**ELIZABETH DE SOUZA ROCHA**

# Is sealing an alternative to restoration for moderate caries lesions on occlusal surfaces in primary teeth?

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# Is sealing an alternative to restoration for moderate caries lesions on occlusal surfaces in primary teeth?

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Thesis presented to the School of Dentistry, University of São Paulo, by the Graduate Program in Dental Sciences to obtain the degree of PhD in Sciences.

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*"Quem caminha sozinho pode até chegar mais rápido, mas aquele que vai acompanhado, com certeza vai mais longe."* (*Clarice Lispector*)

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*"Aonde quer que eu vá, serei luz, e em cada caminho que passar vão saber." (Thiago Barbosa)*

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*"A mente grata é aquela que atrai para si as melhores coisas."* (Platão)

*"Nunca se afaste de seus sonhos, pois se eles se forem*
*você continuará vivendo, mas terá deixado de existir."*
*Charles Chaplin*

## ABSTRACT

Rocha ES. Is sealing an alternative to restoration for moderate caries lesions on occlusal surfaces in primary teeth? [thesis]. São Paulo: University of São Paulo, School of Dentistry, 2019. Corrected Version.

In Dentistry, despite the current use of minimal intervention, a significant proportion of dentists still intervene invasively in caries lesions that were clinically or radiographically confined to enamel, or even minimally into dentine. Indeed, some non-frankly cavitated caries may present a risk for caries progression that seems to be higher than initial caries lesions, deserving special attention in controlling their progression. The aim of this study was to investigate the risk of progression moderate caries lesions (ICDAS 3-4) and to evaluate if caries sealing may be an alternative to restorations for controlling these lesions on occlusal surfaces of primary molars, guiding further clinical decision-making related to management of this type of lesions. This volume presents a compilation of a systematic review and a randomized clinical trial associated to an economic evaluation, whose reports were guided by the PRISMA, CONSORT, and CHEERS recommendations. We performed a systematic review, whose literature search sought for evaluating the impact of clinical and radiographic characteristics of caries lesions on their progression in primary teeth. With this study it was possible to know that lesions presenting cavitation, even clinically confine clinically into enamel and nor exposing dentine, had higher risk of progression. In addition, a non-inferiority randomized clinical trial was designed to evaluate the longevity (no need of reinterventions) of sealing moderate caries lesions with glass ionomer cement as an alternative to restorations with the same material. An economic evaluation was associated with this clinical trial to assess cost-effectiveness of implementing this alternative treatment. A societal perspective and a 2-year time horizon. In this clinical trial, children with 3 to 6 years-old, with at least one occlusal surface classified as scores 3 or 4 of ICDAS were randomized. Children were treated and reassessed biannually for 24 months. The primary endpoint to assess clinical efficacy of treatments was the need for reintervention (sealant/restoration repairments, replacements and caries lesions progression). For the economic evaluation, costs of treatments and reinterventions were assessed.

The incremental cost-effectiveness ratio to verify the efficiency of substituting the use of restorations by sealants on moderate caries lesion. For that, both patient-centered (children' acceptability assessed by Wong-Baker Facial Scale) and professional-centered (no caries progression) as health effects. After 2-year follow-up, sealing of moderate caries lesion with glass ionomer cement sealants demanded more replacement than restorations. On the other hand, no differences in caries progression were observed between groups. When professional-centered view was considered, sealants offered a 30%-probability of being an optimal cost-effective option to substitute restorations in order to avoid caries progression, while using the children acceptability this probability increased to 50%. Considering that moderate caries lesions present a high-risk to progress, sealing may be an alternative to manage the moderate caries in primary teeth compared to restorations, but a higher number of replacements may be necessary. On the other hand, it is important to consider this alternative treatment can benefit different groups in different ways and besides, their benefit can be influenced by the perspective is heard for decision-making (professional or patient-centered). Exploration about these differences are motivation for further studies.

Keywords: Tooth, Deciduous. Glass Ionomer Cements. Systematic Review. Survival Analysis. Economic Evaluation.

# RESUMO

Rocha ES. O Selante é uma alternativa as restaurações para lesões de cárie moderada na superfície oclusal de dentes decíduos? [tese]. São Paulo: Universidade de São Paulo, Faculdade de Odontologia; 2019. Versão Corrigida.

Na Odontologia, apesar do conceito da mínima intervenção, uma proporção significativa de dentistas ainda intervém de maneira invasiva em lesões de cárie, clinicamente ou radiograficamente confinadas ao esmalte, ou até minimamente em dentina. Algumas lesões não francamente cavitadas apresentam um risco de progressão maior que lesões iniciais, merecendo atenção especial no controle de sua progressão. O objetivo desse trabalho foi investigar o risco de progressão de lesões de cárie moderada (ICDAS 3-4) e avaliar se o selamento pode ser uma alternativa as restaurações no controle de em superfícies oclusais de molares decíduos. Este volume apresenta um compilado de uma revisão sistemática e um ensaio clínico randomizado associado a uma avaliação econômica cujas redações foram orientados pelas recomendações dos guias PRISMA, CONSORT e CHEERS. Realizamos uma revisão sistemática, cuja pesquisa bibliográfica buscou avaliar o impacto das características clínicas e radiográficas das lesões de cárie na sua progressão em dentes decíduos. Assim, foi possível observar que lesões apresentando cavidades mesmo que clinicamente confinadas em esmalte ou sombra, apresentavam maior risco de progressão. Adicionalmente, um ensaio clínico randomizado de não inferioridade foi delineado, para avaliar a longevidade (não necessidade de reintervenções) do selamento de lesões de cárie moderada com cimento de ionômero de vidro como alternativa as restaurações com o mesmo material. Uma avaliação econômica foi associada a este ensaio clínico para avaliar a custo-efetividade da implementação desse tratamento alternativo. Uma perspectiva societal e um horizonte temporal de 2 anos. No estudo clínico, crianças entre 3 a 6 anos, que apresentaram superfícies oclusais classificadas como escores 3 ou 4 do ICDAS foram randomizadas. As crianças foram tratadas e reavaliados bianualmente por 24 meses por 2 examinadores treinados. O desfecho primário foi a necessidade de reintervenção nos dentes inicialmente tratados (falhas que demandassem a reparo, substituição dos selantes e restaurações, bem como progressão de lesões

que demandassem nova restauração). Os custos dos tratamentos e reintervenções foram calculados para se avaliar a razão de custo-efetividade incremental para avaliar a eficiência da substituição da restauração pelos selantes em lesões de cárie moderadas. Para isso, efeitos de saúde centrados no paciente (aceitabilidade dos tratamentos usando a escala da Wong-Baker) e no profissional (ausência de progressão de cárie) foram usados. Após 2 anos de acompanhamento, o selamento de lesões de cárie moderada com cimento de ionômero de vidro demandou maior número de substituições que as restaurações. Por outro lado, não houve diferença quanto à progressão de cárie. Quando a visão do profissional foi colocada, os selantes ofereceram uma probabilidade de 30% de ser uma ótima opção custo-efetiva em alternativa à restauração para evitar progressão de cárie, enquanto usando a aceitabilidade pela criança, essa probabilidade aumentou para 50%. Assim, considerando que as lesões moderadas realmente apresentam um alto risco de progressão, selar pode ser uma alternativa à restauração para controlar esse tipo de lesão, mas um maior número de reintervenções pode ser necessário. Por outro lado, é importante considerar que esse tratamento alternativo pode beneficiar grupos diferentes de formas diferentes e ainda, esse benefício pode variar com a perspectiva ouvida para a tomada de decisão (se é centrada no paciente ou no profissional). A investigação futura sobre essas diferenças faz-se ainda necessária.

Palavras-chave: Cárie Dentária. Dente decíduo. Cimento de Ionômero de Vidro. Revisão Sistemática. Análise de Sobrevida. Avaliação Econômica.

## SUMMARY

# 1 INTRODUCTION

Nowadays, there is still a gap between the clinical practice and scientific evidence about the management of caries lesions. Historically, in Dentistry, caries diagnosis had been only limited to the detection of cavitated lesions and restorations were often used as exclusive option to control these caries lesions (1). In this context, restorations have been indicated as a way to control biofilm in the lesions (2), acting as a mechanical barrier and preventing the caries progression. However, with the advent of minimal intervention, the management of dental caries has been changing. The invasive treatments that resulted in large loss of healthy tissues have been replaced by procedures that aimed to preserve the dental structure (3). In this sense, caries detection at early stages would allow the professional to manage lesions earlier and possible using less invasive treatments (4).

Despite the current use of minimal intervention, a significant proportion of dentists still intervene invasively in caries lesions that were clinically or radiographically confined to enamel, or even minimally into dentin (5). Indeed, some non-frankly cavitated caries (moderate caries lesions classified as score 3 or 4 of International Caries Detection and Assessment System - ICDAS ) may present a risk for caries progression that seems to be higher than initial caries lesions (6–8), deserving special attention in controlling their progression. We believe their behavior tend to be different from earlier lesions because some of them are indeed confined (even minimally) into dentin (9).

A recent expert consensus on caries management pointed out the sealants as an alternative, for occlusal surfaces, to intervene on micro-cavitated caries lesions radiographically extending into enamel and in outer half of dentin (10). Sealants can act as a mechanical barrier over the lesion, limiting the direct contact between dental surface and the biofilm and controlling caries progression (11,12). Some evidence has been created for sealing of microcavitated/moderate caries lesions using resin-based sealant as an alternative for caries lesion management (13,14). Although both restorations and sealants treatments can act to arrest caries lesions, to guarantee restorative material insertion in restorations, some dental tissue needs to be removed, differently from caries sealing. Therefore, if sealants have the same effect to control the caries lesions, it could be a better option compared to restorations.

Moreover, these evidences (13,14) realized the treatment with rubber dam, once, to perform a perfect moisture control in children could be difficult, therefore high viscosity glass ionomer cement (HVGIC) could be raised as a possible alternative for sealing moderate caries lesions in primary teeth. This idea emerges considering this material has a relatively short time of work and is less sensitive to moisture than resin-based materials (15,16). On the other hand, due to the differences in their adhesive/retention properties, the glass ionomer cement (GIC) could present lower retention than resin-based sealants (17). Therefore, differences in findings related to caries lesion control or even, demand for a higher number of re-interventions could be expected, negatively impacting on efficiency of implementing such treatment option. That is why this simpler alternative using HVGIC should be deeper explored scientifically.

There is growing demand, for less invasive and simpler techniques, especially for children, looking for minimizing difficulties in children's behavioral management during restorative dental treatments (18). In this sense, new researches in this field are relevant as an opportunity to learn and expand the knowledge about less invasive options to children looking for the best management of caries lesions for children, as well to motivate evidence-based changes in professionals' decisions for intervene on some caries lesions, as moderate lesions.

Based on the rationale exposed above, this thesis consists of three chapters. The first chapter is a systematic review and meta-analysis aiming to evidence the real need for extra-controlling of moderate caries lesions compared to other non-frankly cavitated lesions based on their progression rates along the time. The second and third-chapters report results related to a non-inferiority Randomized Clinical Trial (RCT) in which we opted for testing sealing using HVGIC as an alternative to restorations when managing moderate caries lesions on occlusal surface of primary molars. These two chapters contain the first 2-year results from this trial. The 2$^{nd}$ chapter focus specifically on clinical performance of two caries management alternatives (sealing vs. restoring), evidencing the impact of computing successive failures of these treatments to access their performance. Finally, the 3$^{rd}$ chapter evidences the economic impact of opting for the sealant as an alternative to restoration both when treatment success and patients' acceptability are considered as health effects. At the end, we expected the readers could have a rationale for

indicating appropriate treatments for moderate caries lesions as well as comprehend the biological and economic impact of using different approaches for managing them.

## 2 PROPOSITION

This study aims to contribute creating evidences if caries sealing may be an alternative to restorations for controlling moderate caries lesions (ICDAS 3-4) in occlusal surfaces of primary molars, guiding further clinical decision-making related to management of this type of lesions.

Based on that, the following specific purposes were outlined:

a. To identify, analyze and synthesize scientific evidence about patterns of progression of moderate caries lesions in primary teeth.

b. To explore the clinical performance of sealing occlusal moderate caries lesions in primary teeth using the HVGIC compared to restore them with the same material, including analysis of multiple successive failures (an unusual approach in Dentistry).

**c.** To perform a trial-based economic evaluation to check if sealing is an efficient option to substitute restorations used for some dentists in controlling moderate caries lesions, both when treatment success (caries arrestment) or patient-reported acceptability are considered as possible health effects.

# 3 CHAPTER I:

## How can lesion severity impact on caries progression in primary teeth? A systematic review and network meta-analysis

### 3.1 Introduction

Modern management of dental caries involves to detect and to assess caries lesions in early stages, identifying if the disease is actually present, establishing a prognosis based on patient's caries risk status, managing patients focused on prevention and caries lesions aiming their arrestment/reversal as well as postponing the restorative treatment until really necessary (19). Due to that, a growing interest in detecting noncavitated lesions in epidemiological studies has been observed in the last few years (20). The earlier detection has been advocated as an important aspect to guarantee early caries lesions management, avoiding the beginning of a repetitive restorative cycle (1) and reducing costs with the restorative treatment (19,21,22).

Besides patient's features, e.g. caries risk, clinical decision-making has been extensively based on caries lesions characteristics assessed clinically either radiographically (10,23). These guidelines have been mainly based on transversal studies which investigated caries severity and its relationship with histological and microbiological patterns (24,25). Although we could expect a high correlation between these parameters and progression of caries lesions, few longitudinal studies have explored that relationship systematically. Longitudinal studies are essential to provide a dental practitioner with an important information about the transition of the lesion (7). Additionally, guidelines usually extrapolate for primary teeth results observed in permanent dentition. Recognizing which caries lesions patterns (e.g. caries severity) are really related to higher caries progression in primary teeth is an important key to improve detection/assessment of these characteristics and to actually define their weight on decision-making process.

In addition, different characteristics have been studied in different samples and populations, presenting their own specificities. Aiming to create a guide possible to

be extrapolated, it is necessary to compile findings of these different scenario. Systematic reviews are a useful tool to summarize original studies on a subject for the profession, patients and policy makers, and consequently to support the correct translation, implementation and adoption of research knowledge in everyday practice (26).

To the best of the authors' knowledge, no previous studies have performed a systematic review, using direct and indirect evidences, to evaluate the impact of clinical and radiographic characteristics of caries lesions on their progression in primary teeth. Therefore, the purpose of this study was to evaluate how some caries lesions patterns, including caries severity used as threshold for decision-making guidelines/consensus, can influence on caries lesions progression to frankly cavitations into dentin (clinically assessed) or even, inner third of dentine (radiographically assessed). At the end, we aimed to provide a more robust rationale to guide clinical decision-making related to caries control in primary teeth.

## 3.2 Materials and methods

This paper was reported according to the Preferred Reporting Items for Systematic Reviews and Network Meta-Analyses (PRISMA - NMA extension) (Appendix A) (27). A review protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) database under the registration number #CRD 42017062388.

### 3.2.1 Literature Search

The electronic literature search was conducted through MEDLINE (PubMed) and included articles published until March 2019. The references of the included articles were also verified for checking possible studies not identified by the initial search. The bibliographic database chosen was PubMed, because some areas, such

Dentistry, it appears as a tool for complete search (28), and no language restrictions were applied. The complete search strategy is shown below (Figure 3.1).

Figure 3.1 – Search Strategy, chart containing the strategy for electronic databases

((((((((((((((((((cohort studies[MeSHTerms]) OR retrospective studies[MeSHTerms]) OR Prospective*[Text Word]) OR Longitudinal*[Text Word]) OR Cohort*[Text Word]) OR Retrospective*[Text Word]) OR prospective studies[MeSHTerms]) OR longitudinal studies[MeSHTerms]) OR follow up studies[MeSHTerms]) OR prognos*[Text Word]) OR episode[Text Word]) OR predict*[Text Word]) OR course*[Text Word]) OR progress*[Text Word]) OR evolution*[Text Word]) OR advance*[Text Word]))

AND

((((((((((tooth, deciduous[MeSHTerms]) OR "deciduous tooth"[Text Word]) OR "deciduous dentition*"[Text Word]) OR "primary dentition*"[Text Word]) OR "milk tooth"[Text Word]) OR "primary teeth"[Text Word]) OR "deciduous teeth"[Text Word]) OR "milk teeth"[Text Word]) OR "baby teeth"[Text Word]) OR "baby tooth"[Text Word]) OR "primary tooth"[Text Word])))

AND

((((((((((((((((((((carie*[Text Word]) OR "dental caries"[Text Word]) OR dental caries[MeSHTerms]) OR "caries lesion*"[Text Word]) OR carious[Text Word]) OR tooth demineralization[MeSHTerms]) OR "tooth demineralization"[Text Word]) OR "teeth demineralization"[Text Word]) OR cariology[Text Word]) OR dentin[MeSHTerms]) OR dentin*[Text Word]) OR cavit*[Text Word]) OR decay*[Text Word]) OR "teeth decay"[Text Word]) OR "tooth decay"[Text Word]) OR "dental white spot"[Text Word]) OR "white spot"[Text Word]) OR "white spot lesion*"[Text Word]) OR "white spot"[Text Word]) OR "dental white spots"[Text Word]) OR "enamel lesion*"[Text Word]) OR "enamel demineralization"[Text Word]) OR "dentin lesion"[Text Word])

Source: Author

### 3.2.2 Study Selection and Eligibility Criteria

Initially, the titles and abstracts of studies identified using the databases were evaluated by two independent reviewers (E.S.R. and F.R.R.). Disagreements were discussed with an expert (M.M.B.) to reach a consensus. The studies were considered eligible if fulfilled the following inclusion criteria. They had to assess caries lesions in primary teeth in longitudinal in vivo studies. After the first evaluation, the papers whose titles and abstracts met the inclusion criteria had their text fully reviewed. Those studies with at least one exclusion criterion were considered as ineligible. The exclusion criteria were: a) articles that reported any kind of interventions on caries lesions except for fluoride treatments, considered as standard care; b) papers that did not evaluate the caries lesions progression related to some

clinical and radiograph pattern. Some studies had data collected from permanent and primary teeth, but in this systematic review only the primary data was used. The researchers had been previously trained and calibrated for study selection (Kappa 0.87).

Attempts to access the studies were done through Internet, search in the library of the School of Dentistry, University of São Paulo, School of Clinical Dentistry, University of Sheffield and other libraries participating in the information sharing system. Only one paper could not be assessed even using all these strategies and it was also excluded from our sample. Papers that fulfilled the inclusion criteria and were not eliminate through the exclusion criteria were finally accepted for further data extraction and assessment of bias.

### 3.2.3 Data extraction

From the full texts of the included articles, data was extracted using a standardized form. The required information was collected by one reviewer (E.S.R.) and afterward verified by a second author (M.M.B.) that independently checked and approved collected data.

The following information was extracted from studies: publication details (authors and year), surface evaluated (smooth, proximal, or occlusal), sample size, dropout rate, follow up duration, clinic or radiographic characteristics registered, method, period and place when/where study was conducted, fluoridated water supply and use of fluoridated toothpaste, children's age range. Authors of the included studies were contacted via email to provide additional data (not available in the paper) when needed.

The primary outcome of interest was the caries lesions progression. Depending in data available, clinic or radiographic progression was considered. The clinical progression was considered when the surface initially scored as sound or carious progressed to frankly cavitated dentin caries lesions (ICDAS 5 or 6) or to a condition related to symptoms of reversible pulpits treated requiring endodontic treatment or extraction. Radiographic progression was considered when the surface initially scored as sound or carious progressed to inner third of dentine.

Considering each outcome, total sample size (number of surfaces) and the number of events per surface were registered in each category of clinical/radiographic pattern of each included study.

### 3.2.4 Assessment of risk of bias

After data collection, each selected study was qualitatively evaluated using the Newcastle Ottawa Quality Assessment scale for cohort studies (29) by one independent reviewer (E.S.R.). The risk of bias of the included studies was evaluated based on questions regarding the selection (representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and demonstration that outcome of interest was not present at start of study), comparability of the cohort and the outcome of the study (assessment of outcome and adequacy of follow up of cohorts). If the study fulfilled the criteria checked, a star was registered for it. In this systematic review, a grade was not given to studies based on the number of stars. We classified the studies in high risk of bias, if most part of the domain were not awarded by the star or low risk of bias, if most part of the domain were awarded by the star, as used in a previous systematic review (30). Besides, the domains with potential risk of bias were identified. To classify the study thresholds for converting the Newcastle-Ottawa scales to Agency for Health Research and Quality (AHRQ) standards was adapted as follows (Table 3.1).

Table 3.1 Newcastle-Ottawa scales

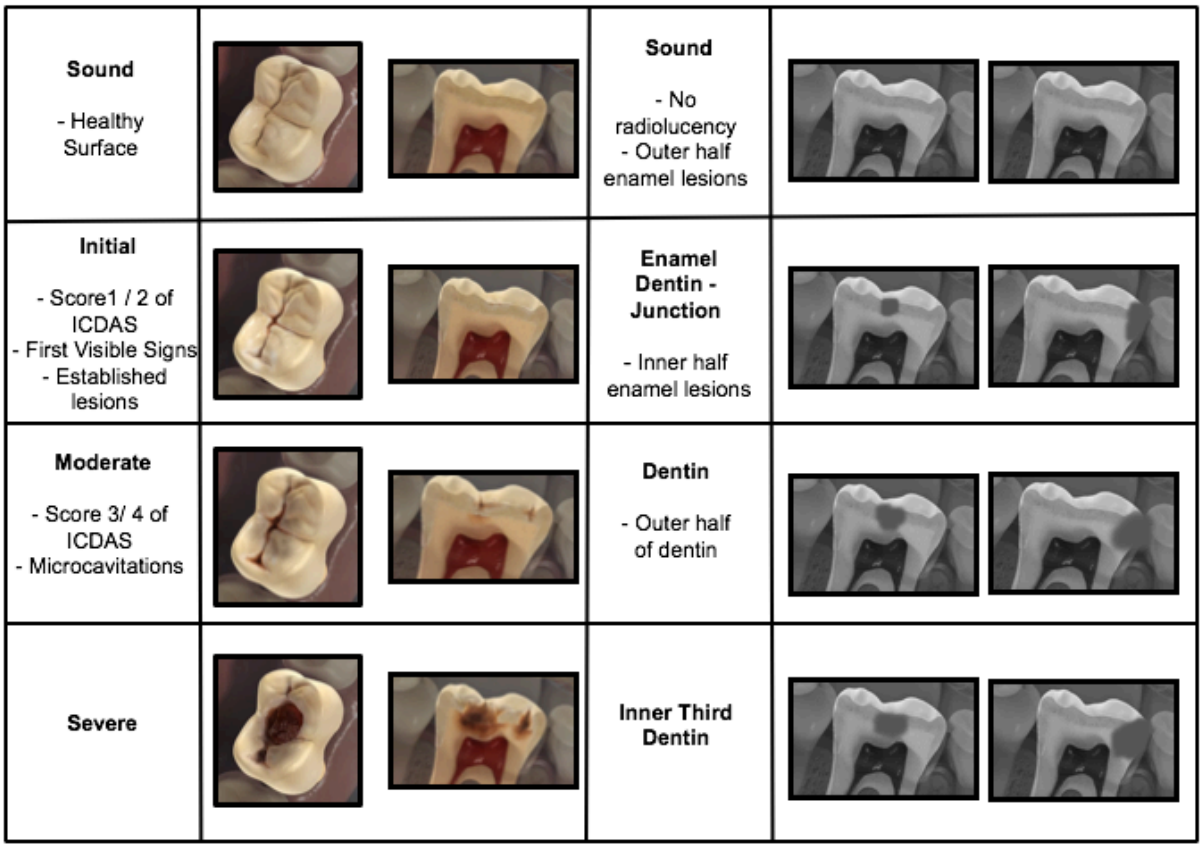
| **Selection** | | | | **Comparability** | **Outcome** | | | **Study** |
|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 1 | 1 | 2 | 3 | |
| 1 – 2 stars: high | | | | 0 star: high | 0 – 1 star: high | | | High |
| 3 – 4 stars: low | | | | 1 – 2 stars: low | 2 – 3 stars: low | | | Low |
| 2 stars: high | | | | 1 – 2 stars: low | 2 – 3 stars: low | | | Moderate |

Source: Author

### 3.2.5 Statistical Analyses

The analyses were performed to be focused on assessing which characteristics were associated with caries lesions progression in two years of follow up. Two different analyses were performed considering the two chosen outcomes: clinical and radiographic progression. To be included in one of these analyses, the study should present data required for that (total sample and number of events (clinical and/or radiographic progression). If data was available for both analyses, the study could be considered for both of them. Studies that did not present similar data about caries lesions progression, or 2-year-follow-up were excluded from the quantitative analyses. For studies with the same data set, only one were included in the meta-analysis, the study considered most complete and with the follow-up of two years. To explore the influence of caries lesions patterns on caries progression, we classified clinical lesion severity in sound surfaces, initial caries lesions, moderate caries lesions and severe caries lesions. The radiographic severity was categorized as: no radiolucency, radiolucency into enamel dentin junction, and radiolucency into dentin (Figure 3.2).

