) and they can be used to analyse events that occur within a Markov cycle (Siebert *et al.*, 2012).

For example, Figure 5.8 shows a Markov cycle tree model, where a circle with an M inside represents a Markov node. Such a node means that intervention A is repeated n times (cycles) and intervention B is performed just once. In this example, the probabilities of the Markov node are constants, meaning the probability of healing is constant after each intervention.

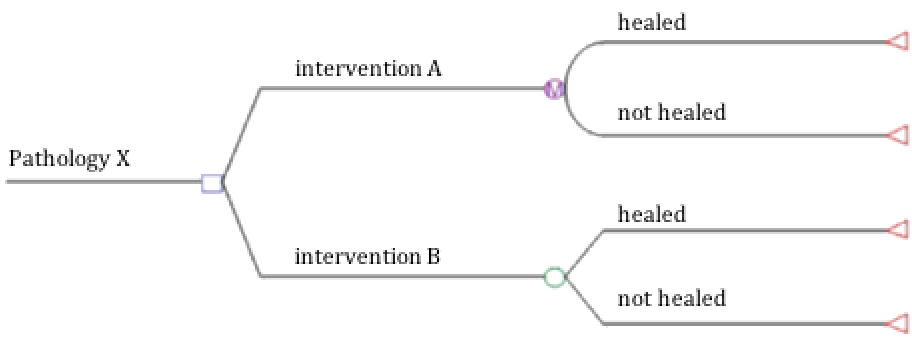


Figure 5.8. Markov cycle tree model.

5.6 Identifying and synthesizing the evidence

Given that RCTs are considered a powerful instrument to calculate the relative effectiveness of health interventions (Donaldson *et al.*, 2002), DAMs should aim to use this type of source. However, RCTs should not be arbitrarily selected and the principles of evidence-based medicine should be followed (Petrou and Gray, 2011). Such principles emphasise that evidence should not be identified selectively (Drummond *et al.*, 2005) and that a systematic approach is needed; consequently, the use of systematic reviews, and meta-analyses of RCT data should be the main source of data for relative effectiveness.

In such cases where obtaining data from RCTs is either not possible or extremely difficult, other sources of data should be identified. Alternative sources include, among others, epidemiological studies, economic studies, national datasets, and expert opinions. The source should be clearly stated regardless of the type of data used; otherwise, the choice or assumption, if used, should be clearly explained and justified (Philips *et al.*, 2006). Evidence synthesis is treated in more detail in Chapters 9 and 10.

Sometimes, as was commented on by Petrou and Gray (2011), even the data provided by an RCT is not sufficient to estimate the value for a model input parameter. A typical example occurs when the RCT source gives a probability calculated for a period that is different than the length of a Markov cycle. Under such circumstances, such a probability should be transformed into a transition probability before populating the model. This can be done by transforming a probability, for a specific time interval, into a rate and then transforming this rate into a new probability for a different time interval; this topic is covered in more detail in Chapter 11.

5.7 Discounting

Drummond *et al.* (2005) state that most economists agree that costs and outcomes that occur at different times should be weighted differently. This is based on the time preference for individuals to incur costs later in the future rather than at the present because a specific cost is considered to be worth more today than the identical amount of the cost is in the future. For example, receiving $100 is considered to be worth more now then say receiving $100 in 10 years. (Rudmik and Drummond, 2013). Therefore, the cost and outcomes of an intervention should be adjusted for time preference and present value of all costs and benefits should be presented to decision-makers regardless of when these costs might be incurred or benefits received.

Along the same lines, NICE (2013) noted that cost-effectiveness analyses should reflect the present value of all costs and benefits accruing over the time horizon of the analysis and that they should adjust future costs and effects by applying a discount rate to them. Nevertheless, Husereau *et al.* (2013a) established that the use of such discounted values is not universal and proposed using local economic evaluation guidelines to establish the value that the discount rate should take.

Therefore, this thesis will use the discount rate as defined by the Chilean guideline for economic evaluation (MINSAL, 2013c), which suggests the use of a discount rate of 3% for both costs and benefits in the baseline scenario and a range between 0 and 5% in the sensitivity analyses.

5.8 Uncertainties

As was discussed by Petrou and Gray (2011), uncertainty (and concepts such as heterogeneity and variability) affects DAMs and needs to be properly addressed so that that decision-makers can trust the results of such analyses. Uncertainty is inherent to decision analytic models and, according to Afzali and Karnon (2015), is due to the lack of perfect information in making choices during the model development process.

Unfortunately, there is some confusion about the definition of such terms as they have not been used consistently in the literature; which, as was commented by Briggs *et al.* (2012), reflects the multidisciplinary nature of decision modelling in health care. This section of the chapter describes a classification proposed by Bilcke *et al.* (2011), which is less complex than the classification proposed by Briggs *et al.* (2012); the former, considers three types (methodological, structural, and parameter) of uncertainty.

5.8.1 Methodological uncertainty

As was described by Bilcke *et al.* (2011), uncertainty around methodological choices occurs when there are different views about what is the correct approach for optimum decision making. This uncertainty is related, for example, to the perspective taken, the way that health gains are valued, and the type of outcome used. This kind of uncertainty also considers uncertainty around parameters associated with normative views about economic evaluations such as time horizon and discount rate.

The way to deal with this kind of uncertainty is to adopt national guidelines about economic evaluations, such as the "Methodological guideline for economic evaluations of health interventions in Chile" (MINSAL, 2013c), for example.

5.8.2 Structural uncertainty

Structural uncertainty involves deciding what structural aspects should be incorporated to capture the relevant characteristics of the disease and intervention being investigated. Some examples are related to the health states to be incorporated and whether the transition rate between disease states is static (constant) or dynamic (variable) over time. An inappropriate structure for a decision analytic model could invalidate estimates of an economic evaluation.

This kind of uncertainty arises due to limitations in the availability and/or quality of supporting evidence, either due to lack of evidence, or conflicting or unclear evidence. Sculpher (2014) argues that this kind of uncertainty can be handled using two approaches, the use of sensitivity analysis or model averaging. However, despite this type of uncertainty affecting the credibility of the models, there is little guidance about how to deal with this phenomenon (Afzali and Karnon, 2015).

5.8.3 Parameter uncertainty

Parameter uncertainty can be defined as the precision of a parameter with respect to the true value of such a parameter. Briggs *et al.* (2011) attribute this uncertainty to the fact that parameters are estimated for populations based on limited data. Decision analytic models should be able to reflect the impact of such uncertainty on both cost and consequence estimates (Gray *et al.*, 2011); to do so, two types of sensitivity analyses are used, deterministic and probabilistic.

Silva *et al.* (2017) included in this type of uncertainty the concept of heterogeneity, which can be defined as the difference between patients that can be explained. Gray *et al.* (2011) argued that heterogeneity can be caused by two factors, either variations between subgroups in baseline characteristics (age, gender, SES, etc.) or subgroup variability in both baseline characteristic and the relative effect of treatment. Heterogeneity can be treated by running different models for populations with different characteristics (or subgroups); this is important because, as was discussed by (Briggs *et al.*, 2011), it is possible that a health policy decision may vary between subgroups.

Deterministic sensitivity analyses

Deterministic sensitivity analysis measures the impact of each parameter on the results of the model incorporating the uncertainty of such parameters in the equation. The simplest way is by conducting a one-way analysis where the uncertainty is incorporated by replacing just one parameter at a time with either a lower or upper value (for example, by using the low and high values from a confidence interval) and then re-running the model. One issue with this type of analysis is that, depending on the number of variables in the models, the analysis is time consuming. Also, as was discussed by Petrou and Gray (2011), this approach does not properly reflect the role of joint uncertainty and the possible correlation between variables. Another approach would be testing two or more variables at the same time (multi-way analysis); this has also been described as scenario analysis (Gray *et al.*, 2011).

Probabilistic sensitivity analysis

A more complex way to incorporate the parameter uncertainty is by using a probabilistic approach, which is based in Bayesian statistics (MINSAL, 2013c). In probabilistic sensitivity analysis, the parameter uncertainty of all parameters in the model is incorporated at the same time in the model by assigning each parameter a statistical distribution. Monte Carlo simulations are run; with each simulation drawing a random value for each parameter distribution and using these as data inputs into the model. The result are then estimated and recorded (Gray *et al.*, 2011). After several simulations, normally several thousand, it is possible to get an average result with a 95% confidence interval, sometimes called an uncertainty interval (UI), such as in Cobiac and Vos (2012). Gray et al (2011) described that 1,000 is the commonly used number of simulations; nevertheless, 10,000 simulations are not rare in economic evaluations of health technologies (Dong and Buxton, 2006;Caporale *et al.*, 2011;Lee *et al.*, 2012).

One way to present the results of these simulations is using a cost-effective scatterplot, where the cost-effectiveness results are presented as clusters whose shapes represent the joint uncertainty of the model and each point represents a random simulation. For example, Figure 5.9 shows the comparison of two interventions (red and blue) reducing the number of individuals with "X" pathology, where it is possible to see that simulations of the blue intervention are more effective, producing more individuals without the pathology on average. Also, it is possible to observe that the red cluster is above the blue one, indicating that the former simulations are slightly more expensive on average.

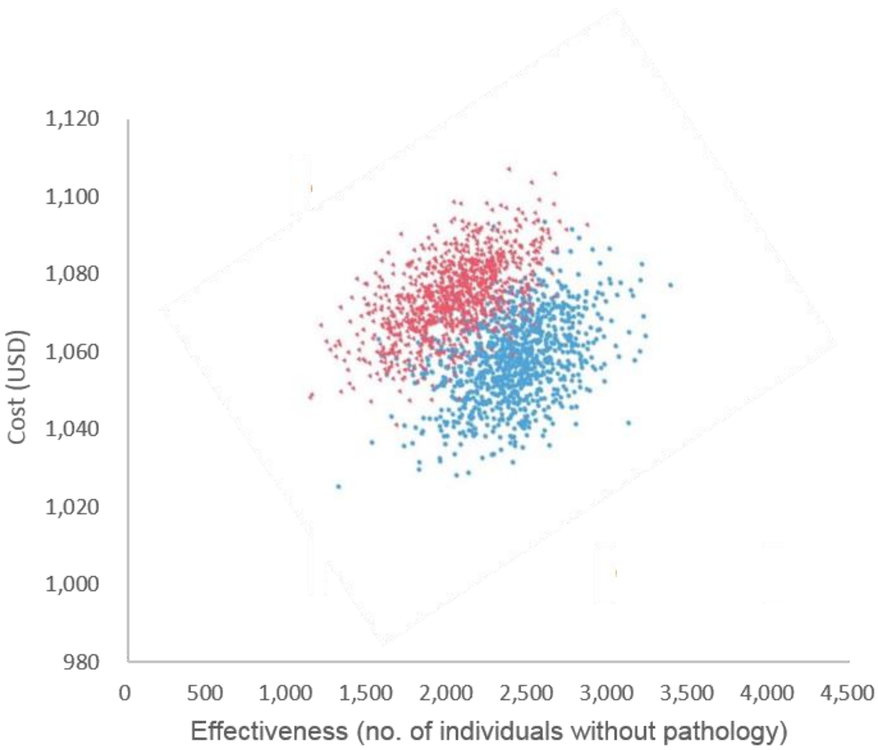


Figure 5.9. Cost-effective scatterplot of two intervention.

A second way to present the results is by employing a cost-effectiveness acceptability curve (CEAC). A CEAC shows the probability that an intervention is cost-effective at different thresholds of willing-to-pay (WTP) per unit of effect. Such a curve is plotted on a graph whose axes represents the probability of being cost-effective (y-axis) and the value of threshold ratio (x-axis).

As was highlighted in the Chilean guideline for economic evaluations (MINSAL, 2013c), this type of graphic representation is not a useful tool for decision-makers because it only reports the probability of being cost-effective and does not consider costs and outcomes separately. Conversely, Gray *et al.* (2011) conclude that acceptability curves give important information to decision-makers who know their maximum WTP for a health gain.

5.8.4 Model evaluation

Petrou and Gray (2011) indicate that model evaluation is an important part in the development of a DAM and is usually overlooked. They describe three types of validation that might be undertaken for any model. The first type is the descriptive validation, where both the assumptions and structure of the model may be reliably, sensibly, and intuitively explained. This may require testing the models with null or extremes values.

A second type of validation is internal validation. Internal validation looks at whether we can replicate the model result when we reconstruct the model using alternative software. This is related to the internal consistency or mathematical logic of the model (Philips *et al.*, 2006). The final type of validation is the external validity. It evaluates if the models can predict future events using a population or a time horizon not used in the model.

5.9 Outlining the ingredients needed for a decision model

Given the complexity of decision modelling in heath economics, several authors (Drummond *et al.*, 2005;Briggs *et al.*, 2011;Petrou and Gray, 2011) and national institutions (MINSAL, 2013c;NICE, 2013), have developed guidelines to try to order such complexity. These guidelines contain the components required to develop economic evaluations (and decision models), and hence can be used to assess economic evaluations. Also, there have been international efforts directed to improve the way that economic evaluations are be reported; these efforts have produced checklists. Such checklist can also be used to assess decision models.

Table 5.1 outlines the components required for a decision model using the CHEERS checklist (Husereau *et al.*, 2013b), and indicates where each element is discussed in this thesis.

Element	Chapter	Section	Subsection
Introduction			
Background and objectives	1 - 5	11.1	
Methods			
Target population and subgroups	6, 7		
Setting and location	8		
Study perspective			11.3.1
Comparators	8		11.3.2
Time horizon	9		11.3.2
Discount rate			11.3.14
Choice of health outcomes	1, 6		
Measurement of effectiveness	9		11.3.6
Estimating resources and cost	10		11.3.5
Currency, price date, and conversion		10.1	
Choice model			11.3.2
Assumptions	10	11.2, 11.3	6.5.1, 7.4.2, 9.4.1, 9.4.2
Analytic methods		11.3	
Results			
Study parameters		11.4	
Incremental cost and outcomes		11.4	
Characterizing heterogeneity	7		11.2, 11.4.1
Discussion			
Study findings, limitations, generalizability, and current knowledge	12	11.5	
Others			
Source of funding	1		
Conflicts of interest	1		

Table 5.1. Outline of elements need for a decision model. Based on CHEERS checklist.

5.10 Summary

This chapter covers basic concepts of economic evaluations, with an emphasis on cost-effectiveness analysis, and highlighted the small number of economic evaluations in dentistry.

This chapter also described theoretical considerations related to decision analytic models such as, for example, the definition of decision problems, structure, evaluation, and presentation of such models. Similarly, this chapter covered important points on how to manage parameter uncertainty using of both deterministic and probabilistic sensitivity analyses.

Chapters 8 to 11 of this thesis develop in more detail the topics cover by this chapter in an empirical setting.

Chapter 6. Proxy of Caries Prevalence in the Chilean Preschool Population

6.1 Introduction

This thesis considers, as part of the main study, the execution of a DAM relating to the use of FV in caries prevention in the Chilean preschool population. Basically, a DAM is a model that allows the costs and consequences of a specific programme or strategy to be calculated, bearing in mind the variability and uncertainty associated with such programmes.

Depending on the structure of these models, they need different types of evidence and require the use of a time horizon that properly reveals the differences in costs and consequences of all alternatives analysed (Briggs *et al.*, 2011); in other words, they require an understanding of the progression of the pathology through different stages of life or the natural history of caries. In simple terms, the natural history of caries is important because such information allows one to obtain the probabilities of developing caries at a specific age; these data are crucial to model costs and consequences of FV application.

The concept of natural history denotes understanding the evolution, in a specific population, of a pathology over different ages and implies a follow-up of many years. This type of data is usually obtained using prospective cohort studies that help to calculate incidence and detect risk factors. However, these studies are difficult to perform, mainly due to the costs, the long-time invested, and difficulties with follow-up (Peres *et al.*, 2011)

As was commented on in Chapter 2, there are few caries-related cohort studies. Furthermore, dental caries has different behaviours depending on the generation and country under analysis (Petersen, 2003). This implies that using the studies of Dunedin, Pelotas, or others as the main input in a decision modelling analysis for the present Chilean population may not be the best alternative, assuming more relevant data are available.

Similarly, such cohorts do not share the same criteria used by MINSAL to classify the socioeconomic status of children, which is a proxy based on the type of school (public, subsidised and private) and has been used to target childhood populations; see Chapter 4 for more detail. For example, Peres *et al.* (2003) used a completely different classification of socioeconomic status (bourgeoisie plus new petit bourgeoisie, traditional petit bourgeoisie, and proletariat) to describe children aged 6-years in the Pelotas cohort. Consequently, the information provided by such cohort studies is unlikely to be useful in the Chilean context.

These factors have led to the decision to obtain the required natural history data from Chilean sources. Unfortunately, Chile lacks any national longitudinal studies that show the development of caries in the preschool population. For these reasons, this chapter describes the analyses of four cross-sectional studies to obtain a proxy of the natural history of caries in a preschool Chilean population. Simultaneously, through such a proxy, this chapter provides data needed to get both initial and transitional probabilities to be used in the DAM (see 11.2.2).

6.2 Description of datasets

6.2.1 General description

Two datasets have been analysed, both obtained from the Oral Health Department of the Ministry of Health of Chile (MINSAL) specifically for this thesis. The first dataset (6-year-old children) is the result of a single unpublished study called "National Diagnosis of Oral Health in 6-year-olds Children" (Soto *et al.*, 2007a). This study was framed by the Chilean Health Objectives for the Decade 2000-2010 (MINSAL, 2002) and was a fundamental piece of evidence in the incorporation of the population of 6 year old children into the national plan of explicit warranties in health (MINSAL, 2005) (see Chapter 4 for more details). The second dataset (2 and 4-year-old children) was drawn from a study completed by MINSAL (2012a), which is a summary of three unpublished studies, all of which were based on children between the ages of 2 and 4 years that attended preschool education throughout the country (Ceballos *et al.*, 2007;Soto *et al.*, 2009;Hoffmeister *et al.*, 2010). It is important to highlight here, that all of these studies used the methodology proposed by the World Health Organization (WHO, 1997) for epidemiological studies in oral health including a clinical examination and a survey; hence they share the same diagnostic criteria.

A complicating factor for this analysis was an administrative change during the latter part of 2007, resulting in a division of two regions and the creation of two new ones. This explains why the first dataset (Soto *et al.*, 2007a) has 13 regions and the second (MINSAL, 2012a) has 15 regions. In order to solve this issue, the present study uses the current administrative division proposed by MINSAL (2012a) which created a new larger type of division called 'zones', of which there are eight. More information about the composition of each zone can be found in Appendix B.

6.2.2 6-year-olds dataset description

Methodology

This dataset is based on a study by Soto et al. (2007a). The research was conducted between the years 2006 and 2007. The universal population was defined as the Chilean population at age 6 who attended the first year of elementary school. The populations who resided in the extremely hard-to-access zones of Easter Island, Juan Fernandez Island, and the Antarctic

Region	Name zone	Zone	Sample size (n)			Date of fieldwork		Study
			2-year-olds	4-year-olds	6-year-olds	2 & 4-year-olds	6-year-olds	
Arica y Parinacota	Northern	1	113	56	70	2008-2009	2006	2,4
Tarapacá			137	84		2008-2009		
Antofagasta			80	118	67	2008-2009	2006	
Atacama			12	37	50	2008-2009	2006	
Coquimbo			165	100	88	2008-2009	2006	
Valparaíso	Centre I	2	280	387	216	2008-2009	2006-2007	2,4
Metropolitana	Metropolitan	3	484	506	746	2007	2006-2007	1,4
Libertador General Bernardo O'Higgins	Centre II	4	328	253	118	2008-2009	2006-2007	2,4
Maule			245	213	159	2008-2009	2006	
Biobío	Centre-Southern	5	311	410	311	2009-2010	2006	3,4
Araucania	Southern I	6	338	434	125	2009-2010	2006	3,4
Los Ríos	Southern II	7	322	235	167	2009-2010	2006	3,4
Los Lagos			80	88		2009-2010		
Aysén	Southernmost	8	146	172	48	2009-2010	2006	3,4
Magallanes y Antártica Chilena			173	261	55	2009-2010	2006	
Total			3,214	3,354	2,220			

Table 6.1. Administrative divisions, sample sizes, dates of fieldwork and studies by zone. Study no.1 done by Soto *et al.* (2007a), no.2 by Ceballos *et al.* (2007), no.3 by Soto *et al.* (2009), and no.4 by Hoffmeister *et al.* (2010).

Territory of Chile were excluded. For determining the sample size, a caries prevalence level of 63%, a confidence level of 95%, and an estimated error rate of 2% were used. The sample size was 2,220 children. See Table 6.1.

A multi-stage and stratified random sampling was used. The sample was stratified by region, county, socioeconomic status (SES), and gender. The male/female proportion of each region and county was kept in the sample. Counties were selected at random in each region and stratified into urban/rural areas, so that the urban/rural proportion of each region was maintained. The schools within each region and county were classified by SES using the classification used by the Ministry of Education that divides the educational institutions into public schools, private schools, and government subsidised schools (see Chapter 4 for more details). At each school, the children were selected using a table of random numbers. Every child had the positive consent of his or her parent or guardian for the oral examination and inclusion in the survey.

Clinical data and sociodemographic variables

Caries was defined using the criteria suggested by WHO (1997), which considers caries as a lesion present in a pit, fissure, or in a smooth dental surface with a visible cavity, undermined enamel, or a wall or floor appreciably softened. Therefore, a $d_3$mft diagnostic criteria was used. See Chapter 2 for more information about dmf index.

As described above, the school type was used as a proxy for socioeconomic status. All children attending public schools were classified as low SES. Children attending subsidised schools were classified as medium SES and the high SES classification was assigned to all students in private schools.

Fieldwork

The fieldwork was conducted during the years 2006 and 2007 (Table 6.1). The calibration of the examiners was performed in collaboration with the Pan American Health Organization (PAHO), through the efforts of MINSAL. The mean inter-examiner agreement was Kappa >0.8. The range obtained by the internal examiners ranged from 0.8 to 1 in the Kappa test. The researchers were organised into fieldwork teams, each of them composed of a dentist who conducted the clinical dental health examination and a dental-assistant who recorded the survey.

For the clinical examination, the children were lying on a table, with the examiner located behind the head of the student. Lighting was provided with a portable lamp headband. To avoid variations in illumination, the room did not face any natural light source. Near to the examiner was a table with dental instruments and containers in which to deposit the instruments when they had been used. Also, to reduce errors in the data transcription process, the dental-assistant was sitting near the examiner.

6.2.3 2 and 4-year-old dataset description

Methodology

This dataset is drawn from the work done by MINSAL (2012a) and contains information collected by three different cross-sectional studies (Ceballos et al., 2007, Soto et al., 2009, Hoffmeister et al., 2010) that share the same methodology and were conducted in Chile in three consecutive stages between the years 2007-2010, see Table 6.1. The first study (Ceballos et al., 2007) included the region of the capital city, the second one (Soto et al., 2009) considered the north and centre of the country, and the last one (Hoffmeister et al., 2010) studied the central and southern parts of Chile. Across the three studies, the entire country was covered.

The population was defined as all children aged 2 years attending "sala cuna" (nursery) and all children aged 4 years attending "pre-kinder" (preschool). At the time of the study, it was estimated that the 4-year-old population attending preschool/nursery education was 61% of the total Chilean population for this age and 21% for the 2-year-old group. This means that a significant percentage of the Chilean population was excluded from this study (79% of 2-year-olds and 31% of 4-year-olds). In terms of calculating the sample size of the study of the Metropolitan Region (Ceballos *et al.*, 2007), the prevalence of dental caries was estimated at 48%, with a confidence interval of 95% and an estimated error of 5%. For the studies of Soto *et al.* (2009) and Hoffmeister *et al.* (2010), the prevalence of caries was 17% for 2 year-olds and 48% for 4 year-olds, with confidence intervals of 95% and an estimated error of 5%. The sample size for each study and age in shown in Table 6.1.

The design was probabilistic, stratified by SES. Counties were selected in a first stage. The selection of institutions was done in a second stage, with probability proportional to the number of students per school and number of students to be selected in the stratum, also considering replacement of 15% of the sample.

Clinical data and sociodemographic variables

Caries was defined in the same way as the study of 6-year-old children using the diagnostic criteria suggested by WHO (1997); hence, a dmft index was used again. At 4 years of age, socioeconomic status was again classified according by the institution they belonged to using the type of school as a proxy for socioeconomic status; this means that all children attending public schools were classified as low SES, children attending subsidised schools were classified as medium SES, and those children attending private schools were classified as high SES.

Special attention must be given to children aged 2 years, given that there are no subsidised nurseries. Consequently, they were classified as low or high SES only. Those attending public institutions as such as JUNJI and INTEGRA foundation (Chapter 4), were classified as low SES, and those children attending private nurseries were classified as high SES.

Fieldwork

Data collection was conducted between May 2007 and July 2010 (Table 6.1), depending on the zone. Clinical variables were obtained from a clinical exam conducted by six pairs of dentists (examiner and recorder) who were calibrated in caries diagnosis with a high concordance among them (Kappa >0.8). The calibration was performed in 20 preschool children under conditions similar to the study. The examination was conducted in schools and data were recorded on a pre-coded epidemiological record, following the recommendations of the WHO (1997).

The researchers were divided into pairs, composed of an examiner and an assistant to record the findings. These studies followed the same methodological recommendation proposed by the WHO (1997) and used by Soto (2007).

6.3 Statistical Analysis

For this thesis, for each dataset, the name of all variables was translated from Spanish to English and imported from Excel (Microsoft Corporation, Redmond, Washington) to Stata 14 (Statacorp, College Station, Texas). No missing data were found in the most important variables (region, zone, county, gender, SES, decayed, missing, and filled teeth).

Descriptive analyses were performed, which provided both absolute and relative frequencies. National and zonal parameters were estimated considering caries prevalence (history of caries positive) when dmft was bigger than zero (dmft > 0); Clopper–Pearson confidence intervals were estimated at 95%. Data were compared by socioeconomic status, gender, and geographic location using Pearson's chi-squared test. Differences were considered significant at $p < 0.01$.

A dmft index, which is not part of the scope of this thesis, was calculated as a reference as well. Caries severity was compared by socioeconomic status, gender, and geographic location using Mann-Whitney and Kruskal-Wallis statistical tests. Differences were also considered significant at $p < 0.01$.

6.4 Results

The follow section contains the caries prevalence of Chilean preschool population between years 2006 and 2010; prevalence is given as a percentage and was analysed according to age, gender, geographical zone, and SES.

6.4.1 Sample size

The sample included 3,214 2-year-old children, of which 1,582 were males (49.2%) and 1,632 were females (50.8%). By socioeconomic status, 18.1% (582 children) of the sample were classified as high SES and 81.9% (2,632 children) as low SES. The full details are shown by zone in Appendix B.

The 4-year-old population consisted of 3,354 children, of which males represented 52.9% of the sample and females represented 47.1%. According to socioeconomic status, 13.1% of the sample were classified as high SES, 24% as medium SES, and 62.9% as low SES (see Appendix B).

For 6-year-old children, the sample size included 2,220 children. By gender, 50.4% of population were female and 49.6% were male. According to socioeconomic status, 14.2% were classified as high SES, 33.5% as medium SES, and 52.3% as low SES (see appendix B).

Size of each zone

Table 6.2 shows in detail the relative weight of each zone by age. For example, in 2-year-olds, zone 3 (or region of the capital city, Santiago of Chile) represents 15.09% of the sample population, and in 4-year-olds, zone 8 (or Patagonian regions of the country) represents 12.91% of the sample.

	2-year-olds		4-year-olds		6-year-olds	
Zone	No.	%	No.	%	No.	%
1	507	15.77	395	11.78	275	12.39
2	280	8.71	387	11.54	216	9.73
3	484	15.06	506	15.09	746	33.60
4	573	17.83	466	13.89	277	12.48
5	311	9.68	410	12.22	311	14.01
6	338	10.52	434	12.94	125	5.63
7	402	12.51	323	9.63	167	7.52
8	319	9.93	433	12.91	103	4.64
total	3,214	100	3,354	100	2,220	100

Table 6.2. Sample size and relative weight (%) of each zone.

6.4.2 Prevalence of caries

2-year-olds

At 2 years of age, the national percentage of children with experience of dental caries was 17.5% (95% CI, 16.2% to 18.9%), see Table 6.3. No statistically significant difference was observed between genders; 18.5% of males and 16.6% of females developed caries ($p = 0.17$), see Table 6.3. At the national level, children belonging to low SES showed three times more caries prevalence than children of high SES, with 19.9% and 6.7%, respectively ($p < 0.01$) (Table 6.4).

Zone 5 had the highest percentage of caries prevalence of all zones, the highest prevalence of females, and the highest percentage of low and high socioeconomic status. See tables 6.3 and 6.4.

4-year-olds

1,689 children developed caries, which corresponded to 50.4% (95% CI, 48.7% to 52.1%) of the national sample (Table 6.5). A difference between zones was observed (Table 6.5); zone 5 showed the highest prevalence (65.1%) and zone 7 had the lowest prevalence (41.2%).

No statistically significant difference between genders was observed; 51.8% of males and 48.7% of females developed caries ($p = 0.08$) (Table 6.5). The prevalence of caries by SES was 24.2%, 48.6%m and 56.5% for high, medium, and low socioeconomic status, respectively, with a significant difference between them ($p < 0.01$) (Table 6.6).

	2-year-olds									
	Total			Male			Female			
Zone	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	p-value
1	14.99	12.00	18.4	15.3	11.3	20.05	14.60	10.27	19.89	0.826
2	14.29	10.41	18.94	15.6	10.04	22.66	12.95	7.86	19.69	0.526
3	16.53	13.33	20.14	18.38	13.63	23.94	14.80	10.64	19.82	0.29
4	20.07	16.86	23.59	22.83	18.01	28.24	17.51	13.36	22.32	0.112
5	24.44	19.76	29.6	22.01	15.84	29.26	26.97	20.10	34.76	0.309
6	21.01	16.79	25.74	16.03	10.65	22.74	25.27	19.14	32.24	0.037
7	12.19	9.16	15.79	13.98	9.34	19.81	10.65	6.87	15.55	0.309
8	17.55	13.54	22.18	23.49	16.94	31.12	12.35	7.81	18.26	*0.009
total	17.52	16.22	18.88	18.46	16.57	20.46	16.61	14.83	18.50	0.167

(*) statistically significant difference (p<0.01).

Table 6.3. Prevalence of caries (%) at 2-year-olds, in total sample and by gender.

	2-year-olds						
	High SES			Low SES			
Zone	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	p-value
1	5.84	2.55	11.18	18.38	14.56	22.71	*<0.001
2	4.11	0.86	11.54	17.87	12.91	23.79	*0.004
3	9.46	3.89	18.52	17.80	14.22	21.86	0.075
4	6.76	3.29	12.07	24.71	20.68	29.09	*<0.001
5	11.11	3.71	24.05	26.69	21.47	32.44	0.024
6	7.14	1.98	17.29	23.76	18.91	29.17	*0.005
7	3.03	0.08	15.76	13.01	9.75	16.87	0.093
8	6.25	0.16	30.23	18.15	13.98	22.96	0.223
total	6.70	4.81	9.05	19.91	18.40	21.49	*<0.001

(*) statistically significant difference (p<0.01).

Table 6.4. Prevalence of caries (%) at 2-year-olds by SES.

The difference between SES was observed in all zone with the exception of zone 5 (Table 6.6). Zone 5 again showed the highest caries prevalence in both genders and in all socioeconomic statuses (Tables 6.5 and 6.6).

6-year-olds

At the national level, 69.6% (95% CI 67.6% to 71.5%) of the sample developed caries (Table 6.7). The zone that showed the highest prevalence was zone 4 (76.5%) and the zone with the lowest proportion was zone 2 (59.7%), see Table 6.7. In the national sample, 70.6% of males developed caries and females developed 68.5% (Table 6.7), with no statistically significant difference observed between genders (p = 0.29).

	4-year-olds									
	Total			Male			Female			
Zone	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	p-value
1	47.85	42.83	52.9	49.74	42.52	56.97	46.00	38.95	53.17	0.456
2	53.23	48.12	58.29	55.72	48.56	62.71	50.54	43.13	57.93	0.307
3	47.43	43.01	51.88	48.97	43.1	54.86	45.33	38.53	52.26	0.417
4	53.43	48.79	58.04	53.39	46.81	59.89	53.48	46.81	60.06	0.985
5	65.12	60.29	69.73	66.81	60.26	72.92	63.04	55.63	70.03	0.426
6	45.39	40.64	50.21	47.96	41.22	54.77	42.72	35.99	49.66	0.273
7	41.18	35.76	46.76	38.37	31.07	46.08	44.37	36.30	52.67	0.274
8	48.04	43.24	52.86	51.08	44.44	57.69	44.55	37.58	51.69	0.175
total	50.36	48.45	52.06	51.80	49.45	54.15	48.73	46.24	51.23	0.076

Table 6.5. Prevalence of caries (%) at 4-year-olds, in total sample and by gender.

	4-year-olds									
	High SES			Medium SES			Low SES			
Zone	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	p-value
1	21.15	11.06	34.7	40.00	31.34	49.14	58.72	51.87	65.32	*<0.001
2	28.26	15.99	43.46	57.14	48.02	65.92	56.28	49.37	63.01	*0.001
3	29.00	20.36	38.93	25.00	7.27	52.38	53.08	47.99	58.12	*<0.001
4	27.78	16.46	41.64	57.05	48.69	65.12	56.65	50.43	62.73	*<0.001
5	47.06	29.78	64.87	60.22	49.54	70.22	68.90	63.16	74.25	0.022
6	9.09	3.41	18.74	41.58	31.86	51.82	55.81	49.62	61.86	*<0.001
7	14.89	6.20	28.31	33.80	23.00	46.01	49.76	42.72	56.8	*<0.001
8	22.50	10.84	38.45	47.20	38.21	56.33	52.24	46.08	58.35	*0.002
total	24.15	20.21	28.43	48.64	45.13	52.15	56.47	54.32	58.6	*<0.001

(*) statistically significant difference (p<0.01).

Table 6.6. Prevalence of caries (%) at 4-year-olds by SES.

Related to socioeconomic status, the national sample showed a prevalence of caries of 39.4%, 70.4%, and 77.2% for high, medium, and low SES, respectively (Table 6.8). A significant difference between SES (p < 0.01) was detected in most zones (Table 6.8). As opposed to other age groups, there was no a clear difference between zones in 6-year-olds (Tables 6.7 and 6.8).

	6-year-olds									
		Total			Male			Female		
Zone	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	p-value
1	69.82	64.02	75.19	70.37	61.91	77.92	69.29	60.94	76.80	0.845
2	59.72	52.85	66.32	60.75	50.84	70.05	58.72	48.88	68.06	0.761
3	67.29	63.80	70.65	66.39	61.25	71.25	68.13	63.23	72.76	0.612
4	76.53	71.09	81.4	78.63	70.61	85.30	74.66	66.80	81.49	0.436
5	73.63	68.36	78.45	72.90	65.19	79.72	74.36	66.76	81.01	0.771
6	73.60	64.97	81.08	80.26	69.54	88.51	63.27	48.29	76.58	0.035
7	72.46	65.02	79.07	78.65	68.69	86.63	65.38	53.76	75.80	0.056
8	65.05	55.02	74.18	64.58	49.46	77.84	65.45	51.42	77.76	0.926
total	69.55	67.59	71.46	70.57	67.78	73.25	68.54	65.73	71.26	0.299

Table 6.7. Prevalence of caries (%) at 6-year-olds, in total sample and by gender.

	6-year-olds									
		High SES			Medium SES			Low SES		
Zone	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	p-value
1	47.50	31.51	63.87	66.67	55.95	76.26	77.93	70.30	84.39	*0.001
2	20.00	8.44	36.94	66.67	55.95	76.26	68.13	57.53	77.51	*<0.001
3	38.40	29.84	47.52	69.4	63.51	74.86	75.92	71.11	80.29	*<0.001
4	53.33	34.33	71.66	71.43	60.00	81.15	82.94	76.43	88.27	*0.001
5	40.00	24.87	56.67	78.57	67.13	87.48	78.61	72.29	84.06	*<0.001
6	50.00	15.70	84.3	73.58	59.67	84.74	76.56	64.31	86.25	0.275
7	29.63	13.75	50.18	79.66	67.17	89.02	81.48	71.30	89.25	*<0.001
8	60.00	26.24	87.84	59.46	42.10	75.25	69.64	55.90	81.22	0.565
total	39.37	33.93	45.00	70.43	67.01	73.69	77.17	74.65	79.56	*<0.001

(*) statistically significant difference (p<0.01).

Table 6.8. Prevalence of caries (%) at 6-year-olds by SES.

6.4.3 Caries increment in primary dentition

Proxy of natural history

For modelling purposes, specifically to obtain a proxy of transitional probabilities (Chapter 5), it was necessary to obtain the natural history of caries, i.e. the increment of caries prevalence through different preschool ages. Unfortunately, Chile lacks any national longitudinal studies that show the natural history of caries in these populations at such ages. To solve this problem, the four cross-sectional studies (which cover all the Chilean territory) were combined and treated as if they were a single cohort study; this kind of analysis gave a proxy of the natural history of caries.

Therefore, where increments are referred to below, they are not true increments because they were not calculated from a true cohort study. However, the word increment was retained, highlighting that this thesis works with a proxy of natural history of caries in the preschool Chilean population.

Prevalence of caries

Prevalence of caries increased four times through the ages from 17.5% (95% CI 16.2% to 18.9%) in 2-year-olds to 69.6% (95% CI 67.6% to 71.5%) in 6-year-olds. Related to gender, the prevalence ratio by gender (male/female) remained similar through the ages (Figure 6.1).

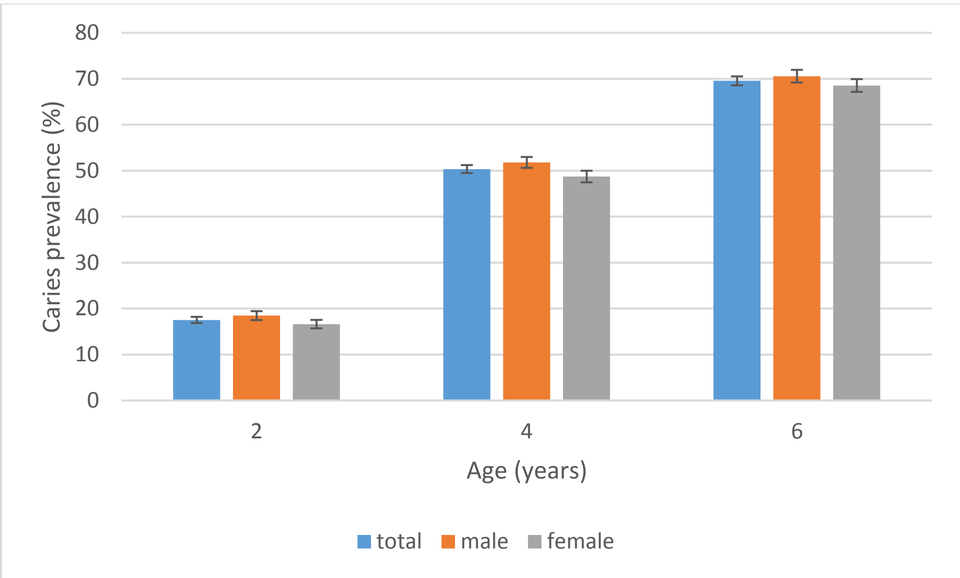


Figure 6.1. Distribution of prevalence of caries through ages by gender.

In the case of prevalence by SES (Figure 6.2), there was a constant increment in prevalence in all socioeconomic status groups.

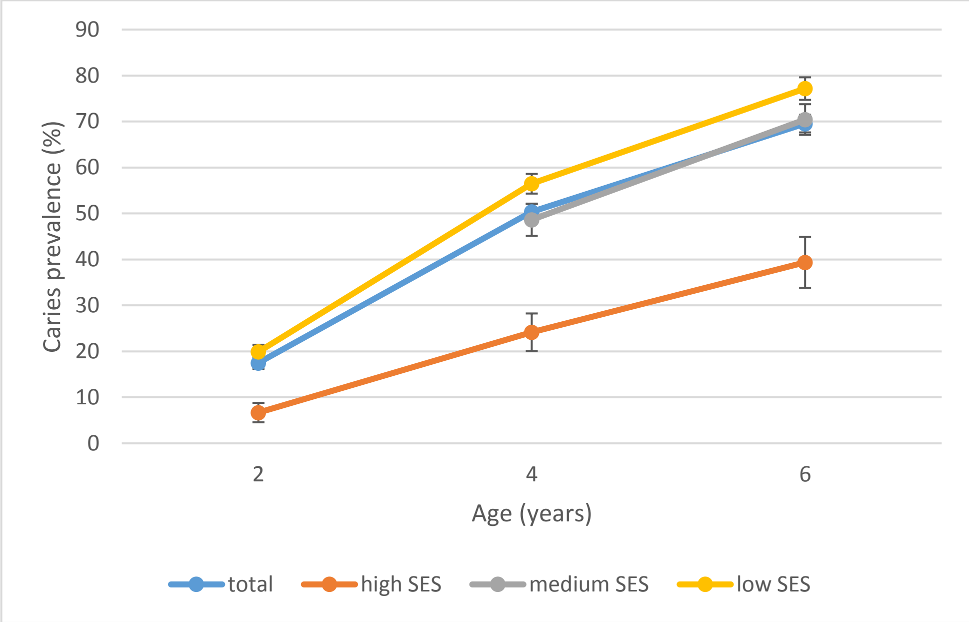


Figure 6.2. Distribution of prevalence of caries by ages and SES.

dmft index

The sample showed a mean dmft of 0.51 in 2-year-olds; the decayed component (d) was 0.5 and represented most of the dmft; see Figure 6.3 and Table 6.9. An important finding was that zone 5 presented the highest dmft ranking between all zones (Appendix B). By socioeconomic status, high SES children showed a dmft of 0.18 and low SES sample had a mean of 0.59 with a statistically significant difference ($p < 0.01$) observed between them (Appendix B). See Figure 6.4 and Table 6.10.

In 4-year-olds, the index was 2.25 (95% CI, 2.15 to 2.36); also, there was a difference between zones, where the highest dmft (3.32) was again observed in zone 5 (Appendix B). By SES, the dmft was 0.81, 1.98, and 2.66 for high, medium, and low SES, respectively; with a statistically significant difference ($p < 0.01$) observed between them (Appendix B).

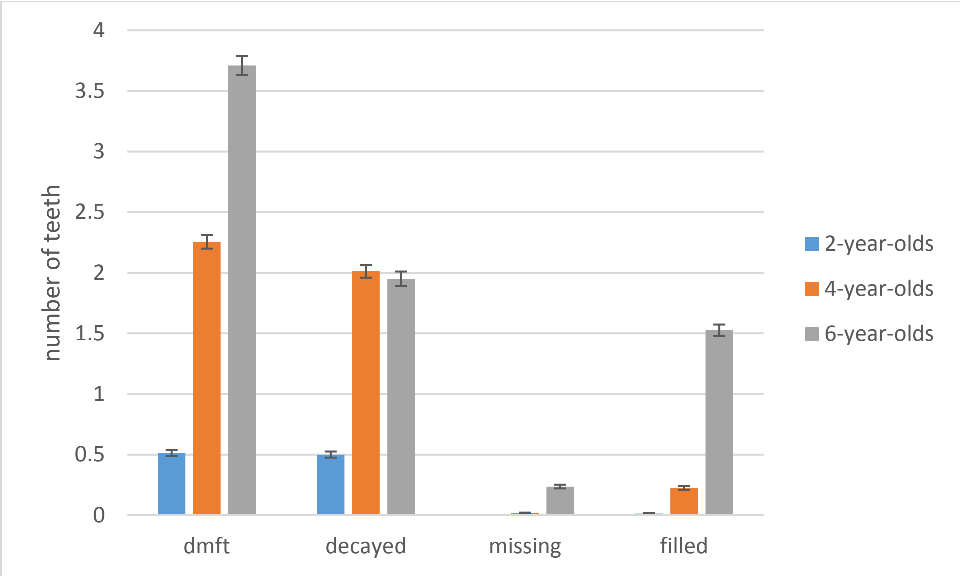


Figure 6.3. Distribution of dmft index and its components by age.

	2-year-olds			4-year-olds			6-year-olds		
dmft index	Mean	Low CI	Upper CI	Mean	Low CI	Upper CI	Mean	Low CI	Upper CI
d	0.50	0.45	0.55	2.01	1.91	2.11	1.95	1.83	2.07
m	0.00	0.00	0.00	0.02	0.01	0.02	0.24	0.21	0.27
f	0.01	0.00	0.02	0.23	0.19	0.26	1.53	1.43	1.62
dmft	0.51	0.46	0.56	2.25	2.15	2.36	3.71	3.56	3.86

Table 6.9. Distribution of dmft index and its components by age.

The average dmft at 6-year-olds was 3.71 (95% CI 3.56 to 3.86). By socioeconomic status, dmft was 1.36 for high SES, 3.6 for medium SES, and 4.4 for low SES, with a statistically significant difference ($p < 0.01$) observed between them (Appendix B).

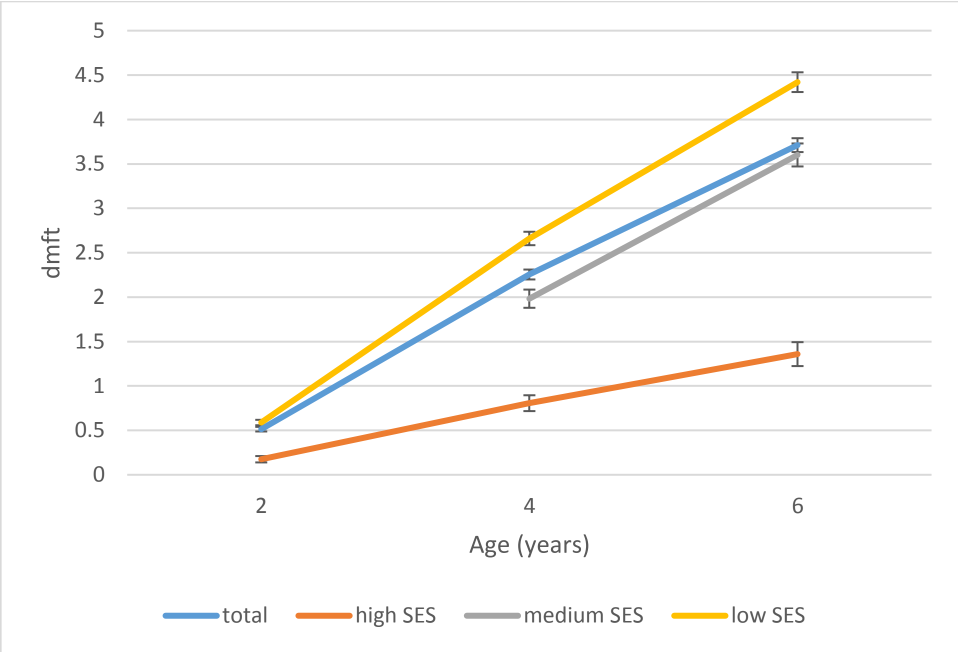


Figure 6.4. Distribution of dmft by age and SES.

