Carla Massignan

SINAIS E SINTOMAS DA ERUPÇÃO DOS DENTES DECÍDUOS: UMA REVISÃO SISTEMÁTICA E META-ANÁLISE

Dissertação submetida ao Programa de Pós Graduação da Universidade Federal de Santa Catarina para a obtenção do Grau de Mestre em Odontologia
Orientadora: Profa. Dra. Michele Bolan
Coorientadora: Profa. Dra. Mariane Cardoso

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Esta Dissertação foi julgada adequada para obtenção do Título de "Mestre", aprovada em sua forma final pelo Programa de Pós Graduação em Odontologia

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_____
Profa. Dra. Izabel Cristina Santos Almeida
Coordenadora do Curso

Banca Examinadora:

_____
Profa. Dra. Michele Bolan
Orientadora
Universidade Federal de Santa Catarina

_____
Profa. Dra. Lucianne Cople Maia de Faria
Universidade Federal do Rio de Janeiro (Videoconferência)

_____
Profa. Dra. Maria Marlene de Souza Pires
Universidade Federal de Santa Catarina

_____
Prof. Dr. João Luiz Dornelles Bastos
Universidade Federal de Santa Catarina

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RESUMO

O objetivo da pesquisa foi estimar a prevalência de sinais e sintomas locais e sistêmicos durante a erupção dos dentes decíduos. Realizou-se busca eletrônica nas bases de dados: LILACS, PubMed, ProQuest, Scopus e Web of Science e busca parcial da literatura cinzenta através do Google Scholar. As listas de referências dos estudos incluídos foram analisadas buscando artigos que inadvertidamente tenham sido excluídos nas buscas eletrônicas. Baseado na estratégia PECOS, foram incluídos estudos observacionais que verificaram a ocorrência de sinais e sintomas durante a erupção dos dentes decíduos através de relato de sintomas pelos pais e medida de temperatura corporal, além da análise clínica do dente em erupção, em crianças de 0-36 meses. A extração dos dados dos artigos selecionados foi realizada por dois revisores de forma independente. As informações foram conferidas para confirmar a precisão. O processo de seleção ocorreu em duas fases. Do total de 1.179 documentos identificados, 16 estudos foram incluídos. A análise qualitativa foi realizada através da avaliação do risco de viés dos estudos incluídos, enquanto a síntese quantitativa foi realizada através de meta-análise. A heterogeneidade encontrada entre os estudos nas meta-análises variou de 93,01 a 99,75% ($p<0,0001$), foi usado modelo aleatório. A prevalência geral de sinais e sintomas durante a erupção dos dentes decíduos em crianças entre 0-36 meses foi de 70,5% (amostra total = 3506, 95% IC 54,19 a 84,62). Inflamação gengival (86,81%), irritabilidade (68,19%) e aumento de salivação (55,72%) foram os mais frequentes. Alguns estudos apresentaram: ausência de relato sobre os fatores de confundimento, uso de medidas subjetivas e exames em intervalos longos. Concluiu-se que a prevalência de sinais e sintomas durante a erupção dos dentes decíduos foi alta. Não houve a ocorrência de febre durante a erupção dos dentes decíduos, mas um leve aumento da temperatura corporal.

Palavras-chave: Erupção Dentária. Sinais e Sintomas. Dente Decíduo. Revisão.

ABSTRACT

Symptoms associated with the primary tooth eruption have been extensively studied but it is still controversial. The objective of the study was to to assess the occurrence of local and systemic signs and symptoms during primary tooth eruption through a systematic review. LILACS, PubMed, ProQuest, Scopus and Web of Science were searched. A partial grey literature search was taken using Google Scholar and the reference lists of the included studies were scanned. Observational studies assessing the association of eruption of primary teeth with local and systemic signs and symptoms in children aged 0-36 months were included. Two authors independently collected the information from the selected articles. Information was crosschecked and confirmed for its accuracy. A total of 1,179 papers were identified and after a 2-phase selection 16 studies were included. The qualitative analysis was performed by assessing the risk of bias of the included studies, while quantitative synthesis was performed by meta-analysis. The heterogeneity found among studies in the meta-analysis ranged from the 93.01 to 99.75% ($p < 0.0001$), a random model was used. Overall prevalence of signs and symptoms occurring during primary tooth eruption in children between 0-36 months was 70.5% (total sample=3506 95% CI 54,19 a 84,62). Gingival inflammation (86.81%), irritability (68.19%) and drooling (55.72%) were the most frequent ones. As limitations, different general symptoms were considered among studies. Some studies presented: lack of confounding factors, use of subjective measures and examinations in long intervals. It was concluded that the prevalence of signs and symptoms during the eruption of primary teeth was high. There was no occurrence of fever during the eruption of primary teeth, but a slight increase of body temperature.

Keywords: Teething. Tooth eruption. Signs. Symptoms. Primary tooth. Review.

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LISTA DE ABREVIATURAS E SIGLAS

COBE- Centro Brasileiro de Pesquisas Baseadas em Evidência
GATA H.T.H.- GATA Haydarpasa Teaching Hospital
CG- Control Group
CI- Confidence interval
CS- Cross sectional
High- High risk of bias
HSV- Herpes simplex virus
I- Infected
Low- Low risk of bias
MDT- Mean daily temperature
Moderate- Moderate risk of bias
MTED- Mean temperature in eruption days
MTNED- Mean temperature in non-eruption days
MTPE- Mean temperature pre-eruption
MTP- Mean temperature post-eruption
NA- Not applicable
NC- Not clear
NI- Not informed
N- No
NoI- Non-infected
PF- Prognostic factor
PS- Prospective study
QUIPS- Quality in Prognosis Studies Tool
RS- Retrospective study
SD- Standard deviation
SG- Study group
USP- Universidade de São Paulo
UFSC- Universidade Federal de Santa Catarina
Y- Yes

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1 CONTEXTUALIZAÇÃO

O primeiro ano representa um período de grandes transformações na vida das crianças e de suas famílias. Mudanças no comportamento das crianças são esperadas e fazem parte do seu crescimento e amadurecimento. É nessa fase que começa a erupção dos dentes decíduos. A erupção do primeiro dente geralmente acontece por volta do sexto mês e os últimos são esperados até os 30 meses.

A erupção dental é um processo fisiológico normal, onde o dente se movimenta da sua posição de formação dentro do osso alveolar até o rompimento gengival na cavidade bucal (MARKS; SCHROEDER, 1996; CRADDOCK; YOUNGSON, 2004). Pode ser dividida em três fases: 1) Crescimento folicular - a cripta do dente em desenvolvimento expande simetricamente nos sentidos vertical e mésio-distal. Esta aparente imobilidade persiste até que toda a coroa seja calcificada; (STEEDLE; PROFFIT, 1985); 2) Movimento pré-eruptivo - movimento intraósseo com a formação das raízes na medida em que o dente começa um período de erupção rápida na direção oclusal através dos processos de reabsorção dos tecidos sobrepostos, criando uma caminho eruptivo conforme se aproxima do rompimento gengival; (CAHILL; MARKS, 1980); e, finalmente, 3) Movimento pós-eruptivo - onde o dente se move da posição de rompimento inicial até o plano oclusal (PROFFIT; FRAZIER-BOWERS, 2009).

Embora faça parte do desenvolvimento infantil normal, a relação entre a erupção dos dentes decíduos e a saúde geral das crianças ainda é controversa (HONIG, 1975; GIBBONS; HEBDON, 1991, DALLY, 1996, MACKNIN et al., 2000, MCINTYRE; MCINTYRE, 2002, ROMERO-MAROTO; SÁEZ-GÓMEZ, 2009, OWAIS; ZAWAIDEH, BATAINEH, 2010, ZAKIRULLA; ALLAHBAKSH, 2011).

Há a crença, entre os pais, de que a erupção dos dentes decíduos está associada com alterações comportamentais e sistêmicas (CASTIGLIA, 1992, WAKE; HESKETH; ALLEN, 1999, BAYKAN, et al., 2004, SARRELL et al., 2005, FELDENS, 2010; KAKATKAR et al., 2012). Nesse período de dois anos que corresponde à fase de erupção dental, há grandes alterações nos hábitos das crianças. Os padrões de sono e de alimentação sofrem transformações. Algumas crianças manifestam ansiedade de separação dos pais. Há, ainda, os quadros de enfermidades. Muitas vezes essas alterações no comportamento causam angústia e confusão nos pais, que podem acabar relacionando tais eventos, que levam à noites de choro e sem dormir, ao processo de erupção dental. Assim, o momento da erupção dental pode ser

preocupante para os pais, principalmente quando se trata do primeiro filho. Muitos pais não sabem como identificar os sinais da erupção dental no seu filho (PLUTZER; SPENCER; KEIRSE, 2011, KOZUCH; PEACOCK; D'AURIA, 2015).

Em uma tentativa de aliviar os sintomas da criança, os pais podem recorrer a medicamentos orais ou tópicos sem orientação profissional (SEWARD, 1969). Em alguns países africanos, as crenças culturais podem levar a práticas como "gum lancing", ou corte gengival, que é referido como o ato de cortar a gengiva que recobre o dente em erupção, realizado geralmente por pais ou avós da criança, como um remédio para a "diarreia da dentição", com graves consequências que vão desde desidratação grave até sepse generalizada (OLABU et al., 2013).

Muitos profissionais da saúde também acreditam na associação entre sinais e sintomas e a erupção dos dentes decíduos. Pesquisas com pediatras e outros profissionais responsáveis pela saúde das crianças revelam que as crenças sobre os sintomas são comuns e variam pouco entre o grupo profissional estudado (HONIG, 1975, WAKE; HESKETH, 2002, FARACO JUNIOR et al., 2008). Falta de apetite, diarreia e febre, frequentemente associados com a erupção dental podem estar relacionados à outras alterações sistêmicas e até mesmo à doenças mais graves (SWANN, 1979) . É importante que os profissionais da saúde sejam capazes de informar adequadamente aos pais o que pode ser esperado do processo de erupção dental a fim de evitar que doenças mais graves sejam diagnosticadas tardiamente. Alguns estudos tendem a considerar que a erupção dental causa poucos sintomas, se houver, e que nenhuma doença deveria ser atribuída à erupção dental (JABER; COHEN; MOR, 1992, WAKE; HESKETH; LUCAS, 2000).

Investigações relacionadas às alterações gengivais locais nessa fase através da biópsia a partir da membrana mucosa que cobre o dente antes do rompimento e em torno do dente que já apresenta perfuração gengival, mostrou a presença de degenerações na mucosa e células inflamatórias em ambos os casos. Não houve diferença histológica entre crianças com ou sem alterações sistémicas (SOLIMAN, SOLIMAN, 1978). Exames da cor da mucosa das mesmas regiões não revelaram qualquer correlação evidente com alterações patológicas (TASANEN, 1969). Da mesma forma, foi observado um aumento dos níveis de citocinas inflamatórias no fluido crevicular gengival dos dentes em processo de erupção (SHAPIRA, et al., 2003).

Tigue e Roe (2007) conduziram uma revisão da literatura para identificar a existência de quaisquer sinais e sintomas patognomônicos

da erupção dental. Embora a análise tenha mostrado uma variedade de sintomas que podem ocorrer simultaneamente, não houve evidências que sugerissem a existência de quaisquer sinais ou sintomas que pudessem sugerir a erupção dental.

A Academia Americana de Odontopediatria em suas Diretrizes sobre Saúde Bucal Infantil (DENTISTRY AAOP, 2014) apresenta orientações de que a erupção dos dentes decíduos leva ao desconforto local, alteração de humor com irritação e aumento da salivação. O tratamento sugerido inclui analgésicos orais e mordedores.

O uso de anestésicos géis para aplicação tópica nas gengivas durante a erupção dos dentes decíduos não é recomendado por representar risco à saúde (SOOD; SOOD, 2010). Os agentes anestésicos locais comumente encontrados nessas preparações representam risco de desenvolvimento de reações de hipersensibilidade e efeitos adversos graves (TSANG, 2011). Em 2011, a Agência Governamental Americana do Departamento de Saúde, FDA (US-Food and Drug Administration) advertiu que o uso tópico de géis de benzocaína para a erupção dos dentes decíduos tem o potencial de causar methaemaglobinaemia. Em 2014, a FDA recomendou o não uso de solução oral de lidocaína por crianças pequenas devido ao risco de deglutição acidental. Essa prática pode resultar em convulsões, lesão cerebral grave e problemas cardíacos (FDA, 2014).

Assim, ao conhecer as implicações que a erupção dental tem nesse período de vida da criança, esse trabalho tem o propósito de contribuir para esclarecer quanto a compreensão e conduta dos pais em relação às possíveis alterações de comportamento que a criança pode manifestar durante a erupção dos dentes decíduos.

Dessa forma, a proposta desse estudo foi realizar uma revisão sistemática para responder a seguinte pergunta focada: “Em crianças entre zero e 36 meses de idade, há a ocorrência de sinais e sintomas locais e sistêmicos durante a erupção dos dentes decíduos?”

Devido à importância das publicações para o aprimoramento da pesquisa e para o Programa de Pós Graduação em Odontologia, esta dissertação foi desenvolvida e está apresentada em forma de artigo a ser submetido à revista Pediatrics.

2 OBJETIVO

2.1 OBJETIVO GERAL

Pretende-se, através de uma revisão sistemática da literatura, verificar a prevalência de sinais e sintomas locais e sistêmicos durante a erupção dos dentes decíduos.

3 ARTIGO

Artigo a ser submetido à revista:
Pediatrics

Signs and symptoms of primary tooth eruption: a meta-analysis

Carla Massignan DDS[a], Mariane Cardoso DDS, MsC, PhD[a], André Luís Porporatti DDS[b], Secil Aydinoz, MD[c], Graziela De Luca Canto, DDS, MsC, PhD[a,d,e], Luis Andre Mezzomo DDS, MsC, PhD[a,e] Michele Bolan DDS, MsC, PhD[a]

Affiliations:
[a]Department of Dentistry, Federal University of Santa Catarina, Florianopolis, Santa Catarina, Brazil;
[b]Bauru School of Dentistry, Bauru, São Paulo, Brazil;
[c]Gulhane Military Medical Academy, Istanbul, Turkey;
[d]Department of Dentistry, University of Alberta, Edmonton, Canada
[e]Brazilian Centre for Evidence-based Research, Federal University of Santa Catarina, Florianopolis, Santa Catarina, Brazil

Address correspondence to: Michele Bolan, Departamento de Odontologia, Universidade Federal de Santa Catarina, UFSC, Campus Universitário, CCS-ODT-Trindade Florianópolis, Santa Catarina, Brasil 88040-900 [michelebolan@hotmail.com], +55483721-9920

Short title: Signs and symptoms of primary tooth eruption

Keywords: Teething, tooth eruption, signs, symptoms, primary tooth, review

ABSTRACT

Context: Symptoms associated with the primary tooth eruption have been extensively studied but it is still controversial.

Objective: To assess the occurrence of local and systemic signs and symptoms during primary tooth eruption.

Data Sources: LILACS, PubMed, ProQuest, Scopus and Web of Science were searched. A partial grey literature search was taken using Google Scholar and the reference lists of the included studies were scanned.