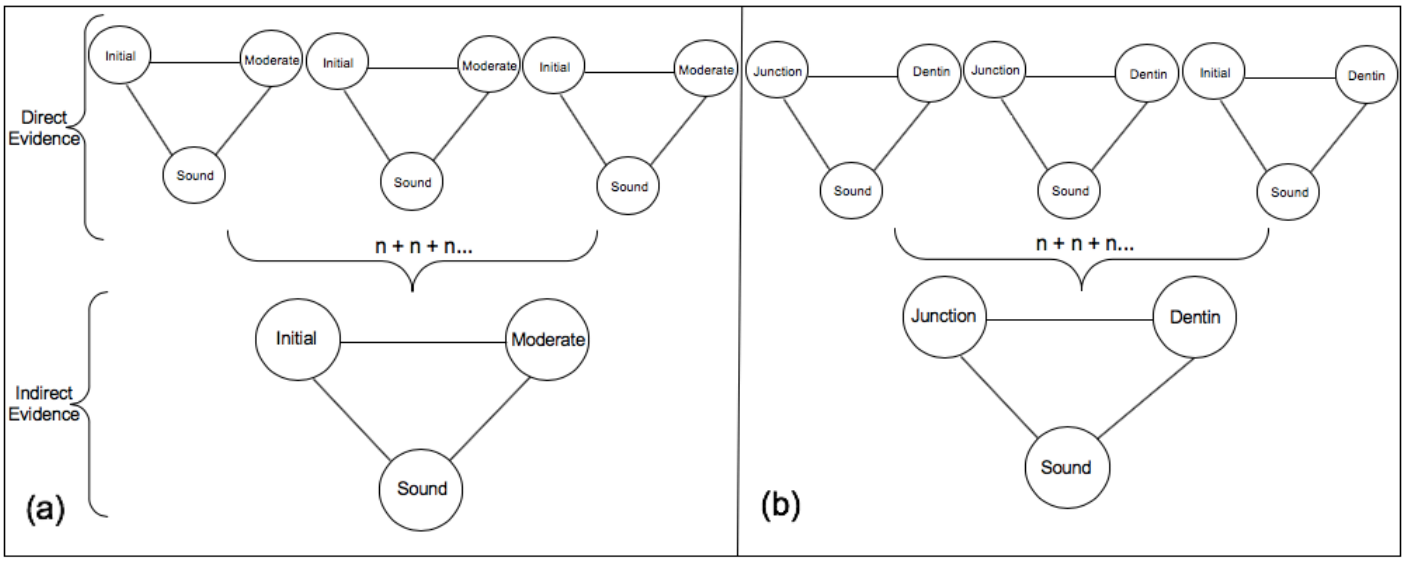
Figure 3.2 Caries lesions progression considering clinical and radiographic lesion severity




Source: Images from Virtual Man Project: Caries lesion formation and severity stages according to ICDAS (31).

Meta-analyses were performed using direct and indirect comparisons. Direct evidence was pooled based on data about progression for each category above in a same study. The indirect evidences were extracted by comparisons from different conditions (categories) from different studies. We used the Mixed treatment comparisons (MTC) strategy to estimation of metrics for all possible comparisons using the same model, combining direct and indirect evidences Figure 3.3. Both MTC and Network Meta-Analysis (NMA) are strategies to compare two or more set of treatments, however, in this study, we extrapolated this strategy to combine evidences from cohort studies, expecting a similar product given the limitations of this type of extrapolation discussed elsewhere. In addition, the MTC also allows the calculation of ranking probabilities (32) related to caries progression of different conditions studied.

Figure 3.3 – Scheme of direct and indirect evidence comparison considering clinical and radiographic lesion severity




For direct comparisons, meta-analyses were performed using the “meta” package, R software (R Studio, Version 1.0.143). Results from individual studies were pooled using a random-effects model. Meta-analyses used the inverse variance method and the DerSimonian-Laird estimator for tau^2. The pooled results were estimated using the Risk Ratio (RR) and 95% CIs. The presence of heterogeneity was checked via Cochran’s Q test and inconsistency was assessed using the I-squared ($I^2$).

Different dental surfaces (occlusal surfaces vs. free or proximal smooth surfaces) were considered as subgroups in subsequent direct comparisons. The idea was to check if caries progression presented the same patterns despite the surface considered. Differences between subgroups were tested using the “meta” package, R software (R Studio, Version 1.0.143). We could not explore the heterogeneity through meta-regressions and also, the publication bias, due to the low number of studies included.

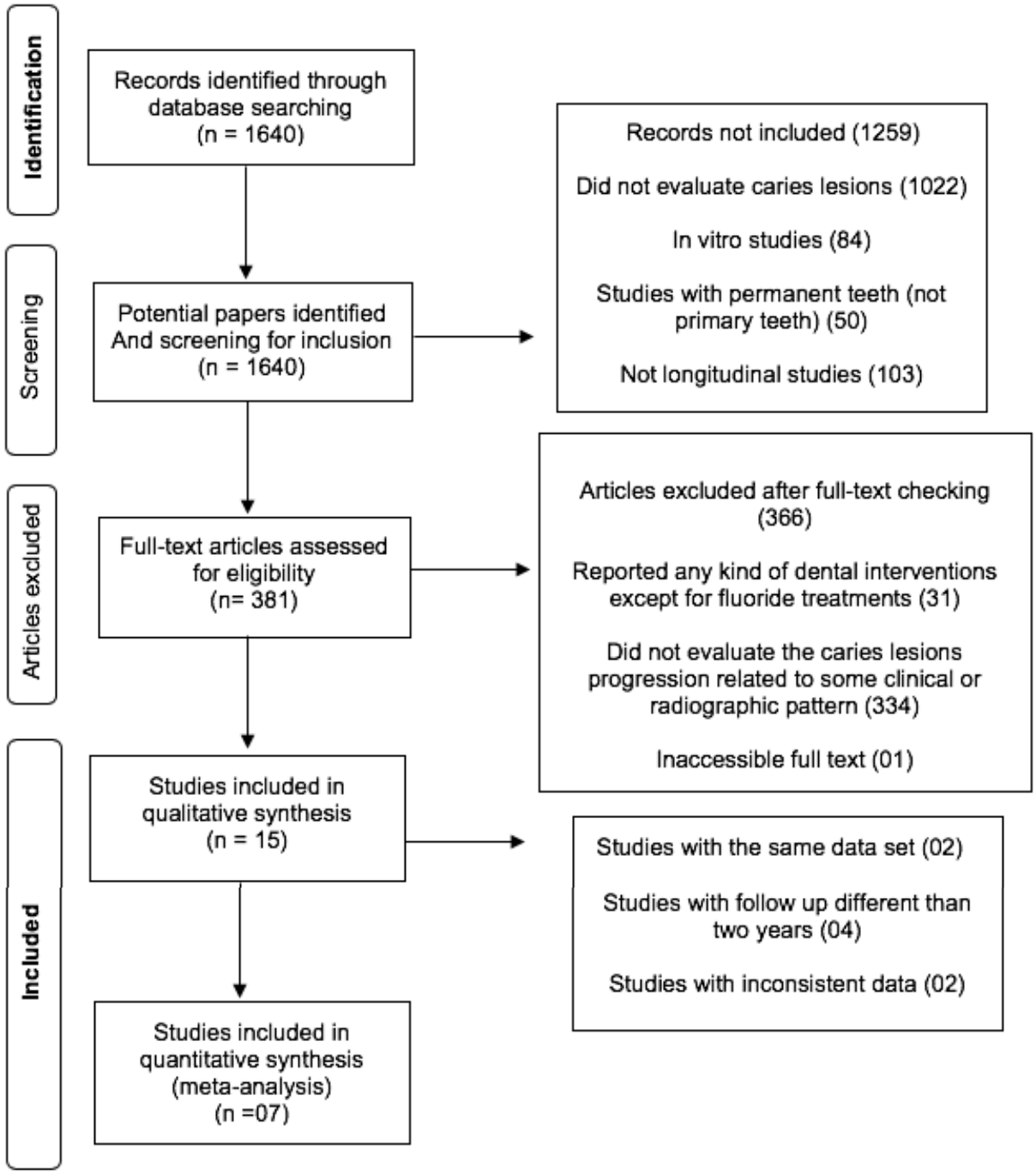
For mixed comparisons, we used the MTC strategy, that is based on a Bayesian hierarchical framework. The estimates were obtained by Markov-Chain Monte Carlo (MCMC) simulations, and the effect measures such Risk Relative (RR) with 95% confidence intervals (95%CI) were calculated for each pair of categories related to the clinical or radiographic characteristic evaluated. All analysis was conducted using the R statistical software with the GeMTC – package, version 0.8 and the rJAGSpackage to estimate the models. The choice between fixed and random effects was performed through the comparison of competing models with the Deviance Information Criteria (DIC). The goodness-of-fit to data was evaluated using residual deviance, for each model (33). Each chain used 5000 interactions with a burn-in of 350.000 and a thinning interval of 30. For all models Vague prior distributions were used. According to the values of DIC, the random effect model presents the best fit. It was also calculated the expected ranking of caries lesions progress based on the posterior probabilities (34) (e.g., in our study, the probability of to be condition that progress less, the second less until that one that progress more than all). Using the same approach, it was also performed subgroups analysis creating models for each subgroup separately.

## 3.3 Results

### 3.3.1 Study Selection

In total, 1.640 papers were identified through the search strategy, after screening title and abstracts, 1259 studies were not related to the topic under investigation. From the eligible studies, 366 manuscripts were excluded, mainly because instead of caries lesions, the studies evaluated children or risk factors (91%). A final number of 15 articles met the eligibility criteria and were included in the qualitative synthesis. Seven papers (3 studies related clinical characteristics of caries lesions and 4 studies related to radiographic features related to the lesions) with sufficient data to be included in the meta-analysis. 8 studies were not included in quantitative analyses, as well the severe caries lesion. Figure 3.4 shows the study selection process and the details of this systematic review.

Figure 3.4 – Flowchart diagram of identification, screening, and assessment of studies for checking their eligibility for this systematic review. Number between parentheses means quantity of studies in each category




Source: Author

### 3.3.2 Study characteristics

The major characteristics of datasets from included studies are displayed in Table 3.2 Publication years ranged from 1978 to 2017. The majority of the studies followed the patients for 2 - 2.5 years (53.3%), and 3.5 - 4 years (40.1%), and only one paper had the follow-up of 1 year (6.6%). From these studies, 2 pairs of studies comprised same samples but followed for different periods (35) or describing different set of data (36).

Furthermore, eight of manuscripts were performed in developed countries (53.3%), but three of these papers had a sample size with high determinants of low income. Seven studies were performed in undeveloped countries (46.7%). The most of the papers used fluoride in some way (water, toothpaste, topical application) (73.3%). Seven studies evaluated the clinical characteristics (46.7%), and eight evaluated the radiographic characteristics of caries lesions (53.3%). Only one study evaluated the activity of the caries lesions.

Table 3.2 – Main data characteristics from included studies.

| Author/Year | Country | Sample size | Age brackets | Fluoride | Follow up period | Drop Out | Clinical Characteristics (Severity) | Clinical Characteristics (Activity) | Radiographic exams |
|---|---|---|---|---|---|---|---|---|---|
| **Pitchika et al., 2016** | Germany | 320 Children | 2-3 Years Old | 500 ppm toothpaste 0.2 ppm water Fluoride varnish | 2 years | 80 Children (25%) | Yes | No | No |
| **Ismail et al., 2015** | USA | 654 Children | 0-5 Years Old | - | 2 years | 136 Children (20,7%) | Yes | No | No |
| **Ismail et al., 2010** | USA | 638 Children | 0-5 Years Old | - | 4 years | 152 Children (23,3%) | Yes | No | No |
| **Guedes et al., 2016** | Brazil | 469 Children | 1-5 Years Old | 0.7mg/L water | 2 years | 170 Children (36%) | Yes | No | No |
| **Guedes et al., 2014** | Brazil | 469 Children | 1-5 Years Old | 0.7mg/L water | 2 years | 170 Children (36%) | Yes | Yes | No |
| **Warren et al., 2005** | Sweden | 692 Children | 3-5 Years Old | Fluoride varnish | 4 years | - | Yes | No | No |
| **Xuan et al., 2013** | China | 305 Children | 7-9 Years Old | - | 3.5years | - | Yes | No | No |
| **Martignon et al., 2010** | Colombia | 91 Children | 4-6 Years Old | - | 2.5 years | 35 Children (38%) | No | No | Yes |
| **Vanderas et al., 2006** | Greece | 314 Children | 6-8 Years Old | Fluoride gel <0.03 ppm water | 4 years | 118 Children (37%) | No | No | Yes |
| **Peyron et al., 1992** | Sweden | 468 Children | 3-6 Years Old | Fluoride varnish 0.2 ppm water | 2 years | - | No | No | Yes |
| **Gruythuysen et al., 1992** | Netherlands | 549 Children | 4-15 Years Old | Fluoride | 2.5 years | - | No | No | Yes |
| **Murray et al., 1978** | United Kingdom | 301 Children | 5 Years Old | Fluoride varnish | 2 years | - | Yes | No | Yes |
| **Ammari et al., 2017** | Brazil | 50 Children | 5-9 Years Old | Fluoridated toothpaste and varnish | 1 year | 08 Children (16%) | No | No | Yes |
| **Basili et al., 2017** | Chile | 61 Children | 8-10 Years Old | 1,100ppm toothpaste | 3.5 years | 16 Children (26%) | No | No | Yes |
| **Tickotsky et al., 2017** | Israel | 95 Children | 5-12 Years Old | Fluoride water | 3 years | - | No | No | Yes |

Source: Author

### 3.3.3 Assessment of risk of bias

The assessment of the risk of bias per domains are displayed in Table 3.3. Nearly 27% of studies presented moderate risk of bias regarding the selection of the exposed cohort, and the great majority of the studies were scored as having weak evidence, once they had more than 20 % of the drop out (46.7%), and in some studies the drop out number was not described (40%). Most of the studies (73.3%) were performed with children in the school or in the community of the city with a representativeness of the exposed cohort (Table 3.3).

Table 3.3 – Risk of bias assessment using the Newcastle-Ottawa Scale

| Study (year) | Selection | | | | | Comparability | | Outcomes | | | | Study Risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | Risk of bias | 1 | Risk of bias | 1 | 2 | 3 | Risk of bias | |
| **Pitchika et al., 2016** | * | * | * | * | Low | * | Low | * | * | | Low | Low |
| **Ismail et al., 2015** | * | * | * | * | Low | * | Low | * | * | * | Low | Low |
| **Ismail et al., 2010** | * | * | * | * | Low | * | Low | * | * | | Low | Low |
| **Guedes et al., 2016** | * | * | * | * | Low | * | Low | * | * | | Low | Low |
| **Guedes et al., 2014** | * | * | * | * | Low | * | Low | * | * | | Low | Low |
| **Warren et al., 2005** | * | | | * | High | * | Low | | * | | High | Moderate |
| **Xuan et al., 2013** | * | * | * | * | Low | * | Low | * | * | | Low | Low |
| **Martignon et al., 2010** | * | * | * | * | Low | * | Low | * | * | | Low | Low |
| **Peyron et al., 1992** | * | | | * | High | * | Low | | * | | High | Moderate |
| **Vanderas et al., 2006** | * | * | * | * | Low | * | Low | * | * | | Low | Low |
| **Gruythuysen et al., 1992** | * | | | * | High | * | Low | | * | | High | Moderate |
| **Murray et al., 1978** | * | | | * | High | * | Low | | * | | High | Moderate |
| **Ammari et al., 2017** | * | * | * | * | Low | * | Low | * | * | * | Low | Low |
| **Basili et al., 2017** | * | * | * | * | Low | * | Low | * | * | | Low | Low |
| **Tickotsky et al., 2017** | * | * | * | * | Low | * | Low | * | * | | Low | Low |
| | 1. Representativeness of the exposed cohort<br>2. Selection of the non-exposed cohort<br>3. Ascertainment of exposure<br>4. Demonstration that outcome of interest was not present at start of study | | | | | 1. Comparability of cohorts on the basis of the design factor | | 1. Assessment of outcome<br>2. Was follow-up long enough for outcomes to occur<br>3. Adequacy of follow up of cohorts | | | | |

Source Author

### 3.3.4 Qualitative Synthesis of results

The mean age of the children included in the studies was 5 years- old. Studies evaluated transition of sound surfaces/caries lesions to more advanced scores (46.7% clinical, 53.3% radiographic) and also, the transition to more robust outcomes, as frankly cavitations or radiolucency into the inner half of dentine (27%). Pooled quantitative results related to these studies will be presented in the following session.

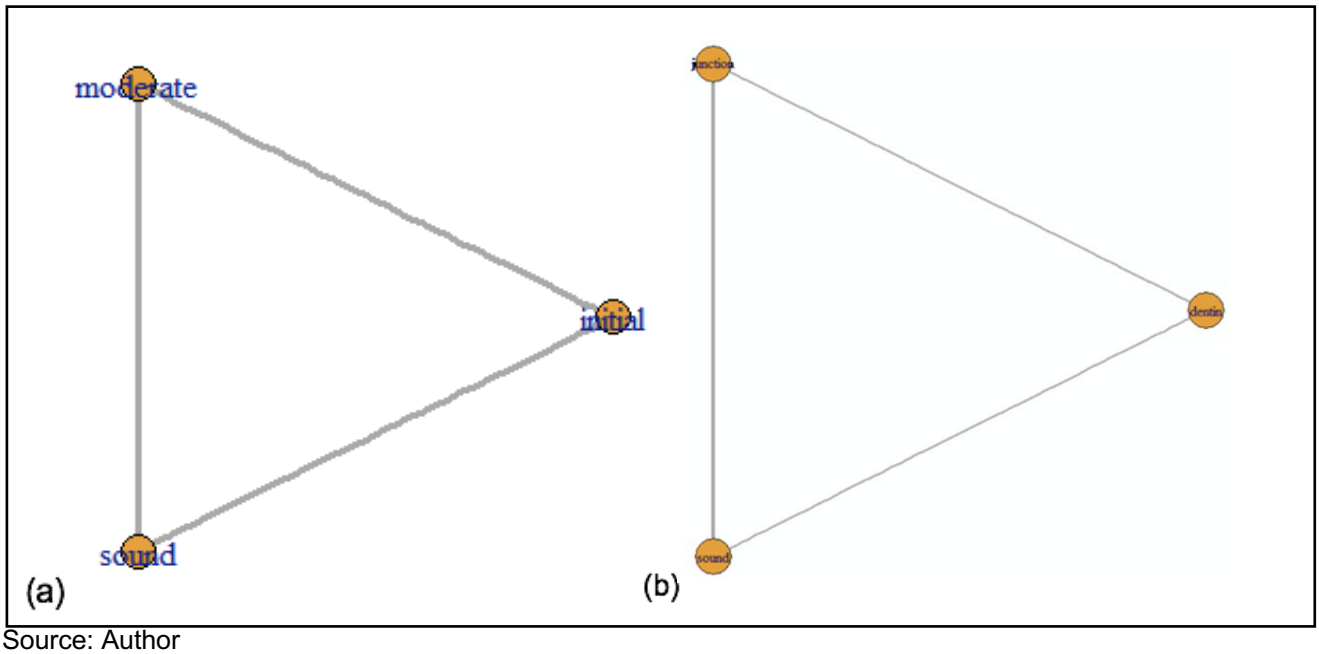
One study evaluated the progression of the severe caries lesions (37). This study evaluated toothache, swelling and fistulae as the outcome. The large majority (81.5%) of frankly cavitated primary teeth in this population (on average, 8-year-old-children), exfoliated without symptoms. Toothache was the symptom most frequently related both to exfoliated restored teeth (6.1%) and to exfoliated untreated (open) cavitated teeth (18.5%) (37). One manuscript evaluated the caries progression related to the activity status of caries lesions. Active lesions progressed approximately 70% more than inactive lesions, even considering different levels of severity (36).

One paper evaluated caries lesions progression using the radiographic characteristics for only 1-year follow-up, the control group (fluoridated toothpaste + flossing) was included in this paper, and lesions progression were observed in 33.3% of primary molars, six teeth progressed of radiolucency confined to the outer half of enamel for radiolucency involving the inner half of enamel, and four teeth progressed to radiolucency in the middle third of dentin. Another four teeth progressed of radiolucency in the outer third of dentin for radiolucency in the middle third of dentin (38). One study followed-up the caries lesions progression for three years using the radiographic characteristics, and in this study for the carious lesion to progress from the dentino-enamel junction to the inner half of the dentin it took only about 1.4 years (39). One study detected the caries progression clinically and radiographically, and 44 (18.3%) of the lesions assessed using both methods had progressed into dentin (40). Finally, four manuscripts followed-up the caries progression for more than 3.5 years, thus were not included in the meta-analysis (41– 44).

### 3.3.5 Meta-analysis – Direct and Indirect comparisons

For the meta-analysis, considering the majority of studies and the biological plausibility for caries progression, we included papers whose follow-up period had been 2-2.5 years. In the quantitative syntheses, three papers linking clinical caries severity to lesions progression (6–8), and also four papers linking radiographic characteristics to caries lesions progression (42,45–47) were included. The evidence comparing the caries lesions progression clinically or radiographically characteristics included in this systematic review are displayed in the network presented in Figure 3.5.

Figure 3.5 – Network of the comparisons of caries lesions progression according to the score: (a) Clinical Network and (b) Radiographic Network




Source: Author

Three possible pair-wise comparisons were performed among different conditions for clinical (n=3) and radiographic (n=3) assessments of caries lesion severity, as detailed in the Figure 3.2.

Both direct and mixed (direct+indirect) comparisons showed any caries lesion detected clinically (despite the severity) progressed more than sound surfaces (Table 3.4). Moderate caries lesion (lesions presenting microcavitated lesions clinically

restricted to enamel or presence of shadows evidencing undermined dentin) presented a three-time higher risk of progression than initial caries lesions (presenting non enamel discontinuity, only spots) (Table 3.4). The mixed evidence tended to corroborate the direct evidence, except for comparisons between moderate vs. initial lesions in which the confidence interval comprised values lower than 1 (Table 3.4).

Table 3.4– Relative Risks with 95% of confidence interval – RR; 95%CI) of different caries lesions severity assessed clinically progress to frankly cavitated lesions after 2 years. Estimates produced by direct and mixed comparison (direct+indirect evidences)

| **Pair-wise Comparison** | **Direct Comparison RR (95%IC)** | **$I^2$** | **Mixed Comparison* RR (95%IC)** | **$I^2$** |
|---|---|---|---|---|
| Initial vs. Sound | 4.8 (2.88 – 8.22) | 96.3% (92.1% – 98.2%) | 4.9 (1.4 – 17.0) | 12% |
| Moderate vs. Sound | 16.2 (9.07 – 29.02) | 96.56% (93.0% – 98.4%) | 16.0 (4.4 – 54.0) | |
| Moderate vs. Initial | 3.37 (2.26 – 5.01) | 88.1% (66.9% – 95.7%) | 3.3 (0.92 – 11.0) | |

* Random effects model, Model fit: residual deviance; DIC= 17.932

Source: Author

Indeed, the sound surfaces presented the highest probability (98%) of progress less than all conditions evaluated clinically, while for moderate caries lesions presented the highest probability of progressing more than all other conditions (96%) (Table 3.5). The initial caries lesions also presented 95% of probability of presenting an intermediate condition between the previous ones, considering caries lesion progression (Table 3.5).

Table 3.5 – Raking of probabilities of caries progression among different severities of caries assessed clinically

| Score | Position 1 | Position 2 | Position 3 |
|---|---|---|---|
| Sound | **0.9868** | 0.0123 | 0.0008 |
| Initial | 0.0124 | **0.9571** | 0.0301 |
| Moderate | 0.0007 | 0.0301 | **0.9690** |

Bold values are the highest values in the selected columns.
Position 1= probabilities of progressing less among all the categories, Position 3=probabilities of progressing more among all the categories

For radiographic assessments, those surfaces which presented radiolucency involved the enamel-dentine junction tended after 2-2.5 years progressed approximately 3.5 times more than those surfaces with no radiolucency (Table 3.6). Similar trend was observed for direct comparisons between radiolucency into outer half dentine vs. sound surfaces (Table 3.6). Although the radiolucencies into outer half of dentine did not present a higher risk than radiolucencies into enamel and enamel-dentine junction (confidence intervals included values lower than 1), in the mixed comparisons, we could observed a 20% higher risk of progression among radiolucencies into outer half dentine compared to those restricted to enamel or involving up to enamel-dentine junction (Table 3.6).