	2-year-olds			4-year-olds			6-year-olds		
dmft index	Mean	Low CI	Upper CI	Mean	Low CI	Upper CI	Mean	Low CI	Upper CI
High	0.18	0.11	0.25	0.81	0.63	0.98	1.36	1.09	1.62
Medium				1.98	1.78	2.18	3.60	3.35	3.85
Low	0.59	0.53	0.65	2.66	2.51	2.81	4.42	4.20	4.64
p value	*<0.01			*<0.01			*<0.01		
Total	0.51	0.46	0.56	2.25	2.15	2.36	3.71	3.56	3.86

(*) statistically significant.

Table 6.10. Distribution of dmft by age and SES.

6.5 Discussion

6.5.1 Datasets

The decision to use datasets given by MINSAL was made based on the fact that all of these studies were undertaken using the same methodology (WHO, 1997), and under the assumption that between the years of 2007 and 2010, as MINSAL (2012a) mentioned, there were no significant changes in provisions of oral healthcare for preschool Chilean population.

The studies and their datasets have limitations, as following:

- The sample size by zone, compared with data obtained from a national socioeconomic survey (MIDEPLAN, 2009), does not properly represent children who attend preschool education. For example, in 2-year-olds, zone 3 represented 15% of national sample by size; however, this population should represent 40% (Table 6.2). As another example, in 4-year-olds, the sample population in zone 8 represents 13%, but the real proportion of such zone should be around 2%.

  The concept of zones used may generate risks of bias, either over or underestimating the sample population. Consequently, adjustments on size samples by zones are required to obtain a more accurate proxy of the natural history of caries.
- Despite the researchers of each study being internally calibrated, an external calibration (between the studies) does not exist.
- In the study of 6-year-old children, the sample of each county was equilibrated according to an urban/rural rate; however, the studies of 2- and 4-year-old children did not consider such adjustments.
- The classification of socioeconomic statuse did not consider the family income; the type of school was used instead.

Also, some characteristics of the studies provided by MINSAL can be considered as weaknesses of this approach, that is, the use of a cross-sectional study as a proxy of a cohort, as follows:

- These studies were not cohort based. Also, because the first chronological (Soto et al., 2007) study worked with the oldest population (6-year-olds), they do not follow a temporal sequence.
- The population of 2-year-old children that attends nurseries was 21% of the national population of this age. So, the sample would be unrepresentative of the entire 2-year-old population.

Notwithstanding the limitations and weaknesses, the use of nationwide surveys allows estimates to be obtained to be used in decision analytic models at the nationwide level. In other words, this is the best proxy available of the natural history of caries in the Chilean preschool population.

6.5.2 Geographic variation

Zone 5 showed the highest values for prevalence in 2- and 4-year-olds. This phenomenon was observed in both genders and in all socioeconomic status groups. Similar findings were related to dmft index.

The present study raises the possibility that something is causing this variation in a subgroup of the population. Knowing what oral health risks are associated with such a difference is important to predict the effect of a nationwide FV programme. A plausible explanation may be that zone 5 (or the Biobío Region) is the only Chilean region that lacks fluoridated water. This finding is in concordance with numerous studies (Armfield, 2010;Young *et al.*, 2015) that related fluoridated water and caries prevalence; this topic is covered in more detail in Chapter 3. However, further investigation is necessary to explain this regional difference.

6.5.3 Gender variation

Caries prevalence showed no significant difference between genders; a finding that, as was explained in Chapter 2, is consistent with most studies of gender and caries prevalence.

6.5.4 Socioeconomic differences

At all ages, a clear statistical difference between SES (at zone and national levels) was observed, where high SES (private schools) showed less prevalence than medium (subsidised schools) and low SES (public schools). This is consistent with the results reported in others countries by Al-Malik *et al.* (2001), Piovesan *et al.* (2011), and Hoffmann *et al.* (2004), which showed that children who attended public schools had more caries than children who attended private schools. Nevertheless, SES and type of school do not have exactly the same distribution, as Piovesan *et al.* (2011) established in a study about preschool children in Brazil; however, it is possible to utilise type of school as a proxy of socioeconomic statuse.

Considering this, the results agree with the findings of numerous other studies, in which the authors showed a higher prevalence of caries and severity in pathology in socioeconomically deprived populations. For example, Levin *et al.* (2009) showed a socioeconomic inequality in the prevalence and severity of caries in the more deprived 5-year-old population in Scotland.

Similar oral health inequalities were found by Borges *et al.* (2012) in a cross-sectional study of 4- to 6-year-olds in the Brazilian city of Araçatuba, where children from families with low socioeconomic status had an increased probability of developing caries (OR 1.23; 95% CI, 1.12 to 2.13).

An increase in the prevalence of caries by age was observed with clear differences between SES, where low and medium socioeconomic status groups developed a greater prevalence of caries at a faster rate, and with more extensive caries than high SES groups. This increment is consistent with several studies that describe the natural history of caries in the preschool population (Ferreira *et al.*, 2007;Andre Kramer *et al.*, 2013) and could be explained by two concepts: different oral health determinants and intrinsic characteristics of oral health indices. The former is associated with the influence that each oral health determinant has over each socioeconomic status (Chapter 2); the latter is related to the fact that prevalence is cumulative over the time.

The decreased prevalence ratio (figure A.5.5) of caries between low and high SES by age could be explained as a characteristic of the dental index used by MINSAL, which records a history of caries of each individual. This means that it is generally expected that the gap will decrease as the population with no caries develops the pathology.

One unanticipated finding was the fact that the dmft ratio (Figure 6.5) between low and high SES did not change significantly by age. This implies that a noticeable difference in severity of caries exists between socioeconomic status groups, and more importantly, that this inequality appears early in the population and remains almost constant over the time. Despite this not being a primary outcome of the thesis, this finding reinforces the idea that is necessary to prevent this pathology as early as possible.

In the international context, when it is used an estimation of prevalence for 5-year-olds (60%), and based on data published by the Brazilian Ministry of Health (Ministerio da Saude, 2011), the Chilean population has more children with a history of caries than Brazil, who has 53.4% (95% CI, 50.6 to 56.1). Also, using the same Chilean estimation at 5 years of age (Chapter 11), Chile has a higher prevalence of caries than children of Welsh, England, and Northern Ireland populations (40%) at the same age, using visual dentine caries as diagnostic criteria (Vernazza et al., 2016).

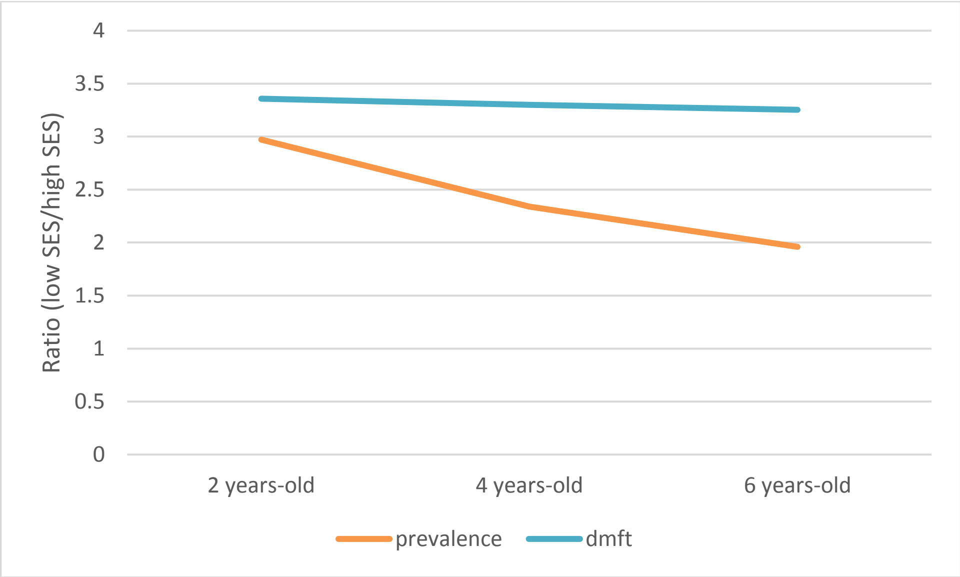


Figure 6.5. Ratio of oral health indices by age.

6.6 Conclusions

Despite the limitations of this study, the proxy of natural history of caries shows a clear percentage increase in caries prevalence by age; these increases presented clear differences between socioeconomic status groups, where low and medium SES groups developed more children with caries than high SES groups.

Zone 5 (Biobío Region) presented the highest caries prevalence of all zones; further research should be undertaken to determine the factors associated with this finding.

Chapter 7. Relationship between Oral Risk Indicators and Caries Prevalence in the Chilean Preschool Population

7.1 Introduction

One important finding in Chapter 6 was the fact that the Biobío Region (zone 5) consistently presented the highest caries prevalence for both 2- and 4-year-olds. It is possible that different zones might have different baselines of caries prevalence, so the potential effect of FV might be difficult to establish without controlling for the characteristics of the zones. In this chapter, regression methods were applied to investigate the relationship between caries prevalence and oral health factors.

As explained in Chapter 2, the evidence shows that caries is a multifactorial and complex issue, and several risk factors (or determinants) have been related to its development. For example, a systematic review by Harris *et al.* (2004) showed that more than 100 determinants were associated with caries prevalence and caries severity in preschool populations. Among them, the determinants related to socioeconomic status were highly significant (Levin *et al.*, 2009;Piovesan *et al.*, 2010), suggesting the existence of socioeconomic inequalities in oral health.

However, the Biobío Region presented the highest national prevalence values in all type of schools (private, subsidised, or public), so it is possible that something else is affecting caries prevalence irrespective of socioeconomic status. It is important to understand what could be affecting caries prevalence in this region, so that systematic differences between regions could be explained. As commented in Chapter 6, a special model for the Biobío Region should be developed in the main empirical study of this thesis.

A possible explanation for the regional difference is the absence of fluoridated water because the Biobío Region is the only non-fluoridated Chilean region. There are numerous studies that show the association between caries prevalence and fluoridated water. For example, Armfield (2010), found that in Australian children aged 5 years living in low fluoridated areas (<0.3 ppm), 29.1% ($p<0.01$) developed more caries (dmft) than those living in optimally fluoridated areas (≥0.7 ppm). In the same age group, Young *et al.* (2015), found that children living in fluoridated areas have 28% ($p<0.01$) less caries prevalence ($d_3$mft) than those living in non-fluoridated areas in an ecological study in England.

Based on the evidence, it is likely that such a relationship between caries prevalence and fluoridated water may also exist in the Chilean preschool context. This chapter examines the relationship between oral health determinant factors, in particular, the presence or absence of fluoridated water, and caries prevalence in the Chilean preschool population. The objective of this chapter is to investigate if previously detected variations in caries prevalence can be explained as subgroup variation (Gray et al., 2011) or heterogeneity.

7.2 Methodology

7.2.1 Sources

The main source of data was based on a cross-sectional study by Hoffmeister *et al.* (2010) and commissioned by the Chilean Ministry of Health; this dataset (Hoffmeister dataset) contains a clinical examination of 1,600 children aged 4 years and a parental completed questionnaire. The Hoffmeister dataset contains 68 questions on socioeconomic status, oral health behaviours, and demographic information.

The clinical examination included the dmft index, which was obtained using the methodology proposed by the WHO (1997), and thus considered only cavitated lesions. More details on the dmft index were presented in Chapter 2.

A stratified multistage probability sampling method was used. The first stage of sampling was at the county level using a probability proportional to the number of 4-year-olds per county. The second stage of sampling was at the school level using a probability proportional to the number of students per school. The sampling also considered replacing a sample of 15% (MINSAL, 2012a).

The Hoffmeister dataset was divided into 4 geographical zones, each one containing approximately a quarter of the total sample. However, this approach does not represent the true proportion of the preschool population in each zone. For example, the Biobío Region population should correspond to 42.92% of the sample population but it was underrepresented in the survey (25.63%). Consequently, all variables were weighted in the analysis using data from a national survey of socioeconomic characterization (MIDEPLAN, 2009), which showed the percentage of preschool children in each zone. Details of the zones are shown in Table B.6.1.

A second source of data was obtained through personal communications with Dr Carolina del Valle of the Department of Oral Health of Chilean Ministry of Health (MINSAL, 2014). This data provided the information on the presence of fluoride in drinkable water in the year 2010 and was merged with the Hoffmeister dataset at the county level.

7.2.2 Statistical analyses

Independent variables were classified in the following types: sociodemographic factors, feeding habits, oral hygienic habits, and dental health services factors; Table 7.1 contains all variables by category.

Type	Variables
Sociodemographic	Gender of child, educational level of caregiver, fluoridated water, educational level of head of household, monthly income of household, absence of teeth of the mother, type of school, geographic zone, relative position of child among other children, relationship with caregiver, family composition, age of caregiver, number of adults living with the child, gender of caregiver, and number of children living with the child.
Feeding habits	Intake liquids with sugar (juice or milk) before bed, intake of tea during the day, breastfeeds at night, intake of soft drinks or juices with sugar, breastfed exclusively, intake of sweets/fruits or drinks juice between meals during the day, use of baby bottle, and intake of tap water during the day.
Oral hygienic habits	Frequency of tooth brushing, intake of toothpaste, use of toothpaste, brushing during week, brushing autonomy, brushing during weekend, brushing before bed, and type of toothpaste.
Oral health care system	Perceived need of dental care, previous dentist experience, and previous education in oral health care.

Table 7.1. Classification of variables by type.

Univariate and multivariate logistic regressions were conducted to investigate the relationship between sociodemographic factors and prevalence of caries, controlling for other relevant factors. The dependent binary variable was caries prevalence based on the dmft (decayed, missing and filled) index, where children with dmft > 0 were considered as having developed caries.

The reason why a logistic regression was used was because this mathematical model approach can describe the relationship of several independent variables with a dichotomous dependent variable, in this case, the presence or not of caries. Despite the existence of other modelling approaches, according to Kleinbaum *et al.* (2010), this is the most popular modelling procedure used in epidemiology when the dependent variable (or illness measure) is dichotomous.

All variables were first analysed in a univariable logistic regression model; and then, except for gender, only those variables with a significance level of 90% or more (using an X^2 test) were used in a multivariate logistic regression model.

In the multivariate analysis and, following a hierarchical model of determination similar to that used by Peres *et al.* (2003), a stepwise selection method was used (Hosmer and Lemeshow, 2000). This meant that all statistically significant variables were ranked (low-to-high) within each type of variable and were added one by one to the multivariate model using the stepwise selection process and, with gender included in all models, followed by sociodemographic, feeding habits, hygienic habits, and dental health care system categories.

Categorical variables were included when at least one of its categories was statistically significant ($p < 0.05$). When a variable that was already incorporated into the model became non-statistically significant after the addition of another variable that was significant, the non-statistically significant variable was eliminated.

7.3 Results

Table 7.2 shows the significance levels of the variables examined in univariate models. Information on the univariate models can be found in Appendix B. After the hierarchical modelling of determination (stepwise process) within each type of variable, 9 variables remained. The multivariate regression result is shown in Table 7.3.

The fluoridated water variable was highly significant ($p < 0.001$) in both univariate and multivariate analyses. The odds ratio was 0.42 (95% CI 0.34 to 0.51) in the univariate model and 0.36 (95% CI 0.28 to 0.47) in multivariate model, indicating that those children with no fluoridated water had a higher risk of developing caries.

Independent variables	Categories	Caries-free	%	With caries	%	Total	p-value in univariate model
gender of child							0.386
	male	359	48.26	384	51.74	743	
	female	395	46.09	462	53.91	857	
educational level of caregiver							<0.001*
	primary uncomplete	46	30.98	103	69.02	149	
	primary complete	49	37.59	81	62.41	129	
	secondary uncomplete	98	41.69	137	58.31	235	
	secondary complete	243	45.90	287	54.10	530	
	tertiary uncomplete	106	52.44	96	47.56	202	
	tertiary complete	198	60.36	130	39.64	328	
	no education	4	31.77	9	68.23	13	
fluoridated water							<0.001*
	no	239	34.88	447	65.12	686	
	yes	514	56.27	399	43.73	913	
educational level of head of household							<0.001*
	primary uncomplete	46	30.31	107	69.69	153	
	primary complete	45	30.00	105	70.00	151	
	secondary uncompleted	111	47.38	123	52.62	234	
	secondary complete	208	44.97	255	55.03	463	
	tertiary uncomplete	69	48.60	73	51.40	142	
	tertiary complete	198	62.13	121	37.87	319	
	postgraduate	30	80.60	7	19.40	37	
	no education	9	50.77	8	49.23	17	
monthly income of household (SCL)							<0.001^
	less than 80,000	60	37.61	99	62.39	159	
	between 81,000 and 150,000	157	39.25	242	60.75	399	
	between 151,000 and 220,000	143	42.01	198	57.99	341	
	between 221,000 and 280,000	91	48.19	98	51.81	189	
	between 281,000 and 450,000	97	48.91	101	51.09	198	
	between 451,000 and 780,000	70	61.87	43	38.13	113	
	more than 780,000	99	83.67	19	16.33	118	
absence of teeth of the mother							<0.001*
	5 or more teeth	94	35.80	169	64.20	263	
	between 4 and 2	254	45.64	303	54.36	557	
	only one	179	51.68	167	48.32	346	
	none	182	54.41	153	45.59	335	
type of school							<0.001*
	high	124	73.31	45	26.69	170	
	medium	114	52.32	104	47.68	219	
	low	514	42.48	697	57.52	1211	
geographic zone							<0.001^^
	Biobio	239	34.88	447	65.12	686	
	Araucanía	191	54.61	159	45.39	351	
	Los Ríos and Los Lagos	258	58.82	181	41.18	439	
	Aysén and Magallanes	64	51.96	59	48.04	124	
relative position of child among other children							0.005*
	1st	317	50.38	312	49.62	629	
	2nd	237	46.66	271	53.34	508	
	3rd	97	40.60	142	59.40	240	
	4th	37	44.66	46	55.34	83	
	5th	15	35.32	28	64.68	44	
	6th or less	8	24.23	27	75.77	35	
gender of caregiver							0.01*
	male	56	59.32	38	40.68	94	
	female	689	46.35	798	53.65	1487	
relationship with caregiver							0.016
	mother	637	46.00	748	54.00	1385	
	father	55	60.92	35	39.08	90	
	uncle/aunt	4	21.15	15	78.85	20	
	grand father/mother	34	55.72	27	44.28	61	
	brother/sister	5	49.71	5	50.29	10	
	another relative	2	56.41	2	43.59	4	
	another people	5	58.18	4	41.82	8	
age of caregiver							0.073
	less than 20	7	42.79	9	57.21	16	
	20-29	279	46.03	327	53.97	606	

	30-39	323	50.18	321	49.82	644	
	40-49	111	40.31	164	59.69	274	
	50-59	20	53.64	17	46.36	37	
	60 or more	8	100.00	0	0.00	8	
number of adults living with the child							0.096
	1	60	48.02	65	51.98	126	
	2	394	50.14	392	49.86	786	
	3	133	42.93	177	57.07	310	
	4	81	40.36	120	59.64	202	
	5	42	45.05	51	54.95	93	
	6 or more	25	42.76	34	57.24	59	
family composition							0.146
	father & mother	512	48.36	547	51.64	1059	
	father	5	34.41	10	65.59	15	
	mother	194	42.75	260	57.25	455	
	another people	19	52.21	18	47.79	37	
number of children living with the child							0.213
	0	265	49.13	274	50.87	539	
	1	286	46.18	333	53.82	619	
	2	131	48.06	142	51.94	273	
	3	33	37.24	56	62.76	89	
	4 or more	23	40.05	35	59.95	58	
frequency of tooth brushing							<0.001*
	always	576	50.46	565	49.54	1141	
	nearly always	133	37.50	222	62.50	355	
	sometimes	31	39.82	46	60.18	77	
	never	1	15.53	7	84.47	9	
brushing autonomy							<0.001*
	seft-brushing	58	33.83	113	66.17	171	
	seft-brushing, with a	513	50.12	510	49.88	1023	
	with help of another	18	41.79	25	58.21	43	
	by an adult	127	47.31	141	52.69	268	
intake of toothpaste							0.017*
	no	439	49.52	448	50.48	887	
	yes	275	43.33	360	56.67	635	
brushing before bed							0.034*
	always	395	49.74	400	50.26	795	
	nearly always	206	43.43	268	56.57	474	
	sometimes	66	41.31	94	58.69	160	
	rarely	38	56.82	29	43.18	67	
	never	33	41.63	46	58.37	80	
use of toothpaste							0.05*
	always	607	48.39	648	51.61	1255	
	nearly always	93	41.49	131	58.51	224	
	sometimes	23	44.54	29	55.46	52	
	rarely	5	30.48	12	69.52	17	
	never	6	26.76	16	73.24	22	
brushing during weekend							0.102
	once per day	114	47.07	129	52.93	243	
	twice per day	332	48.97	345	51.03	677	
	3 times per day	231	47.63	254	52.37	486	
	4 times or more per day	51	36.65	88	63.35	140	
	no brushing	15	41.17	21	58.83	36	
brushing during week							0.229
	once per day	148	43.01	196	56.99	343	
	twice per day	377	48.27	404	51.73	780	
	3 times per day	170	48.80	179	51.20	349	
	4 times or more per day	36	46.43	42	53.57	78	
	no brushing	8	31.55	17	68.45	25	
type of toothpaste							0.475
	children toothpaste	587	48.23	630	51.77	1217	
	adult toothpaste	48	41.05	69	58.95	117	
	sometimes children to	97	45.72	115	54.28	212	
	no toothpaste	9	45.63	11	54.37	19	
intake liquids with sugar (juice or milk) before bed							<0.001*
	always	316	42.26	432	57.74	748	
	nearly always	104	44.68	129	55.32	234	
	sometimes	106	46.62	122	53.38	228	
	rarely	93	56.98	70	43.02	163	
	never	114	60.98	73	39.02	187	

intake of tea during the day							<0.001*
	always	69	46.19	81	53.81	150	
	nearly always	41	37.04	69	62.96	110	
	sometimes	137	39.69	209	60.31	346	
	rarely	171	52.49	155	47.51	327	
	never	313	50.60	306	49.40	618	
breastfeeds at night							0.003*
	always	9	38.39	14	61.61	22	
	nearly always	0	2.94	9	97.06	10	
	sometimes	9	56.12	7	43.88	16	
	rarely	2	15.91	10	84.09	12	
	never	701	47.51	774	52.49	1475	
intake of soft drinks or juices with sugar							0.01*
	always	128	43.82	164	56.18	291	
	nearly always	171	42.08	235	57.92	406	
	sometimes	270	47.12	303	52.88	572	
	rarely	140	53.50	122	46.50	262	
	never	25	62.01	15	37.99	41	
breastfed exclusively							0.02*
	yes, breastfed exclusive	586	45.26	709	54.74	1295	
	no, breastfed and for	103	54.68	85	45.32	189	
	no, formula exclusive	43	54.60	36	45.40	79	
intake of sweets/fruits or drinks juice between meals during the day							0.065*
	once per day	222	46.77	252	53.23	474	
	twice per day	313	50.37	309	49.63	622	
	3 times per day	122	44.27	154	55.73	277	
	4 or more per day	66	38.84	103	61.16	169	
	no intake	20	53.43	18	46.57	38	
use of baby bottle							0.337
	always	316	48.20	340	51.80	656	
	nearly always	60	47.38	66	52.62	126	
	sometimes	31	39.24	48	60.76	78	
	rarely	45	53.90	39	46.10	84	
	never	281	45.38	338	54.62	619	
intake of tap water during the day							0.651
	always	399	47.53	441	52.47	840	
	nearly always	150	48.38	160	51.62	310	
	sometimes	105	44.44	131	55.56	236	
	rarely	45	43.58	58	56.42	103	
	never	26	40.52	38	59.48	64	
perceived need of dental care							<0.001*
	yes	549	42.39	746	57.61	1295	
	no	173	68.94	78	31.06	251	
previous dentist experience							<0.001*
	yes	389	39.89	586	60.11	974	
	no	318	58.80	223	41.20	541	
education in oral health care							0.014*
	yes	658	79.75	167	20.25	826	
	no	369	81.21	85	18.79	454	

(*) statistically significant. (^) eliminated because collinearity with type of school. (^^) eliminated because collinearity with fluoridated water.

Table 7.2. Statistical significance of variables in the univariate model.

The children whose mothers had secondary incomplete (OR 0.55; 95% CI 0.33 to 0.90) or tertiary complete (OR 0.55; 95% CI 0.33 to 0.92) level of education were less likely to have caries than those children whose mothers did not finish primary school. The number of teeth the child's mother lost is also a predictor of the child's caries - children whose mothers had lost only one (OR 0.53; 95% CI 0.35 to 0.78) or no teeth (OR 0.58; 95% CI 0.39 to 0.87) presented less caries prevalence than those whose mothers had lost 5 or more teeth.

Variable		OR	Lower CI	Upper CI	p-value	
Fluoridated water						
	no					
	yes	0.3617	0.2775	0.4714	< 0.001	**
Educational level of head of household						
	primary incomplete					
	primary complete	1.3642	0.7613	2.4447	0.297	
	secondary incomplete	0.5472	0.3321	0.9018	0.018	*
	secondary complete	0.6987	0.4445	1.0982	0.12	
	tertiary incomplete	0.6835	0.3903	1.1971	0.183	
	tertiary complete	0.5531	0.331	0.924	0.024	*
	postgraduate	0.3135	0.097	1.013	0.053	
	no education	0.4332	0.0981	1.9127	0.27	
No. teeth lost by mother						
	5 or more					
	between 4 and 2	0.7316	0.5113	1.0467	0.087	
	only one	0.5267	0.3547	0.7822	0.001	*
	none	0.5783	0.386	0.8665	0.008	*
Type of School						
	high					
	medium	2.0221	1.1359	3.5995	0.017	*
	low	1.7219	1.0183	2.9115	0.043	*
Frequency of toothbrushing						
	always					
	nearly always	1.4233	1.0463	1.936	0.025	*
	sometimes	0.9282	0.4959	1.7372	0.816	
	never	1.3237	0.0781	22.4322	0.846	
Toothbrushing autonomy						
	self-brushing					
	self-brushing, with adult sup	0.4437	0.2903	0.6782	< 0.001	**
	with help of another child	0.5602	0.232	1.353	0.198	
	by an adult	0.4716	0.2875	0.7735	0.003	*
Intake liquids with sugar before bed						
	always					
	nearly always	0.849	0.5963	1.2086	0.364	
	sometimes	0.8975	0.6241	1.2907	0.56	
	rarely	0.464	0.2993	0.7192	0.001	*
	never	0.5421	0.363	0.8097	0.003	*
Perceived need of dental care						
	yes					
	no	0.334	0.2328	0.4791	< 0.001	**
Previous dental experience						
	yes					
	no	0.4659	0.3588	0.605	< 0.001	**
Cons		9.203	4.0006	21.1709	< 0.001	

* p < 0.05; ** p < 0.001

Table 7.3. Multivariate logistic regression model.

The type of school (private, subsidised, or public) showed statistically significant differences when subsidised and public nurseries were compared with private schools. The adjusted analysis indicated that children who attended subsidised schools were 2.02 (95% CI, 1.14 to 3.60) times more likely to experience caries and children who attended public schools were 1.72 (95% CI, 1.02 to 2.91) times more likely to experience caries than those who attended private schools.

Children who rarely or never consumed sugary liquids (e.g., milk, fruit juice, soft drinks, or tea) before bedtime had a lower risk of caries than that always consumed sweeten liquids as shown by the odd ratios in the multivariate model: 0.46 (95% CI, 0.30 to 0.72) and 0.54 (95% CI, 0.36 to 0.81), respectively.

In terms of tooth brushing habits, children who nearly always brushed their teeth were 1.42 (95% CI, 1.05 to 1.95) times more likely to have caries than those who always brushed their teeth. Regarding tooth brushing autonomy, children were less likely to experience caries when adults participated in tooth brushing compared to children who practiced self-brushing; the OR was 0.44 (95% CI 0.29 to 0.68) when an adult supervised tooth brushing and the OR was 0.47 (95% CI, 0.29 to 0.77) when an adult performed tooth brushing.

Finally, children whose parents did not perceive the need of dental care presented less caries risk with an OR of 0.33 (95% CI, 0.23 to 0.48). Additionally, children who had no previous dental experience had less caries than those who had already had dental treatment, with an OR of 0.47 (95% CI, 0.36 to 0.61).

7.4 Discussion

The aim of this study was to statistically model the determinants of caries prevalence as shown in the epidemiological study performed in Chapter 6. Special attention was given to the role of fluoridated water.

7.4.1 Key findings

The most important finding was that the presence of fluoridated water was highly correlated with caries prevalence of preschool children, which is in agreement with existing evidence in the literature (Bramlett *et al.*, 2010;Iheozor-Ejiofor *et al.*, 2015;Young *et al.*, 2015). However, given that this study only used information obtained from 4-year-old children, further research is required to understand the role of fluoridated water in other age groups.

Education level of the head of household showed a significant correlation with children's caries prevalence in the univariate model, in which caries risk increased with reduced educational level; this was also found by Congiu *et al.* (2013). However, this gradient was no longer significant when caries experience was analysed in the multivariate model; thus, the protective role of education level of the head of household may be confounded by other factors that are also correlated with caries prevalence.

The children whose mothers lost more teeth had less risk of caries prevalence, so it is plausible that the number of teeth lost by the mother could be associated with the importance given by mothers to oral health and mother's dental experience.

One unexpected finding in the multivariate models was the fact that children who attended subsidised schools had more risk of caries than those who attended public schools. One explanation could be that parents of children who attended subsidised (medium socioeconomic status) school were wealthier and, therefore, more likely to purchase cariogenic foods. At the same time, their households may have lacked other protective factors (Chapter 2). This result contradicts with findings from others studies (Al-Malik *et al.*, 2001;Hoffmann *et al.*, 2004;Piovesan *et al.*, 2010), where public school children were found to have a higher caries prevalence than private school children.

Regarding tooth brushing frequency, the multivariate model showed that those children who always brushed their teeth had less caries than those who brushed teeth less often. This result is similar to Machry *et al.* (2013) who, using the ICDAS classification (Chapter 2), found a statistically significant difference between those children that brushed their teeth and those that did not among Brazilian children aged between 1 and 5 years.

In contrast, using the WHO (1997) methodology, Borges *et al.* (2012) did not find a significant difference between those children who brushed their teeth less frequently (0 or once per day) and those that frequently brushed their teeth (twice or more per day) in another Brazilian population, though this result was based on a population of children aged 4 to 6 years.

Children who always consumed sugary drinks before bedtime had an increased risk of caries, indicating that teeth were not brushed when children fell asleep, which facilitates fermentation of sugar. This result is consistent with data obtained by Al-Malik *et al.* (2001).

Those children who had never visited the dentist demonstrated lower caries prevalence. This could be an indication of the perceived dental care needs by the public and dental care providers, in that people only seek treatment when problems arise. In this case, children only had their first dental visits when they had already developed caries and pain (Chapter 2). Similar findings have also been documented by Nunn *et al.* (2009), Borges *et al.* (2012), Congiu *et al.* (2013), and Nobile *et al.* (2014).

7.4.2 Strengths and weaknesses

The strength of this study is that the findings can be extrapolated to the entire country. This is because this study included approximately half of the Chilean continental territory, from the Biobío Region (36° 46′ 22.08″ S) to Magallanes Region (53° 9′ 45″ S) and, even more importantly, the sample represented nearly 25% of 4-year-olds in the Chilean population.

This study also allows the opportunity to compare with similar studies examining a similar type of population (preschool aged children); however, direct comparisons are not straightforward because there is no consistency in the variables chosen. Limitations of this study are also noted. One major limitation is that this study used data from two sources, and the data on fluoridated water came from the main cites of each county; however, there was no record on what city (of each county) was sampled by Hoffmeister et al., so it was assumed that Hoffmeister et al. sampled the main cities to match with the fluoride water dataset. This assumption was made for three reasons. First, the selection of school was done using a probability proportional to the number of students per school; consequently, the likelihood of selecting a school in a small city was low. Second, the distances between cities in the southern part of the country, particularly in Patagonia, are huge; therefore, to facilitate the sampling and reduce costs, it is highly likely that small cities (villages) were not included in the sample. Finally, given that an urban/rural variable does not exist in the Hoffmeister dataset, it is unlikely that they sampled small cities in rural areas.

7.4.3 Research implications

Results on the correlation between both fluoridated water and type of school with caries prevalence would allow policies to target preschool children at the population level.

This research confirms the hypothesis that the lack of fluoridated water was associated with the high caries prevalence found in the Biobío Region in Chapter 6. Consequently, the high values of caries prevalence may be partially explained by variations between subgroups in baseline characteristics as a result of heterogeneity (Gray *et al.*, 2011). This finding justifies the incorporation of fluoridated water scenarios in the decision analytic model in Chapter 11.

7.5 Conclusions

This study found that that fluoridated water have an important role in caries prevalence in Chilean preschool populations, even after controlling for other demographic and socioeconomic factors. At the same time, the type of school was also found to be an important indicator of caries prevalence. Therefore, this study demonstrates the need to include both variables in decision analytic models. Further studies should focus on determining the effect of fluoridated water at different ages.

Chapter 8. Selection of Comparators

8.1 Introduction

Many authors (Sculpher *et al.*, 2000;Philips *et al.*, 2004;Briggs *et al.*, 2011) suggest that a decision model should consider all feasible alternatives and should not be limited to a comparison with current clinical practice alone. The range of feasible alternatives can be difficult to determine but to prevent biases, the choice of comparators should be systematic and reproducible.

Philips *et al.* (2006) recommend including all feasible comparators that are practical to deliver within the relevant health system. They go on to argue that the alternatives must be mutually exclusive. The alternatives may be found in literature reviews or through expert opinions, and incorporate evidence of local guidelines and treatment patterns. Nevertheless, comparators should not be influenced completely by the opinion of decision-makers, data availability, and current practice. The Chilean guideline for economics evaluations (MINSAL, 2013c) adds that alternatives must be technically feasible and accepted by the population. While these principles appear reasonable, practical guidance as to how to identify comparators is not available.

The main aim of this chapter is to outline a method to identify relevant comparators for inclusion into a decision analytic model. This approach was used to find relevant health interventions for the delivery of FV application in the preschool Chilean population. This chapter considers also a health intervention proposed by MINSAL and evaluates other innovative alternatives such as the application of FV by primary care staff during well-child check-ups.

The goal of this chapter is to identify feasible health interventions; it does this by following a structured assessment to identify which of the different health interventions can be eliminated from further evaluation.

8.2 Methodology

The selection process of comparators was composed of five stages that can be divided into two parts. The first part involved stages that were related to a creative process of health interventions and the second part involved stages associated with discarding a process of health interventions (Figure 8.1).

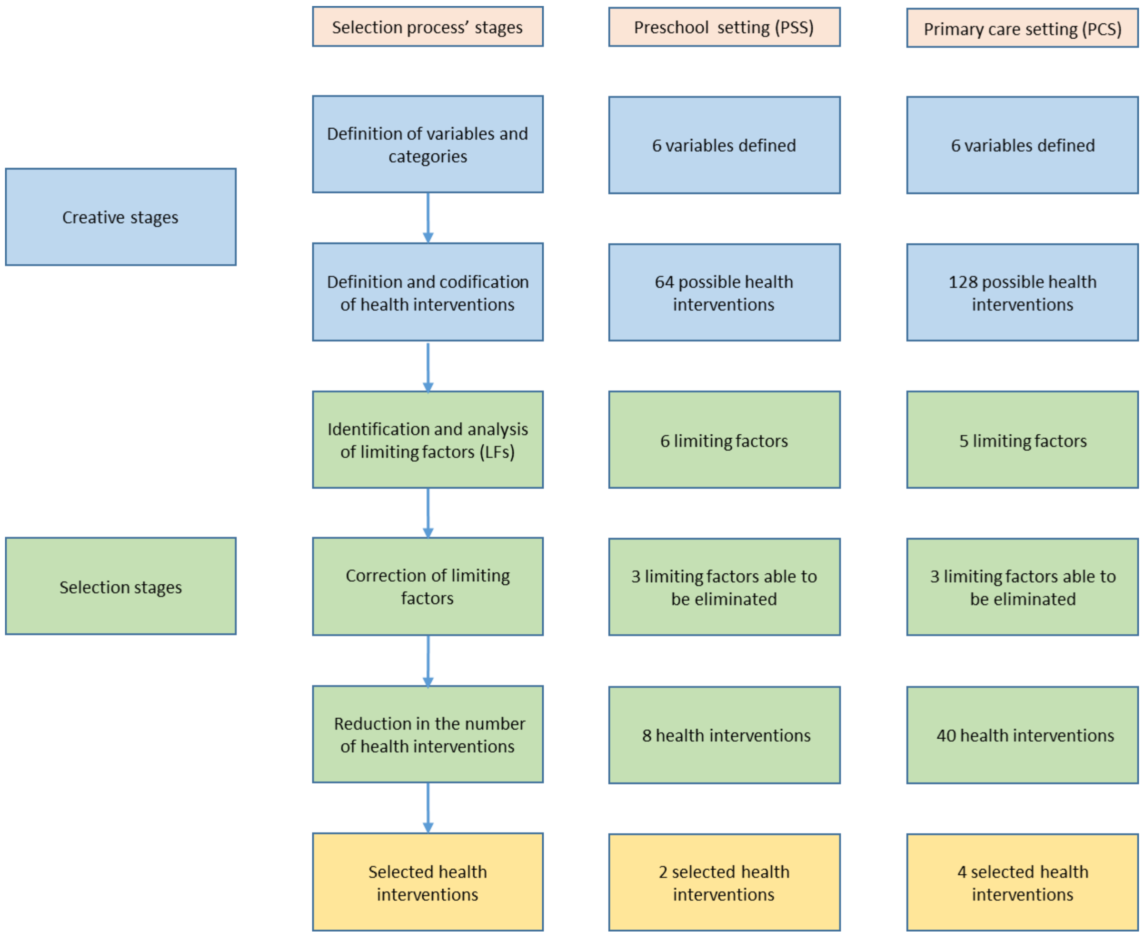


Figure 8.1. Summary of the selection process in both preschool and primary care settings.

8.2.1 Definition of variables and categories

To be sure that all alternative methods of applying FV were considered in the analysis, a process that assembled the most important variables of the application process and its categories was used. As an initial point of reference for this, the guideline issued by the Chilean Ministry of Health, entitled "Guideline of brushing and community application of fluoridated varnish for interventions in preschool population" was used (MINSAL, 2012c).

All stages of application directly related to application technique such as directions before application, supplies, application position, application technique itself and directions after application were considered as constants as these were clearly defined in the guideline. However, the steps of the clinical application process not directly associated with application technique were considered as elements that could vary; an exception was made with informed consent that was considered as a constant. Such variables included setting and the person applying the varnish as well as the clinical (screening and education in oral health) and administrative procedures (referral and booking) before and after application. This allowed the identification of the most relevant variables of application process of FV. These variables are outlined as follows:

1. Variable “setting”: Defined as the premise where the application is performed. Categories: nursery school and primary care.
2. Variable “applicator”: Person who applies the FV. Categories: dentist, dental assistant, dental nurse, dental team, physician, nurse, health assistant, and health team.
3. Variable “education”: Whether the person who applies the FV gives oral health education. This point excludes the instructions post-FV application that should not vary between heath interventions. Categories: with education and without education.
4. Variable “screening”: If application is a result of a previous screening. According to the Chilean guideline of FV application (MINSAL, 2012c), the FV application must be administered after an examination and a diagnosis performed by a dentist. In such a diagnosis, the professional verifies that the child meets the indications for application of FV. Categories: with screening and without screening.
5. Variable “referral”: If the applicator refers the child for further treatment. It does not include referral for a new FV application. Categories: with referral and without referral.
6. Variable “booking”: Where a child who cannot attend a first appointment is booked into a new appointment. Categories: with booking and without booking.

The main goal of the decision analytic model (Chapter 11) is to evaluate the cost-effectiveness of FV for a preschool population. Therefore, in terms of the potential strategies, the mode of access to the target population was the initial point where health interventions to provide a FV might differ. One way to access the preschool population is, within the Chilean context, via the well-child programme (WCP) which is based in primary care (Chapter 4). This programme currently gives promotional and preventive services to both preschool and school children from 0- to 9-year-olds (MINSAL, 2013d). The other way to access to preschool aged children is via nursery schools; therefore, the categories for each variable were defined including two central strategies of FV application: one based in the preschool setting (PSS) and the other based in the primary care setting (PCS).

In the PSS setting, the consideration of alternative comparators was bounded by the assumption that the only staff involved would be dental personnel, because it is difficult to justify PCS staff leaving the premises to perform an activity that is not their direct responsibility.

Within the PCS setting, there are several alternatives that make use of the personnel and infrastructure already working on the WCP. The application of FV might be fitted within the current activities carried out by physicians, dentists, nurses, and auxiliary health personnel during the WCP check-up. See Chapter 3 for more information.

8.2.2 Definition and codification of health interventions

For this process of analysis, Professor Jimmy Steele helped in areas of public health and oral health services, Dr Christopher Vernazza collaborated in areas of paediatric dentistry and health economics, and Raul Palacio brought expertise in the areas of health management, primary care, and the Chilean health system.

Descriptive system

After combining all categories, a very large number of potential health interventions (192) were obtained. To make this set of health interventions more manageable, a descriptive system was created. In this descriptive system, a code of six characters was used, as described in Table 8.1 in the appendices. How this works is illustrated by using code 210001 as an example. This code means that application is done in primary care institutions (1st digit) by a dentist (2nd digit), does not include education (3rd digit), screening (4th digit), or referral (5th digit); however, it does contain a rebook (last digit).

Flow chart of health interventions.

Once the descriptive system was used to describe each possible health intervention, a flow diagram was developed for each of the more complex codes to better portray the health interaction followed. The purpose of this work was merely to aid understanding of the care process for each of the alternative ways of providing care; Figures 8.2 and 8.3 provide illustrative examples of health interventions.

Variable	Position of variable in code	Category of variable	Number of category
Place	1st	At school	1
		At primary health care institution	2
Applicator	2nd	Dentist	1
		Dental assistant	2
		Dental nurse	3
		Dental team	4
		Physician	5
		Nurse	6
		Health assistant	7
		Health team	8
Education	3rd	with education	1
		with no education	0
Screening	4th	with screening	1
		with no screening	0
Referral	5th	with referral	1
		with no referral	0
Re-booking	6th	with rebook	1
		with no rebook	0

Table 8.1. Codification of variables and its categories.

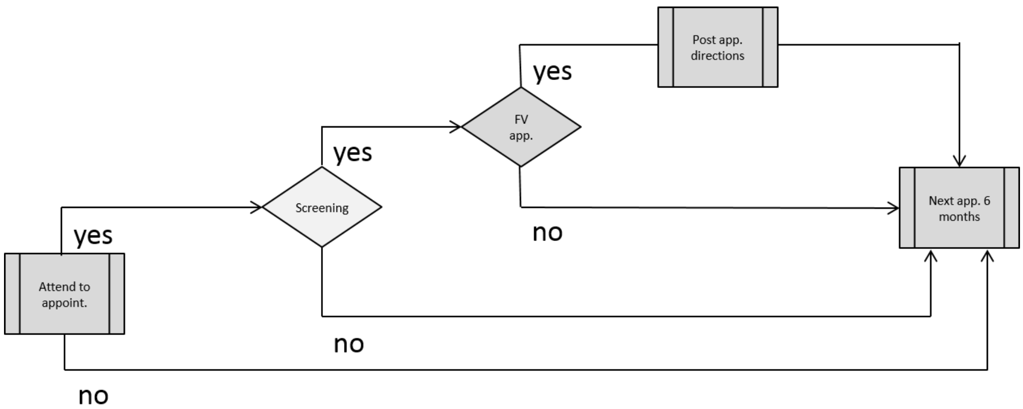


Figure 8.2. Example of flow diagram for health intervention 110100.

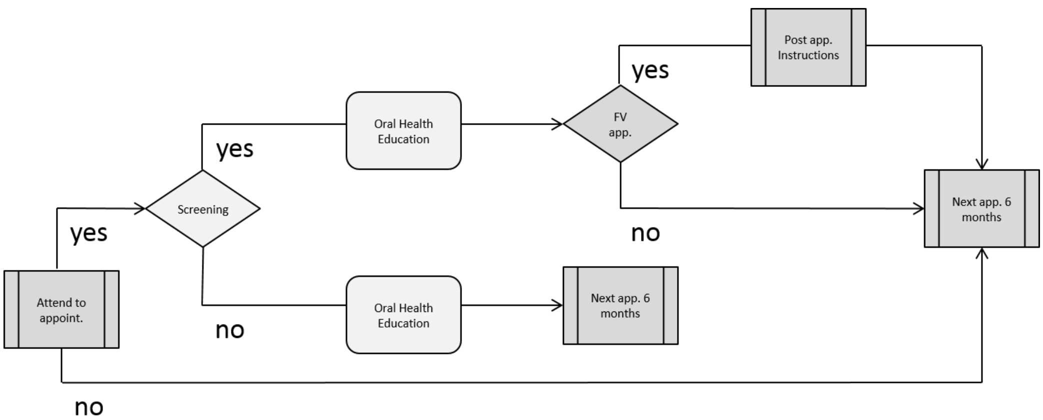


Figure 8.3. Example of flow diagram for health intervention 211100.

Identification and analysis of limiting factors

Each health intervention and its respective flow diagram was analysed with the help of dentists (PhD candidate and his supervisors), looking for issues that might act as limiting factor, which is a factor that might prevent its use in practice. As a result, seven limiting factors were identified.

Every identified limiting factor was analysed one by one to determine whether they were able to eliminate or not eliminate a health intervention. The following section shows the analysis undertaken and its respective conclusion.

8.2.3 Preschool setting

Direct supervision

The guideline for FV application published by the Chilean Ministry of Health (MINSAL) in 2012 established that the application of FV can be performed by a dentist, dental nurse (Técnico en Odontología de Nivel Superior), or dental hygienist; also, according to decree 1704 of MINSAL (2013b), it can be performed by a dental assistant (Auxiliar Paramédico de Odontología) under the direct supervision of a dentist. This variation in responsibilities is reflected in a difference in wage between both technicians; a dental nurse earned a mean salary 5.6% higher than dental assistants in the Chilean public health sector in 2012.

Dental hygienists are the rarest form of dental auxiliary personnel in Chile, with few of them working in the public health system. Therefore, though it is clinically plausible that they could be involved in the provision of FV due to their training and experience, in practice the lack of personnel demonstrates that it is not viable that they can routinely be used as part of the FV application process in the foreseeable future. As a consequence, they will not be considered in the modelling process.

The requirement for direct supervision is a legal limiting factor but, as with all legal aspects, requirements can be modified. Chile has some recent experience with changes in its laws related to the health workforce. For example, in 2010, the lack of ophthalmologists led to a modification that allowed medical technologist specialists in ophthalmology to prescribe spectacles (National Congress, 2010). However, changing the requirement for direct supervision could be even easier than the example of medical technologists. The legal normative that contains such limiting factors is a decree issued by MINSAL (2013b), this means that a possible modification is within the domain of the Ministry of Health and would not need to pass through the National Congress to be approved.

A second argument that supports the elimination of this limiting factor is related to the simplicity of FV application. The procedure requires "painting" teeth surfaces with FV using a special brush. The complete procedure usually takes less than five minutes and the training for applications is short. Therefore, there is no necessity for highly trained personnel to perform it.