Study Selection: Observational studies assessing the association of eruption of primary teeth with local and systemic signs and symptoms in children aged 0-36 months were included.

Data Extraction: Two authors independently collected the information from the selected articles. Information was crosschecked and confirmed for its accuracy.

Results: A total of 1,179 papers were identified and after a 2-phase selection process 16 studies were included. The registration of symptoms revealed significant heterogeneity. Ten studies had data enough to conduct meta-analysis. Overall prevalence of signs and symptoms occurring during primary tooth eruption in children between 0-36 months was 70.5% (total sample=3506). Gingival inflammation (86.81%), irritability (68.19%) and drooling (55.72%) were the most frequent ones.

Limitations: Different general symptoms were considered among studies. Some studies presented: lack of confounding factors, no clear definition of the diagnostic methods, use of subjective measures and examinations in long intervals.

Conclusions: There is evidence of the occurrence of signs and symptoms during primary tooth eruption. For body temperature analyses, it can lead to a rise in temperature, but it was not characterized as fever.

INTRODUCTION

Tooth eruption is a physiological process in which teeth move from its development position within the alveolar bone to break the gum towards the oral cavity.[1] Nevertheless, this mechanism and the source of the eruptive force has not been established nor completely understood.[2] Despite being a natural process of child development, the impacts of primary tooth eruption on the overall health of children are still controversial. Recent studies have suggested that tooth eruption could be accompanied by different benign symptoms, such as increased salivation, irritability, loss of appetite for solid foods and rise in body temperature.[3,4,5,6,7,8,9,10,11]

Moreover, the eruption of primary teeth has been assumed among parents to be associated with behavioral and systemic changes.[12,13,14,15,16,17] The period of time that tooth eruption occurs can be very frustrating and stressful for parents, especially when it happens

to their first offspring. Many parents do not know how to identify the signs of tooth eruption in their children and, therefore, do not feel confident to relieve the discomfort of the child.[18,19] Likewise, many health professionals also believe that there is an association between some signs and symptoms and the eruption of primary teeth. Surveys with pediatricians and other child health professionals showed that these beliefs are common.[3,20,21] The use of this diagnostic label may lead either parents not manage a likely illness[10] or the doctors to ignore significant symptoms and fail in diagnoses.[22]

Nevertheless, consistent evidences on the association of tooth eruption and general signs and symptoms are rather low and out of date. In a review conducted by Tighe et al[23] in 2007 to identify the existence of any pathognomonic sign and symptom of dental eruption, a variety of symptoms that may occur simultaneously with the tooth eruption was demonstrated and no evidence suggested the existence of any signs or symptoms that could predict the tooth eruption.

Thus, the purpose of this systematic review was to answer the following focused question: "In children aged 0 up to 36 months, are there local or systemic signs and symptoms during the eruption of the primary teeth?"

METHODS

This systematic review was oriented following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol.[24]

Protocol Registration

The systematic review protocol was recorded at the International Prospective Register of Systematic Reviews (PROSPERO)[25] under number CRD 42015020822.

Eligibility criteria

Inclusion criteria

Observational studies assessing the occurrence of local and systemic signs and symptoms during the spontaneous eruption of primary teeth in healthy children aged between 0 and 36 months, by means of either clinical examination or a questionnaire directed to the parents or health care professionals, were included. The local and systemic signs and symptoms evaluated were all reported complications

related to teething described in the studies (e.g., decreased appetite, diarrhea, drooling, fever, inflammation, swelling, vesicles or ulceration of the gum, irritability, rash, rhinorrhea, sleeping disturbances, vomiting).

Exclusion criteria

Exclusion of the studies was performed in two phases. In phase one (titles and abstracts) the exclusion criteria were as follows: 1 - Studies conducted in children aged over 36 months old; 2 - Reviews, letters, conference abstracts; 3 - Studies in which the sample included genetic syndromic patients (e.g., Down syndrome, craniofacial anomalies, neuromuscular disorders, etc.); 4 - Studies in which the sample included malignancies, malnutrition and chronic diseases; 5 - Studies in which the sample included non-spontaneous eruption of primary teeth; 6 - Studies in which the eruption of primary teeth was not the primary outcome. Besides the six cited criteria, in phase two (full-text) the following exclusion criteria were added: 7 - Studies in which clinical exam was not performed by a health care professional and, 8- Articles that evaluated the same sample.

Information sources and search strategies

A systematic search was conducted on the following electronic databases: Latin American and Caribbean Health Sciences (LILACS), PubMed, ProQuest Dissertations and Theses Database, Scopus and Web of Science, for titles and abstracts relevant to the research question. The syntax has been adapted to each database (Appendix 1). A partial grey literature search was taken using Google Scholar limited to the first 100 most relevant articles published in the past 5 years. The reference lists of the included studies were scanned to identify additional studies of relevance. All references were managed by reference manager software EndNote® Basic (Thomson Reuters, New York, EUA) and duplicate hits were removed. The end search date was May 6th, 2015. No language or date restrictions were applied.

Study Selection

The selection occurred in a 2-phase process in order to minimize bias. In phase 1, studies were independently screened by 2 reviewers (CM, MB) based on the titles and, if available, the abstracts derived from the search. Any study that clearly did not fulfill the inclusion criteria was discarded. In phase 2, the full text of relevant papers was retrieved for further analysis by the same 2 reviewers (CM, MB) and

was either included or excluded in the review on the basis of the eligibility criteria. Disagreements of inclusion/exclusion were handled through discussion and the third reviewer (MC) was consulted to make a final decision.

Data Collection Process

Two authors (CM, MB) independently collected the required information from the selected articles. After, all the collected information was crosschecked and confirmed for its accuracy. Again, any disagreement was resolved by discussion and mutual agreement between the authors. The third author (MC) was involved, when required, to make a final decision.

Data Items

For all of the included studies the following structured information was recorded: study characteristics (authors, year of publication, country, study design, setting), population characteristics (sample size, age of participants), intervention characteristics (type of diagnostic approach - clinical exam, body temperature, questionnaire) and, finally, outcome characteristics (assessed teeth, symptoms, mean temperature in non-eruption days, mean temperature in eruption days and conclusions pertaining to the occurrence of local and systemic signs and symptoms during the eruption of primary teeth). Authors were contacted for further details when relevant information was not reported or there was doubt remaining about duplicate publication.

Risk of Bias in Individual Studies

Two reviewers (CM, MB) independently assessed the methodological quality of the included studies, using the "Quality in Prognosis Studies Tool" (QUIPS).[26] The QUIPS tool comprises 6 domains: Study Participation, Study Attrition, Prognostic Factors Measurement, Outcome Measurement, Study Confounding and Statistical Analysis and Reporting to guide ratings of high, moderate or low risk of bias. Disagreements were resolved through consensus when possible, or a third reviewer (MC) made the final decision.

Summary Measures

Presence of local and systemic signs and symptoms and differences in body temperature during the eruption of primary teeth were considered the main outcomes. For body temperature, the threshold point was considered according to a recent meta-analysis on

accuracy of infrared tympanic thermometry,[27] between 37.4°C to 37.8°C for tympanic temperature and 38.0°C for rectal temperature. Any type of related outcome measurement was computed (categorical variables and continuous variables).

Synthesis of results

A meta-analysis was planned within the studies presenting enough data. The occurrence of signs and symptoms of the eruption of primary teeth was analyzed by two types of meta-analysis, for fixed and random effects following the appropriate Cochrane Guidelines.[28] Meta-analysis was performed with the aid of MedCalc Statistical Software version 14.8.1 (MedCalc Software, Ostend, Belgium). Heterogeneity was calculated by inconsistency indexes (I^2), and a value greater than 50% was considered an indicator of substantial heterogeneity between studies.[29] The significance level was set at 5%.

Risk of bias across studies

Clinical heterogeneity (differences in participants, interventions and outcomes) and methodological heterogeneity (study design, risk of bias) were explored.

RESULTS

Study Selection

The search identified 1,318 citations across 5 databases. After duplicates removal, 1,179 papers were screened in phase 1. A total of 65 papers met criteria for full-text screening. Additionally, 100 citations from Google Scholar were considered. From these, 4 further studies met the inclusion criteria. A hand search on the reference lists was performed for any study that might have been inadvertently missed by the electronic search procedures and 6 additional references were identified. Based on exclusion criteria for phase 2 (full-text screening), 59 articles were excluded. Two articles evaluated the same sample and one was not found. The reasons for exclusion are compiled in a comprehensive list (Appendix 2). Therefore, 16 articles were selected for data collection with the aim of answering the review question. A flowchart of the process of identification and selection of studies is shown in Figure 1.

Study Characteristics

The reviewed studies were conducted in 8 different countries: Australia,[10,30] Brazil,[31,32,33] Colombia,[34] Finland,[35] India,[36,37,38] Israel,[11,39,40] Senegal[41] and United States.[42,43] The sample size ranged widely from 16[40] to 1,165[32] children. The search involved papers published between 1969[35,39] to 2012.[38] A summary of the study descriptive characteristics can be found in Table 1.

Risk of Bias Within Studies

The reported methodological quality of the included studies ranged between low and high risk of bias following QUIPS[26] domains. Studies selected have shown to be heterogeneous considering bias, 7 presented high[11,31,32,36,37,41,43] risk of bias, 4 moderate[34,38,39,42] and 5 low.[10,30,33,35,40] None of them fulfilled all the methodological criteria. Summarized assessment considering risk of bias can be found in Table 2. Detailed results on the use of QUIPS[26] tool in selected studies can be found in Appendix 3.

Results of Individual Studies

There were 2 researches that investigated exclusively local modifications.[30,36] Other studies evaluated, besides general problems, local disturbances that could be involved on primary tooth eruption.[32,35,37,41] Hulland et al[30] observed that 85% of 128 teeth in 21 children presented gingival hyperemia in the early stages of eruption. Chakraborty et al[36] reported that anterior teeth erupted with less local signs than posterior. King et al[43] suggested that local signs could be confounded with oral herpetic infection.

Shapira et al[40] observed an increase in inflammatory cytokine levels in the gingival crevicular fluid surrounding erupting teeth, while Galili et al[39] found that multiple eruption occurring at the same time were associated with diseases. Bengtson et al,[31] Carpenter,[42] Cunha et al[32] and Yam et al[41] observed that eruption of primary teeth were associated with symptoms. Kiran et al,[37] Noor-Mohammed at al[38] and Peretz at al[34] found more symptoms associated with the eruption of the incisors. Tasanen[35] evaluated that mild symptoms like sucking finger, rubbing gum an drooling increased during teething while Wake et al[10] reported that primary tooth eruption was not associated with symptoms. Jaber et al[11] found that children erupted their teeth with fever and Ramos-Jorge at al[33] that there was a slight rise in body temperature.

The frequency of body temperature measurement varied between studies. In some of them daily registration could be assessed,[11,31,33,35,39] whereas in others every week day,[10] twice a week[40] or monthly.[42] From

the studies in which type of thermometer and measurement were informed, four studies used rectal temperature[11,35,39,42] and two tympanic.[10,33] In studies that presented this data, the cutoff point to consider a child with high temperature ranged from 37.5ºC over a period of two days (rectal)[39] to 39ºC in a single assessment (not informed).[34] A summary of body temperature assessment can be found on Table 3.

In relation of individual signs and symptoms, some investigations demonstrated that fever,[11,31,32,34,37,38,39,40,41,42] drooling,[31,33,34,35,37,38,42] diarrhea,[31,32,33,34,37,38,41,42] irritability,[31,32,33,37,40,42] loss of appetite;[31,33,35,37,42] sleeping problems[31,32,33,35,37] and rhinorrhea[31,32,33,37,42] were associated with primary teeth eruption. In the opposite site, other studies exposed that the same symptoms – fever,[10,35] irritability,[10] sleep disturbances[10,39] and loose stools[10,39] - had no association with the eruption.

Synthesis of results

To easily interpret the results, the studies were clustered into overall prevalence of signs and symptoms (Figure 2) and separately prevalence for each individual sign or symptom (Figure 3). A total of ten studies were included in the meta-analysis. Eight studies had sufficient data to conduct meta-analysis[11,32,34,37,38,40,42,43] of general prevalence of signs and symptoms. Another two studies were included in the meta-analysis of individual signs or symptoms. [33,35]

Because of the heterogeneity between the studies a random model was choosen.[44] All the information about the meta-analysis of individual studies is described in Figure 2 and Appendix 4. The results from this meta-analysis revealed that the overall prevalence of signs and symptoms associated with primary tooth eruption in children between 0-36 months was 70.5% (total sample=3506; Figure 2), where gingival irritation, irritability and drooling were the most frequent ones with 86.81%, 68.19% and 55.72%, respectively. Additional information regarding the meta-analysis can be found on Appendix 4 and 5.

Risk of bias across studies

The studies were heterogeneous and had different designs. Analysis revealed that the weakness in methods was not considered important confounders capable to mask possible signs and symptoms related to other diseases that could occur simultaneously with primary tooth eruption.

DISCUSSION

This systematic review investigated the available evidence about primary tooth eruption and local and systemic signs and symptoms. Currently, American Academy of Pediatric Dentistry guidelines have indications that eruption of primary teeth leads to local discomfort, irritation and drooling.[45]

Parents follow the development of children and witness any change in behavior, mood or health. Thus, they can be helpful to assist the detection of related problems.[46] Although cooperative, parents retrospectively reported symptoms associated with primary tooth eruption showed to be memory biased. In a retrospective study about parents' beliefs related to primary tooth eruption, the mean number of symptoms reported per child was 11 while in the study sample the mean number was 8.[10] Similarly, fever was reported five times more often in the retrospective than children experienced fever during teething period in the prospective study.[33] Limitations of these studies are represented by the subjectivity of the parents' observations. In this context, a study that had the collaboration of parents which daily measured children temperature, checked for tooth eruption and kept a daily log of symptoms, despite presented adequate methods, was excluded based on the criteria for this systematic review because children did not receive health professional examination during the follow-up. There was a significant association to tooth emergence: biting, drooling, gum rubbing, irritability, sucking, sleep awakenings, ear rubbing, rash on face, decreased appetite for solids, and slight temperature elevation.[6]

Regarding the local signs, the most frequent was inflammation of the gum[36] or gingival reddish (hyperemia),[30] mostly in posterior teeth. The timing of eruption of the primary teeth (6 months onwards) coincides with age when babies start to explore the environment. In this phase, the introduction of the hands and objects into the mouth is normal; this, in turn, can bring harmful microorganisms and cause infection.[47] Even sucking behavior, nutritive and nonnutritive, may lead to bruise or traumatize the gums causing inflammation.[48]

Regarding the most frequent general symptoms during primary tooth eruption; irritability and drooling were the most observed followed by decreased appetite, sleeping problem, rhinorrhea, fever, diarrhea, rash and vomiting. Eruption was associated with fever,[40] did not influence the body temperature[35] or leads to a slight rise in body temperature.[33] In contrast, symptoms that were not related to primary tooth eruption in the selected studies were in this sequence: sickness,[10,35,39] sleeping disturbances,[10,39] loose stools,[10,39] drooling,[10,39] vomiting[39] and fever.[10,35] Three of most robust studies in this

systematic review showed that sucking finger, gum rubbing, daytime restlessness, loss of appetite,[35] sleep disturbance, increased salivation, rash, rhinorrhea, diarrhea, irritability[33] and coughing[40] increased during teething.