Table 3.6 – Relative Risks with 95% of confidence interval – RR; 95%CI) of different caries lesions severity assessed radiographically progress to frankly cavitated lesions after 2-2.5 years. Estimates produced by direct and mixed comparison (direct+indirect evidences)

| Pair-wise comparison | Direct Comparison RR (95%IC) | $I^2$ | Mixed Comparison* RR (95%IC) | $I^2$ |
|---|---|---|---|---|
| Enamel dentine junction vs No radiolucency – | 3.42 (2.24 – 5.21) | 78.5% (42.3% – 92.0%) | 3.4 (1.6 – 6.5) | 93% |
| Outer half of dentin vs. No radiolucency | 4.68 (3.36 – 6.53) | 76.8% (00.0% – 94.7%) | 4.0 (1.5 – 9.6) | |
| Outer half of dentin vs. Enamel-dentine Junction | 0.99 (0.50 – 1.95) | 97.1% (92.7% – 98.9%) | 1.2 (0.49 – 9.6) | |

* Random effects model, Model fit: residual deviance; DIC= 20.548

Source: Author

The post-probability calculated in the mixed comparison analyses corroborated the surfaces presenting no radiolucency are more prone (99%) to have less caries progression than other categories (Table 3.7). Lesions into outer half of dentine presented approximately 70% of probability of being the radiographic condition that progress more than all while radiolucencies up to enamel-dentine junction presented the same probability of presenting an intermediate progression between other two categories scored radiographically (Table 3.7).

Table 3.7 –Raking of probabilities of caries progression among different severities of caries assessed radiographically

| Score | Position 1 | Position 2 | Position 3 |
|---|---|---|---|
| Sound | **0.9889** | 0.0100 | 0.0010 |
| Junction | 0.0039 | **0.6881** | 0.3079 |
| Dentin | 0.0071 | 0.3018 | **0.6910** |

Bold values are the highest values in the selected columns
Position 1= probabilities of progressing less among all the categories, Position 3=probabilities of progressing more among all the categories

Source: Author

Sub-group analyses considering the type of surfaces (occlusal or smooth surfaces) presented similar trends described above (Table 3.8). No differences were found for any subgroup (Table 3.8).

Table 3.8 – Relative Risks with 95% of confidence interval – RR; 95%CI) of different caries lesions severity assessed clinically progress to frankly cavitated lesions after 2 years. Estimates produced by direct and mixed comparison (direct+indirect evidences) obtained in subgroup analysis per type of surface (occlusal and free or proximal smooth surfaces)

| | Occlusal Surface | | | | Smooth Surface | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Pairwise comparison** | **Direct Comparison RR (95%IC)** | **$I^2$** | **Mixed Comparison* RR (95%IC)** | **$I^2$** | **Direct Comparison RR (95%IC)** | **$I^2$** | **Mixed Comparison* RR (95%IC)** | **$I^2$** | **Test for subgroup comparison** |
| Initial vs. Sound | 2.80 (1.73 – 4.51) | 89.3% | 2.80 (0.46 – 17.0) | 12% | 4.91 (2.11 – 11.4) | 97.4% | 5.0 (1.50 – 17.0) | 11% | p=0.16 |
| Moderate vs. Sound | 6.22 (1.69 – 22.8) | 98.3% | 6.22 (0.94 – 37.0) | | 20.38 (12.93 – 32.10) | 89.0% | 19.0 (5.50 – 63.0) | | p=0.09 |
| Moderate vs. Initial | 2.33 (1.06 – 5.11) | 93.9% | 2.20 (0.34 – 14.0) | | 3.87 (2.02 – 7.38) | 91.0% | 3.8 (1.10 – 13.0) | | p=0.37 |

*Fixed effects model, Model fit: residual deviance; DIC= 17.929 occlusal – DIC=17.705 smooth

Source: Author

The level of heterogeneity for all comparisons performed was higher than 75% (Tables 3.4 and 3.6). Similar figures were observed even performing subgroup analyses considering the type of surface for clinical lesion severity assessment (Table 3.8). Indeed, the sound occlusal surface and smooth surface presented the highest probability (88%) and (98%) respectively of progress less than all conditions evaluated, and moderate caries lesions presented the highest probability of progressing more than all other conditions (83%) in occlusal surface and (97%) in smooth surface (Table 3.9).

Table 3.9 – Raking of probabilities of caries progression among subgroup analysis per type of surface

| | **Occlusal Surface** | | | **Smooth Surface** | | |
|---|---|---|---|---|---|---|
| **Score** | **Position 1** | **Position 2** | **Position 3** | **Position 1** | **Position 2** | **Position 3** |
| Sound | **0.8865** | 0.0988 | 0.0145 | **0.9885** | 0.0108 | 0.0006 |
| Initial | 0.0951 | **0.7500** | 0.1548 | 0.0106 | **0.9692** | 0.0200 |
| Moderate | 0.0183 | 0.1510 | **0.8306** | 0.0007 | 0.0199 | **0.9793** |

Bold values are the highest values in the selected columns
Position 1= probabilities of progressing less among all the categories, Position 3=probabilities of progressing more among all the categories

Source: Author

## 3.4 Discussion

Few longitudinal researches have been done in primary teeth to check the actual contribution of some characteristics observed in caries lesion assessment. Caries severity is definitely the more explored characteristic related to the caries lesions in this sense. Non-cavitated caries lesions are considered the initial stages of more severe and frankly cavitated caries (48,49). Historically, several still used criteria for caries lesion assessment has been based on histological and microbiological characteristics of caries lesions (50,51). The rationale surrounding this idea is an assumption that these characteristics can predict caries progression, however, there is a lack of information to confirm their role in the prognosis of detected caries lesions.

The present findings produced evidence and estimates compiling different populations validating the use of criteria used for caries assessment as a manner to

predict caries progression (establish a prognosis) and state the clinical relevance of caries detection, a still underexplored topic in most studies of accuracy of methods for caries diagnosis (52). The present results also contribute to show that a differential “value” could be really attributed to different severities of caries lesions, both clinically or radiographically assessed, impacting on clinical decision-making.

Different risk to progress may impact on choosing of the most appropriate therapeutic approach for each case. A recent expert consensus about intervene in caries lesion may reflect this differential possibilities (10). Detecting the presence of the cavity (observed, for example, in moderate caries lesions) is an important aspect to be assessed regarding caries lesion severity because this condition significantly increases the risk for caries progression. Such condition may often demand some type of intervention that could control locally the caries lesion progress in order to minimize other possible factors which could be related to caries progression. This higher rate of progression may be caused by some lesions that are into dentine (53), and tend to become cavitated more easily because of their specific structure and composition (54), and as a result of a higher level of infection of the enamel-dentine junction (51).

Certainly different types of cavitations could be expected since those that could be cleaned by toothbrushing (as a small pit) up to those for which sealing or restoring is the alternative to controlling biofilm over the lesion associated with the use of fluoride-containing toothpaste (55,56). In this sense, there is growing consensus that, even in such situations, invasive treatments should be used for lesions that reached a more severe stage, where caries could not be sealed, or restorations should be required to restore aesthetics, function or structural integrity (57–59).

In the last decades, the early detection of caries lesions has raised researchers and clinicians’ interest (50,60). Knowing the probability of progression of an initial caries lesion is approximately 5x-higher to a frankly cavitation compared to a sound surface is a motivation to opt for some treatment aiming to arrest the caries process. On the other hand, considering differential risks for progression when initial and moderate caries lesions are compared, it is evident that a differential attention may be done to these lesions both in terms of the option for treat/arrest the lesion and the moment to do that. If you needed to prioritize one of them to treat, certainly that one with the worst prognosis would be chosen. Based on that, the current

guidelines for conducting epidemiological surveys related to caries recommends data collection of robust information (cavitations) that could have a stronger health impact on populations (61). This is an important aspect to be weighed when deciding public health policies, but also to order procedures in individual clinical decision-making.

Lesions involving enamel-dentine junction radiographically or involving outer half of dentin showed a relative approximation of the clinical microcavitations or presence of shadows (moderate caries lesions). At this point, we should the meta-analysis for radiographic assessment only considered proximal surfaces. Considering the caries progression on proximal surfaces, when the lesion reaches the enamel dentine junction, demineralized dentin is present, and lesion progress quickly, since it is in dentin and this tissue is less mineralized, an additional substantial demineralization may be observed despite the absence of cavitation into dentin (42). Despite approximation between results observed for caries lesions prognosis, lower estimates were observed when radiographic assessment of lesions severity was compared to clinical assessment. Even considering only the subgroup of smooth surfaces evaluated by clinical criteria (including proximal lesions), trends were not changed. Based on these findings, we could suggest the clinical assessment could be more helpful in determining the prognosis and scrutinize those lesions really more prone to progress and demanding more urgent or controlled interventions.

In this systematic review, it was difficult to evaluate the progression of severe caries lesions. Some studies registered these lesions at the baseline (7,8), but in the follow-ups, it is not possible to discriminate if they were restored because they were immediately indicated for restorative treatment as manner of controlling the lesion or if they progressed to worse conditions and then, they received the operative intervention. That is why this clinical condition was not included in the meta-analysis. One study evaluates the progression of cavitated lesions to endodontic treatment or tooth extraction. This would be a valid alternative to escape from differentiation of restorations as a measurement of progression or achievement of immediate treatment when severe caries lesions are followed. On the other hand, depending on the context, some ethical questions can be raised if the population usually is referred for treatment after surveys like that, being a possible reason why such findings are not available. Specifically for this study, most part of severe lesions which were followed did not progress and teeth were exfoliated without complications or symptoms (37). These results should be interpreted with caution since older children

were included (on average, 8-year-old children), teeth were close to the exfoliation and probably more open (wide) cavities were included favoring the arrestment by plaque control associated with use of fluoridated toothpaste (55).

Evidences presented reflects combination of data from different studies using both direct and indirect evidences. The strategy used for that (MTC) is a relatively recent development that allowed the estimation of metrics for all possible comparisons with the same model. It is usually a technique to compare three or more interventions in a single analysis. In this paper, we provide a solution of comparing different conditions (clinical or radiographic categories), instead of comparing treatments as usual observed in publications. Using this meta-analytic approach, the outcomes are estimates of the relative effect between any pair of interventions, with the advantage to facilitates indirect comparisons (32), e.g., evidences of comparison between different studies. Despite these adaptations, we believe our results are clear could be interpreted similarly to a meta-analysis of international studies.

In this review, as all conditions were present in all studies, the indirect evidences contributed to increase the sample size analysed (Figure 3.4). On the other hand, the adjustment proposed for standard error in indirect comparisons, for example using the Bucher´s method, tend to produce wider confidence intervals (62). Specially when few trials are included in the analysis, indirect comparisons may be underpowered and results should be interpreted with caution because of potential inclusion of type I error (63). That is why we should not consider, for example, those cases in which mixed comparisons eliminate possible effects previously showed by direct comparisons, as observed when comparing moderate lesions vs. clinically sound surfaces, a possible occurrence of the type 1 error in the mixed estimates. In these cases, we can consider the direct evidence is more truthful. Besides, probably the greater advantage to use the MTC in our systematic review was to provide information about the ranking of post-probabilities among conditions (severities) evaluated as predictors for caries progression (prognosis), using a Bayesian framework. In this sense, we could corroborate differential “values” among the conditions used in caries detection both clinically and radiographically, ordering priorities according to prognosis in order to provide adequate caries management to control caries lesions.

A high level of heterogeneity was observed, as expected, since observational studies were included. However, heterogeneity was considered in our meta-analyses

(random-effects models) and explored (subgroup analyses), contributing to an appropriate judgment about the findings and helping in identifying potential sources of heterogeneity. We highlighted methodological and clinical sources of heterogeneity. For population recruitment, it was necessary to establish a number of examiners, and there were differences between the studies, it was possible to find studies that performed the exams with one calibrated examiner and other with fifteen. Both visual inspection and radiographic examination are methods subjective and dependent of examiners' interpretation. Further, another difference between the studies was the fluoride varnish application, a recent systematic review highlight that the use of fluoride varnish may be an effective treatment on the reversal of incipient caries lesions in primary and permanent teeth (64).

A lack of evidence showing the relationship between caries progression and other clinical characteristics (different from severity) related to caries lesions. Even considering the assessment of activity status of caries lesions, a topic that has been eminently studied through longitudinal studies (36), with this systematic review, it was not possible to explore the real benefits of this type assessment in primary dentition. Further studies should be conducted to provide evidence about the role of these additional features on prognosis of caries lesions in primary teeth.

The main source of bias detected among the included studies is related to the outcome measurement (in this case, the caries progression). Approximately half of the included papers with a dropout rate greater than 20% or even, did not mention about the dropout rate in the study. From those which presented a dropout rate higher than 20%, very few demonstrated the similarity between baseline and followed sample. Some studies did not also permit a complete outcome evaluation, since they did not set a reasonable follow-up period to detect significant changes in terms of caries progression. Considering evidences for caries progression in primary teeth, 2 years of follow-up seems to be adequate (7). These findings demonstrate the lack of rigor in the such type publications when reporting outcomes and should be considered when planning further studies similar to those ones. The use of guidelines for reporting longitudinal studies may be useful to provide required methodological rigor and information, minimizing risk of bias among compiled studies.

In general, the evidence brought in this paper, especially pooled in the meta-analysis, was based mainly in studies with low risk of bias. More caution should be taken when interpreting findings studies related to radiographic assessment of caries

lesion severity since some of them seem to have included high risk of bias. The risk of bias analysis performed on the longitudinal studies showed that almost 27% of the study presented moderate risk of bias regarding the representativeness of the exposed cohort, with incomplete outcome data.

Clinicians and researches will be benefited with the information of these systematic review, once it is possible to know which lesions we have to arrest and considerate their potential of progression (prognosis) when making clinical decisions, not necessarily opting for operative treatment, but also using non-operative options, carefully monitoring and maybe avoiding or postponing restorative intervention. Under a public health perspective, the evidences raised permit to create an evidence-based strategy both for detecting and directing treatment for different caries lesion severities across the population. Therefore, this knowledge should support and guide the implementation of adequate approaches to caries management both individually or collectively.

## 3.5 Conclusion

Given the exposed above, caries severity, especially when assessed clinically, is an important characteristic related to the lesion and should be considered in caries lesion assessment to guide clinical decision-making. Lesions presenting cavitations (even appearing to clinically confine into enamel) or presenting shadows suggesting undermined enamel should be detected the soonest possible and more attention should give to them based on their higher risk of progression.

# 4 CHAPTER II:

## Sealing moderate caries lesions using glass ionomer cement as an alternative to restorations: a multiple failure-time survival analysis on exploring treatments success in a non-inferiority randomized controlled trial followed for 2 years

### 4.1 Introduction

Dental caries is an international public health challenge, especially amongst young children (65). Its consequences can affect the immediate and long-term quality of life of the child and family (66,67). With the advent of minimally invasive dentistry, sealing microcavitated and/or dentine caries lesions has appeared as an option of treatment instead of operative treatment (13,14,68). A recent expert consensus on caries management pointed out the sealants as an alternative, for occlusal surfaces, to intervene on micro-cavitated caries lesions radiographically extending into enamel and in outer half of dentin (10). However, a recent systematic review showed that a significant proportion of dentists still intervene invasively on caries lesions in such type of caries lesions (5).

In primary teeth, moderate caries lesions (including microcavitations clinically into enamel and/or shadows suggested undermined enamel) may frequently extend histologically into dentine(53,69). As mentioned in the previous chapter, these lesions present higher progression rate compared to sound surfaces or even initial caries lesions. Due to that, they should be detected and managed appropriately since we believe, if untreated, the condition tends to worsen gradually (65).

Restorations or sealants may act as a mechanic barrier created between the caries lesion and the biofilm, preventing the progression of these lesions (11,12,70). Nevertheless, especially for non-frankly cavitated caries lesions, it is necessary the lesion access/cavity opening (dental sound tissue removal) to guarantee the minimum requirements for performing further restoration. Since getting access to the microcavity demands use of high-speed burs or manual instruments (if using

Atraumatic Restorative Treatment approaches), this clinical step, besides more invasive, can represent a more stressful experience, especially in Paediatric Dentistry.

Some evidence has been created for sealing of microcavitated/moderate caries lesions as an alternative to restorations in caries lesion management for primary teeth (13,14). Alternatives like this may be sufficient to permit the primary teeth exfoliate without other interventions and avoid invasive treatments (53). This sealing approaches been proposed using resin-based sealants (68,71). Such type of materials present good mechanical properties and high longevity (72) because of their adhesive characteristics (73). Longevity of sealants are, however, strongly related to an adequate control of moisture (73). The perfect moisture control in children is actually a big deal. Besides, the risk of failure of resin sealants tends to increase significantly with unsatisfactory child's behaviour (74). Furthermore, the use of rubber dam to guarantee moisture control increases significantly the complexity of this procedure, and, sometimes, decreases children`s acceptability to the treatment (75). Thus, the use of a material less sensitive to moisture could be desirable when sealing caries lesions in children.

Facing this situation, it was raised the idea of using, the high viscous glass ionomer cement (HVGIC) as an alternative material for sealing caries lesions in attempt for controlling them. This material is not as sensitive to moisture as the resin-based materials and has a favourable setting time inferior to 5 min (76). These conditions could bring a clinical solution to improve paediatric dental treatment. On the other hand, due to the differences in their adhesive/retention properties, the HVGIC could present lower retention than resin-based sealant and consequently a higher number of failures, possibly increasing the need for reinterventions on treated surfaces (72).

In Dentistry, survival analyses are useful for analyzing time-related events. Currently, in the literature, only the first failures (events) related to dental treatments have been considered in survival analysis. However, in the real life, treatments may fail more than once and might demand several successive reinterventions after that. In biomedical sciences, some statistical approaches have been used to lead with multiple failure-time events (77,78). For that, within-group (in our case, restoration/sealant) dependency should be considered and variance-adjusted models were used (79). These alternative statistical models are important to be used,

especially in situations in which we expect event could be repeated several times, impact treatment success. In these cases, insisting on traditional methods could imply an inefficient use of data (79).

Aiming to test the efficacy of HVGIC sealants (a known less invasive approach) as an alternative to restorations in the management of moderate occlusal caries lesions in primary teeth, a non-inferiority clinical trial was designed. To efficacy estimation the need of reintervention was set as primary outcome and the actual impact of use a multiple failure-time survival analysis was then considered.

## 4.2 Materials and methods

This manuscript was written according to the extension of the CONSORT Statement to Noninferiority and Equivalence Randomized Trials (80) (Appendix B).

### 4.2.1 Study design and ethical approval

This is a two-parallel-arm non-inferiority study (allocation tax – 1:1), controlled and patient-randomized and followed for 2 years. This clinical trial was nested within another trial “Caries Detection in Children-2” (NCT02473107) which tested diagnostic strategies for caries detection. The study was approved by the Research Ethics Committee of Dental School, University of São Paulo (protocol 659.006) (Annex A), and it has been registered on ClinicalTrials.gov (NCT03005405).

Informed consent was obtained from children’s parents or guardians before participation in the study (Appendix C). Participant’s confidentiality was ensured using identification code numbers, and the information recorded was available only to researchers.

### 4.2.2 Setting of the study

The study was conducted in a mobile dental unit (Motor Trailer ®), that is located in a public school at the municipality of Barueri – SP, metropolitan area of Sao Paulo city. – Complexo Educacional Carlos Osmarinho de Lima. Presenting a Human Development Index (HDI) of 0.786 and water supply of 0.7 mg/L F (81) (Appendix D).

### 4.2.3 Sample size calculation

The website Sealed Envelope Ltd. 2012 (http://sealedenvelope.com) was used for the sample size calculation. For that, we considered a non-inferiority trial and a non-inferiority limit of 20%. An alpha error of 5% and power of 90% were used. We considered 7% of failure of HVGIC restorations in 1-single surface after 2 years (82) increased 20% to compensate eventual non-compliance with the protocol or losses of follow-up. Finally, as more than one tooth could be included per child, additional 40% was added to compensate the clustering effect. Thus, 96 children were expected to be included in the study, 48 children per group.

### 4.2.4 Participant selection

Children who sought dental treatment in the mobile dental unit were invited to participate in the study.

Eligible children were those from 3 to 6 years old, with at least one occlusal moderate caries lesion - scores 3 or 4 according to International Caries Detection and Assessment System (ICDAS) on primary molars and presenting no special medical conditions. Children were excluded from the sample if they (or their guardians) refused to participate in the study.

### 4.2.5 Allocation

The selected children were assigned, by random allocation, to have their tooth treated with restoration (control group) or sealant (experimental group). Both approaches were performed with HVGIC. The randomization sequence was generated by an external research (M.M.B) using the website Sealed Envelope Ltd. 2012 (http://sealedenvelope.com). To guarantee allocation concealment different sizes of blocks (2 to 6) were used and generated sequence was distributed in opaque, sealed envelopes by another external research (M.E.F.G). Envelopes were opened by the operator at the moment in which the treatment would be carried-out.

Child was considered the experimental unit and all teeth that required intervention were treated according to the group in which each child had been allocated.

### 4.2.6 Examiners and Operators

Five operators (postgraduate paediatric students – E.S.R, L.A.P, I.M.P.U, I.C.L. N.M.L) were trained by a single trainer (T.K.T) to perform all procedures for both intervention groups according to the following sequences. They firstly received a theoretical explanation and then an 8h-session clinical training about how to prepare (if necessary) and insert the material into the cavity and protect material after finishing the procedure. The trainer was in charge for solving all doubts during this training, or, even when appeared during the treatments. Operators were considered prepared to begin dental treatments when performing the correct sequence of procedures related to treatments.

Three examiners (I.F, L.Y, T.K.T) were trained to examine caries using the World Health Organization (WHO) (61) and ICDAS criteria (83). Firstly, they examined images and extracted teeth simulating all possible conditions of caries. Then, they proceed to clinical evaluation until reaching an agreement almost perfect or substantial Kappa (>70%). The examiners were also trained to using a criteria to

assess restoration/sealant integrity (84) using a similar training strategy.

One examiner (I.F) was responsible for examining children at the baseline to using the visual inspection. The criteria used to classify the surfaces was the ICDAS. This examination was previous to the children's allocation.

Other examinations, during the follow-ups, were carried out by other two examiners (L.Y, T.K.T) who did not participate neither in the baseline assessment nor in the treatment phase. They were blind to the child's allocation and to the initial tooth condition.

All examinations were performed after professional tooth cleaning with prophylactic paste and rotating toothbrushes. Surfaces were assessed with the aid of an oral mirror and a ball-ended probe.

### 4.2.7 Interventions

**Test Arm:** Sealant with HVGIC (Fuji IX, GC Corp, Leuven, Belgium). No caries lesion access or caries removal were performed. Afterwards, the HVGIC was inserted on the entire occlusal surface using hand filling instruments and digital pressure with petroleum jelly was performed.

**Control Arm:** Restoration with HVGIC (Fuji IX, GC Corp, Leuven, Belgium). Lesion was accessed using the high-speed burs under refrigeration and selective removal of carious tissue with a hand excavator was performed. The HVGIC was inserted into the cavity with the aid of filling hand instrument and digital pressure with petroleum jelly was performed.

The operators and the children were not blind to the treatments, because the differences between the intervention groups.

For both groups, surfaces were cleaned with prophylactic paste and rotating toothbrush before the procedure. The HVGIC was used in the powder-liquid ratio: 1:1. The first drop was dispensed because it may have a bubble. This drop of polyacrylic acid was applied into the lesion with the aid of tweezer and a cotton ball by 10 seconds. The surface was cleaned with three cotton balls soaked in water, and another three cotton balls were used to dry the cavity. For manipulation of the material the first part of the powder was mixed with the liquid for 10 seconds, then,

the other part of the powder was incorporated and mixed for 10 to 20 seconds. After HVGIC insertion and initial setting (becomes dull), a thin layer of petroleum jelly was applied over the procedure performing digital pressure. Occlusal interference was checked with articulating paper. The patient was instructed not to drink liquids or consume solid foods for 1 hour after the procedure.