Finally, a third strong argument in favour of eliminating direct supervision is the fact that there is almost no evidence about side effects (Marinho *et al.*, 2013) and, as described in the literature (Milgrom *et al.*, 2014), FV is safe even for young children (see Chapter 3).

Conclusion: Although modifying a Chilean decree could be laborious, it can be done. Therefore, elimination of this limiting factor (LF) was considered possible.

Prescriptions

Although dental nurses are entitled to work without a dentist's direct supervision, they cannot do the entire procedure of application due to the Chilean guideline (MINSAL, 2012c) that specifies that a dentist must perform a clinical diagnosis first; therefore, the dentist must indicate (prescribe) the FV application. Under Chilean law, the only professionals allowed to prescribe a medication are physicians, dentists, and midwives. This means, for example, that a dental nurse cannot be sent on their own to perform FV application because FV requires a prescription, which requires a dentist. However, as in the case of direct supervision, the legal normative that contains this limiting factors is a decree issued by MINSAL; consequently, it is a political decision.

Other studies wherein the application was performed by non-dental personnel, such as in Lawrence *et al.* (2008) where the application was performed by dental hygienists, support the participation of non-dental personnel in a possible health programme of FV application. A similar point of view about task delegation was shared by Vermaire *et al.* (2014) who considered the use of auxiliary dental personnel in the application of FV in a study of caries prevention programmes in the Netherlands.

Within Chile, the main point is not about the capability of non-dental personnel to carry out FV applications, but about their inability to provide a diagnosis. Nevertheless, the need to make a diagnosis of caries in low SES children is redundant when almost 80% of low SES children experience caries by age six (Chapter 6). Therefore, this raises the question as to why all low SES populations should not be considered as a high-risk population. In this case, there would be no need for a diagnosis, and hence prescription.

Chile has had some experience in targeting the entire population for a preventive programme. For example, a national sub-programme of fluoridated mouthwash was focused on children attending public schools in locations without natural or artificial fluoridated water. This programme also did not require a diagnosis or prescription to be applied, suggesting that a prescription for FV can be eliminated provided that FV can be incorporated as part of a national programme.

Conclusion: Prescriptions as a limiting factor was considered feasible to be corrected, because it depends on a political decision that should made by MINSAL.

Second visit to school

A second visit to the school is difficult and expensive to correct due to the low attendance rates at preschools by Chilean children, estimated at 78% by Arbour *et al.* (2014). If the intention is to get access to the maximum number of possible children, a second trip, at least, would be required. This logic means that costs associated with the transport of the health team would double.

An important argument against a second visit to the school is the time consumed by the health team for each visit. The opportunity cost of being in the dental practice working with patients rather than trying to "capture" the non-attending children, could be high and questioned by society. As Monsalves (2012) commented, dentists in the public health system are few compared to private sector; this is in agreement with Goic (2015), who estimated that just 22% of dentists work in the public sector. Also, as was commented on in Chapter 4, dentists in the public sector provide dental care to about 82% of the Chilean population; hence, they are under a high demand for dental care.

Conclusion: Second school visits as a limiting factor was not considered modifiable, because of the high demand for dental care in the public sector.

Parental attendance

This point is related to the concept of oral health education (OHE). This point is difficult to correct due to the low participation of parents in activities related to schools in large urban areas (Kain *et al.*, 2010).

An important reason for low participation in school activities is that such activities coincide with the working hours of parents' jobs (Cáceres and Alegría, 2008); this implies difficulties in getting permission to leave their job and the possibility that absence from work will reduce the income of an already poor group.

Conclusion: Parental attendance was not considered readily modifiable, so it was not planned to evaluate education in oral health (OHE) in the PSS setting in a further decision analytic model (DAM) study.

Risk of cross infection

Theoretically, different health interventions carry different cross infection risks, and therefore different adjustments might be required, some of which would be feasible and some of which would not. The risk of cross infection increases when the procedure requires more than one person.

The risk of cross infection could be reduced by the adherence to guidelines that clearly indicate what the risk of cross infection is, and how to reduce it. It would be anticipated that adhering to these guidelines would entail the use of more consumables. Specifically, the guideline should highlight the avoidance of re-using gloves (and other consumables) by the dentist and auxiliary personnel.

Conclusion: The elimination of the risk of cross infection as a limiting factor was judged feasible.

Over demand on health system

When a dentist completes an oral examination, and makes a diagnosis, she or he has the ethical and legal obligation to share this information with the parents. Once the parents have this information, they could demand dental attention. This means that a FV application programme could increase the demand of services. Unfortunately, the Chilean health system is not able to absorb anything other than the most modest increases in demand. To avoid this possible rise of dental demand, the examination should be just a screening and not a complete oral examination.

Something similar happened with the referral of children for further treatment. Given the prevalence of caries in preschool population (MINSAL, 2012a), the risk of overloading the current health system is high. Consequently, referral of all children with caries is not recommended. An intermediate solution could be a referral or suggested action, just for those children with pain or oral infection.

Conclusion: Given that solving this limitation would require excessive amounts of money, this limiting point was judged as not modifiable. Thus, the DAM will not consider the variable of referral.

8.2.4 Primary care setting

Direct supervision

The delivery of FV in this setting has the same limitations as the delivery in the PSS setting.

Conclusion: Similar to the PSS setting.

Prescriptions

As with the PCS setting, prescriptions are an important limiting factor in this setting.

Conclusion: Similar to the PSS setting.

Lack of infrastructure

Plausibly, auxiliary personnel can apply FV without supervision by a dentist. However, there is no way to know if every primary care institution has sufficient additional room to perform the application. Also, splitting the dental team will negatively affect the dentist's productivity.

Conclusion: This limiting factor was not considered modifiable, so the decision analytic model (DAM) does not include the application of FV by auxiliary dental personnel in this setting.

Risk of cross infection

Conclusion: Similar to the PSS setting.

Over demand on the health system

This issue could be more important in this setting; it is extremely difficult to explain to parents that the child cannot be treated because there are no appointments available when they already have access to an examination.

Unlike the PSS setting, parents in the PCS setting can attend and receive dental health education. Nevertheless, provision of education in oral health at each application of FV (4 times at a minimum) is time consuming, and therefore expensive. The health system would be overloaded with the extra work.

Considering the previous argument and given that there is no evidence about how effective FV is if parents do not receive oral education in each appointment, oral health education is not considered for further analysis.

Conclusion: The DAM phase will not analyse oral health education as a variable.

8.2.5 Correction of limiting factors

Two main questions (or difficulties) were found: how does a limiting factor influence the entire application process, and how does a combination of factors affect a specific health intervention? To cope with these difficulties and to begin to analyse the limiting factors, all possible health interventions (codes) and limiting factors were tabulated.

The table was constructed by placing the coded health interventions on the left-hand side of each row and each limiting factor (for each setting) was used as a header for each column. Then, the code for every health intervention was copied into the columns where the health intervention was affected by a limiting factor. Those health interventions whose codes were not affected by any limiting factor were considered as feasible without modification.

The selection of all relevant health interventions was based on the feasibility of each alternative where feasibility was determined by the possible elimination of each limiting factor. In other words, the removal or not of a limiting factor determines the feasibility of a health intervention.

Although the decision whether to keep a health intervention or not was not based exclusively on the opinion of decision-makers (MINSAL), the analysis did consider the point of view and range of action of the Chilean Ministry of Health; for example, improving parental attendance was not possible because MINSAL cannot act directly on this point.

In the PSS setting

Only three (3/64) possible health interventions in this setting were considered feasible at the beginning of this analysis (i.e., before consideration of removal of limiting factors). All of them had the dentist as the main professional.

Of the limiting factors identified, diagnosis, second visit to school, parental attendance, and over demand had the most influence on the process, with each one of them placing a limitation on 32 possible health interventions. Cross infection affected 24 health interventions and direct supervision affected 16.

Following this first stage, it was next considered what would happen if it were possible to remove some of the limiting factors. First, the elimination of just one limiting factor at a time was analysed (prescription, risk of cross infection, and direct supervision) then a combination of two limiting factors (prescription + risk of cross infection, direct supervision + prescription, and risk of cross infection + direct supervision) and, finally, three limiting factors (prescription + risk of cross infection + direct supervision) were removed. This process showed which additional health interventions became available for consideration in the decision model. A table with the results of this process can be found in Appendix B.

The minimum number of feasible health interventions was 3, identified at the starting point, where all limiting factors were considered to be in place and, the maximum number of health interventions was 8, which occurred after 3 limiting factors were removed. When just the need of a dentist prescription and risk of cross infection were removed, there were 6 feasible health interventions.

In the PCS setting

Over demand and need for dental prescriptions had the most influence, affecting 64 health interventions. Lack of infrastructure affected 48 health interventions, direct supervision affected 16 health interventions, and risk of cross infection affected only 8 health interventions.

A similar process was then followed to determine the impact of removing limiting factors. Such a process found that the minimum number of feasible health interventions was 24, detected at the starting point and removing either risk of cross infection, direct supervision, or both had no effect on the number of LPs (see Appendix B). On the other hand, the maximum number of feasible health interventions (40) was found when prescription was removed and elimination of more LPs did not improve that number.

8.2.6 Reduction in the number of health interventions

The selected health interventions varied in the PSS setting in terms of who applied the FV and the inclusion or not of a screening element. In the case of PCS, the health interventions varied in the same aspects as PSS, plus whether or not education was provided.

There were 8 health interventions selected for in the preschool setting that were finally reduced to 2 (110000 and 110100); only those interventions associated with dentists were retained. This was because there was no evidence to suggest there was a difference in the efficacy between the personnel who applied the FV. Given that the dentists are the only oral health professionals that do not require either a prescription or supervision to apply the FV in the Chilean context, retaining the dentist (as a kind of "Chilean standard") was decided. The dropped interventions at this level are included as part of the sensitivity analysis in Chapter 11.

In the primary care setting, the elimination process resulted in 40 feasible health interventions (in Appendix B). After further consideration of the context of the Chilean WCP, it was decided that the variable education would not be modelled directly in a further DAM (see Discussion). Consequently, a reduction in the number of codes was performed and like the preschool setting, the dropped health interventions were studied as part of the sensitivity analysis. Finally, 4 health interventions were selected for the primary care setting (210000, 210001, 210100 & 210101).

8.3 Discussion

8.3.1 Discussion about selected variables

This section contains a discussion about each selected variable and the reason(s) why such variables were or were not eliminated from further analysis.

Setting

This thesis proposed a different setting than that proposed by MINSAL: the application of FV in primary care appointments during well-child check-ups. Despite the fact that such an alternative is relatively new in the Chilean context, the use of well-child check-ups to perform activities related with dentistry is not new, either to deliver oral health education (Hallas *et al.*, 2011) or to perform FV application (Achembong *et al.*, 2014).

Considering that MINSAL currently promotes the use of such check-ups to deliver oral health education by nurses and physicians (MINSAL, 2013d), it is perfectly logical to think about extending the role of well-child check-ups in caries prevention.

Human resources (applicator)

Several repetitions of health interventions were detected in both settings, most of them were related to the variable applicator. The elimination of most of these health interventions from further analysis was due to lack of evidence about the difference in effectiveness between the personnel who apply the varnish, especially between dentists and dental auxiliary personnel (Dyer *et al.*, 2014). Although FV is applied by non-dental professionals in others countries (Hendrix *et al.*, 2013), almost no evidence exists about their relative effectiveness compared with dentists undertaking the application. Some authors have reported relative effectiveness, using some ad hoc outcomes, such as the number of caries-related treatments (Pahel *et al.*, 2011). These data suggest that performance is comparable.

Consequently, it can be concluded that the difference in the type of professional who applied the FV would be explored in a sensitivity analysis that would explore the trade-off between cost and effectiveness rather than designing different comparator arms in the decision model for each type of potential. Although there is a lack of evidence on effectiveness, this form of analysis would allow consideration of whether a difference in effectiveness, as predicted by the model, would be plausible.

The selection of variables only considered clinical aspects, meaning the clinical facet of diagnosis, i.e., screening. However, the selection of limiting factors allowed consideration of other aspects of diagnosis such as prescription and legal limitations. For example, lack of ability to prescribe FV was the most important modifiable limiting factor in both settings. Allowing other carers to prescribe allowed a further set of care health interventions to be provided.

Nevertheless, there are some legal problems with eliminating restrictions on who can prescribe as currently in some of the HIs that would not be legal, such as 120100 or 130100, as dental nurses and dental assistant are not allowed to perform a diagnosis.

Oral health education

Performing oral health education (OHE) in the PSS setting is difficult, mostly due to limited participation by parents in preschool activities. This phenomenon should not happen in the PCS setting as parents are the ones that take children to the WCP. The main problem is the lack of infrastructure that does not allow oral health examinations to be performed by dental assistants and dental nurses. Furthermore, the lack of infrastructure does not allow the dental team to be separated, as there is unlikely to be enough physical space to provide the care required.

In the PCS setting, 20 health interventions with variable education were considered feasible. This means that OHE can be done in this setting. However, given that there is no evidence about the efficacy of FV with or without oral health education (OHE) and the only variation related to education is the cost (wage/hour), further exploration of the impact of this variable using sensitivity analyses was chosen.

Screening

One important consideration detected in this study was related to the concepts of diagnosis and screening, as both are intimately related. Both concepts were defined by Ireland (2010), in the Oxford Dictionary of Dentistry, as follows:

Diagnosis

"The process of arriving at the nature of a disease or condition from consideration of the patient's signs and symptoms and when appropriate, any additional diagnostic tests such as radiographs, biopsy, and blood or saliva analysis. The diagnosis of a condition or disease often involves comparison with other conditions which produce similar signs or symptoms (differential diagnosis)".

Screening

"The process of testing a large number of asymptomatic or apparently healthy people to separate those who may have a specific disease and would benefit from further testing from those who probably do not. Screening is usually targeted at individuals who are most at risk of the disease, such as screening heavy smokers for oral cancer. Factors which need to be taken into account to determine the appropriateness of screening include the epidemiology of the disease, efficacy and availability of treatment, safety, acceptability, cost, sensitivity, and specificity of the test. Screening for diseases that affect general health, such as diabetes and cardiovascular disease, may be undertaken within a primary dental care setting".

According to Ireland (2010), and given that the Chilean guideline (MINSAL, 2012c) establishes that a dentist must perform a diagnosis in order to detect which children meet the criteria for application of FV, dentists would be performing the screening rather than the diagnosis.

Screening helps detect those individuals with high risk of developing caries and may help prioritising the allocation of resources. But due to the complexity of caries, there is no clear method to identify those children that are likely to develop caries and, unluckily, one stronger predictor of future caries is previous experience of caries (Masood *et al.*, 2012). So, the question is, how do we detect high-risk individuals when the goal of a programme is to avoid any experience of caries?

The fact that almost 80% percent of those with a low SES have a caries history by 6 years of age (Soto *et al.*, 2007a) is a strong argument against individual screening. Paradoxically, the guideline of FV application (MINSAL, 2012c) established as a clinical indication for application, is that the child must be in a low SES group. This leads to questions about the sense of having a dentist just for screening when the entire population of the school would be considered as having low SES, and hence, at high risk of caries; such a question is highly related to opportunity costs.

Referral

All the health interventions related to referral were blocked because of the potential for possible over demand on the health system. It would not be reasonable to refer all children with caries because the Chilean health system does not have the capacity to treat all preschool patients with a history of caries. The treatment cost could be enormous due to the high prevalence of caries (approximately 50% of the population aged 4 years) and, the fact that most children are very young. Such preschool children require special care and highly trained personnel as well.

Here an ethical question arises: what is the utility of determining an oral health diagnosis knowing that children will not be treated nor referred and their parents must find money to pay a private dentist? More broadly, research is also needed to answer this question.

Booking

This study showed that an important number of health interventions are blocked by difficulties related to a second visit to the school. Also, the argumentative analysis of this limiting factor demonstrated that a possible second visit in the PSS setting is hard to do because there is a low probability of catching those children that did not attend the first visit. By contrast, there were no major problems about rescheduling a visit in the PCS setting.

8.3.2 Discussion: Methodological considerations

This approach represents a new methodology for identifying the comparators that should be included in an economic model. Current guidance for the design of economic evaluation models lacks any clear explanation about how this might be best accomplished. Therefore, for this study, an approach that incorporates sequential steps that allow the selection of relevant alternatives in an economic model was developed.

The use of combinatory and sequential processes helped to incorporate more alternatives, identify the role of each factor and how they interact with each other and, and define which alternative could be executed. Also, this method was able to order and manage a large number of health interventions. Given that this approach is straightforward and useful, it could be replicated in other clinical research areas where the consideration of numerous alternatives is necessary.

Here the decision-making context heavily influenced the choice of comparators. Specifically, the work considered the decision-makers (MINSAL) range of action. Nevertheless, the international evidence and researchers allowed the inclusion of more alternatives. The determination and evaluation of limiting factors required the judgment of experts experienced in primary health care and public health as well as knowledge about the Chilean context.

Should this approach be repeated in another setting, a key lesson is that this methodology allowed the step by step analysis of the clinical process and this could be useful for researchers without a clinical background, but ideally it requires the collaboration of the key stakeholders. For this study, it required the collaboration of experts with a clinical background and experience.

There are other ways in which to establish a consensus about what comparators to consider in this thesis. One option might be a Delphi panel for instance, where experts in specific areas of knowledge participate in an anonymous way (Cramer *et al.*, 2008). However, due to time restrictions this alternative was not considered in this thesis.

8.4 Conclusions

The lack of any clear explanation about how to identify and select comparators in the current guidance on economic evaluation models, led to the development of this new approach. This methodology was also created as an answer to the concept that the current clinical practice is not necessarily the best alternative and that there was a need to manage a huge number of health interventions.

This approach was based on two features, the first one was based on a sequence that allowed to us give an order to the entire process, and a second one based on combinatory sequences that permitted consideration of all theoretically available health interventions.

This methodology outlined a sequence to identify the alternative health interventions for FV application in the Chilean context that could be compared in an economic decision model. The approach also provided a structure that allowed the identification of the potential impact of factors that might affect specific health interventions and to determine whether a health intervention is feasible or not.

Chapter 9. Fluoride Varnish Efficacy

9.1 Introduction

Given that the objective of the decision analytic model in this thesis is modelling the effect of fluoride varnish (FV) on caries incidence in an initially caries-free population, a value for the efficacy of FV is required. However, determining this value is extremely difficult due to two main factors: one related to the scarce number of studies of FV efficacy that report caries incidence from a caries-free baseline and the other one being that several outcomes have been used to measure the efficacy of FV (see Chapter 3).

While there are some studies that analyse FV efficacy in a preschool population, currently, there are almost no studies on caries-free populations. One example is the study performed by Weintraub *et al.* (2006) on disadvantaged preschool aged children in California. They found that caries incidence was higher in those children receiving counselling only compared to those children that received FV applications. They also found a difference in caries incidence, depending on the length of the follow-up period. O'Neill et al. (2017), in a recently published study, found no statistically significant difference ($p = 0.81$) in caries prevalence (at dmft>0 or caries-free level) between intervention group (FV) and control group (no FV).

Other studies, such as that performed by Holm (1979), have recorded the sample to be caries-free at baseline; she included children with caries, but those who were caries-free at baseline were presented as a sub-group. Such information would allow FV efficacy in caries-free populations to be estimated. In other words, other reports may include details that allow a sub-group with a caries-free baseline to be analysed.

Therefore, there might be evidence about caries-free population but such evidence should be collected systematically. To optimise the search efforts, we decided to update a previous systematic review. The systematic review selected was the Cochrane systematic review performed by Marinho *et al.* (2013). This study was selected because the methodology of Cochrane literature reviews is accepted and used worldwide.

Additionally, the Marinho et al. (2013) systematic review is an update of a previous systematic review performed by the same main author (Marinho et al., 2003) that, as was explained in Chapter 4, was used as evidence in the Chilean protocol of FV application (MINSAL, 2012).

To summarise, the main goal of this chapter is to determine a parameter of efficacy for the application of FV. To achieve this objective, this chapter uses the systematic review performed by Marinho *et al.* (2013) as a baseline. Similarly, this chapter analyses the evidence about safety and acceptance of FV in preschool populations.

9.2 The original systematic review

The objectives of the Marinho *et al.* (2013) systematic review were to determine the effectiveness and safety of FV in preventing caries in both child and adolescent populations. Also, the researchers examined whether the effect of FV is affected by other factors such as initial level of caries, background exposure to other sources of fluoride, and concentration and application features.

9.2.1 Measurement of treatment effect

They used prevented fraction as the measure of treatment effect on caries increment and for caries incidence (dichotomous outcome), they calculated risk ratios (RR).

9.2.2 Risk of bias

The risk of bias was assessed based on eight domains (Higgins and Green, 2011), as follows: sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, baseline balance, and free from contamination or co-intervention. Each domain was then classified either as “low risk of bias” or “high risk of bias”, or in those cases where it was not possible to obtain data, were classified as “unclear risk of bias”.

9.2.3 Results

Marinho *et al.* (2013) performed several meta-analyses. One of these meta-analyses showed that FV reduced the number of decayed, missing, and filled tooth surfaces (dmfs) in the primary dentition by 37% (95% CI, 24% to 76%; $p < 0.01$). Regardless of the beneficial effect detected in reduction of surfaces affected (dmfs), another meta-analysis, which used teeth as the unit of measurement (dmft), found no statistically significant difference (RR.81; 95% CI, 0.62 to 1.06; $p > 0.05$) between FV and no treatment or placebo in the development of one or more new carious teeth.

However, given that the decision analytic model requires the caries incidence in a caries-free population, the meta-analyses done by Marinho et al. (2013) on primary dentition cannot be used because, unfortunately, they considered preschool populations with and without caries at baseline.

9.3 Methodology

The same Cochrane methodology for the systematic review used by Marinho *et al.* (2013) was used in this chapter. However, given that the objectives of Marinho *et al.* (2013) were slightly different than the objectives of both this chapter and this thesis, meta-analyses of a subgroup of studies included in the original systematic review were performed.

The literature search done by Marinho et al. (2013) was repeated for the years since the initial review was undertaken. Only works written in English, Spanish, or Portuguese were included.

9.3.1 Inclusion criteria for this review

The criteria used by Marinho *et al.* (2013) were partially maintained in this research and are shown in italics below. The adjustments (if any) made for this review are then described after each excerpt.

Type of studies

"Randomised or quasi-randomised controlled trials using or indicating blind outcome assessment, in which fluoride varnish is compared concurrently to a placebo or no treatment group during at least one year"

Related to the type of studies, this chapter considered the same parameters as Marinho et al. (2013).

Type of participants

"Children or adolescents aged 16 or less at the start of the study (irrespective of initial level of dental caries, background exposure to fluorides, dental treatment level, nationality, setting where intervention is received or time when it started). Studies where participants were selected on the basis of special (general or oral) health conditions were excluded."

Unlike in Marinho *et al.* (2013), given that one of the main objectives of this thesis is analysing the cost-effectiveness of FV in the incidence of caries in a preschool population, this chapter was based on children aged 5 years or less at the start of the study with an initial level of caries equal to zero (dmft = 0), but other inclusion and exclusion criteria were maintained.

Type of interventions

"Topical fluoride in the form of varnishes only, using any fluoride agent, at any concentration (ppm F), amount or duration of application and with any technique of application, prior or post-application. However, frequency of application should have been at least once a year. The control group is placebo or no treatment resulting in the following comparison: Fluoride varnish compared with a placebo or no treatment. Studies where the intervention consisted of any other caries preventive agent or procedure (e.g. other fluoride-based measures, chlorhexidine, sealants, oral hygiene interventions, xylitol chewing gums) used in addition to fluoride varnish were excluded."

Related to the type of intervention, this chapter considered the same parameters as Marinho *et al.* (2013).

Type of outcome

"The primary outcome measure in this review was caries increment, as measured by change from baseline in the number of decayed, (missing) and filled permanent surfaces / number of decayed, (extracted/missing) and filled primary surfaces (D(M)FS / d(e/m)fs). Caries is defined here as being recorded at the dentine level of diagnosis. If caries data only reported caries at both dentine and enamel lesions combined then this was used in the analysis"

Unlike Marinho *et al.* (2013), who analysed caries increment in both primary and adult dentition, this chapter measured caries incidence in primary dentition only. Also, this chapter studied such caries incidence from a caries-free baseline, i.e., dmft = 0. Therefore, any useful information that allowed the calculation of a relative risk (RR) of caries incidence from a caries-free baseline was used. Chapter 2 contains information about caries measurements. Also, as a secondary outcome, all references about acceptability and safety were considered.

9.3.2 Methodology for studies contained in Cochrane literature review

All studies contained in the Marinho et al. review on primary dentition were re-analysed under the new selection criteria; those that did not meet the criteria were not considered in the quantitative analysis.

9.3.3 Methodology for studies not contained in Cochrane literature review

For data collection, the same databases and search parameters used by Marinho et al. were used to search for new studies. The search period was set from May 2013 (the final date of the Marinho et al. review) to March 2015.

Abstracts were retrieved and compared against revised inclusion criteria. Full text was retrieved for those studies that met these inclusion criteria. Finally, those studies that fully met the criteria were used during qualitative synthesis. The complete process of selection and analysis was performed by the author of this thesis with the help of his supervisors.

9.3.4 Quantitative synthesis

Although Marinho et al. did not perform a calculation of a measure of FV efficacy by socioeconomic status (SES) but rather pooled all data in a single analysis, for this chapter, differentiation by SES was required. There are two reasons to justify this requirement.

First, the natural history of caries is affected by several risk factors but is strongly affected by SES (Chapters 2, 6, and 7); therefore, an assumption that FV has different efficacy depending on SES is reasonable. Indeed, there is evidence that would suggest variations in efficacy, e.g., as demonstrated by Jiang et al. (2014) that argued that one of the reasons why they did not find a difference between FV and placebo was due to the high percentage of children that belonged to high socioeconomic status. A second argument is that the studies had completely different target populations; for example, as was also discussed in the introduction of this chapter, Weintraub et al. (2006) studied low income and under-served Hispanic and Chinese populations.

Both arguments suggest that a pooled measure of FV efficacy cannot easily be applied to the target population of this thesis, which studies the Chilean population of low socioeconomic status (or baseline study, see Chapter 11).

Consequently, and only after the studies passed all selection criteria, we decided to create three different scenarios; L (low SES), ML (medium and low SES) and HML (high, medium, and low SES). Such scenarios are also in agreement with the incremental incorporation of socioeconomic status, as suggested by MINSAL (Chapter 4).

9.4 Results for fluoride varnish efficacy

9.4.1 Studies contained in Cochrane literature review

For this analysis, all of the studies used by Marinho et al. that included the primary dentition were considered. The characteristics of such studies were tabulated according to type of treatment, study duration, number of children randomized, number of children analysed, type of study, child age, vanish manufacturer, concentration of fluoride, and annual frequency of FV application (see Appendix B).

Those studies that did not meet the inclusion criteria were ruled out as follows: the studies of Clark *et al.* (1985), Hardman *et al.* (2007), and Gugwad *et al.* (2011) were based in populations with mixed dentitions; Frostell *et al.* (1991) and Chu *et al.* (2002) were ruled out due to the population not being caries-free at baseline; and Borutta *et al.* (2006) had incomplete data. Despite the study by Lawrence *et al.* (2008) that recorded a caries-free population at baseline, the dental index used was dfs, and was thus excluded. There was no evidence about a caries-free population in the study by Yang *et al.* (2008), the same situation was observed in the Master's thesis of Salazar (2008). The reasons why each study was discarded appear in Appendix B.

Therefore, the studies remaining for more exhaustive analysis were those of Holm (1979) and Weintraub *et al.* (2006).

Holm (1979)

The author analysed a Swedish preschool population with a mean age of 3 years at baseline and 5 years and 1 month at the end of study. The years of the study were not reported. Holm established that there were no significant differences between groups (control and test) regarding SES but did not specify characteristics used to judge SES. However, they would not belong mainly to a low SES, this assumption is based on the following comment by the author:

“It should be remembered that the children in this study had a rather low caries activity, probably because the parents were well informed about caries prophylaxis. In a group of children with high caries activity, the results might have been different.”

Fluoride varnish (Duraphat®, ICN, Pharmaceuticals GmbH & Co., Eschwege, West Germany) was applied every 6 months for a 2-year follow-up period. The time spent on the application was not reported.

The diagnostic criteria used was visuo-tactile, and children had access to fluoridated water (0.3 ppm). Despite the study using dmfs index as outcome, it was possible to obtain a proxy of dmft = 0 as the author described the proportion of caries-free children at baseline and their status after 2 years, as follows:

“At baseline examination 69% of the children in the test group and 75% of the children in the control group were caries-free. The result after 2 years showed that 38% of the children in the test group and 27% in the control group were still caries-free”.

Considering that the total number of children was 113 in the control group and 112 in test group, the number of caries-free children was calculated, giving 77 (77.28) children at baseline and 43 (42.56) after 2-year follow-up for the test group, and 85 (84.75) children at baseline and 31 (30.51) at the end of the study for the control group.

The author concluded that FV had a caries-inhibitory effect when applied to primary dentition.

Risk of bias, according to Marinho et al. (2013) is shown in Appendix B. For example, the authors considered that this research has a high risk of bias related to selection, performance, and reporting.

Weintraub et al. (2006)

The authors examined preschool populations of San Francisco, California, at two public health centres that served low income and underserved populations (Hispanic and Chinese). Children were aged 6-44 months at the beginning of the trial and were followed for 2 years. The study began in 2000.

The primary outcome of this study was caries incidence; consequently, all children were caries-free at baseline. They used the NIDCR diagnostic criteria (Chapter 2) for dental caries for assessing cavitated, decayed, and filled surfaces on primary teeth. Also, they recorded adverse events. Children were exposed to fluoridated water (~1 ppm).

The FV used was Duraphat® (Colgate Oral Pharmaceuticals, New York, NY, USA). The tooth surface was dried with a gauze. FV was applied with a brush using 0.1 ml per arch. The time taken to perform the application was not reported.

Children were randomized into three groups: parental counselling and FV application every 6 months (GP1), parental counselling and FV application every 12 months (GP2), and parental counselling only (GP3). Although this study is a 3-arm RCT, only two arms (GP1 and GP3) were considered for a quantitative synthesis. The once/year group was excluded from this analysis due to the criteria for this quantitative analysis only considering FV application every 6 months.

The same methodology used by Marinho et al. (2013) was used in the updated analysis for this chapter to count the number of children in both control and test groups. To calculate the number of children with caries (or number of events), the number of children with caries at 12 months was added to the number of children with caries at 24 months; the total number of children was obtained adding the number of caries-free children at 24 months to the number of events.

The group with parental counselling only started with 90 children at baseline with no caries and finished with 48 caries-free children, and the test group (parental counselling and FV application twice/year) started with 81 and ended with 67 caries-free children.

An important aspect of this study is that the authors used an intention-to-treat (ITT) approach, meaning that the final number of children was calculated based on the initial treatment assignment and not on the number of FV applications that they received. Indeed, only one child received four FV applications.

The authors concluded that the use of FV along with parental counselling is efficacious in reducing caries incidence and they did not report any adverse effects.

Risk of bias, according to Marinho et al. (2013), is shown in Appendix B. Despite a protocol deviation, where children received a placebo varnish instead an active product, the authors concluded that this research had a low risk of bias and the only unclear risk was related to the attrition bias.

9.4.2 Studies not contained in the original Cochrane literature review

An updated search from May 2013 to March 2015 was conducted using the same parameters and databases used by Marinho *et al.* (2013). One thousand fifty-five records were identified through database searches and 16 full-text studies were considered as potentially eligible. Figure 9.1 shows a summary of the steps performed during the update of Marinho *et al.* (2013) literature review.

Twelve studies were excluded because they were not randomised controlled trials (RCT). Four RCTs were excluded for the following reasons: there was no record of caries-free population in Mohammadi *et al.* (2015). Divaris *et al.* (2013), which was a secondary analysis of Slade *et al.* (2011), included other fluoride-based intervention. Similarly, Agouropoulos *et al.* (2014) evaluated efficacy of FV along with the use of fluoridated toothpaste (1,000 ppm) and supervised toothbrushing. The studies of Oliveira *et al.* (2014) and Jiang *et al.* (2014) were similar; both included oral health advice and supervised toothbrushing at each follow-up visit. However, and despite the fact that a risk ratio could be obtained from Oliveira *et al.* (2014), this study was excluded because this study provided another source of fluoride, fluoridated toothpaste (1,450 ppm) at each follow-up visit (or every six-months). Studies with oral hygiene advice and instructions were included in the systematic review of Marinho *et al.* (2013); hence, despite parents receiving oral hygiene advice and instructions, Jiang *et al.* (2014) was not excluded from the quantitative synthesis.

Therefore, Jiang *et al.* (2014) was the only trial included in the quantitative analysis. For more details see Appendix B.

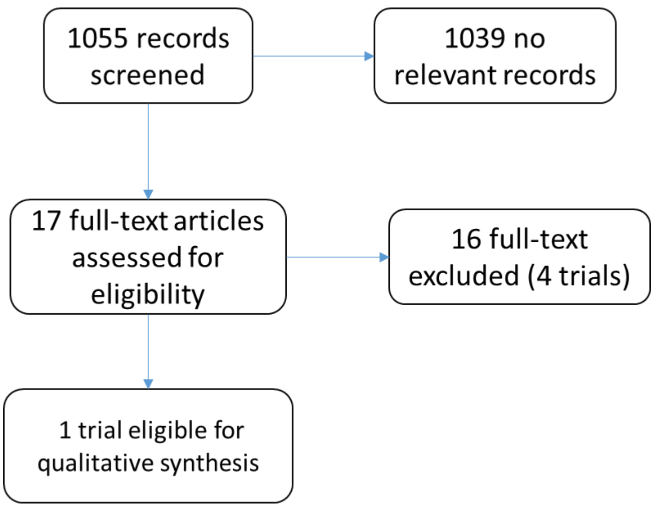


Figure 9.1. Summary of the steps performed during the update.

Jiang *et al.* (2014)

The authors studied, during 2010, a low risk population of Hong Kong children aged 8-23 months that were recruited in parenting education centres and child day care centres. The initial sample was 450 children, 45% boys and 55% girls. The retention rate after two years was 92% (415 children). Two percent of the sample had caries at baseline with no statistically significant differences between the control and test groups. Children were exposed to other sources of fluoride such as fluoridated water (0.5 ppm), and the diagnostic criteria included in the quantitative synthesis was ICDAS codes 2-6.

The sample was distributed randomly across three groups. The first one (GP1), the control group, was provided with oral health education and printed materials. Group number 2 (GP2) received the same treatment as GP1 plus hands-on training on brushing and a FV placebo application every 6-months. The last group (GP3) received the same treatment as GP2, but a 5% sodium fluoride varnish (Clinpro White Varnish, 3M ESPE Dental Products, St. Paul, USA) was used instead of placebo. Also, both GP2 and GP3 groups were provided with new child-sized toothbrushes at every follow-up visit.

After the 2-year study period, the average incidence of caries was 13.7% (57/415). There were no statistically significant differences in caries incidence between the three groups ($p > 0.05$). GP 2 included 144 children from which 17 (11.8%) developed caries after 24-months of follow-up. In GP 3, a total of 137 children finished the follow-up period and 24 (17.5%) of them developed caries. Sixty percent (167 children) of this subsample was considered as high socioeconomic status. The data was retrieved from incidence at level 1 (non-cavitated and cavitated lesions) according to the authors; this level was selected because it was more sensitive than level 2 (cavitated lesions).

The authors concluded that application of FV might be not effective in young children younger than 3 years with a low risk of caries. For more information about risk of bias, based on Higgins and Green (2011), see Appendix B.

To include this study in the pooled quantitative synthesis, two aspects need to be considered. First, an assumption must be made that the sample had no caries at baseline. Second, only GPs 2 and 3, which were equal except for FV, should be included.

9.4.3 Quantitative synthesis

Following the Cochrane Handbook for Systematic Reviews of Interventions (2011), the relative risk of developing at least one tooth with caries from a caries-free baseline (dmft = 0) was calculated using a random effects model in the software Revision Manager 5.3 (The Cochrane Collaboration, London, United Kingdom). The same software was used to obtain forest plots. Regarding the diagnostic criteria of caries, the same methodology used by Marinho *et al.* (2013) was used; all studies were polled together disregarding the type of diagnostic criteria used. The same methodology was used for all scenarios.

One scenario (Sce 1) analyses specific branches of the RCT performed by Weintraub et al. (2006) and represents a low-income population; RR was 0.37 (95% CI, 0.22 to 0.63) with $p < 0.001$. A second scenario (Sce 2) includes scenario 1 plus data obtained from Holm (1979) and characterises low and medium SES; the risk ratio for overall effect was 0.53 (95% CI, 0.28 to 0.99) with $p = 0.05$. The last scenario (Sce 3) includes Sce 2 plus information from 2 branches of Jiang et al. (2014) and represents the combination of low, medium, and high SES; with a RR 0.72 (95% CI, 0.37 to 1.38) and $p > 0.05$. All scenarios are shown in Figure 9.2.

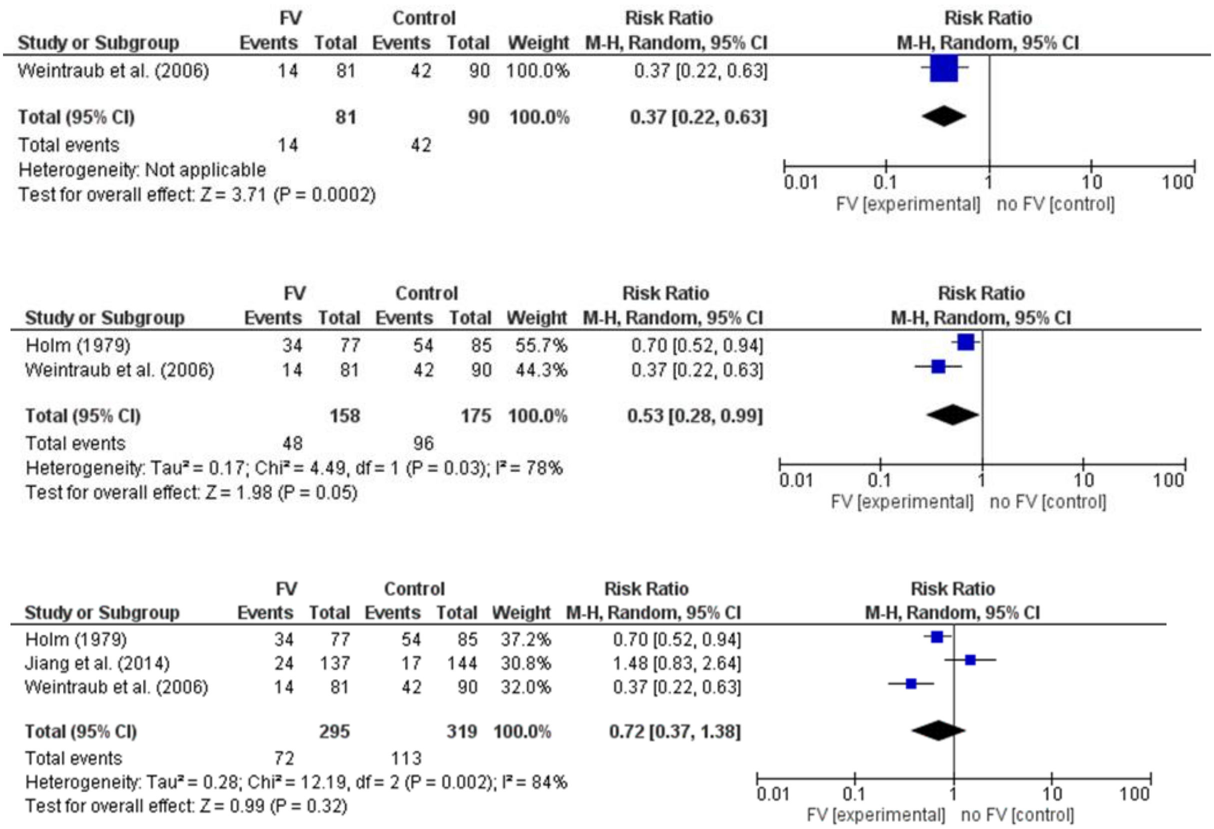


Figure 9.2. Relative risks of the application of fluoride varnish in several scenarios.

9.5 Results of safety and acceptance of fluoride varnish

The data for both variables were obtained either from the studies on primary dentition selected by Marinho *et al.* (2013) or, in those studies not contained in the Cochrane systematic review, from the 17 full-text studies considered as potentially eligible.

9.5.1 Safety

Few reports of safety outcomes were made. For example, Weintraub et al. (2006) reported only one adverse event that was not associated with FV application. Lawrence et al. (2008) found no cases of contact stomatitis in their sample and state that the product is safe even for children with asthmatic conditions.

Oliveira et al. (2014) reported just 2 complaints about FV, one associated with the colour and the other related to a "burning sensation" that is explained by authors as an effect of ethanol. In the study of Jiang et al. (2014), the parents did not report adverse effects after a 2-year follow-up. Agouropoulos et al. (2014) published that no serious adverse effects were detected.

9.5.2 Acceptance

There are almost no data about acceptance of FV for children during RCTs and the evidence that does exist is difficult to summarise because it was measured using different parameters.

For example, in children aged between 2 and 5 years, Agouropoulos et al. (2014) reported 1.4% (6 out of 424) of total eligible children were not cooperative, and therefore were excluded of study. Also, they reported 3.9% (16 out of 409) of those included in the trial were not cooperative. On the other hand, Holm (1979) described that a 9% of an original group of children would not cooperate at baseline and were excluded from the trial; the mean age was 3 years.

One interesting aspect related to the reception for FV was described by Oliveira et al. (2014). They detected, using a specific behavioural scale, that child behaviour improved as children received more FV applications.

9.6 Discussion

9.6.1 Efficacy

The results show that the efficacy of FV in a caries-free population was better, at least, in two (L and ML) scenarios (RRs 0.37 and 0.53, respectively) than in the meta-analysis performed by Marinho *et al.* (2013) that pooled five studies with and without caries-free population (RR 0.81). Unlike Marinho *et al.* (2013), two scenarios (1 and 2) were statically significant with p-values less than 0.001 and equal to 0.05, respectively. Explanation for this difference in FV efficacy could be due to the heterogeneity of studies pooled by Marinho *et al.* (2013), or the fact that the caries-free population contained a higher proportion of lower risk children, or perhaps FV was more effective on caries-free teeth than already carious teeth. More research is needed to better explain this finding.

These results coincide with Oliveira *et al.* (2014) who, using the $d_3$mfs dental index, found that the effect of FV was higher in those children with no caries experience at baseline; caries incidence was 82.3% for those children with caries and 25% for those without history of caries.

Although not statistically significant, similar findings were published by Lawrence *et al.* (2008) who registered the number of children with a decayed or filled surface equal to zero (dfs = 0) at baseline. After two years of follow-up, 57.9% of caries-free children developed caries in the control group and the incidence of caries in the test group was only 44.4% with an OR 1.60 (95% CI, 0.86 to 2.98) and $p > 0.05$. Notably, they did not consider the missing component of dmft index, meaning that children may have been classified as caries-free but with a dmft > 0.

The same pattern was found by Divaris *et al.* (2013), but at surface level using the $d_3$mfs index in Aboriginal Australian preschool children. The conclusion was that FV had greater efficacy when applied on surfaces that are sound at baseline.

The analysis showed that FV efficacy increased as the population became poorer. However, this result is only valid assuming that data extracted from Holm (1979) were correctly classified and represent a medium income population; consequently, this assumption could be considered as a weakness. Although previous systematic reviews (Petersson *et al.*, 2004;Carvalho *et al.*, 2010;Marinho *et al.*, 2013) do not mention the role of SES on FV efficacy, they do consider the relationship between caries risk and efficacy. Given that the relationship between caries risk and SES has been well documented (Chapters 2, 6, and 7), it might be expected that there would be a relationship between SES and FV efficacy.

9.6.2 Safety and acceptance

This systematic review showed that few side effects of FV have been reported. However, there is a general opinion that FV is a safe method of delivery fluoride and, as was commented in Chapter 3, is safe even in toddlers (Milgrom *et al.*, 2014). The Cochrane systematic review does not provide evidence about the likelihood of side effects as well. More research is required in this area.

Similarly, there is little evidence about the acceptance of this product in preschool children. Lack of cooperation, or refusal, could be due to two reasons: one related to a behavioural problem and another associated with the presence of some acute pathology that was causing pain. This latter point is significant when the finding by Evans et al. (2013) are kept in mind. Evans et al. (2013) reported that 1.58% of children were excluded from FV application as they had either a dental abscess or a sore mouth. Future studies investigating FV acceptance would be very interesting.

9.6.3 Strengths and weaknesses

The main weakness of this chapter is the lack of evidence about efficacy, safety, and acceptance of FV application on preschool populations.

Given that such evidence about the efficacy in caries-free populations is even scarcer, it was necessary to perform a systematic review and meta-analysis. Executing this analysis is not simple as, except for a study by Weintraub et al. (2006) and a protocol designed by Tickle *et al.* (2011), there are no studies specifically designed to evaluate caries incidence in a caries-free population.

These difficulties mean that some estimation of the value of FV efficacy is necessary. For example, data from Holm (1979) had to be calculated based on a percentage of the sample who were caries-free and the data extracted from Weintraub *et al.* (2006) and Jiang *et al.* (2014) were calculated from 2 out of 3 branches. The limited evidence found also implies that comparisons of these results with other studies are not straightforward and caution must be applied.

The analyses performed by socioeconomic scenarios would not be in complete agreement with the Cochrane methodology. Also, the assumption made about the SES of Holm's population could be considered as a weakness. However, it would not be easy to argue why a pooled result should be used in a low socioeconomic population knowing that target populations of all studies were different in relation to SES.

As was suggested by Jiang *et al.* (2014), it is possible that FV may not be effective in high SES groups that are also associated with good health behaviours and low caries risk (Chapters 2, 6, and 7). Using such efficacy would mask the effect of FV on low SES. Similarly, it was thought that this way was the better alternative to deal with the heterogeneity associated with SES, detected in Chapters 6 and 7.

On the other hand, to the best of the author's knowledge, this is the first systematic review and meta-analysis focused exclusively on a caries-free population. Also, the fact that this chapter was based on the Cochrane methodology, updating an already completed Cochrane systematic review validates this research to a degree.

9.7 Conclusions

This study shows that efficacy of fluoride varnish is, in primary dentition, higher in caries-free populations than those that have already developed caries. Such efficacy would increase as the population is poorer.

The evidence would indicate that application of fluoride varnish is a safe procedure even for younger children. Also, there is no conclusive evidence about the acceptance of the procedure.

Chapter 10. Costing Study

10.1 Introduction

The costing element of the economic evaluation was based on the protocol of the intervention, provided by the Protocol of Brushing and Community Application of Fluoridated Varnish for Intervention in Preschool Population issued by the Chilean Ministry of Health (2012c). This protocol, here onward called the Chilean fluoride varnish (FV) protocol, detailed all materials required for the procedure. It also described the quantities required for the some of the products to be used.

The process of FV application is an extremely simple procedure that consists of the application of a thin film of fluoride onto the surface of the teeth (VOCO, 2015); indeed, it is so simple that it has been defined as "painting" the surface of the teeth (Colgate-Palmolive, 2014) with a resin using a small brush, probe, or swab. It does not require any special equipment and can be performed in any setting.