Another robust study,[10] that accompanied 90 erupting teeth from 21 children every weekday, reported that fever, mood disturbance, illness, sleeping disturbance, drooling, diarrhea, strong urine, red checks or rashes did not have association with primary tooth eruption.

The stage of eruption considered to represent the day of eruption for the studies differed from the first day the edge of an incisor or a cusp of a molar could be seen or felt emerging through the gum,[10,33] palpable with the finger nail;[35] clinical crown of the tooth visible but not exceeding 3mm of exposure above the gingiva[34,37,38] to any portion of the occlusal surface penetrated the gingiva.[39] Besides that, the frequency of clinical exam varied from a single assessment in cross sectional studies to daily investigation in some prospective investigations. This is an important information since Hulland et al[30] found out that the mean duration of primary tooth eruption from imminent eruption to completion of emergence phase was in an average rate of 0.7mm per month. Those studies that evaluated the eruption as the tooth crown visible through gingiva but not exceeding 3 mm or those that clinical examinations occurred in monthly intervals may have lost or overestimated some signs or symptoms.

It seems that symptoms associated with primary tooth eruption decrease with age. Most manifestations were observed during the eruption of primary incisors[32,34,37,38] or were studied only in incisors.[11,33,40] Also there was a significant difference between the mean age at which eruptions were accompanied by disturbances (11.8 months) and the average age (14.8 months) at which teeth erupted without general disturbances. On the other hand, there seems to be an association between multiple eruption with fever and respiratory and alimentary illnesses that could be due to the stress that lead to the low resistance of the body against infections.[39]

Accurate determination of body temperature is essential to diagnose fever.[49] A recent systematic review investigating the accuracy of infrared tympanic thermometry used in the diagnosis of fever in children, disclosed that the accuracy of this kind of thermometer is high, using rectal measurement as the "gold standard". Besides, as temperature measured by tympanic thermometry was always 0.6°C to 0.2°C less than rectal temperature, the threshold of fever diagnosed by tympanic thermometry can be decreased. Therefore, if 38.0°C is the

fever diagnosed by rectal temperature, the threshold of infrared tympanic thermometry should be 37.4°C to 37.8°C.[27] Under these circumstances, in this systematic review, in one study using rectal temperature, mothers on a daily basis verified temperature and threshold point was not informed. Fever was associated with teething and the mean daily temperature in days of non-eruption was between 36.90ºC and 37.10ºC, and in the eruption day 37.60ºC.[11] Two studies with moderate risk of bias used rectal temperatures above 37.77ºC (100ºF)[42] and above 37.50ºC;[39] these authors stated that fever was associated to tooth eruption, but mean daily temperature was not informed. Analyzing the three most robust studies, one used rectal temperature and detected that eruption did not interfere in body temperature with mean daily temperature in non-infected children (37.0ºC in non-eruption days and 36.9ºC in eruption days) in twice daily examinations.[35] The others used tympanic measurements. One study discovered a slight rise from 36.39ºC in non-eruption days to 36.51ºC in eruption days in a daily check by dentists,[33] while the other one stated that children do not have fever in teething period, with 36.18ºC in non-eruption days and 36.21ºC in eruption days every weekday by the dental therapist.[10]

Limitations

Some methodological limitations of this review should be considered. Different general symptoms were considered among studies and not all studies related confounding factors, like other disease that might have occurred with tooth eruption, or several symptoms happening at the same time. All of these may obscure the actual findings.

Most studies failed in expose a clear definition of the diagnostics methods. Examinations were performed in long intervals that could compromise adequate data collection. Besides, some symptoms did not use objectives measures, but parents' observation, like irritability and loss of appetite. In addition, some symptoms need more specific exam, like diarrhea that may be caused by infection and, without a virology study the diagnostic is not conclusive.

Most of the selected studies demonstrated high risk of bias especially with relation to study design. Articles with lower risk of bias had small samples - 21 to 126 children evaluated. The longest samples were found in studies with high risk of bias, although a random effect for meta-analysis was used, this might be affected the results.

Conclusions

There is evidence of the occurrence of signs and symptoms during primary tooth eruption. Gingival inflammation, irritability and drooling were the most common. For body temperature analyses, it was possible to evaluate that during the eruption of primary teeth there was a rise in temperature, but it was not characterized as fever.

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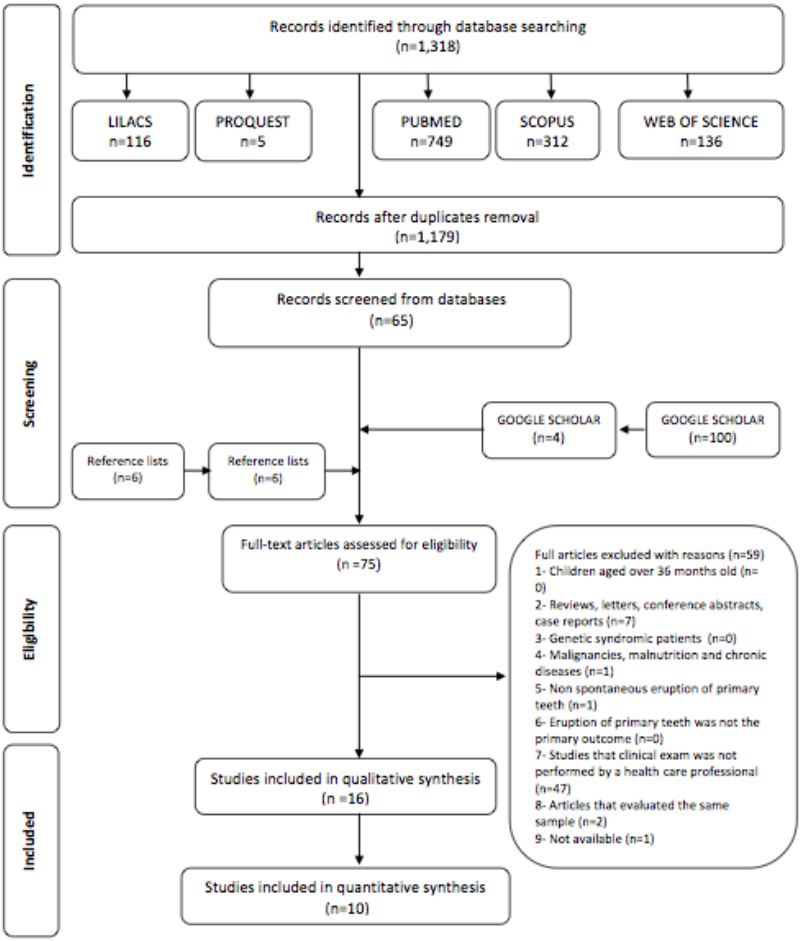
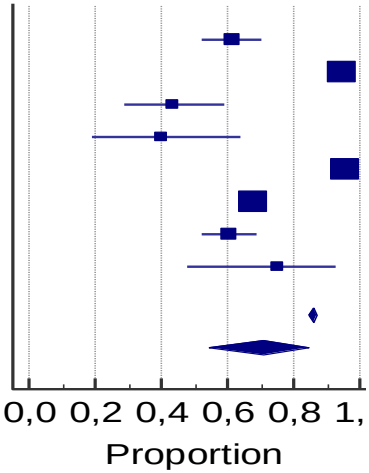


FIGURE1. Flow diagram of literature search and selection criteria.[1]

[1]Adapted from PRISMA

Study	Sample size	Proportion (%)	95% CI
Carpenter, 1978	120	61,667	52,350 to 70,393
Cunha, et al, 2004	1165	94,764	93,325 to 95,971
Jaber et al, 1992	46	43,478	28,934 to 58,893
King et al, 1999	20	40,000	19,119 to 63,946
Kiran et al, 2011	894	95,749	94,212 to 96,975
Noor-Mohammed et al, 2012	1100	68,000	65,152 to 70,751
Peretz et al, 2003	145	60,690	52,243 to 68,690
Shapira et al, 2003	16	75,000	47,623 to 92,734
Total (fixed effects)	3506	85,616	84,412 to 86,761
Total (random effects)	3506	70,591	54,198 to 84,622



Test for heterogeneity	
Q	578,7393
DF	7
Significance level	P < 0,0001
I^2 (inconsistency)	98,79 %
95% CI for I^2	98,39 to 99,09

FIGURE 2. Forest plot for all signs and symptoms that occurred during the eruption of primary teeth. Sample = 3,506.

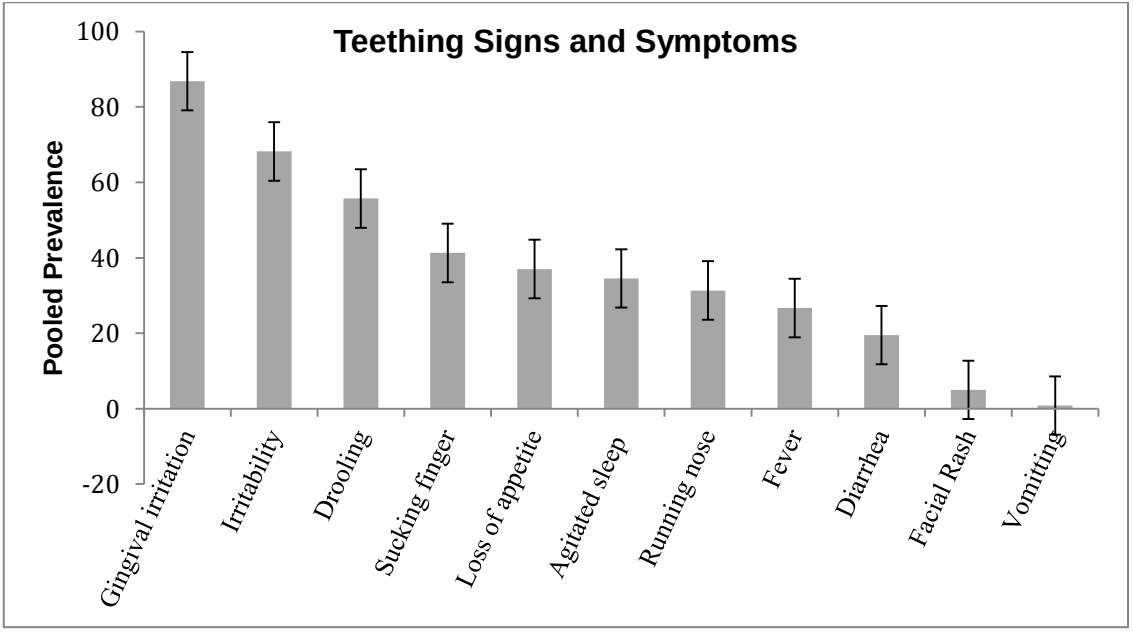


FIGURE 3. Pooled prevalence for each individual sign or symptom that occurred during the eruption of primary teeth**.**

TABLE1. Summary of descriptive characteristics of included articles (n=16).

STUDY			POPULATION		INTERVENTION			OUTCOME				
Author, Year, Country[a]	Study design	Setting	Total *n*	Age Mean or Range (Months)	Clinical Assessment	Body Temperature ºC (Who/How)	Questionnaire	Assessed Teeth	Symptoms	Follow-Up Period	MTNED/ MTED (ºC)	Main Conclusion
Bengtson et al 1988 Brazil[31]	PS	Institutionalized children living in a shelter	36	5 - 11	Children were examined for admission to the research. Examiner NI	Nurses/Daily. Type of thermometer, measurement NI	Nurse daily registered salivation, diarrhea, sleeping trouble, irritability, runny nose, rash, fever, decreased appetite, vomiting, strong urine, itching hearing, physical difficulty	72	88.88% had salivation, 87.50% diarrhea, 72.22% sleeping trouble, 69.44% irritability, 68.05% runny nose, 61.11% rash, 58.33% fever, 50.00% decreased appetite, 11.40% no symptoms	4 months	NI/NI	Children had their teeth erupted with symptoms
Carpenter 1978, United States[42]	RS	Well-baby clinic of a medical university hospital (South Carolina)	120 records	4 - 10	Medical student and a board certified pediatrician. Records utilized in the study indicated teeth were erupting that time or in previous visit one month before	Medical student and a board certified pediatrician/ Monthly Rectal temperatures of less than 37.77[a] were not recorded as fever	N	Number of teeth NI. Inferior primary central incisors	39.16% had one disturbance and 22.50% had two or more disturbances (fever, vomiting, diarrhea, drooling, irritability, facial rash and rhinorrhea) concurrent with teething; 17 patients had fever	NI	NI/ NI	There is a correlation between teething process and the occurrence of systemic disturbances
Chakraborty et al 1994, India[36]	PS	Pediatric departments of different hospitals of Calcutta and pedodontic department Dr. R. Ahmed Dental College	201	6 - 12	Dentist/2 months interval	NA	Parents were asked direct questions on the appointment day on extend and nature of local disturbances (inflammation of the gum, non specific oral ulcers, cheek flush, cheek rash, eruption cyst), within 2 months period	NI	80.08% suffered from at least one complication in relation to anterior teeth and 92.53% from posterior teeth. Inflammation of the gum was the most common complication	NI	NA	Eruption of anterior teeth was associated with less number of complications than posterior teeth