All children were instructed regarding oral health care including dental floss use, toothbrushing with fluoridated toothpaste after meals and dietary habits. Every 6 months, they received oral hygiene instructions and a kit containing a toothbrush and fluoridated toothpaste.

### 4.2.8 Outcome assessment

To evaluate the efficacy of the interventions, the outcome of this study was considered as:

The need of reintervention on treated surface. Children were followed-up for 24 months and treated teeth assessed biannually by trained examiners. Examiners were blind regarding the treatment received at the baseline.

To need of reintervention were composed by need for repairments, replacements or caries lesions progression. The restoration/sealant integrity was assessed according to the adapted criteria for Atraumatic Restorative Treatment (ART) restorations/ sealants (84) (Table 4.1). The width and depth of the marginal defects, and excessive surface wear or lack of material were measured with the aid of a ball ended probe. The Table 4.1 showed the circumstances in which repairments or replacement of sealant/restoration were indicated. For caries progression, surfaces were assessed using WHO criteria. If frankly cavitation was observed on the treated surface, caries progression was recorded. On summary, an event was registered: 1- when there was a defect in the filling greater than 0.5 mm but less than 1.0 mm, and repair was needed; or 2- when the restoration/sealant was not present, or it has almost completely disappeared, thus, the restoration needed to be replaced; 3- when caries lesion has clinically progressed resulting into a frankly cavity exposing dentine.

External assessors checked the follow-up and baseline codes in order to guarantee coherence between them. In case of divergence, the possible errors were corrected after a re-examination and then, registered in the database.

Table 4.1 – Evaluation criteria for ART restorations and glass ionomer sealants (84)

| ***Score*** | ***Criteria*** |
|---|---|
| 0 | Present, good |
| 1 | Present, slight marginal defect for whatever reason, at any one place which is less than 0.5mm in depth; **no repair is needed** |
| 2 | Present, marginal defect for whatever reason, at any one place which is deeper than 0.5 mm but less than 1.0 mm; **repair is needed** |
| 3 | Present, gross defect of more than 1.0 mm in depth; **replacement is needed** |
| 4 | Not present, restoration has (almost) completely disappeared; treatment is needed; **replacement** |

Source: Adapted from Frencken

For sealants, if some material was present and no moderate (or more severe) lesion registered, the success was registered. Although it was supposed the entire surface should have been sealed, we considered that some small portion of the surface could be left unsealed. Those procedures that never presented failures, or those that present, slight marginal defect for whatever reason, at any one place which is less than 0.5mm in depth and no repair is needed were both considered as success, only one tooth exfoliate before complete eighteen months of follow-up and was also considered as success.

As secondary outcomes also related to efficacy of treatments, we set: need for major interventions (including need for restoration/sealant replacement-major failures + need for restoration for caries progression) and caries progression.

### 4.2.9 Reinterventions

We opted for performing the reinterventions based on needs indicated by the criteria used. They were performed immediately after their need was detected. Failed

sealants/restorations were replaced or repaired using the same intervention of baseline, whenever necessary for 2 years follow-up. Caries lesions progression was indicated to be restored. Although the steps were the same for restorations of moderate lesions, in this case, severe caries lesions were supposed to be restored and neither more considered for analysis regarding the efficacy of treatments.

Successive failures that occurred in re-restored/sealed teeth were treated in the same way than primary failures.

### 4.2.10 Data Analysis

All statistical data were analysed by Stata software, version 13.1 (StataCorp LP, Texas, USA).

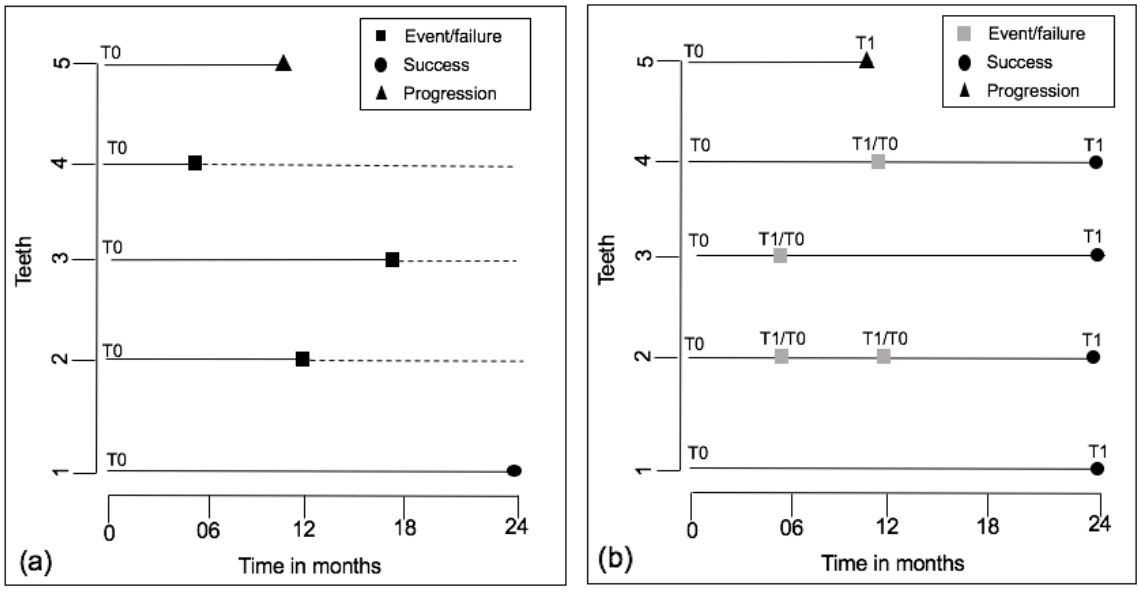
Intra-examiner reliability was calculated by Cohen or weighted Kappa test, depending on the criteria used for examination. The survival of treatments (efficacy) was based on proportion of surfaces that did not present the events. Firstly, the primary outcome was used in the survival analysis and then, other secondary were also used.

The survival analyses were performed using Cox regression analysis associated with two different types of models. Firstly, traditional approach for survival analyses used in Dentistry was used. Firstly, only single first were considered (Figure 4.1a) and then, multiple ordered failures along 24 months were analysed (Figure 4.1b).

For single failures, proportional hazards regressions with shared fragility were set. For successive failures, conditioned risk set models were used (79). In these models, time to each event was measured from the entry time. For those sealants/restorations which failed more than once, the T0 for subsequent intervention was defined as the time when the treatment was done or replaced, and T1 the time when a new failure or survival were observed (Figure 4.1b). A variable (strata) was created in these models to identify if the event was recurrent (77,78), and the order such event has in a sequence of events creating a connection among events that happens in the same surface.

Besides the intervention received, sex (female vs. male), children age (5-to-6-year-old vs. 3-to-4-year-old children), caries experience (dmft+DMFT>3 vs. dmft+DMFT≤3), operator (general operators vs. team leader), tooth type (2nd vs. 1st molar), side (left vs. right), and dental arch (lower vs. upper) were tested and considered to adjust the models, if appropriate.

Figure 4.1 – Schematic representation a time-to-event considering models for: Single First Failures (a), and Multiple Ordered Failures (b). Note that in single failure model (a) reinterventions are not considered for analysed (dotted line), differently from observed in real life. In the ordered events (b), when a restoration; sealant fails and it is repaired/replaced, a new restoration is considered under risk (gray symbols) and possible new events were taken into account considering new time-to-event and incorporation time span since the baseline




Source: Author

For each model, the Hazard Ratio (HR) related to each independent variable was calculated with 95% confidence interval (CI). Kaplan-Meier survival curves were plotted, and log rank test were used using the intervention as moderators. The significant level for the tests was considered as 5%.

As this trial is a non-inferiority trial for comparing the sealing as an alternative to restorations on controlling moderate caries lesions, the p-value and CI were adjusted deriving a one-tailed test from two tailed output. For each cox regression coefficient, the tested null hypothesis is that the coefficient is equal to zero. Thus, to get the p-value for the one-tailed test of the variable “intervention” having a

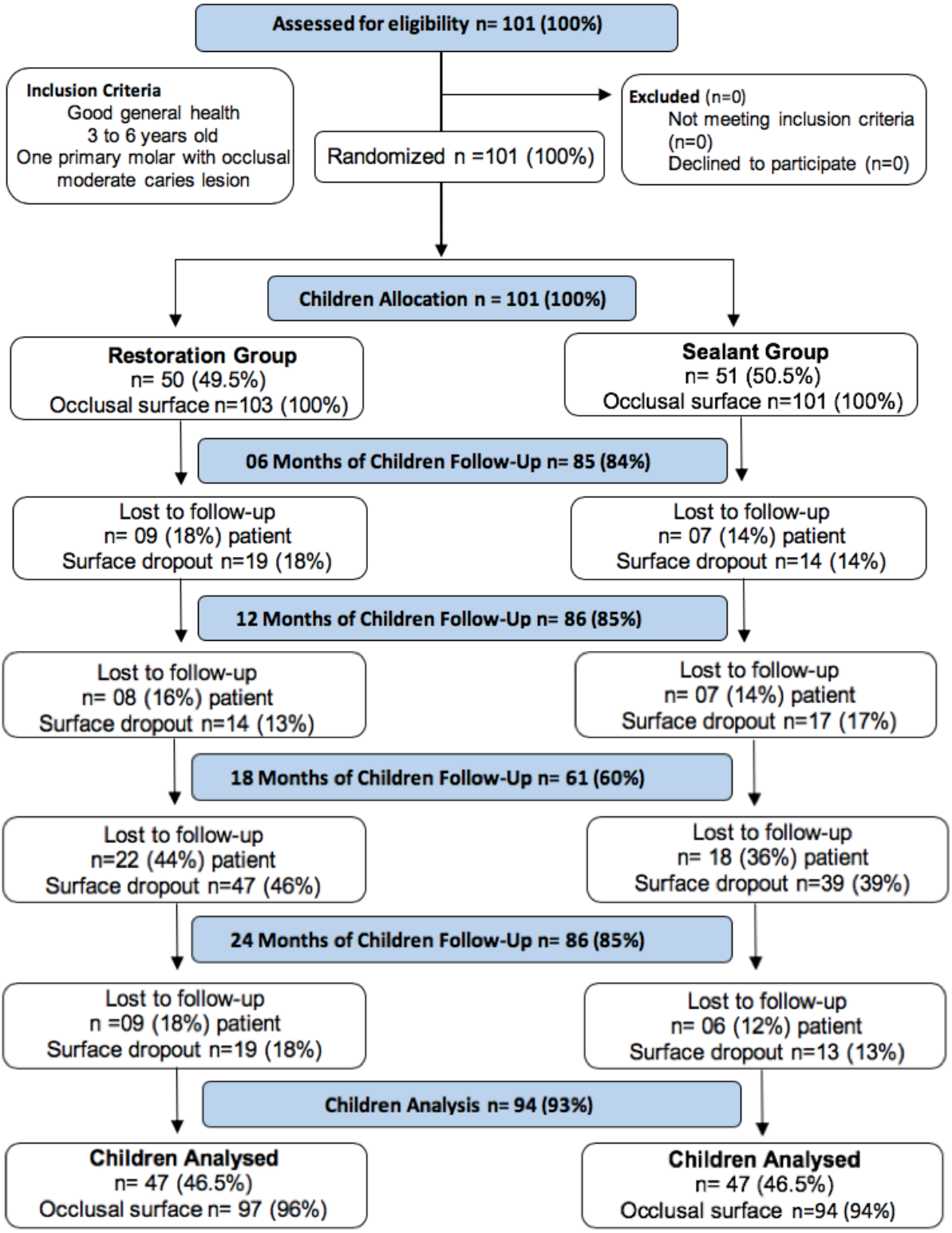
coefficient greater than zero, the p-value obtained in the analyses were divided by 2, since the effect is going in the predicted direction (85). As we are testing the hypotheses if sealants were not inferior to restorations (one-sided test), we constructed a one-sided 95% CI. In a one sided interval we can get 95% coverage with 50% below the mean and 45% above the mean (79). HR values were converted into logHR to fit normal distribution. Since 45% above the mean in a normal distribution is 1.64 according to 4.3 e 4.4 tables, the superior limit adjusted using the adjustedlogLS=logcentralestimate+1.64*(sd/(√sample size). The inferior limit would be -∞representing 50% below the mean in such circumstances (79). Finally, logHR were reconverted into HR to permit appropriate interpretation.

## 4.3 Results

101 children aged between 3 to 6 years old (mean age: 4.5 ± 0.8) were included in the study (Figure 4.2). A positive response rate of 100% was achieved. A total of 204 occlusal surfaces of primary molars were treated (on average, 2 teeth/child). Occlusal surfaces presented lesions classified as ICDAS scores 3 (81%) and 4 (19%).

After randomization, groups were considered similar (Table 4.2). A dropout rate of 15% was registered in the 2-year-follow-up (Figure 4.2). Similar drop-out rates were observed in both groups (p=0.44). The main reason for dropouts was the non-attendance at the scheduled appointment (Figure 4.2).

Figure 4.2 – Flow-chart diagram of the study regarding participant enrolled, followed-up and analyzed




Source: Author

Table 4.2 – Baseline characteristics after allocation in sealant and restoration groups.

| | **Restoration HVGIC** | **Sealant HVGIC** |
|---|---|---|
| Children Number n (%) | 50 (49.5) | 51 (50.5) |
| Mean Teeth included per children n (%) | 2.06 | 1.98 |
| **Variables related to children** | | |
| *Sex n (%)* | | |
| Male | 23 (22.8) | 31 (30.6) |
| Female | 27 (26.7) | 20 (19.9) |
| *Age n (%)* | | |
| 3-4 years 11months | 25 (24.8) | 18 (17.8) |
| 5-6 years 11months | 25 (24.8) | 33 (32.7) |
| *Biofilm n (%)* | | |
| = or > 1 | 20 (19.8) | 23 (22.8) |
| > 1 = or > 2 | 23 (22.8) | 24 (23.8) |
| > 2 | 03 (3.0) | 03 (3.0) |
| No answered | 02 (2.0) | 01(1.0) |
| *Caries Experience (dmft-s) n (%)* | | |
| Low | 19 (18.8) | 17 (16.8) |
| High | 31 (30.7) | 34 (33.7) |
| *Familiar Budget n (%)*** | | |
| Till 1 | 08 (7.9) | 00 (00) |
| Between 1 and 2 | 21 (20.8) | 21 (20.8) |
| 2 or more | 15 (14.9) | 26 (25.7) |
| No answered | 06 (5.9) | 04 (4.0) |
| *Mother's schooling n (%)* | | |
| School incomplete | 22 (21.8) | 15 (14.9) |
| School complete | 23 (22.8) | 25 (24.8) |
| High School incomplete | 01 (1.0) | 02 (2.0) |
| High School complete | 04 (4.0) | 09 (8.9) |
| **Variables related to teeth** | | |
| *Clinical evaluation (ICDAS) n (%)* | | |
| Score 3 | 85 (41.7) | 81 (39.7) |
| Score 4 | 18 (8.8) | 20 (9.8) |

**In minimum familiar wage. 1 Brazilian minimum wage =R$ 788.00 or $ 388.00– at the beginning of the study (2014)

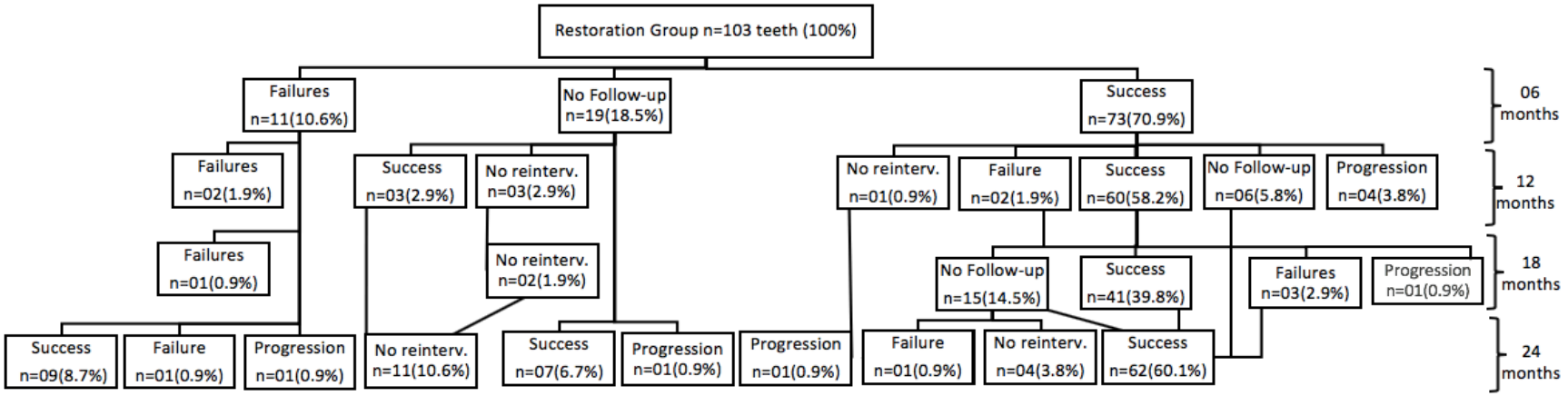
Source: Author

When having any follow-up data for a child, she/he was included in the analyses, even if her/his last follow-up information were not available. Therefore, 94 children (191 occlusal surfaces) were included in the final analyses, totalizing an analytic dropout of approximately 7%.

After 24 months, the success rates were observed for both interventions (restoration= 75% and sealant= 66%), the flowchart illustrate the natural history of treatments failures, and caries lesions progression (Figure 4.3 and Figure 4.4).

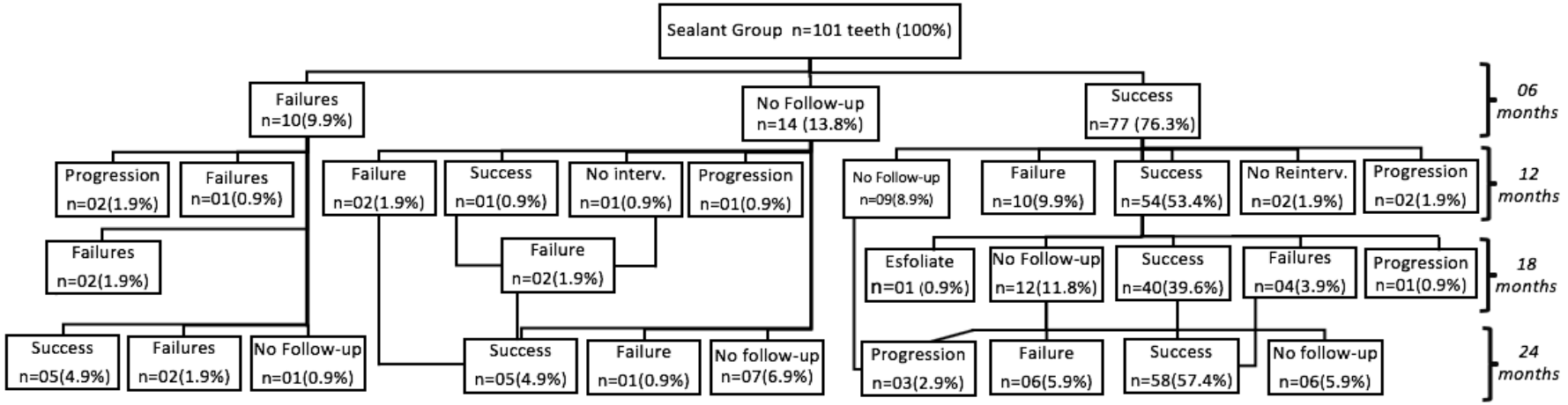
Considering all failures (minor failures + major failures + progression), the sealant was not an inferior treatment, both when single first failures and multiple failures were analyzed (Table 4.3 and Figure 4.5). Around 25-35% of occlusal surfaces initially treated required retreatment after the first intervention (restorations: 24%, sealants: 34%). When successive failures were computed, these figures slightly changed (restorations: 26%, sealants: 38%). Younger children presented more failures (including repetitions) than older ones independently of intervention received (Table 4.3).

Figure 4.3 – Flowchart of restauration group per teeth considering, failures, success, and caries lesions progression over 24 months of follow-up




Source: Author

Figure 4.4 – Flowchart of sealant group per teeth considering, failures, success, and caries lesions progression over 24 months of follow-up




Source: Author

Table 4.3 - Cox regression models considering as outcome the composed outcome minor failures (requiring repair), major failures (requiring replacement) and caries progression (requiring a new restoration)

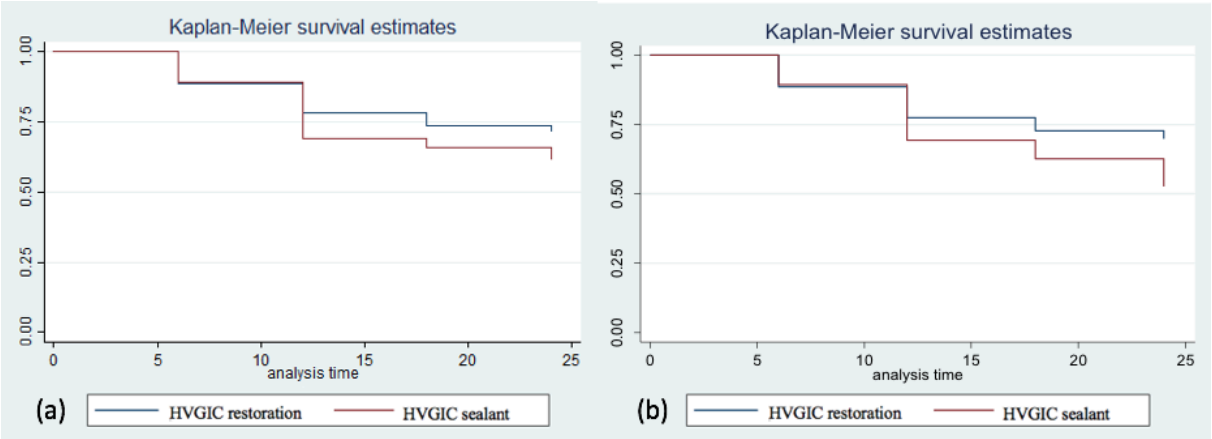
| ALL FAILURES | Single First Failure | | | | Multiple Failures | | | |
|---|---|---|---|---|---|---|---|---|
| Independent Variable | Brute HR (95%CI) | P Value | Adjusted HR (95%CI) | P Value | Brute HR (95%CI) | P Value | Adjusted HR (95%CI) | P Value |
| **Group❖** | | | | | | | | |
| **Restoration (ref)** | | | | | | | | |
| **Sealant** | 0.95 (0.48 – 1.82) | 0.905 | 1.72 (0.91 – 3.28) | 0.094 | 1.68 (1.17 – 1.80) | 0.058 | 1.50 (1.05 – 1.61) | 0.106 |
| **Sex** | | | | | | | | |
| **Male (ref)** | | | | | | | | |
| **Female** | 1.04 (0.63 – 1.72) | 0.862 | - | - | 1.02 (0.26 – 0.98) | 0.476 | - | - |
| **Age** | | | | | | | | |
| **3 to 4 yrs-old (ref)** | | | | | | | | |
| **5 to 6 yrs-old** | 0.88 (0.65 – 1.19) | 0.432 | - | - | 0.43 (0.11 – 0.42) | 0.07 | 0.36 (0.09 – 0.34) | 0.001 |
| **Caries Experience** | | | | | | | | |
| **dmft+DMFT<3 (ref)** | 1.04 | | 3.28 | | 0.98 | | | |
| **dmft+DMFT > /= 3** | (0.95 – 1.13) | 0.326 | (1.00 –10.8) | 0.050 | (0.20 – 1.18) | 0.487 | - | - |
| **Operator** | | | | | | | | |
| **Team Leader (ref)** | 0.91 | | 0.40 | | 0.57 | | | |
| **General Operators** | (0.14 – 1.44) | 0.442 | (0.16 – 0.98) | 0.046 | (0.11 – 0.72) | 0.119 | - | - |
| **Tooth Type** | | | | | | | | |
| **1° molar (ref)** | 0.76 | | | | 1.17 | | | |
| **2° molar** | (0.20 – 0.73) | 0.204 | - | - | (0.28 – 1.21) | 0.329 | - | - |
| **Side** | | | | | | | | |
| **Right (ref)** | 0.63 | | | | 0.83 | | | |
| **Left** | (0.34– 1.06) | 0.442 | - | - | (0.21 – 0.81) | 0.296 | - | - |
| **Dental Arch** | | | | | | | | |
| **Upper (ref)** | 1.34 | | | | 1.71 | | 2.08 | |
| **Lower** | (0.81– 2.22) | 0.239 | - | - | (0.44– 1.67) | 0.055 | (0.52 – 2.05) | 0.017 |

- Variables tested, but not associated in multiple model HR = Hazard ratio; 95%CI = 95% confidence intervals

❖The p-value and CI were adjusted deriving a one-tailed test from two tailed output. (Bruin,J. 2006 Statistical Consulting Group). (Open access https://stats.stackexchange.com/questions/257526/can-one-sided-confidence-intervals-have-95-coverage/257528#257528 accessed in October 22st,2019)

Source: Author

Figure 4.5 – Kaplan-Meier curves for survival of restorations and sealants with HVGIC, considering all failures - (a. Single first failure analyses and b. Multiple failures analysis.)