Nevertheless, the Chilean FV protocol did provide an estimate of the time spent on conducting the procedure. Consequently, an average time of 5 minutes was defined based on Hawkins et al. (2004) who found that the average time used in children aged 3-6 years by a dental therapist was 5.22 minutes. In other words, average costs were calculated on a non-patient-specific basis (Gray *et al.*, 2011), assuming that all children had a FV application of 5 minutes.

Given that this study was in collaboration with the Chilean Ministry of Health (MINSAL) and its target population was the Chilean preschool population, the perspective adopted by this research was the Chilean public health system perspective; thus, only the costs incurred by public health institutions were considered. The currency used was the Chilean peso and all prices were adjusted using the consumer price index (CPI) for March 2015 using data obtained from the webpage of the Chilean National Institute of Statistics (INE, 2015).

Two settings, each with different costs structure were studied, included preschool and primary care settings. The former is based on the Chilean FV protocol and the latter was based on the results presented in Chapter 8. The preschool setting (PSS) required that the dental team was transported to and from either nurseries or preschool institutions; meaning that health professionals went to where the children were gathered to perform the FV application. The primary care setting (PCS) required that children go to where the FV application was given.

The costs for providing FV in either setting consisted of several items. Most of these items were applied to both settings but some were specific to a single setting. For example, transport costs were applied only to the preschool setting and equipment was included in the primary care setting only.

10.2 Data sources

When using secondary data, the Methodological Guide for the Economic Evaluation of Health Interventions in Chile (MINSAL, 2013c) suggests the use of public datasets from public institution such as the Health National Fund (FONASA) and ChileCompra for studies conducted on behalf of MINSAL or FONASA. Consequently, when estimating costs data from these two sources, they were used as outlined below.

10.2.1 PUC study

This Chilean study was commissioned by the Health National Fund (FONASA), which is the public national health insurance system and was conducted by the Department of Public Health of Pontifical Catholic University of Chile (PUC). The research was defined by the Head of FONASA as the first serious attempt to detect the real costs of health in Chile (PUC, 2012). The study was performed in the year 2010 and published in 2013. Dr Camilo Cid, the head researcher, kindly facilitated access to the dataset of this study.

This research used both main approaches of costing: gross-costing (or top-down costing) and micro-costing (or bottom-up costing). The latter was used to calculate the direct costs of interventions, and the former was used to obtain the indirect costs. The study considered 130 health interventions performed either in hospitals or primary care institutions or both. Although PUC's study included different types of health institutions, this research only considered primary care institutions.

10.2.2 ChileCompra

ChileCompra is the Chilean public system for procurement of good and services. The objective of this system is link the public buyers with suppliers, and to ensure high levels of transparency and efficiency (UN, 2010). The contracting system is based on Law 19,886 (2003) whose Article 20 states:

“Public agencies must use the information systems established by the Public Procurement and Contracting Bureau to publish the basic information regarding their procurement processes and all other information required by the regulations. Such information must be comprehensive and appropriate, including the calls for tenders, reception of bids, clarifications, replies and changes to the bidding specifications, as well as the results of the tendering processes for the acquisition of goods and contracting of services, manufacture and works, all according to the regulations”. Consequently, ChileCompra allows access to the results of all public tenders; hence, the price of goods and services.

10.3 Human resources

As FV application was not included in the PUC study, and the aim of this research was to explore the impact of the FV application performed by other professionals that currently do not perform this procedure, other health interventions were selected to calculate the wage rate per hour for other health professionals.

In the case of dental staff, a simple oral health intervention was selected to obtain the costs. The intervention chosen was “oral health examination”, which is performed by a dentist assisted either by a dental nurse or a dental assistant. In the case of physicians, the health intervention selected was “primary-care physician control”, and for nurses, “primary-care nurse control”.

10.3.1 Primary care setting

As discussed in the Introduction section, the time taken for the procedure was 5 minutes and that was applied to all personnel except for administrative staff. This exception was because the PUC study found that administrative personnel spent 5.4 minutes to schedule every appointment. The time for dental well-child programme (DWCP) was estimated as taking 30 minutes. This was taken from the document National Health Program for Children with Integral Approach (MINSAL, 2013d). Also, it was assumed that each session was fully used either with FV or other care. The results are shown in Appendix B.

Regarding the dental staff, it is important to note that there are two types of dental auxiliary personnel (Chapter 8), the dental nurse and the dental assistant. Hence, an average wage was calculated and called dental personnel. Combinations of staff were created assuming that the FV application was a team effort. For example, when FV was applied by a dentist in the PCS the wage rates of the dentist, dental personnel, and administrative personnel were used. See Appendix B for more details.

10.3.2 Preschool setting

A different approach was used in this setting. The estimated time to perform the application to a class, with an average of 27 children (MINEDUC, 2015), was 4 hours, or a half-day.

- This time included the transport time from the closest primary care institution to the school and back.
- Arrangements prior to FV application such as preparation of classroom, measures to prevent possible cross-infections, meetings with school authorities, etc.
- All those activities performed after the application such as cleaning of the classroom used.

Using data from the PUC study, the cost of human resources (dentist + dental personnel) per half-day was estimated was divided by the average number of children per school.

$$\text{cost human resources per half-day} = \text{wage rate per hour} * 4$$

$$\text{cost of human resources per application} = \text{cost human resources per half-day}/27$$

$$\text{cost of human resources per application} = \text{CLP } 2{,}015$$

10.4 Equipment

The equipment item was applied to the PCS only and where the standard procedure of application was performed in the dental practice by dental staff. This item was defined as all furniture and equipment present in the dental practice. This approach was selected because it was judged that there was an opportunity cost in using the equipment. Although FV application is a simple procedure and even if the equipment (especially the dental chair) is not necessary, FV application in a dental practice implies that no other oral health intervention can be performed at the same time.

The cost per hour per item of equipment was calculated, in every primary care institution by dividing the price of all equipment by service life expressed in years (both data obtained from the PUC study) and then, dividing the result by an estimated number of hours worked per year (2,016 hours). Then, the cost per hour of each equipment was adjusted by the time taken (5 minutes) for FV application and by 30 minutes for DWCP. Finally, the average was calculated between all primary care institutions (see Appendix B).

cost equipment per hour = price per unit / (service life * hours worked per year)

cost equipment per health intervention = cost equipment per hour * (tech. coefficient. *(1/60))

The number of hours worked per year was estimated under the assumption that the year has 48 working weeks and each week has 42 working hours. Interestingly, the number or working hours obtained in this study (2,016) was similar to that obtained by OECD, which estimated an average of 2,015 hours (OECD, 2013).

10.5 Instruments

As was explained in Chapter 8, the protocol includes an oral health evaluation or screening that must be performed by a dentist but does not require specific instruments or lightning conditions. This item was defined for those FV strategies that include screening. The items consist of a dental mirror, dental explorer, and cotton pliers. It was assumed that instruments were sterilised once per day in the PSS and twice per day in the PCS, so the cost of the instrument per use could be estimated. The estimate was obtained by dividing the price of instruments by their service life, expressed in years, and the number of working days (240) in the preschool setting, and by the number of sessions (i.e., half working days, 480) in the primary care setting. See Appendix B for more details.

cost instrumental PSS per day = price per unit / (service life * days worked per year)

cost instrumental PCS per day = price per unit / (service life * half days worked per year)

10.6 Fluoride varnish

The data for this consumable was obtained from ChileCompra. Usually, a primary care institution purchases several products at the same time; therefore, the searching process was made more complicated. To identify purchases of this product, only purchases made from the beginning of 2013 regardless of location in Chile (i.e. even from extreme geographic zones) were included.

Suppliers offered two types of FV products, multi-doses (10 ml) and single-dose (0.25 ml). Based on Marinho *et al.* (2013), for the estimation it was assumed that a tube of 10 ml contains 20 doses of 0.5 ml each; this proportion was also included in some calls for tenders.

The average price per dose of FV was CLP 963 (SD 185), the average price per dose in multi-dose preparation was CLP 982 (SD 150), and the average price of a single-dose was 941 (SD 246); see Appendix B.

Unexpectedly, it was found that the price of a single-dose was less expensive than the multi-dose per application. This finding suggests that, along with the other advantages of a single dose product (easier storage and better hygiene), this approach may be more efficient. However, this finding should be taken with caution given the magnitude of the standard deviation obtained.

10.7 Oral hygiene kit

The Chilean FV protocol establishes that a children's toothbrush and a children's toothpaste (up to 500 ppm of fluoride ion) must be given to the children so that they brush their teeth themselves prior to FV application. The protocol also mentions that such brushing should be supervised by either a dentist or a teacher.

The information on the cost of the kit was obtained from ChileCompra but those purchases for the current FV programme (Chapter 4) were selected. The toothpaste average price was CLP 786 (SD 213) and toothbrush average price was CLP 524 (SD 278). More information is provided in Appendix B.

10.8 Transport

Even though almost every primary care institution has a vehicle, there are no studies about the average cost of such transport in Chile; therefore, the cost of renting a car (pick-up car) with a driver and fuel was used as an alternative approach to obtaining the cost of transport. The values for transport were obtained from ChileCompra, considering transport for personnel only (Appendix B).

A value per hour was calculated (CLP 9,226; SD 2,115) considering 8 worked hours per day and 20 days per month, then the same approach was utilised to calculate the cost of human resources in the PSS was used, as follows:

$$\text{cost transport per half-day} = \text{cost per hour} * 4$$

$$\text{cost of transport per application} = \text{cost transport per half-day} /27$$

$$\text{cost pf transport per application} = \text{CLP } 1{,}367$$

10.9 Indirect costs

All of those costs that are directly related to health interventions (human resources, FV, and consumables) should be considered as direct costs. On the other hand, all those costs that are not directly associated with FV application should be considered as indirect costs; for example, electricity, water, heater, security, sterilization, storage, etc. There is no study about indirect costs associated with FV application in Chile.

Thus, an alternative approach was used. The indirect cost estimated by PUC for the health intervention "oral health examination" in primary care institutions. The PUC study estimated this cost as a percentage of total cost, as follows:

$$\text{total cost} = \text{direct cost} + \text{indirect cost}$$

$$\text{total cost} = \text{direct cost} + (\text{direct cost} * \text{indirect cost rate})$$

The average rate of indirect cost calculated in the PUC study for primary care institutions performing an "oral health examination" was 0.14 (SD 0.02).

10.10 Other costs

Others clinical consumables were obtained from ChileCompra such as gloves, masks, and paper towels. The cost of soap was obtained from the PUC study as well as all the stationary items. For more information, see Appendix B.

10.11 Discussion

The costs studied in this chapter included costs of human resources, equipment, instruments, FV, oral hygiene kit, transport of personnel, and indirect costs related to the intervention.

Two sources were used: a costing study commissioned by Health National Fund, which was performed by the Department of Public Health of Pontifical Catholic University of Chile (PUC); and a public database that is part of a public system for procurement of good and services (ChileCompra). Consequently, the main strength of this chapter is based on the fact that all costs came from Chilean data.

Both the PCS and the PSS were studied independently because they have a different cost structure; however, costs were calculated assuming that application time was 5 minutes in both settings. In the PSS, it is assumed that the dental team was transported to and from either nurseries or preschool institutions; whereas in the PCS, it was assumed that children go where the FV application is provided – a "well-child programme" appointment.

The greatest difficulty of this study was probably the estimation of the costs of both transport and human resources in the preschool setting, which required making an assumption about the average number of children that can be treated per travel episode. At present, there is no evidence about productive efficiency relating to these points. Further work is needed to explore productive efficiency.

Another weakness of this chapter is related to the fact that the PUC study does not include FV application, which requires obtaining the costs from other interventions. More studies, at the national scale are needed to improve the cost estimates in the PCS.

Finally, most of the costs were composite, based on estimations from two or more items. Consequently, few confident intervals around the mean estimates of costs could be obtained. As explained in Chapter 11, confident intervals of mean estimates of costs were not used in the decision analytic model.

Chapter 11. Decision Analytic Models

11.1 Introduction

Dental caries is considered a chronic disease whose course can be modified by addressing several risk factors, including socioeconomic status. As was described in Chapter 6, at the national level, 30% of 6-year-old children were caries-free in 2007, with a clear difference in caries prevalence between the types of schools (public, subsidised, and private), which was used as a proxy of socioeconomic status; illustrating important health inequalities. To address the high prevalence of caries, the Chilean Ministry of Health (MINSAL) has established as a public health goal for the year 2020 to increase the caries-free population by 35%, i.e., from 30% to 40.5%.

In order to meet this objective, MINSAL proposed the use of fluoride varnish (FV) and the reinforcement and expansion of the model of promotional and preventive interventions at preschool and school levels (MINSAL). One way to reduce the gap between socioeconomic status is to increase efforts in those disadvantaged populations. For this reason, MINSAL planned to promote the application of fluoridated varnish in children attending those public schools with a caries-free rate of 22.8%. This approach would reduce oral health inequalities between socioeconomic groups.

However, the evidence states that although FV reduces the number of caries, there is no evidence that it will prevent the development of new caries (DMFT/dmft > 0) in both primary and adult dentition (Marinho *et al.*, 2013). Furthermore, as the evidence came from RCTs, it is possible that the efficacy of FV (i.e., how well FV works in tightly controlled research settings) is higher than the effectiveness that could be achieved in an oral public health programme. This is given because, by definition, a randomized controlled trial must have a well-controlled environment that may be far from real scenarios where FV application is planned to be done.

The Chilean Department of Oral Health proposed the application of FV in a preschool setting with a previous screening (MINSAL, 2012c) in all those children receiving public education before they turn 6 years old. In other words, they proposed a national oral public health programme. They were clear that the implementation of such national programme would be costly, and hence the expenditure must be justified.

For these reasons, it is reasonable to consider whether the FV intervention proposed by MINSAL would have some effect on preschool population and if taxpayer money would be wisely expended. To address these questions, it is necessary to estimate the performance of FV in realistic scenarios. Consequently, a type of "framework" that allows an estimation of whether this programme is cost-effective or not is needed; this would allow testing of whether there are other interventions where FV application could be more effective and cost-effective. Furthermore, a methodological approach is needed that allows the consideration of the evidence beyond systematic reviews and meta-analyses. Here, the use of decision analytic models (DAMs) can play an important role.

As was explained in Chapter 5, a decision analytic model is defined as a systematic approach that allows us to incorporate all information related to clinical scenarios, interventions, settings, variabilities, and uncertainties in a mathematical model. DAMs can be used to explore alternative courses of action, such as different ways the application of FV could be implemented, in terms of its expected costs and outcomes. DAMs include a set of analytic tools quite different from those used in economic evaluations conducted as part of an empirical study such as a trial but can be seen as complementary to them (Briggs *et al.*, 2011). Mariño *et al.* (2013) described that the literature reporting economic evaluations (which usually contains DAMs) on caries prevention programmes in dentistry is scarce. Therefore, it is reasonable to think that there are few of examples where DAMs have been used to evaluate preventive programmes in dentistry.

Subsequently, the aim of this chapter is to evaluate the performance of the current Chilean FV programme in realistic scenarios using DAMs. Similarly, this chapter will test whether different interventions of FV application can be more cost-effective than that proposed by the Chilean Ministry of Health.

11.2 Transition probabilities of caries

As was commented on in Chapter 5, transition probabilities should be obtained from cohort studies because these kinds of studies allow one to understand the natural history of the disease. Unfortunately, Chile lacks such studies, and due to different populations having different natural histories of caries, working with a proxy of natural history of caries was decided to be the best option for this thesis (Chapter 6). Consequently, the transition probabilities obtained in this section are not proper transition probabilities, rather they use data to proxy the transition probabilities.

11.2.1 For the entire population

To obtain caries transition probabilities, the consolidated dataset utilised in the previous epidemiological study (Chapter 6) was used. However, given that the concept of zones used in such a dataset could either over or underestimate the sample population, a weighting process was necessary. The adjustments were based on population values obtained from a national survey of socioeconomic characterization (MIDEPLAN, 2009). The dataset used the decayed, missing, and filled dental index (dmft) using the whole tooth as a basic unit.

To calculate the probabilities for each cycle, some assumptions were made:

- Caries prevalence has a constant incremental rate.
- Dental caries begins after one year of age.
- One cycle has lapsed when children reach 1.5 years of age.
- Ten cycles have lapsed when children reach 6 years of age.

After these assumptions, average caries prevalence for each age (2, 4, and 6 years) and scenario (L, ML, and HML) were calculated. Then caries prevalence was extrapolated every six months, as follows:

$$\text{prevalence}_{4.5L} = \text{prevalence}_{4} + (((\text{prevalence}_{6L} - \text{prevalence}_{4L})/4)*t)$$

$$\text{prevalence}_{4.5L} = 0.562 + (((0.772 - 0.562)/4)*1)$$

$$\text{prevalence}_{4.5L} = 0.615$$

Where, $\text{prevalence}_{4.5L}$ is the expected prevalence at 4.5 years of age in low socioeconomic scenarios and, t is number of cycles elapsed. Figure 11.1 and Table 11.1 contain a summary of the estimated prevalence.

Average caries prevalence was considered as the probability of having caries (dmft > 0) from one-year-old (cycle 0) to a specific age (or n number of cycles). Then, using the same methodology discussed for the estimation of the effects of FV (Section 10.2.6), these probabilities were transformed into rates. Finally, these rates were converted in probabilities for each cycle.

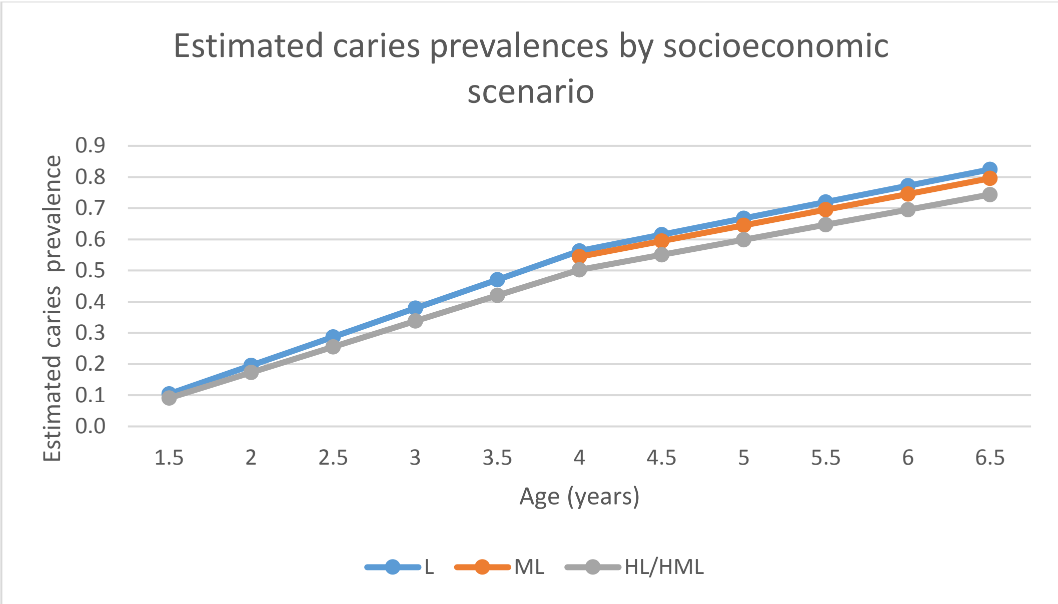


Figure 11.1. Estimated caries prevalence by different socioeconomic scenario.

For example, considering that the number of elapsed cycles from 1 year to 4.5 years of age is equal to 7 and the estimated probability of having caries at 4.5 years of age in the low socioeconomic scenario is 0.615.

Transform the probability for 4.5-year-olds in a rate.

$$r = -[\ln(1-p)]/t$$

$$r = -[\ln(1-0.615)]/7$$

$$r = 0.136$$

Transform the rate for 7 cycles (4.5-year-olds) in a probability for 1-cycle

$$p = 1-\exp(-rt)$$

$$p = 1-\exp(-0.136*1)$$

$$p = 0.127$$

Where, t is equal to 1 cycle.

In other words, this example gives the probability of developing caries during the next six months (one cycle) after children have reached 4 years of age, based on the assumption that prevalence of caries has a constant incremental rate (Fleurence and Hollenbeak, 2007;Briggs *et al.*, 2011).

These data allowed transition probabilities to be estimated based on the natural history of caries (NHC) and these estimates were used as both initial and transition probabilities in the Markov models. The results showed that estimated probabilities of caries progression were curvilinear (Figures 11.2 and Table 11.1).

	Cycles	1	2	3	4	5	6	7	8	9	10	11
	Year-olds	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5
caries prevalence	L	0.104	**0.196**	0.287	0.379	0.471	**0.562**	0.615	0.667	0.719	**0.772**	0.824
	ML						**0.544**	0.595	0.645	0.695	**0.745**	0.796
	HL/HML	0.091	**0.173**	0.256	0.338	0.420	**0.503**	0.551	0.599	0.647	**0.695**	0.744
rate	L	0.110	0.109	0.113	0.119	0.127	0.138	0.136	0.137	0.141	0.148	0.158
	ML						0.131	0.129	0.129	0.132	0.137	0.144
	HL/HML	0.095	0.095	0.098	0.103	0.109	0.116	0.114	0.114	0.116	0.119	0.124
probability	L	0.104	0.103	0.107	0.112	0.119	0.129	0.127	0.128	0.132	0.137	0.146
	ML						0.123	0.121	0.121	0.124	0.128	0.134
	HL/HML	0.091	0.091	0.094	0.098	0.103	0.110	0.108	0.108	0.109	0.112	0.116

Table 11.1. Estimated caries prevalence, rates, and transitional probabilities in the preschool Chilean population by socioeconomic scenarios (2006-2010). In bold, the prevalence estimated directly from the consolidated dataset.

Similar calculations were done to obtain transition probabilities from lower and upper confidence intervals of this NHC; see Appendix B. As transition probabilities were not constant over time, they were used in TreeAge as transition tables; this is the reason why these models are more correctly considered as Markov processes rather than as Markov models. Lower and upper confident intervals of initial and transition probabilities can be found in Appendix B.

An important point of the analysis is that the initial probability of being caries free for the two settings to be tested were not the same. This was due to the average age estimated for the transition level 1 (pre-kinder) at the PSS (CASEN, 2013), which was 4.5 years and, the starting age in the PCS was estimated as 4 years. In other words, a higher caries prevalence was expected in the preschool setting as the programme starts later.

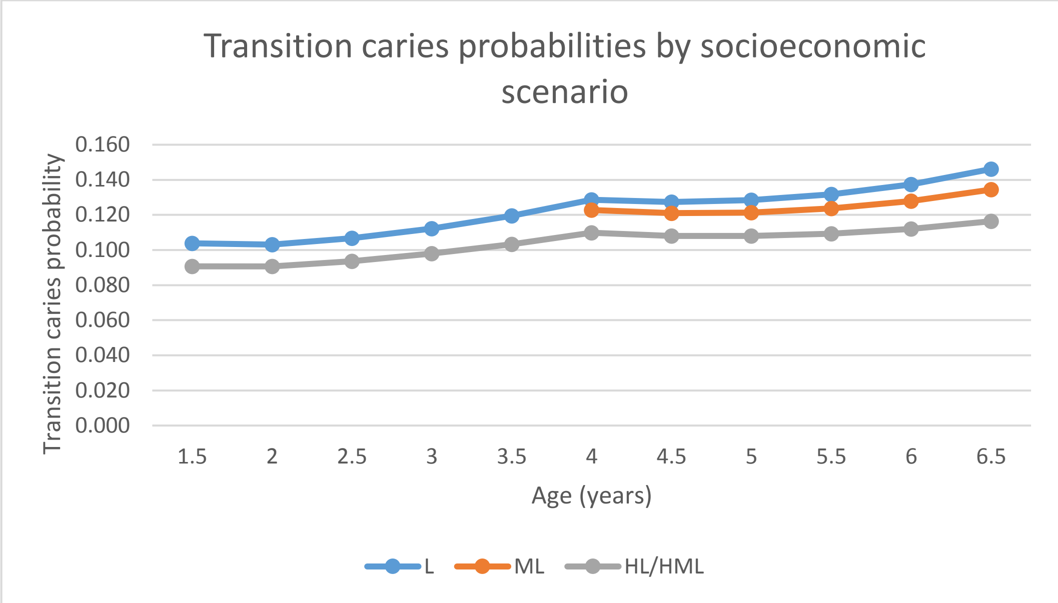


Figure 11.2. Probability of having caries by age in years according to socioeconomic scenario.

The initial probabilities were inputted in TreeAge Pro as initial probabilities for each Markov cohort. As the transition probabilities were different for each age, they were inputted as transition tables.

11.2.2 For fluoridated water-related population

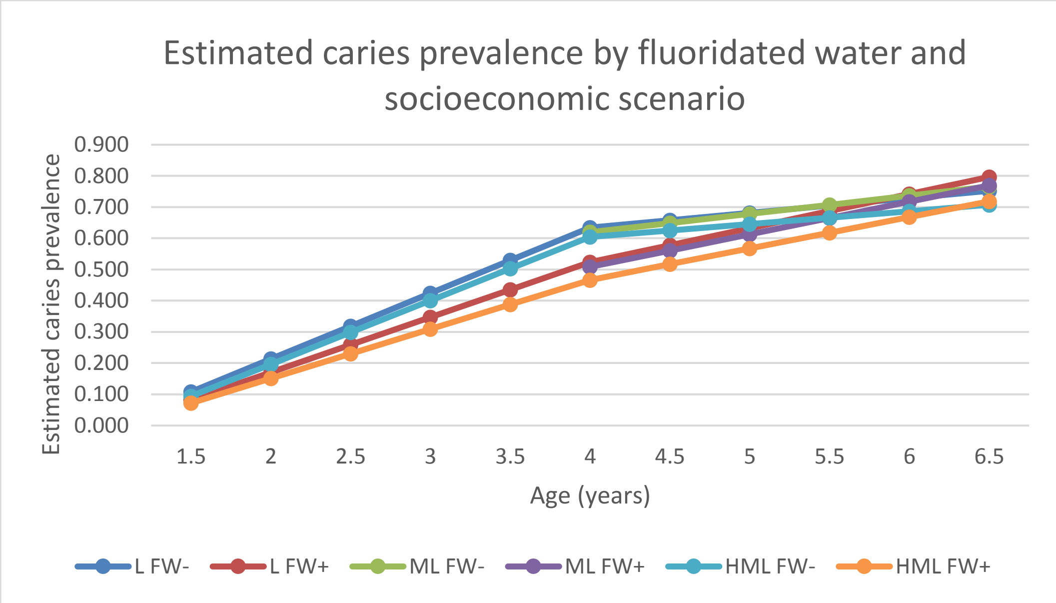
The econometric analysis (Chapter 7), informed by the work of Hoffmeister *et al.* (2010), found that the absence of fluoridated water was highly related to caries prevalence. This finding led to scenarios being created where the presence or not of fluoridated water was included.

The fluoridated water data were incorporated into a consolidated dataset using a similar approach used in the econometric analysis (Chapter 6). After that, a weighted caries prevalence for 2, 4, and 6-year-olds were obtained considering both socioeconomic scenarios (L, ML, and HML) and presence (or not) of fluoridated water. This utilised the same methodology used for transition probabilities by SES, weighted prevalence was transformed into rates that were finally converted into probabilities.

	cycles	1	2	3	4	5	6	7	8	9	10	11
	years	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5
Estimated prevalence	L FW-	0.108	**0.213**	0.319	0.424	0.529	**0.635**	0.658	0.682	0.705	**0.729**	0.752
	L FW+	0.083	**0.171**	0.259	0.347	0.435	**0.523**	0.578	0.633	0.687	**0.742**	0.797
	ML FW-						**0.620**	0.649	0.678	0.708	**0.737**	0.766
	ML FW+						**0.509**	0.561	0.613	0.665	**0.717**	0.770
	HML FW-	0.094	**0.196**	0.298	0.401	0.503	**0.605**	0.625	0.646	0.667	**0.687**	0.708
	HML FW+	0.072	**0.151**	0.230	0.309	0.388	**0.467**	0.517	0.567	0.618	**0.668**	0.718
Rates	L FW-	0.114	0.120	0.128	0.138	0.151	0.168	0.153	0.143	0.136	0.131	0.127
	L FW+	0.086	0.094	0.100	0.107	0.114	0.124	0.123	0.125	0.129	0.135	0.145
	ML FW-						0.161	0.150	0.142	0.137	0.133	0.132
	ML FW+						0.118	0.118	0.119	0.122	0.126	0.133
	HML FW-	0.099	0.109	0.118	0.128	0.140	0.155	0.140	0.130	0.122	0.116	0.112
	HML FW+	0.075	0.082	0.087	0.092	0.098	0.105	0.104	0.105	0.107	0.110	0.115
Probabilities	L P(C+IFW-)	0.108	0.113	0.120	0.129	0.140	0.155	0.142	0.133	0.127	0.122	0.119
	L P(C+IFW+)	0.083	0.089	0.095	0.101	0.108	0.116	0.116	0.118	0.121	0.127	0.135
	ML P(C+IFW-)						0.149	0.139	0.132	0.128	0.125	0.124
	ML P(C+IFW+)						0.112	0.111	0.112	0.114	0.119	0.125
	HML P(C+IFW-)	0.094	0.104	0.111	0.120	0.130	0.143	0.131	0.122	0.115	0.110	0.106
	HML P(C+IFW+)	0.072	0.079	0.083	0.088	0.093	0.099	0.099	0.099	0.101	0.104	0.109

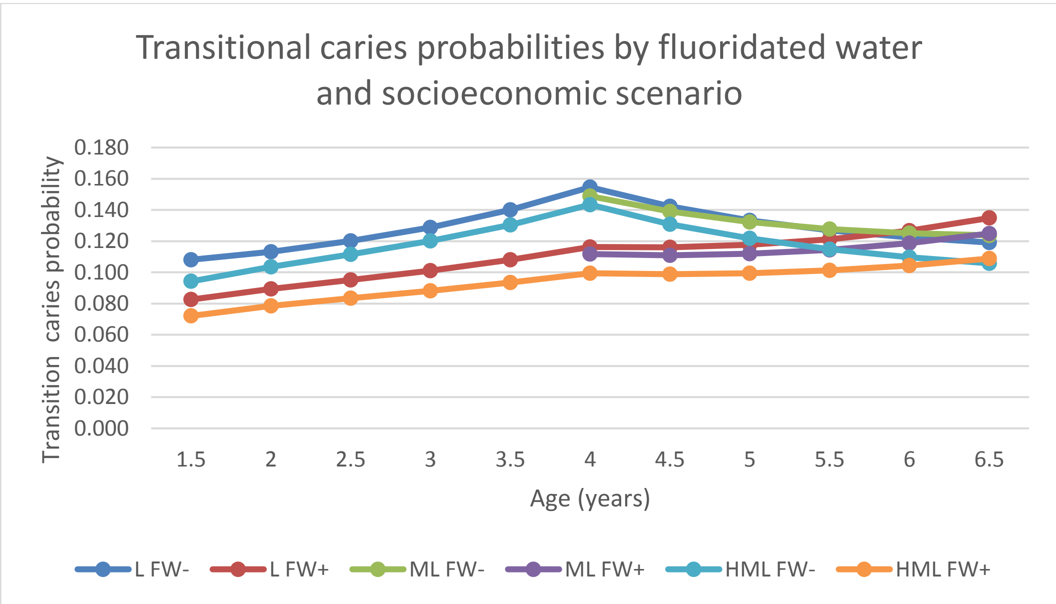
Table 11.2. Estimated prevalence, rates, and transition probabilities of caries in the preschool Chilean population by socioeconomic scenarios and fluoridated water (2006-2010). In bold, the prevalence estimated directly from consolidated dataset. FW+, fluoridated water positive and FW-, fluoridated water negative.

Figures 11.3, 11.4, and Table 11.2 show the results that were used as both initial and transition probabilities in the Markov processes; the confidence intervals of such results can be found in the Appendix B.



FW+, fluoridated water positive and FW-, fluoridated water negative.

Figure 11.3. Estimated prevalence by fluoridated water and socioeconomic scenario.



FW+, fluoridated water positive and FW-, fluoridated water negative.

Figure 11.4. Transitional probabilities by fluoridated water and socioeconomic scenario.

11.3 DAM Methodology

11.3.1 Defining the decision problem

The decision problem was intimately linked to MINSAL's goal of increasing the 6-year-old caries–free population by 35% during this decade in the entire population by the year 2020 (MINSAL, 2012c).

Since the work reported in this thesis was completed in collaboration with the Chilean Ministry of Health (MINSAL), and bearing in mind the Chilean guide for economic evaluations (MINSAL, 2013c), a public health system perspective was used. It meant that the only costs associated were those expended by the public sector and did not include out of pocket expenditures by the families of the children.

11.3.2 Structuring a decision model

Given that the objective of this chapter was to also evaluate other ways to perform the FV application, the target population of the model included all those preschool children able to be targeted either through preschool education or primary health care. Two settings were considered for the FV application: PSS and PCS. The percentage of caries-free population (dmft = 0) was used as measure of effect in the DAM.

The econometric study (Chapter 7) found a relationship between caries prevalence and fluoridated water; this finding showed that not all preschool populations have the same risk determinants and specific models for such populations were required. To develop the comparators for the DAM, a logic analysis using information on the Chilean context and protocols of FV application was conducted (Chapter 8). Seven comparators or interventions were chosen.

The use of three socioeconomic scenarios in the DAM were focused on. This was based on the findings of the systematic review and meta-analysis performed (Chapter 9) as well as the fact that caries prevalence has different behaviours depending on the socioeconomic statuses. These socioeconomic scenarios selected were: low SES, low-medium SES, and low-medium-high SES. Since low socioeconomic status is the socioeconomic group prioritised by the Chilean Ministry of Health, this group was selected as the base case scenario in this chapter.

The time horizon was defined for all DAMs as two-years long; this implies a biannual FV application from age 4 to 6 years. This was defined considering that the time horizon of DAMs of this thesis should be based in primary dentition only (Chapter 5), and taking into account MINSAL's goal of reducing caries prevalence in 6-year-olds. Also, the frequency of FV application was based on the findings of the systematic review performed in Chapter 9, which gave a cycle length of 6 months. This length reflects the frequency of application of FV in most studies analysed by Marinho et al. (2013) in primary dentition.

The models were required to be able to calculate expected values of prevalence and costs after 4 applications but allowing parameters to change after each application or cycle. Also, the models were required to replicate the natural history of caries; hence, caries prevalence would change for each application. The models were also required to incorporate events that occur within the cycles. Given these issues, a Markov cycle tree process was selected for the modelling framework, where the decision tree was used to estimate the proportion of the population in each of the Markov states at the end of every 6-month-length cycle; see Chapter 5 for more details. Using only decision tree models would have been difficult due to the high quantity of branches generated. To simplify presentation, the Markov cycle tree processes are called Markov models from here onward.

Markov models were developed in TreeAge Pro 2015 (TreeAge Software Incorporated. Massachusetts, USA) using the comparators or interventions obtained in Chapter 8. One comparator represents counselling-only (000000), two models were related to preschool settings (110000 & 110100), and four models represent different ways of organising FV in a primary health care setting (210000, 210001, 210100 & 210101). Table 10.3 contains the description of each intervention.

In all models, every branch ended in two possible terminal nodes, either caries or caries-free. Therefore, to recreate the possible outcomes after each cycle, two Markov states were created, caries and caries-free. The Markov state of caries was defined as an absorbing state, meaning that no transitions out of this state were possible. Defining the model in this way allowed the estimation of the prevalence of caries after the fourth cycle to be obtained. For example, Figure 11.5 shows the Markov model developed for the preschool setting without screening (110000). The rest of the models can be found in Appendix A.

Intervention	Definition
000000	Counselling-only at dental well-child programme
110000	FV application at preschool setting without screening
110100	FV application at preschool setting with screening
210000	FV application at primary care setting without screening
210001	FV application at primary care setting without screening and with re-appointment
210100	FV application at primary care setting with screening
210101	FV application at primary care setting with screening and with re-appointment

Table 11.3. Definition of interventions to be compared.

The application was simulated in the entire population, i.e., for both caries and caries-free children. This decision was grounded in two arguments, the first related to the positive effect of FV in those children that already have dental caries (Marinho *et al.*, 2013) and the second is related to the formal principle of justice in bioethics that establishes that equals must be treated equally (Beauchamp and Childress, 2013). Consequently, calculating the outcomes of FV application in both populations (those already with caries and caries-free) was necessary.

11.3.3 Cost-effectiveness analysis

All comparators, henceforth interventions, were finally put together in the DAM to allow the calculation of the cost and effect of each intervention and the incremental cost-effective ratios (ICERs) as well. The result was represented graphically using cost-effective planes.

11.3.4 Selection of scenarios and base case scenario

Since the epidemiological study showed that there was a clear difference existing between children of different socioeconomic status and that there were regional divisions, specific analyses of such variables were required to deal with the heterogeneity detected. Subsequently and, considering that the econometric analysis (Chapter 7) showed a statistical significant difference between those populations with and without fluoridated water, several scenarios were required to simulate all those settings and variables.

In the end, six FV scenarios were used. They were base case (L), fluoridated water positive (FWP), fluoridated water negative (FWN), medium and low socioeconomic status (ML), all socioeconomic statuses (HML), and best-case scenario (BCS). The main scenario was the base

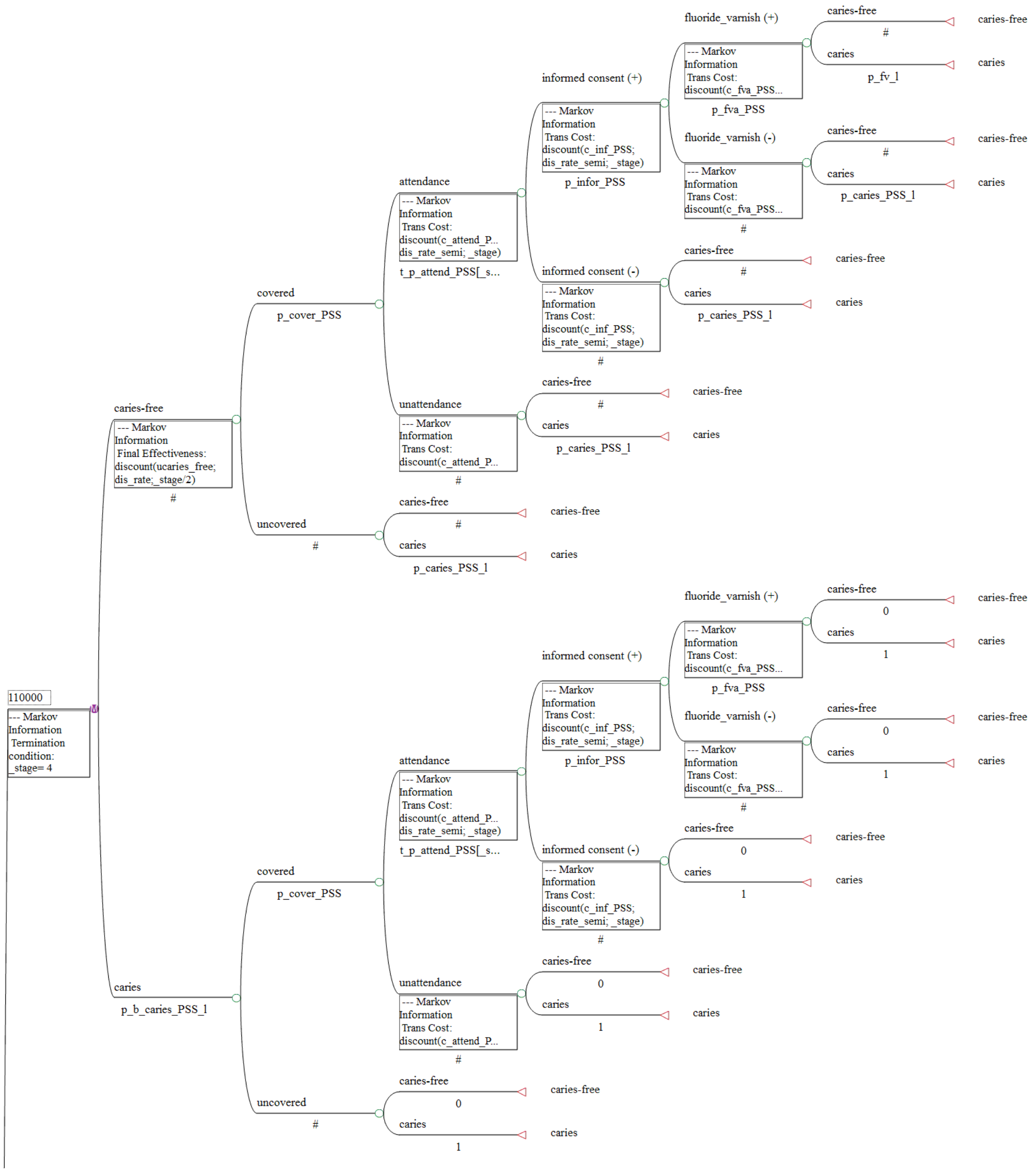


Figure 11.5. Preschool setting without screening (110000).

case, which included the low socioeconomic status only and the presence (or not) of fluoridated water was not considered. The relationship between the rest of the scenarios and socioeconomic status and fluoridated water is shown in Appendix B.

11.3.5 Costs

Chapter 10 contains the costing methodology and results. All costs were calculated in Chilean pesos (CLP) in March 2015 prices and the duration it took to apply the FV was defined as five minutes. The selected time for application was based on a study by Hawkins *et al.* (2004) who calculated in a population aged 3 to 6 years an average time of 5.22 minutes per application.

To construct Markov models that allow modification of as many parameters as possible, disaggregated costs were used. For example, the cost of a child attending the primary care setting (c_attend_PCS) was defined as the sum of the cost of human resources (c_HR_PCS) plus the cost of equipment (c_equip_PCS) both multiplied by indirect costs (c_ind_cost).

$$c\_attend\_PCS = (c\_HR\_PCS + c\_equip\_PCS) * c\_ind\_cost$$

$$c\_attend\_PCS = (1{,}402+66)*1.14$$

$$c\_attend\_PCS = 1{,}673.52 \text{ Chilean pesos}$$

Consequently, some operational definitions were created to enable such disaggregated costs to be entered into the models constructed within TreeAge. This approach permitted more reliable deterministic analyses to be performed. The complete list of costs and their definitions can be found in Appendix B.

11.3.6 Efficacy of fluoride varnish

The probability of FV effect on the caries-free preschool population was obtained for different socioeconomic scenarios (low, medium-low, and high-medium-low) from the systematic review and meta-analysis performed in Chapter 9. This was in agreement with a possible incremental implementation of different types of schools.

However, since FV efficacy data was calculated for three socioeconomic scenarios, initial and transition probabilities were calculated for the same scenarios (L, ML, and HML); see Chapters 6 and 9. This arrangement allowed the addition, in an incremental way, of all types of schools in the simulations. Given that the probability that FV would be effective was based upon a follow-up period of two-year data with application every 6 months, calculating the probability for one application (or cycle) was necessary.

The attributable risk of being exposed, which is the probability of having caries after a 2-year follow-up or 4 Markov cycles in the exposed group, was calculated using data obtained in Chapter 9.

$$\text{attrib. risk exposed} = \text{attrib. risk unexposed} - \text{relative risk}$$

Then the probability was transformed in a rate for 4 Markov cycles (t = 4) using the formula below.

$$r = - [\ln (1-p)]/t$$

Finally, such rate was converted again into a probability for each Markov cycle (t = 1).

$$p = 1-\exp (-rt)$$

All conversions were done under the assumption that caries prevalence increased at a constant rate over the 2-year follow-up period (Briggs et al., 2011). Results of all these conversions are presented in Table 11.2; here lower and upper ranges of FV effect were obtained by multiplying the attributable risk obtained from Chapter 9 by 0.75 and 1.25, respectively.

Scenarios	Range	Probability for four cycles	Rate for four cycles	Probability for one cycle
Low		0.173	0.047	0.046
Medium & low		0.291	0.086	0.082
High, medium & low		0.255	0.074	0.071
Low	lower	0.130	0.035	0.034
Medium & low	lower	0.228	0.065	0.063
High, medium & low	lower	0.183	0.051	0.049
Low	upper	0.216	0.061	0.059
Medium & low	upper	0.380	0.119	0.113
High, medium & low	upper	0.305	0.091	0.087

Table 11.4. Effect of fluoride varnish for 6 months (one Markov cycle).

11.3.7 Probabilities related to Chilean health system

Based on Letelier (2010), the coverage of dental well-child programme (DWCP) at 2 and 4 years of age was 33% and 32%, respectively. Subsequently, the counselling-only scenario (000000) considered a probability of coverage of 0.32. Given that Letelier used the number of children that have been already treated in DWCP for her report, the attendance probability for DWCP was assumed as equal to 1.

11.3.8 Coverage and attendance of well-child programme

The coverage of well-child programme (WCP) was estimated by socioeconomic scenario (L, ML and HML) using the national socioeconomic survey CASEN (MIDEPLAN, 2013). A percentage was calculated using the number of children of the relevant age who had attended the WCP divided by the total number of children of that same relevant age who were eligible to attend the WCP. First, coverage was calculated by socioeconomic status (Appendix B) and then by socioeconomic scenario (Table 11.5).

The probability of attendance for the DWCP was assumed as 1, this was because MINSAL calculates the coverage of this programme using all those children who had already attended their appointments only.

SES scenarios	3-year-olds	4-year-olds	5-year-olds
L	0.51	0.47	0.41
ML	0.50	0.46	0.40
HML	0.50	0.44	0.39

Table 11.5. Coverage of well-child programme by socioeconomic scenarios, from CASEN survey 2013.

11.3.9 Probability of rescheduling a child.

Unfortunately, the Department of Oral Health of the Chilean Ministry of Health did not provide this information; therefore, all the comparators with this variable (210001 & 210101) could not be included in the DAM stage of this study. Further work will consider these comparators when the relevant data becomes available.

11.3.10 Probabilities related to Chilean educational system

Coverage of preschool education was obtained from CASEN (MIDEPLAN, 2013). Here, a couple of problems were solved since academic year and child age usually do not coincide and the fact that CASEN does not discriminate between transition level 1 (pre-kinder/NT1) and transition level 2 (kinder/NT2).

First, given that the natural history of caries used as a baseline came from several surveys that only considered children aged 2, 4, and 6 years, the coverage was calculated by age and not by educational level. Second, children aged 2 or 4 years that effectively attended preschool education (NT1 or NT2) were included in the analysis for this coverage; those children who did not attend either nursery or primary school were excluded. The following assumptions were made for the estimation:

- The number of not covered children (whose children who have never attended) was proportional to every educational level.
- 100% of children aged 4 years who attended preschool education, go to NT1.
- 50% of children aged 5 years who attended preschool education, go to NT2.

The probability of coverage of preschool education was 0.81 (95% CI 0.79 to 0.83) and 0.95 (95% CI 0.98 to 1) for 4- and 5-year-olds, respectively (Table 11.6). More information is presented in Appendix B. Confidence intervals were estimated using the Wald method.

Age	Coverage	Lower CI	Upper CI
4-year-olds	0.81	0.79	0.83
5-year-olds	0.95	0.94	0.97
6-year-olds	0.99	0.98	0.99

Table 11.6. Summary of coverage of preschool education from the CASEN survey 2013.