Cunha, et al 2004, Brazil[32]	RS	Baby clinic of Araçatuba dental School	1165 records	0 -36	Examiner NI/ 2 months intervals	Parents were asked regarding the occurrence of fever, Type of thermometer, measurement NI	Parents were asked regarding the occurrence of disturbances during eruption. Gingival irritation, runny nose, diarrhea, fever, general agitation, increased salivation, agitated sleep, was analyzed	889[b]	95% of the records reported some type of manifestation, 85% gingival irritation, 74% agitation, 70% increased salivation, 46% fever, 39% agitated sleep, 35% diarrhea, 26% runny nose. The most frequent teeth involved were the lower central incisors 52%, maxillary central incisors 20%	Records from Jan 1996 to Dec 2001 were analyzed	NI/NI	Children showed some type of disturbance during eruption of teeth
Galili et al. 1969, Israel[39]	PS	Institutionalized children residents of a Wizo Baby Home, Jerusalem	43	5 -23 Mean 11.07 (± 0.8)	Author/Weekly. Eruption was registered if any portion of the occlusal surface had penetrated the gingiva	Nurses/Daily/Rectal temperature of at least 37.5ºC over a period of 2 days was designated as fever	Nurses daily registered stool, consistence and number, vomiting, sickness, drooling and restlessness. They referred the child to the resident pediatrician in case of any sign of disturbance	93	The difference between eruptions in periods with fever of unknown origin and those in period of health is significant. The association between eruption and fever without apparent cause is significant. Multiple eruptions associated with fever and illness was significant	4 months	NI/ NI	There was no association between tooth eruption and systemic disturbances. Eruption and fever without recognizable cause was associated. Multiple eruption and disease (respiratory and alimentary) was associated
Hulland et al. 2000, Australia[30]	PS	3 day-care centers	21	6 - 24 Mean 14.4 (± 4.9)	Dental hygienist examined (tactile and visual) the alveolar ridges to identify redness or swelling and	NA	NA	128	Only 16 observation of swelling. Redness occurred in 85% of teeth in the early stages of eruption	7 months	NA/ NA	During eruption most of teeth showed signs of gingival reddening (hyperemia) and soft tissue swelling is uncommon

					stage of tooth eruption/ Every weekday, mid-morning							
Jaber et al. 1992, Israel[11]	PS	Author's private clinic to confirm tooth eruption	46	6 - 18	Mothers examined gums daily. Professional confirmation of tooth eruption	Mothers/Daily/ Rectal	Mothers, daily noted if there was any diarrhea, convulsions, bronchial symptoms, or any other diseases; medications and medical examinations. All data refer to the previous 20 days	Number of teeth NI. Only data collected up to the eruption of the first tooth (incisors) were analyzed	Since the day that tooth eruption was registered was referred to day 0, and all data refer to the previous 20 days, the results of comparison of days 0 to 9 and 10 to 19 showed 47 versus 67 days of otitis media, 85 versus 72 days of diarrhea, and 52 versus 58 days with cough; no convulsions occurred	NI	MTNED MDT 36.9 and 37.1 from day 19 to day 4. Three days before the tooth eruption occurred the MDT increased to 37.14 (0.66) on day 3, 37.2 (0.68) on day 2, 37.4 (0.76) on day 1. MTED 37.6 (0.85) on the day the tooth erupted (95% CI 37.33 to 37.86)	Infants cut their teeth with fever
King et al 1999, United States[43]	CS	SG patient at a dental school pediatric dentistry clinic, a community hospital, and the private offices of a pediatric dentist and a pediatrician. CG selected by age-matching to SG, at local church's infant	40 Total 20 SG distress from tooth eruption 20 CG no distress	7 - 30	Responsible personnel at each location made exam and viral sampling protocol for HVS, for SG and one of the authors for CG subjects. Samples for viral culture were obtained from subject's gingiva in both	Examiner NI/Type of thermometer, measurement and frequency NI. When temperatures were obtained by other than the oral method (skin tape, rectal), they were adjusted to oral values for comparison purposes	N, only that information obtained on each subject was recorded on a prepared form and included name, age, gender, temperature, and oral findings	NI	SG Positive cultures for HVS in 9 infants, they presented inflammation, swelling, vesicles, ulceration limited to area adjacent/ beyond to erupting tooth (teeth). CG all negative for HVS and normal oral findings	NA, Single clinical assessment	MTNED NA MTED SG 7 from 9 positive for HVS had temperature >37.77[a] from 11 negative 5 presented elevated temperature CG all negative for HVS normal	Children had elevated temperature that could not be explained by other diseases during teething period

		care facility			groups						temperature	
Kiran et al 2011, India[37]	PS	Department of Paediatric and Preventive Dentistry, Institute of Dental Sciences, and the Department of Paediatrics, Rohilkhand Medical College	894	6 - 36	Examiner NI/3 months interval. Eruption was defined as visible clinical crown of the tooth, but not exceeding 3 mm of exposure in the oral cavity	Nurse/After dental examination. Type of thermometer, measurement NI	Parents were asked about the occurrence of local and systemic disturbances. Analysis of the records showed the presence of the following symptoms: gingival irritations; diarrhea; fever; loss of appetite; irritability; increased salivation; running nose; agitated sleep; fever with diarrhea; fever with increased salivation; diarrhea with increased salivation; fever with diarrhea and increased salivation	Number of teeth NI. Incisors, canines, and molars.	95.7% reported some type of manifestations, gingival irritation was observed in 95.9%, irritability in 92.1%, fever in 78.0%. In the control group 92.1% of infants did not manifest any symptom	11 months	NI/NI	Local and systemic manifestations were more pronounced during eruption of primary incisors. There was association between primary tooth eruption and incidence of signs and symptoms
Noor-Mohammed et al 2012, India[38]	CS	Child health institute and research center	1100	4 - 36	One of the authors. Eruption was determined if the clinical crown of the tooth was visible, but not exceeding 3 mm exposure above the gingiva	Mothers complete a short and simple questionnaire in a yes/no manner including fever. Type of thermometer, measurement NI. Frequency NA	Parents completed a questionnaire in a yes/no manner about three objective manifestations noted during the eruption of the primary teeth including drooling, diarrhea, fever, and the combination of these symptoms	Number of teeth NI. Incisors, canines, and molars	The most frequent clinical manifestations were: fever (16%), drooling (12%), diarrhea (8%), fever-drooling (15%), fever-diarrhea (8%), drooling-diarrhea (6%) and the combination of fever- drooling-diarrhea 3%	NA, Single clinical assessment	NI	There was association between general objective signs (drooling, fever, and diarrhea) and the eruption of primary teeth. Most signs appeared during the eruption of the primary incisors
Peretz et al 2003, Colombia[34]	CS	Public child center	585 145 SG 340 CG	4 - 36	Dentist/ Single assessment	Nurse/Frequency NA/Type of thermometer,	Parents accompanying the child completed a	Number of teeth NI. Incisors,	CG 93% of the children did not present any clinical	NA, Single clinical	NI	An association has been shown between general

					Eruption was determined if the clinical crown of the tooth was visible, but not exceeding 3 mm exposure above the gingiva	measurement NI. Fever was recorded when exceeded 39°C.	questionnaire. Information was relayed in a yes/no manner about 3 objective manifestations noted during the eruption of the primary teeth, including drooling, diarrhea, fever, and the combination of these symptoms. The dentist and the nurse confirmed drooling and fever during the clinical check up	canines, and molars.	manifestation. In the SG, only 39%. The most frequent clinical manifestations were: drooling (15%), diarrhea (13%), and drooling-diarrhea (8%), fever and fever- diarrhea (8%)	assessment		objective signs (drooling, fever, diarrhea) and the eruption of primary teeth with drooling being the most prevalent sign. Most signs appeared during the eruption of the primary incisors
Ramos-Jorge et al 2011, Brazil[33]	PS/ RS	Residences of the infants. Non-institutionalized	47	5 - 15 Mean 8.9 (± 2.7)	11 validated trained dentists/ Daily. The day of eruption was defined as the first day on which the incisor edge emerged in the oral cavity without being completely covered by gingival tissue.	11 validated trained dentists/ Daily/ Infrared auricular thermometer and a digital axillary thermometer.	Mothers were interviewed to investigate the occurrence of signs and symptoms such as increased salivation, rash, runny nose, diarrhea, loss of appetite, cold, irritability, fever, smelly urine, constipation, vomiting, colic, and seizure, in the previous 24 hours and one week after the end of data collection, the mothers answered the same questionnaire.	23(incisors). Mean number of teeth per infant was nearly 5 (range=2-8)	The associations between signs and symptoms reported by mothers and tooth eruption were statistically significant The most common symptoms on days of eruption were irritability, increased salivation, runny nose, and loss of appetite. Fever was reported five times more often in the RS	8 months	MTNED Tympanic 36.39 (0.26) Axillary 35.98 (0.36) MTED Tympanic 36.51 (0.20) Axillary 35.99 (0.46)	There are associations between teething and sleep disturbance, increased salivation, rash, runny nose, diarrhea, loss of appetite, irritability, and a slight rise in temperature. Fever was more frequently reported in the RS
Shapira et al, 2003, Israel[40]	PS	Day Care Center	16	5 - 14	Pediatric dentist/ Twice weekly. Eruption of the teeth was	Information provided by parents/caregivers. Twice weekly. Type of	The children's signs and symptoms for each day were recorded by the examining	50 teeth (anterior), evaluated and samples from 21 of	During the teething period, behavioral problems were observed in 50% of the infants,	5 months	MTNED During the control period, 8% of the children	Teething was associated with fever, behavioral problems, coughing, and

					referred to the act of teeth breaking out the gum. Fluid from the sulcus was collected on the day of eruption or on 1 of the following 3 days. And was again collected for the control group from the same tooth 1 month later	thermometer, measurement NI. A child with a temperature of under 37.5°C was classified as having "no fever." A temperature of 37.6°C to 38.5°C was regarded as low/moderate fever, and a temperature over 38.5°C was classified as high fever	dentist on the basis of the information provided by parents as well as caregivers at the day care center. The following signs and symptoms were recorded: fever; vomiting; gastrointestinal disturbances; drooling; behavioral problems; sleep disturbances; coughing; appetite disturbances; and biting; sucking	them for the test and the control group (fluid from the sulcus)	compared to 16% in the control period (P<0.01); fever was observed in 24% of the infants during tooth eruption and in 8% of the infants during the control period (P=.04); and coughing was observed in 12% during tooth eruption compared to 2% (P=.06) of the infants during the control period. In teething period vomiting (2%), drooling (12%), and appetite disturbances (12%), but were absence during the control period		exhibited low/moderate fever, no episodes of high fever were found. MDT NI MTED In the teething period, 14% of the children exhibited low/moderate fever and 10% exhibited high fever MDT NI	the cytokine TNFα levels
Tasanen, 1969, Finland[35]	PS/CS	Nursery, day-nursery, welfare center SG: PS: 42 nursery GI 43 day-nursery GII 41 welfare center GIII CG: CS: 107 the same locals	126 SG 107 CG +50 newborn and 50 teething children for evaluation of the gum color +17 mucosal specimens	0 - 30	1 investigator with both medical and dental qualifications, daily- groups I /II and summoned when eruption occurred- group III. Eruption: first time the edge of incisor/ cusp of molar emerges through gingiva and is palpable with the fingernail. Coincidental infection: if	Same investigator: rectal temperature, twice daily (morning/ afternoon), one-minute thermometer ªC	Behavior disturbances: nursing staff/mothers. Symptoms: sleep, daytime restless, rubbing the cheek and ear, rubbing gum and sucking the finger, drooling, appetite and loose stools. Questionnaire maternal opinion: 200 mother, 100 more than 40 years old. Symptoms: fever, sleep disturbances, restlessness during	192 (incisive, canine, molar).	Infection during eruption: 26% SG, 15% CG. Temperature: NoI was in average of 0.1ªC lower in pre and post eruptive phase. Sedimentation rate: during and after eruption not significant. White blood cells during eruption: significant only for lymphocyte ratio in SG compared CG. Disturbances in behavior: statistical difference only for restless	Average period of 13.3 days	MTPE NoI 37.0 I 37.2 MTED NoI 36.9 I 37.3 MTP NoI 37.0 I 37.3	Eruption did not influence the body temperature or increase the possibility of infection. Sucking finger, rubbing gum, drooling, daytime restlessness, loss of appetite increased during teething. There was no change in the color of mucosa in one third of the erupting teeth. There were some

					fever or other signs of infection was noted one week before or 5 days after eruption, child was place in the infected group. Blood investigation: sedimentation rate per hour and total white blood cell count. Local investigations: condition of the mucosa: normal, slight redness and deep red. Sensitivity of gingiva: finger palpation, moderate pressure. Sensitivity of tooth to pressure: with special equipment 800g. Histological investigation: gum at the eruption site		the day, gum rubbing and finger sucking, cheek and ear rubbing, appetite, drooling, diarrhea, convulsion		ness and drooling in SG and appetite showed little decrease for SG. Local observation: gum color chance: in 40% was deep red. Changes in mucosa: 28 in 126 cases showed slight hemorrhages, moderate pericoronorite, fistulas, swelling or eruption cyst. No difference could be found in relation to the other findings. Pain was not found in pressure to the gingiva or to the erupting teeth. No investigation was made concerning correlation between clinical and histologic findings. At least 20% of mothers believed their children could present some of the investigated symptoms			local complications during teething. Mother attributed some disease to teething
Wake et al 2000, Australia[10]	PS/ RS	3 child-care centers	21	6 – 24 Mean 14.4 (± 4.9)	Dental therapist examined for tooth eruption every weekday (midmorning). An *eruption day* was defined as the first day that the edge of an	Dental therapist Every weekday (midmorning)/ Infrared tympanic thermometer	Two questionnaires: to staff (afternoon) and parents (morning) inquired about the child's mood, wellness/illness, drooling/ dribbling, sleep,	90 (incisive, canine, molar).	Analysis did not indicate a relationship between tooth eruption and fever. All parents retrospectively reported that their own child had suffered teething	7 months	MTNED 36.18 MTED 36.21	Tooth eruption is not associated with fever, mood disturbance, illness, sleep disturbance, drooling, diarrhea, strong urine, red cheeks, or

					incisor or cusp of a molar crown could be seen or felt emerging through the gum		stools, wet diapers, and rashes/flushing over the preceding 24 hours were answered every weekday. At the end of the study, parents completed a questionnaire about their beliefs and experiences related to teething		symptoms			rashes/ flushing on the face or body
Yam et al, 2002, Senegal[41]	PS	Child health institute Centre de Protection Maternelle et Infantile in Dakar-Médina	499	5 - 30	Medical service/ Monthly. Mothers should bring the children if there were any sign or symptoms in this period	Information provided by parents. Type of thermometer, measurement NI	NI	Number of teeth NI. Incisors, canines, and molars.	Local observation: 7 hematoma of eruption, 5 widespread gingivitis, 297 local gingivitis. At least 60% of the children had one or more of the symptoms: hyperthermia, vomiting, diarrhea and appetite problems	NI	NI/NI	Children cut their teeth with local and systemic disturbances

CG, Control Group; CI, Confidence interval; CS Cross sectional; HSV, herpes simplex virus; I, Infected; MDT, Mean daily temperature; MTED, Mean temperature in eruption days; MTNED, Mean temperature in non-eruption days; MTPE, Mean temperature pre-eruption; MTP; Mean temperature post-eruption; NA, Not applicable; NI, Not informed; N, No; NoI, Non-infected; PS, Prospective study; RS, Retrospective study; SD, Standard deviation; SG, Study group

[a] Data were modified by authors (ºF to ºC)

[b] Data calculated by authors

TABLE 2. Risk of bias summarized assessment (QUIPS[26]).*

Biases	Bengtson et al 1988[31]	Carpenter 1978[42]	Chakraborty et al 1994[36]	Cunha et al 2004[34]	Galili et al 1969[39]	Hulland et al 2000[30]	Jaber et al 1992[11]	King et al 1999[43]	Kiran et al 2011[37]	Noor-Mohammed et al 2012[38]	Peretz et al 2003[34]	Ramos-Jorge et al 2011[33]	Shapira et al 2003[40]	Tasanen 1969[35]	Wake et al 2000[10]	Yam, et al 2002[41]
Study Participation	high	mod	low	low	mod	low	mod	low	low	low	low	low	low	low	low	high
Study Attrition	high	x	mod	x	high	high	high	x	low	low	high	mod	high	mod	mod	high
PF Measurement	high	mod	high	high	high	mod	high	high	high	high	low	low	mod	low	low	high
Outcome Measurement	high	low	high	high	low	low	high	high	high	high	mod	low	low	low	low	high
Study Confounding	high	low	high	high	low	low	high	high	high	high	high	low	low	low	low	high
Statistical Analysis and Presentation	high	high	low	high	low	low	high	high	high	low	low	low	low	low	low	high
Overall	high	mod	high	high	mod	low	high	high	high	mod	mod	low	low	low	low	high

* Abbreviations: QUIPS, Quality in Prognosis Studies Tool; PF, Prognostic factor. Ratings: High, moderate, and low indicates high, moderate, and low risk of bias, respectively.