Source: Author

Considering the major failures when only the single 1st failure was considered sealants were also not inferior than restorations (need for replacement – restorations: 18%/ sealants: 27%) and the survival mean time until 1st failure was observed among groups receiving different treatments (t=23months). Besides increasing failure rates, inclusion of successive events increased the difference between interventions. Sealants presented more failures (37%) than restorations (22%), rejecting the hypothesis the sealant was not inferior (Table 4.4 and Figure 4.6). Besides, the mean time-to-event were different between interventions using this model.

Table 4.4 – Cox regression models considering as a composed outcome major failures (requiring replacement) + caries progression (requiring placement of new restorations)

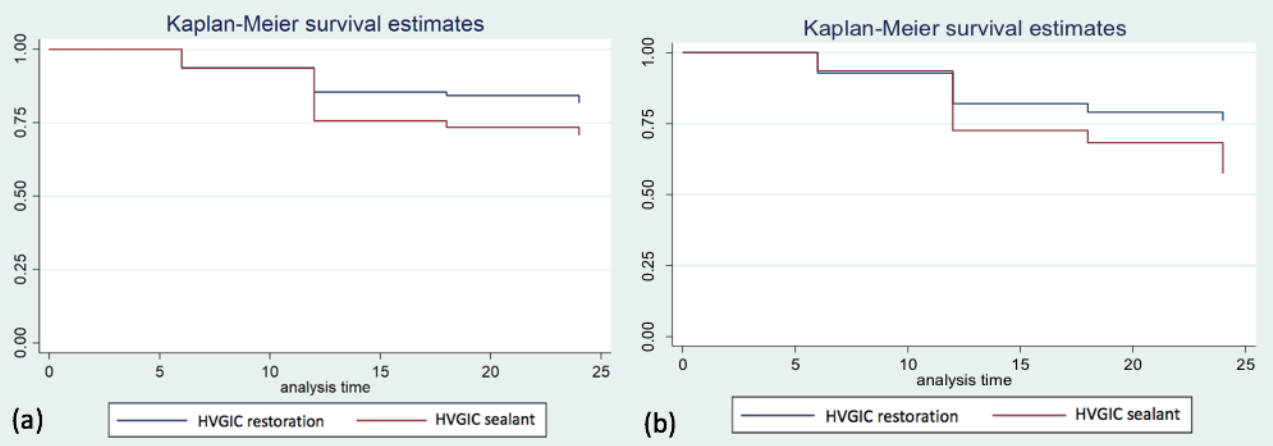
| MAJOR FAILURES | Single First Failure | | | | Multiple Failures | | | |
|---|---|---|---|---|---|---|---|---|
| Independent Variable | Brute HR (95%CI) | P Value | Adjusted HR (95%CI) | P Value | Brute HR (95%CI) | P Value | Adjusted HR (95%CI) | P Value |
| **Group ❖** | | | | | | | | |
| **Restoration (ref)** | 1.68 | | 1.69 | | 1.48 | | 1.97 | |
| **Sealant** | (0.87 – 2.97) | 0.116 | (0.88 – 3.25) | 0.109 | (1.17 – 1.59) | 0.164 | (1.35 – 2.10) | 0.040 |
| **Sex** | | | | | | | | |
| **Male (ref)** | 0.95 | | | | 1.01 | | | |
| **Female** | (0.50 – 1.82) | 0.894 | - | - | (0.47 – 2.18) | 0.963 | - | - |
| **Age** | | | | | | | | |
| **3 to 4 yrs-old (ref)** | 0.73 | | | | 0.74 | | | |
| **5 to 6 yrs-old** | (0.38 – 1.38) | 0.338 | - | - | (0.49 – 1.11) | 0.151 | - | - |
| **Caries Experience** | | | | | | | | |
| **dmft+DMFT<3 (ref)** | 3.47 | | 3.28 | | 1,24 | | 1.36 | |
| **dmft+DMFT > /= 3** | (1.04 – 11.6) | 0.043 | (1.00 – 10.8) | 0.050 | (0.42 – 3.58) | 0.690 | (0.51 – 3.58) | 0.533 |
| **Operator** | | | | | | | | |
| **Team Leader (ref)** | 0.36 | | 0.40 | | 0.28 | | 0.76 | |
| **General Operators** | (0.14 – 0.87) | 0.023 | (0.16 – 0.98) | 0.046 | (0.87 – 0.95) | 0.042 | (0.34 – 1.71) | 0.520 |
| **Tooth Type** | | | | | | | | |
| **1° molar (ref)** | 0.76 | | | | 2.29 | | 2.55 | |
| **2° molar** | (0.39 – 1.46) | 0.418 | - | - | (1.65 – 3.19) | 0.001 | (1.79 – 3.78) | 0.001 |
| **Side** | | | | | | | | |
| **Right (ref)** | 0.68 | | | | 1.02 | | | |
| **Left** | (0.34– 1.17) | 0.151 | - | - | (0.23 – 1.08) | 0.948 | - | - |
| **Dental Arch** | | | | | | | | |
| **Upper (ref)** | 1.34 | | | | 1.83 | | | |
| **Lower** | (0.72 – 2.48) | 0.151 | - | - | (0.85 – 3.93) | 0.121 | - | - |

- Variables tested, but not associated in multiple model HR = Hazard ratio; 95%CI = 95% confidence intervals

❖The p-value and CI were adjusted deriving a one-tailed test from two tailed output (Bruin, J. 2006 Statistical Consulting Group). (Open access https://stats.stackexchange.com/questions/257526/can-one-sided-confidence-intervals-have-95-coverage/257528#257528 accessed in October 22st,2019)

Source: Author

Figure 4.6 – Kaplan-Meier curves for survival of restorations and sealants with HVGIC, considering major failures (requiring replacement) + caries progression (requiring placement of new restorations) (a) Single first failure analyses and (b) Multiple failures analysis




Source: Author

Indeed, we could observe a higher increase in failures among sealants than among restorations at the 12-month follow-up (Figures 4.3, 4.4 and 4.6). Furthermore, mostly sealants (70%) replaced at this moment failed again at 18- or 24-month follow-up.

Analyzing survival curves, during the first year of the study, reintervention needs of restoration tended to be higher than sealants considering both needs of repair and replacement (all failures). Nevertheless, in the 2$^{nd}$ year, difference in survival rate tended to be diminished (Figure 4.7). When only the replacement (major failures) were considered, after one year the failures demanding replacement of sealants and were higher than for restorations, what continues until the 2-year follow-up.

Caries progression was observed in few cases (6%), and there were no differences between the treatments despite of the model of failure used in the analyses (Table 4.5 and Figure 4.7). Among failed sealants 22% were replaced (Table 4.4). Among those surfaces which were to retreat, any progression was observed during the study.

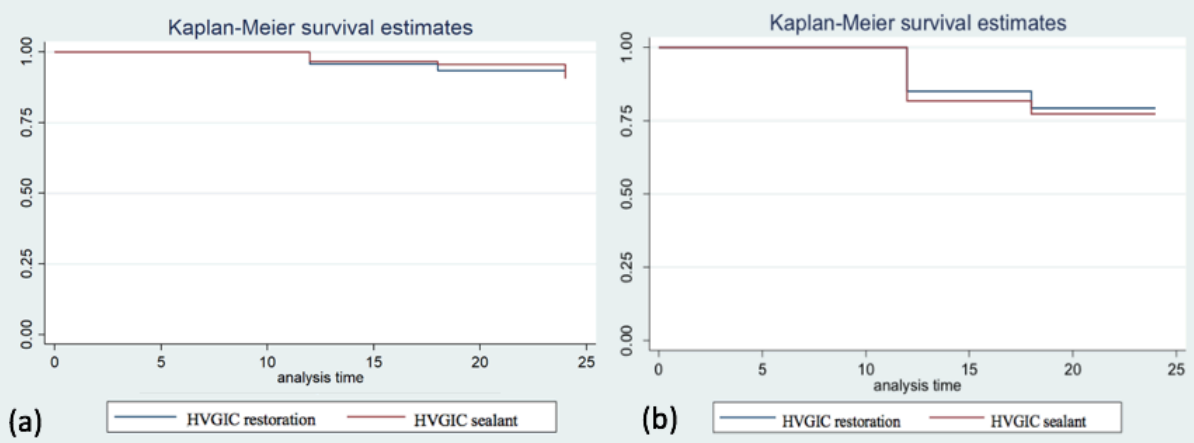
Table 4.5 – Cox regression models considering only caries lesion progression

| PROGRESSION ✣ | Single First Failure | | Multiple Failures | |
|---|---|---|---|---|
| **Independent Variable** | **Brute HR (95%CI)** | **P Value** | **Brute HR (95%CI)** | **P Value** |
| **Group** | | | | |
| **Restoration (ref)** | 1.34 | | 0.84 | |
| **Sealant** | (0.46 – 3.87) | 0.584 | (0.24 – 2.92) | 0.792 |
| **Sex** | | | | |
| **Male (ref)** | 0.70 | | 0.70 | |
| **Female** | (0.20 – 2.47) | 0.583 | (0.20 – 2.47) | 0.583 |
| **Age** | | | | |
| **3 to 4 yrs-old (ref)** | 0.87 | | 0.48 | |
| **5 to 6 yrs-old** | (0.30 – 2.53) | 0.812 | (0.20 – 2.47) | 0.073 |
| **Caries Experience** | | | | |
| **dmft+DMFT < 3 (ref)** | 1.04 | | 2.68 | |
| **dmft+DMFT > /= 3** | (0.87 – 1.24) | 0.642 | (0.31 – 22.8) | 0.365 |
| **Operator** | | | | |
| **Team Leader (ref)** | 0.66 | | 1.08 | |
| **General Operators** | (0.18 – 2.36) | 0.524 | (027 – 4.34) | 0.905 |
| **Tooth Type** | | | | |
| **1° molar (ref)** | 0.77 | | 0.39 | |
| **2° molar** | (0.25 – 2.29) | 0.60 | (0.10 – 1.44) | 0.160 |
| **Side** | | | | |
| **Right (ref)** | 0.82 | | 0.69 | |
| **Left** | (0.29 – 2.36) | 0.724 | (0.18 – 2.58) | 0.588 |
| **Dental Arch** | | | | |
| **Upper (ref)** | 1.48 | | 1.94 | |
| **Lower** | (0.50 – 4.10) | 0.497 | (0.51 – 7.35) | 0.329 |

- Variables tested, but not associated in multiple model HR = Hazard ratio; 95%CI = 95% confidence intervals.
✣Final model were not adjusted for other variables

Source: Author

Figure – 4.7 Kaplan-Meier curves for survival of restorations and sealants with HVGIC, considering the caries lesion progression (a) Single first failure analyses and (b) Multiple failures analysis.)




Source: Author

## 4.4 Discussion

After a 2-year perspective, sealing moderate caries lesions using HVGIC may be used to arrest the lesions progress on occlusal surface of primary teeth, but more failures along the time may demand more reinterventions compared with the restoration using the same material. To the best of our knowledge, this is the first study to perform multiple ordered failure-time events to evaluate the efficacy of these two dental treatment approaches. These findings seem to indicate that the use of HVGIC, even used less invasive approaches, could be useful to control moderate caries lesions in children. Invasive treatments that resulted in loss of sound tissue have been replaced by treatments that aimed to preserve the tooth structure (86). In addition, even for more advanced lesions, more invasive treatments have not demonstrated superiority to more conservative in terms of avoiding dental pain in children (87) .

As discussed in the Chapter I, moderate caries lesions (presenting microcavitations or shadow into dentine), showed higher risk of progression (worse prognosis) than initial caries lesions, probably because they involve cavitations, present a more complicate biofilm control and are often histologically involving dentine (53,69). Although restorative treatment has been traditionally indicated to the

treatment of dentine caries lesions (2,88) and are being the some professionals' option (5), efforts should be concentrated on these lesions to prevent their progression to stages in which the restorative treatment could be really unavoidable. Therefore, in these conditions in which frankly cavitation is not observed, sealants, as more conservative options, may be considered.

Glass ionomer cements have been widely used in Brazil in Paediatric Dentistry to due to the clinical advantages of the technique (89) has been pointed out as an alternative to resin composite that is more moisture sensitive. The HVGIC performance in primary teeth may be a reasonable explanation for that. A systematic review performed with only Randomized Clinical Trial (RCTs) concluded that ART with HVGIC restorations have similar survival percentages to conventional treatment of amalgam and resin composite restorations (90). Other study showed that ART/HVGIC sealants can be used with a high level of success in high caries risk pits and fissures, evidencing prevention of dentine carious lesion along 5 years (91). HVGIC ART/sealants approach has been consistently shown as an effective evidence-based option for managing carious lesions (91).

On the other hand, in this study, the purpose of using HVGIC was slightly different from those exposed until now. Clinically, we do not believe the surface to be sealed could imply in some difference and impact on intervention success, since only only a microcavitation would be the differential to teeth sealed in other studies. In fact, we observed similar survival rates than those observed in the literature when HVGIC used as sealants in permanent teeth (84,92). Nevertheless, the clinical condition would be more critical (a moderate instead of initial caries lesions), demanding more controlled care, as discussed in Chapter I. That is why assessing successive failures, if they occurred permit a more real understanding about the proposed intervention, as also would approximate the results to the real life.

In Dentistry, Cox proportional hazard model is commonly used for clinical trial data and provides survival times estimates and the relative risk associated with time-to-event occurrence. However, to calculate the survival time in the standard Cox model, only the first event is considered and any information after the event is used (93). One possible solution is to use multiple failures instead of only the first, and all recurrent events (failures) and the patients continue to be observed even after the first event (77,78).

There are different multifailure survival methods to analyze time to multiple occurrences (93,94). In this study, we used the conditional risk set model (time from entry) (79), with multiple events ordered by stratification, which is based on the prior number of events during the follow-up (78). Using this strategy, we observed a shift in the direction of results compared to the single failure analysis. Besides the higher failure rates for both groups when such type of model is used, we evidenced different time to events between the two different tested treatments. Thus, our hypothesis of non-inferiority of HVGIC sealants compared to restorations in the mentioned purpose was rejected. The same could not be proved when the conventional survival analysis (single failures) was used. Therefore, using multiple failure-time models permit we have a more realistic understanding of treatment patterns in the real life. That is why multiple events, when applicable, should be considered for testing efficacy of treatments in Dentistry. Further studies in different fields may use such type of strategy in order to provide more accurate results and minimize the gap between the research and the clinic.

Another important observation should be done related to the type of failures and related to the interventions. In a short-term analysis, a higher number of repairments is required for restored teeth, while sealants showed more distant failures, but requiring replacement. This fact may be a condition related to the type of intervention by itself, since the sealant is often placed on a microcavitated, or even non-cavitated surface, being a lower mechanical retention compared to cavities which were restored. On the other hand, these findings can be reflecting the sealant/restoration assessment, in which if sealant was only considered as failed when the moderate lesion was appearing. Probably, small losses of sealing material were unregistered in the protocol.

Despite studies have shown the HVGIC can be effective in controlling caries although fails in sealant retention (84), given the unfavourable prognosis of moderate caries lesions if they were not treated we cannot affirm, based on our findings, what could have happened if lesions had not been resealed, since many of them are into dentine (53). In this protocol, due to ethical reasons, we opted for retreat all failures when detected, especially because microcavities, depending on randomization, could have been opened to be restored. Then, to avoid a potential source of difference between interventions (retreat or not), we opted to retreat both groups. Due to that, in cases where sealant was lost exposing the moderate lesion initially sealed, we

considered as a need for re-intervention. Further studies could be performed in order to test the prognosis when the reintervention is not performed in such cases.

In this study radiographs were not taken to detect moderate caries lesions on occlusal surface, because its known that clinicians are able to detect lesions and predict activity and severity based on visual inspection (95). Moderate caries lesions often present no radiographic image, or a radiolucent zone restricted to the enamel-dentin junction, despite the presence of clinically evident dark shadow from dentin (50,51). Not necessarily the presence of enamel breakdown is associated with the presence/ depth of the radiolucent image (96). However, radiographs could be useful to determine caries management on lesions (95), but, in this protocol, we opted for indicating the interventions based on clinical condition. Indeed, as showed in Chapter I, typical clinical characteristics as microcavitations and dentine shadows were more associated with caries progression than lesions depth. We believe this aspect could be more evident for occlusal lesions, as treated in this study.

Although restoration group presented less failures demanding major interventions (replacement or new restorations for progression), the survival rates seems to be lower than those found in the current scientific literature for 1-surface restoration in primary teeth (91), in which we indeed based our sample size calculation. We believe the higher failure rate is related to type of cavity created when a moderate lesion is opened. Following the concepts of minimal invasion, the minimum removal of dental tissue is expected. Since many moderate lesions may present minimum (or none) involvement of dentine, the cavity design may be unfavourable for enhancing mechanical retention of material. This fact may be an additional motivation to opt for sealants instead restorations when controlling moderate caries lesions is the deal.

Small caries progression rates were observed independently of the group. This fact could evidence the success of the strategies to controlling caries lesions at the time horizon explored. Indeed, approximately 50% of moderate caries lesions on occlusal surfaces of primary teeth progressed after 2 years (6–8). Considering less than 10% of progression was observed, we can corroborate the caries control was achieved despite the intervention used.

In this clinical trial, it was not possible to blind operators and the participants, because the difference between the procedure techniques. In the restoration group the high-speed burns was used, and selective removal of carious tissue with a hand

excavator, in the sealants group no caries removal were performed. In addition, when the participant had more than one eligible tooth, and it was not possible to perform all teeth at the same session, the allocation confidentiality was broken from the second treatment session, as the child was randomized only once. Nevertheless, the evaluation was carried out by two examiners and they were blind to the allocation group, and they did not participate of the treatment phase. As we used the same material for both interventions and even opening cavities for restoring, these cavities presented minimum size, knowing which intervention had been performed in each tooth. Therefore, we believe these methodological strategies could have minimized inclusion of bias in our study.

Sealing moderate caries lesions using HVGIC could be an efficacious alternative to arrest these lesions progress in primary teeth, however a higher number of replacements are necessary. This evidence could be useful in private and public contexts representing an easier and efficacy option to treatment of moderate carious lesions in children. It is important to highlight that not only the local treatment should be considered as the responsible for the control of caries lesions on occlusal surfaces. Other preventive factors such as diet control, good hygiene and children's and their family motivation should be also associated to preserve oral health.

## 4.5 Conclusion

After a 2-year perspective, sealing moderate caries lesions using HVGIC seems to have similar longevity than restorations with the same material, but a higher number of replacements may be necessary.

# 5 CHAPTER III:

## Is sealing moderate caries lesions on occlusal surfaces of primary molars using high viscous glass ionomer an efficient therapeutic alternative? A trial-based economic evaluation including professional-centered and patient-centered health effects

## 5.1 Introduction

Usually, dental materials and the performance of restorative techniques are investigated considering their survival rates of the treatments (97). However, other relevant outcomes related to the use of such interventions are important to be investigated before disseminating their regular use clinical practice. In this sense, the economic evaluations (linking effects caused by treatment to the treatment costs-material or not) are extremely relevant for clinical decision-making and implementation of strategies in a regular basis (98).

In the Chapter II, we demonstrated that sealing moderate caries lesions has similar effect than restoring them for controlling caries progression over 2 years. However, a higher number of reinterventions (especially replacements) were expected. Individually, this may be a preference choice for patient and their family. On the other side, increasing the demand for reinterventions, and retreatments, which is still frequent in public and private dental practices, consumes a significant amount of clinical time and imposing high financial costs for health systems (99). Thus, it is important to understand the economic impact of the treatments and reinterventions in children (100).

In recent years, economic evaluations of healthcare programs has become more important. Even being underexplored in Dentistry (101), they are accepted tool to evaluate the benefits of different interventions (102) and provide a constantly improvement of health care programs (103,104). Clinicians and caregivers tend to choose for the treatment that is based on techniques that are cost-effective and evidence-based (102). Since economics is founded on the principle of scarcity (105)

and to make decisions and choices about how best to use and allocated the resources worldwide, economic analysis are desirable. Using the economic analysis, it is possible to weigh in the same analysis two different outcomes (costs and effects) to guide the decision-making process.

The Cost-effectiveness analysis (CEA) is one of the most commonly economic evaluation used in health (106). This type of economic analyses link directly the financial aspects to the health implications of different interventions (107). As expected health gains, different outcomes should be considered (98). For decision-making in Pediatric Dentistry, besides professional-centered outcomes as treatment success, e.g. survival of a restoration, patient-centered outcomes would be desirable. A common challenge for clinicians and parents is allowing child to experience dental treatment and empower her/him to maximize their ability to accept and to cooperate with the treatment (18). Furthermore, it is growing the evidence that different types of procedures might influence child's behavior and perceptions of dental treatment (108–110). This brings an important glance since sealing does not demand neither the use of rotatory instruments, tending to be more acceptable for children.

In this sense, this study proposed a trial-based economic evaluation to investigate if sealing moderate caries lesions is an efficient option to allocate resources compared to restoring them, even considering more reinterventions should be done. To analyze the efficiency in allocating resources, two different health effects were chosen. One of them was a professional-centered outcome, based on the success of the treatment, hence considered as no caries progression after 2 years. The other one is a patient-centered reported outcome focusing on children's acceptability to the interventions. At the end, we expected to create subsides to guide (or not) implementation of the proposed strategy when both actors involved in the intervention are considered.

## 5.2 Materials and methods

The present study was written following the guidelines proposed in the ISPOR Good Research Practices Task Force Report for cost-effectiveness analysis

alongside clinical trials (111), and to the checklist “Consolidated Health Economic Evaluation Reporting Standard’s” (CHEERS) (Appendix E).

### 5.2.1 Clinical trial

This study performed an economic evaluation alongside a clinical trial (NCT03005405) planned to check if sealing was not an inferior treatment compared to restorations to manage moderate caries lesions on occlusal surfaces of primary teeth. The protocol was approved by the Research Ethics Committee of Dental School, University of São Paulo (protocol 659.006) (Annexe A). Details about the study protocol may be found elsewhere (in Chapter II).

### 5.2.2. Definitions for economic evaluation

A time horizon of two years and a societal perspective were chosen for this evaluation. We opted for using CEA to make possible to analyze the relationship about costs and both professional-centered and patient-centered health effects.

### 5.2.3 Health effects

The health effects considered were the treatment success (absence of caries progression) and patient-reported acceptability. Child was used as the unit of analysis for this economic evaluation.

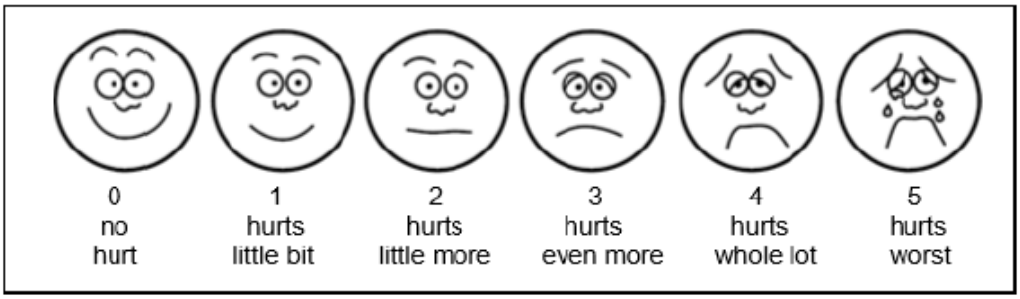
### 5.2.4 Treatment success (professional-centered outcome)

Children were followed and treated teeth were assessed biannually for 24 months to success was considered when caries  lesion in treated teeth did not progress to a frankly cavity exposing dentine, according to WHO criteria (61). The success rate per child (ranging from 0 to 1) was considered the health effect. It was calculated by the ratio between number of teeth without caries progression and the total number of treated teeth.