Arbour *et al.* (2014) determined, in a sample of public schools in Santiago City, that the average non-attendance frequency for preschool education was 22.9% of academic days for transition level 1 (approximately children aged 4 years) and 20.8% for transition level 2 (5-year-olds). Hence, the base case scenario in the preschool setting had an attendance probability of 0.77 (95% CI, 0.76 to 0.78) and 0.79 (95% CI, 0.78 to 0.80) for 4- and 5-year-olds, respectively. Personal communications with Dr MaryCatherine Arbour from Harvard University allowed the confidence intervals for this variable to be obtained and highlighted the need to consider the seasonal variation of school attendance. There are clear differences in the attendance percentages depending on the seasons, with a maximum in the autumn and a minimum in winter; this phenomenon could be explored in further studies.

11.3.11 Probabilities related to informed consent

Given that it was not possible to obtain Chilean data about the positive (or accepted) informed consent rate in a fluoride varnish programme, obtaining such information from international literature was necessary. Buckingham and John (2013) published a pilot study about recruitment and participation in a preschool-based FV programme in the South-Central region of England that showed a positive consent rate of 96.8% (487 out of 503); such a rate was high considering that this study involved children aged between 3 and 7 years and who were not enrolled as part of a public health programme. However, this study must be treated cautiously as 14.6% of families did not respond to recruitment letters. By contrast, Evans *et al.* (2013b) reported an average positive consent rate of 64.5%. This study was performed in East London schools in a preschool population aged between 3 and 5 years. The authors suspected that the lower positive consent rate might be a product of both language and literacy barriers.

The Chilean scenario could be more similar to results described by Buckingham and John (2013) given that the application of FV will be part of a public health programme; hence, a high positive informed consent rate would be expected. Therefore, a rate of 90% positive informed consent was estimated for the base case scenario at PSS and a 95% for the PCS. A higher rate is expected at the PCS as applicators can answer directly any question from parents or caregivers.

11.3.12 Probabilities of acceptance of fluoride varnish application

Despite some authors concluding that acceptance of FV is high (Oliveira *et al.*, 2014), there is no conclusive evidence about the level of acceptance of FV (Marinho *et al.*, 2013). Unfortunately, few authors have quantified the acceptance rates. A proxy could be obtained from Agouropoulos *et al.* (2014) who reported that 4.9% (9 out of 181) of children did not co-operate with the application of FV in the control group. Similarly, Humphris and Zhou (2014) reported a 5% refusal rate (12 out of 238) in a study where FV was applied by extended duties dental nurses. However, Quissell *et al.* (2014) reported that no children refused the application of FV in their study.

This lack of cooperation or refusal could be due to two reasons: one is related to behavioural problems and the other is associated with the presence of some acute pathology that was causing pain. This latter point is significant if the finding by Evans *et al.* (2013b) are kept in mind. Evans *et al.* (2013b) reported that 1.58% of children were excluded from FV application as they had either a dental abscess or a sore mouth. Interestingly, in the protocol for Northern Ireland caries prevention in practice trial or NIC-PIP trial, Tickle *et al.* (2011) estimated discontinuing the application of fluoride varnish in just 1% of cases due to both reasons: dislike of fluoride varnish intervention and concerns about effectiveness of such an intervention.

Therefore, a conservative estimate about the percentage of children that, for one reason or another, might refuse FV application was estimated in the range of 5%. A lower level of cooperation was expected for PCS (90%) given that this setting is not the natural environment for children.

11.3.13 Screening

Other parameters affect screening such as, for example, the child's acceptance of this procedure. Again, trying to find data was difficult because there is little information about this in published studies; consequently, a proxy was estimated. Agouropoulos *et al.* (2014) reported that 1.49% (5 out of 424) of eligible children were excluded from their study because they were non-cooperative. A study performed by Holm (1979) reported that 25 out of 275 (9%) children did not cooperate and were excluded. Unfortunately, which part of study they were excluded from is not clear. Therefore, based on the very limited evidence about the number of children who refuse screening, a refusal percentage of 5% was assumed to be reasonable.

With regards to the decision problem is the percentage of children that refuse screening. The Markov models evaluate the effectiveness and cost-effectiveness of FV in a caries-free population but the screening proposed by MINSAL cannot be used to separate those children with caries from those without. Therefore, the question that arises here is: what is the screening for?

There are a couple of alternatives that could answer this question. One alternative is to assume that screening is a type of legal requirement for FV application. This is highlighted in the Chilean guideline (MINSAL, 2012c) that requires a diagnosis prior to application of FV. Furthermore, under = Chilean law, this diagnosis must be performed by a dentist. But, as was commented on in Chapter 8, a question arises here: what is the sense of performing such a diagnostic test if the health system is unable to treat all children?

Another alternative is to think about screening as a kind of filter to detect those children that have a contraindication for FV. Unfortunately, this is not necessarily helpful because at the ages of the children considered, the children are not able to answer all questions and, even worse, parents are not required to be present during the screening in the intervention proposed by MINSAL, so they cannot provide the information on the child's behalf.

Using this logic, there is no sense in performing screening; however, this must be included in the model as it is a legal requirement, and hence we must demonstrate its effect on the programme. Regardless of the relevance of screening, this procedure incurs a cost and has an effect. A probability of one was selected for the base case scenario in both settings. This was done because all children attending public school were considered as low socioeconomic status, and hence at a a high risk of developing caries.

11.3.14 Discount rate

The Chilean methodological guide for economic evaluation states that a generic discount rate of 3% should be used. The same guide suggests, for sensitivity analysis, a discount rate varying between 0 and 5% for both costs and outcomes should be used and that rates of 3% and 1.5% for costs and outcomes, respectively should be used (MINSAL, 2013c).

$$y=a\ (1+ ((r/n))\ exp\ (-nx)$$

The TreeAge built-in discounting function (TreeAge, 2014) for the discounted value is:

Discount (utility; rate; time)

So, the formula of discount value for cost was:

Discount (cost; 0.03/2; _stage)

Where *cost* represents the cost to be discounted; *_stage* is the TreeAge keyword (Markov cycle counter starting at 0) to perform discounting in each cycle. Since the discount value is expressed as an annual rate, the value (0.03/2) represents a semi-annual discount.

In the case of effectiveness, measured as a final effectiveness after a two-year follow-up, discounting was incorporating using the function:

Discount (ucaries_free; 0.03; 2)

Where *ucaries-free* denotes the utility of caries-free at the end of a follow-up period whose length is two years.

11.3.15 Payoffs in TreeAge

Given that the objective of this chapter was to simulate caries prevalence in 6-year-olds, counting the number of caries-free children at the end of four cycles was necessary. TreeAge was set to assign a one-time reward in all terminal nodes at the end of cycle four; the values used were 1 for caries-free and 0 for caries. Likewise, these models did not use a half-cycle correction due to the short length of each cycle (less than one year) and because the rewards were not counted after each cycle (TreeAge, 2014).

As was noted previously, all those non-constant transition probabilities were inputted into TreeAge Pro using transition tables.

11.3.16 Evaluation of validity and consistency of model.

Several tests were done in TreeAge Pro to evaluate the internal validity of the Markov models. Among the parameters evaluated were discount rates, TreeAge rewards, costs, and the prediction capability. The outcome estimation was tested in a simple model in both Excel and TreeAge, using initial and transition probabilities obtained in 4-year-olds, from a multivariable logistic regression model (Chapter 7). This logistic model allowed a constant caries rate to be obtained that was used to extrapolate caries prevalence in 6-year-olds. After having run the model for 4 Markov cycles, the value obtained in 6-year-olds was the same as that obtained using the multivariate logistic regression model.

In the same way, an ex-post validity test was done to evaluate the predictive value of decision analytic model (DAM). This was done in all scenarios comparing the expected caries-free rates, from natural history of caries (NHC), against the obtained caries-free rates (from DAMs) of the counselling-only interventions. This allowed us to obtain a percentage of variation of the DAM with respect to natural history of caries.

$$\text{Model variation} = (\text{caries-free}_{NHC} - \text{caries-free}_{DAM}) / \text{caries-free}_{DAM}$$

11.3.17 Deterministic sensitivity analysis

With the intention of evaluating the parameter of uncertainty and the impact of every variable on the baseline CEA, univariate deterministic sensitivity analyses (DSAs) were run for every variable in the base case scenario. Given that this analysis estimates the impact of one variable at once, it helps to simulate specific and highly likely situations. For example, what would happen in very isolated zones (in Patagonia for example) where costs of both human resources and transport are higher than the rest of the country?

In the other scenarios, to be more efficient in the deterministic sensitivity analysis, not all variables were analysed; the variables with higher impact in base case scenario plus some variables related specifically to each scenario were used.

11.3.18 Probabilistic sensitivity analysis

Deterministic sensitivity analyses do not allow consideration of the possible impact of a combination of parameters. To solve this problem, a Monte Carlo simulation with 1,000 iterations was performed as probabilistic sensitivity analysis (PSA). This approach allowed us to explore the impact of the uncertainty in all parameters at the same time. This PSA was executed for the base case scenario only.

To populate the uncertainty of the parameter in the model, it is necessary to choose a parameter distribution, and this distribution should reflect the nature of the data (Gray et al., 2011). The same author recommends using either gamma or log-normal distributions for costs, because both distributions can reflect the skewed nature of cost data.

However, given that all costs were calculated, it was not possible to obtain any standard errors that are required to obtain confidence intervals. Therefore, triangular distributions were used in all cost parameters, considering ±25% as a range of uncertainty. Beta distributions were used for those probability parameters obtained from binomial data; given that such distribution is constrained on the interval [0,1], it can be used to reflect the probabilities of two mutually exclusive events (Gray et al., 2011).

All parameter definitions are shown in Table 11.7. Parameters used in probabilistic sensitivity analysis can be found in Tables 11.8 and 11.9.

Similarly, a cost-effectiveness acceptability curve was obtained using the ICER of the intervention proposed by MINSAL (210100) compared to counselling-only as a threshold. This value was selected due to there being no evidence about how much either society or MINSAL are willing to pay for a caries-free child; consequently, it was assumed that MINSAL is willing to pay for its current proposal.

11.3.19 Adjustment of populations

Given that both settings have different potentially eligible populations, to properly compare all interventions, some adjustments of populations were required. Such adjustments were done in all interventions at the base case scenario.

This adjustment of population allowed the consideration of those children who were caries-free as result of FV intervention, and those who were caries-free as it naturally occurs as part of the natural history of caries. More importantly, this allowed the estimation of the effect of each intervention in the entire population.

First the eligible populations, or populations in which the application is going to be done, were defined. The eligible population of preschool setting (PSS), or public education population, included all those preschool children that attend to public institutions (school, nurseries, etc.). On the other hand, the primary care population was composed by all those preschool children entitled to receive benefits from the National Health Fund (FONASA); called FONASA population henceforth.

To get an estimate for both populations, the projection of the entire preschool population for 2015 performed by the Chilean National Institute of Statistics (INE, 2014) was used. This population was then adjusted using data from the CASEN survey (MIDEPLAN, 2013). As result (appendix B), 141,691 children were considered as the eligible population in the preschool setting and 211,002 children were eligible in the primary care setting. The entire preschool population was used as a proxy of a reference cohort.

Name	Description
c_attend_PCS	Cost of attendance at PCS
c_attend_PSS	Cost of attendance at PSS
c_cons_DWCP	Cost of consumables at DWCP
c_DWCP	Cost of dental well-child programme (equipment, consumables and human resources)
c_equip_DWCP	Cost of equipment at DWCP
c_equip_PCS	Cost of equipment
c_fv_dose	Cost of one dose of fluoride varnish
c_fva	Cost of FV application
c_fva_PCS	Cost of FV application at PCS
c_fva_PSS	Cost of FV application at PSS
c_hr_DWCP	Cost of human resources at DWCP
c_hr_PCS	Cost of human resources at PCS
c_hr_PSS	Cost of human resources at PSS
c_hyg_kit	Cost of oral hygiene kit
c_ind_cost	Indirect cost (%)
c_inf_PCS	Cost of informed consent
c_inf_PSS	Cost informed consent at PSS
c_inst	Cost of instrumental
c_inst_PCS	Cost of instrument at PCS
c_inst_PSS	Cost of instrumental at PSS
c_scr_coef	Screening coefficient (%)
c_scr_PCS	Cost of screening at PCS
c_scr_PSS	Cost of screening at PSS
c_trans	Cost of transport to and from school
dis_rate	Discount rate
dis_rate_semi	Semi-annual discount rate
p_attend_DWCP	Dental well-child programme attendance
p_attend_PCS	Well-child programme attendance
p_attend_PSS	Preschool attendance
p_b_caries_48_l	Baseline of caries experience at 48-month-olds in low SES
p_b_caries_54_l	Baseline of caries experience at 54-month-olds in low SES
p_b_caries_DWCP_l	Baseline of caries experience at DWCP in low SES
p_b_caries_PCS_l	Baseline of caries experience at PCS in low SES
p_b_caries_PSS_l	Baseline of caries at NT1
p_caries_DWCP_l	Natural history of caries at DWCP in low SES
p_caries_48_l	Natural history from 48-month-olds in low SES
p_caries_54_l	Natural history from 54-month-olds in low SES)
p_cover_DWCP	Dental well-child programme coverage
p_cover_PCS	Well-child programme coverage
p_cover_PSS	Preschool coverage
p_fv_l	Efficacy of FV at low SES scenario
p_fva_PCS	Probability of FV acceptance at PCS
p_fva_PSS	Probability of FV application acceptance at PSS
p_infor_PCS	Probability of informed consent positive at PCS
p_infor_PSS	Probability of informed consent positive at PSS
p_scr_l	Screening positive at low SES scenario
p_scra_PCS	Screening acceptance at PCS
p_scra_PSS	Screening acceptance at PSS
ucaries	Reward of caries (TreeAge)
ucaries_free	Reward of caries-free (TreeAge)

Table 11.7. Parameters definitions.

Variable	Distribution	Parameter 1	Parameter 2	Parameter 3
d_c_cons_DWCP	triangular	125	166	208
d_c_DWCP *	triangular	2,174	8,699	10,874
d_c_equip_DWCP	triangular	297	396	495
d_c_equip_PCS	triangular	50	66	83
d_c_fv_dose	triangular	844	1,125	1,406
d_c_hr_DWCP	triangular	5,302	7,069	8,836
d_c_hr_PCS	triangular	1,052	1,402	1,753
d_c_hr_PSS	triangular	850	1,133	1,416
d_c_hyg_kit	triangular	983	1,310	1,638
d_c_ind_cost	triangular	1.105	1.14	1.175
d_c_inf_PSS	triangular	17	22	28
d_c_inst	triangular	58	77	96
d_c_scr_coef	triangular	0.38	0.5	0.63
d_c_trans	triangular	1025	1367	1709
d_dis_rate	triangular	0	0.03	0.05
d_p_attend_PSS	Beta	inputted in TreeAge as table, from t_p_attend_PSS		
d_p_b_caries_48_l	Beta	0.562	0.027	
d_p_b_caries_54_l	Beta	0.615	0.026	
d_p_caries_48_l	Beta	inputted in TreeAge as table, from t_p_caries_48_l		
d_p_caries_54_l	Beta	inputted in TreeAge as table, from t_p_caries_54_l		
d_p_cover_DWCP	Beta	0.32	0.08	
d_p_cover_PCS	Beta	inputted in TreeAge as table, from t_p_cover_PCS		
d_p_cover_PSS	Beta	inputted in TreeAge as table, from t_p_cover_PSS		
d_p_fv_l	Beta	0.046	0.012	
d_p_fva_PCS	triangular	0.68	0.9	1
d_p_fva_PSS	triangular	0.71	0.95	1
d_p_infor_PCS	triangular	0.71	0.95	1
d_p_infor_PSS	triangular	0.68	0.9	1
d_p_scra_PCS	triangular	0.68	0.9	1
d_p_scra_PSS	triangular	0.71	0.95	1

(*) cycle one only.

Table 11.8. Parameters for probabilistic sensitivity analysis (I) for the low socioeconomic scenario or base case.

Variable	Cycle	Parameter 1	Parameter 2
t_p_attend_PSS	1	0.771	0.01
	2	0.771	0.01
	3	0.792	0.01
	4	0.792	0.01
t_p_caries_48_l	1	0.127	0.008
	2	0.128	0.008
	3	0.132	0.009
	4	0.137	0.09
t_p_caries_54_l	1	0.128	0.008
	2	0.132	0.009
	3	0.137	0.009
	4	0.146	0.01
t_p_cover_PCS	1	0.47	0.016
	2	0.47	0.016
	3	0.42	0.02
	4	0.42	0.02
t_p_cover_PSS	1	0.8062	0.019
	2	0.9539	0.011
	3	0.9539	0.011
	4	0.985	0.004

Table 11.9. Parameters for probabilistic sensitivity analysis (II) in the low socioeconomic scenario or base case.

Then, to identify the number of caries-free children in each intervention, the number of caries-free children in the eligible population was calculated by multiplying the effect of each intervention by either the public education or the FONASA population. A non-eligible population was calculated for each intervention by subtracting each population from the entire population. Then, the number of caries-free children in the non-eligible population was calculated, assuming the effect of a do-nothing intervention, multiplying the non-eligible population by caries-free prevalence in both medium and high (HM) socioeconomic statuses; 38.8% in 6-year-olds and 33.5% in 6.5-year-olds. Finally, the number of all caries-free children in each intervention was obtained by adding the number of caries-free children of the not eligible population to the number of caries-free children of each intervention in the eligible population.

The cost of each intervention was estimated multiplying the cost per child, obtained from DAM, by the eligible population, either the public school or FONASA population.

The data obtained from this population adjustment allowed a new cost-effectiveness analysis to be performed, including all interventions of base case scenario.

11.4 Results

11.4.1 Internal validity test

An ex-post internal validity test was performed in all scenarios at counselling-only interventions, results of which are presented in Table 11.10. The result shows that the base case scenario had a variation of -3% with respect to the natural history of caries (NHC), the ML scenario had no differences (0%), the HML scenario a 3% difference, the fluoridated water scenario a -7% difference, the fluoridated water negative scenario had a 29% difference and, the best-case scenario was -3% different.

As is explained in the discussion, consideration of the validity of the results for the fluoridated water scenarios led to the exclusion of these scenarios from further consideration.

			Caries-free	
Scenarios	NHC	DAM	(NHC-DAM)	(NHC-DAM)/NHC
Low SES	0.228	0.235	-0.01	-3%
Medium and low SESs	0.255	0.254	0.00	0%
High, medium and low SESs	0.305	0.295	0.01	3%
Fluoridated water positive	0.231	0.247	-0.02	-7%
Fluoridated water negative	0.214	0.152	0.06	29%
Best-case scenario	0.228	0.235	-0.01	-3%

NHC, natural history of caries and DAM, decision analytic model.

Table 11.10. Ex-post internal validity test.

11.4.2 Cost-effectiveness analysis of base case scenario

After a 2-year follow-up, this cost-effectiveness analysis (or baseline analysis) showed that 23.5% of the eligible population was caries-free in the counselling-only intervention with a cost of CLP 2,784 per child. FV application in a primary care setting without screening (210000) was the only undominated FV intervention; this intervention had an average cost of CLP 7,620 per child and resulted in 27.2% of caries-free children in the eligible population. Compared with counselling-only, this intervention increased the caries-free population by 3.7% at an extra cost of CLP 4,836 per child; the ICER was CLP 130,849 per additional caries-free child. See Table 11.11 and Figure 10.6 for more details.

The cost-effectiveness plane (Figure 11.6), shows that there was almost no difference in effectiveness between both settings with respect to counselling-only. For example, the more effective intervention (PCS without screening) resulted in just 16 additional caries-free children per 1000 when compared with the less effective FV intervention (PSS with screening). On the other hand, there was a clear difference in costs per child between both settings, where the costliest intervention (PSS with screening) had a cost that was 209% greater than the cost of the only undominated FV intervention (PCS without screening).

Interventions	Cost	Incr. cost	Effect	Incr. effect	ICER	Dominance
Excluding dominated						
000000	2,784		0.235			
210000	7,620	4,836	0.272	0.037	130,849	
All						
000000	2,784	-	0.235	0	-	
210000	7,620	4,836	0.272	0.037	130,849	
210100	8,662	1,042	0.269	-0.004	-268,558	
110000	19,344	11,724	0.26	-0.012	-947,188	
110100	23,514	15,894	0.257	-0.016	-1,024,417	
All referencing common baseline						
000000	2,784		0.235			undominated
210000	7,620	4,836	0.272	0.037	130,849	undominated
210100	8,662	5,878	0.269	0.033	177,690	abs. dominated
110000	19,344	16,560	0.26	0.025	673,612	abs. dominated
110100	23,514	20,730	0.257	0.021	966,637	abs. dominated
All by Increasing effectiveness						
000000	2,784		0.235			
110100	23,514		0.257			
110000	19,344		0.26			
210100	8,662		0.269			
210000	7,620		0.272			

Table 11.11. Ranking of strategies in the low socioeconomic scenario or base case scenario.

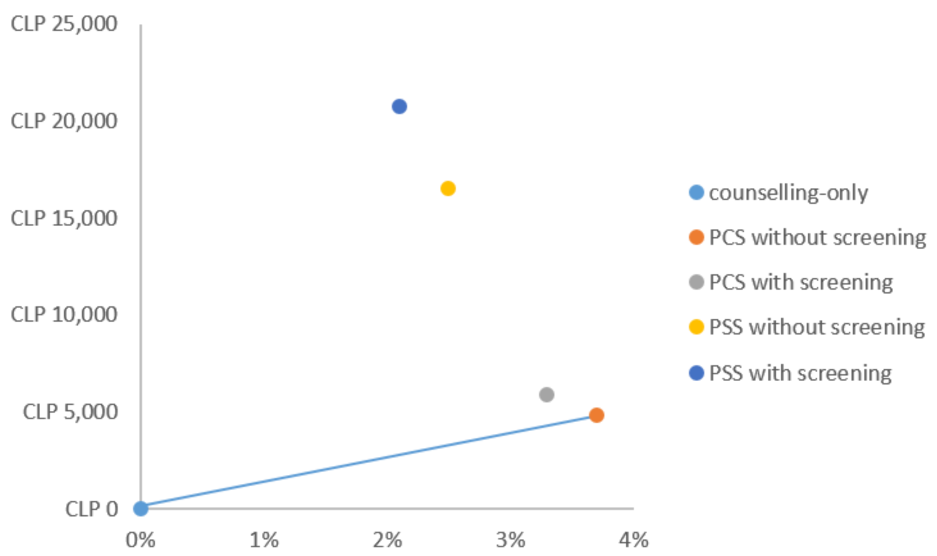


Figure 11.6. Cost-effectiveness plane of the base case scenario (L).

11.4.3 Deterministic sensitivity analysis of base case scenario

There were two simulations where an intervention delivered in the preschool setting was more effective and more costly than the primary care intervention. Both were related to initial caries probabilities. The first situation occurred when the initial caries probability at PCS was increased; therefore, the most cost-effective FV intervention was the application in the preschool setting without screening (110000). The second situation occurred when the initial caries probability at PSS was reduced; in this case, the more costly but more effective intervention was also 110000. For more details about this analysis, see Appendix B.

The lowest average cost (CLP 5,148) per child was observed when the oral hygiene kit was eliminated; the second lowest cost (CLP 5,715) was observed when coverage of the PCS was reduced. The highest average cost (CLP 19,344) was estimated when either the initial caries prevalence was increased in the PCS or reduced in the PSS.

The highest effect was 28.9%, which occurred when either the discount rate was not included or when the initial caries prevalence was reduced at PCS. The lowest effect (25.6%) was observed in the primary care setting (210000) when the initial caries prevalence was increased in the PCS. The second lowest effect (26%) was observed in the preschool setting (110000), also when the initial caries prevalence was increased at PCS.

The highest ICER (CLP 2,656,093) was observed when the initial caries prevalence increased at PCS and the second highest ICER (CLP 2,262,376) was detected when the initial caries prevalence in the PSS was reduced; both ICERs were observed when the PSS without screening intervention was compared to the PCS without screening intervention. The third highest ICER (CLP 175,542) was detected when the acceptance of FV at the PCS was reduced; this ICER was observed when the PCS without screening intervention was compared to counselling-only.

Interestingly, when the cost of the oral hygiene kit was equal to zero, the ICER dropped to its minimum (CLP 63,969). The second lowest ICER (CLP 107,218) was observed when the coverage of the WCP was reduced. The third lowest ICER (CLP 112,013) was detected when the cost of human resources was reduced at the PCS. All ICERs were observed when the intervention at the PCS without screening was compared with counselling-only.

11.4.4 Probabilistic sensitivity analysis of base case scenario

All simulations were more effective but more costly than counselling-only. The estimated outcomes averages of the interventions showed small differences in effectiveness and, as can be seen in Appendix B, larger differences in cost. The only undominated FV intervention was the application at the PCS without screening (210000); in this case, a 26.9% caries-free population was estimated with an average cost of CLP 7,314 per child. The additional number of children without caries, compared with the counselling-only intervention, was 33 additional children per 1000 with an incremental cost of CLP 4,535 per child, in other words, a cost of CLP 140,275 per extra caries-free child.

The scatterplot (Figure 10.7) shows that the iterations of each intervention presented large variations in effect and small variations in cost; a big difference in cost was also detected between both settings. Similarly, there was a clear difference in cost between both PSS interventions; however, this difference was not clearly observable in the PCS interventions due to an overlapping of iterations.

The cost acceptability curve (Figure 11.8) shows that when cost of a caries-free child is less than CLP 96,664, it is highly probable (78.5%) that the counselling-only intervention is cost-effective. When the cost is above such a value, intervention 210000 is more likely to be cost-effective, having a probability of 47.2% at CLP 144,996. On the other hand, the intervention and setting proposed by MINSAL have almost no probability of being cost-effective. More details can be seen in Table Appendix B.

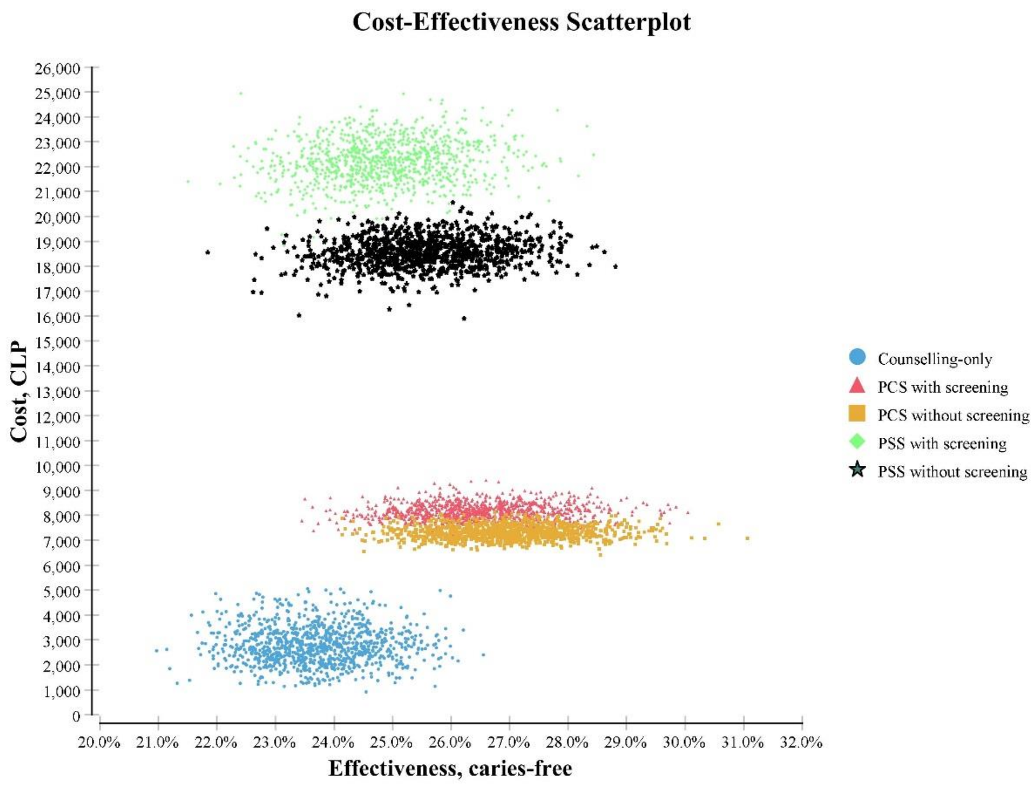


Figure 11.7. Cost-effectiveness scatterplot of base case scenario.

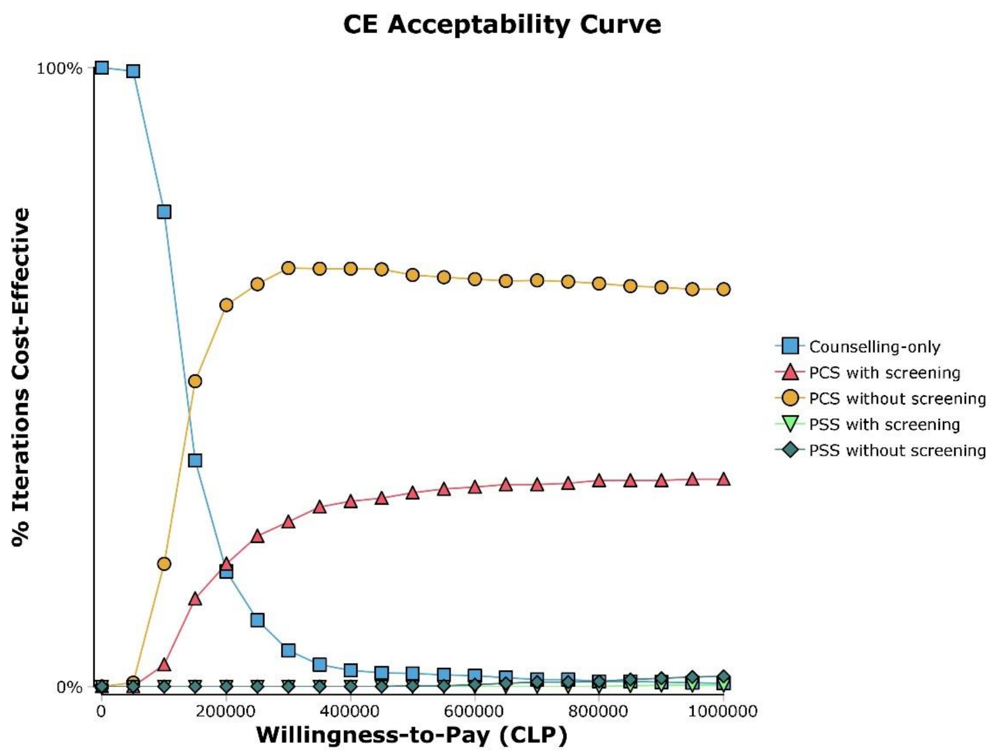


Figure 11.8. Cost-effectiveness acceptability curve.

11.4.5 Low and medium socioeconomic statuses scenario

The counselling-only intervention (000000) was estimated as resulting in 25.4% of the eligible population being caries-free. The only undominated FV intervention was 210000, which presented an average cost of CLP 7,365 with 27.2% children being caries free. This intervention, when compared with 000000, also had an incremental cost of CLP 4,581 per child and an incremental effect of 1.8%, giving an incremental cost of CLP 253,758 per additional caries-free child. More details are provided in Appendix B.

All of the variables deemed important in the base case scenario plus the coverage of preschool education were used for this DSA (Appendix B). The only undominated FV intervention in all sensitivity analyses was 210000.

The lowest cost (CLP 5,148) was observed when the oral hygiene kit was not included; the highest cost (CLP 9,525) was observed when the coverage of the WCP increased. The lowest effect (25.8%) was detected when the efficacy of FV decreased; the highest effect (28.9%) was detected when a discount rate was not used.

When comparing PCS without screening with counselling-only: the lowest ICER (CLP 126,331) was detected when the oral hygiene kit was eliminated, and the second lowest ICER (CLP 174,912) was when the efficacy of FV increased (decreasing the attributable risk exposed from 0.173 to 0.130). The highest ICER (CLP 1,052,081) was observed when the efficacy of FV decreased and the second highest ICER (CLP 344,267) was observed when the acceptance of FV application in the primary care setting was reduced.

11.4.6 Low, medium, and high socioeconomic status scenarios

The counselling-only intervention had a cost of CLP 2,784 per child with an estimate of 29.5% of the eligible population without caries. FV application in the primary care setting without screening (210000) presented 31.3% of caries-free population with an average cost of CLP 7,107 per child; this meant an incremental cost of CLP 4,323 per child with an incremental effect of just 18 children per 1000 treated. The cost per extra caries-free child was CLP 235,563. See Appendix B for more details.

The deterministic sensitivity analyses were very similar to the ML scenario. The only undominated FV intervention was again the application at the primary care setting without screening (210000), which was more effective and less costly than other FV interventions. The lowest effect (30.1%) was observed when the initial caries prevalence increased at the PCS. The higest effect was (33.3%) when the discount rate was not considered; the second higest effect (32.7%) was observed when the initial caries prevalence decreased at the PCS. The lowest cost (CLP 4,976) was detected when the oral hygiene kit was not included and the highest cost (CLP 9,525) observed was the coverage of the WCP increased.

The lowest ICERS always occurred for the comparisons of the PCS without screening with counselling-only. The lowest ICER (CLP 115,211) was observed when the oral hygiene kit was eliminated. The second lowest ICER (CLP 150,689) occurred when the efficacy of FV increased. The highest ICER (CLP 418,722) occurred when the efficacy of FV decreased and the second higest ICER (CLP 320,537) occurred when the acceptance of FV at the PCS decreased.

11.4.7 Best-case scenario

This scenario included the same parameters as the base case scenario with the exception that the Markov model was run for a period of 3 years beginning in 3-year-olds. This meant that variables such as initial caries probabilities, transition caries probabilities, human resources, and WCP coverage were changed. See Table Appendix B for more details. The FV efficacy was maintained at a constant rate over the follow-up period extrapolating the data reported in the literature review by one year.

Almost twenty-four percent (23.9%) of the eligible population was caries-free with the oral health counselling intervention (000000) with a cost of CLP 2,784 per child. The intervention 210000 or FV application at the PCS without screening was the only undominated FV intervention. This intervention resulted in 31.1% of the population being caries-free at an average cost of CLP 7,541 per child. Compared with counselling-only, the incremental cost was CLP 4,758 per child and the incremental effect was 7 children per 1000 treated. The cost of one additional caries-free child was CLP 66,021 (see Appendix B).

The deterministic sensitivity analysis showed that the highest average cost (CLP 12,409) was observed when oral the oral hygiene kit was included and the lowest average cost (CLP 7,010) was observed when the cost of human resources decreased in the PCS. The lowest effect (28.2%) was detected when the acceptance of FV was reduced in the PCS. The highest effect (34%) was detected when the discount rate was not included. The second highest effect (32.3%) was detected when the initial caries prevalence was decreased in the PCS.

When comparing the PCS without screening with counselling-only, the highest ICER (CLP 133,564) was observed when the oral hygiene kit was included. The second highest ICER (CLP 111,318) was observed when the acceptance of FV decreased in the PCS. The lowest ICER (CLP 54,802) was observed when the initial caries prevalence decreased in the PCS and the second lowest ICER (CLP 56,006) was observed when the coverage of the DWCP increased. See Appendix B.

11.4.8 Costs and effects in the entire preschool population

An adjustment of population, aimed to determine an estimation of effect of each intervention on the whole population (Appendix B), was performed in all interventions in the base case scenario.

This adjustment showed an increment on the effect of all interventions with respect to the results obtained from DAM. For example, intervention 110000 went from 26% to 29.3%, 110100 augmented from 25.5% to 29.1%, and intervention 210000 increased from 27.2% to 26%. Related to cost, the intervention proposed by MINSAL had a cost of CLP 3,331,715,092 and the most-effective FV intervention was (210000) CLP 1,607,838,311.

Related to the incremental effect of each FV alternative compared to counselling-only, for example, 110100 had an incremental effect of 12.3% and 21000 presented 12.1% of an incremental effect.

The cost-effective analysis that included all base case interventions (Figure 11.9) showed that both interventions in the PCS without screening (210000) and in the PSS without screening (110000) were undominated. Intervention 210000 had an incremental effect of 7,807 caries-free children with an incremental cost of CLP 1,020,407,621 with respect to counselling-only and an ICER of CLP 130,703. In contrast, compared to 210000, the intervention 110000 had an incremental effect of just 599 caries-free children, an incremental cost of CLP 1,133,026,567 and an ICER of CLP 1,893,077.

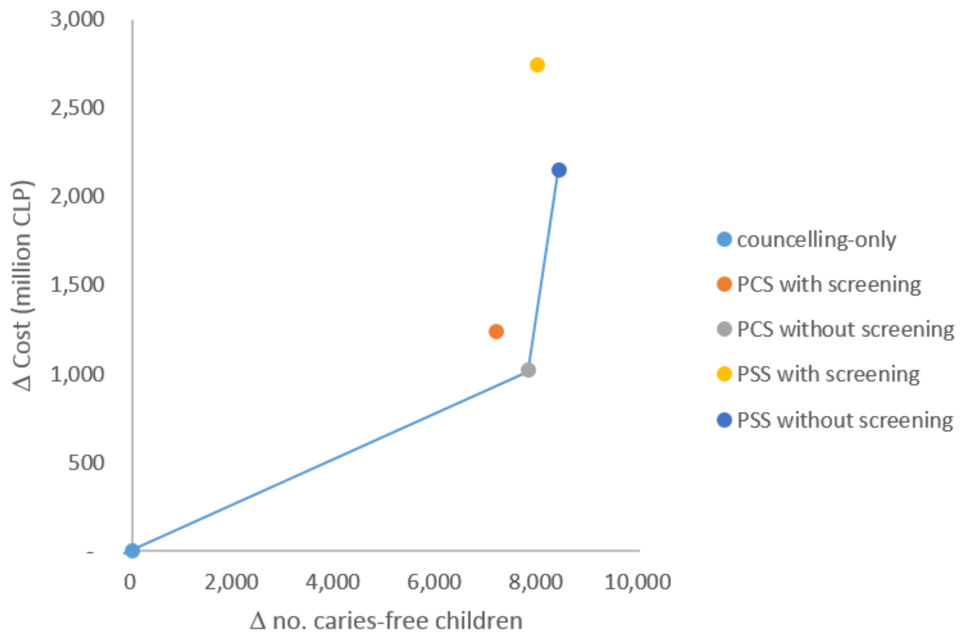


Figure 11.9. Cost-effectiveness plane in the entire preschool population.

11.5 Discussion

11.5.1 Cost-effectiveness analysis in the base case scenario

The results showed that all FV interventions increased the caries-free proportion on eligible populations, but at an additional cost compared to counselling-only. The application in the PCS with no screening was the only undominated FV intervention.

Contrary to expectations, this study did not find a large difference between the effectiveness of all FV interventions. A possible explanation for these results may be the clinical similarities between all FV interventions and the fact that all interventions used the same value of FV efficacy. As mentioned in Chapter 9, the evidence of the efficacy of FV in the caries-free population is scarce; therefore, it is not possible to improve this aspect with the currently available data.

Despite the limited impact on effectiveness, it should be noted that the analysis to date may miss important aspects of effectiveness. For example, the study does not include the effect of FV on children that already have caries, in other words, on the extension of caries disease. Further research should be undertaken to investigate such an effect.

An important finding was related to the large differences in costs between FV interventions; this difference may be given by the fact that both settings have different production costs.

When the costs were disaggregated, the greatest production cost difference was found in the cost of attendance, where the cost in the PSS was 102% greater than in the PCS. This finding is explained by the transport costs and the low productive efficiency of human resources in the PSS due to the relatively fewer children seen. This last point is relevant in the Chilean context given the scarcity of dentists in the public health system; as was explained in Chapter 4. Highly qualified (and costly) dental personnel would be utilised more efficiently by performing either preventive or restorative interventions at primary care institutions.

11.5.2 Deterministic sensitivity analysis is base case scenario

The deterministic sensitivity analyses conducted showed that the results were sensitive to the cost of human resources, presence or not of the oral hygiene kit, initial caries probability, coverage of WCP and DWCP, and FV efficacy and its acceptance in the PCS.

Initial caries prevalence

As was commented on in these results, there were two situations where an intervention delivered in the PCS (110000) was undominated was was primary care intervention (210000), and both were related to initial caries prevalence. This observation could be explained by a reduction in the effect between both settings caused by either an increment of caries prevalence in the PCS or a decrement in the PSS. Given that the difference in the initial caries prevalence between both settings is a product of different starting points, any change in such starting points would cause differences on the effect of interventions and in dominance of one intervention over the others.

The highest ICERs were detected every time when a PSS intervention was more effective than a PCS one. This phenomenon would be due to both a very small difference in effect and a large difference in cost between both settings. Such differences cause the production costs of an extra caries-free children to be extremely large. In other words, it might be more effective but more costly for MINSAL to perform the FV application in the preschool setting. Nevertheless, a note of caution is due here since the difference of cost between both settings is large.

Contrary to expectations, the results also showed that when initial caries prevalence in the PCS was reduced, the ICER was not greatly altered (it reduced by 6%) between the PCS without screening and PCS with counselling-only. However, the impact of initial caries prevalence on effects in the PCS was extremely important; both lower and upper confidence interval bounds caused the highest (28.9%) and lowest (25.6%) percentage of caries-free children, respectively. These findings lead to the question, what would be the result if FV was applied in a population with an initial caries prevalence even smaller than that used in this deterministic sensitivity analysis such as in younger populations, for example.

Fluoride varnish acceptance

Another parameter that caused the ICER to increase was FV acceptance in the PCS. When acceptance was reduced, the ICER increased by 34% with respect to baseline analysis (base case scenario). This is a complex topic because there are multiple reasons why children would reject the application. However, as was previously explained in this chapter, there is little evidence on this topic. For example, Humphris and Zhou (2014) found, in their cross sectional study performed in Scotland, that both an initial anxious behaviour and no previous experience of children (of FV application) increased the child's refusal rate. They also found that some dental nurse behaviours could affect the child's response. Undoubtedly, further work is required to establish a more accurate value of FV acceptance rate.

Oral hygiene kit

The analyses showed that the elimination of the oral hygiene kit reduced the ICER by 51%, compared to baseline analysis. The rationale for oral hygiene kit elimination was mostly based on several Cochrane literature reviews. One review by Marinho et al. (2013) excluded any other fluoridated-based measure. Consequently, given that this study was used as a reference to obtain the FV efficacy for this thesis, the effect of FV used did not consider the effect of fluoridated toothpastes. A second review performed by Cooper et al. (2013), concluded that there is also insufficient evidence about of school-based behavioural interventions, which includes toothbrushing, in dental caries reduction.

According to a third Cochrane review (Walsh et al., 2010), there was also little evidence about the effect of fluoridated toothpastes on caries prevention in primary dentition, either at dmft or dmfs levels. Similar results were found by Wright et al. (2014) in another systematic review. They concluded that there is limited scientific evidence to support the fluoridated toothpaste efficacy in children younger than 6 years old.

Regardless of the setting, the elimination of the oral hygiene kit would allow MINSAL to realise an important amount of money savings, compared to baseline analysis. For example, CLP

538,142,488 (19.6%) for the PSS without screening intervention and CLP 521,588,915 (32.4%) at PCS without screening intervention, during a period of two years.

Well-child programme coverage

When the WCP coverage was reduced, the ICER decreased by 18% compared with the baseline analysis. This finding could be explained by the multiplicative effect of all transition probabilities that causes a non-linear relationship between costs and effects. For example, when the number of children covered by the WCP decreases, the number of eligible children during all cycles also decreases; such a reduction would cause both an important reduction in cost and a small reduction in effect, which causes a reduction in the ICER. In the same way, an increment of well-child coverage causes an increase in the value of the ICER.

Therefore, given that both effects and costs do not have a linear relationship, MINSAL should expect an important increase in the ICER when coverage at the PCS increases because this will cause a small increment in effect and a big increment in cost.

Human resources

The cost of human resources in the PCS had an impact on ICER as well. A reduction in the human resource costs led to the ICER dropping by 14% compared with the baseline analysis. This is mainly because the human resources item represents approximately 30% of the total cost of all FV interventions. So, any move to reduce this component would reduce the ICER.

Something could be done in the primary care setting; however, it is necessary to consider two specific characteristics of this setting. First, as was commented on in Chapter 8, the primary care setting considers that FV applications are performed exclusively by dentists. Second, the human resources costs in the PCS includes both dentists and dental assistants. Therefore, the only alternative to reduce human resources costs would be through the participation of other less costly health professionals. This might be achieved by incorporating either nurses or physicians or both into the application process; both professionals do not require a health assistant. Based on Chapter 8, a legal modification would be required to incorporate the nurses without the need of a prescription. Without this, the only alternatives to reduce staff costs would be the substitution of physicians for dentists.

Efficacy of fluoride varnish

As was expected, the efficacy of FV, measured as the probability of having caries given that FV was applied (P(C+|FV+), was also significant in both directions; as efficacy decreased (or upper value), ICER increased, and vice versa.

Transport

Interestingly, it was initially thought that transport costs would play a significant role in the definition of the most cost-effective intervention. However, the results were not sensitive to the value of this parameter over the ranges considered, even when the transport cost was equal to zero.

Other analyses

An attempt was made to use upper and lower bound estimates from international studies to investigate how the impact of such data would have on the decision model. However, except for FV varnish efficacy, the variables that were significant in the deterministic analysis were almost exclusive of the Chilean context. Consequently, the comparison with the international literature was not so straightforward. This argument was supported by the publication of the results of the NIC-PIP study (O`Neill et al., 2017); for more information, see the discussion of the best-case scenario in this section. Regarding FV efficacy, the base case scenario simulation was run using the upper bound estimate found in the literature.

11.5.3 Probabilistic sensitivity analysis is the base case scenario

The average values of the probabilistic sensitivity analysis presented are basically the same results than baseline CEA, with important differences in cost and tiny differences in effect between all interventions.

On the contrary, as can be seen in the scatterplot (Figure 10.2), the iterations of FV interventions had a small variation in cost and a large variation in effect. This variation in effect is due to the small effect of FV on the caries-free population. This means that a small variation in any other parameter (e.g., coverage or attendance) would cause a considerable variation in the effectiveness of an intervention. This would lead one to think, uncertainties included, that the difference between the interventions is not given by the effect, it is given by the cost instead. MINSAL should consider this last point carefully, to avoid spending money unnecessarily.

Correspondingly, the cost-effectiveness acceptability curve showed that both preschool setting interventions have a very low probability of being cost-effective.

11.5.4 Fluoridated water cost-effectiveness analyses

The ex-post internal validity test showed a 29% difference with respect to the natural history of caries (NHC). This important difference cannot be only explained as a mathematical artefact as the product of the conversion of caries prevalence into a transition probability. This explanation was given for the differences found in the other non-fluoridated water scenarios. For more details, see Appendix B.

Some possible explanations for fluoridated water scenarios could be as follows:

- An underdiagnosis in caries in non-fluoridated zones (Biobío Region) in 6-year-olds.
- An overdiagnosis of caries in the Biobío Region in both 2- and 4-year-old populations.
- Natural history of caries is not precise for non-fluoridated zones because one cannot always precisely state which area a person is in.
- Predicted DAM estimates were underestimated because of the way that the transition probabilities were estimated.

It is possible that one (or a combination) of these possible explanations has caused the difference detected between the expected and obtained caries prevalence. Considerably more work would need to be done to explain this finding further, which would be out of the scope of this thesis.