TABLE 3. Summarized body temperature assessment.

Measurement	MTNED	MTDE	Study reference	Association
Rectal[42]	NI	NI	37.7ºC	Yes
Rectal[39]	NI	NI	37.5ºC	Yes
Rectal[11]	36.9 – 37.1ºC	37.6ºC	NI	Yes
Rectal[35]	37.0ºC	36.9ºC	37.5ºC	No
Tympanic[33]	36.39ºC	36.51ºC	NI	Yes (slight rise)
Tympanic[10]	36.18ºC	36.21ºC	NI	No

NI, Not informed; MTED, Mean temperature in eruption days; MTNED, Mean temperature in non-eruption days.
It was not possible to calculate the weighted average because data was insufficient.

APPENDIX 1. Search strategy (PubMed). May 6th, 2015*.

Step	Search Strategy
#5	(#1 AND #2 AND #3 AND #4)
#4	(eruption OR teething)
#3	(symptom* OR signs OR fever OR "body temperature" OR diarrhoea OR diarrhea OR appetite OR "irritable mood" OR irritability OR salivation OR sleep OR erythema OR biting OR "runny nose" OR "nasal congestion" OR cough OR drooling OR sialorrhea OR "ear pulling" OR rash OR vomiting OR "sucking behavior" OR sucking OR sign)
#2	("deciduous tooth" OR deciduous OR "primary dentition" OR "primary dentitions" OR "primary teeth" OR "primary tooth" OR "milk teeth" OR "milk tooth" OR "baby teeth" OR "baby tooth" OR milk-tooth OR "deciduous teeth")
#1	(infant OR baby OR babies OR preschool OR child OR children OR infants OR pediatric OR paediatric)

* This search strategy was adapted for other databases (LILACS, ProQuest Dissertations and Theses Database, Scopus and Web of Science).
Corresponding terms in Portuguese and Spanish were used for LILACS.

APPENDIX 2. Excluded articles with reasons for exclusion (n=59).

Author, Year	Reason for Exclusion*
Abujamrra et al 1994[1]	7
Abreu-Correa et al 1997[2]	7
Adimorah et al 2011[3]	7
Agbaje et al 2012[4]	7
Andrade et al 1999[5]	7
Aragão et al 2007[6]	7
Bankole et al 2004[7]	7
Bankole et al 2005[8]	7
Barlow et al 2002[9]	7
Baykan et al 2004[10]	7
Bengtson et al 1994[11]	8
Bennett 1986[12]	7
Bhavneet et al 2012[13]	7
Casaretto et al 2007[14]	7
Coldebella et al 2008[15]	7
Coreil et al 1995[16]	7
Crispim et al 1997[17]	7
Cross et al 2009[18]	7
De Castro et al 2013[19]	7
De Rezende et al 2010[20]	7
Denloye et al 2005[21]	7
De Rudder et al 1960[22]	2
Faraco et al 2008[23]	7
Feldens et al 2010[24]	7
Freitas et al 2001[25]	7
Honig et al 1975[26]	7
Illingworth 1969[27]	2
Ispas et al 2013[28]	7
Kakatkar et al 2012[29]	7
Kasangaki 2004[30]	7
Macknin et al 2000[31]	7
Mota-Costa et al 2010[32]	7
Noronha et al 1985[33]	7
Olabu et al 2013[34]	5
Og Uti et al 2005[35]	7
Owais et al 2010[36]	7
Oyejide et al 1991[37]	7
Oziegbe et al 2009[38]	7
Oziegbe et al 2011[39]	7
Pierce et al 1986[40]	7
Plutzer et al 2012[41]	7
Rocha et al 1988[42]	7
Ramos-Jorge et al 2013[43]	8

Sarrell et al 2005[44]	7
Seward et al 1971[45]	7
Seward et al 1969[46]	7
Seward et al 1972[47]	7
Seward et al 1972[48]	7
Soliman et al 1978[49]	7
Sood et al 2010[50]	2
Steward et al 1988[51]	2
Swann et al 1979[52]	4
Szpringer-Nodzak et al 1990[53]	9
Tighe et al 2007[54]	2
Vasques 2010[55]	7
Vogelsberg et al 1972[56]	2
Wake et al 1999[57]	7
Wake et al 2002[58]	7
Wilson et al 2002[59]	2

* 1 = studies in children aged over 36 months old; 2 = reviews, letters, conference abstracts; 3 = studies which the sample included genetic syndromic patients; 4 = studies which the sample included malignancies, malnutrition and chronic diseases; 5 = studies which the sample included non spontaneous eruption of primary teeth; 6 = studies where the eruption of primary teeth was not the primary outcome; 7 = studies that clinical exam was not performed by a health care professional; 8 = articles that evaluated the same sample; 9 = not available.

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**APPENDIX 3. ***QUIPS[26] Risk of Bias Assessment Instrument for Prognostic Factor Studies.

Biases	Issues to consider for judging overall rating of "Risk of bias"	Studies							
		Bengtson et al 1988[31]	Carpenter 1978[42]	Chakraborty et al 1994[36]	Cunha et al 2004[32]	Galili et al 1969[39]	Hulland et al 2000[30]	Jaber et al 1992[11]	King et al 1999[43]
		Rating of reporting	Rating of reporting	Rating of reporting	Rating of reporting	Rating of reporting	Rating of reporting	Rating of reporting	Rating of reporting
1. Study Participation	Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).								
Source of target population	The source population or population of interest is adequately described for key characteristics.	Y	Y	Y	Y	Y	Y	Y	Y
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	Y	Y	Y	Y	Y	N	Y	Y
Recruitment period	Period of recruitment is adequately described	Y	Y	N	Y	Y	Y	Y	Y
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	Y	Y	Y	Y	Y	Y	Y	Y
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including	N	Y	Y	N	Y	Y	Y	Y

	explicit diagnostic criteria or "zero time" description).								
Adequate study participation	There is adequate participation in the study by eligible individuals	N	N	Y	Y	N	Y	N	N
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for key characteristics.	N	N	Y	Y	N	Y	N	Y
Summary Study participation	The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.	High	Mod	Low	Low	Mod	Low	Mod	Low
	Rating of "Risk of bias"								
2. Study Attrition	Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).								
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	N	N	Y	NA	NC	Y	NC	NA
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	N	NA	N	NA	N	N	NC	NA
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	N	NA	Y	NA	N	N	NC	NA
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics.	N	NA	Y	NA	N	Y	NC	NA
	There are no important differences between key characteristics and outcomes in participants who completed the study and those who did not.	NC	NC	NC	NC	NC	Y	NC	NC

Study Attrition Summary	Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.	High	X	Mod	X	High	Mod	High	X
	Rating of "Risk of bias"								
3. Prognostic Factor Measurement	Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).								
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	N	N	N	N	Y	Y	N	N
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	N	N	N	N	Y	N	N	N
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	N	Y	N	N	Y	Y	N	N
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Y	Y	Y	Y	Y	Y	Y	Y
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	N	Y	Y	Y	N	N	N	N
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	NA	NA	NA	NA	NA	NA	NA	NA
PF Measurement	*PF* is adequately measured in study	High	Mod	High	High	Mod	Mod	High	High

Summary	participants to sufficiently limit potential bias.								
	Rating of "Risk of bias"								
4. Outcome Measurement	Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).								
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	Y	Y	Y	Y	Y	Y	Y	N
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	N	N	N	N	Y	Y	N	N
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	N	Y	Y	Y	Y	Y	Y	Y
Outcome Measurement Summary	*Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.	High	Low	High	High	Low	Low	High	High
	Rating of "Risk of bias"								
5. Study Confounding	Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).								
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model), are measured.	N	Y	N	N	Y	Y	N	N
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	N	Y	N	N	Y	Y	N	N

Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	N	Y	N	N	Y	Y	N	N
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	NC	Y	NC	Y	Y	Y	NC	NC
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	NA	NA	NA	NA	NA	NA	NA	NA
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	N	Y	N	N	Y	Y	N	N
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	N	Y	N	N	Y	Y	N	N
Study Confounding Summary	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*. Rating of "Risk of bias"	High	Low	High	High	Low	Low	High	High
6. Statistical Analysis and Reporting	Goal: To judge the risk of bias related to the statistical analysis and presentation of results.								
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	N	N	Y	N	N	Y	N	N
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	N	N	Y	N	Y	Y	N	N
	The selected statistical model is adequate	N	Y	Y	N	NC	Y	N	Y

	for the design of the study.								
Reporting of results	There is no selective reporting of results.	Y	N	N	N	Y	Y	Y	Y
Statistical Analysis and Presentation Summary	The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.	High	High	Low	High	Low	Low	High	High
	Rating of "Risk of bias"								

Biases	Issues to consider for judging overall rating of "Risk of bias"	Studies							
		Kiran et al 2011[37]	Noor-Mohammed et al 2012[38]	Peretz et al 2003[34]	Ramos-Jorge et al 2011[33]	Shapira et al 2003[40]	Tasanen 1969[35]	Wake et al 2000[10]	Yam et al 2002[41]
		Rating of reporting	Rating of reporting	Rating of reporting	Rating of reporting	Rating of reporting	Rating of reporting	Rating of reporting	Rating of reporting
1. Study Participation	Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).								
Source of target population	The source population or population of interest is adequately described for key characteristics.	Y	Y	Y	Y	Y	Y	Y	Y
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	Y	Y	Y	Y	Y	Y	Y	Y
Recruitment period	Period of recruitment is adequately	Y	Y	Y	Y	Y	Y	Y	N

	described								
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	Y	Y	Y	Y	Y	Y	Y	Y
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	N	Y	Y	Y	Y	Y	Y	N
Adequate study participation	There is adequate participation in the study by eligible individuals	Y	Y	Y	Y	Y	Y	Y	N
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for key characteristics	Y	Y	Y	Y	Y	Y	Y	N
Summary Study participation	The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.	Low	Low	Low	Low	Low	Low	Low	High
	Rating of "Risk of bias"								
2. Study Attrition	Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).								
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Y	Y	N	Y	Y	NC	Y	N
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	Y	NA	NA	N	N	N	N	N
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	Y	Y	N	Y	N	N	N	N
Outcome and prognostic factor	Participants lost to follow-up are adequately described for key	Y	Y	N	Y	N	N	Y	N

information on those lost to follow-up	characteristics. There are no important differences between key characteristics and outcomes in participants who completed the study and those who did not.	NC	Y	N	Y	Y	NC	Y	N
Study Attrition Summary	Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.	Low	Low	High	Mod	High	High	Mod	High
	Rating of "Risk of bias"								
3. Prognostic Factor Measurement	Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).								
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	N	N	Y	Y	N	Y	Y	N
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	N	N	N	Y	N	Y	Y	N
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	N	N	Y	Y	Y	Y	Y	N
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Y	Y	NC	Y	Y	Y	Y	Y

Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	Y	Y	Y	Y	N	Y	Y	Y
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	NA	NA	NA	NA	NA	NA	NA	NA
PF Measurement Summary	*PF* is adequately measured in study participants to sufficiently limit potential bias.	High	High	Low	Low	Mod	Low	Low	High
	Rating of "Risk of bias"								
4. Outcome Measurement	Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).								
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	N	NA	Y	Y	Y	Y	Y	N
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	N	N	N	Y	Y	Y	Y	N
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	N	N	N	Y	Y	Y	Y	Y
Outcome Measurement Summary	*Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.	High	High	Mod	Low	Low	Low	Low	High
	Rating of "Risk of bias"								
5. Study Confounding	Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).								
Important	All important confounders, including	Y	N	N	Y	Y	Y	Y	N

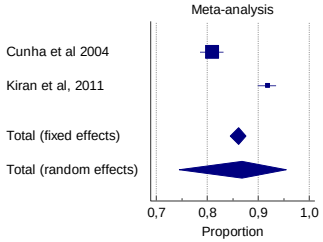
Confounders Measured	treatments (key variables in conceptual model), are measured.								
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	N	N	N	Y	Y	Y	Y	N
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	N	N	N	Y	Y	Y	Y	N
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	N	N	N	N	Y	Y	Y	N
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	NA	NA	NA	NA	NA	NA	NA	NA
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Y	N	N	Y	Y	Y	Y	N
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	N	Y	Y	Y	Y	Y	Y	N
Study Confounding Summary	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*. Rating of "Risk of bias"	High	High	High	Low	Low	Low	Low	High
6. Statistical Analysis and Reporting	Goal: To judge the risk of bias related to the statistical analysis and presentation of results.								
Presentation of	There is sufficient presentation of data to	N	Y	Y	Y	Y	Y	Y	N

analytical strategy	assess the adequacy of the analysis.								
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	N	Y	Y	Y	Y	Y	Y	N
	The selected statistical model is adequate for the design of the study.	N	Y	Y	Y	Y	Y	Y	N
Reporting of results	There is no selective reporting of results.	Y	Y	Y	Y	Y	Y	Y	Y
Statistical Analysis and Presentation Summary	The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.	High	Low	Low	Low	Low	Low	Low	High
	Rating of "Risk of bias"								

* Abbreviations: QUIPS, Quality in Prognosis Studies Tool; PF, Prognostic factor. Ratings: High, moderate, and low indicates high, moderate, and low risk of bias, respectively. NA, Not Applicable; NC, Not Clear, N, No; Y, Yes.