### 5.2.5 Acceptability (patient-centered outcome)

The child's acceptability was inferred by the self-reported discomfort by her/him immediately at the end of treatment. A facial image scale of Wong-Baker (112) (Figure 5.1) was presented for all children by an external examiner and they had to answer how he/she was feeling during the procedure through the question: "How did you feel after taking care of your teeth today?". The answer was given only by the child, without interference from parents or professionals and was recorded in a standardized form (Appendix F). Participants with more than one tooth treated in the study answered to the scale more than once. If, during the -year follow-up, treated teeth needed some repair or replacement, the sealants/restorations were replaced using the same intervention of baseline, and the discomfort was self-reported again by the children. The worst score reported by child in the intervention was considered.

Figure 5.1 – Facial Image scale of Wong-Baker




Source: Wong-Baker (112)

The acceptability rate per child was used as another health effect. This rate was calculated using similar formula to success rate (number of interventions in which child reported discomfort divided by the number of interventions received).

### 5.2.6 Costs

The cost per child was calculated over 24 months. In the calculations, costs related to all treated teeth were summed up. Final costs are considered as the sum of the direct costs (costs related to the procedure) and the indirect costs (costs related to the patient and caregivers) in the baseline treatments and other interventions (e.g. sealants/restorations repairment or replacement) carried out during follow-ups. In case of caries progression and need of a new restoration placement, teeth received atraumatic restorative treatment (ART) and direct and indirect cost was calculated.

Costs were valued in Brazilian Real (BRL) and converted to International dollars (USD), for the conversion it was used the Purchasing Power Parities (PPP) 2018 with a conversion rate=2.029 (113).

For all procedures, information about quantity and specifications of all dental materials was recorded in a standardized form (Appendix F).The clinical time spent, and the materials used in each session was recorded in the form by an external operator (who was not in the diagnostic or treatments exams). Also, the number of sessions and the clinical time spent in the treatments over the 2 years of follow-up were recorded for further calculations.

As direct costs, we considered those costs related to dentist and dental assistant, the equipment, and the dental material used during the treatments and the accommodation:

For professional costs, 40 working hours per week were considered to the dentist ($28.82/h) and 30 working hours to the dental assistant ($10.00/h), as suggested by Brazilian Federal Law (16.665) (114). The value per hour was calculated using as reference the minimum wage for the state of Sao Paulo. Professional cost was finally calculated considered the time spent during all visits/child.

For the costs of accommodation, equipment and maintenance the total time spent in all procedures were considered. The accommodation cost was calculated using the rental mean cost. The mean price per $m^2$ from properties in the municipality of the Barueri-SP was considered. Then, we calculated the cost per hour of the mobile dental unit with 13.5 $m^2$. Summarized to this, the estimate of electricity use was also measured following the same methodology.

A cost per hour of utilization of dental chair, peripheral equipments and dental instruments was estimated. A useful life of 5-year for equipments and 3-year for instruments was considered and a monthly use of 160 hours, resulting in the average cost of these goods per hour.

The material cost was calculated using the quantities recorded for each intervention. A mean value of selling prices for materials was also calculated. The selling price was obtained in three different dental stores (last update in Jan 14$^{th}$ 2019). For the restorative materials (HVGIC), portions were recorded using a precision scale (Analytical Electronic Scale, QUIMIS® ISO 9001, Model Q500L210C, Standard Deviation ± 0,1mg). The price per unit was calculated dividing the total price per number of portions obtained in product package.

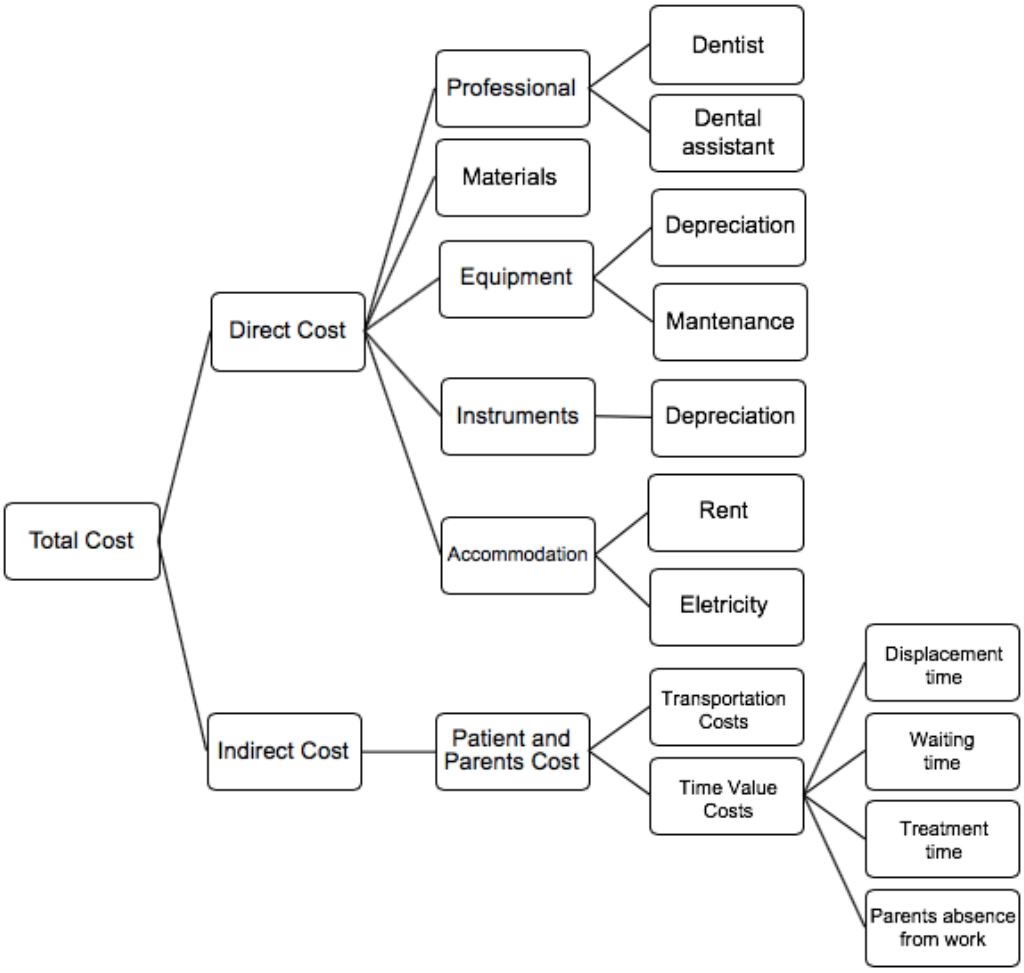
As indirect costs, we considered the patient and parent's transportation, patient and parent's time value and parent's absenteeism in the workplace for all dental visits.

The number of sessions were considered to the costs of transportation, which were calculated based on the type of transportation (car, public transportation or on foot). If parents used their own car, both the average price for fuel as informed by the National Agency and the distance from the mobile dental unit to their house were considered. It was used a fixed ratio of 8.5 kilometres per litre of fuel. For public transportation an average fare of the last four years was calculated. Round-trip fares were assumed for the child and her/his parent. When patients went on foot no fare were considered.

Patient's and parent's time value was based on time spent for transportation (round trip) plus waiting and treatment time in the dental unit. To calculate the transportation time, we considered the information available in a database for transportations (GoogleMaps), which estimate the time from the family's residence to the dental unit. 15 minutes was considered as waiting time per session. For the treatment time it was used the procedures duration. To estimate the value to

accompanying person's time, the average for month of Brazilian income from 2012 to 2017 was used a value per hour was calculated (US$ 6.16 per hour), considering 8 work hours per day (business day). The minimum wage rate for Sao Paulo was the reference for calculating the patient's time and same parameters above were used (US$ 2.61/hour). It was important to know if the accompanying person missed the work, if the answer was yes, we have to consider an additional cost (a day of work). Therefore, the total time of transportation, waiting time and treatments time per session were calculated in order to obtain the total value of child and accompanying person (Figure 5.2).

Figure 5.2 – Diagram evidencing direct and indirect costs estimated to CEA




Source: Author

### 5.2.7 Data Analyses

The bootstrapping quantile regression analysis was used to compare the costs between the interventions. The analysis estimates the model with bootstrap standard errors, and with assumption of independent errors, and they are analogous to standard errors in the linear regression. Bootstrapping replications have been defined such 1000, and a fixed seed was determined (115). The bootstrapping quantile regression analysis was also performed. The variables tested for incremental costs were: the treatment (HVGIC sealant vs HVGIC restoration), sex (male, female), caries experience (dichotomized by the median: <3 vs >3), age (3 to 4 years vs. 5 to 6 years), Familiar Budget (between $388 to $776, more than $776) and mother's schooling (less than 8 years, more than 8 years). The unit of analysis was set as the child.

Health effects were, in a first attempt, considered as dichotomized (success vs. insucess and with discomfort vs. with no discomfort). Poisson regression analyses were performed to compare the health effects in tooth level. Then, the success rate and the acceptability rate per child were compared using the bootstrapping analysis and the same strategy for creating the models were used. These last analyses used the child as the unit to be analyzed.

The cost and effect of performing sealants as an alternative to restoration were used in two different cost-effectiveness analyses (one for each chosen effect). Since HVGIC restoration was considered as the control group, it was used as the reference for calculations of incremental cost-effectiveness ratio (ICER). The ICER was calculated dividing the incremental cost of performing HVGIC sealants instead HVGIC restoration by the incremental effect of the same substitution.

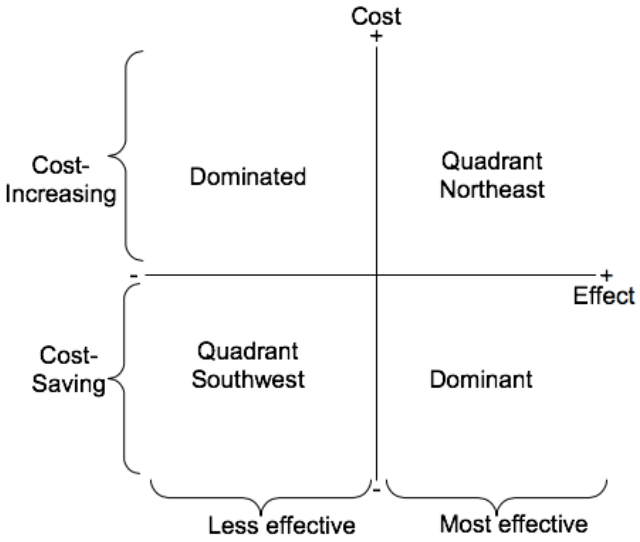
As effect, we set: the treatment success (no caries progression) and the treatment acceptability, as detailed in previous sections. ICERs express the cost difference per gained or lost in effectiveness.

$$ICER = \frac{\text{Cost HVGIC sealant} - \text{Cost HVGIC restoration}}{\text{Effect HVGIC sealant} - \text{Effect HVGIC restoration}}$$

A cost-effectiveness plane was drawn using 10.000 simulated situations by Monte-Carlo simulation. Bayesian approach was adopted to explore the uncertainties of cost-effectiveness analysis (CEA). Then, the costs and effects were described by statistical distributions using XLSTAT 2018 (Addinsoft SARL, Paris, France). The simulated values of effects and cost were plotted on a cost-effectiveness plan (scatter plot – in the axis X: effects, axis Y: costs).

To analyse the uncertainties about the variables, the probability was also visually assessed in this plane the uncertainty according to the decision estimated. The best option would be the quadrant southeast (most effective, less costly), in quadrant northeast (most effective, more costly), and in quadrant southwest (less effective, less costly) the alternative maybe would be acceptable depending on decision rules. The quadrant northwest (less effective, more costly), the alternative treatment would be dominated (Figure 5.3).

Figure 5.3 – Cost-Effectiveness Plan




Source: Adapted from Cohen and Reynolds (113)

We calculated the incremental benefit using the equation: Incremental Net Benefit = Incremental Effect* Ceiling Ratio – Incremental Cost. Taking the value 1 for a positive coefficient and 0 for a negative coefficient value. Thus, for the interpretation, if the difference is greater than zero (the value 1), it means that for one

additional unit of effectiveness the incremental cost is below the Ceiling Ratio (the maximum value that decision makers is willing to pay). If the difference is less than zero (the value 0), then for one additional unit of effectiveness the incremental cost is above the Ceiling Ratio (117).

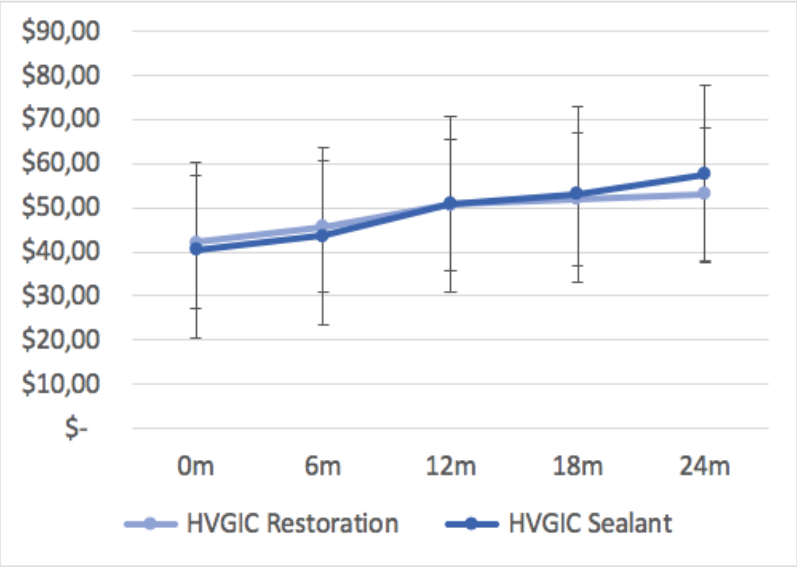
Finally, cost-effectiveness acceptability curves (CEAC) were drawn using the incremental net benefit framework and assuming different ceiling ratios (from 0 to 500000). Probabilities for the sealant treatment being a cost-effective option were calculated for all ceiling rates assumed. The CEAC is a graph summarising the impact of uncertainty, this graph plots on the horizontal axis a range of cost-effectiveness thresholds (representation of ceiling ratio), and on the vertical axis the probability that the sealant intervention will be cost-effective (118).

## 5.3 Results

101 children aged between 3 to 6 years old (mean age: 4.5±0.8) were included and 204 occlusal surfaces of primary molars were treated (on average, 2 teeth/child). More detailed description about participants can be found elsewhere, in the Chapter II.

In the baseline (t0), the total costs (direct costs + indirect costs) were, on average, similar between the restoration ($42.15 ± 3.3) and sealant groups ($40.44 ± 4.6). After 2-year follow-up, the costs tended to increase more evidently for the sealant group, but there was no statistically significant difference. ($53.02 ± 10.6; $57.70 ± 15.2) (p=0.977) (Figure 5.4) and (Table 5.1).

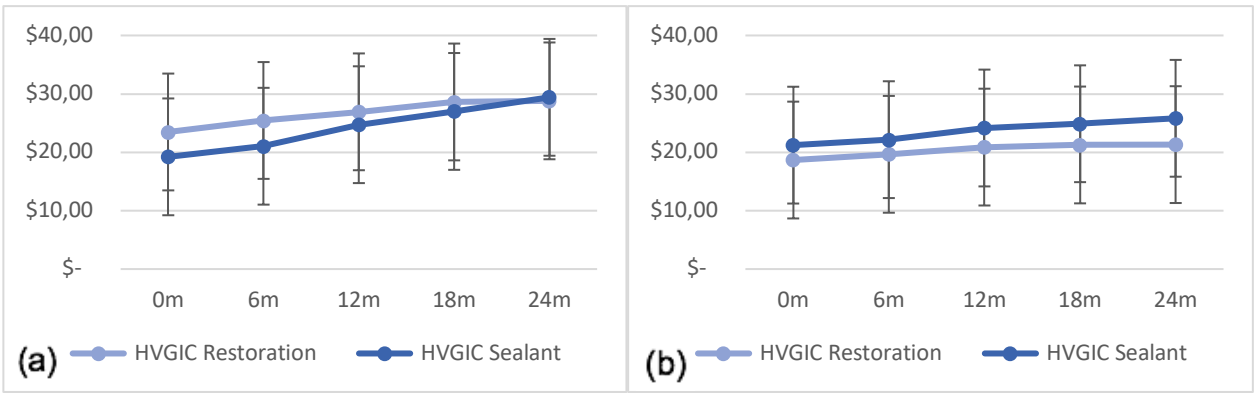
Figure 5.4 – Accumulated total cost of HVGIC restorations and sealants in 24 months of follow-up




Source: Author

Although no statistically significant difference has been observed, considering the directs cost in the baseline (t0), HVGIC restoration tended to be more expensive ($23.47) than HVGIC sealant ($19.22). This difference seems to be diminished after 2 years (Figure 5.5a). Constant patterns for indirect costs were observed over the time (Figure 5.5b).

Figure 5.5 Direct (a) and indirect (b) costs of HVGIC restorations and sealants accumulated over 24 months of follow-up




Source: Author

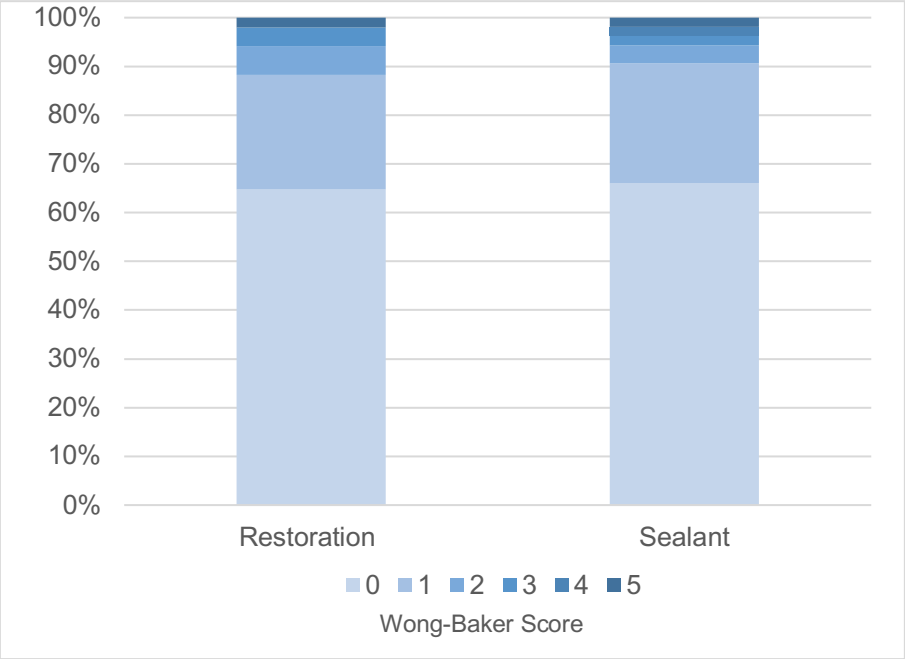
Table 5.1 – Bootstrapping Quantile Regression Analysis by children

| Independent Variable | Univariate | | Multivariate | |
|---|---|---|---|---|
| | Coef. (95%CI) | P Value | Coef. (95%CI) | P Value |
| **Group** | | | | |
| **Restoration (ref)** | 0.37 | | 0.37 | |
| **Sealant** | (- 0.00 – 0.74) | 0.055 | (- 0.16 – 0.72) | 0.040 |
| **Sex** | | | | |
| **Male (ref)** | - 0.31 | | | |
| **Female** | (- 0.78 – 0.16) | 0.202 | - | - |
| **Caries Experience** | | | | |
| **dmft+DMFT < 3 (ref)** | 0.11 | | -5.77 | |
| **dmft+DMFT > /= 3** | (- 0.34 – 0.56) | 0.631 | (- 0.37 – 0.37) | 1.000 |
| **Age** | | | | |
| **3 to 4 yrs-old (ref)** | - 0.12 | | | |
| **5 to 6 yrs-old** | (- 0.40 – 0.16) | 0.413 | - | - |
| **Familiar Budget** | | | | |
| **$388 to $776 (ref)** | 0.02 | | | |
| **More than $776** | (- 0.41 – 0.45) | 0.916 | - | - |
| **Mother's schooling** | | | | |
| **Less than 8 years** | 0.06 | | | |
| **More than 8 years** | (- 0.58 – 0.70) | 0.854 | - | - |

Source: Author

Around 65% of children reported no level of discomfort (happier face). Considering the score distribution of Wong-Baker facial scale, there were no statistic difference between the groups (RR = 0.96, IC 95%= 0.56 – 1.63) p=0.88. The Figure 5.6 show us the percentage of scores between the treatments.

Figure 5.6 – Distribution of Wong-Baker Scale Scores by the type of treatment




Source: Author

At a 2-year perspective, on average, the incremental cost of sealing instead restoring moderate caries lesions was approximately $5. Although no statistically significant differences have been observed between groups, the direction of incremental effects are opposite when patient or professional-centered was considered (Table 5.2).

As a negative mean incremental effect was observed for success rate, a negative ICER was observed (less effective, more costly), representing, on average the studied sample would be represented in the northwest quadrant of CE plan (Figure 5.7). On the other side, when acceptability was considered, the incremental cost and effect were positive and the mean point would be in the northeast quadrant (more costly, more effective) of the CE plan. (Figure 5.8)

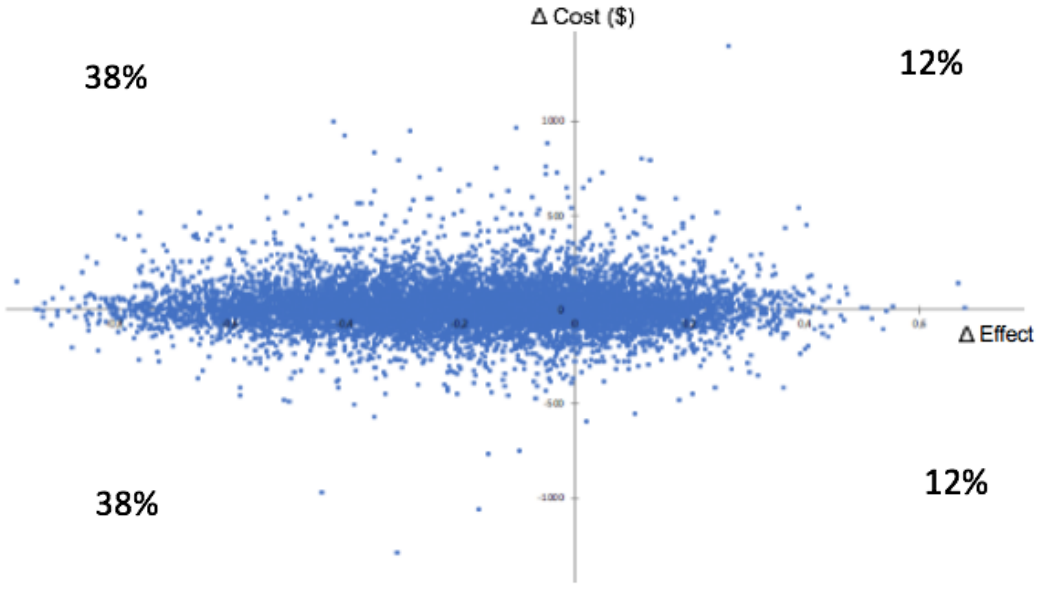
Table 5.2 – Economic analysis considering the cost of using HVGIC sealants as an alternative to HVGIC restoration

| Treatment | HVGIC Sealants | HVGIC Restorations | Delta Incremental |
|---|---|---|---|
| *Survival rates* | | | |
| Costs | $ 57.70 | $ 53.02 | $ 4.68 |
| Effect | 0.898 | 0.951 | - 0.053 |
| ICER | - | - | $ - 88.30 |
| *Acceptability* | | | |
| Costs | $ 57.70 | $ 53.02 | $ 4.68 |
| Effect | 0.816 | 0.764 | 0.052 |
| ICER | | | $ 90.00 |