In conclusion, the data regarding fluoridated water were not appropriate for the decision analytic model. Consequently, it is not possible to draw any policy conclusions.

11.5.5 The impact of socioeconomic statuses

The only undominated FV intervention, in both ML and HML CEAs, was FV application in the primary care setting without screening. Even though that population of both scenarios have a lower caries prevalence, the incremental effects of such interventions compared with counselling-only were just 1.9%, almost half of the effect of the baseline CEA. This finding could be caused by the lower FV efficacy in both scenarios. This result is in agreement with those obtained by Jiang *et al.* (2014) who found no significant effect of FV in a medium-high income preschool population.

The deterministic sensitivity analysis was also similar in both scenarios. The more important variable here was the cost of human resources in PCS, both lower and upper bounds had an important impact on ICER. Interestingly, the analysis of preschool coverage, the variable that is highly related to socioeconomic status, did not cause any significant change in ICERs.

11.5.6 What if? The best-case scenario

The best-case scenario presented, was as expected, the one with the highest effect (7%) and the lowest cost of all scenarios considered. The explanation for these findings is based on two facts, one related to a very early start of the programme and the other associated with the reduction of cost. Interestingly, the percentage of caries-free population from counselling-only was 32.2%, which is very close to MINSAL's goal.

Also, the time frame of this simulation coincided with the study of O'Neill *et al.* (2017) shows the results of the NIC-PIP study (Tickle *et al.*, 2011). As was commented on in Chapter 3, this RCT study, with a CEA included, evaluated the biannual application of fluoride varnish in caries-free children aged 2-3 years in 22 NHS dental practices in Northern Ireland with a follow-up period of 3 years. This study reported an incremental effect of 5%, which is close to the 7% obtained in this simulation. With regards to the cost prevented from converting a caries-free child to caries (ICER), the NIC-PIP study estimated an average cost of £2,093, and this simulation estimated an average cost of £76.2. However, due to differences in cost structure, the cost comparison between both studies is not straightforward.

An unanticipated and remarkable finding was that the PCS was more effective and less costly than the PSS, even when FV acceptance was reduced to 50%. In other words, even if cooperation in young children is low in the PCS, we would obtain better results than the PSS. Another important finding in the sensitivity analysis was that despite including the oral hygiene kit, the PSS was always less effective and more costly than the PCS. This could be explained by the large difference in caries prevalence between both settings at cycle 0.

The variable human resources in the PCS was also significant and both lower and upper bounds represented different human resources (applicators) in the deterministic analysis. The lower bound represented the less expensive human resource (nurse) and the upper bound simulated the most expensive human resource (dentist plus dental nurse).

Due to an extrapolation of FV effect that was used in this CEA, these results need to be interpreted with caution. However, it is clinically plausible to assume that the efficacy of FV calculated for 6 months can be extrapolated over three years. This assumption was based on two arguments, the lack of contraindications and the lack of evidence about a decrement of efficacy when the product was used for more than two years. Marinho et al. (2013) concluded after several univariate meta-regression analyses that there is no evidence that the relative effect of FV was affected by the length of follow-up. Consequently, this finding has important implications for developing an earlier FV application programme. Undoubtedly, more studies are required in this area.

11.5.7 Real costs and effects

Given than not one of the FV interventions covers the entire preschool population, as was MINSAL's objective, some adjustments were done to allow the effect of each intervention in the population to be determined. To get this effect estimation, all caries-free children had to be included. This required including those caries-free children that are the product of the effect of FV and those that would be naturally occurring in the populations (or caries-free children in the non-eligible population). The incorporation of the latter one in the analysis showed that the PSS without screening (110000) intervention became undominated and produced an increment on effect of all interventions as well.

PSS without screening was more effective but more costly than PCS without screening (210000). The incremental effect was so small that the production cost of one extra caries-free children, compared to 210000, was 1,448% higher than the production cost of PCS without screening compared to counselling-only.

As was commented on earlier, the incorporation of caries-free children caused changes in the effect of all interventions. The more manifest changes were those related to the PSS, where the caries-free children in the non-eligible population were almost equal to the number of caries-free children caused by FV application. This phenomenon could be explained by the difference in caries prevalence between socioeconomic groups, where those populations belonging to medium and, especially, high socioeconomic groups have more caries-free children. More studies are required to explain this finding further.

In other words, the relative effectiveness improvement in the PSS would be related to the existing oral health inequalities. Also, given that the eligible population is bigger in the primary care setting, selecting any primary care setting intervention would potentially allow more children to benefit than any preschool setting alternative. Therefore, such interventions would potentially reduce oral health inequalities. MINSAL should consider this point carefully.

All interventions produced results far from MINSAL's goal of increasing the caries-free population by 35%. The most effective (but most costly) intervention was the application at the PSS without screening, and this intervention resulted in just a 13% incremental effect compared with counselling-only.

11.5.8 Implication for health policies

Given that all cost-effectiveness analyses, apart from the best-case scenario, showed a small increment in the number of caries-free children and an important increment in cost, MINSAL should carefully consider the incorporation of any FV interventions. To help make judgements, MINSAL could use a threshold value for the cost per caries free child. Unfortunately, there is no evidence about how much the Chilean (or any) society is willing-to-pay for a 6-year-old caries-free child. Further studies, which take this point into account, will need to be examined.

Based on this estimation and, from a pure financial perspective, the Chilean Government would save millions of pesos by just providing counselling-only interventions. However, as was noted, this study does not include the effect of FV on the extension or severity of caries, measured as dmft index for example. Rather, it assumes that any decay is equally bad, regardless of the extent or severity. More studies about the extension or severity of caries are needed, such studies would allow us to estimate caries progression (using dmft for instance) for those children who have existing disease.

The Chilean Government could reduce the cost of a fluoride varnish programme by opting for a more cost-effective intervention compared with the proposal from MINSAL. However, as was analysed in Chapter 3, except for fluoridated water which is already in use, no other intervention is supported by strong evidence of efficacy.

In the case of MINSAL deciding to launch a nationwide FV programme, they should keep in mind the following points:

- The simulations showed that PCS interventions were almost always the more effective and less costly ones. Also, in those simulations where a preschool setting intervention was undominated, very high ICERs were estimated. Therefore, MINSAL should consider the primary care alternatives and avoid application in the preschool setting. This would reduce the costs and it would also reach more children. This would theoretically reduce oral health inequalities, even more than interventions provided in the preschool setting.
- Based on this study, it is possible to say that increasing the coverage of a possible nationwide FV programme to medium and high socioeconomic statuses children would not produce an important number of caries-free children due to the lesser effect of FV on children from higher SES backgrounds. Therefore, the proposed incremental incorporation of SES into the programme (Chapter 4) should be discarded by MINSAL.
- Interventions with screening were always dominated; this result may be explained by the fact that screening had no effect on caries-free populations and only added an extra cost to the programme. So, MINSAL should not consider screening as part of the FV application.
- A reduction in the initial caries prevalence had an important impact on the undominated FV intervention (210000); it can therefore be assumed that beginning applications earlier would improve the effect of FV. MINSAL may explore alternatives where the application of FV begins even earlier.
- The impact of human resources on ICER was substantial in all CEAs. MINSAL would save an important amount of money by allowing the participation of other non-dental related health professionals. Legally speaking, physicians could apply FV with no problems. However, nurses would require a prescription to perform the application (Chapter 7). To solve this problem, FV application should be part of a nationwide public health programme, compulsory for all of the population, as vaccines are (MINSAL, 2015). However, this alternative would generate another problem; MINSAL would be required to treat the whole population, which, as was previously discussed in this section, is less effective and more costly than the base case scenario. Consequently, MINSAL should explore the legal framework for this type of change.

- Basically, any reduction in production costs of primary care interventions will improve the productive efficiency and reduce the ICER. One area to reduce cost is by not supplying the oral hygiene kit. Keeping in mind that there is limited scientific evidence (Walsh *et al.*, 2010;Wright *et al.*, 2014) to support fluoridated toothpaste efficacy in preschool children as well; MINSAL should consider re-evaluating its policies, at least, in reference to the use of fluoridated toothpaste in a nationwide FV programme.
- Finally, this study showed the impact of coverage of the WCP. Consequently, MINSAL should try to maximise such coverage. An interesting point here is the fact that FV may increase such coverage, acting as an incentive to take children to the WCP. Further work is required to test this hypothesis.

11.5.9 Weaknesses and strengths

To run these models, specific data about transition probabilities of caries prevalence were required and, given the limited available data, two important epidemiological assumptions were made to obtain such transition probabilities. First, the natural history of caries was obtained from several studies assuming that they were a single cohort study; therefore, a proxy of natural history of caries was used (Chapter 5).

Second, this data was converted into a proxy of transition probabilities assuming caries prevalence had a constant six-month rate in 1- to 6.5-year-olds. This assumption could lead to potential bias in both directions, and this is the main weakness of this thesis. Available data does not always fit with research requirements and, as was highlighted by Mariño *et al.* (2013), this is a significant limitation of an important proportion of economic evaluations performed in dentistry.

This weakness highlights the need for longitudinal epidemiological programmes. An alternative approach to obtain the natural history of caries may be using serial epidemiological studies or through administrative data. However, such data are not easy to generate in the Chilean context, especially in the dental area (MINSAL, 2017a).

Another weakness is related to problems with the data detected in the fluoridated water scenarios that led to such scenarios being dropped from the analysis. As was explained in the discussion, trying to explain in more detail the causes of this finding is out of the scope of this thesis.

An important weakness of this study was that data for some variables came from few sources, for example, FV efficacy in the baseline CEA (Weintraub *et al.*, 2006), FV acceptance, and informed consent. A special circumstance was the cost of human resources that came from a single study performed for FONASA by the Pontifical Catholic University of Chile (PUC, 2012). However, this study was selected following the indications of the Chilean Methodological Guideline for Economic Evaluations of Health Interventions (MINSAL, 2013c)

Despite the fact that all FV interventions were more effective than counselling-only, a note of caution is due here since the CEAs were run under the Markovian assumption that caries-free children at the end of cycle 4 received 4 FV applications or doses. Nevertheless, there is no way to assure that children have received all doses (Chapter 4). This assumption means that getting poorer outcomes is still possible. This is an important issue for both future research and for decision-makers.

On the other hand, the use of a huge and validated Chilean dataset (CASEN survey), as well as well-known Chilean studies (Ceballos *et al.*, 2007;Soto *et al.*, 2007a;Soto *et al.*, 2009;Hoffmeister *et al.*, 2010;PUC, 2012), makes the study relevant to decision-makers. The utilization of all these studies means that this research used the best available Chilean data.

Also, this study simulated numerous FV interventions using several sources of data. This was particularly important because it allowed this study to model not just clinical effects, but health and educational policies as well. This would be highly relevant for policies that require the collaboration of several Chilean ministries.

Another important strength of this study is its originality. There are only a few studies using decision analytic models to evaluate dental programmes (Chapter 3) and even fewer economic evaluations about the effect of FV (Mariño *et al.*, 2013). To the best of the author's knowledge, this is one of the first health economic analyses performed to study the effect and cost of FV on a caries-free population (dmft = 0). The closest study, methodologically speaking, was performed by Quinonez *et al.* (2006) who used a Markov model to simulate the effect of FV on children during a well-child visit; however, the results cannot be compared given that the authors used a different definition of caries-free children (d = 0) compared to this thesis and used different outcomes (the number of months without cavities per child) as well.

This research was able to evaluate ex-ante FV interventions. The model capability permitted the evaluation of more realistic scenarios, avoiding costly and time-consuming clinical trials. Moreover, the decision analytic models could evaluate the heterogeneity of several caries-free populations and, given the top-to-bottom decision-making model followed by the Chilean Ministry of Health, such capability could be extremely important for decision-makers.

11.6 Conclusions

This research provided the simulation of the performance of FV in realistic scenarios incorporating important aspects of health and education policies. The effect between all FV interventions was quite similar and small compared to counselling-only. The PSS was always more costly than the PCS. Application in the PCS without screening was the most cost-effective intervention.

Although none of the interventions reached Chilean Ministry of Health's (MINSAL) goal of 35% of children being caries free at 6 years of age, the results of this study suggest that the Chilean Government could reduce the cost of a possible fluoride varnish programme opting for a more cost-effective intervention compared with the proposal done by MINSAL . Also, MINSAL could get even better value for the money if they started the application at earlier ages, eliminated the oral hygiene kit, and incorporated non-dental professionals. The methodology can be useful for both policy and decision-makers.

Chapter 12. General Discussion and Conclusions

12.1 Introduction

The aim of this thesis was to analyse a possible nationwide FV application programme that seeks to increase the number of caries-free children in the preschool Chilean population and to demonstrate how health economics methodologies, especially in economic evaluations, can aid in decision-making in oral health.

Various studies were performed in order to obtain data to be used as inputs to the main study; a decision analytic model (DAM) study, where several FV interventions, including an intervention proposed by Chilean Ministry of Health (MINSAL, 2012c), were compared with a counselling-only (or do-nothing) alternative.

The objective of this chapter is to summarise all empirical chapters and show how they are linked. Also, it analyses the strengths and limitations of this thesis, its contributions, and its implications. Finally, this chapter answers the aims of this thesis.

12.2 Summary of empirical chapters

Chapter 6

To simulate the impact of FV, a proxy for the natural history of caries in Chile was determined using epidemiological data. Several datasets from published and unpublished nationwide cross-sectional studies were included.

This study showed no clear difference between genders. Statistical differences were observed between SESs, at both regional and nationwide levels, where the children attending public schools presented the lowest percentage of caries-free population. The caries-free population decreased from 2 to 6 years of age. This decrement occurred in all SESs but was less evident in the high SES and in those children who attended to private schools. This data was used to obtain transition probabilities in Chapter 11.

Differences in caries prevalence between geographic zones were also detected.

Chapter 7

Due to the differences between geographic zones detected, an econometric analysis was performed to determine if such differences could be explained. As fluoridated water was one of the potential influencing factors found in the epidemiological analysis, the analysis was performed looking for the relationship between water fluoridation and the prevalence of caries, controlling for socioeconomic status and other risk indicators.

This study demonstrated, in the Chilean context, a relationship between fluoridated water and caries prevalence; consequently, the detected difference between Chilean regions found in the epidemiological study can be partially explained and considered as heterogeneity (Gray *et al.*, 2011). This finding justified the incorporation of fluoridated water as a scenario in the decision analytic model.

Chapter 8

Chapter 8 outlined a new method to select relevant interventions for the delivery of FV application in the preschool Chilean population during the later preschool ages. This approach was grounded in a sequence that allowed an order to be given to the entire process and was based on combinatory sequences that permitted consideration of all theoretically available interventions as well.

This chapter provided four interventions, two in the PCS and two in the PSS. PSS considered the FV application with and without screening. The PCS considered applications with and without screening as well.

Chapter 9

The objective of the decision analytic model (DAM) of this thesis was simulate the effect of FV on caries-free population; hence, a FV efficacy value on caries-free populations was required. This chapter was conducted to determine such a parameter of efficacy. Similarly, this chapter analysed the safety and acceptability of FV.

The Cochrane systematic review performed by Marinho *et al.* (2013) was used as the main source but was updated to March 2015. The only outcome measured was incidence of caries in primary dentition from a caries-free baseline, in other words, a dmft > 0 from a baseline of dmft = 0.

Meta-analyses, with data on the effect of FV on caries-free populations only, were performed using the incremental incorporation of SES proposed by MINSAL. They showed that efficacy of FV decreased as the analysis incorporated more advantaged populations.

Chapter 10

This chapter reported on the costs of interventions considered within this thesis. Two main sources were used here: a costing study commissioned by Health National Fund (FONASA) that was performed by the Department of Public Health of Pontifical Catholic University of Chile (PUC), and a public database that is part of a public system for procurement of goods and services (ChileCompra).

Given that both PCS and PSS have a different cost structures, they were studied independently. The costs studied were, among others, those associated with human resources, equipment, instruments, FV, oral hygiene kit, transport of personnel, and indirect costs.

Chapter 11

This was the main chapter of this thesis and was performed with the objective to create a mathematical framework able to estimate the outcomes of several FV interventions.

Three scenarios were created based on the findings of Chapters 4 and 8, as well as, the incremental incorporation of type of schools (proxy of SESs) proposed by MINSAL. Scenarios included: low SES status only or baseline scenario (L); medium and low SESs (ML); and low, medium, and high SES (HML). Two scenarios were based on findings of Chapter 6 and associated with fluoridated water. A sixth scenario, or best-case scenario, was tested based on the results of the baseline scenario.

In the baseline scenario (L), CEA showed that the effect in all FV interventions were slightly better that counselling-only, and there was almost no difference in effectiveness between the two settings as well; however, the primary care setting was clearly less costly than the preschool one. The most cost-effective and only undominated FV intervention was the application of FV at the PCS without screening. All other FV interventions were less effective and more costly than the former.

The incremental effect of the application of FV in the primary care setting without screening was only 3.7 % more effective than counselling-only with an incremental cost of CLP 7,620 per child and an ICER of CLP 130,849 per extra caries-free child.

A deterministic sensitivity analysis showed that the ICER decreased if other health professionals, rather than dentists, provided the FV application. Also, increasing the starting age of the application raised the incremental cost-effectiveness ratio. The probabilistic sensitivity analysis presented the same average results as the baseline CEA; however, such analysis showed that FV interventions presented a wider range of uncertainties related to effects.

The FV intervention in the preschool setting without screening was also the most cost-effective and only undominated FV intervention in ML, HML, and best-case scenarios. Due to limitations with data, both fluoridated water related scenarios were eliminated.

An adjustment was performed to analyse the impact of each intervention in the Chilean context, i.e., the effect in the entire preschool population and the total cost of each intervention. The results of a cost-effectiveness analysis showed that two FV interventions, in the primary care setting without screening and in the preschool setting also without screening, were undominated. The former one had a total cost of CLP 1,607,838,311 with a total effect of 29% and an ICER of CLP 130,703 per extra caries-free child compared with the counselling-only alternative; the latter one, presented a total cost of CLP 3,331,715,092 with a total effect of 29.3% and an ICER of CLP 1,893,077 per extra caries-free compared with the primary care setting without screening intervention.

The effects produced by all FV interventions were far from MINSAL's goal of increasing the caries-free population by 35%. The most effective but not least expensive FV intervention, in the PSS without screening, presented an incremental effect of just 13% compared with counselling-only.

12.3 Strengths and weaknesses of research

12.3.1 Strengths

A key strength of the present study, which can be considered as a systematic analysis of costs and effects of a possible nationwide FV programme, was the incorporation of different areas of knowledge such as dentistry and health economics for example. This research was made possible by integrating several sets of analytic tools incorporated from different fields and methodologies such as statistics, epidemiology, econometrics, evidence-based dentistry, costing, modelling, and economic evaluation.

Despite the numerous sources of data on which this thesis was based, this work includes the best reliable data available. To obtain these data, this thesis followed validated methodologies and Chilean standards such as the Cochrane methodology for systematic reviews (Higgins and Green, 2011) and the Chilean guideline for economics evaluations (MINSAL, 2013) for example. Furthermore, the fact that most of the data come from Chilean official sources, such as natural history of caries and costs for example, ensures the validity of this study in the Chilean context.

This is not the first study where the cost-effectiveness of FV has been evaluated using a Markov model. For example, in a study performed in North Carolina-USA, Quinonez *et al.* (2006) evaluated FV during attendance to a Medicaid well-child appointment. However, this study included clinical data only and used the number of months without cavities per child as the outcome. Such an outcome is very difficult, if not impossible, to use in a public health programme because it is both difficult to measure and lacks of clinical significance. On the other hand, the DAM used in this thesis utilised an outcome with a high clinical significance (caries-free). Also, this is the first DAM that includes health and educational variables.

During the execution of this thesis, a pilot study (RCT with an embedded CEA) of FV in a caries-free preschool population was performed in Northern Ireland (O'Neill *et al.*, 2017) and, the results were published at the beginning of 2017. This study found just 5% efficacy after 3 years of biannual application of FV. This value was close to the 7% detected in the simulation of the best-case scenario, which also had a follow-up period of 3 years.

On the other hand, this thesis is the first study that analyses the effects and costs of FV in a caries-free population in a broader context, considering both health and educational policies. Furthermore, this thesis has allowed the construction of a flexible model that would be useful to evaluate future changes in both such types of policies.

This is a very policy relevant piece of research and directly addresses questions that MINSAL should be answering. Similarly, this thesis has demonstrated the prediction capability of decision analytic models in dentistry allowing, as was suggested by Pitts *et al.* (2011) and

Petersen and Kwan (2011), a reduction in the implementation gaps between clinical sciences and public health policies.

12.3.2 Weaknesses

The main weakness of this thesis was related to data. For example, the lack of prospective epidemiological studies meant that proxies needed to be used: both a proxy of natural history of caries and the type of school as a proxy of socioeconomic status. The former led to work with a proxy of transition probabilities. As was discussed by Mariño *et al.* (2012), cross-sectional studies are usually used in dental economic evaluations as the source of epidemiological data.

In another example, the scarce number of studies about FV efficacy meant that it was necessary to run the base case scenario based on a single study. The use of a single study as source of efficacy is not a problem unique to dentistry. For example, in a systematic review of the quality of cost-effective analyses in Spain, Catala-Lopez *et al.* (2016) described that 39% of analyses are based on a single study.

This study relied heavily on epidemiological data, meaning that any error in such data caused important mis-estimations in the outcomes. An aspect related to this subject concerned a problem related to the influence of fluoridated water related data; this implied excluding a large volume of existing work.

Another weakness of this thesis was the model itself. Given that models assume that all children receive every FV application, the simulations represent the most optimistic scenarios. This would mean that the effect of FV on caries-free population would be even less. Considerably more work will need to be done to determine what would happen in scenarios where children did not receive all FV applications.

The public health system perspective, suggested by the Chilean guideline for economic evaluation (MINSAL, 2013c), used in this thesis meant that this study did not consider a wider point of view, and can be considered as a limitation. More studies are required to understand, for example, how the cost incurred by parents taking their children to well-child appointments would affect the cost-effectiveness of FV interventions. It may be possible that parents are not willing to (or cannot) take children to every application.

12.4 Contribution of the thesis

This thesis has contributed, through Chapter 7, to the establishment of an association between fluoridated water and caries incidence/prevalence in the Chilean context. Some studies (Mariño, 2013;Olivares-Keller *et al.*, 2013) have analysed the relationship between fluoridated water and caries prevalence in Chilean school populations comparing caries prevalence pre- and post-fluoridated water implementation in very specific areas of the country. However, as was stated by Quinteros (2016), studies that quantify the benefits of reducing the incidence of caries in the population with fluoridated water in Chile are not available. This thesis may be the first step in such a direction.

The results of this chapter were presented in two conferences, the 25th Congress of the International Association of Paediatric Dentistry (Glasgow, 2015) and 35th Conference of the Spanish Health Economics Association (Granada, 2015). Documents in Appendix C, show the posters presented at both conferences.

Interestingly, with the exception of Weintraub *et al.* (2006) and Tickle et al. (2016), there are no studies evaluating the effect of FV on caries-free populations. This thesis evaluated, through a systematic review and meta-analysis, the existing evidence about the efficacy of FV on caries-free populations. As was discussed in Chapter 8, this is the first systematic review on this topic.

Several guidelines and reviews, such as Husereau *et al.* (2013a) and Rudmik and Drummond (2013) for example, suggest using all relevant comparators including "do-nothing" and "current-practice" if they are suitable. The problem with this approach is that they did not specify how such comparators must be chosen.

Assuming that most economic evaluations have few possible clinical alternatives and enough data to be used as imputed parameter, the comparator selection should be relatively easy. However, in those cases where the economic evaluation considers variables not directly related to clinical practice, such as health and education policies for example, the number of plausible alternatives may be excessive. This research provides a framework for the exploration of a new methodology to obtain relevant interventions to be compared, helping researchers to systematise the search of such comparators.

In the Chilean context, this thesis determined of the small effect of FV interventions on caries-free populations and estimated the impact of FV interventions in both FONASA (public health insurance) and public school populations. This information has been discussed (MINSAL, 2017a) with the Department of Oral Health of the Chilean Ministry of Health and more discussion is expected to follow in the near future. In other words, this thesis should have a direct impact on decisions that affect the Chilean population.

The present study is particularly valuable for estimating costs and effectiveness of FV interventions in realistic scenarios as well as contributing to the incorporation of economic evaluations in dentistry. This work was orally presented at the International Association for Dental Research General Meeting (Seoul, 2016). More details can be found in Appendix C.

12.5 Implications for policy

The results of this research support the idea that the use of FV in the later stages of preschool education is not a good method to increase the caries-free children population. In other words, MINSAL should be thinking about a different programme. Unfortunately, the evidence shows that few interventions are both effective and safe for preschool children. More research is required here.

MINSAL should explore programmes that deliver care to very young children as Childsmile Practice does. In this programme, children as young as 6-month-olds are seen either at general dental service practices or primary care salaried services (Macpherson *et al.*, 2010). However, replicating such a programme in Chile is not so straightforward because the Chilean public health sector would not be able to absorb the demand; consequently, MINSAL should explore how to incorporate the private health sector first.

The results of this study indicate that the incorporation of all the Chilean preschool populations, i.e., from all socioeconomic statuses, into a nationwide FV programme would not be recommended under any circumstance. The finding also suggests that the most cost-effective FV intervention was in both the PCS (without screening) and in children of low socioeconomic status. Consequently, in the case that MINSAL decides to run a nationwide programme anyway, they should focus on this intervention and this socioeconomic status rather than other alternatives.

Based on this study, both effects and costs can be improved in the most cost-effective intervention: in the former case, through the inclusion of younger children; and in the latter case, by eliminating the oral hygiene kit and allowing the participation of other health professionals in the application of FV.

The involvement of other health professionals has already been supported by other investigations such as in Achembong *et al.* (2014) and Taylor et al.(2014) for example. However, such incorporation would not be completely viable under the current legal framework; thus, MINSAL would have to modify the legal framework first.

Even more importantly, this study strengthens the idea that economic evaluations of health interventions should become the standard in Chile. This would allow the analysis of the health problem (and solutions) from a wider perspective, helping to make the best decisions.

12.6 Implications for further research

As was commented on earlier in this chapter, the main weakness of this study was related to the lack of Chilean longitudinal epidemiological data, which led us to use several assumptions. This study highlights the need for having longitudinal epidemiological surveys, serial epidemiological studies, and more administrative data. This would allow construction of more accurate models facilitating both research and decision making. More sources of epidemiological data should be explored.

As was commented on above, MINSAL may explore in more details the role, feasibility, and benefits of including other health professionals. Further research might explore the application of FV in earlier stages of the WCP as well.

It would be also interesting to assess other potential benefits of FV, for example, the reduction of caries progression in the primary dentition and the relationship between other types of interventions alongside FV application such as the use of fluoridated toothpastes for example. This may require the development and evaluation of complex health interventions to promote the use of fluoridated toothpastes.

Another area of future research could be the participation of parents in this preventive intervention, for example, to investigate if FV would work as an incentive to take children to

WCP appointments. This topic could be explored through discrete-choice experiments, as demonstrated by Clark *et al.* (2014).

In a broader context and in a negative way, this study also highlights the lack of evidence about the effect of FV in caries-free children. This is important for two reasons: the first is related to the increasing number of this type of children, mostly in developed countries; the second one is associated with the fact that increasing this population has been a heath objective of several countries. Researchers and governments should be aware of how to maintain and increase the proportion of such children so they can understand how preventive procedures specifically affect such populations.

12.7 General conclusion

The economic evaluations performed in this thesis conclude that the use of FV as a method to increase the Chilean preschool caries-free population during the last preschool ages, has a small incremental effect and a large incremental cost compared with a counselling-only alternative. Thus, from an economic perspective only, the use of fluoride varnish in a nationwide programme is not recommended.

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Appendices

Appendix A. Figures

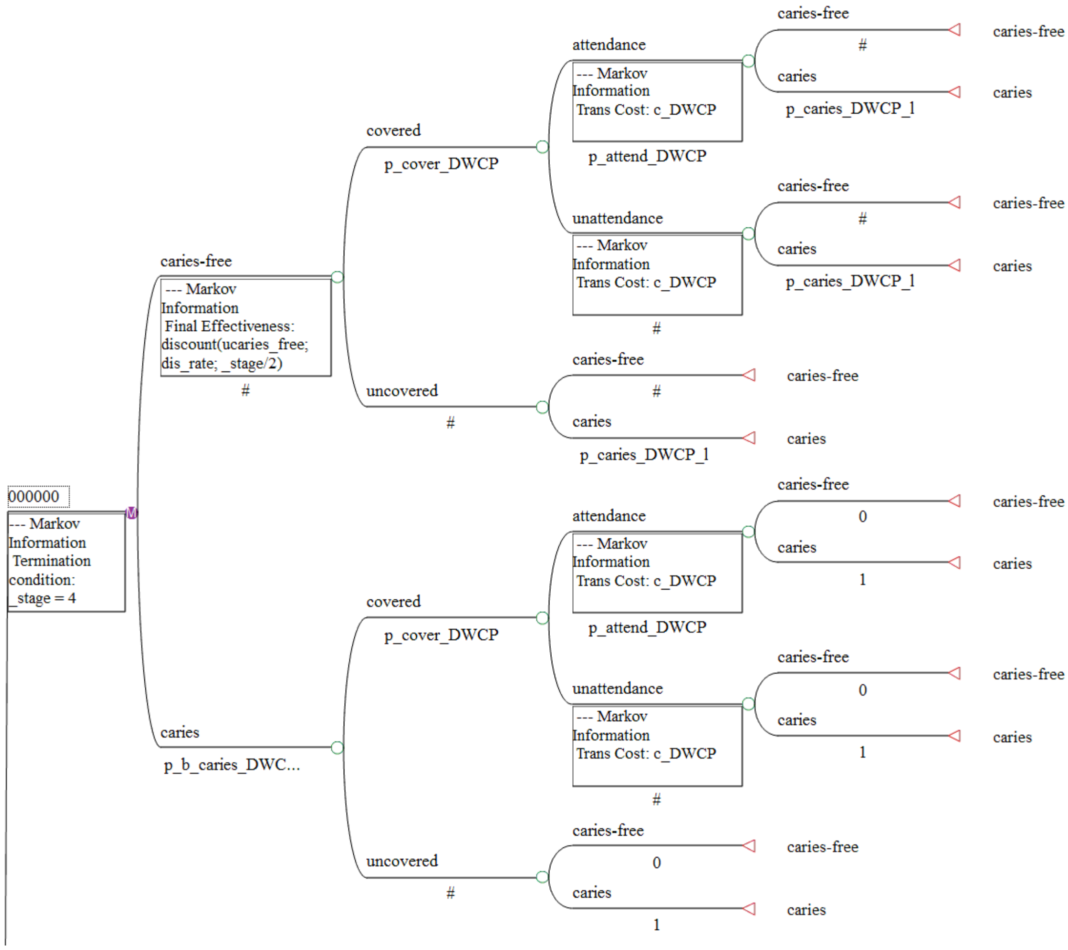

Figure A.1. Counselling-only (000000).

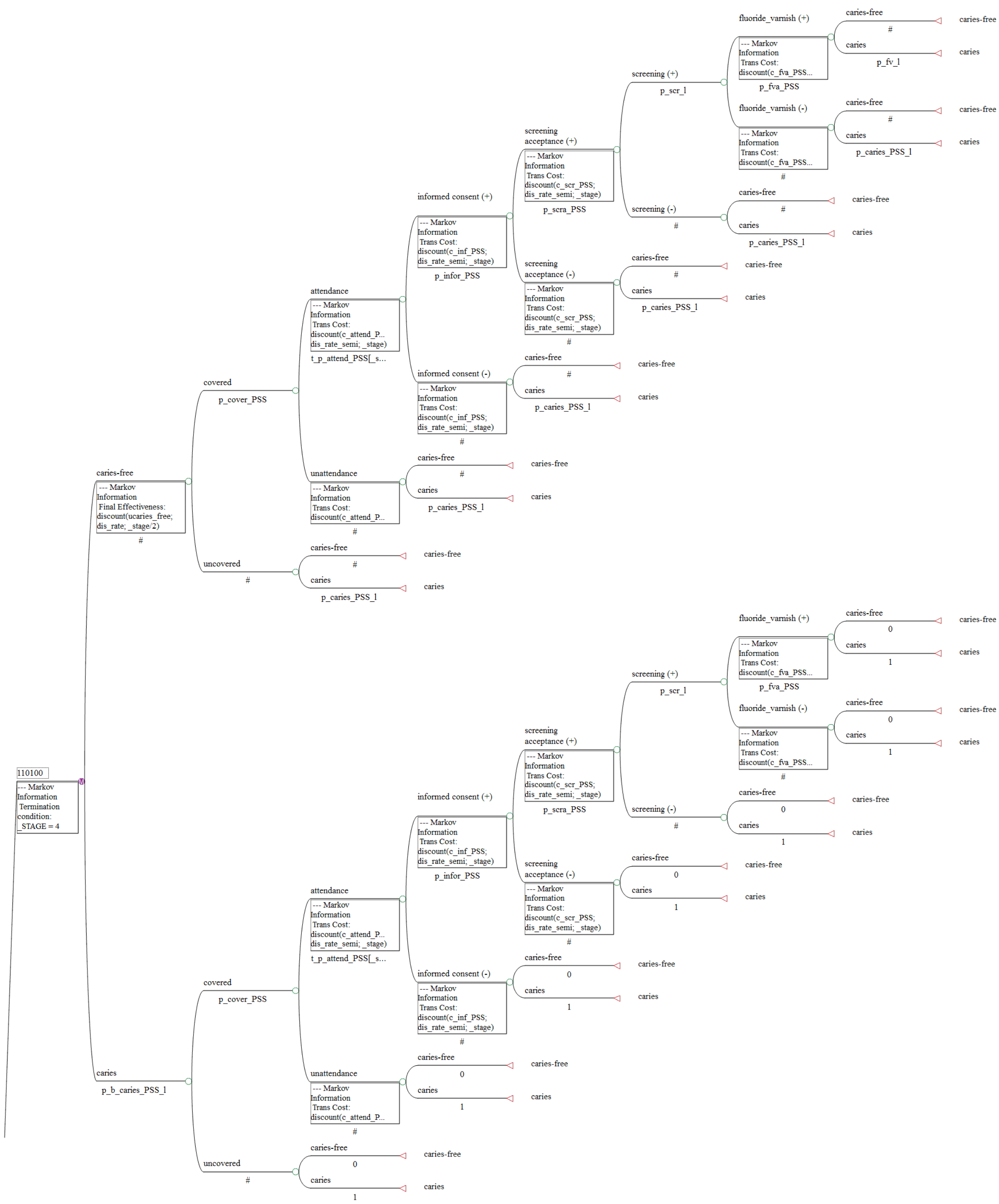

Figure A.2. Preschool setting with screening (110100).

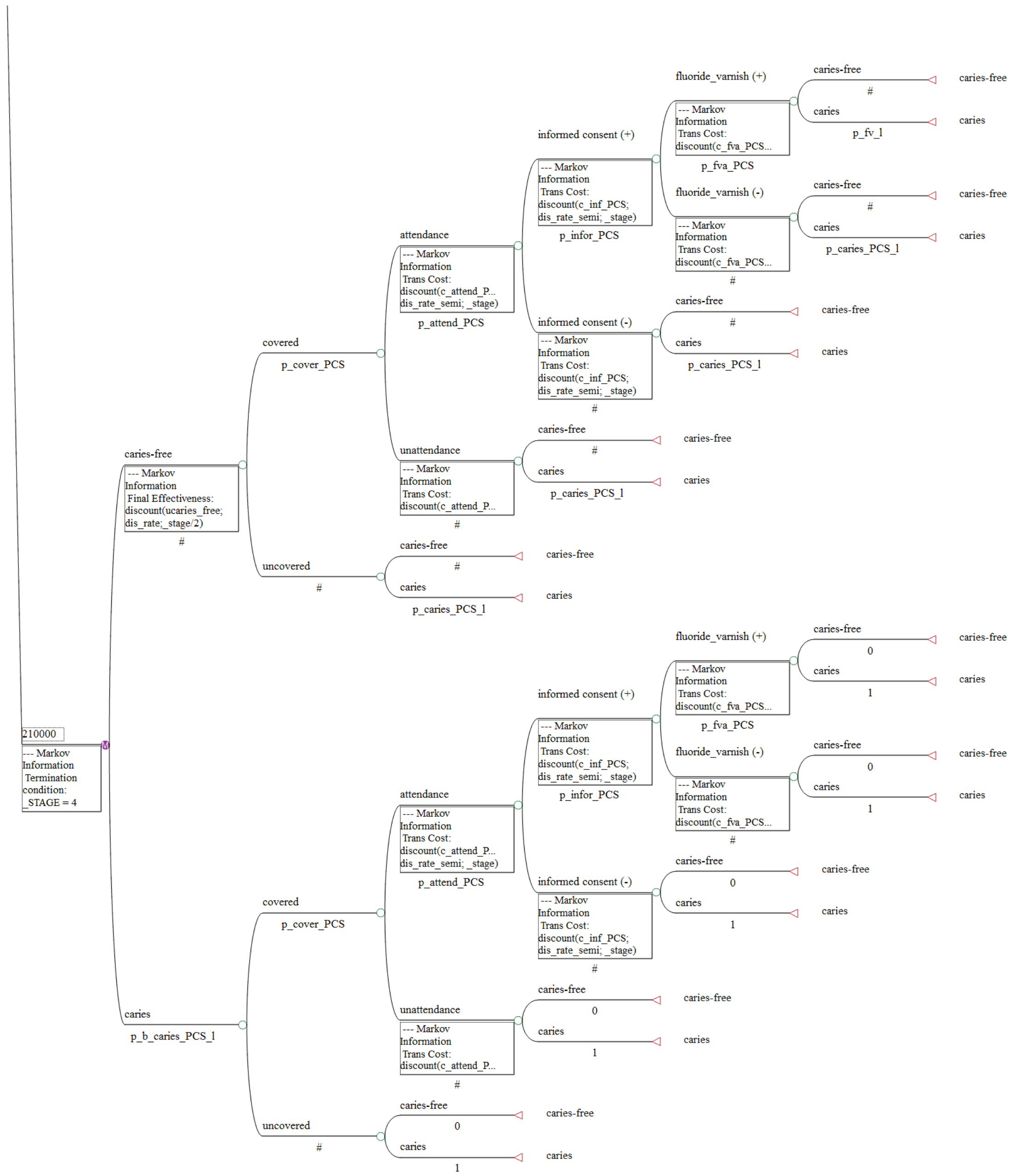

Figure A.3. Primary care setting without screening (210000).

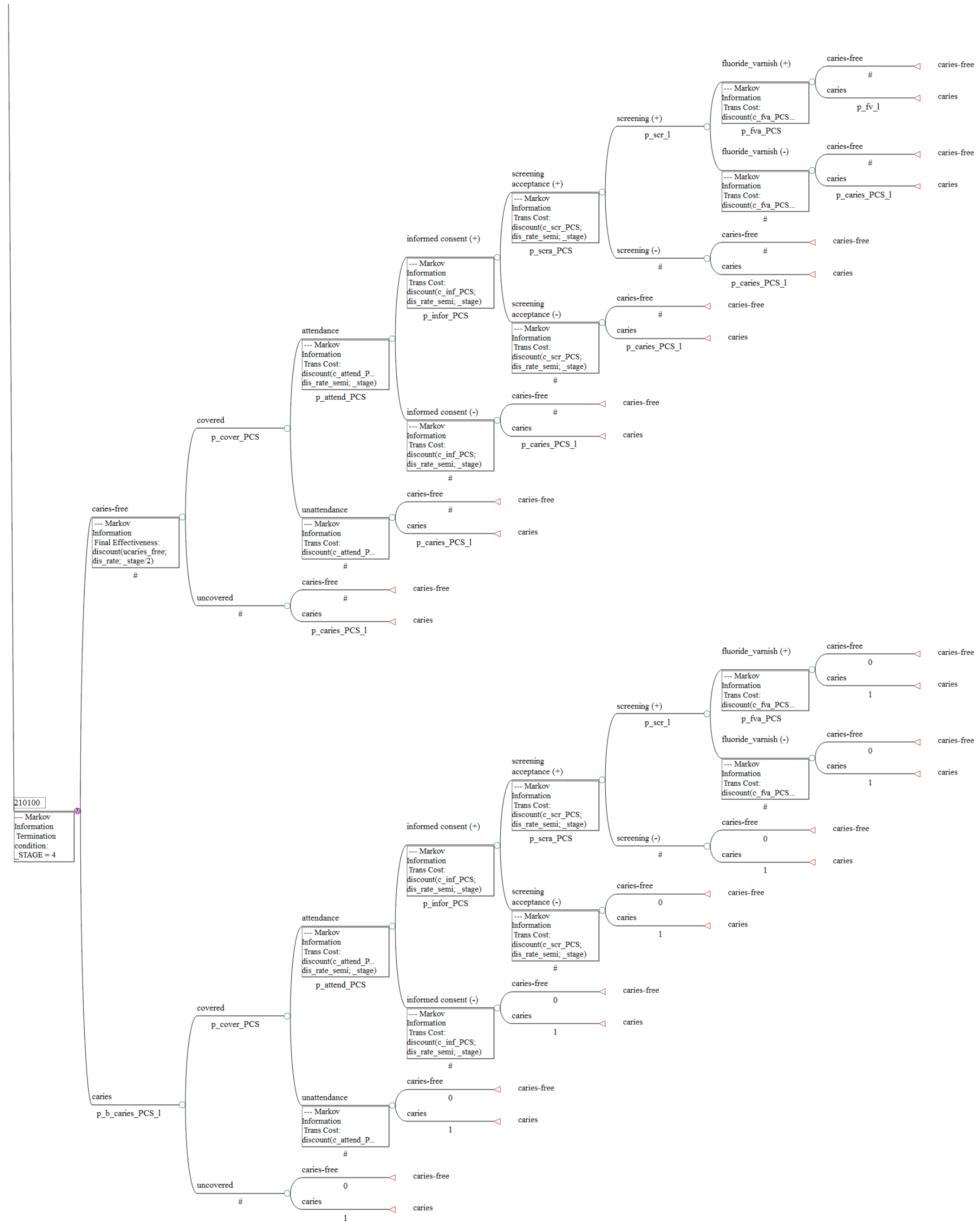

Figure A.4. Primary care setting with screening (210100).

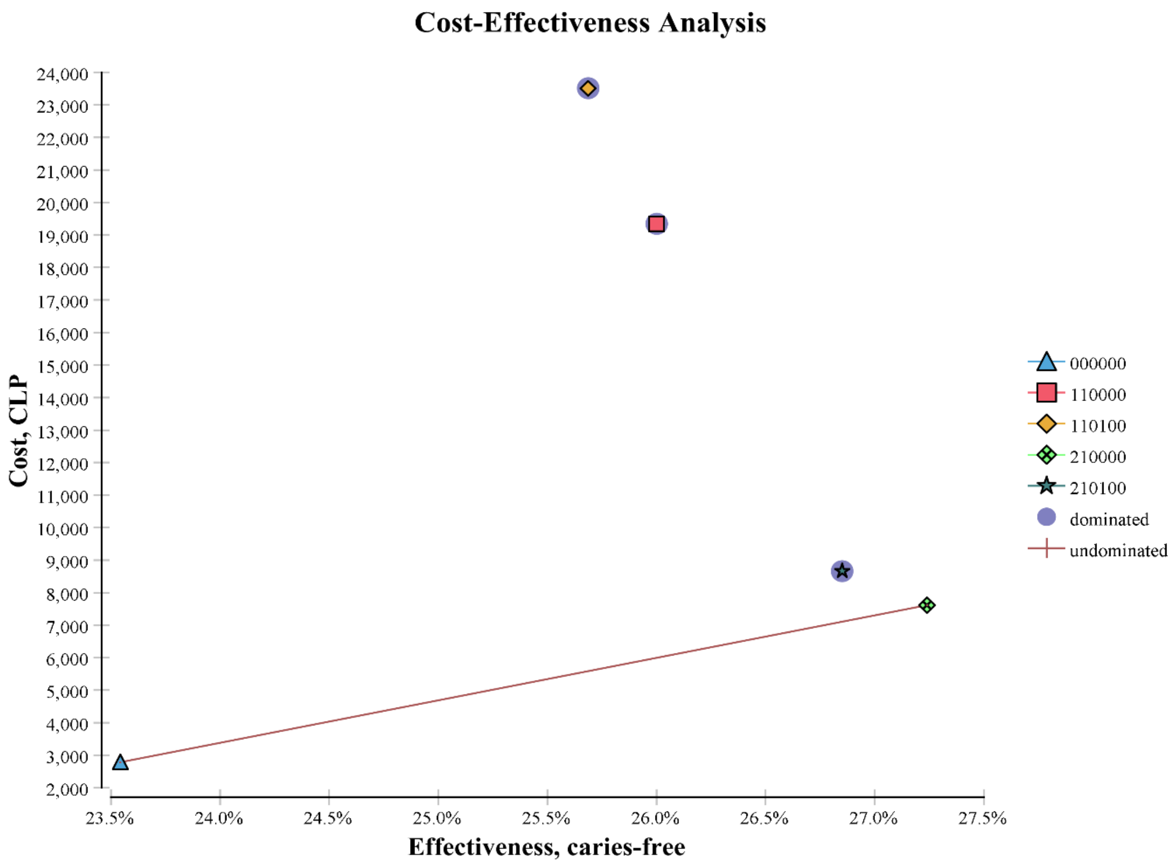

Figure A.5. Cost-effectiveness analysis of low socioeconomic status (L) or base case scenario.

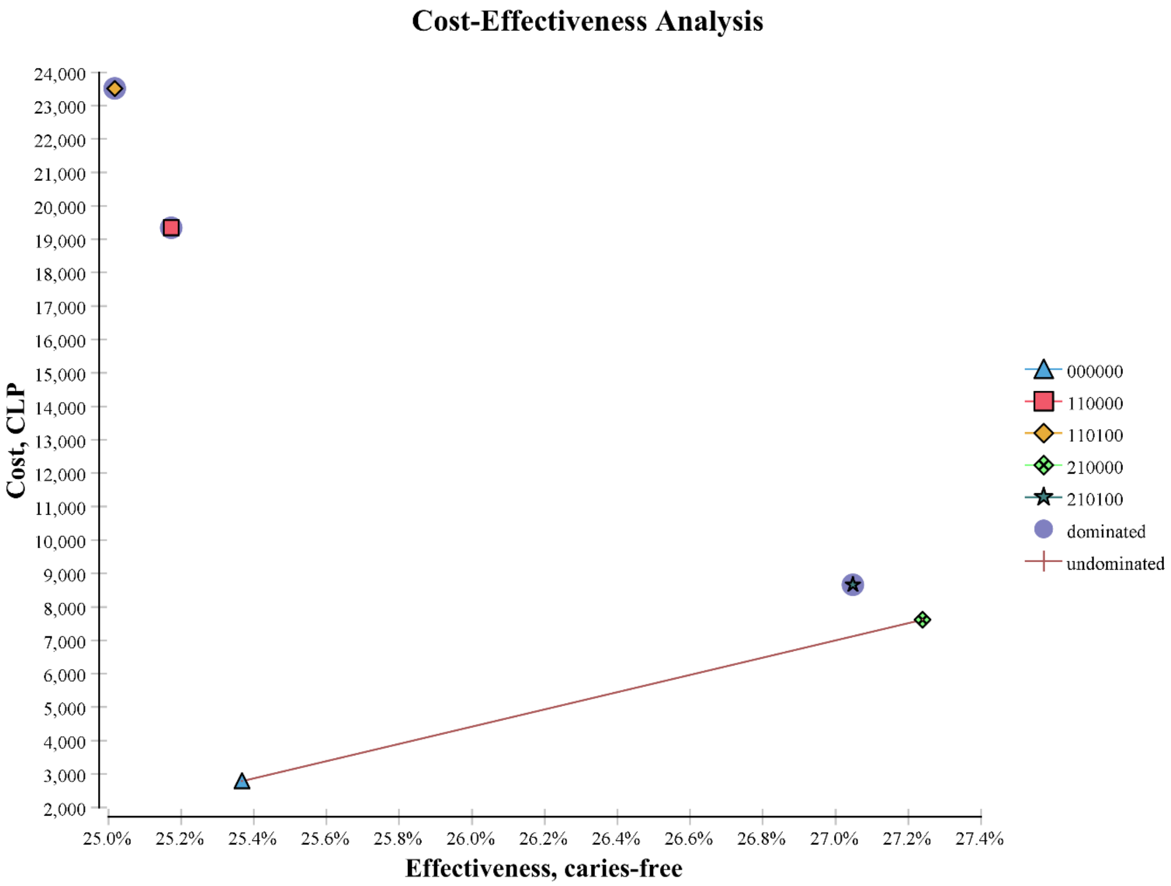

Figure A.6. Cost-effectiveness analysis in medium and low (ML) socioeconomic status scenario.