APPENDIX 4. Forest plot of prevalence for each individual sign or symptom. A, Forest plot for gingival irritation. Sample = 2059. B, Forest plot for irritability. Sample = 2215. C, Forest plot for drooling. Sample = 4364. D, Forest plot for loss of appetite. Sample = 1050. E, Forest plot for agitated sleep. Sample = 2215. F, Forest plot for runny nose. Sample = 2226. G, Forest plot for fever. Sample = 3719. H, Forest plot for diarrhea. Sample = 2576

A. Gingival Irritation



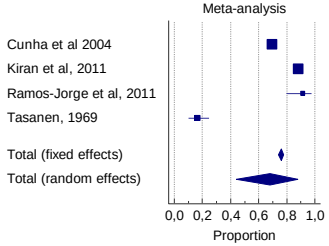
Variable for studies	Author__Year Author, Year
Variable for total number of cases	Total_n Total n
Variable for number of positive cases	Gingival_irritation Gingival irritation

Study	Sample size	Proportion (%)	95% CI
Cunha et al 2004	1165	80,944	78,569 to 83,162
Kiran et al, 2011	894	91,834	89,842 to 93,545
Total (fixed effects)	2059	86,106	84,537 to 87,571
Total (random effects)	2059	86,818	74,464 to 95,516

Test for heterogeneity

Q	52,7809
DF	1
Significance level	P < 0,0001
I^2 (inconsistency)	98,11 %
95% CI for I^2	95,62 to 99,18

B. Irritability



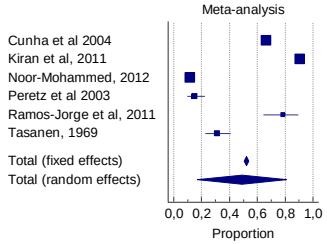
Variable for studies	Author__Year Author, Year
Variable for total number of cases	Total_n Total n
Variable for number of positive cases	Irritability

Study	Sample size	Proportion (%)	95% CI
Cunha et al 2004	1165	69,700	66,970 to 72,329
Kiran et al, 2011	894	88,255	85,962 to 90,293
Ramos-Jorge et al, 2011	47	91,489	79,621 to 97,632
Tasanen, 1969	109	16,514	10,091 to 24,837
Total (fixed effects)	2215	76,050	74,218 to 77,813
Total (random effects)	2215	68,194	44,145 to 87,965

Test for heterogeneity

Q	302,8950
DF	3
Significance level	P < 0,0001
I^2 (inconsistency)	99,01 %
95% CI for I^2	98,52 to 99,34

C. Drooling



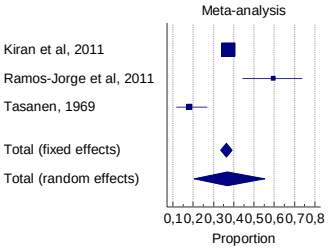
Variable for studies	Author__Year Author, Year
Variable for total number of cases	Total_Sample Total Sample
Variable for number of positive cases	Drooling

Study	Sample size	Proportion (%)	95% CI
Cunha et al 2004	1165	66,352	63,557 to 69,064
Kiran et al, 2011	894	90,492	88,378 to 92,335
Noor-Mohammed, 2012	1110	11,892	10,046 to 13,943
Peretz et al 2003	145	15,172	9,759 to 22,065
Ramos-Jorge et al, 2011	47	78,723	64,336 to 89,297
Tasanen, 1969	109	31,193	22,662 to 40,775
Total (fixed effects)	3470	52,085	50,409 to 53,758
Total (random effects)	3470	48,789	17,044 to 81,096

Test for heterogeneity

Q	1868,7453
DF	5
Significance level	P < 0,0001
I^2 (inconsistency)	99,73 %
95% CI for I^2	99,67 to 99,78

D. Loss of Appetite



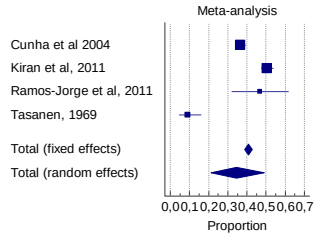
Variable for studies	Author__Year Author, Year
Variable for total number of cases	Total_n Total n
Variable for number of positive cases	Loss_of_appetite Loss of appetite

Study	Sample size	Proportion (%)	95% CI
Kiran et al, 2011	894	37,472	34,289 to 40,738
Ramos-Jorge et al, 2011	47	59,574	44,266 to 73,631
Tasanen, 1969	109	18,349	11,583 to 26,906
Total (fixed effects)	1050	36,314	33,404 to 39,302
Total (random effects)	1050	37,031	20,560 to 55,231

Test for heterogeneity

Q	28,6221
DF	2
Significance level	P < 0,0001
I^2 (inconsistency)	93,01 %
95% CI for I^2	82,92 to 97,14

E. Agitated Sleep



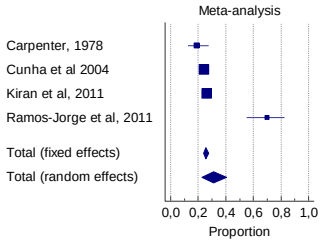
Variable for studies	Author__Year
Variable for total number of cases	Total_n
Variable for number of positive cases	Agitated_sleep

Study	Sample size	Proportion (%)	95% CI
Cunha et al 2004	1165	36,652	33,879 to 39,493
Kiran et al, 2011	894	50,559	47,229 to 53,886
Ramos-Jorge et al, 2011	47	46,809	32,112 to 61,922
Tasanen, 1969	109	9,174	4,488 to 16,225
Total (fixed effects)	2215	40,780	38,727 to 42,859
Total (random effects)	2215	34,539	21,354 to 49,066

Test for heterogeneity

Q	106,7486
DF	3
Significance level	P < 0,0001
I^2 (inconsistency)	97,19 %
95% CI for I^2	95,05 to 98,40

F. Runny Nose



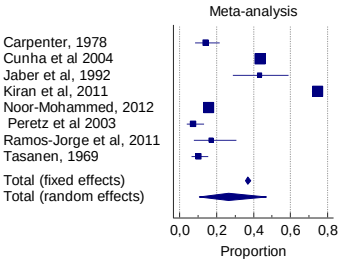
Variable for studies	Author__Year Author, Year
Variable for total number of cases	Total_n Total n
Variable for number of positive cases	Runny_nose Runny nose

Study	Sample size	Proportion (%)	95% CI
Carpenter, 1978	120	19,167	12,555 to 27,358
Cunha et al 2004	1165	24,206	21,771 to 26,772
Kiran et al, 2011	894	26,174	23,319 to 29,187
Ramos-Jorge et al, 2011	47	70,213	55,106 to 82,661
Total (fixed effects)	2226	25,627	23,825 to 27,492
Total (random effects)	2226	31,321	22,714 to 40,631

Test for heterogeneity

Q	44,3541
DF	3
Significance level	P < 0,0001
I^2 (inconsistency)	93,24 %
95% CI for I^2	85,89 to 96,76

G. Fever



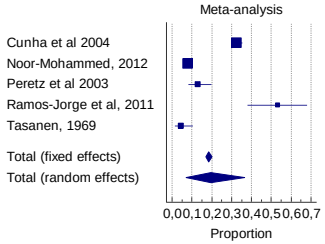
Variable for studies	Author__Year Author, Year
Variable for total number of cases	Total
Variable for number of positive cases	Fever

Study	Sample size	Proportion (%)	95% CI
Carpenter, 1978	120	14,167	8,474 to 21,711
Cunha et al 2004	1165	43,777	40,904 to 46,681
Jaber et al, 1992	46	43,478	28,934 to 58,893
Kiran et al, 2011	894	74,720	71,737 to 77,540
Noor-Mohammed, 2012	1110	15,856	13,755 to 18,140
Peretz et al 2003	145	7,586	3,848 to 13,168
Ramos-Jorge et al, 2011	47	17,021	7,647 to 30,809
Tasanen, 1969	192	10,417	6,480 to 15,629
Total (fixed effects)	3719	37,081	35,528 to 38,655
Total (random effects)	3719	26,701	10,545 to 46,995

Test for heterogeneity

Q	1034,1251
DF	7
Significance level	P < 0,0001
I^2 (inconsistency)	99,32 %
95% CI for I^2	99,14 to 99,46

H. Diarrhea



Variable for studies	Author__Year Author, Year
Variable for total number of cases	Total_n Total n
Variable for number of positive cases	Diarrhea

Study	Sample size	Proportion (%)	95% CI
Cunha et al 2004	1165	32,704	30,014 to 35,482
Noor-Mohammed, 2012	1110	7,928	6,407 to 9,676
Peretz et al 2003	145	13,103	8,077 to 19,704
Ramos-Jorge et al, 2011	47	53,191	38,078 to 67,888
Tasanen, 1969	109	4,587	1,506 to 10,381
Total (fixed effects)	2576	18,468	16,988 to 20,020
Total (random effects)	2576	19,526	6,960 to 36,473

Test for heterogeneity

Q	288,2248
DF	4
Significance level	P < 0,0001
I^2 (inconsistency)	98,61 %
95% CI for I^2	97,95 to 99,06

APPENDIX 5. Prevalence of each sign or symptom occurred during the eruption of primary teeth.

Author, Year	Total	Complication	Teething Signs and Symptoms	Percentage
Cunha et al 2004[32]	1165	943	Gingival irritation	80.94
Kiran et al, 2011[36]	894	821	Gingival irritation	91.83
			Mean from Meta-Analysis	86.81 (74.46 to 95.51)
			I^2 (Inconsistency)	98.11% (95.62 to 99.18)
Cunha et al 2004[32]	1165	812	Irritability	69.70
Kiran et al, 2011[36]	894	789	Irritability	88.26
Ramos-Jorge et al, 2011[33]	47	43	Irritability	91.49
Tasanen, 1969[34]	109	18	Irritability	16.51
			Mean from Meta-Analysis	68.19 (44.14 to 87.96)
			I^2 (Inconsistency)	99.01% (98.52 to 99.34)
Cunha et al 2004[32]	1165	773	Drooling	66.35
Kiran et al, 2011[36]	894	809	Drooling	90.49
Noor-Mohammed, 2012[38]	1110	132	Drooling	11.89
Peretz et al 2003[34]	145	22	Drooling	15.17
Ramos-Jorge et al, 2011[33]	47	37	Drooling	78.72
Tasanen, 1969[34]	109	34	Drooling	31.19
			Mean from Meta-Analysis	48.79 (17,044 to 81,096)
			I^2 (Inconsistency)	99.73% (99,67 to 99,78)
Tasanen, 1969[34]	109	45	Sucking finger	41.28
Kiran et al, 2011[36]	894	335	Loss of appetite	37.47
Ramos-Jorge et al, 2011[33]	47	28	Loss of appetite	59.57
Tasanen, 1969[34]	109	20	Loss of appetite	18.35
			Mean from Meta-Analysis	37.03 (20.56 to 55.23)
			I^2 (Inconsistency)	93.01% (82.92 to 97.14)
Cunha et al 2004[32]	1165	427	Agitated sleep	36.65
Kiran et al, 2011[36]	894	452	Agitated sleep	50.56
Ramos-Jorge et al, 2011[33]	47	22	Agitated sleep	46.81
Tasanen, 1969[34]	109	10	Agitated sleep	9.17

			Mean from Meta-Analysis	34.53 (21.35 to 49.06)
			I^2 (Inconsistency)	97.19 % (95.05 to 98.40)
Carpenter, 1978[42]	120	23	Runny nose	19.17
Cunha et al 2004[32]	1165	282	Runny nose	24.21
Kiran et al, 2011[36]	894	234	Runny nose	26.17
Ramos-Jorge et al, 2011[33]	47	33	Runny nose	70.21
			Mean from Meta-Analysis	31.32 (22.71 to 40.63)
			I^2 (Inconsistency)	93.24% (85.89 to 96.76)
Carpenter, 1978[42]	120	17	Fever	14.17
Cunha et al 2004[32]	1165	510	Fever	43.78
Jaber et al, 1992[11]	46	20	Fever	43.48
Kiran et al, 2011[36]	894	668	Fever	74.72
Noor-Mohammed, 2012[38]	1110	176	Fever	15.86
Peretz et al 2003[34]	145	11	Fever	7.59
Ramos-Jorge et al, 2011[33]	47	8	Fever	17.02
Tasanen, 1969[34]	192	20	Fever	10.42
			Mean from Meta-Analysis	26.70 (10.54 to 46.99)
			I^2 (Inconsistency)	99.32% (99.14 to 99.46)
Cunha et al 2004[32]	1165	381	Diarrhea	32.70
Noor-Mohammed, 2012[38]	1110	88	Diarrhea	7.93
Peretz et al 2003[34]	145	19	Diarrhea	13.10
Ramos-Jorge et al, 2011[33]	47	25	Diarrhea	53.19
Tasanen, 1969[34]	109	5	Diarrhea	4.59
			Mean from Meta-Analysis	19.52 (6.96 to 36.47)
			I^2 (Inconsistency)	98.61% (97.95 to 99.06)
Carpenter, 1978[42]	120	6	Facial Rash	5.00
Carpenter, 1978[42]	120	1	Vomiting	0.83

4 CONSIDERAÇÕES FINAIS

Os resultados dessa revisão sistemática apontam que podem ocorrer sinais e sintomas durante a erupção dos dentes decíduos, porém de menor gravidade como inflamação gengival, irritabilidade e aumento de salivação. Febre não esteve relacionada à erupção dos dentes decíduos, embora tenha sido observado leve aumento da temperatura corporal nos dias de erupção dental.

Pesquisas com delineamento mais apurado, envolvendo grupo controle e determinação dos fatores de confundimento são necessárias. Sintomas mais graves, como a diarreia, embora tenham sido relatados durante a erupção dos dentes decíduos em alguns estudos, precisam de investigação do diagnóstico através de exame por um profissional de saúde.

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APÊNDICES

APÊNDICE A – ESTRUTURA PERGUNTA PECOS

A pergunta focada, nesta revisão sistemática foi: Em crianças entre 0 e 36 meses, há a ocorrência de sinais e sintomas locais e sistêmicos durante a erupção dos dentes decíduos?

A pergunta focada tem o objetivo de auxiliar os revisores a pensar claramente sobre o escopo da revisão. A definição da pergunta focada é o primeiro passo da revisão sistemática (NEEDLEMAN, 2002). O acrônimo PICO (ou PECO) auxilia a fragmentar a questão em quatro partes: Paciente/Problema; Intervenção/Exposição; Comparação e Desfecho (MAIA, ANTONIO, 2012). Ainda pode ser acrescentado o tipo de estudo, componente S do acrônimo conforme Tabela 1.

Tabela 1 – Estrutura da pergunta PECO.

PECOS	
Participantes (P)	Crianças entre 0-36 meses
Exposição (E)	Erupção do dente decíduo
Comparação (C)	Não há
Outcome ou desfecho (O)	Sinais e sintomas locais e sistêmicos
Tipo de estudo (S)	Estudos observacionais

APÊNDICE B – CRITÉRIOS DE ELEGIBILIDADE E ESTRATÉGIA DE BUSCA COMPLETA

Nessa revisão foram incluídos estudos observacionais avaliando a ocorrência de sinais e sintomas locais e sistêmicos durante a erupção espontânea dos dentes decíduos em crianças saudáveis com idade entre 0 e 36 meses, por meio de exame clínico ou questionário dirigido aos pais ou profissionais de saúde. Os sinais e sintomas locais e sistêmicos avaliados foram os relatados como relacionados com a erupção dos dentes decíduos descritos nos estudos (por exemplo, diminuição do apetite, diarreia, aumento da salivação, febre, inflamação, ulceração gengival, irritabilidade, erupções cutâneas, rinorreia, perturbações do sono, vômitos).

Os critérios de exclusão foram aplicados nas duas fases de seleção dos artigos. Na primeira fase, de leitura de títulos e resumos, foram considerados os seguintes critérios de exclusão:

1 - Estudos realizados em crianças com idade superior a 36 meses;
2 - Revisões, cartas, resumos de congressos;
3 - Estudos em que a amostra incluiu pacientes com síndromes genéticas (por exemplo, síndrome de Down, anomalias craniofaciais, doenças neuromusculares, etc.);
4 - Estudos em que a amostra incluiu malignidades, desnutrição e doenças crônicas;
5 - Estudos em que a amostra incluiu erupção não-espontânea dos dentes decíduos;
6 - Estudos em que a erupção dos dentes decíduos não foi o desfecho primário.

Além dos seis critérios citados, na segunda fase, de leitura de texto completo, foram adicionados os seguintes critérios de exclusão:

7 - Estudos em que o exame clínico não foi realizado por um profissional de saúde e,
8 - Artigos que avaliaram a mesma amostra.