Source: Author

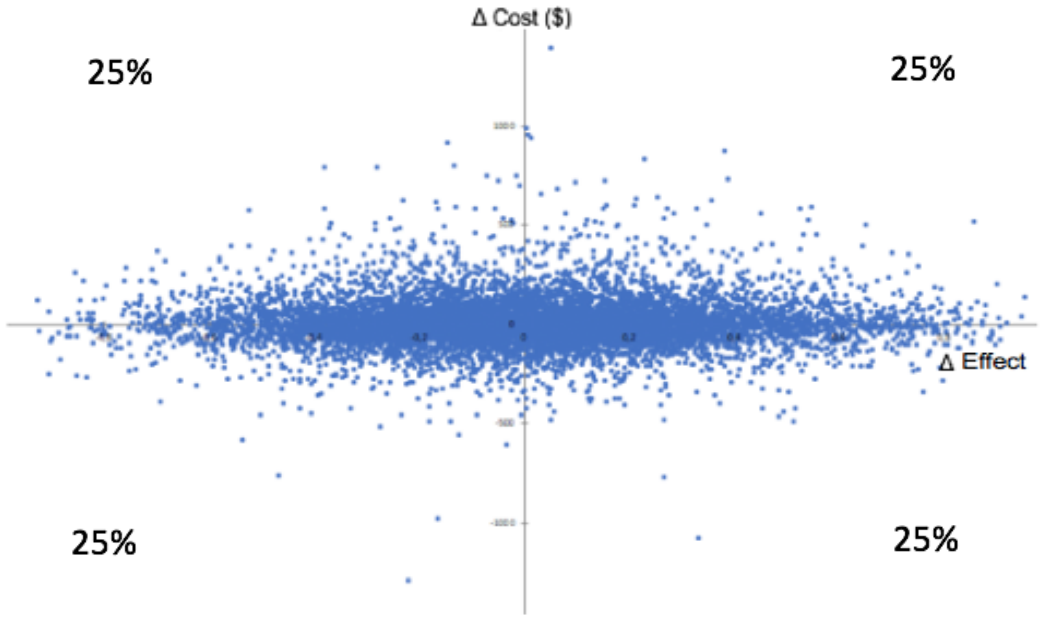
When treatment efficacy (success - no caries progression) was considered, 30% of simulations represent HVGIC sealants as a cost-effective option compared to restorations Figure 5.7. As the perspective was the patient-centred outcome, this probability increased to 50%. Figure 5.8

Figure 5.7 – Cost-effectiveness plan of using HVGIC sealants as an alternative to HVGIC restoration considering the treatment success




Source: Author

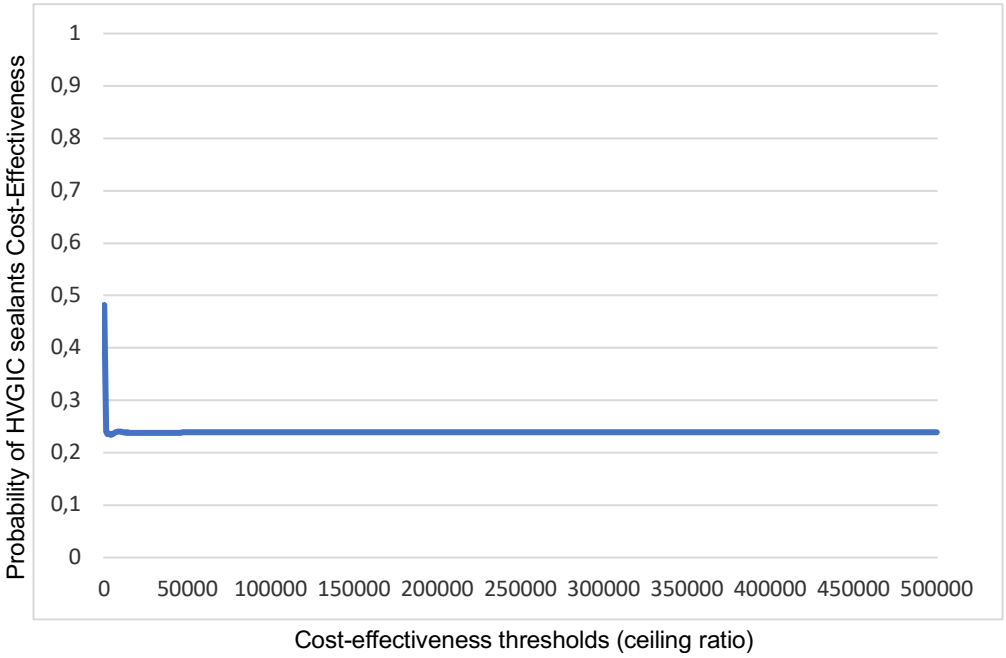
Figure 5.8 – Cost-effectiveness plan of using HVGIC sealants as an alternative to HVGIC restoration considering the acceptability




Source: Author

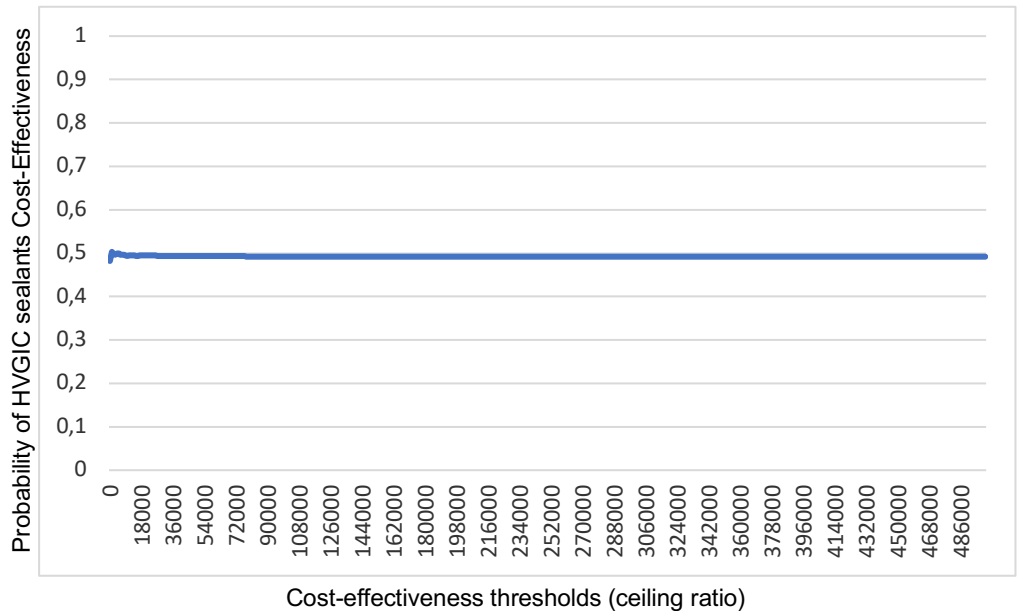
For the professional centered effect varied -$484.828 to $340.432, while for the patient-centered effect, the value of incremental net benefit ranged of -$463.320 to 476.793. The acceptability curves showed that the probability of sealants to be a cost-effectiveness option is of 40% (ceiling ratio=0) or lower around 20%, when progression is the effect considered. On the other hand, this probability increased to 50%, despite the ceiling ratio assumed, when the possibility of not causing discomfort to children is assumed as outcome (Figure 5.9) e (Figure 5.10).

Figure 5.9 – Cost-effectiveness acceptability curves of using HVGIC sealants as an alternative to HVGIC restoration considering the professional-reported outcome




Source: Author

Figure 5.10 – Cost-effectiveness acceptability curves of using HVGIC sealants as an alternative to HVGIC restoration considering the patient-reported outcome




Source: Author

## 5.4 Discussion

The economic analyses have been used in Pediatric dentistry (100,119) and they are important to understand the real outgoing of specific dental treatments. Thus, with these analyses, it is possible to find out if an alternative of treatment is an efficient way to allocate resources than another one, that have been currently used. Using probabilistic decision models and uncertainties, the decision makers may choose the maximum value that they willing to pay for an extra unit of health gain. Besides the efficacy of treatment, this step in the decision-making process may be important to guide changes in clinical practice. Considering restoration is still a reality for several dentists throughout the world, showing the impact of introducing a new alternative may be an important motivation to change the current scenario. In this sense, this is the first attempt to evaluate the incremental cost-effectiveness of using HVGIC sealants instead of HVGIC restorations, as option to the treatment of moderate caries lesions on occlusal surface of primary molars.

This trial-based economic analysis allowed us to consider the short and long-term impact on costs and efficacy related to the implementation of HVGIC sealants for moderate caries lesions. A clinical trial study has several advantages when considered as a vehicle for an economic evaluation. Firstly, we have the possibility of registering the real costs related to the interventions (98). The random allocation reduces the inclusion of bias for selecting information from different studies, e.g. when modeling, and the study design with prospective follow-up, it is possible to ensures the treatment time and number of appointments (120). In the present trial, a time horizon of two years. This horizon was set based on the rationale about failures in restoration in primary teeth (81) and progression of moderate caries lesions (6 – 8). That is why we believe our study horizon was sufficient to consider both initial and re-treatment costs into our estimates.

As discussed in the Chapter II, after 2-year follow-up, the use of HVGIC sealants seems to have similar efficacy in controlling moderate caries lesions compared with HVGIC restorations, but a higher number of replacements were necessary. Then, a societal perspective was chosen, since we intended to calculate and compute the real impact of failures in the evaluation. For that, indirect costs related with treatment and the need of reintervention are necessary to be included,

once patient and her/his parent's dismissed time to go to the treatment, and this time has a value. This is a strength of this study, since many economic evaluations were conducted using only the payer perspective and excluding possible impacts that implementation of a strategy could cause for patients, their family and in a wider analysis, for the society in general.

In terms of cost, the strategy proposed implied in a small increase in costs over a 2-year perspective. Although trial-based economic evaluations allow to test conventionally the significance of differences between costs, this association provide other important contributions to the analyses (121), rather than the significance by itself. Although no statistical difference has been observed, some aspects relevant to a possible implementation of the strategy should be considered. Even demanding more reintervention, sealing seems not alter the indirect costs. Regarding the direct cost, mainly the professional cost explained the difference in the baseline cost. Thus, the HVGIC restorations were more expensive, because its take longer time to be performed than HVGIC sealants. However, after 2 years the needs of reinterventions in the sealants group were responsible for impacting on economic aspects, minimizing possible initial differences between the strategies.

Considering the advent of minimally invasive Dentistry, "child friendly" treatments have been often advocated. Therapies that do not cause any (or even) stress to patients, preserve pulp vitality, and guarantee the teeth remain symptomless until it exfoliates naturally tend to be preferred in this context (18,122). It is important to consider patient-centered outcome (especially those reported by the own patients or any proxy) once it is an assessment of the patient's own health status, instead of to be used by an external examiner. Although physical, physiological and biomechanical information can be estimated through medical evaluation, there are some data that can only be obtained from the patient's report, such as symptoms, feelings and the impact of the disease (123). That is our motivation for considering in these analyses both the treatment success (no caries progression) and patient-reported acceptability, then the cost-effectiveness analyses were performed in order to sight the economic benefit of these approaches under these two manners of interpreting the treatment implementation.

Interestingly, we observed some important differences when the patient-centered outcome was set as the health effect in the economic evaluation. Introducing such type of outcome reduced the uncertainties related to adopting the

proposed alternative for controlling moderate caries lesions. The amount of tissue removed is actually the differential between the two techniques evaluated in the study. What is more, the no need of using high-speed motors are an important aspect that may cause discomfort in children. A Facial Image Scale (112) was used in this study to assess the discomfort and try to detect possible different children's perception after treatment. Although no statistically significant differences have been observed for this outcome, children tended to report more "discontent" or "uncomfortable" scores in the scale, increasing approximately twice the probability of being considered a more effective alternative under a patient-centred perspective. Certainly, at this point, we have to consider the absence of differences in the sample may be caused by the controlled setting we have in a clinical trial (120), in which dentists are specialists and tried to be friendly, establishing an effective communication and a trusting relationship among child, caregivers and dentist. This is another motivation to trust in probabilities observed in the economic evaluation aiming to simulate the real-life and increasing the power of generalization of an evaluation like that.

Evidently, we have to consider as a limitation of our study, as a trial-based economic evaluation using piggyback approach, we do not have a sample size calculation specifically for this purpose. That is one of the reasons we use simulations to estimate probabilities we could observed in the population, since our paper focused on how to use and allocated the resources in public health.

All empirical comparisons carry some amount of uncertainty. Usually, in clinical studies, this uncertainty is measures such as confidence intervals, power, and p values (116). However, features of economic data and cost-effectiveness studies require some methods for measure and express uncertainty (116). These uncertainties could be visualized in the cost-effectiveness plan in this economic evaluation. If, we have a greater number of uncertain parameters in a study, complex sensitivity analysis is necessary to conduct and report data. The use of Monte Carlo simulation intends to make an extrapolation from the sample to a real situation, creating innumerous sample conceptually like that one studies and, thereby assessing the true impact of the joint uncertainty in each parameter on a model's overall findings (124-125). These techniques help to establish the confidence for a model conclusion by reporting the proportion of iterations that favor one or another strategy (116). Based only in the average effects and costs, results of statistical tests

sealing could be totally discarded for all patients, preventing a real benefit for a considerable part of the population. On the opposite, the uncertainties analyses permit to find out some children could be benefited from the implementation of the strategy. These children would correspond to those points located in the optimal (or quasi-optimal) quadrants (NE and SE quadrants) in the cost-effectiveness plane.

Based on findings from epidemiological surveys in Brazilian children with primary dentition, we could expect approximately 0.03% of surfaces are moderate caries lesions (126) and from these 62% are located on occlusal surfaces (6). Considering, as in this study, a mean age of 4 years-old and a mean of 2 lesions per child, we could estimate 16% of children could be indicated for sealing moderate caries lesions. Considering the distribution of the Brazil population according to groups of age, we would have a universe of 14.969.375 3-to-9-year-old children 2.395.100 children eligible to receive such treatment. If we considered only average of results (statistically assessed), all these children could not receive the treatment, since the evidence could not be strong enough to change professionals' conviction (apparent non-additional benefits).

Even knowing many professionals could not change their own practices based on findings of economic evaluations (127), decision-makers may have varying preferences for outcomes in different quadrants of cost-effectiveness plane (128). Bringing this idea to our findings, considering the probability of being cost-effective under a patient-centred point-of-view (50%), considering the Brazilian scenario described above, 1.197.550 children would benefit from the treatment and other 1.197.550 would not benefit. Besides, if the professional-centered view is set, 718.530 children could still be benefited by the strategy. Considering these absolute numbers, beside other inferences, is important to recognize the actual economic impact that the implementation of a strategy could bring to certain population. On the other hand, it is imminent that further sensitivity analyses should be conducted to find to which groups the strategy could bring potential benefits in a population (129). Besides, other settings could be explored as a step of valuating and guarantying generalisability of results (130).

To complement this rationale, the net-benefit approach framework is insightful in evaluate cost-effectiveness considering a public health perspective (117), minimizing some problem with ICERs, once the simulations of the same sign but in opposite quadrants of the cost-effectiveness plane (131) and the need of establishing

a decision rule of the ICER, that helps the decision makers to choose the maximum value that they will be willing to pay for an extra unit of health gain (117). In this sense, cost-effectiveness acceptability curve (CEAC), graphically represents the incremental net benefit framework and assuming different ceiling ratios and probabilities for the treatment being a cost-effective option, summarising the impact of uncertainty, then the CEAC helps the decision-maker to understand how to use and allocated the resources, regardless the threshold. It is clear the findings brought for this study are independent from a ceiling-ratio. This is an important point to be highlighted since there is no available value of willingness-to-pay for neither for not having discomfort reported on child dental care sessions nor for not having caries progression.

Finally, it is also important to measure the preference of patient between the two treatments alternative, to show the intervention options, and ask, what do they prefer. In our case, the restoration treatment, a more invasive procedure, that required less reintervention sessions, or sealant treatment, less invasive, however demanded greater number of sessions after 2-year follow-up. We can hear from those would be really benefited which aspects would be relevant and more important for them. Researchers would be considering children and young people as able to be active participants on their own health (132).

Our findings highlighted that based only in the average effects and cost, sealing moderate caries lesions with HVGIC could be totally discarded for all patients, preventing a real benefit for a considerable part of the population. Although, HVGIC sealants may be a cost-effective alternative to restorations for 30-50% of children depending if success or discomfort are used as expected effects. If uncertainties were ignored, sealing option might be erroneously forgone for the entire children population and its possible benefits ignored. Besides, patient-centered health effects may bring additional contributions to the analyses. In this way, it is always important to consider the patient's voice and their engagement, some information and preferences can only be obtained from the patient.

## 5.5 Conclusion

After a 2-year perspective, sealing moderate caries lesion using HVGIC may be used to arrest the caries lesions progress in primary teeth compared to restorations and may be benefit part of the population, being important to consider not only central mean estimates but the uncertainties related to them in decision-making process. Besides, patient-centered view may bring additional resources for decision-making being important to be considered when implementing this alternative in the real life. Who the actual benefited patients could be and how to reach them is still a matter of further research, besides patient's preferences regarding outcome evaluated.

# 6 FINAL CONSIDERATIONS

The advances in the field of Cariology regarding the understanding of caries as a disease have challenged treatment approaches to manage lesions. Therefore, moderate caries lesions should be detected the soonest possible and more attention should give to them, based on their higher risk of progression as shown in our systematic review. Clinicians and researches will be benefited with this information, once is important to know which kind of lesion we must arrest, when making clinical decisions, glimpsing, whenever possible, the option for non-operative treatments.

Randomized clinical trials are useful to prove, when well delineated the efficacy of one intervention compared to another, being an instrument for evidence-based medicine and it is the basis for translate research into clinical practice. Nevertheless, the treatment success is not only guaranteed by the efficacy of procedures. Thus, economic outcomes can be measured alongside clinical trials and provide an additional dimension to the assessment of treatments, but for a treatment to be more accepted by the society, the studies must also focus on patient-centered outcomes.

In this perspective, restoration and sealants using high viscous glass ionomer cement may be used to arrest moderate caries lesion progression in primary teeth after 2-year follow-up, but a higher number of treatment failures may require more interventions in sealants group. Therefore, considering the cost-effectiveness, sealants may be an alternative to restoration, but it is important to consider the uncertainties and that different groups may be differently benefitted from this strategy compared to others. As soon, this thesis has brought and discussed important findings related to management of moderate caries lesions in primary teeth and have the opportunity to give to the pediatric dentists' evidences that will help them in the decision-making process, and it will guide researchers in further studies.

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APPENDIX A – PRISMA - NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

| Section/Topic | Item # | Checklist Item | Reported on Page # |
|---|---|---|---|
| **Title** | | | |
| Title | 1 | Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).* | 33 |
| | | | |
| **Abstract** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable:<br>**Background:** main objectives<br>**Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.*<br>**Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.*<br>**Discussion/Conclusions:** limitations; conclusions and implications of findings.<br>**Other:** primary source of funding; systematic review registration number with registry name. | - |
| | | | |
| **Introduction** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.* | 34 |
| Objectives | 4 | Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 33-34 |
| | | | |
| **Methods** | | | |
| Protocol and registration | 5 | Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number. | 34 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).* | 35 |

| | | | |
|---|---|---|---|
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 35 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 35 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 35 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 36 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 36 |
| **Geometry of the network** | **S1** | Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers. | 38 |
| Risk of bias within individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 37 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.* | 39 |
| Planned methods of analysis | 14 | Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to:<br>• *Handling of multi-arm trials;*<br>• *Selection of variance structure;*<br>• *Selection of prior distributions in Bayesian analyses; and*<br>• *Assessment of model fit.* | 40 |
| **Assessment of Inconsistency** | **S2** | Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found. | 40-41 |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 47 |
| Additional analyses | 16 | Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following:<br>• Sensitivity or subgroup analyses;<br>• Meta-regression analyses; | 41 |

| | | | |
|---|---|---|---|
| | | • *Alternative formulations of the treatment network; and*<br>• *Use of alternative prior distributions for Bayesian analyses (if applicable).* | |
| | | | |
| **Results†** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 41 |
| **Presentation of network structure** | **S3** | Provide a network graph of the included studies to enable visualization of the geometry of the treatment network. | 52 |
| **Summary of network geometry** | **S4** | Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure. | 52 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 43-45 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment. | 47-49 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.* | 51 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented. | 53-56 |
| **Exploration for inconsistency** | **S5** | Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network. | 53-56 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies for the evidence base being studied. | 51 |
| Results of additional analyses | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth). | 55 |

| | | | |
|---|---|---|---|
| **Discussion** | | | |
| Summary of evidence | 24 | Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers). | 56 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).* | 57-60 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 61 |
| | | | |
| **Funding** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network. | - |

APPENDIX B – Consort Statement - Checklist for Non-inferiority and Equivalence Trials

| ***PAPER SECTION*** **And topic** | **Item** | **Descriptor** | **Reported on Page #** |
|---|---|---|---|
| *Title & Abstract* | 1 | How participants were allocated to interventions (e.g., "random allocation", "randomized", or "randomly assigned"), specifying *that the trial is a non-inferiority or equivalence trial.* | 63 |
| *Introduction* Background | 2 | Scientific background and explanation of rationale, *including the rationale for using a non-inferiority or equivalence design.* | 63 |
| *Methods* Participants | 3 | Eligibility criteria for participants *(detailing whether participants in the non-inferiority or equivalence trial are similar to those in any trial(s) that established efficacy of the reference treatment)* and the settings and locations where the data were collected. | 64-65 |
| Interventions | 4 | Precise details of the interventions intended for each group *detailing whether the reference treatment in the non-inferiority or equivalence trial is identical (or very similar) to that in any trial(s) that established efficacy, and how and when they were actually administered.* | 68 |
| Objectives | 5 | Specific objectives and hypotheses *including the hypothesis concerning non-inferiority or equivalence*. | 65 |
| Outcomes | 6 | Clearly defined primary and secondary outcome measures *detailing whether the outcomes in the non-inferiority or equivalence trial are identical (or very similar) to those in any trial(s) that established efficacy of the reference treatment* and, when applicable, any methods used to enhance the quality of measurements (*e.g.*, multiple observations, training of assessors). | 69 |
| Sample size | 7 | How sample size was determined *detailing whether it was calculated using a non-inferiority or equivalence criterion and specifying the margin of equivalence with the rationale for its choice*. When applicable, explanation of any interim analyses and stopping rules (*and whether related to a non-inferiority or equivalence hypothesis*). | 66 |
| Randomization -- Sequence generation | 8 | Method used to generate the random allocation sequence, including details of any restrictions (*e.g.*, blocking, stratification) | 67 |
| Randomization -- Allocation concealment | 9 | Method used to implement the random allocation sequence (*e.g.*, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned. | 67 |
| Randomization -- Implementation | 10 | Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups. | 67 |
| Blinding (masking) | 11 | Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated. | 68 |
| Statistical methods | 12 | Statistical methods used to compare groups for primary outcome(s), *specifying whether a one or two-sided confidence interval approach was used*. Methods for additional analyses, such as subgroup analyses and adjusted analyses. | 71-72 |

| | | | |
|---|---|---|---|
| *Results*<br>Participant flow | 13 | Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons. | 73 |
| Recruitment | 14 | Dates defining the periods of recruitment and follow-up. | 74 |
| Baseline data | 15 | Baseline demographic and clinical characteristics of each group. | 75 |
| Numbers analyzed | 16 | Number of participants (denominator) in each group included in each analysis and whether the analysis was *"intention-to-treat" and/or alternative analyses were conducted*. State the results in absolute numbers when feasible (*e.g.*, 10/20, not 50%). | 76 |
| Outcomes and estimation | 17 | For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (*e.g.*, 95% confidence interval). *For the outcome(s) for which non-inferiority or equivalence is hypothesized, a figure showing confidence intervals and margins of equivalence may be useful*. | 79-84 |
| Ancillary analyses | 18 | Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory. | 79-84 |
| Adverse events | 19 | All important adverse events or side effects in each intervention group. | - |
| *Discussion*<br>Interpretation | 20 | Interpretation of the results, taking into account the *non-inferiority or equivalence hypothesis and any other* study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes. | 84-87 |
| Generalizability | 21 | Generalizability (external validity) of the trial findings. | 84-87 |
| Overall evidence | 22 | General interpretation of the results in the context of current evidence. | 88 |

APPENDIX C – Informed consent

**VIA DO RESPONSÁVEL**

**TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO**

Por esse documento, o Sr(a) está sendo *convidado* para que seu (sua) filho (a) participe voluntariamente da pesquisa intitulada "**Custo-efetividade, aplicabilidade e impacto na qualidade de vida da detecção e avaliação de lesões de cárie iniciais em dentes decíduos: estudo controlado randomizado"** coordenada pela Profa. Dra. Mariana Minatel Braga e realizada pela Faculdade de Odontologia da Universidade de São Paulo em parceria com a Prefeitura Municipal de Barueri, SP. Este documento também dará maiores informações sobre os procedimentos a serem realizados, que serão detalhados a seguir. Sua participação *não é obrigatória* e não haverá prejuízo algum, caso se recuse a participar.