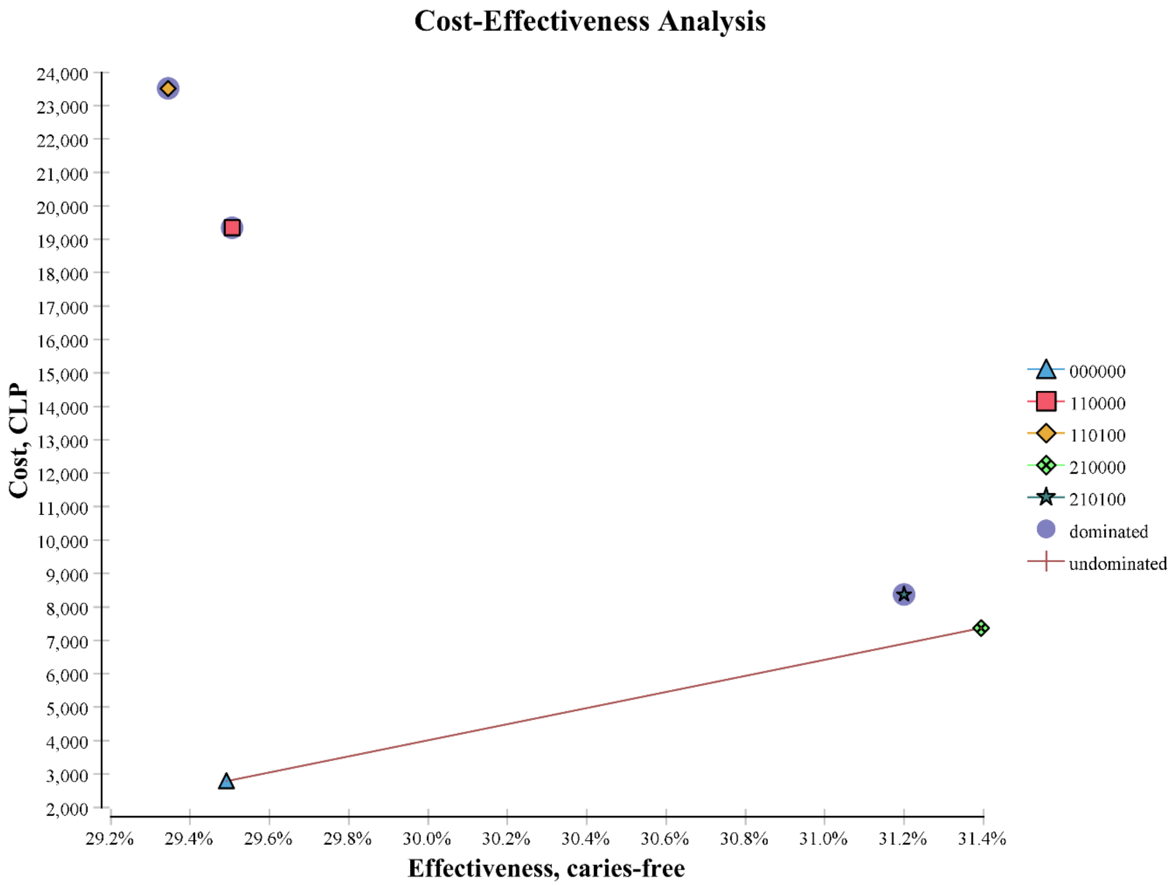

Figure A.7. Cost-effectiveness analysis in high, medium, and low (HML) socioeconomic status scenario.

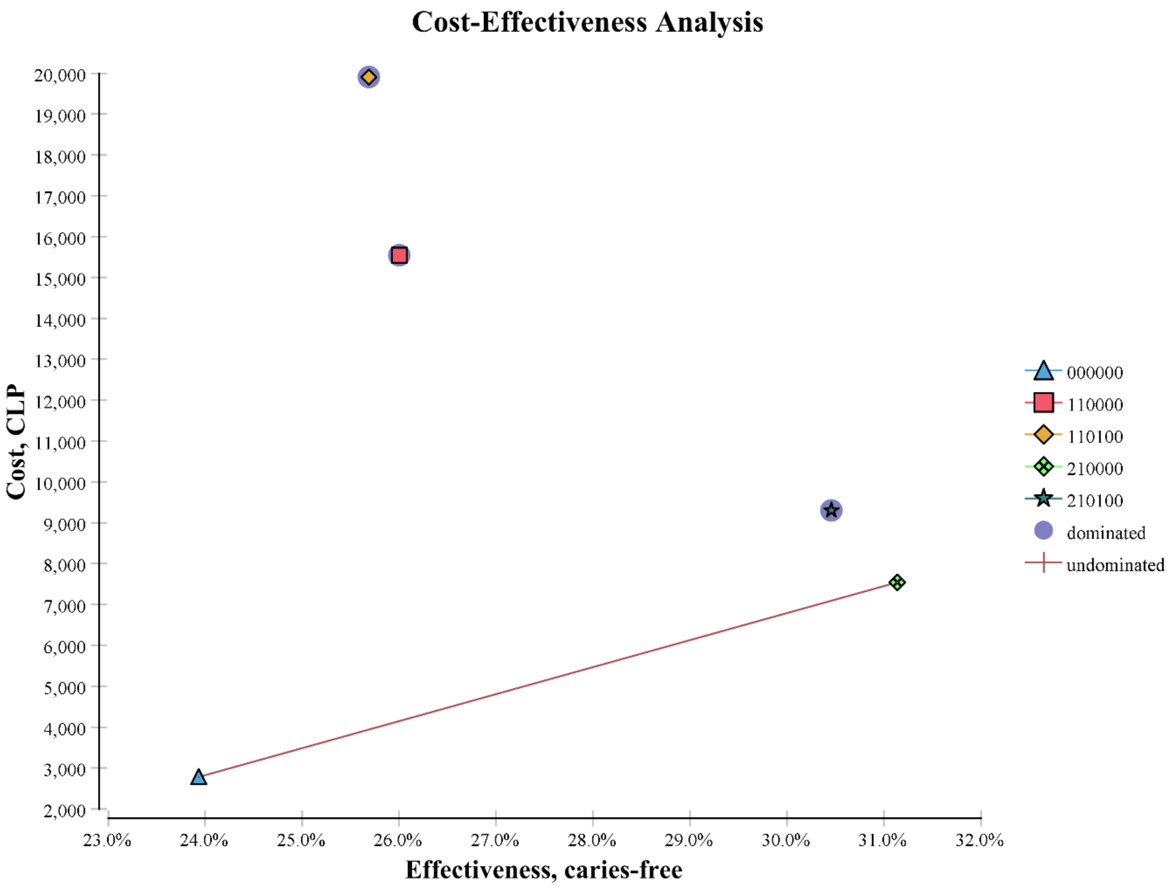

Figure A.8. Cost-effectiveness analysis in the best-case (BC) scenario.

Appendix B. Tables

	2-year-olds							
	Gender				SES			
	Male		Female		High		Low	
Zone	No.	%	No.	%	No.	%	No.	%
1	281	55.42	226	44.58	137	27.02	370	72.98
2	141	50.36	139	49.64	73	26.07	207	73.93
3	234	48.35	250	51.65	74	15.29	410	84.71
4	276	48.17	297	51.83	148	25.83	425	74.17
5	159	51.13	152	48.87	45	14.47	266	85.53
6	156	46.15	182	53.85	56	16.57	282	83.43
7	186	46.27	216	53.73	33	8.21	369	91.79
8	149	46.71	170	53.29	16	5.02	303	94.98
total	1,582	49.22	1,632	50.78	582	18.11	2,632	81.89

Table B.1. Sample size by gender and SES in the 2-year-old population.

	4-year-olds									
	Gender				SES					
	Male		Female		High		Medium		Low	
Zone	No.	%	No.	%	No.	%	No.	%	No.	%
1	195	49.37	200	50.63	52	13.16	125	31.65	218	55.19
2	201	51.94	186	48.06	46	11.89	126	32.56	215	55.56
3	292	57.71	214	42.29	100	19.76	16	3.16	390	77.08
4	236	50.64	230	49.36	54	11.59	149	31.97	263	56.44
5	226	55.12	184	44.88	34	8.29	93	22.68	283	69.02
6	221	50.92	213	49.08	66	15.21	101	23.27	267	61.52
7	172	53.25	151	46.75	47	14.55	71	21.98	205	63.47
8	231	53.35	202	46.65	40	9.24	125	28.87	268	61.89
total	1,774	52.89	1,580	47.11	439	13.09	806	24.03	2,109	62.88

Table B.2. Sample size by gender and SES in the 4-year-old population.

	6-year-olds									
	Gender				SES					
	Male		female		High		Medium		Low	
Zone	No.	%	No.	%	No.	%	No.	%	No.	%
1	135	49.09	140	50.91	40	14.55	90	32.73	145	52.73
2	107	49.54	109	50.46	35	16.20	90	41.67	91	42.13
3	360	48.26	386	51.74	125	16.76	268	35.92	353	47.32
4	131	47.29	146	52.71	30	10.83	77	27.80	170	61.37
5	155	49.84	156	50.16	40	12.86	70	22.51	201	64.63
6	76	60.80	49	39.00	8	6.40	53	42.40	64	51.20
7	89	53.29	78	46.71	27	16.17	59	35.33	81	48.50
8	48	46.60	55	53.40	10	9.71	37	35.92	56	54.37
total	1,101	49.59	1,119	50.41	315	14.19	744	33.51	1,161	52.30

Table B.3. Sample size by gender and SES in the 6-year-old population.

	MINSAL's datasets						CASEN 2009	
	2-year-olds		4-year-olds		6-year-olds		0 to 5-year-olds	6 to 13-year-olds
Zone	No.	%	No.	%	No.	%	%	%
1	507	15.77	395	11.78	275	12.39	13.60	13.13
2	280	8.71	387	11.54	216	9.73	9.95	10.50
3	484	15.06	506	15.09	746	33.60	40.12	38.26
4	573	17.83	466	13.89	277	12.48	11.10	10.74
5	311	9.68	410	12.22	311	14.01	10.83	12.36
6	338	10.52	434	12.94	125	5.63	5.53	6.15
7	402	12.51	323	9.63	167	7.52	6.92	7.42
8	319	9.93	433	12.91	103	4.64	1.95	1.42
total	3,214	100	3,354	100	2,220	100	100	100

Table B.4. Sample size and relative weight (%) of each zone, and relative weight (%) of each zone, according to national socioeconomic characterization survey (CASEN) by MIDEPLAN (2009).

Variable	OR	Lower CI	Upper CI	p-value	
Educational level of carer					
primary incomplete					
primary complete	0.745	0.453	1.225	0.246	
secondary incomplete	0.628	0.407	0.969	0.035	*
secondary complete	0.529	0.359	0.779	0.001	*
tertiary incomplete	0.407	0.261	0.634	< 0.001	**
tertiary complete	0.295	0.195	0.445	< 0.001	**
no education	0.964	0.285	3.261	0.953	
Gender of carer					
male					
female	1.688	1.105	2.578	0.015	*
Relationship between carer and child					
mother					
father	0.546	0.353	0.846	0.007	*
uncle/aunt	3.176	1.070	9.426	0.037	*
grandfather/grandmother	0.677	0.404	1.135	0.139	
brother/sister	0.862	0.248	2.993	0.815	
another relative	0.658	0.087	4.963	0.685	
other people	0.612	0.156	2.406	0.482	
Fluoridated water					
no					
yes	0.416	0.339	0.510	< 0.001	**
Educational level of head of household					
primary incomplete					
primary complete	1.015	0.622	1.657	0.953	
secondary incomplete	0.483	0.314	0.742	0.001	*
secondary complete	0.532	0.360	0.786	0.002	*
tertiary incomplete	0.460	0.286	0.741	0.001	*
tertiary complete	0.265	0.176	0.400	< 0.001	**
postgraduate	0.105	0.043	0.254	< 0.001	**
no education	0.422	0.152	1.167	0.096	
Type of School					
high					
medium	2.503	1.626	3.854	< 0.001	**
low	3.720	2.599	5.326	< 0.001	**

* $p < 0.05$; ** $p < 0.001$

Table B.5. Univariate logistic regression models.

Variable	OR	Lower CI	Upper CI	p-value	
Monthly average income of household (CLP)					
less than 81,000					
between 81,000 and 150,000	0.933	0.639	1.363	0.720	
between 151,000 and 220,000	0.832	0.565	1.225	0.351	
between 221,000 and 280,000	0.648	0.422	0.996	0.048	
between 281,000 and 450,000	0.630	0.412	0.963	0.033	*
between 451,000 and 780,000	0.372	0.226	0.611	< 0.001	**
more than 780,000	0.118	0.066	0.211	< 0.001	**
Ranking of child among household's children					
1st					
2nd	1.161	0.918	1.467	0.212	
3rd	1.486	1.099	2.008	0.01	*
4th	1.258	0.795	1.992	0.327	
5th	1.860	0.981	3.526	0.057	
6th or less	3.175	1.443	6.985	0.004	*
Number of teeth lost by mother					
5 or more					
between 4 and 2	0.664	0.491	0.898	0.008	*
only one	0.521	0.375	0.724	< 0.001	**
none	0.467	0.335	0.651	< 0.001	**
Zone					
Biobío Region					
Araucanía Region	0.445	0.342	0.579	< 0.001	**
Los Ríos and Los Lagos Regions	0.375	0.293	0.480	< 0.001	**
Aisén and Magallanes Regions	0.495	0.337	0.728	< 0.001	**
Breastfeeding					
yes, breastfed exclusively					
no, breastfed and formula	0.685	0.504	0.931	0.016	*
no, formula exclusively	0.687	0.436	1.084	0.107	
Frequency of toothbrushing					
always					
nearly always	1.698	1.330	2.168	< 0.001	**
sometimes	1.539	0.962	2.464	0.072	
never	5.541	0.886	34.666	0.067	

* $p < 0.05$; ** $p < 0.001$

Table B.6. Univariate logistic regression models, continuation.

Variable	OR	Lower CI	Upper CI	p-value	
Intake of soft drinks or juices with sugar					
always					
nearly always	1.073	0.792	1.455	0.648	
sometimes	0.875	0.659	1.163	0.358	
rarely	0.678	0.485	0.948	0.023	*
never	0.478	0.243	0.938	0.032	*
Intake liquids with sugar before bed					
always					
nearly always	0.906	0.674	1.218	0.514	
sometimes	0.838	0.622	1.129	0.245	
rarely	0.553	0.392	0.778	0.001	*
never	0.468	0.337	0.650	< 0.001	**
Toothbrushing autonomy					
self-brushing					
self-brushing, with adult supervision	0.509	0.362	0.714	< 0.001	**
with help of another child	0.712	0.359	1.411	0.331	
by an adult	0.569	0.383	0.847	0.005	*
Toothbrushing before bed					
always					
nearly always	1.289	1.025	1.620	0.03	*
sometimes	1.406	0.997	1.984	0.052	
rarely	0.752	0.455	1.243	0.266	
never	1.387	0.870	2.213	0.169	
Previous education in oral health					
yes					
no	0.754	0.601	0.945	0.014	*
Previous dental experience					
yes					
no	0.465	0.375	0.576	< 0.001	**
Perceived need of dental care					
yes					
no	0.332	0.248	0.443	< 0.001	**

* p < 0.05; ** p < 0.001

Table B.7. Univariate logistic regression models, continuation.

Setting	Domain	Specific limiting factor	Feasibility of correction
Preschool	Legal	Direct supervision	Yes
		Prescription	Yes
	Logistic	Second visit to school	No
		Parent's attendance	No
	Clinical	Risk of cross infection	Yes
	Political	Over demand on health system	No
Primary care	Legal	Direct supervision	Yes
		Prescription	Yes
	Logistic	Lack of infrastructure	No
	Clinical	Risk of cross infection	No
	Political	Over demand on health system	No

Table B.8. Limiting factors and the feasibility of being corrected by setting.

Limiting factors or combination of them eliminated	No. of feasible health interventions	Code of health intervention
Starting point at school setting	3	**110000, 110100, 140000**
Prescription	4	110000, 110100, **130000,** 140000
Risk of cross infection	4	110000, 110100, 140000, **140100**
Direct supervision	3	110000, 110100, 140000
Prescription + risk of cross infection	6	110000, 110100, 130000, **130100,** 140000, 140100
Direct supervision + prescription	5	110000, 110100, **120000**, 130000, 140000
Risk of cross infection + direct supervision	4	110000, 110100, 140000, 140100
Prescription + risk of cross infection + direct supervision	8	110000, 110100, 120000, **120100**, 130000, 130100, 140000, 140100

Table B.9. Clinical pathways feasible after elimination of limiting factors the in school setting. In bold, those health interventions not previously considered as feasible.

Limiting factors or combination of them eliminated	No. of feasible health interventions	Code of health intervention
Starting point at school setting	24	**210000, 210001, 210100, 210101, 211000, 211001, 211100, 211101, 250000, 250001, 250100, 250101, 251000, 251001, 251100, 251101, 280000, 280001, 280100, 280101, 281000, 281001, 281100, 281101**
Prescription	40	210000, 210001, 210100, 210101, 211000, 211001, 211100, 211101, 250000, 250001, 250100, 250101, 251000, 251001, 251100, 251101, **260000, 260001, 260100, 260101, 261000, 261001, 261100, 261101, 270000, 270001, 270100, 270101, 271000, 271001, 271100, 271101,** 280000, 280001, 280100, 280101, 281000, 281001, 281100, 281101
Risk of cross infection	24	Similar to starting point
Direct supervision	24	Similar to starting point
Prescription + risk of cross infection	40	Similar to prescription only
Direct supervision + prescription	40	Similar to prescription only
Risk of cross infection + direct supervision	24	Similar to starting point
Prescription + risk of cross infection + direct supervision	40	Similar to prescription only

Table B.10. Clinical pathways feasible after elimination of limiting factors in the primary health care setting. In bold, those health interventions not previously considered as feasible.

Study	Holm	Clark	Frostell	Chu	Weintraub	Borutta	Hardman	Lawrence	Yang	Salazar	Gugwad
published (year)	(1979)	(1985)	(1991)	(2002)	(2006)	(2006)	(2007)	(2008)	(2008)	(2008)	(2011)
no treatment (NT) or placebo	NT	NT	NT	placebo	placebo	NT	NT	NT	placebo	placebo	NT
study duration (years)	2	5	2	2.5	2	2	2	2	2	1	1
number randomized	250	787	206	146	376	288	2091	1275	150	200	250
number analysed	225	676	206	123	280	200	664	1160	111	148	211
cluster RCT	no	no	no	no	no	yes	yes	yes	no	no	no
setting	clinic	school	unclear	school	clinic	nursery	school	clinic	nursery	clinic	unclear
age (year-olds)	mean 3	**6 to 7**	4	3 to 5	1 to 4	2 to 4	**6 to 8**	1 to 5	3	1 to 4	**6 to 7**
FV brand	Duraphat	Duraphat Fluor Protec.	Duraphat	Duraphat	Duraphat	Duraphat Fluoridin	Duraphat	Durofluor	Fluor Protector	Duraphat	Cavity Shield
FV concentration (ppm)	22,600	22,600 7,000	22,600	22,600	22,600	22,600 22,600	22,600	22,600	5,000 1,000	22,600	22,600
Frequency (per year)	2	2	2	4	1 to 2	2	2	2 to 3	2	2	3 times in 1 week
caries-free at baseline	yes	**N/A**	**no**	**no**	yes	**N/A**	**N/A**	**No**	**N/A**	**no**	**N/A**
language	ENG	ENG	ENG	ENG	ENG	**GER**	ENG	ENG	**CHI**	POR	ENG
included in this review	yes	no	no	no	yes	no	no	No	no	no	no

N/A, no access.

Table B.11. Summary of papers analysed by Marinho et al. (2013). Reason why paper was excluded from this meta-analysis in bold.

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Baseline characteristic balanced	Free of contamination-intervention
Holm (1979)	high	high	high	Low	low	low	high	unclear
Weintraub et al. (2006)	low	low	low	Low	unclear	low	low	low

Table B.12. Risk of bias of selected studies, according to Marinho *et al.* (2013).

Study	Holm	Clark	Frostell	Chu	Weintraub	Borutta	Hardman	Lawrence	Yang	Salazar	Gugwad
published (year)	(1979)	(1985)	(1991)	(2002)	(2006)	(2006)	(2007)	(2008)	(2008)	(2008)	(2011)
no treatment (NT) or placebo	NT	NT	NT	placebo	placebo	NT	NT	NT	placebo	placebo	NT
study duration (years)	2	5	2	2.5	2	2	2	2	2	1	1
number randomized	250	787	206	146	376	288	2091	1275	150	200	250
number analysed	225	676	206	123	280	200	664	1160	111	148	211
cluster RCT	no	no	no	no	no	yes	yes	yes	no	no	no
setting	clinic	school	unclear	school	clinic	nursery	school	clinic	nursery	clinic	unclear
age (year-olds)	mean 3	**6 to 7**	4	3 to 5	1 to 4	2 to 4	**6 to 8**	1 to 5	3	1 to 4	**6 to 7**
FV brand	Duraphat	Duraphat Fluor Protec.	Duraphat	Duraphat	Duraphat	Duraphat Fluoridin	Duraphat	Durofluor	Fluor Protector	Duraphat	Cavity Shield
FV concentration (ppm)	22,600	22,600 7,000	22,600	22,600	22,600	22,600 22,600	22,600	22,600	5,000 1,000	22,600	22,600
Frequency (per year)	2	2	2	4	1 to 2	2	2	2 to 3	2	2	3 times in 1 week
caries-free at baseline	yes	**N/A**	**no**	**no**	yes	**N/A**	**N/A**	**No**	**N/A**	**no**	**N/A**
language	ENG	ENG	ENG	ENG	ENG	**GER**	ENG	ENG	**CHI**	POR	ENG
included in this review	yes	no	no	no	yes	no	no	No	no	no	no

Table B.13. Reasons why papers were not included in this meta-analysis.

Bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“The recruited subjects were randomly allocated into three groups through stratified block randomization by a statistician who was not involved in this study.”
Allocation concealment (selection bias)	Low risk	“Children were divided into two subgroups according to their gender and were sequenced according to their age in each subgroup. A block randomization list was produced for each subgroup separately and the block size was six, generating 90 different combinations. Children were allocated according to the randomly chosen combinations generated by computer software.”
Blinding of participants and personnel (performance bias)	Low risk	“Follow-up visits were made every 6 months by a dentist who was not involved in the outcome assessment so as to reinforce the dental health messages and to monitor the practice of parental toothbrushing. Toothpaste without fluoride was applied onto the child’s teeth with a microbrush as placebo in the follow-up visits, to blind parents from knowing whether their child received fluoride varnish or not.”
Blinding of outcome assessment (detection bias)	Low risk	“At baseline and 24-month follow-up, the study children were clinically examined by a trained dentist who did not know the group assignment of the children.”
Incomplete outcome data (attrition bias)	Low risk	“In this study, only 8% of the parents and their children dropped out over 2 years and the retention rate was very high.”
Selective reporting (reporting bias)	Low risk	Outcome reported: dmft increment using ICDAS criteria, at 24 months follow-up.
Baseline characteristic balanced	Low risk	“There were no statistically significant differences between the three groups in terms of the children’s age, gender, family, income, parents’ education level, parental toothbrushing and child self toothbrushing at baseline.”
Free of contamination-intervention	Unclear	No information provided.

Table B.14. Risk of bias by Jiang et al. (2014).

	Physician	Nurse	Dentist	Dental nurse	Dental assistant	Dental personnel	Adm. personnel
average wage (per hour)	10,434	7,875	10,187	4,125	3,056	3,412	2,966
time taken (minutes)	5	5	5	5	5	5	5.4
average wage (per 5 min)	870	656	849	344	255	284	269

Table B.15. Wage (CLP) per each staff in fluoride varnish application. Based on study done by PUC (2012) for FONASA.

Combination of personnel	Cost per intervention
Dental well-child programme	
dentist + dental personnel + administrative personnel	*7,069
Preschool setting	
dentist + dental personnel	2,015
Primary care setting	
dentist + dental personnel + administrative personnel	1,402
physician + administrative personnel	1,139
nurse + administrative personnel	925

Table B.16. Cost per intervention (CLP) using different staff combinations. (*) DWCP was calculated considering 30 minutes per intervention.

Primary care institution	Equipment per hour	Equipment per hour adjusted	Instruments per day	Instruments per day adjusted	Instruments per half day	Instruments per half day adjusted
Antofagasta	940	1086	42	48	21	24
Cerro Navia	550	636	88	101	44	51
San Joaquin	550	635	75	86	37	43
El Bosque	532	615	79	92	40	46
Puente Alto	550	635	80	92	40	46
Talcahuano	988	1142	34	39	17	20
Average	685	792	66	77	33	38
SD	217	251	22	26	11	13

Table B.17. Cost of equipment per hour (CLP). Cost of instruments per day and half a day, in the PCS and PSS, respectively. The values were adjusted using the consumer price index (CPI) to March 2015.

	Cost equipment (per hour)	Time taken (min)	Cost equipment (per min)
dental box in dental well-child programme	792	30	396
dental box in primary care setting	792	5	66

Table B.18. Cost of equipment per oral health intervention (CLP). Counselling-only in DWCP and fluoride varnish application in the PCS.

Name	Brand	Presentation	Brushes	Price per unit n/VAT	Price per dose n/VAT	Price per dose w/VAT	Month	Year	CPI variation (Mar 2015)	Adjusted price per dose	Council
Profluorid	VOCO	10 ml	20	14300	715	851	May	2014	3.5	881	Temuco
Profluorid	VOCO	10 ml	20	14300	715	851	Mar	2014	5.1	894	San Antonio
Profluorid	VOCO	10 ml	20	14300	715	851	Jan	2014	5.8	900	Diego de Almagro
Profluorid	VOCO	10 ml	20	14300	715	851	Aug	2013	7.8	917	Puchuncavi
Profluorid	VOCO	10 ml	20	16300	815	970	Dec	2014	0.6	976	Pitrufquen
Profluorid	VOCO	10 ml	20	16300	815	970	Jun	2014	3.2	1001	Laja
Duraphat	Colgate	10 ml	20	20924	1046	1245	Mar	2014	5.1	1308	Penco
Durashield	Sultan	single-dose	1	529	529	630	Dec	2014	0.6	633	Hualqui
Profluorid	VOCO	single-dose	1	639	639	760	Nov	2013	6.8	812	Ovalle
Durashield	Sultan	single-dose	1	732	732	871	Mar	2015	0	871	Paine
Profluorid	VOCO	single-dose	1	679	679	808	Jul	2013	8.1	873	Concepcion
Profluorid	VOCO	single-dose	1	924	924	1100	Jun	2014	3.2	1135	La Florida
Durashield	Sultan	single-dose	1	1066	1066	1269	Apr	2014	4.2	1322	Rio Negro, Palena

	average price per dose (CLP)	SD
total	963	185
single-dose	941	246
multi-doses	982	150

Table B.19. Values of fluoride varnish. The values were adjusted using the consumer price index (CPI) to March 2015.

Name	Brand	Price per unit n/VAT	Price per unit w/VAT	Month	Year	CPI variation (Mar 2015)	Adjusted price per unit	Source
Dental care	no data	210	250	Jun	2014	3.2	258	Laja
Premier ultra-kids	Colgate	250	298	Jul	2014	3.1	307	Santa Barbara
Premier ultra-kids	Colgate	261	311	Jun	2014	3.2	321	Talcahuano
Premier ultra-kids	Colgate	261	311	Jun	2014	3.2	321	Calle Larga
Premier ultra-kids	Colgate	275	327	Jun	2013	8.7	356	Curico
Premier ultra-kids	Colgate	300	357	Apr	2014	4.2	372	Chanco
Premier ultra-kids	Colgate	320	381	Sep	2014	2.6	391	San Francisco
Premier ultra-kids	Colgate	540	643	May	2013	8.7	699	Puerto Aysen
Premier ultra-kids	Colgate	598	712	Apr	2014	4.2	742	Rio Negro, Palena
Premier ultra-kids	Colgate	685	815	Jul	2014	3.1	840	La Union
PHB petit	PHB	974	1159	Dec	2014	0.0	1159	Diego de Almagro

average adjusted price (CLP) per unit	524
standard deviation	278

Table B.20. Value of children’s toothbrushes. The values were adjusted using the consumer price index (CPI) to March 2015.

Name	Brand	ppm	Price per unit n/VAT	Price per unit w/VAT	Month	Year	CPI variation (Mar 2015)	adjusted price per unit	Council
no data	no data	422	340	405	Jul	2014	3.1	417	Santa Barbara
no data	Strickland	422	450	536	Dec	2014	0.6	539	Diego de Almagro
Plaza Sesame	no data	422	538	640	Jun	2014	3.2	661	Laja
no data	no data	500	597	710	Jun	2014	3.2	733	Talcahuano
no data	Colgate	500	600	714	Apr	2014	4.2	744	Chanco
Barney smile	Colgate	500	639	760	May	2014	3.5	787	Rio Negro, Osorno
Barney smile	Colgate	500	655	779	Jun	2014	3.2	804	Calle Larga
Barney smile	Colgate	500	800	952	Sep	2014	2.6	977	San Francisco
Barney smile	Colgate	500	850	1012	May	2013	8.7	1100	Puerto Aysen
no data	Colgate	500	890	1059	Apr	2014	4.2	1104	Rio Negro, Palena

average adjusted price (CLP) per unit	786
standard deviation	213

Table B.21. Value of children's toothpaste. The values were adjusted using the consumer price index (CPI) to March 2015.

Service	Unit	Price per month	Price per hour	Price per hour plus VAT	Month	Year	CPI variation (Mar 2015)	Adjusted price per hour
Dirección de Sanidad Municipal	Puerto Varas	848,487	5,303	6,311	Sep	2014	2.9	6,494
Subsecretaria de Salud Pública	VI	875,000	5,469	6,508	Apr	2015	0	6,508
Subsecretaria de Salud Pública	XIII	900,000	5,625	6,694	Jun	2014	3.2	6,908
Subsecretaria de Salud Pública	VI	1,000,000	6,250	7,438	Apr	2015	0	7,438
Subsecretaria de Salud Pública	XIII	1,000,000	6,250	7,438	Aug	2014	2.9	7,653
Subsecretaria de Salud Pública	XIII	1,099,000	6,869	8,174	Aug	2014	2.9	8,411
Subsecretaria de Salud Pública	VII	1,049,999	6,562	7,809	May	2013	8.7	8,489
Subsecretaria de Salud Pública	VII	1,120,000	7,000	8,330	Sep	2014	2.6	8,547
Subsecretaria de Salud Pública	VII	1,100,000	6,875	8,181	May	2013	8.7	8,893
Subsecretaria de Salud Pública	VII	1,195,000	7,469	8,888	Jan	2015	1.1	8,986
Subsecretaria de Salud Pública	VI	1,240,000	7,750	9,223	Jan	2015	1.1	9,324
Subsecretaria de Salud Pública	VI	1,450,000	9,063	10,784	Jan	2014	5.8	11,410
Subsecretaria de Salud Pública	VI	1,550,000	9,688	11,528	Jan	2015	1.1	11,655
Subsecretaria de Salud Pública	VIII	1,490,000	9,313	11,082	Feb	2013	8.8	12,057
Subsecretaria de Salud Pública	VIII	1,490,000	9,313	11,082	Feb	2013	8.8	12,057
Subsecretaria de Salud Pública	VI	1,700,000	10,625	12,644	Jan	2015	1.1	12,783

	cost per hour (CLP)
average	9,226
standard deviation	2,115

Table B.22. Cost of transport of personnel. Calculated considering 8 hours per day with driver and fuel included. The values were adjusted using the consumer price index (CPI) to March 2015.

	Gloves	Mask	Gauze	Paper towel	Soap	Notebook	Ball pen	Tipp-ex	Record file	Leaflet	Informed consent
average cost per unit	48.1	19.9	5.8	6.4	4.9	728.5	144.4	858.4	22.1	22.1	22.1
source	CC	CC	CC	CC	PUC	PUC	PUC	PUC	PUC	PUC	PUC
unit	pair	unit	unit	sheet	ml	unit	unit	unit	sheet	sheet	sheet
time taken	1	0.02	1	4	10	0.01	0.01	0.001	0.02	1	1
cost (p*q)	48.1	0.4	5.8	25.8	49.4	7.3	1.4	0.9	0.5	22.1	22.1

CC ChileCompra, PUC Catholic Pontifical University of Chile.

Table B.23. Other costs (CLP) associated with fluoride varnish application. The values have already been adjusted using the consumer price index (CPI) to March 2015.

Scenario	Abbrev.	SES	Fluoridated water	Deterministic sensitivity analysis	Probabilistic sensitivity analysis
Baseline	L	L	.	complete	yes
Medium & low	ML	ML	.	partial	no
High, medium & low	HML	HML	.	partial	no
Fluoridated water positive	FWP	L	yes	partial	no
Fluoridated water negative	FWN	L	no	partial	no
Best-case	BCS	L	.	partial	no

Table B.24. Summary of scenarios.

Description	Root definition
Cost of attendance at PCS	(c_hr_PCS+c_equip_PCS)*c_ind_cost
Cost of attendance PSS	c_hr_PSS+c_trans
Cost of consumables at DWCP	166
Cost of dental well-child programme	t_c_DWCP[_stage]
Cost of equipment at DWCP	396
Cost of equipment	66
Cost of one dose of fluoride varnish	1,125
Cost of FV application	(c_fv_dose+c_hyg_kit)*c_ind_cost
Cost of FV application at PCS	c_fva+c_equip_PCS
Cost of FV application at PSS	c_fva
Cost of human resources at DWCP	7,069
Cost of human resources at PCS	1,402
Cost of human resources at PSS	1,133
Cost of oral hygiene kit	1,310
Indirect cost (%)	1.14
Cost of informed consent	0
Cost informed consent at PSS	22
Cost of instrumental	77
Cost of instrument at PCS	(c_inst/2)*c_ind_cost
Cost of instrumental at PSS	c_inst*c_ind_cost
Screening coefficient (%)	0.5
Cost of screening at PCS	((c_equip_PCS+c_attend_PCS)*c_scr_coef)+ c_inst_PCS
Cost of screening at PSS	((c_attend_PSS)*c_scr_coef)+c_inst_PSS
Cost of transport to and from school	1367
Discount rate	0.03
Semi-annual discount rate	dis_rate/2
Dental well-child programme attendance	1
Well-child programme attendance at 4-year-olds	1
Preschool attendance	t_p_attend_PSS[_stage]
Baseline of caries experience at 4-year-olds in low SES	0.562
Baseline of caries experience at 4.5-year-olds in low SES	0.615
Baseline of caries experience at DWCP in low SES	p_b_caries_48_l
Baseline of caries experience at PCS in low SES	p_b_caries_48_l
Baseline of caries at NT1	p_b_caries_54_l
Natural history of caries at DWCP in low SES	t_p_caries_48_l[_stage]
Natural history of caries at PCS in low SES	t_p_caries_48_l[_stage]
Natural history of caries from NT1 in low SES	t_p_caries_54_l[_stage]
Dental well-child programme coverage	0.32
Well-child programme coverage	t_p_cover_PCS_48[_stage]
Preschool coverage	t_p_cover_PSS[_stage]
Efficacy of FV at low SES scenario	0.046
Probability of FV acceptance at PCS	0.9
Probability of FV application acceptance at PSS	0.95
Probability of informed consent positive at PCS	0.95
Probability of informed consent positive at PSS	0.9
Screening positive at low SES scenario	1
Screening acceptance at PCS	0.9
Screening acceptance at PSS	0.95
Reward of caries	0
Reward of caries-free	1

Table B.25. Cost and probabilities of reference scenario (L).

Description	Root definition
Cost of attendance at PCS	(c_hr_PCS+c_equip_PCS)*c_ind_cost
Cost of attendance PSS	c_hr_PSS+c_trans
Cost of consumables at DWCP	166
Cost of dental well-child programme	t_c_DWCP[_stage]
Cost of equipment at DWCP	396
Cost of equipment	66
Cost of one dose of fluoride varnish	1,125
Cost of FV application	(c_fv_dose+c_hyg_kit)*c_ind_cost
Cost of FV application at PCS	c_fva+c_equip_PCS
Cost of FV application at PSS	c_fva
Cost of human resources at DWCP	7,069
Cost of human resources at PCS	1,402
Cost of human resources at PSS	1,133
Cost of oral hygiene kit	1,310
Indirect cost (%)	1.14
Cost of informed consent	0
Cost informed consent at PSS	22
Cost of instrumental	77
Cost of instrument at PCS	(c_inst/2)*c_ind_cost
Cost of instrumental at PSS	c_inst*c_ind_cost
Screening coefficient (%)	0.5
Cost of screening at PCS	((c_equip_PCS+c_attend_PCS)*c_scr_coef)+c_inst_PCS
Cost of screening at PSS	((c_attend_PSS)*c_scr_coef)+c_inst_PSS
Cost of transport to and from school	1367
Discount rate	0.03
Semi-annual discount rate	dis_rate/2
Dental well-child programme attendance	1
Well-child programme attendance	1
Preschool attendance	t_p_attend_PSS[_stage]
Baseline of caries experience at 4-year-olds in low SES & FWP	0.546
Baseline of caries experience at 4.5-year-olds in low SES & FWP	0.602
Baseline of caries experience at DWCP in low SES & FWP	p_b_caries_48_l_FWP
Baseline of caries experience at PCS in low SES & FWP	p_b_caries_48_l_FWP
Baseline of caries at NT1	p_b_caries_54_l_FWP
Natural history of caries at DWCP in low SES & FWP	t_p_caries_48_l_FWP[_stage]
Natural history of caries at PCS in low SES & FWP	t_p_caries_48_l_FWP[_stage]
Natural history of caries from NT1 in low SES & FWP	t_p_caries_54_l_FWP[_stage]
Dental well-child programme coverage	0.32
Well-child programme coverage	t_p_cover_48[_stage]
Preschool coverage	t_p_cover_54[_stage]
Efficacy of FV at low SES scenario	0.046
Probability of FV acceptance at PCS	0.9
Probability of FV application acceptance at PSS	0.95
Probability of informed consent positive at PCS	0.95
Probability of informed consent positive at PSS	0.9
Screening positive	1
Screening acceptance at PCS	0.9
Screening acceptance at PSS	0.95
Reward of caries	0
Reward of caries-free	1

Table B.26. Costs and probabilities of fluoridated water positive scenario (FWP).

Description	Root definition
Cost of attendance at PCS	(c_hr_PCS+c_equip_PCS)*c_ind_cost
Cost of attendance PSS	c_hr_PSS+c_trans
Cost of consumables at DWCP	166
Cost of dental well-child programme	t_c_DWCP[_stage]
Cost of equipment at DWCP	396
Cost of equipment	66
Cost of one dose of fluoride varnish	1,125
Cost of FV application	(c_fv_dose+c_hyg_kit)*c_ind_cost
Cost of FV application at PCS	c_fva+c_equip_PCS
Cost of FV application at PSS	c_fva
Cost of human resources at DWCP	7,069
Cost of human resources at PCS	1,402
Cost of human resources at PSS	1,133
Cost of oral hygiene kit	1,310
Indirect cost (%)	1
Cost of informed consent	0
Cost informed consent at PSS	22
Cost of instrumental	77
Cost of instrument at PCS	(c_inst/2)*c_ind_cost
Cost of instrumental at PSS	c_inst*c_ind_cost
Screening coefficient (%)	0.5
Cost of screening at PCS	((c_equip_PCS+c_attend_PCS)*c_scr_coef)+c_inst_PCS
Cost of screening at PSS	((c_attend_PSS)*c_scr_coef)+c_inst_PSS
Cost of transport to and from school	1367
Discount rate	0.03
Semi-annual discount rate	dis_rate/2
Dental well-child programme attendance	1
Well-child programme attendance	1
Preschool attendance	t_p_attend_PSS[_stage]
Baseline of caries experience at 4-year-olds in low SES & FWN	0.689
Baseline of caries experience at 4.5-year-olds in low SES & FWN	0.713
Baseline of caries experience at DWCP in low SES & FWN	p_b_caries_48_l_FWN
Baseline of caries experience at PCS in low SES & FWN	p_b_caries_48_l_FWN
Baseline of caries at NT1	p_b_caries_54_l_FWN
Natural history of caries at DWCP in low SES & FWN	t_p_caries_48_l_FWN[_stage]
Natural history of caries at PCS in low SES & FWN	t_p_caries_48_l_FWN[_stage]
Natural history of caries from NT1 in FWN	t_p_caries_54_l_FWN[_stage]
Dental well-child programme coverage	0.32
Well-child programme coverage	t_p_cover_PCS_48[_stage]
Preschool coverage	t_p_cover_PSS[_stage]
Efficacy of FV at low SES scenario	0.046
Probability of FV acceptance at PCS	0.9
Probability of FV application acceptance at PSS	0.95
Probability of informed consent positive at PCS	0.95
Probability of informed consent positive at PSS	0.9
Screening positive	1
Screening acceptance at PCS	0.9
Screening acceptance at PSS	0.95
Reward of caries	0
Reward of caries-free	1

Table B.27. Costs and probabilities of fluoridated water negative scenario (FWN).

Description	Root definition
Cost of attendance at PCS	(c_hr_PCS+c_equip_PCS)*c_ind_cost
Cost of attendance PSS	c_hr_PSS+c_trans
Cost of consumables at DWCP	166
Cost of dental well-child programme	t_c_DWCP[_stage]
Cost of equipment at DWCP	396
Cost of equipment	66
Cost of one dose of fluoride varnish	1,125
Cost of FV application	(c_fv_dose+c_hyg_kit)*c_ind_cost
Cost of FV application at PCS	c_fva+c_equip_PCS
Cost of FV application at PSS	c_fva
Cost of human resources at DWCP	7,069
Cost of human resources at PCS	1,402
Cost of human resources at PSS	1,133
Cost of oral hygiene kit	1,310
Indirect cost (%)	1.14
Cost of informed consent	0
Cost informed consent at PSS	22.1
Cost of instrumental	77
Cost of instrument at PCS	(c_inst/2)*c_ind_cost
Cost of instrumental at PSS	c_inst*c_ind_cost
Screening coefficient (%)	0.5
Cost of screening at PCS	((c_equip_PCS+c_attend_PCS)*c_scr_coef)+c_inst_PCS
Cost of screening at PSS	((c_attend_PSS)*c_scr_coef)+c_inst_PSS
Cost of transport to and from school	1367
Discount rate	0.03
Semi-annual discount rate	dis_rate/2
Dental well-child programme attendance	1
Well-child programme attendance	1
Preschool attendance	t_p_attend_PSS[_stage]
Baseline of caries experience at 4-year-olds in ML SESs	0.544
Baseline of caries experience at 4.5-year-olds in ML SESs	0.595
Baseline of caries experience at DWCP in ML SESs	p_b_caries_48_ML
Baseline of caries experience at PCS in ML SESs	p_b_caries_48_ML
Baseline of caries at NT1	p_b_caries_54_ML
Natural history of caries at DWCP in ML SESs	t_p_caries_48_ML[_stage]
Natural history of caries at PCS in ML SESs	t_p_caries_48_ML[_stage]
Natural history of caries from NT1 in ML SESs	t_p_caries_54_ML[_stage]
Dental well-child programme coverage	0.32
Well-child programme coverage	t_p_cover_PCS[_stage]
Preschool coverage	t_p_cover_PSS[_stage]
Efficacy of FV at low SES scenario	0.082
Probability of FV acceptance at PCS	0.9
Probability of FV application acceptance at PSS	0.95
Probability of informed consent positive at PCS	0.95
Probability of informed consent positive at PSS	0.9
Screening positive	1
Screening acceptance at PCS	0.9
Screening acceptance at PSS	0.95
Reward of caries	0
Reward of caries-free	1

Table B.28. Costs and probabilities of medium and low socioeconomic status scenario (ML).

Description	Root definition
Cost of attendance at PCS	(c_hr_PCS+c_equip_PCS)*c_ind_cost
Cost of attendance PSS	c_hr_PSS+c_trans
Cost of consumables at DWCP	166
Cost of dental well-child programme	t_c_DWCP[_stage]
Cost of equipment at DWCP	396
Cost of equipment	66
Cost of one dose of fluoride varnish	1,125
Cost of FV application	(c_fv_dose+c_hyg_kit)*c_ind_cost
Cost of FV application at PCS	c_fva+c_equip_PCS
Cost of FV application at PSS	c_fva
Cost of human resources at DWCP	7,069
Cost of human resources at PCS	1,402
Cost of human resources at PSS	1,133
Cost of oral hygiene kit	1,310
Indirect cost (%)	1.14
Cost of informed consent	0
Cost informed consent at PSS	22.1
Cost of instrumental	77
Cost of instrument at PCS	(c_inst/2)*c_ind_cost
Cost of instrumental at PSS	c_inst*c_ind_cost
Screening coefficient (%)	0.5
Cost of screening at PCS	((c_equip_PCS+c_attend_PCS)*c_scr_coef)+c_inst_PCS
Cost of screening at PSS	((c_attend_PSS)*c_scr_coef)+c_inst_PSS
Cost of transport to and from school	1367
Discount rate	0.03
Semi-annual discount rate	dis_rate/2
Dental well-child programme attendance	1
Well-child programme attendance	1
Preschool attendance	t_p_attend_PSS[_stage]
Baseline of caries experience at 4-year-olds in HML SESs	0.503
Baseline of caries experience at 4.5-year-olds in HML SESs	0.551
Baseline of caries experience at DWCP in HML SESs	p_b_caries_48_HML
Baseline of caries experience at PCS in HML SESs	p_b_caries_48_HML
Baseline of caries at NT1	p_b_caries_54_HML
Natural history of caries at DWCP in HML SESs	t_p_caries_48_HML[_stage]
Natural history of caries at PCS in HML SESs	t_p_caries_48_HML[_stage]
Natural history of caries from NT1 in low SES	t_p_caries_54_HML[_stage]
Dental well-child programme coverage	0.32
Well-child programme coverage	t_p_cover_PCS_48[_stage]
Preschool coverage	t_p_cover_PSS[_stage]
Efficacy of FV at low SES scenario	0.071
Probability of FV acceptance at PCS	0.9
Probability of FV application acceptance at PSS	0.95
Probability of informed consent positive at PCS	0.95
Probability of informed consent positive at PSS	0.9
Screening positive	1
Screening acceptance at PCS	0.9
Screening acceptance at PSS	0.95
Reward of caries	0
Reward of caries-free	1

Table B.29. Costs and probabilities of high, medium, and low socioeconomic status scenario (HML).