Para identificar os estudos elegíveis, foi realizada busca eletrônica nas seguintes bases de dados: Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), PubMed, ProQuest Dissertations and Theses Database, Scopus e Web of Science. Ainda foram adicionadas à busca, a pesquisa de parte da literatura cinzenta no Google Scholar, sendo considerados as primeiras 100 referências excluindo-se patentes e citações; e a busca manual nas referências dos

artigos incluídos para qualquer referência que possa ter sido inadvertidamente excluída durante as buscas eletrônicas. Não houve limitação quanto ao idioma nem data de publicação dos artigos. A busca em todas as bases de dados foi realizada em 6 de maio de 2015. As estratégias de busca em cada base de dados está exposta na Tabela 2. A sintaxe foi adaptada para cada base de dados.

Tabela 2 – Estratégia de busca para cada base de dados. Realizada em 6 de maio de 2015.

Base de dados	Estratégia de busca
LILACS	(tw:((decidu* OR "Dente Decíduo" OR "Dentição primaria" OR "primeira Dentição" OR "dente de leite" OR "dentes de leite" OR "diente primario" OR "dientes primarios" OR "primary dentition" OR "primary teeth" OR "primary tooth" OR "milk teeth" OR "milk tooth" OR "baby teeth" OR "baby tooth") AND (erupção OR erupti* OR erupcion OR irrompimento OR irromper OR nascer OR nascimento OR "Movimentação Dentária" OR "tooth emergence" OR "tooth movement"))) AND (tw:((sintoma* OR febre OR "Temperatura Corporal" OR diarreia OR apetite OR irrita* OR coriza OR saliva* OR tosse OR orelha OR vomit* OR sucção OR mord* OR dor* OR symptom* OR "fever" OR "body temperature" OR "diarrhoea" OR "diarrhea" OR "appetite" OR "irritable mood" OR "nose" OR "nasal congestion" OR "cough" OR "sialorrhea" OR "drooling" OR "ear pulling" OR "rash" OR "vomiting" OR "pain" OR "sucking"))) AND (instance:"regional") AND (db:("LILACS"))
PubMed	(infant OR baby OR babies OR preschool OR child OR children OR infants OR pediatric OR paediatric) AND ("deciduous tooth" OR deciduous OR "primary dentition" OR "primary dentitions" OR "primary teeth" OR "primary tooth" OR "milk teeth" OR "milk tooth" OR "baby teeth" OR "baby tooth" OR milk-tooth OR "deciduous teeth") AND (symptom* OR signs OR fever OR “body temperature” OR diarrhoea OR diarrhea OR appetite OR “irritable mood” OR irritability OR salivation OR sleep OR erythema OR biting OR “runny nose” OR “nasal congestion” OR cough OR drooling OR sialorrhea OR “ear pulling” OR rash OR vomiting OR “sucking behavior” OR sucking OR sign) AND (eruption OR teething)
ProQuest	(all(("deciduous" OR ("primary" AND "dentition*") OR ("primary" AND "teeth") OR ("primary" AND "tooth") OR ("milk" AND "teeth") OR ("milk" AND "tooth") OR

	("baby" AND "teeth") OR ("baby" AND "tooth")) AND (erupt* OR ("tooth" AND "emergence") OR ("tooth" AND "movement"))) OR all(teething)) AND all(symptom* OR "fever" OR "body temperature" OR "diarrhoea" OR "diarrhea" OR "appetite" OR "irritable mood" OR "nose" OR "nasal congestion" OR "cough" OR "sialorrhea" OR "drooling" OR "ear pulling" OR "rash" OR "vomiting" OR "pain" OR "sucking")
Scopus	(((TITLE-ABS-KEY("deciduous" OR ("primary" W/5 "dentition") OR ("primary" W/5 "teeth") OR ("milk" W/5 "teeth") OR ("baby" W/5 "teeth")) AND TITLE-ABS-KEY("erupti*" OR ("tooth" W/5 "emergence") OR ("tooth" W/5 "movement")))) OR (TITLE-ABS-KEY("teething"))) AND (TITLE-ABS-KEY((symptom* OR "fever" OR "body temperature" OR "diarrhoea" OR "diarrhea" OR "appetite" OR "irritable mood" OR "nose" OR "nasal congestion" OR "cough" OR "sialorrhea" OR "drooling" OR "ear pulling" OR "rash" OR "vomiting" OR "pain" OR "sucking")))
Web of Science	#1 OR #2 = #3 #3 AND #4 1= (("deciduous" OR ("primary" AND "dentition*") OR ("primary" AND "teeth") OR ("primary" AND "tooth") OR ("milk" AND "teeth") OR ("milk" AND "tooth") OR ("baby" AND "teeth") OR ("baby" AND "tooth")) AND (erupti* OR ("tooth" AND "emergence") OR ("tooth" AND "movement"))) 2 = ("teething") 3 = (symptom* OR "fever" OR "body temperature" OR "diarrhoea" OR "diarrhea" OR "appetite" OR "irritable mood" OR "nose" OR "nasal congestion" OR "cough" OR "sialorrhea" OR "drooling" OR "ear pulling" OR "rash" OR "vomiting" OR "pain" OR "sucking")
Google Scholar	teething signs OR symptoms "eruption of primary teeth"

As referências foram importadas para o programa gerenciador de referências EndNote® Basic (Thomson Reuters, New York, EUA) e as duplicadas foram eliminadas.

APÊNDICE C – EQUIPE DA REVISÃO SISTEMÁTICA E SUAS FUNÇÕES

A triagem dos estudos foi realizada por dois revisores (CM, MB) de maneira independente em duas etapas. O processo de avaliação começou pela leitura dos títulos e resumos, quando disponíveis, e uma etapa posterior de confirmação, pela leitura do manuscrito em forma de texto completo. Nos casos em que o resumo não estava disponível, se o título fosse sugestivo de inclusão, o artigo foi lido na íntegra para avaliar a sua elegibilidade. Caso, depois da leitura do texto completo, ainda houvesse quaisquer dúvidas em relação ao estudo, os autores foram contatados.

As discordâncias entre os revisores foram resolvidas por consenso. Quando o consenso não foi possível, o terceiro revisor (MC) auxiliou na tomada de decisão. A seleção final foi baseada na leitura do texto completo. A equipe da revisão sistemática e suas funções correspondentes estão dispostas na Tabela 3.

Tabela 3 - Equipe da revisão sistemática, suas afiliações e funções correspondentes.

Autor	Afiliação	Contribuições
1. Carla Massignan	UFSC	1R
2. Michele Bolan	UFSC	2R
3. Mariane Cardoso	UFSC	3R
4. André Luís Porporatti	USP	E
5. Secil Aydinoz	GATA H.T.H.	E
6. Graziela de Luca Canto	COBE UFSC	SC
7. Luis Andre Mendonça Mezzomo	COBE UFSC	C

1R = Primeiro Revisor (Conceituação e Desenho do estudo / Busca e seleção / Coleta de dados / Análise de dados / Preparação do manuscrito). 2R = Segundo Revisor (Conceituação e Desenho do estudo / Busca e seleção / Coleta de dados / Análise de dados / Preparação do manuscrito). 3R = Terceiro Revisor (Análise de dados). E = Expert (Conceituação e Desenho de estudo / Análise de dados). SC = Subcoordenador (Conceituação e Desenho de estudo / Análise de dados). C = Coordenador (Conceituação e Desenho de estudo / Análise de dados).
Todos os autores: revisão do manuscrito.

Os dados foram coletados separadamente por cada um dos dois revisores (CM, MB). Qualquer divergência foi resolvida por meio de discussão e acordo mútuo entre ambos. Quando o acordo não foi possível, o terceiro revisor (MC) auxiliou na decisão final.

APÊNDICE D – CRITÉRIOS USADOS PELOS AUTORES PARA CLASSIFICAR O RISCO DE VIÉS DOS ARTIGOS SELECIONADOS PARA A REVISÃO SISTEMÁTICA SEGUNDO A FERRAMENTA DE AVALIAÇÃO DA QUALIDADE QUIPS (QUALITY IN PROGNOSIS STUDIES TOOL)

O risco de viés dos estudos incluídos foi verificado através da ferramenta de avaliação da qualidade Quality in Prognosis Studies Tool (QUIPS - Avaliação da Qualidade em Estudos de Prognóstico – em tradução livre) (HAYDEN, et al., 2013). Dois revisores (CM, MB), de forma independente, avaliaram a qualidade dos estudos e o terceiro revisor (MC) foi consultado quando não houve consenso. Os critérios utilizados para cada um dos seis domínios da ferramenta - Study Participation, Study Attrition, Prognostic Factors Measurement, Outcome Measurement, Study Confounding and Statistical Analysis and Reporting – para classificar os estudos incluídos como sendo de alto, moderado ou baixo risco de viés, estão dispostos na Tabela 4.

Tabela 4 – Critérios usados pelos autores para classificar o risco de viés dos artigos selecionados para a revisão sistemática segundo a ferramenta de avaliação da qualidade QUIPS*

1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**	
Source of target population	The source population or population of interest is adequately described for key characteristics.	- A proveniência dos bebês está descrita adequadamente
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	- Apresenta adequadamente número da amostra, idade
Recruitment period	Period of recruitment is adequately described	- Apresenta adequadamente período de seleção da amostra
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	- Apresenta adequadamente o local/lugar de seleção da amostra
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic	- Apresenta adequadamente os critérios de inclusão/exclusão como crianças saudáveis,

	criteria or "zero time" description).	crianças com doença, crianças na época de erupção dos dentes decíduos, etc.
Adequate study participation	There is adequate participation in the study by eligible individuals	- Apresenta a abrangência da amostra; se é só uma creche, de creches de várias partes da cidade, mães que trabalham, que não trabalham, abrange várias classes econômicas
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for key characteristics.	- Apresenta adequadamente os bebês que entraram na amostra final
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.** **Rating of "Risk of bias"**	
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**	
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	-A taxa de resposta é adequada (considerar maior que 70%)
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	- Apresenta informação quanto à tentativa de rechamada dos participantes perdidos
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	- Razões de perda são descritas
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics .	- Apresenta informação quanto aos participantes perdidos
	There are no important differences between key characteristics and outcomes in participants who completed the study and those who did not.	- Não há diferença nos participantes perdidos e os que completaram o estudo

Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.** **Rating of "Risk of bias"**	
3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**	
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	- **Apresenta como foi feito o diagnóstico da erupção dental?** Sim(+), não (-) Tátil, visual, com iluminação (+) não relata (-) Dente emergindo através da gengiva (++), dente com 3mm de coroa exposta (+), não relata (-) Quem fez o exame: profissional de saúde (+), relato de pais (-) Quem fez o exame foi o mesmo que mediu a temperatura? (-) Que fez entrevista? (-) - **Apresenta como foram medidos os sintomas?** Sim(+), não (-) Relato dos pais, exame físico (+), medição de temperatura (+) **- Quando os exames bucal, temperatura e relato dos sintomas foram feitos?** Frequência: Diariamente (++), mensalmente (+) não relata (-) Período: mesmo horário (++), 1 x/dia (+), >1x/dia (++) Tipo de termômetro (+) não relata (-)
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	- Cita algum cegamento dos examinadores - Apresenta grupo controle - Mãe não sabe qual foi a temperatura do bebê antes de responder ao questionário

	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	- Apresenta ponto de corte para temperatura corporal
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	- O método de medida é o mesmo para todos os participantes?
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	- Proporção da amostra é adequada para os dados?
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	- Apresenta métodos de imputação de dados
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.** **Rating of "Risk of bias"**	
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**	
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	- Apresenta resultado claro, incluindo o tempo de acompanhamento (nos transversais não teremos isto)
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	- Os métodos de medição foram adequados
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	- Métodos de medição adequados à todos os participantes
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.** **Rating of "Risk of bias"**	

5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**	
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model), are measured.	-Todos os fatores confundidores são medidos como outras doenças não relacionadas ao dente (as crianças eram examinadas por médico ou encaminhadas para detecção de outra doença?) - Os exames foram realizados antes, durante e após a erupção dental?
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	- Apresenta definição dos fatores confundidores? (outras doenças)
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	- Apresenta fatores de confundimento plausíveis
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	-Os fatores confundidores são aplicáveis em todos os participantes?
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	- Apresenta métodos de imputação de dados
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	-Os fatores confundidores são levados em consideração no delineamento do estudo?
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	-Os fatores confundidores são levados em consideração na análise dos dados?
Study Confounding	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship**	

Summary	**between *PF* and *outcome*.** **Rating of "Risk of bias"**	
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**	
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	-Apresenta dados suficientes para análise?
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	- Estratégia de inclusão das variáveis no modelo estatístico é apropriada
	The selected statistical model is adequate for the design of the study.	- Modelo estatístico é adequado para o desenho do estudo?
Reporting of results	There is no selective reporting of results.	- Apresenta os resultados reais, não seletivo
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.** **Rating of "Risk of bias"**	

***** Quality in Prognosis Studies Tool

ANEXO

ANEXO A – REGISTRO PROSPERO

A fim de aumentar a disponibilidade e acessibilidade dos métodos a priori para revisões sistemáticas, reduzir a duplicação de esforços na condução das revisões e reduzir o viés de publicação, há um portal on-line, International Prospective Register of Ongoing Systematic Reviews (PROSPERO), que permite registrar a intenção de realizar uma revisão sistemática, mesmo antes de ser iniciada (BOOTH, et al., 2011). A documentação dos métodos a priori, aumenta a transparência no processo de revisão, permitindo que os leitores de revisões sistemáticas possam comparar métodos, resultados e análises realizadas com as planejadas com antecedência. O registro no PROSPERO permite a documentação permanente de 22 itens obrigatórios e 18 opcionais sobre o projeto a priori e a condução de uma revisão (MOHER, et al., 2015). Assim, o protocolo dessa revisão sistemática foi registrado no PROSPERO sob número CRD 42015020822 (PROSPERO, 2015)

PROSPERO International prospective register of systematic reviews

Review title and timescale

1 Review title
Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.
Signs and symptoms of eruption of primary teeth: a systematic review and meta-analysis

2 Original language title
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3 Anticipated or actual start date
Give the date when the systematic review commenced, or is expected to commence.
11/02/2015

4 Anticipated completion date
Give the date by which the review is expected to be completed.
01/09/2015

5 Stage of review at time of this submission
Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started ×

Review stage	Started	Completed
Preliminary searches	No	Yes
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

Review team details

6 Named contact
The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Dr Bolan

7 Named contact email
Enter the electronic mail address of the named contact.
michelebolan@hotmail.com

8 Named contact address
Enter the full postal address for the named contact.
Universidade Federal de Santa Catarina UFSC Campus Universitário CCS-ODT-Trindade Florianópolis, Santa Catarina, Brasil 88040-900

9 Named contact phone number
Enter the telephone number for the named contact, including international dialing code.
+55483721-9920

10 Organisational affiliation of the review
Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.
Brazilian Centre for Evidence-based Research, Federal University of Santa Catarina
Website address:
http://ufsc.br

11 Review team members and their organisational affiliations
Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Dr	Carla	Massignan	Federal University of Santa Catarina
Dr	Mariane	Cardoso	Federal University of Santa Catarina
Dr	André	Porporatti	Bauru School of Dentistry, Bauru, São Paulo, Brazil
Dr	Secil	Aydinoz	Military Medical Academy Uskudar-Istanbul-Turkey
Dr	Graziela	De Luca Canto	Brazilian Centre for Evidence-based Research, Federal University of Santa Catarina
Dr	Luis	Mezzomo	Brazilian Centre for Evidence-based Research, Federal University of Santa Catarina
Dr	Michele	Bolan	Federal University of Santa Catarina

12 Funding sources/sponsors
Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.
none

13 Conflicts of interest
List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
Are there any actual or potential conflicts of interest?
None known

14 Collaborators
Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details
Ms	Maria Gorete	Savi	Federal University of Santa Catarina

Review methods

15 Review question(s)
State the question(s) to be addressed / review objectives. Please complete a separate box for each question.
In children aged 0 up to 36 months, are there local or systemic signs and symptoms during the eruption of the primary teeth?