Nesta pesquisa seu filho receberá todo o tratamento odontológico necessário inicialmente. Entretanto, o objetivo da pesquisa é avaliar a influência de formas diferentes de diagnóstico das lesões de cárie na escolha dos tratamentos para as lesões de cárie. Por isso, para algumas crianças o exame será feito considerando as lesões de cárie que estiverem mais iniciais (sem cavidade) e para outras não. Também, para algumas crianças serão tratadas todas as lesões de cárie que forem encontradas, paralisadas ou não, mas para outras, serão tratadas apenas as lesões de cárie que tiverem chance de aumentar. Apenas o dentista que fará o diagnóstico saberá o grupo em que a criança está. Nem os responsáveis, nem a criança, nem o dentista que tratará a criança saberão se as lesões iniciais foram ou não identificadas. As lesões avançadas (com cavidade), que são as que oferecem maior risco de causar dor e aumentarem, serão sempre tratadas. Todas as crianças deverão usar pasta de dente com flúor de 1000 ppm ou 1500 ppm, que receberão durante o estudo.

Algumas pesquisas anteriores já mostraram que as lesões de cárie iniciais (manchas) podem, muitas vezes, paralisar sozinhas apenas com o uso de da pasta de dente com flúor. Além disso, elas demoram mais para progredir e caso isso ocorra com seu filho, que estará em acompanhamento no estudo, isso será prontamente identificado e tratado. Portanto, a criança não estará sendo prejudicada por participar do estudo. Se qualquer coisa diferente for notada ao longo do estudo, o (a) Sr. (a) podem e devem procurar os membros da equipe para esclarecimento e/ou atendimento odontológico de seu filho (a), se necessário for. Considerando que há diversas formas para diagnóstico de cárie e que eles avaliam as lesões em diferentes estágios, é muito importante que se saiba a partir de qual estágio se deve diagnosticar e tratar as lesões.

Todas as crianças, independente do grupo, realizarão uma limpeza profissional dos dentes e serão examinadas com um espelho para avaliação das lesões de cárie. Em seguida, elas receberão o tratamento odontológico necessário. Para participarem do estudo as crianças deverão aceitar participar do estudo. Se chorarem ou não aceitarem mesmo após o dentista conversar e explicar sobre o atendimento, elas não serão incluídas na pesquisa.

As crianças serão submetidas a uma sessão de exame inicial e as sessões necessárias para o tratamento, dependendo de cada caso; as consultas serão agendadas para não atrapalhar o rendimento escolar. O exame clínico oferece desconforto e risco mínimo para a criança. Os procedimentos de tratamento oferecem os riscos inerentes à sua execução, minimizados por detalhada entrevista inicial, seguimento das normas de biossegurança e alto rigor técnico.

Todos os procedimentos serão realizados em um trailer que possui um consultório odontológico montado em seu interior, que ficará no terreno do Complexo Educacional Carlos Osmarinho Silva. Terminado o tratamento, a criança será reexaminada após 12 e 24 meses. Após 6 e 18 meses, a criança será revista para orientações de higiene. Todos os procedimentos serão realizados por membros da equipe da pesquisa e por alguns profissionais do município de Barueri, SP. Após 24 meses do fim do tratamento, com o término da pesquisa, a criança continuará assistida pelos dentistas da rede pública de Barueri-SP e casos mais complexos, podem ser encaminhados para atendimento na Faculdade de Odontologia da Universidade de São Paulo, na Disciplina de Odontopediatria.

O responsável pelo participante terá escolha em não participar da pesquisa, tendo a possibilidade de retirar seu consentimento posteriormente, caso mude de opinião por qualquer motivo. Não será revelada, sob nenhuma hipótese, a identidade do participante bem como de seu responsável, mesmo na divulgação dos resultados. Os resultados obtidos serão publicados, independentemente de serem favoráveis ou não. Os pesquisadores garantem o caráter confidencial das informações e se colocam à disposição para esclarecer qualquer dúvida a qualquer momento.

Como benefício direto da pesquisa, as crianças participarão de atividades de educação em saúde bucal e prevenção de cárie, além de receber tratamento odontológico necessário. Para os que não participarem da pesquisa, o atendimento odontológico pelo município continuará sendo garantido.

Havendo qualquer problema ou dúvida durante a realização da pesquisa, a professora Mariana Minatel Braga, responsável pela pesquisa, pode ser encontrado pelo telefone 11-992014818 ou no Departamento de Odontopediatria, pelo telefone 11-39017835. A pesquisadora Isabela Floriano Nunes Martins pode também ser encontrada para resolução de dúvidas ou problemas 11-96314-6444 (inclusive ligações a cobrar). Eventuais dúvidas poderão ser esclarecidas pelas pesquisadoras responsáveis, na própria sede da Faculdade de Odontologia da Universidade de São Paulo – FOUSP – sito à Av. Lineu Prestes 2227, 05508-000 São Paulo. Dúvidas sobre a ética da pesquisa entre em contato com o Comitê de Ética em Pesquisa da FOUSP, (Av. Lineu Prestes 2227 | 05508-000 | São Paulo/SP | (11) 30917960 | e-mail cepfo@usp.br).

| | |
|---|---|
| **Profa. Dra. Mariana Minatel Braga** | **Isabela Floriano Nunes Martins** |
| **CRO SP 81102** | **CRO SP 104865** |

**Consentimento pós-informação**

**Eu, _____, de RG _____, certifico que fui esclarecido pelas pesquisadoras sobre todos os itens do estudo aqui descrito e dúvidas que apresentei e concordo com a participação do meu filho/minha filha, o(a) menor _____, por qual sou responsável legal, participe de forma voluntária desta pesquisa. Informo também ter recebido uma cópia desse documento.**

**Declaro que, em caso de necessidade de uso de dados decorrentes dessa pesquisa para outras pesquisas:**

( ) NÃO autorizo a utilização de dados em outra pesquisa.

( ) SIM autorizo a utilização de dados ou em outra pesquisa

**Se a resposta for SIM, para utilizar esses dados em outra pesquisa, declaro que:**

( ) NÃO quero ser consultado da utilização dos dados de meu/minha filho(a) em outra pesquisa, desde que a nova pesquisa seja aprovado pelo Comitê de Ética em Pesquisa,

( ) SIM quero ser consultado da utilização dos dados de meu/minha filho(a) em outra pesquisa

**Barueri, _____ de _____ de 2015**

**Nome do Responsável: _____**

**RG: _____**

**CPF: _____**

_____

**Assinatura do Responsável**

APPENDIX D - Description of Research Setting

This research was developed in a mobile dental unit (Motor Trailer ®), that is located in a public school - EMEF Complexo Educacional Carlos Osmarinho de Lima in the city of Barueri – SP. Barueri is located 26 Kilometers from Sao Paulo city, with 262.275 inhabitants.

All the children were treated in this mobile dental unit since July 2014, purchased with financial resources from Fundação de Amparo á Pesquisa de São Paulo – FAPESP (process - 2012/50716-0), and the Dental materials were obtained with financial resources of Conselho Nacional de Desenvolvimento Científico e Tecnológico – CNPq (process 448013/2014-2), and FAPESP (process 2013/27206-8). The mobile dental unit consist in a dental chair, compressor, x-ray machine and sterilizers.

Figure 2a. Mobile dental unit (Motor Trailer ®), external (a) and internal structure(b).


Source: Author

Prof. Dra. Mariana Minatel Braga are the research coordinator, Fernanda Rosche was an assistant. The staff per day of treatment was composed of two external researchers, dentist as operators or examiners, and undergraduate students. Below is the name of all the team and the status during the study follow-up. (Figure 2b)

*Research coordinator of specific studies:*

- Isabela Floriano Nunes Martins (I.F)
- Luciana Antonio Pion (L.A.P)
- Maria Eduarda Franco Viganó (M.E.F.V)
- Jhandira Daibelis Yampa Vargas (J.D.Y.V)
- Nathalia de Miranda Ladewing (N.M.L)
- Elizabeth de Souza Rocha (E.S.R) (present study)

*Operators:*

- Elizabeth de Souza Rocha (E.S.R) - Dentist, PhD student FOUSP
- Issac Murisi Pedroza Uribe (I.M.P.U) - Dentist, Master student FOUSP
- Isabella Cristina Louzada (I.C.L) - Dentist
- Jhandira Daibelis Yampa Vargas (J.D.Y.V) - Dentist, PhD student FOUSP
- Karina Haibara de Natal (K.H.N) - Dentist, PhD student FOUSP
- Luciana Pion Antonio (L.A.P) - Dentist, Master student FOUSP
- Nathalia de Miranda Ladewing (N.M.L) - Dentist, PhD student FOUSP

*Examiners:*

- Isabela Floriano Nunes Martins (I.F) - Dentist, PhD student FOUSP
- Laysa Yoshioka (L.Y) - Dentist, PhD student FOUSP
- Tamara Keber Tedesco (T.K.T) – Dentist and Prof. Dra.

*Undergraduate students (researches):*

- Gabriela Manco Machado
- Renata Anonangelo Corrêa Gomes

*Undergraduate Student:*

- Aline Ramos Carlucci
- Ana Carolina Correia
- Ana Clara Moronte Dias de Souza
- Ana Victória Saboia Bertoletti
- Aryane Valeck
- Bárbara Aline Bernardino
- Gabriel de Freitas
- Giulia Duarte
- Jennifer Cavalcanti
- Livia Goron Bergamin
- Maria Clara Lembo Teixeira
- Mariana Hercules Loesch
- Mariana Xavier
- Natássia Jurisberg Corre
- Nicole Fontana
- Raissa Andujas Carlos Pereira
- Raquel Stephani Gomes Guttierrez

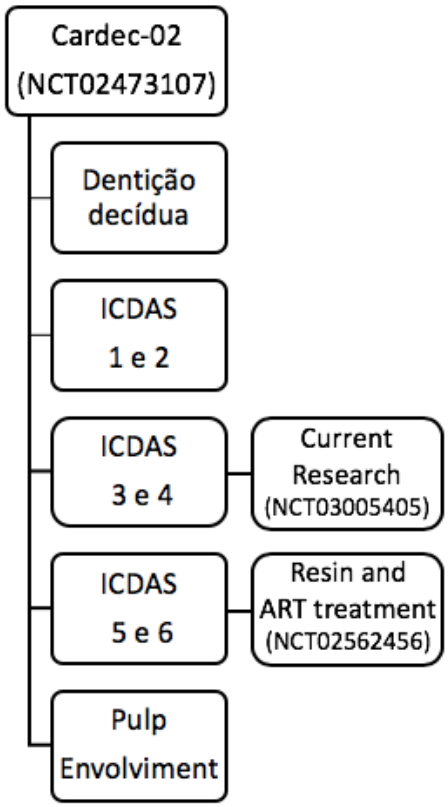
- Renan Yamamoto
- Thalita Barreto Louzada
- Thaís dos Reis

Figure 2b - Participants involved in different phases of the study


Source: Mobil Dental Unit Team

The study “Cost-effectiveness, applicability and impact on quality of life of detection and evaluation of initial caries lesions in primary teeth: a randomized controlled trial (CARDEC - 02)” (NCT02473107), is this research that our study is nested:

Figure 2c – Origin of research participants




Source: Author

APPENDIX E – Checklist of "Consolidated Health Economic Evaluantion Reporting Standards" (CHEERS)

| Section/item | Item No | Recommendation | Reported on page Nº |
|---|---|---|---|
| **Title and Abstract** | | | |
| Title | 1 | Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared. | 89 |
| Abstract | 2 | Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions. | – |
| **Introduction** | | | |
| Background and Objectives | 3 | Provide an explicit statement of the broader context for the study.<br>Present the study question and its relevance for health policy or practice decisions. | 89/90 |
| **Methods** | | | |
| Target population and subgroups<br>Setting and location | 4 | Describe characteristics of the base case population and subgroups analyses, including why they were chosen. | 91 |
| | 5 | State relevant aspects of the system(s) in which the decision(s) need(s) to be made. | 91 |
| | 6 | Describe the perspective of the study and relate this to the costs being evaluated. | 91 |
| | 7 | Describe the interventions or strategies being compared and state why they were chosen. | 92-93 |
| | 8 | State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate. | 96 |
| | 9 | Report the choice of discount rate(s) used for costs and outcomes and say why appropriate. | 94 |
| | 10 | Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed. | 96 |
| | 11a | *Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data. | 91 |

| | | | |
|---|---|---|---|
| Measurement and valuation of preference based outcomes | 11b | *Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data. | 92-95 |
| Estimating resources and costs | 12 | If applicable, describe the population and methods used to elicit preferences for outcomes. | 9 |
| | 13a | *Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost.<br>Describe any adjustments made to approximate to opportunity costs. | 91 |
| | 13b | *Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research | – |
| Currency, price date, and conversion | 14 | Methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. | 95 |
| Choice of model | 15 | Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate. | 95 |
| Assumptions | 16 | Describe and give reasons for the specific type of decision- analytical model used. Providing a figure to show model structure is strongly recommended. | 96 |
| Analytical methods | 17 | Describe all structural or other assumptions underpinning the decision-analytical model. | 96-97 |
| | | Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty. | 96-97 |

| | | | |
|---|---|---|---|
| Study parameters | 18 | Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended. | 100-103 |
| Incremental costs and outcomes | 19 | For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios. | 99 |
| Characterising uncertainty | 20a | *Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective). | 102 |
| | 20b | *Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions. | – |
| Characterising heterogeneity | 21 | If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information. | 103-104 |
| **Discussion** | | | |
| Study findings, limitations, generalizability, and current knowledge | 22 | Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge. | 105-108 |
| **Other** | | | |
| Source of funding | 23 | Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support. | – |
| | 24 | Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors | – |

APPENDIX F – Time and costs sheets used in the treatments

Nº _____ Sessão nº ____

## TEMPO E CUSTO DOS PROCEDIMENTOS

| Data | Procedimento | Tempo (s) |
|---|---|---|
| | | |
| | | |
| | | |

**Dentista / Auxiliar:** _____

**Material**

| | | |
|---|---|---|
| Abridor de boca **(unidade)** | Escova de dente **(unidade)** | Papel para radiografia **(unidade)** |
| Ácido fosfórico **(1cm)** | Escova para macromodelo OHB | Paramonoclorofenol **(gota)** |
| Ácido poliacrílico **(gota)** | Escova para profilaxia **(unidade)** | Pasta de dente **(unidade)** |
| Adesivo dentinário **(porção)** | Espátula de inserção nº1 | Pasta profilática **(1 cm)** |
| Água para autoclave **(300 ml)** | Espátula de madeira **(unidade)** | Pedra pomes **(1 porção)** |
| Agulha curta **(unidade)** | Espátula de manipulação de CIV | Película raio-x adulto **(unidade)** |
| Agulha extra curta **(unidade)** | Espátula Hollemback **(unidade)** | Película raio-x infantil **(unidade)** |
| Alavancas **(jogo)** | Espátula nº7 **(unidade)** | Pinça porta-grampo de Palmer |
| Álcool 70 **(50 ml*)** | Espelho de mão OHB **(unidade)** | Porta agulha **(unidade)** |
| Alicate perfurador de Ainsworth | Evidenciador Replak **(gota)** | Porta matriz **(unidade)** |
| Anestésico **(tubete)** | Filme PVC **(30 cm)** | Posicionador radiográfico **(jogo)** |
| Anestésico tópico **(1 cm)** | Fio de sutura **(unidade)** | Pote Dappen **(unidade)** |
| Arco de Young **(unidade)** | Fio dental **(10 cm)** | Régua endodôntica **(unidade)** |
| Avental descartável **(unidade)** | Fixador **(50 ml)** | Resina composta **(incremento)** |
| Babador **(unidade)** | Fórceps **(unidade)** | Revelador **(50 ml)** |
| Banda matriz 5 mm **(unidade)** | Gaze **(1 compressa)** | Rifocort **(1 cm)** |
| Bandeja **(unidade)** | Guta percha **(1/5 bastão)** | Saco de geladinho **(unidade)** |
| Bisturi **(unidade)** | Iodofórmio **(1 cm)** | Seringa carpule **(unidade)** |
| Bloco de espatulação **(1 folha)** | Ionômero Fuji IX **(porção)** | Seringa descartável **(unidade)** |
| Broca diamantada **(unidade)** | Ionômero Riva **(cápsula)** | Sobreluva **(unidade)** |
| Cabo para bisturi **(unidade)** | Jogo clínico | Soro fisiológico **(50 ml)** |
| Calcador de Ward **(unidade)** | Lençol de borracha **(unidade)** | Sugador **(unidade)** |
| Canudo p/ tríplice **(1/3 unidade)** | Lima endodôntica **(1 jogo)** | Sugador endodôntico **(unidade)** |
| Cariostático **(gota)** | Líquido de Dakin **(50 ml)** | Tesoura reta **(unidade)** |
| Colgadura **(unidade)** | Luva descartável **(1 par)** | Tira de acabamento **(unidade)** |
| Colher de dentina **(unidade)** | Macromodelo para OHB | Tira de lixa de aço **(1/2 unidade)** |
| Cunha de madeira **(unidade)** | Mandril **(unidade)** | Tira de poliéster **(1/2 unidade)** |
| Descolador de Molt **(unidade)** | Máscara descartável **(unidade)** | Touca descartável **(unidade)** |
| Disco de acabamento **(unidade)** | Microbrush **(unidade)** | Vaselina **(1 cm)** |
| Envelope 19 x 37 cm **(unidade)** | Óculos de proteção **(unidade)** | Verniz Duraphat **(1 cm)** |
| Envelope 9 x 26 cm **(unidade)** | Papel carbono **(1/3 folha)** | |

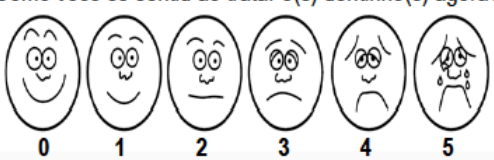
**Custo**

Meio de transporte usado para comparecer à consulta? ( ) A pé ( ) Ônibus ( ) Carro ( ) Moto ( ) Outro

O responsável precisou faltar ao trabalho? ( ) Não ( ) Sim. Vai ser descontado do salário? _____

**DESCONFORTO**

"Como você se sentiu ao tratar o(s) dentinho(s) agora?"




**Dentista**, como a criança reagiu nesta sessão?

( ) Criou muita dificuldade
( ) Criou alguma dificuldade
( ) Indiferente
( ) Cooperou razoavelmente
( ) Cooperou bem

ANNEXE A – Research Ethic's Committee Approval

FACULDADE DE ODONTOLOGIA DA UNIVERSIDADE DE SÃO

Plataforma Brasil

## PARECER CONSUBSTANCIADO DO CEP

**DADOS DO PROJETO DE PESQUISA**

**Título da Pesquisa:** CUSTO-EFETIVIDADE, APLICABILIDADE E IMPACTO NA QUALIDADE DE VIDA DA DETECÇÃO E AVALIAÇÃO DE LESÕES DE CÁRIE INICIAIS EM DENTES DECÍDUOS: ESTUDO CONTROLADO RANDOMIZADO

**Pesquisador:** Mariana Minatel Braga

**Área Temática:**

**Versão:**

**CAAE:** 31159114.2.0000.0075

**Instituição Proponente:** Universidade de Sao Paulo

**Patrocinador Principal:** Financiamento Próprio
FUNDACAO DE AMPARO A PESQUISA DO ESTADO DE SAO PAULO

**DADOS DO PARECER**

**Número do Parecer:** 659.006

**Data da Relatoria:** 23/05/2014

**Apresentação do Projeto:**

"O estudo tem como objetivo avaliar o impacto de se detectar lesões iniciais e/ou avaliar a atividade das lesões de cárie em dentes decíduos em termos de efetividade, custo-efetividade, aplicabilidade (aceitabilidade e satisfação) e qualidade de vida. Para isso, 372 crianças de 2 a 5 anos e com dentição decídua completa serão examinadas e tratadas em uma unidade odontológica móvel, que ficará temporariamente sediada em escola vinculada à Prefeitura Municipal de Barueri (SP). O diagnóstico de cárie das crianças será realizado utilizando o International Caries Detection and Assessment System (ICDAS) e, quando necessário, critério adjunto para avaliação da atividade de cárie. Inicialmente, as crianças serão randomizadas quanto ao limiar do diagnóstico, em Grupo A (serão detectadas e tratadas apenas as lesões avançadas) e Grupo B (lesões iniciais e avançadas). Num segundo momento, apenas as crianças já alocadas no Grupo B serão novamente randomizadas quanto a avaliação da atividade de cárie, em Grupo B.1 (sem) e Grupo B.2 (com). Uma vez feito o diagnóstico, o plano de tratamento de cada criança será elaborado e realizado
conforme a estratégia à qual a criança foi randomizada. Dados relativos à custo efetividade dos procedimentos, aceitabilidade/satisfação das crianças e qualidade de vida serão coletados após o diagnóstico, ao fim do tratamento e 12 e 24 meses após o exame inicial. Para comparação entre os

**Endereço:** Av Prof Lineu Prestes 2227
**Bairro:** Cidade Universitária **CEP:** 05.508-900
**UF:** SP **Município:** SAO PAULO
**Telefone:** (11)3091-7960 **Fax:** (11)3091-7814 **E-mail:** cepfo@usp.br

grupos, análises de regressão de Poisson serão realizadas. O desfecho primário será o número de superfícies com necessidade de tratamento operatório durante os períodos de acompanhamento e os desfechos secundários serão a custo-efetividade de cada estratégia, a aceitabilidade/satisfação da criança e o impacto na qualidade de vida."

**Objetivo da Pesquisa:**

"Avaliar o impacto de se detectar lesões iniciais e/ou avaliar a atividade das lesões de cárie em dentes decíduos em termos de efetividade, custo-efetividade, aplicabilidade (aceitabilidade e satisfação) e qualidade de vida."

**Avaliação dos Riscos e Benefícios:**

Riscos: " Os riscos em relação à variação do limiar de detecção das lesões de cárie, que ocorrerá dependendo do grupo em que a criança for alocada, não será um risco por parte das crianças, já que todas estarão expostas ao uso de dentifrício fluoretado de no mínimo 1000 ppm, o que tem se mostrado efetivo para controle de lesões de cárie iniciais nessa faixa etária, além de se ter evidências de que a maioria dessas lesões se auto-resolvem, como mencionado na seção de Introdução. Além disso, as crianças estarão sob acompanhamento e em caso de qualquer intercorrência em virtude do estudo, os pesquisadores, bem como os dentistas do município de Barueri estarão trabalhando em parceria para assisti -los ao longo da realização do estudo. É importante ressaltar que as únicas lesões que não seriam tratadas em alguns grupos seriam as iniciais, como já mencionado, passíveis de controle com o próprio dentifrício fluoretado e que se evoluírem, serão prontamente identificadas e tratadas pelos pesquisadores, o que poderia ocorrer mesmo se a pesquisa não estivesse sendo realizada".

Benefícios: "Pode ser citado como principal benefício a realização do tratamento odontológico de cada sujeito, em conformidade com protocolos que seguem o mais alto nível de evidência disponível, com qualidade técnica e respeitando as normas de biossegurança. Além disso, o sujeito e seus pais/responsáveis receberão orientações de higiene bucal, essenciais à manutenção do tratamento realizado. A criança receberá, ainda, acompanhamento de sua saúde bucal durante o período de realização da pesquisa e receberá atendimento necessário durante esse período. Embora as reavaliações sejam realizadas após 12 e 24 meses, as crianças serão revistas semestralmente para garantir a adesão e se captar possíveis intercorrências advindas da pesquisa."

**Comentários e Considerações sobre a Pesquisa:**

Serão tratadas e acompanhadas 372 crianças de 2 a 5 anos de idades, divididas em grupos específicos, em unidade odontológica móvel, no município de Barueri e acompanhadas por 24

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meses. Riscos e benefícios bem explicados.

**Considerações sobre os Termos de apresentação obrigatória:**

Apresenta:

- Folha de rosto: adequada;
- Carta de autorização e parceria com a prefeitura de Barueri: adequada;
- Projeto de pesquisa anexado: adequado;
- TCLE: adequado.

**Recomendações:**

Tendo em vista a legislação vigente, devem ser encaminhados ao CEP-FOUSP relatórios parciais semestrais referentes ao andamento da pesquisa e relatório final ao término do trabalho. Qualquer modificação do projeto original deve ser apresentada a este CEP, de forma objetiva e com justificativas, para nova apreciação.

**Conclusões ou Pendências e Lista de Inadequações:**

Aprovado.

**Situação do Parecer:**

Aprovado

**Necessita Apreciação da CONEP:**

Não

**Considerações Finais a critério do CEP:**

SAO PAULO, 23 de Maio de 2014

**Assinado por:**
**Maria Gabriela Haye Biazevic**
**(Coordenador)**

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