Description	Root definition
Cost of attendance at PCS	(c_hr_PCS+c_equip_PCS)*c_ind_cost
Cost of attendance PSS	c_hr_PSS+c_trans
Cost of consumables at DWCP	166
Cost of dental well-child programme	t_c_DWCP[_stage]
Cost of equipment at DWCP	396
Cost of equipment	66
Cost of one dose of fluoride varnish	1125
Cost of FV application	(c_fv_dose+c_hyg_kit)*c_ind_cost
Cost of FV application at PCS	c_fva+c_equip_PCS
Cost of FV application at PSS	c_fva
Cost of human resources at DWCP	7069
Cost of human resources at PCS (combined)	t_c_hr_PCS_36[_stage]
Cost of human resources at PSS	1133
Cost of oral hygiene kit	0
Indirect cost	1.14
Cost of informed consent	0
Cost informed consent at PSS	22.1
Cost of instrumental	77
Cost of instrument at PCS	(c_inst/2)*c_ind_cost
Cost of instrumental at PSS	c_inst*c_ind_cost
Screening coefficient	0.5
Cost of screening at PCS	((c_equip_PCS+c_attend_PCS)*c_scr_coef)+c_inst_PCS
Cost of screening at PSS	((c_attend_PSS)*c_scr_coef)+c_inst_PSS
Cost of transport to and from school	1367
Discount rate	0.03
Semi-annual discount rate	dis_rate/2
Dental well-child programme attendance	1
Well-child programme attendance	1
Preschool attendance	t_p_attend_PSS[_stage]
Baseline of caries experience at 3.5-year-olds in low SES	0.379
Baseline of caries experience at 4-year-olds in low SES	0.562
Baseline of caries experience at 4.5-year-olds in low SES	0.615
Baseline of caries experience at DWCP in low SES	p_b_caries_48_l
Baseline of caries experience at PCS in low SES	p_b_caries_36_l
Baseline of caries at NT1	p_b_caries_54_l
Natural history of caries at DWCP in low SES	t_p_caries_48_l[_stage]
Natural history of caries at PCS in low SES	t_p_caries_36_l[_stage]
Natural history of caries from NT1 in low SES	t_p_caries_54_l[_stage]
Dental well-child programme coverage	0.32
Well-child programme coverage	t_p_cover_PCS_36[_stage]
Preschool coverage	t_p_cover_PSS[_stage]
Efficacy of FV at low SES scenario	0.046
Probability of FV acceptance at PCS	0.9
Probability of FV application acceptance at PSS	0.95
Probability of informed consent positive at PCS	0.95
Probability of informed consent positive at PSS	0.9
Screening positive at low SES scenario	1
Screening acceptance at PCS	0.9
Screening acceptance at PSS	0.95
Reward of caries	0
Reward of caries-free	1

Table B.30. Costs and probabilities of best-case scenario (BCS).

SES scenarios	Caries exposed	Total exposed	Caries unexposed	Total unexposed	Attributable risk unexposed	Relative risk	Attributable risk exposed from RR
Low	14	81	42	90	0.467	0.37	0.173
Medium & low	48	158	96	175	0.549	0.53	0.291
High, medium & low	72	295	113	319	0.354	0.72	0.255

Table B.31. Attributable risk of those exposed obtained using relative risk. Relative risks were obtained using random-effect models.

	Cycles	1	2	3	4	5	6	7	8	9	10	11
	Year-olds	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5
caries prevalence	L	0.087	**0.177**	0.266	0.356	0.446	**0.536**	0.589	0.642	0.695	**0.748**	0.801
	ML						**0.522**	0.573	0.624	0.675	**0.726**	0.777
	HL/HML	0.076	**0.157**	0.238	0.319	0.400	**0.482**	0.530	0.579	0.628	**0.676**	0.725
rate	L	0.091	0.097	0.103	0.110	0.118	0.128	0.127	0.128	0.132	0.138	0.147
	ML						0.123	0.121	0.122	0.125	0.129	0.136
	HL/HML	0.079	0.085	0.091	0.096	0.102	0.109	0.108	0.108	0.110	0.113	0.117
probability	L	0.087	0.093	0.098	0.104	0.111	0.120	0.119	0.120	0.123	0.129	0.136
	ML						0.116	0.114	0.115	0.117	0.121	0.127
	HL/HML	0.076	0.082	0.087	0.092	0.097	0.104	0.102	0.102	0.104	0.107	0.111

Table B.32. Initial and transition probabilities (lower range) of caries prevalence in preschool Chilean population (2006-2010). In bold, prevalence calculated directly from consolidated dataset.

	Cycles	1	2	3	4	5	6	7	8	9	10	11
	Year-olds	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5
caries prevalence	L	0.121	**0.214**	0.308	0.402	0.495	**0.589**	0.641	0.692	0.744	**0.796**	0.848
	ML						**0.567**	0.617	0.666	0.716	**0.765**	0.814
	HL/HML	0.106	**0.189**	0.273	0.357	0.440	**0.524**	0.572	0.619	0.667	**0.715**	0.762
rate	L	0.129	0.121	0.123	0.128	0.137	0.148	0.146	0.147	0.151	0.159	0.171
	ML						0.140	0.137	0.137	0.140	0.145	0.153
	HL/HML	0.112	0.105	0.106	0.110	0.116	0.124	0.121	0.121	0.122	0.125	0.131
probability	L	0.121	0.114	0.116	0.121	0.128	0.138	0.136	0.137	0.141	0.147	0.157
	ML						0.130	0.128	0.128	0.130	0.135	0.142
	HL/HML	0.106	0.100	0.101	0.104	0.110	0.116	0.114	0.114	0.115	0.118	0.122

Table B.33. Initial and transition probabilities (upper range) of caries prevalence in preschool Chilean population (2006-2010). In bold, prevalence calculated directly from consolidated dataset.

	Cycles	1	2	3	4	5	6	7	8	9	10	11
	Year-olds	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5
Estimated prevalence	L FW-	0.108	**0.213**	0.319	0.424	0.529	**0.635**	0.658	0.682	0.705	**0.729**	0.752
	L FW+	0.083	**0.171**	0.259	0.347	0.435	**0.523**	0.578	0.633	0.687	**0.742**	0.797
	ML FW-						**0.620**	0.649	0.678	0.708	**0.737**	0.766
	ML FW+						**0.509**	0.561	0.613	0.665	**0.717**	0.770
	HML FW-	0.094	**0.196**	0.298	0.401	0.503	**0.605**	0.625	0.646	0.667	**0.687**	0.708
	HML FW+	0.072	**0.151**	0.230	0.309	0.388	**0.467**	0.517	0.567	0.618	**0.668**	0.718
Rates	L FW-	0.114	0.120	0.128	0.138	0.151	0.168	0.153	0.143	0.136	0.131	0.127
	L FW+	0.086	0.094	0.100	0.107	0.114	0.124	0.123	0.125	0.129	0.135	0.145
	ML FW-						0.161	0.150	0.142	0.137	0.133	0.132
	ML FW+						0.118	0.118	0.119	0.122	0.126	0.133
	HML FW-	0.099	0.109	0.118	0.128	0.140	0.155	0.140	0.130	0.122	0.116	0.112
	HML FW+	0.075	0.082	0.087	0.092	0.098	0.105	0.104	0.105	0.107	0.110	0.115
Probabilities	L P(C+IFW-)	0.108	0.113	0.120	0.129	0.140	0.155	0.142	0.133	0.127	0.122	0.119
	L P(C+IFW+)	0.083	0.089	0.095	0.101	0.108	0.116	0.116	0.118	0.121	0.127	0.135
	ML P(C+IFW-)						0.149	0.139	0.132	0.128	0.125	0.124
	ML P(C+IFW+)						0.112	0.111	0.112	0.114	0.119	0.125
	HML P(C+IFW-)	0.094	0.104	0.111	0.120	0.130	0.143	0.131	0.122	0.115	0.110	0.106
	HML P(C+IFW+)	0.072	0.079	0.083	0.088	0.093	0.099	0.099	0.099	0.101	0.104	0.109

Table B.34. Estimated prevalence (lower confidence interval), rates, and transition probabilities of caries in the preschool Chilean population by socioeconomic scenarios and fluoridated water (2006-2010). In bold, the prevalence estimated directly from consolidated dataset. FW+, fluoridated water positive and FW-, fluoridated water negative.

	Cycles	1	2	3	4	5	6	7	8	9	10	11
	Year-olds	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5
Estimated prevalence	L FW-	0.215	**0.320**	0.426	0.532	0.638	**0.743**	0.768	0.793	0.818	**0.843**	0.868
	L FW+	0.110	**0.202**	0.294	0.386	0.477	**0.569**	0.626	0.682	0.739	**0.795**	0.852
	ML FW-						**0.715**	0.745	0.775	0.805	**0.835**	0.865
	ML FW+						**0.548**	0.601	0.654	0.707	**0.760**	0.813
	HML FW-	0.191	**0.292**	0.394	0.495	0.596	**0.698**	0.720	0.742	0.764	**0.786**	0.808
	HML FW+	0.097	**0.178**	0.259	0.340	0.422	**0.503**	0.554	0.606	0.658	**0.710**	0.761
Rates	L FW-	0.242	0.193	0.185	0.190	0.203	0.227	0.209	0.197	0.189	0.185	0.184
	L FW+	0.117	0.113	0.116	0.122	0.130	0.140	0.140	0.143	0.149	0.159	0.174
	ML FW-						0.209	0.195	0.187	0.182	0.180	0.182
	ML FW+						0.132	0.131	0.133	0.136	0.143	0.152
	HML FW-	0.212	0.173	0.167	0.171	0.181	0.199	0.182	0.169	0.160	0.154	0.150
	HML FW+	0.102	0.098	0.100	0.104	0.109	0.116	0.115	0.116	0.119	0.124	0.130
Probabilities	L P(C+IFW-)	0.215	0.176	0.169	0.173	0.184	0.203	0.189	0.179	0.173	0.169	0.168
	L P(C+IFW+)	0.110	0.107	0.110	0.115	0.122	0.131	0.131	0.134	0.139	0.147	0.159
	ML P(C+IFW-)						0.189	0.177	0.170	0.166	0.165	0.166
	ML P(C+IFW+)						0.124	0.123	0.124	0.127	0.133	0.141
	HML P(C+IFW-)	0.191	0.159	0.154	0.157	0.166	0.181	0.166	0.156	0.148	0.143	0.139
	HML P(C+IFW+)	0.097	0.093	0.095	0.099	0.104	0.110	0.109	0.110	0.112	0.116	0.122

Table B.35. Estimated prevalence (upper confident interval), rates, and transition probabilities of caries in the preschool Chilean population by socioeconomic scenarios and fluoridated water (2006-2010). In bold, the prevalence estimated directly from consolidated dataset. FW+, fluoridated water positive and FW-, fluoridated water negative.

	3-year-olds			4-year-olds			5-year-olds		
SES	Total	WCP	WCP/total	Total	WCP	WCP/total	Total	WCP	WCP/total
low	1,183	598	0.505	1,576	747	0.474	1,463	606	0.414
medium	186	93	0.500	777	326	0.420	1,182	439	0.371
high	187	81	0.433	202	60	0.297	194	53	0.273

Table B.36. Coverage of well-child programme (WCP) by socioeconomic status, from the CASEN survey (MIDEPLAN, 2013).

Age	Never attended		Nursery		Preschool		Special education		Primary school		Total		NT1	NT2	1st year	Coverage	Lower CI	Upper CI
	n	%	n	%	n	%	n	%	n	%	n	%	n	n	n			
4-year-olds	0	0	1,307	0.49	1,344	0.50	28	0.01	0	0.00	2,679	1.00	1,344			0.81	0.79	0.83
	644										663		323.1					
5-year-olds	0	0	368	0.13	2,522	0.87	22	0.01	1	0.00	2,913	1.00	1,261	1,261	1	0.95	0.94	0.97
	140										150			60.6				
6-year-olds	0	0	97	0.03	1,392	0.46	20	0.01	1,516	0.50	3,025	1.00			1,516	0.99	0.98	0.99
	46										56				23.1			

Table B.37. Coverage of preschool education from the CASEN survey 2013. Confidence intervals calculated using the Wald method.

Variable	Cycle	L	FWP	FWN	HM	HML	BCS
t_c_DWCP	1	8,699	8,699	8,699	8,699	8,699	8,699
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
t_p_attend_PSS	1	0.771	0.771	0.771	0.771	0.771	0.771
	2	0.771	0.771	0.771	0.771	0.771	0.771
	3	0.792	0.792	0.792	0.792	0.792	0.792
	4	0.792	0.792	0.792	0.792	0.792	0.792
t_p_caries_48	1	0.127	0.123	0.163	0.121	0.108	0.127
	2	0.128	0.125	0.154	0.121	0.108	0.128
	3	0.132	0.13	0.147	0.124	0.109	0.132
	4	0.137	0.136	0.143	0.128	0.112	0.137
t_p_caries_54	1	0.128	0.125	0.154	0.121	0.108	0.128
	2	0.132	0.13	0.147	0.124	0.109	0.132
	3	0.137	0.136	0.143	0.128	0.112	0.137
	4	0.146	0.146	0.14	0.134	0.116	0.146
t_p_cover_PCS (WCP)	1	0.47	0.47	0.47	0.46	0.44	-
	2	0.47	0.47	0.47	0.46	0.44	-
	3	0.41	0.41	0.41	0.40	0.39	-
	4	0.41	0.41	0.41	0.40	0.39	-
t_p_cover_PSS	1	0.806	0.806	0.806	0.806	0.806	0.806
	2	0.954	0.954	0.954	0.954	0.954	0.954
	3	0.954	0.954	0.954	0.954	0.954	0.954
	4	0.985	0.985	0.985	0.985	0.985	0.985
t_c_hr_PCS_36	1	-	-	-	-	-	925
	2	-	-	-	-	-	1,373
	3	-	-	-	-	-	1,402
	4	-	-	-	-	-	925
	5	-	-	-	-	-	1,373
	6	-	-	-	-	-	1,402
t_p_caries_36	1	-	-	-	-	-	0.119
	2	-	-	-	-	-	0.129
	3	-	-	-	-	-	0.127
	4	-	-	-	-	-	0.128
	5	-	-	-	-	-	0.132
	6	-	-	-	-	-	0.137
t_p_cover_PCS_36	1	-	-	-	-	-	0.531
	2	-	-	-	-	-	0.531
	3	-	-	-	-	-	0.474
	4	-	-	-	-	-	0.474
	5	-	-	-	-	-	0.415
	6	-	-	-	-	-	0.415

Table B.38. Transition probabilities and costs used in baseline, fluoridated water positive (FWP), fluoridated water negative (FWN), medium and low socioeconomic status (ML) and, high, medium & low socioeconomic status (HML) scenarios.

	INE 2014		CASEN 2013 (%)		Eligible population	
	4-year-olds	4.5-year-olds	4-year-olds	4.5-year-olds	4-year-olds	4.5-year-olds
population (2015)	250,149	251,491				
health system						
FONASA (ABCD)			0.84	0.83	211,002	209,831
ISAPRE			0.10	0.11	26,123	27,053
others			0.05	0.06	13,024	14,606
educational system						
Public			0.62	0.56	154,299	141,691
Subsidised			0.30	0.36	76,073	91,337
Private			0.08	0.07	19,777	18,463

Table B.39. Estimated population for each setting.

Variable	Range	Magnitude	Dominant int.	Cost	Effect	Incr. cost	Incr. effect	ICER
c_equip_PCS	LV	49.5	210000	7,560	0.272	4,776	0.037	129,223
c_equip_PCS	UV	82.5	210000	7,680	0.272	4,896	0.037	132,475
c_fv_dose	LV	844	210000	7,090	0.272	4,306	0.037	116,503
c_fv_dose	UV	1406	210000	8,150	0.272	5,367	0.037	145,195
c_hr_PCS	LV	1051.5	210000	6,924	0.272	4,140	0.037	112,013
c_hr_PCS	UV	1752.5	210000	8,316	0.272	5,533	0.037	149,685
c_hr_PSS	LV	1511.25	210000	7,620	0.272	4,836	0.037	130,849
c_hr_PSS	UV	2518.75	210000	7,620	0.272	4,836	0.037	130,849
c_hyg_kit	zero	0	210000	5,148	0.272	2,364	0.037	63,969
c_hyg_kit	LV	982.5	210000	7,002	0.272	4,218	0.037	114,129
c_hyg_kit	UV	1637.5	210000	8,238	0.272	5,454	0.037	147,569
c_ind_cost	LV	1.105	210000	7,389	0.272	4,606	0.037	124,610
c_ind_cost	UV	1.175	210000	7,851	0.272	5,067	0.037	137,088
c_inf_PCS	LV	0	210000	7,620	0.272	4,836	0.037	130,849
c_inf_PCS	UV	22.1	210000	7,659	0.272	4,875	0.037	131,891
c_inf_PSS	LV	16.575	210000	7,620	0.272	4,836	0.037	130,849
c_inf_PSS	UV	27.625	210000	7,620	0.272	4,836	0.037	130,849
c_inst	LV	57.75	210000	7,620	0.272	4,836	0.037	130,849
c_inst	UV	96.25	210000	7,620	0.272	4,836	0.037	130,849
c_scr_coef	LV	0.375	210000	7,620	0.272	4,836	0.037	130,849
c_scr_coef	UV	0.625	210000	7,620	0.272	4,836	0.037	130,849
c_trans	zero	0	210000	7,620	0.272	4,836	0.037	130,849
c_trans	LV	1025.25	210000	7,620	0.272	4,836	0.037	130,849
c_trans	UV	1708.75	210000	7,620	0.272	4,836	0.037	130,849
dis_rate	GLV	0	210000	7,785	0.289	5,001	0.039	127,533
dis_rate	GUV	0.05	210000	7,515	0.262	4,731	0.036	133,019
p_b_caries_48_l	LCI	0.535	210000	7,620	0.289	4,836	0.039	123,251
p_b_caries_48_l	UCI	0.589	210000	7,620	0.256	4,836	0.035	139,445
p_b_caries_48_l	UCI	0.589	110000	19,344	0.260	11,724	0.004	2,656,093
p_b_caries_54_l	LCI	0.589	210000	7,620	0.272	4,836	0.037	130,849
p_b_caries_54_l	LCI	0.589	110000	19,344	0.278	11,724	0.005	2,262,376
p_b_caries_54_l	UCI	0.641	210000	7,620	0.272	4,836	0.037	130,849
p_cover_DWCP	LV	0.24	210000	7,620	0.272	5,532	0.037	149,677
p_cover_DWCP	UV	0.4	210000	7,620	0.272	4,140	0.037	112,021
p_fv_l	LV	0.034	210000	7,620	0.278	4,836	0.043	113,738
p_fv_l	UV	0.059	210000	7,620	0.266	4,836	0.031	155,850
p_fva_PCS	LV	0.68	210000	7,620	0.263	4,836	0.028	175,542
p_fva_PCS	UV	1	210000	7,620	0.277	4,836	0.041	117,043
p_fva_PSS	LV	0.71	210000	7,620	0.272	4,836	0.037	130,849
p_fva_PSS	UV	1	210000	7,620	0.272	4,836	0.037	130,849
p_infor_PCS	LV	0.71	210000	6,432	0.263	3,648	0.027	133,918
p_infor_PCS	UV	1	210000	7,868	0.274	5,084	0.039	130,290
p_infor_PSS	LV	0.68	210000	7,620	0.272	4,836	0.037	130,849
p_infor_PSS	UV	1	210000	7,620	0.272	4,836	0.037	130,849
p_scr_l	LV	0.75	210100	7,604	0.260	4,820	0.025	196,698
p_scr_l	LV	0.75	210000	7,620	0.272	16	0.012	1,324
p_scr_l	UV	1	210000	7,620	0.272	4,836	0.037	130,849
p_scra_PCS	LV	0.68	210000	7,620	0.272	4,836	0.037	130,849
p_scra_PCS	UV	1	210000	7,620	0.272	4,836	0.037	130,849
p_scra_PSS	LV	0.71	210000	7,620	0.272	4,836	0.037	130,849
p_scra_PSS	UV	1	210000	7,620	0.272	4,836	0.037	130,849
c_DWCP	LV	table	210000	7,620	0.272	5,532	0.037	149,675
c_DWCP	UV	table	210000	7,620	0.272	5,532	0.037	149,675
p_attend_PSS	LCI	table	210000	7,620	0.272	4,836	0.037	130,849
p_attend_PSS	UCI	table	210000	7,620	0.272	4,836	0.037	130,849
p_caries_48_l	LCI	table	210000	7,620	0.279	4,836	0.034	141,695
p_caries_48_l	UCI	table	210000	7,620	0.266	4,836	0.040	121,037
p_caries_54_l	LCI	table	210000	7,620	0.272	4,836	0.037	130,849
p_caries_54_l	UCI	table	210000	7,620	0.272	4,836	0.037	130,849
p_cover_PCS	LCI	table	210000	5,715	0.263	2,931	0.027	107,218
p_cover_PCS	UCI	table	210000	9,525	0.282	6,741	0.047	143,909
p_cover_PSS	LCI	table	210000	7,620	0.272	4,836	0.037	130,849
p_cover_PSS	UCI	table	210000	7,620	0.272	4,836	0.037	130,849

Table B.40. Parameters for deterministic sensitivity analysis in low socioeconomic scenario or reference case. See Table B.10.2 for description of abbreviations.

	Cost		Effect	
Intervention	Mean	SD	Mean	SD
000000	2,780	755	0.237	0.009
110000	18,582	601	0.256	0.011
110100	22,212	843	0.249	0.011
210000	7,314	287	0.269	0.011
210100	8,102	361	0.265	0.010

Table B.41. Results of probabilistic sensitivity analysis.

Threshold (CLP)	000000	110000	110100	210000	210100
0	1	0	0	0	0
48,332	0.995	0	0	0.005	0
96,664	0.785	0	0	0.186	0.029
144,996	0.392	0	0	0.472	0.136
193,327	0.172	0	0	0.605	0.223
241,659	0.094	0	0	0.635	0.271
289,991	0.06	0	0	0.644	0.296
338,323	0.04	0	0	0.646	0.314
386,655	0.034	0	0	0.645	0.321
434,987	0.026	0	0	0.641	0.333
483,319	0.022	0.001	0	0.638	0.339
531,650	0.019	0.001	0	0.637	0.343
579,982	0.018	0.004	0	0.636	0.342
628,314	0.016	0.005	0	0.634	0.345
676,646	0.013	0.006	0	0.634	0.347
724,978	0.012	0.007	0.001	0.631	0.349
773,310	0.01	0.012	0.001	0.63	0.347
821,641	0.01	0.015	0.003	0.625	0.347
869,973	0.007	0.017	0.003	0.622	0.351
918,305	0.007	0.019	0.003	0.618	0.353
966,637	0.007	0.024	0.003	0.612	0.354

Table B.42. Cost-effectiveness acceptability curve.

Interventions	Cost	Incr. cost	Effect	Incr. effect	ICER	Dominance
Excluding dominated						
000000	2,784		0.254			
210000	7,365	4,581	0.272	0.018	253,758	
All						
000000	2,784	-	0.254	0	-	
210000	7,365	4,581	0.272	0.018	253,758	
210100	8,372	1,007	0.27	-0.002	-545,122	
110000	19,344	11,979	0.252	-0.02	-598,854	
110100	23,514	16,149	0.25	-0.022	-749,137	
All referencing common baseline						
000000	2,784		0.254			undominated
210000	7,365	4,581	0.272	0.018	253,758	undominated
210100	8,372	5,588	0.27	0.016	344,826	abs. dominated
110000	19,344	16,560	0.252	-0.002	(8,488,969)	abs. dominated
110100	23,514	20,730	0.25	-0.004	(5,914,618)	abs. dominated
All by Increasing effectiveness						
110100	23,514		0.25			
110000	19,344		0.252			
000000	2,784		0.254			
210100	8,372		0.27			
210000	7,365		0.272			

Table B.43. Ranking of strategies in medium and low socioeconomic status (ML) scenario.

Variable	Range	Magnitude	Dominant int.	Cost	Effect	Incr. cost	Incr. effect	ICER
c_hr_PCS	LV	1,052	210000	6,924	0.272	4,140	0.019	221,212
c_hr_PCS	UV	1,753	210000	8,316	0.272	5,533	0.019	295,610
c_hyg_kit	zero	0	210000	5,148	0.272	2,364	0.019	126,331
c_hyg_kit	LV	983	210000	7,003	0.272	4,219	0.019	225,441
c_hyg_kit	UV	1,638	210000	8,239	0.272	5,455	0.019	291,482
dis_rate	GLV	0.000	210000	7,785	0.289	5,001	0.020	251,862
dis_rate	GUV	0.050	210000	7,515	0.262	4,731	0.018	262,698
p_b_caries_48_ML	LCI	0.522	210000	7,620	0.286	4,836	0.020	246,518
p_b_caries_48_ML	UCI	0.567	210000	7,620	0.259	4,836	0.018	272,137
p_b_caries_54_ML	LCI	0.573	210000	7,620	0.272	4,836	0.019	258,411
p_b_caries_54_ML	UCI	0.617	210000	7,620	0.272	4,836	0.019	258,411
p_cover_DWCP	LV	0.240	210000	7,620	0.272	5,532	0.019	295,595
p_cover_DWCP	UV	0.400	210000	7,620	0.272	4,140	0.019	221,227
p_cover_PCS_ML	LCI	t_p_cover_PCS_ML	210000	5,715	0.268	2,931	0.014	210,239
p_cover_PCS_ML	UCI	t_p_cover_PCS_ML	210000	9,525	0.277	6,741	0.024	286,232
p_cover_PSS	LCI	t_p_cover_PSS	210000	7,620	0.272	4,836	0.019	258,411
p_cover_PSS	UCI	t_p_cover_PSS	210000	7,620	0.272	4,836	0.019	258,411
p_fv_ML	LV	0.063	210000	7,620	0.281	4,836	0.028	174,912
p_fv_ML	UV	0.113	210000	7,620	0.258	4,836	0.005	1,052,081
p_fva_PCS	LV	0.680	210000	7,620	0.268	4,836	0.014	344,267
p_fva_PCS	UV	1.000	210000	7,620	0.275	4,836	0.021	231,878

Table B.44. Parameters for deterministic sensitivity analysis in medium and low socioeconomic status (ML) scenario. See Table B.10.2 for description of abbreviations.

Interventions	Cost	Incr. cost	Effect	Incr. effect	ICER	Dominance
Excluding dominated						
000000	2,784		0.295			
210000	7,107	4,323	0.313	0.018	235,563	
All						
000000	2,784	-	0.295	0	-	
210000	7,107	4,323	0.313	0.018	235,563	
210100	8,078	972	0.311	-0.002	-518,892	
110000	19,344	12,237	0.295	-0.018	-671,884	
110100	23,514	16,407	0.293	-0.02	-827,619	
All referencing common baseline						
000000	2,784		0.295			undominated
210000	7,107	4,323	0.313	0.018	235,563	undominated
210100	8,078	5,295	0.311	0.016	321,300	abs. dominated
110000	19,344	16,560	0.295	0	119,037,945	abs. dominated
110100	23,514	20,730	0.293	-0.001	-14,075,268	abs. dominated
All by Increasing effectiveness						
110100	23,514		0.293			
000000	2,784		0.295			
110000	19,344		0.295			
210100	8,078		0.311			
210000	7,107		0.313			

Table B.45. Ranking of strategies in high, medium, and low socioeconomic status (HML) scenario.

Variable	Range	Magnitude	Dominant int.	Cost	Effect	Incr. cost	Incr. effect	ICER
c_hr_PCS	LV	1,052	210000	6,692	0.314	3,908	0.019	205,424
c_hr_PCS	UV	1,753	210000	8,038	0.314	5,254	0.019	276,162
c_hyg_kit	zero	0	210000	4,976	0.314	2,192	0.019	115,211
c_hyg_kit	LV	983	210000	6,768	0.314	3,985	0.019	209,445
c_hyg_kit	UV	1,638	210000	7,963	0.314	5,179	0.019	272,236
dis_rate	GLV	0	210000	7,522	0.333	4,738	0.020	234,772
dis_rate	GUV	0.05	210000	7,264	0.302	4,480	0.018	244,729
p_b_caries_48_HML	LCI	0.482	210000	7,365	0.327	4,581	0.020	231,031
p_b_caries_48_HML	UCI	0.524	210000	7,365	0.301	4,581	0.018	251,416
p_b_caries_54_HML	LCI	0.53	210000	7,365	0.314	4,581	0.019	240,793
p_b_caries_54_HML	UCI	0.572	210000	7,365	0.314	4,581	0.019	240,793
p_cover_DWCP	LV	0.24	210000	7,365	0.314	5,277	0.019	277,373
p_cover_DWCP	UV	0.4	210000	7,365	0.314	3,885	0.019	204,213
p_cover_PCS	LCI	t_p_cover_PCS_HML	210000	5,715	0.310	2,931	0.015	199,472
p_cover_PCS	UCI	t_p_cover_PCS_HML	210000	9,525	0.320	6,741	0.025	271,906
p_cover_PSS	LCI	t_p_cover_PSS	210000	7,365	0.314	4,581	0.019	240,793
p_cover_PSS	UCI	t_p_cover_PSS	210000	7,365	0.314	4,581	0.019	240,793
p_fv_HML	LV	0.049	210000	7,365	0.325	4,581	0.030	150,689
p_fv_HML	UV	0.087	210000	7,365	0.306	4,581	0.011	418,722
p_fva_PCS	LV	0.68	210000	7,365	0.309	4,581	0.014	320,537
p_fva_PCS	UV	1	210000	7,365	0.316	4,581	0.021	216,148

Table B.46. Parameters for deterministic sensitivity analysis in high, medium, and low socioeconomic status (HML) scenario. See Table B.10.2 for description of abbreviations.

Interventions	Cost	Incr. cost	Effect	Incr. effect	ICER	Dominance
Excluding dominated						
000000	2,784		0.235			
210000	7,541	4,758	0.311	0.076	62,636	
All						
000000	2,784	-	0.235	0	-	
210000	7,541	4,758	0.311	0.076	62,636	
210100	9,303	1,761	0.305	-0.007	-258,669	
110000	15,546	8,005	0.26	-0.051	-155,816	
110100	19,906	12,365	0.257	-0.055	-226,836	
All referencing common baseline						
000000	2,784		0.235			undominated
210000	7,541	4,758	0.311	0.076	62,636	undominated
210100	9,303	6,519	0.305	0.069	94,277	abs. dominated
110000	15,546	12,762	0.26	0.025	519,133	abs. dominated
110100	19,906	17,123	0.257	0.021	798,409	abs. dominated
All by Increasing effectiveness						
000000	2,784		0.235			
110100	19,906		0.257			
110000	15,546		0.26			
210100	9,303		0.305			
210000	7,541		0.311			

Table B.47. Ranking of strategies in best-case (BC) scenario.

Variable	Range	Magnitude	Dominant int.	Cost	Effect	Incr. cost	Incr. effect	ICER
c_hr_PCS	LV	1,052	210000	7,010	0.311	4,227	0.072	58,654
c_hr_PCS	UV	1,753	210000	9,203	0.311	6,419	0.072	89,081
c_hyg_kit	zero	0	210000	7,541	0.311	4,758	0.072	66,021
c_hyg_kit	LV	983	210000	10,462	0.311	7,679	0.072	106,555
c_hyg_kit	UV	1,638	210000	12,409	0.311	9,625	0.072	133,564
dis_rate	GLV	0	210000	7,813	0.340	5,030	0.086	58,239
dis_rate	GUV	0.05	210000	7,370	0.294	4,586	0.064	72,070
p_b_caries_36_L	LCI	0.356	210000	7,541	0.323	4,758	0.084	56,913
p_b_caries_36_L	UCI	0.402	210000	7,541	0.300	4,758	0.061	78,600
p_b_caries_48_L	LCI	0.536	210000	7,541	0.311	4,758	0.058	82,232
p_b_caries_48_L	UCI	0.589	210000	7,541	0.311	4,758	0.087	54,802
p_b_caries_54_L	LCI	0.589	210000	7,541	0.311	4,758	0.072	66,021
p_b_caries_54_L	UCI	0.641	210000	7,541	0.311	4,758	0.072	66,021
p_cover_DWCP	LV	0.24	210000	7,541	0.311	5,454	0.072	76,165
p_cover_DWCP	UV	0.4	210000	7,541	0.311	4,062	0.073	56,006
p_cover_PCS_36	LCI	t_p_cover_PCS_36	210000	7,240	0.309	4,456	0.069	64,288
p_cover_PCS_36	UCI	t_p_cover_PCS_36	210000	7,841	0.314	5,058	0.075	67,598
p_fv_L	LV	0.034	210000	7,541	0.322	4,758	0.082	57,863
p_fv_L	UV	0.059	210000	7,541	0.301	4,758	0.061	77,537
p_fva_PCS	LV	0.5	210000	7,541	0.282	4,758	0.043	111,318
p_fva_PCS	UV	1	210000	7,541	0.319	4,758	0.080	59,637

Table B.48. Parameters for deterministic sensitivity analysis in best-case (BC) scenario.

	Unit	000000	110000	110100	210000	210100
cost per child (from DAM)	CLP	2,784	19,344	23,514	7,620	8,662
incremental cost	CLP	-	16,560	20,730	4,836	5,878
effect of intervention (from DAM)	%	23.5%	26.0%	25.7%	27.2%	26.9%
incremental effect	%	-	2.5%	2.2%	3.7%	3.4%
whole preschool population	child	250,149	250,149	250,149	250,149	250,149
eligible population for intervention	child	211,002	141,691	141,691	211,002	211,002
not eligible population for intervention	child	39,147	108,458	108,458	39,147	39,147
caries-free children in eligible population	child	49,586	36,840	36,415	57,393	56,760
caries-free in not eligible population	child	15,193	36,344	36,344	15,193	15,193
effectiveness of intervention (no. caries-free children in whole population)	child	64,778	73,184	72,759	72,585	71,952
cost of intervention	CLP	587,430,690	2,740,864,878	3,331,715,092	1,607,838,311	1,827,702,815
incr. cost of intervention compared to do-nothing intervention	CLP	-	2,153,434,188	2,744,284,402	1,020,407,621	1,240,272,125
effect of intervention in whole population (% of population)	%	25.9%	29.3%	29.1%	29.0%	28.8%
incr. effect of in whole pop. compared with counselling-only intervention	%	-	3.4%	3.2%	3.1%	2.9%
% increased of caries-free children in adjusted target population (MINSAL's goal)	%	-	13.0%	12.3%	12.1%	11.1%

Table B.49. Eligible population for each intervention and adjusted costs and effects in the entire Chilean preschool population.

Interventions	Cost	Incr. cost	Effect	Incr. effect	ICER	Dominance
Excluding dominated						
000000	2,784		0.247			
210000	7,620	4,836	0.284	0.037	129,271	
All						
000000	2,784	-	0.247	0	-	
210000	7,620	4,836	0.284	0.037	129,271	
210100	8,662	1,042	0.28	-0.004	-265,729	
110000	19,344	11,724	0.27	-0.015	-795,894	
110100	23,514	15,894	0.266	-0.018	-886,442	
All referencing common baseline						
000000	2,784		0.247			undominated
210000	7,620	4,836	0.284	0.037	129,271	undominated
210100	8,662	5,878	0.28	0.033	175,515	abs. dominated
110000	19,344	16,560	0.27	0.023	730,085	abs. dominated
110100	23,514	20,730	0.266	0.019	1,064,070	abs. dominated
All by Increasing effectiveness						
000000	2,784		0.247			
110100	23,514		0.266			
110000	19,344		0.27			
210100	8,662		0.28			
210000	7,620		0.284			

Table B.50. Ranking of strategies in the fluoridated water positive (FWP) scenario.

Interventions	Cost	Incr. cost	Effect	Incr. effect	ICER	Dominance
Excluding dominated						
000000	2,784		0.152			
210000	7,620	4,836	0.183	0.031	155,764	
110000	19,344	11,724	0.19	0.007	1,611,565	
All						
000000	2,784	-	0.152	0	-	
210000	7,620	4,836	0.183	0.031	155,764	
210100	8,662	1,042	0.179	-0.003	-315,624	
110000	19,344	11,724	0.19	0.007	1,611,565	
110100	23,514	4,170	0.188	-0.003	-1,640,154	
All referencing common baseline						
000000	2,784		0.152			undominated
210000	7,620	4,836	0.183	0.031	155,764	undominated
210100	8,662	5,878	0.179	0.028	211,845	abs. dominated
110000	19,344	16,560	0.19	0.038	432,107	undominated
110100	23,514	20,730	0.188	0.036	579,369	abs. dominated
All by Increasing effectiveness						
000000	2,784		0.152			
210100	8,662		0.179			
210000	7,620		0.183			
110100	23,514		0.188			
110000	19,344		0.19			

Table B.51. Ranking of strategies in the fluoridated water negative (FWN) scenario.

Appendix C. Documents

Factors influencing prevalence of caries in a Chilean preschool population: Econometric analysis.

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Introduction

Many studies worldwide have highlighted different factors influencing caries prevalence and with Chile there appears to be a difference between regions in prevalence[1,2]. The reason for this prevalence differs warrants investigation and additional studies are required to examine the factors associated with this difference. The aim of this study is to examine the relationship of several risk indicators with the prevalence of caries (dmft>0) difference in the Chilean preschool population.

Methods

The data used come from a cross-sectional study directed by the Chilean Ministry of Health. This dataset is drawn from a clinical examination of 1600 4-year-olds children and a parental completed questionnaire carried out in 2010. Variables used in the analysis include type of school (as proxy of socioeconomic status), oral health behaviours, feeding behaviours and, coverage of fluoridated water by county.

Multivariate logistic regressions were conducted to investigate the relationship between these variables and prevalence of caries. Weighted data were used.

Results

Type of school (private, subsidised or public) showed a statistically significantly relationship. Other significant variables were educational level of head of household, mother's number of teeth, frequency of toothbrushing, autonomy of toothbrushing, drinking sugary liquids before bed, previous dentist experience and perceived need for treatment. The presence of fluoridated water was highly significant ($p<0.001$) and had an OR of 0.32 (CI_{95} 0.24-0.43). See Table 1.

Discussion

These results corroborate the findings of numerous studies which establish a relationship between prevalence of caries and existence of fluoridated water. Also, given that the region with the higher prevalence of caries is the only one that lacks fluoridated water, the results could give some hints that explain the difference in caries at this age among Chilean regions.

The results, which indicate that children with highest risk of caries were those with no fluoridated water and who attended either subsidised or public schools (medium or low socioeconomic status), could help to allocate resources in a better way.

Table 1. Multivariate logistic regression of caries prevalence in a Chilean preschool sample aged 4 years.

	OR	SE	lower CI	upper CI	
Fluoridated water					
no	.	.	.	.	
yes	**0.324**	0.047	0.244	0.430	*
Type of school					
private	.	.	.	.	
subsidised	**2.162**	0.655	1.194	3.916	**
public	**1.803**	0.497	1.050	3.096	**
Educational level of head of household					
primary incomplete	.	.	.	.	
tertiary complete	**0.580**	0.154	0.345	0.975	**
no. teeth lost by mother					
5 or more teeth	.	.	.	.	
only one	**0.546**	0.114	0.363	0.823	*
none	**0.578**	0.123	0.381	0.878	**
Intake of toothpaste					
always	.	.	.	.	
sometimes	**0.386**	0.154	0.177	0.843	**
never	**0.317**	0.125	0.147	0.687	*
Brushing autonomy					
seft-brushing	.	.	.	.	
seft-brushing, with adult supervision	**0.408**	0.094	0.260	0.641	*
by an adult	**0.385**	0.103	0.228	0.651	*
Intake of liquid with sugar before bed					
always	.	.	.	.	
rarely	**0.438**	0.102	0.277	0.692	*
never	**0.564**	0.118	0.375	0.849	*
Breastfeeding					
breastfed exclusively	.	.	.	.	
formula exclusively	**0.536**	0.168	0.290	0.990	**
Perceived need of dental care					
yes	.	.	.	.	
no	**0.306**	0.058	0.211	0.444	*
Previous dental experience					
yes	.	.	.	.	
no	**0.471**	0.064	0.360	0.616	*

Table with significant categories only. * *P* value < 0.01, ** *P* value < 0.05.

Conclusion

The absence of fluoridated water was the most significant predictor of caries prevalence. These findings will allow better targeting the preschool population in future studies.

Funding

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References

1.Letelier MJ, Mendoza C, Del Valle C. Informe consolidado del Diagnóstico Nacional de Salud Bucal de los niños y niñas de 2 y 4 años que participan en la educación parvularia. Chile 2007-2010. Ministerio de Salud, Chile. 2012.

2.Hoffmeister L, Moya P, Vidal C, Fuentes R, Silva J. Diagnóstico en Salud Bucal de los niños de 2 y 4 años de edad que asisten a la educación preescolar en la zona sur del país. Ministerio de Salud, Chile. 2010.

How fluoridated water is related to prevalence of caries in a Chilean preschool population.

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Introduction

Existing studies[1,2] have found a difference in caries prevalence among Chilean regions. Further studies are required to determinate the factors associated with this difference. This study aims to examine the relationship between water fluoridation and the prevalence of caries, controlling for school dependency (as proxy of socioeconomic status) and other risk indicators.

Methods

The data used in this research are based on a cross-sectional study directed by the Chilean Ministry of Health. This dataset contains a clinical examination of 1600 4-year-olds children and a parental completed questionnaire carried out in 2010. Variables used in the analysis include type of school, oral health behaviours, and the coverage of fluoridated water by counties in 2010. Weighted data were used.

Multivariate logistic regressions were conducted to investigate the relationship between the variables and prevalence of caries. The dependent variable was the decayed, missing and filled index (dmft).

Results

The presence of fluoridated water was highly significant ($p<0.001$) and had an OR of 0.32 (CI_{95} 0.24-0.43). Dependency of school (private, subsidised or public) showed statistically significantly differences.

Other significant variables were educational level of head of household, mother's number of teeth, autonomy of toothbrushing, drinking sugary liquids before bed, previous dentist experience and perceived need for treatment. See Table 1.

Discussion

These findings coincide with numerous studies which establish a relationship between prevalence of caries and existence of fluoridated water. Also, given that the region with the higher prevalence of caries is the only one that lacks fluoridated water, the results could give some hints that explain the difference in caries at this age among Chilean regions.

The results indicate that children with highest risk of caries were those with no fluoridated water and who attended either subsidised or public schools (medium or low socioeconomic status). These findings could help with the effective allocation of health resources.

Table 1. Multivariate logistic regression of caries prevalence in a Chilean preschool sample aged 4 years.

	OR	SE	lower CI	upper CI	
Fluoridated water					
no	.	.	.	.	
yes	**0.324**	0.047	0.244	0.430	*
School dependency					
private	.	.	.	.	
subsidised	**2.162**	0.655	1.194	3.916	**
public	**1.803**	0.497	1.050	3.096	**
Educational level of head of household					
primary incomplete	.	.	.	.	
tertiary complete	**0.580**	0.154	0.345	0.975	**
no. teeth lost by mother					
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Intake of toothpaste					
always	.	.	.	.	
sometimes	**0.386**	0.154	0.177	0.843	**
never	**0.317**	0.125	0.147	0.687	*
Brushing autonomy					
seft-brushing	.	.	.	.	
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Intake of liquid with sugar before bed					
always	.	.	.	.	
rarely	**0.438**	0.102	0.277	0.692	*
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yes	.	.	.	.	
no	**0.306**	0.058	0.211	0.444	*
Previous dental experience					
yes	.	.	.	.	
no	**0.471**	0.064	0.360	0.616	*

Table with significant categories only. * *P* value < 0.01, ** *P* value < 0.05.

Conclusion

The nonexistence of fluoridated water was the most significant predictor of caries prevalence. These findings will allow better targeting of preschool population in future studies.

Funding

This research is funded by Chilean National Commission for Scientific and Technological Research (CONICYT), as part of funding for the corresponding author.

References

1.Letelier MJ, Mendoza C, Del Valle C. Informe consolidado del Diagnóstico Nacional de Salud Bucal de los niños y niñas de 2 y 4 años que participan en la educación parvularia. Chile 2007-2010. Ministerio de Salud, Chile. 2012.

2.Hoffmeister L, Moya P, Vidal C, Fuentes R, Silva J. Diagnóstico en Salud Bucal de los niños de 2 y 4 años de edad que asisten a la educación preescolar en la zona sur del país. Ministerio de Salud, Chile. 2010.

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TITLE: The Use of Decision Analytic Models in Oral Health Interventions

AUTHORS (FIRST NAME INITIAL LAST NAME): R. A. Palacio[1, 2], C. R. Vernazza[1, 2], J. Steele[1, 2], J. Shen[2], L. Vale[2]

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PREFERRED PRESENTATION TYPE: Oral

CURRENT SCIENTIFIC GROUPS & NETWORKS: Behavioral, Epidemiologic and Health Services Research

ABSTRACT BODY:

Objectives: Decision analytic models (DAMs) allow predictions of effectiveness and costs for a specific health technology to be obtained and, they can be used to evaluate either a new service or an existing one. This study shows the use of DAMs to evaluate whether fluoride varnish application (FV) increases the proportion of caries-free children in the Chilean preschool population at an acceptable cost.

Methods: Different FV strategies were compared with a baseline strategy (oral health counselling only). Fluoride varnish application was tested every 6 months over 2 years in a preschool setting and during a well-child programme appointment in a primary care setting, with and without screening, for areas with and without fluoridated water and, for different socioeconomic statuses. Several Markov models were created to simulate the FV performance; such models were populated with data obtained from Chilean datasets, a systematic review and, a costing study. A Markov model was used to estimate the cost-effectiveness of the different strategies compared and an incremental cost-effectiveness ratio (ICER) was estimated. The robustness of such estimates was tested using one-way deterministic sensitivity analyses and Monte Carlo simulation..

Results: All FV strategies and scenarios presented a small increase in the number of caries free children. The FV application in a primary care setting without screening was dominant in the low SES scenario; this strategy increased the caries-free population by 3.7% at an extra cost of £4.62 per child. The starting age of application significantly affected cost-effectiveness and the ICER decreased if other health professionals, rather than dentists, provided FV applications.

Conclusions: This analysis provided the simulation of the performance of FV in realistic scenarios incorporating important aspects of health and education policies. The FV application in a primary care setting was the most cost-effective strategy. The methodology and results can be useful for both policy and decision-makers.

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TABLE FOOTER: (No Tables)

(No Image Selected)

KEYWORDS: Cost-effectiveness, Health economics, Fluoride varnish, Decision analytic model.

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Special Scheduling Needs - Abstracts:

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Abstract Submission - Track Selection: Not Applicable

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