16 Searches
Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.
We will include observational studies related to the spontaneous eruption of primary teeth and the association with local and systemic signs and symptoms. Detailed individual search strategies for each of the following bibliographic databases will be developed: PubMed, Web of Science, Scopus, Lilacs and ProQuest Dissertations and Theses Database. Hand search of the references cited in the selected articles will be also checked. A partial gray literature search will be taken using Google Scholar. No restrictions will be placed on the publication date or languages.

17 URL to search strategy
If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

I give permission for this file to be made publicly available
Yes

18 Condition or domain being studied
Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.
Many parents and health professionals believe that there is an association between local and systemic signs and symptoms and the eruption of primary teeth. Although it is a part of child development, the association between the eruption of the primary teeth and the general health is still controversial.

19 Participants/population
Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
Children aged between 0 and 36 months

20 Intervention(s), exposure(s)
Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed
Eruption of primary teeth

21 Comparator(s)/control
Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).
Not applicable.

22 Types of study to be included initially
Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.
Observational studies

23 Context
Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.
Inclusion criteria: Observational studies assessing the occurrence of local and systemic signs and symptoms during the spontaneous eruption of primary teeth in healthy children aged between 0 and 36 months, by means of either clinical examination or a questionnaire directed to the parents or health care professionals. Exclusion criteria: Phase 1(titles and abstracts): 1 - Studies in children aged over 36 months old, 2 - Reviews, letters, conference abstracts, 3 - Studies which the sample included genetic syndromic patients (e.g., Down syndrome, craniofacial anomalies, neuromuscular disorders, etc.), 4 - Studies which the sample included malignancies, malnutrition and chronic diseases, 5 - Studies which the sample included non spontaneous eruption of primary teeth, 6 - Studies in which the eruption of primary teeth was not the primary outcome. Phase 2 (full-text):the following exclusion criteria were added: 7 - Studies that clinical exam was not performed by a health care professional and, 8- Articles that evaluated the same sample.

24 Primary outcome(s)
Give the most important outcomes.
Local and systemic signs and symptoms associated with the eruption of primary teeth
Give information on timing and effect measures, as appropriate.

25 Secondary outcomes
List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.
None

Give information on timing and effect measures, as appropriate.
None

26 Data extraction, (selection and coding)
Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.
The selection will be performed in two phases. In phase 1 two reviewers working independently will screen titles and abstracts for inclusion in the group of articles for full-text review. If both authors thought that an article should be included or excluded then that will be the final decision. If the two authors disagree, the third reviewer will be consulted to help resolve the differences. If there are differences remaining, the full article will be assessed. In phase 2, the authors will read the full articles to determine which of them finally meet the inclusion criteria. Any additional articles will be included in the review if they are recommended by the expert or identified through the citations of relevant articles. These articles need to meet the same inclusion criteria as those identified through the search engines.

27 Risk of bias (quality) assessment
State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.
The QUIPS (Assessing bias in studies of prognostic factors) tool will be used to judge bias and applicability.

28 Strategy for data synthesis
Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.
If the data from the studies are relatively homogeneous a meta-analysis will be applied.

29 Analysis of subgroups or subsets
Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.
None planned

Review general information

30 Type of review
Select the type of review from the drop down list.
Prognostic

31 Language
Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.
English
Will a summary/abstract be made available in English?
Yes

32 Country
Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.
Brazil

33 Other registration details
Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.

34 Reference and/or URL for published protocol
Give the citation for the published protocol, if there is one.
Massignan et al. Signs and symptoms of the eruption of primary teeth: a systematic review and meta-analysis
Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available
Yes

35 Dissemination plans
Give brief details of plans for communicating essential messages from the review to the appropriate audiences.
Do you intend to publish the review on completion?
Yes

36 Keywords
Give words or phrases that best describe the review. (One word per box, create a new box for each term)
Review
Teething
Tooth eruption
Signs
Symptoms

36 Keywords
Give words or phrases that best describe the review. (One word per box, create a new box for each term)
Review
Teething
Tooth eruption
Signs
Symptoms
Deciduous tooth

37 Details of any existing review of the same topic by the same authors
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38 Current review status
Review status should be updated when the review is completed and when it is published.
Ongoing

39 Any additional information
Provide any further information the review team consider relevant to the registration of the review.

40 Details of final report/publication(s)
This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.
Give the URL where available.

Fonte: PROSPERO. University of York. Disponível em <http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015020822> Acessado em: 24, set. 2015.

ANEXO B – PRISMA CHECKLIST* - LISTA DE VERIFICAÇÃO DOS ITENS A SEREM INCLUÍDOS NO REPORTE DE UMA REVISÃO SISTEMÁTICA OU META-ANÁLISE.

Essa revisão sistemática foi conduzida usando o PRISMA checklist (MOHER, 2010)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
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.	
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.	

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
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).	
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.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in 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.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
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).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
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.	
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.	

Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
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).	
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).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
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.	

*Fonte: MOHER D, LIBERATI A, TETZLAFF J, ALTMAN DG, THE PRISMA GROUP (2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed.1000097

ANEXO C – NORMAS DA REVISTA PEDIATRICS*

Author Guidelines

Pediatrics is the official peer-reviewed journal of the American Academy of Pediatrics. *Pediatrics* publishes original research, clinical observations, and special feature articles in the field of pediatrics, as broadly defined. Contributions pertinent to pediatrics also include related fields such as nutrition, surgery, dentistry, public health, child health services, human genetics, basic sciences, psychology, psychiatry, education, sociology, and nursing.

Pediatrics considers unsolicited manuscripts in the following categories: reports of original research, particularly clinical research; review articles; special articles; and case reports. When preparing a manuscript for *Pediatrics*, authors must first determine the manuscript type and then prepare the manuscript according to the specific instructions below.

The electronic edition of *Pediatrics* is the journal of record. Some accepted articles may also be presented in full in the print version. The editors reserve the right to determine whether an accepted manuscript will be published in the print edition in addition to the electronic edition of *Pediatrics*.

Acceptance Criteria

Relevance to readers is of primary importance in manuscript selection. The readership includes general and specialist pediatricians, pediatric researchers and educators, and child health policy-makers. *Pediatrics* receives many more high quality manuscripts than can be accommodated based on our available space. The current acceptance rate is approximately 10%. An article that is thought by the editors to be not relevant to readers, outside of scope or very unlikely to be accepted may be rejected without review. All manuscripts considered for publication are peer reviewed. Peer reviewers are selected by the editors based on their expertise in the topic of the manuscript; generally at least 2 reviews are required before a decision is rendered. Authors may suggest appropriate reviewers and may also suggest reviewers who should not review the manuscript.

Authors should carefully follow instructions for manuscript preparation, and ensure that the manuscript is proofread before submission. Manuscripts that do not adhere to the author instructions will not be considered for review. Careless preparation of a manuscript suggests careless execution of the research and therefore makes acceptance

unlikely. Manuscripts are scanned for plagiarism using the latest software; if potential plagiarism is detected, the editors will contact the authors for clarification, and may also contact the authors' institution.

Submissions of original research are judged on the importance and originality of the research, scientific strength, clinical relevance, the clarity of the manuscript, and the number of submissions on the same topic. *Pediatrics* does not publish manuscripts that involve animal research.
Pediatrics accepts review articles, with preference given to systematic reviews, which may include meta-analyses. State-of-the-Art Review Articles and Perspectives are generally solicited by the editors or the associate editors for their respective sections. Special Articles reflect topics or issues of relevance to pediatric health care that do not conform to a traditional study format. Case Reports must challenge an existing clinical or pathophysiologic paradigm; provide a starting point for novel hypothesis-testing clinical research; and/or focus on topics pertinent to the pediatric generalist. Quality Reports provide a venue for manuscripts that describe the implementation and outcome of quality-improvement projects. Authors should review and follow the comprehensive reporting guidelines for a wide variety of study designs that are available at http://www.equator-network.org/home/.

Authors submitting manuscripts involving adverse drug or medical device events or product problems should also report these to the appropriate governmental agency.

Unsolicited commentaries will be considered for publication; however, most commentaries are solicited by the editors. Responses to a published article should be submitted as eLetters (see this section); selected eLetters may be published in the journal as Letters to the Editor.

Incorrect grammar, language use, or syntax may distract readers from the science being communicated and may lead to less favorable reviews. To help reduce this possibility, we strongly encourage authors to have their manuscripts reviewed for clarity by colleagues. If the authors' native language is not English, we strongly encourage review and editing by a colleague whose native language is English or the use of an English language editing service.

Peer reviewers are asked to assess each manuscript for originality; for interest to scientists, practitioners and policy makers; for quality of the analysis; and for quality of the presentation, and are asked to assess the priority of the paper for publication. After the reviews are received, the editors may take one of the following actions: *Accept*; *Accept with Revisions*; *Reject with option to Resubmit*; or *Reject*. A rejected manuscript may not be resubmitted. A manuscript may be rejected with an option to resubmit when additional data or analyses are requested by reviewers, or when extensive revision of the text is needed. The resubmitted manuscript receives an additional round of peer review (which may include new reviewers), and the manuscript may or may not be accepted. A decision of *Accept with Revision* indicates that the editors intend to accept the manuscript contingent on adequate response to reviewers. A decision of *Accept*(which is exceedingly rare on first submission) indicates that the manuscript is ready to place into production without further modification. Decisions by the editors are final.

Publication Ethics

Authorship. An "author" is someone who has made substantive intellectual contributions to a published study. Each author is required to meet ALL FOUR of the following criteria:

1. Substantial contribution(s) to conception and design, acquisition of data, or analysis and interpretation of data; AND
2. Drafting the article or revising it critically for important intellectual content; AND
3. Final approval of the version to be published, AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

NOTE: Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute a sufficient basis for authorship.

All persons listed as authors must meet these criteria, and all persons who meet these criteria must be listed as authors. Although *Pediatrics* does not specifically limit the number of authors (except for Case Reports), articles submitted with an unusual number of authors invite scrutiny by editors and reviewers for clear justification for the presence of each person on the authorship list. *Pediatrics* does not permit more than one author to claim any particular position in the author list (e.g., two first authors, or two senior authors).

Decide authorship issues, including the order, before submission. Except in instances where the editorial office has determined that a person does not qualify for authorship, *Pediatrics* does not allow changes to the author order, including adding or removing authors from a paper or any subsequent revisions.

Conflict of Interest and Disclosure. After a paper is accepted by *Pediatrics* for publication, all authors must submit conflict of interest and disclosure forms. *Pediatrics* adheres to the policy and uses the standardized disclosure form of the International Committee of Medical Journal Editors (ICMJE). The collection of the forms is automated within the online system.

IRB Approval. All studies that involve human subjects must be approved or deemed exempt by an official institutional review board; this should be noted in the Methods section of the manuscript.

Industry Sponsorship. *Pediatrics* generally does not accept reports of studies in which all authors are employed by a commercial entity with a financial interest in the results of the study.

Registration of Clinical Trials. All clinical trials must be registered in a World Health organization-approved Clinical Trial registry prior to enrollment of the first subject. The registry name and registration number should be included on the title page. Reports of unregistered trials will be returned to authors without review. Publication of the results of a trial that was initiated prior to the ICMJE requirement for trial registration will be considered by the editors on a case-by-case basis.

Journal Style

All aspects of the manuscript, including the formatting of tables, illustrations, and references and grammar, punctuation, usage, and scientific writing style, should be prepared according to the most current *AMA Manual of Style*(http://www.amamanualofstyle.com).[1]

Author Listing. All authors' names should be listed in their entirety, and should include institutional/professional affiliations and degrees held.

Authoring Groups. If you choose to include an organization, committee, team, or any other group as part of your author list, you must include the names of the individuals as part of the Acknowledgments section of your manuscript. This section should appear after the main text prior to your References section. The terms "for" or "on behalf of" must also be used when referencing the authoring group in the by-line.

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If a manuscript uses the same or similar data contained in previously published articles, the authors must state this in the initial letter of submission and provide citations to the related or possibly duplicative materials.

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All submissions must contain a Contributors' Statement Page, directly following the Title Page. Manuscripts lacking this page will be returned to the authors for correction.

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> Dr Smith conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted.
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> Ms Green designed the data collection instruments, and coordinated and supervised data collection at two of the four sites, critically reviewed the manuscript, and approved the final manuscript as submitted.

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Authors should number figures in the order in which they appear in the text. Figures include graphs, charts, photographs, and illustrations. Each figure should be accompanied by a legend that does not exceed 50

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- Units of independent variables must be provided in tables and results sections if regression coefficients are provided
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Supplemental Information

Authors may wish to include additional information as part of their article for inclusion in the online edition of*Pediatrics*. References to any online supplemental information must appear in the main article. Such supplemental information can include but are not limited to additional tables, figures, videos, audio files, slide shows, data sets (including qualitative data), and online appendices. If your study is based on a survey, consider submitting your survey instrument or the key questions as a data supplement. Authors are responsible for clearly labeling supplemental information and are accountable for its accuracy. Supplemental information will be peer reviewed, but not professionally copyedited.

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Pediatrics encourages the submission of videos to accompany articles where relevant. Links can be placed in the article for use when it is accessed electronically. All videos must adhere to the same general permission rules that apply to figures (i.e.: parental consent when a patient is identifiable).

All videos should be submitted at the desired reproduction size and length. To avoid excessive delays in downloading the files, videos should be no more than 6MB in size, and run between 30 and 60 seconds in length. In addition, cropping frames and image sizes can significantly reduce file sizes. Files submitted can be looped to play

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Reports of systematic reviews and meta-analyses should use the PRISMA statement (http://www.prisma-statement.org/) as a guide, and include a completed PRISMA checklist and flow diagram to accompany the main text. Blank templates of the checklist and flow diagram can be downloaded from the PRISMA Web site (http://www.prisma-statement.org/statement.htm).
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Cover Letter

The cover letter serves to assure the editors that the article and the authors meet the conditions of publication. A brief paragraph that provides any additional information that may be useful to the editors is welcome, but keep in mind that the need for a long cover letter may indicate that the article does not speak for itself. Reviewers will not see the cover letter; cover letters are not a Title Page.

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